▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Casgevy 4 - 13 × 10^6 cells/mL dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Casgevy (exagamglogene autotemcel) is a genetically modified autologous $CD34^+$ cell enriched population that contains haematopoietic stem and progenitor cells (HSPCs) edited *ex vivo* by CRISPR/Cas9 at the erythroid-specific enhancer region of the *BCL11A* gene.

2.2 Qualitative and quantitative composition

Each patient-specific vial of Casgevy contains exagamglogene autotemcel at a batch-dependent concentration of genetically modified autologous $CD34^+$ cells enriched population. The medicinal product is packaged in one or more vials overall containing a dispersion for infusion of 4-13 × 10^6 cells/mL of viable $CD34^+$ cells enriched population suspended in a cryopreservation solution.

Each vial contains 1.5 to 20 mL of dispersion for infusion.

The quantitative information of medicinal product, including the number of vials (see section 6) to be administered, is presented in the Lot information sheet (LIS) located inside the lid of the cryoshipper used for transport.

Excipient(s) with known effect

This medicinal product contains 50 mg of dimethyl sulfoxide (DMSO) per mL.

This medicinal product contains 3.5 mg of sodium per mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.

A translucent cell dispersion for infusion, free from foreign particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

β-thalassemia

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.

Sickle cell disease

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.

4.2 Posology and method of administration

Casgevy must be administered in an authorised treatment centre by a physician with experience in HSC transplantation and in the treatment of patients with β-haemoglobinopathies and trained for administration and management of patients treated with the medicinal product.

Before mobilisation, apheresis and myeloablative conditioning are initiated, confirm that haematopoietic stem cell transplantation is appropriate for the patient.

Posology

Casgevy is intended for autologous use (see section 4.4).

Treatment consists of a single dose containing a dispersion for infusion of viable $CD34^+$ cells in one or more vials.

The minimum recommended dose of Casgevy is 3×10^6 $CD34^+$ cells/kg of body weight.

See the accompanying Lot information sheet (LIS) for additional information pertaining to dose.

Mobilisation and apheresis

Patients are required to undergo $CD34^+$ HSPC mobilisation followed by apheresis to isolate the $CD34^+$ cells for medicinal product manufacturing.

Maximise $CD34^+$ cell collection for product manufacturing during each mobilisation and apheresis cycle. Perform two consecutive days of cell collection for product manufacturing per cycle, if clinically tolerated. A total collection target of at least 20×10^6 $CD34^+$ cells/kg is recommended for product manufacture. Collected cells should be sent for product manufacturing even if the total collection target is not achieved. In addition, at least 2×10^6 $CD34^+$ cells/kg are required to be collected for back-up unmodified rescue cells. A third day of cell collection can be used to obtain back-up rescue cells, if needed.

If the minimum dose of Casgevy is not met after initial medicinal product manufacturing, the patient will need to undergo additional cycles of mobilisation and apheresis to obtain more cells for additional product manufacture. Each mobilisation and apheresis cycle must be separated by a minimum of 14 days.

The back-up collection of $\geq 2 \times 10^6$ $CD34^+$ cells/kg of unmodified rescue cells must be collected from the patient and be cryopreserved prior to myeloablative conditioning and infusion with Casgevy.

The unmodified cells may be needed for rescue treatment under any one of the following conditions: compromise of Casgevy after initiation of myeloablative conditioning and before Casgevy infusion; neutrophil engraftment failure; or loss of engraftment after infusion with Casgevy.

See section 5.1 for a description of the mobilisation regimen used in the clinical study. Refer to the Summary of Product Characteristics for the mobilisation medicinal product(s) prior to treatment with Casgevy.

β-thalassemia
Prior to apheresis procedure it is recommended that patients receive red blood cell (RBC) transfusion(s) with a goal to maintain total haemoglobin (Hb) concentration ≥ 11 g/dL.

Sickle cell disease
Prior to apheresis it is recommended that patients receive RBC exchange or simple transfusion(s) with a goal of maintaining haemoglobin S (HbS) levels < 30% of total Hb while keeping total Hb concentration ≤ 11 g/dL.

Disease modifying therapies (e.g., hydroxyurea/hydroxycarbamide, crizanlizumab, voxelotor) must be discontinued 8 weeks before the planned start of mobilisation and conditioning.

Granulocyte colony-stimulating factor (G-CSF) must not be administered for mobilisation in patients with sickle cell disease.

Pre-treatment conditioning

Full myeloablative conditioning must be administered before infusion of Casgevy. Conditioning must not be initiated until the complete set of vials constituting the full dose of Casgevy has been received at the authorised treatment centre, and the availability of the back-up collection of unmodified $CD34^+$ cells is confirmed. See section 5.1 for a description of the conditioning regimen used in the clinical study. Refer to the Summary of Product Characteristics for the myeloablative conditioning medicinal product(s) prior to treatment.

β-thalassemia
It is recommended that patients maintain total Hb concentration ≥ 11 g/dL for 60 days prior to myeloablative conditioning.

Sickle cell disease
It is recommended that patients receive RBC exchange or simple transfusion(s) for at least the 8 weeks prior to the initiation of myeloablative conditioning with a goal of maintaining HbS levels < 30% of total Hb while keeping total Hb concentration ≤ 11 g/dL. At initiation of red blood cell exchanges or simple transfusions, discontinue disease modifying therapies (e.g., hydroxyurea/hydroxycarbamide, crizanlizumab, voxelotor).

Iron chelation therapy must be stopped at least 7 days prior to myeloablative conditioning.

Prophylaxis for seizures should also be considered. Refer to the Summary of Product Characteristics for the myeloablative conditioning medicinal product used for information on drug interactions.

Prophylaxis for hepatic veno-occlusive disease (VOD)/hepatic sinusoidal obstruction syndrome should be considered, per institutional guidelines.

Prior to starting the myeloablative conditioning regimen, confirm availability of the complete set of vials constituting the dose of Casgevy, and unmodified rescue cells. See the Lot information sheet (LIS) provided with the product shipment for confirmation of the number of vials and total dose of Casgevy.

Pre-medication

It is recommended that pre-medication with paracetamol and diphenhydramine, or equivalent medicinal products, be administered per institutional guidelines, before the infusion of Casgevy, to reduce the possibility of an infusion reaction.

Special populations

Patients aged 35 years and older

Casgevy has not been studied in patients > 35 years of age. The safety and efficacy of Casgevy in this population has not been established. The benefit of treatment in individual patients should be considered against the risks of HSC transplantation.

Renal impairment

Casgevy has not been studied in patients with renal impairment, defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2. No dose adjustment is required.

Hepatic impairment

Casgevy has not been studied in patients with hepatic impairment. No dose adjustment is required.

Paediatric population

The safety and efficacy of Casgevy in patients < 12 years of age have not been established. No data are available.

Patients seropositive for human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV)

Casgevy has not been studied in patients with HIV-1, HIV-2, HBV, or HCV. Perform screening for HIV-1, HIV-2, HBV, and HCV and any other infectious agents in accordance with local guidelines before collection of cells for manufacturing. Casgevy must not be used in patients with active HIV-1, HIV-2, HBV or HCV.

Patients with prior HSC transplant

Casgevy has not been studied in patients who have received a prior allogeneic or autologous HSC transplant. Treatment with Casgevy is not recommended in these patients.

Method of administration

Casgevy is for intravenous use only.

After completion of the myeloablative conditioning regimen, a minimum of 48 hours must elapse before Casgevy infusion. Casgevy must be administered between a minimum of 48 hours and a maximum of 7 days after the last dose of myeloablative conditioning.

Before thawing and administration, it must be confirmed that the patient's identity matches the unique patient information on the Casgevy vial(s) and accompanying documentation. The total number of

vials must also be confirmed with patient specific information on the Lot information sheet (LIS) (see section 4.4).

Casgevy is administered as an intravenous bolus via a central venous catheter. Casgevy infusion must be completed as soon as possible and no more than 20 minutes after thawing. In the event that more than one vial is provided, **all vials must be administered**. The entire volume of each vial must be infused.

For detailed instructions on preparation, administration, measures to take in case of accidental exposure and disposal of Casgevy, see section 6.6.

After Casgevy administration

Standard procedures for patient monitoring and management after HSC transplantation must be followed after Casgevy infusion, including monitoring of complete blood counts and transfusion needs.

Blood products required within the first 3 months after Casgevy infusion must be irradiated.

Restarting iron chelation after Casgevy infusion may be necessary. Avoid the use of non-myelosuppressive iron chelators for at least 3 months and use of myelosuppressive iron chelators for at least 6 months after Casgevy infusion. Phlebotomy can be used in lieu of iron chelation, when appropriate (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindications to mobilisation and myeloablative conditioning medicinal products must be considered.

4.4 Special warnings and precautions for use

Warnings and precautions of mobilisation and myeloablative conditioning medicinal products must be considered.

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years after expiry date of the medicinal product.

Autologous use

Casgevy is intended solely for autologous use and must not under any circumstances be administered to other patients. Casgevy must not be administered if the information on the product labels and Lot information sheet (LIS) does not match the patient’s identity.

Transmission of an infectious agent

Although Casgevy is tested for sterility, mycoplasma and endotoxins, a risk of transmission of infectious agents exists. Healthcare professionals administering Casgevy must, therefore, monitor patients for signs and symptoms of infections after treatment and treat appropriately, if needed.

Hypersensitivity reactions

There is a potential for hypersensitivity reactions with Casgevy, including due to Cas9. Serious hypersensitivity reactions, including anaphylaxis may occur due to dimethyl sulfoxide (DMSO) or dextran 40 in Casgevy. Patients should be observed closely during and after infusion. Vital signs (blood pressure, heart rate, and oxygen saturation) and the occurrence of any symptoms should be monitored prior to the start of the infusion, and approximately every 30 minutes from when the first vial of Casgevy is infused until 2 hours after the last vial of Casgevy is infused.

Potential neutrophil engraftment failure

Neutrophil engraftment failure is a potential risk in haematopoietic stem cell transplant, defined as not achieving neutrophil engraftment after Casgevy infusion and requiring use of unmodified rescue $CD34^+$ cells. Patients must be monitored for absolute neutrophil counts (ANC) and infections must be managed according to standard guidelines and medical judgement. In the event of neutrophil engraftment failure, patients must be infused with rescue $CD34^+$ cells (see section 4.8).

Delayed platelet engraftment

Longer median platelet engraftment times have been observed with Casgevy treatment compared to allogeneic HSC transplantation. There is an increased risk of bleeding until platelet engraftment is achieved.

Patients should be monitored for bleeding according to standard guidelines and medical judgement. Frequent platelet counts must be conducted until platelet engraftment and platelet recovery are achieved. Blood cell count determination and other appropriate testing must be performed whenever clinical symptoms suggestive of bleeding arise (see section 4.8).

Risk of insufficient mobilisation/apheresis in patients with SCD

Patients with SCD may require more cycles of mobilisation and apheresis compared to patients with TDT and are at higher risk of failure of sufficient mobilisation/apheresis. See section 4.2 for the recommended total $CD34^+$ cell collection target. See section 5.1 for information regarding the average number of cycles of mobilisation and apheresis, and overall discontinuation rates.

Gene-editing related oncogenesis

No cases of myelodysplasia, leukaemia, or lymphoma have been reported in clinical studies with Casgevy. There is a theoretical risk of oncogenesis related to gene editing. Patients should be monitored at least annually (including complete blood count) for 15 years after treatment with Casgevy. If myelodysplasia, leukaemia, or lymphoma are detected, the local representative of the Marketing Authorisation Holder should be contacted to determine appropriate samples for analysis.

The risk of unintended, off-target editing in an individual's edited $CD34^+$ cells cannot be ruled out. A search spanning the human genome identified off-target editing at a single variant site. The variant was identified in 3.3% (3/91) of patient samples analyzed (edited $CD34^+$ cells). The currently

identified off-target site is located in an intron of a gene not expressed in haematopoietic cells so no adverse effects are expected (see section 5.3).

Immunogenicity

No immune-mediated reactions were observed in clinical studies with Casgevy. It is unknown whether pre-formed antibodies to Cas9 including following recent *Streptococcus pyogenes* infection could result in immune-mediated reactions and/or clearance of cells with residual Cas9.

Blood, organ, tissue, and cell donation

Patients treated with Casgevy must not donate blood, organs, tissues, and cells for transplantation.

Long-term follow-up

Patients must be monitored annually (including complete blood counts) according to standard guidelines and medical judgement. Patients are expected to be enrolled in a long-term follow-up scheme in order to better understand the long-term safety and efficacy of Casgevy.

Sodium content

This medicinal product contains 5.3 mg to 70 mg sodium in each vial. This is equivalent to 0.3 to 4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

The drug-drug interaction of mobilisation and myeloablative conditioning medicinal products must be considered.

No formal drug interaction studies have been performed. Casgevy is not expected to interact with the hepatic cytochrome P-450 family of enzymes or drug transporters.

Use of hydroxyurea/hydroxycarbamide must be discontinued at least 8 weeks prior to start of mobilisation and conditioning. There is no experience on the use of hydroxyurea/hydroxycarbamide after Casgevy infusion.

Discontinue the use of voxelotor and crizanlizumab at least 8 weeks prior to start of mobilisation and conditioning, as their interaction potential with mobilisation and myeloablative conditioning medicinal products is not known.

Iron chelators must be discontinued at least 7 days prior to initiation of myeloablative conditioning, due to potential interaction with the conditioning medicinal product. Some iron chelators are myelosuppressive. Avoid the use of non-myelosuppressive iron chelators for at least 3 months and use of myelosuppressive iron chelators for at least 6 months after Casgevy infusion. Phlebotomy can be used instead of iron chelation, when appropriate.

Live vaccines

The safety of immunisation with live viral vaccines during or following Casgevy treatment has not been studied. As a precautionary measure, vaccination with live vaccines is not recommended for at least 6 weeks prior to the start of the conditioning regimens, during Casgevy treatment, and until haematological recovery following treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

A negative serum pregnancy test must be confirmed prior to the start of each mobilisation cycle and re-confirmed prior to myeloablative conditioning. There are insufficient exposure data to provide a precise recommendation on duration of contraception following treatment with Casgevy. Women of childbearing potential and men capable of fathering a child must use effective method of contraception from start of mobilisation through at least 6 months after administration of myeloablative conditioning. Please also refer to the Summary of Product Characteristics for the myeloablative conditioning medicinal product.

Pregnancy

There are no clinical data from the use of exagamglogene autotemcel in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with exagamglogene autotemcel to assess whether it can cause foetal harm when administered to a pregnant woman. It is not known whether exagamglogene autotemcel has the potential to be transferred to the foetus. Casgevy must not be administered during pregnancy because of the risk associated with myeloablative conditioning. Pregnancy after Casgevy infusion should be discussed with the treating physician (see guidance on contraception, above).

Breast-feeding

It is unknown whether exagamglogene autotemcel is excreted in human milk or transferred to the breast-feeding child. There are no data available.

Refer to the Summary of Product Characteristics of the mobilisation and myeloablative conditioning medicinal product(s) for guidance on their use during breast-feeding. Because of the potential risks associated with myeloablative conditioning, breast-feeding should be discontinued during conditioning.

The decision to breast-feed after Casgevy treatment should be discussed with the treating physician, taking into account the benefit of breast-feeding for the child versus any potential adverse events from Casgevy or from the underlying maternal condition.

Fertility

There are no data on the effects of exagamglogene autotemcel on human fertility. Effects on male and female fertility have not been evaluated in animal studies. Data are available on the risk of infertility with myeloablative conditioning. It is therefore advised to consider fertility preservation options such as cryopreservation of semen or ova before treatment if possible.

4.7 Effects on ability to drive and use machines

Casgevy has no influence on the ability to drive or use machines.

The effect of mobilisation and myeloablative conditioning medicinal products on the ability to drive or use machines must be considered.

4.8 Undesirable effects

Summary of the safety profile

The safety of Casgevy was evaluated in two open-label, single-arm studies (study 111 and study 121) and one long-term follow-up study (study 131), in which 97 adolescent and adult patients with TDT or SCD were treated with Casgevy.

Treatment with Casgevy was preceded by peripheral blood mobilisation with granulocyte colony-stimulating factor (G-CSF) and plerixafor in patients with TDT and plerixafor only in patients with SCD, followed by apheresis and myeloablative conditioning with busulfan.

The safety profile was generally consistent with that expected from busulfan myeloablative conditioning and HSC transplant after mobilisation and apheresis.

The median (min, max) duration of follow-up after being administered Casgevy was 22.8 (2.1, 51.1) months for patients with TDT (N=54), and 17.5 (1.2, 46.2) months for patients with SCD (N=43).

Serious adverse reactions attributed to Casgevy occurred in 2 (3.7%) patients with TDT: 1 (1.9%) patient with haemophagocytic lymphohistiocytosis, acute respiratory distress syndrome, idiopathic pneumonia syndrome, and headache; 1 (1.9%) patient with delayed engraftment and thrombocytopenia. No patient with SCD had serious adverse reactions attributed to Casgevy.

A life-threatening serious adverse reaction of cerebellar haemorrhage occurred in 1 (1.9%) patient with TDT and was attributed to busulfan myeloablative conditioning.

One (2.3%) patient with SCD died due to a COVID-19 infection and subsequent respiratory failure. The event was not related to Casgevy.

Tabulated list of adverse reactions

Adverse reactions are listed by MedDRA body system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10) and common (≥ 1/100 to < 1/10). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Tables 1, 2, 3, and 4 are lists of adverse reactions attributed to mobilisation/apheresis with G-CSF and plerixafor, mobilisation/apheresis with plerixafor only, myeloablative conditioning with busulfan, and Casgevy, respectively, experienced by patients with TDT and SCD in clinical studies with Casgevy.

Table 1: Adverse reactions attributed to mobilisation/apheresis in patients with TDT receiving G-CSF and plerixafor (N=59)

System organ class (SOC)	Very common	Common
Blood and lymphatic system disorders		Leukocytosis, thrombocytopenia
Metabolism and nutrition disorders		Hypokalaemia
Nervous system disorders	Headache	
Respiratory, thoracic and mediastinal disorders		Oropharyngeal pain
Gastrointestinal disorders	Nausea	Abdominal pain, vomiting, diarrhoea, oral hypoaesthesia
Musculoskeletal and connective tissue disorders	Musculoskeletal pain *	

General disorders and administration site conditions		Pain, pyrexia

[*] Musculoskeletal pain included back pain, bone pain, musculoskeletal chest pain, neck pain, non-cardiac chest pain, pain in extremity.

Table 2: Adverse reactions attributed to mobilisation/apheresis in patients with SCD receiving plerixafor (N=58)

System organ class (SOC)	Very common	Common
Blood and lymphatic system disorders		Sickle cell anaemia with crisis
Metabolism and nutrition disorders		Hyperphosphataemia, hypomagnesaemia
Nervous system disorders	Headache	
Respiratory, thoracic and mediastinal disorders		Acute chest syndrome
Gastrointestinal disorders	Abdominal pain [*], nausea, Vomiting	Diarrhoea
Musculoskeletal and connective tissue disorders	Musculoskeletal pain [†]	Arthralgia
General disorders and administration site conditions		Pain, fatigue

[*] Abdominal pain included abdominal pain upper.
[†] Musculoskeletal pain included back pain, bone pain, chest pain, neck pain, non-cardiac chest pain, and pain in extremity.

Table 3: Adverse reactions attributed to myeloablative conditioning with busulfan in patients with TDT and SCD (N=97) [*]

System organ class (SOC)	Very common	Common
Infections and infestations		Pneumonia, sepsis, klebsiella sepsis, oral candidiasis, folliculitis
Blood and lymphatic system disorders	Thrombocytopenia, febrile neutropenia, neutropenia, anaemia, lymphopenia [†], leukopenia	Pancytopenia, reticulocytopenia, splenomegaly
Metabolism and nutrition disorders	Decreased appetite, hypokalaemia, hyperphosphataemia, hypomagnesaemia, fluid retention, hypophosphataemia	Hypoalbuminaemia, hypocalcaemia
Nervous system disorders	Headache	Cerebellar haemorrhage, hydrocephalus, peripheral sensory neuropathy, peripheral neuropathy, neuralgia, dysgeusia
Eye disorders		Vision blurred, dry eye
Cardiac disorders		Tachycardia
Vascular disorders		Hypotension, hot flush
Respiratory, thoracic and mediastinal disorders	Epistaxis, oropharyngeal pain	Respiratory failure, idiopathic pneumonia syndrome, hypoxia, dyspnoea, cough
Gastrointestinal disorders	Mucositis [‡], nausea, vomiting, abdominal pain [§], diarrhoea, constipation, gastritis	Colitis, dyspepsia, gingival bleeding, gastrooesophageal reflux disease, haematemesis, oesophagitis, dysphagia, gastrointestinal inflammation, haematochezia, mouth ulceration

System organ class (SOC)	Very common	Common
Hepatobiliary disorders	Veno-occlusive liver disease, hyperbilirubinaemia, alanine aminotransferase increased	Aspartate aminotransferase increased, hepatomegaly, gamma-glutamyl transferase increased
Skin and subcutaneous tissue disorders	Pigmentation disorder [#], skin exfoliation, alopecia, petechiae, dry skin, rash [**]	Pruritus, erythema
Musculoskeletal and connective tissue disorders	Musculoskeletal pain [††]	Arthralgia
Renal and urinary disorders		Dysuria, haematuria
Reproductive system and breast disorders		Amenorrhoea, intermenstrual bleeding, vulvovaginal pain, dysmenorrhoea, menstruation irregular, premature menopause
General disorders and administration site conditions	Pyrexia, fatigue	Pain
Investigations	Weight decreased	International normalised ratio increased, C-reactive protein increased, weight increased
Injury, poisoning procedural complications		Delayed engraftment, subcutaneous haematoma, skin abrasion, skin laceration

[*] Frequency is based on the highest incidence from study 111 in patients with TDT or from study 121 in patients with SCD.
[†] Lymphopenia included CD4 lymphocytes decreased and lymphocyte count decreased.
[‡] Mucositis included anal inflammation, mucosal inflammation, pharyngeal inflammation, and stomatitis.
[§] Abdominal pain included abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and epigastric discomfort.
[#] Pigmentation disorder included nail pigmentation, skin hyperpigmentation, and skin hypopigmentation.
[**] Rash included dermatitis, rash erythematous, rash macular, rash maculo-papular, and rash papular.
[††] Musculoskeletal pain included back pain, bone pain, chest pain and pain in extremity.

Table 4: Adverse reactions attributed to Casgevy in patients with TDT and SCD (N=97) [*]

System organ class (SOC)	Very common	Common
Blood and Lymphatic system disorders	Lymphopenia [†, ‡]	Thrombocytopenia [†], neutropenia [†], anaemia [†], leukopenia [†]
Immune system disorders		Haemophagocytic lymphohistiocytosis
Metabolism and nutrition disorders		Hypocalcaemia [†]
Nervous system disorders		Headache [†], paraesthesia
Cardiac disorders		Tachycardia [†]
Respiratory, thoracic and mediastinal disorders		Acute respiratory distress syndrome, idiopathic pneumonia syndrome [†], epistaxis [†]
Skin and subcutaneous tissue disorders		Rash [†, §], petechiae [†]
General disorders and administration site conditions		Chills [†], pyrexia [†]
Injury, poisoning and procedural complications		Delayed engraftment [†], infusion related reactions [#]

[*] Frequency is based on the highest incidence from study 111 in patients with TDT or from study 121 in patients with SCD.
[†] At least one event was also attributed to busulfan myeloablative conditioning.
[‡] Lymphopenia included CD4 lymphocytes decreased and lymphocyte count decreased.

§ Rash included dermatitis.
# Infusion related reactions included chills, sinus tachycardia, and tachycardia.

Description of selected adverse reactions

Platelet engraftment

Platelet engraftment was defined as 3 consecutive measurements of platelet counts ≥ 20×10^9/L in patients with TDT and 3 consecutive measurements of platelet counts ≥ 50×10^9/L in patients with SCD, obtained on 3 different days after Casgevy infusion without administration of platelet transfusions for 7 days. All patients achieved platelet engraftment.

In study 111, the median (min, max) time to platelet engraftment in patients with TDT was 44 (20, 200) days (n=53), with one remaining patient achieving platelet engraftment after the time of the interim analysis. The median (min, max) time to platelet engraftment was 45 (20, 199) days in adolescent patients and 40 (24, 200) days in adult patients. Patients without a spleen had an earlier median time to platelet engraftment than patients with an intact spleen. Median (min, max) time to platelet engraftment was 34.5 (20, 78) days in patients without a spleen and 46 (27, 200) days in patients with an intact spleen.

In study 121, the median (min, max) time to platelet engraftment for patients with SCD was 35 (23, 126) days (n=43). The median (min, max) time to platelet engraftment was 44.5 (23, 81) days in adolescent patients and 32 (23, 126) days in adult patients.

There was no association observed between bleeding events and time to platelet engraftment after Casgevy treatment.

Neutrophil engraftment

Neutrophil engraftment was defined as 3 consecutive measurements of absolute neutrophil count (ANC) ≥ 500 cells/µL on 3 different days after Casgevy infusion, without use of the unmodified rescue $CD34^+$ cells. All patients achieved neutrophil engraftment, and no patients received rescue $CD34^+$ cells.

In study 111, the median (min, max) time to neutrophil engraftment in patients with TDT was 29 (12, 56) days (n=54). The median (min, max) time to neutrophil engraftment was 31 (19, 56) days in adolescent patients and 29 (12, 40) days in adult patients.

In study 121, the median (min, max) time to neutrophil engraftment in patients with SCD was 27 (15, 40) days (n=43). The median (min, max) time to neutrophil engraftment was 28 (24, 40) days in adolescent patients and 26 (15, 38) days in adult patients.

There was no association observed between infections and time to neutrophil engraftment.

Paediatric population

The safety of Casgevy was evaluated in 31 adolescent patients aged 12 to less than 18 years with TDT or SCD. The median (min, max) age of adolescent TDT patients was 14 (12, 17) years, and for SCD patients was 15 (12, 17) years. The median (min, max) duration of follow-up was 19.6 (2.1, 26.6) months for adolescent TDT patients and 14.7 (2.5, 18.7) months for adolescent SCD patients. The safety profile was generally consistent among adolescent and adult patients. Engraftment times were similar in adolescent and adult patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It

allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other haematological agents, other haematological agents, ATC code: B06AX05

Mechanism of action

Casgevy is a cell therapy consisting of autologous $CD34^+$ HSPCs *ex vivo* edited by CRISPR/Cas9-technology. The highly specific guide RNA enables CRISPR/Cas9 to make a precise DNA double-strand break at the critical transcription factor binding site (GATA1) in the erythroid-specific enhancer region of the *BCL11A* gene. As a result of the editing, GATA1 binding is irreversibly disrupted and BCL11A expression reduced. Reduced BCL11A expression results in an increase in γ-globin expression and foetal haemoglobin (HbF) protein production in erythroid cells, addressing the absent globin in transfusion-dependent β-thalassemia (TDT) and the aberrant globin in sickle cell disease (SCD), which are the underlying causes of disease. In patients with TDT, γ-globin production is expected to correct the α-globin to non-α-globin imbalance, thereby reducing ineffective erythropoiesis and haemolysis and increasing total haemoglobin levels. In patients with severe SCD, HbF expression is expected to reduce intracellular HbS concentration, preventing the red blood cells from sickling.

Clinical efficacy and safety

The efficacy of Casgevy was evaluated in adolescent and adult patients with transfusion-dependent β-thalassemia (TDT) or sickle cell disease (SCD) in two open-label, single-arm studies (study 111 and study 121) and one long-term follow-up study (study 131).

Transfusion-dependent β-thalassemia

Study 111 is an ongoing open-label, multicentre, single-arm study to evaluate the safety and efficacy of Casgevy in adult and adolescent patients with transfusion-dependent β-thalassemia. After completion of 24 months of follow-up in study 111, patients were invited to enrol in study 131, an ongoing long-term safety and efficacy study.

Patients were eligible for the study if they had a history of requiring at least 100 mL/kg/year or 10 units/year of RBC transfusions in the 2 years prior to enrolment. Patients were also required to have a Lansky or Karnofsky performance score of ≥ 80%.

Patients were excluded from the study if they had an available HLA-matched related HSC donor. Patients who had severely elevated iron in the heart (i.e., patients with cardiac T2* less than 10 msec by magnetic resonance imaging [MRI]), or advanced liver disease were excluded from the study. MRI of the liver was performed on all patients. Patients with MRI results demonstrating liver iron content ≥ 15 mg/g underwent liver biopsy for further evaluation. Patients with a liver biopsy demonstrating bridging fibrosis or cirrhosis were excluded.

Of the 59 patients who initiated mobilisation in study 111, 3 patients (5.1%) discontinued prior to Casgevy infusion, all due to withdrawn consent.

The key demographics and baseline characteristics are shown in Table 5 for (1) all patients enrolled in study 111 and (2) all patients infused with Casgevy in study 111.

Table 5: Study 111 demographics and baseline characteristics

Demographics and disease characteristics	Casgevy Enrolled patients (N=59) [§]	Casgevy Infused patients [†] (N=54)
Age (years), n (%)		
Adults (≥ 18 and ≤ 35 years)	39 (66.1%)	35 (64.8%)
Adolescents (≥ 12 and < 18 years)	20 (33.9%)	19 (35.2%)
All ages (≥ 12 and ≤ 35 years)		
Median (min, max)	19 (12, 35)	20 (12, 35)
Sex, n (%)		
Female	28 (47.5%)	25 (46.3%)
Male	31 (52.5%)	29 (53.7%)
Race, n (%)		
Asian	25 (42.4%)	23 (42.6%)
White	19 (32.2%)	18 (33.3%)
Multiracial	3 (5.1%)	3 (5.6%)
Other	3 (5.1%)	2 (3.7%)
Not collected	9 (15.3%)	8 (14.8%)
Genotype, n (%)		
β^0/β^0-like [‡]	38 (64.4%)	33 (61.1%)
Non-β^0/β^0-like	21 (35.6%)	21 (38.9%)
Baseline annualised RBC transfusion volume (mL/kg)		
Median (min, max)	211.2 (48.3, 330.9)	205.7 (48.3, 330.9)
Baseline annualised RBC transfusion episodes		
Median (min, max)	16.5 (5.0, 34.5)	16.5 (5.0, 34.5)
Spleen intact, n (%)	43 (72.9%)	38 (70.4%)
Baseline liver iron concentration (mg/g)		
Median (min, max)	3.5 (1.2, 14.8)	3.5 (1.2, 14.0)
Baseline cardiac iron T2* (msec)		
Median (min, max)	34.1 (12.4, 61.1)	34.4 (12.4, 61.1)
Baseline serum ferritin (pmol/L)		
Median (min, max)	3100.9 (584.2, 10837.3)	3115.5 (584.2, 10837.3)

[§] N represents the total number of enrolled patients who signed informed consent.
[†] Interim analysis conducted based on April 2023 data cut with 54 patients administered Casgevy and 2 patients awaiting Casgevy infusion.
[‡] Low to no endogenous β-globin production (β^0/β^0, β^0/IVS-I-110 and IVS-I-110/IVS-I-110).

Mobilisation and apheresis

To maintain a total Hb concentration ≥ 11 g/dL patients underwent RBC transfusions prior to mobilisation and apheresis and continued receiving transfusions until the initiation of myeloablative conditioning.

To mobilise stem cells for apheresis, patients in study 111 were administered granulocyte-colony stimulating factor (G-CSF). Patients with a spleen were administered a planned dose of 5 mcg/kg G-CSF approximately every 12 hours via intravenous or subcutaneous injection for 5 to 6 days. Splenectomised patients were administered a planned dose of 5 mcg/kg G-CSF once daily for 5 to 6 days. The dose was increased to every 12 hours in splenectomised patients if there was no increase

in white blood cell (WBC) or peripheral blood $CD34^+$ counts. After 4 days of G-CSF administration, all patients received plerixafor at a planned dose of 0.24 mg/kg administered via subcutaneous injection approximately 4 to 6 hours prior to each planned apheresis. Apheresis was carried out for up to 3 consecutive days to achieve the target collection of cells for manufacture and for the unmodified rescue $CD34^+$ cells. The mean (SD) and median (min, max) number of mobilisation and apheresis cycles required for manufacture Casgevy and for the collection of rescue $CD34^+$ cells were 1.3 (0.7) and 1 (1, 4), respectively.

Pre-treatment conditioning
All patients received full myeloablative conditioning with busulfan prior to treatment with Casgevy. Busulfan was administered for 4 consecutive days intravenously via a central venous catheter at a planned starting dose of 3.2 mg/kg/day once daily or 0.8 mg/kg every 6 hours. Busulfan plasma levels were measured by serial blood sampling and the dose adjusted to maintain exposure in the target range. For once daily dosing, four-day target cumulative busulfan exposure was 82 mg*h/L (range: 74 to 90 mg*h/L), corresponding to $AUC_{0\text{-}24h}$ of 5000 μM*min (range: 4500 to 5500 μM*min). For dosing every 6 hours, the four-day target cumulative busulfan exposure was 74 mg*h/L (range: 59 to 89 mg*h/L), corresponding to $AUC_{0\text{-}6h}$ of 1125 μM*min (range: 900 to 1350 μM*min).

All patients received anti-seizure prophylaxis with agents other than phenytoin prior to initiating busulfan conditioning. Phenytoin was not used for anti-seizure prophylaxis because of its induction of cytochrome P-450 and resultant increased clearance of busulfan.

Prophylaxis for hepatic veno-occlusive disease (VOD)/hepatic sinusoidal obstruction syndrome was administered per institutional guidelines.

Casgevy administration
Patients were administered Casgevy with a median (min, max) dose of
8.0 (3.0, 19.7) × 10^6 $CD34^+$ cells/kg as an intravenous infusion. All patients were administered an antihistamine and an antipyretic prior to Casgevy infusion.

After Casgevy administration
G-CSF was not recommended within the first 21 days after Casgevy infusion. As Casgevy is an autologous therapy, immunosuppressive agents were not required after initial myeloablative conditioning.

Efficacy results – β-thalassemia
An interim analysis (IA) was conducted with 42 patients administered Casgevy and eligible for the primary efficacy analysis. The primary efficacy set (PES) was defined as all subjects who had been followed for at least 16 months after Casgevy infusion. At the time of the interim analysis 59 patients were enrolled and 54 patients had been administered Casgevy. The median (min, max) total duration of follow-up was 22.8 (2.1, 51.1) months from the time of Casgevy infusion.

The efficacy of Casgevy was assessed based on evaluation of patients with at least 16 months of follow-up. The primary endpoint was the proportion of patients achieving transfusion independence for 12 consecutive months (TI12), defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time within the first 24 months after Casgevy infusion in study 111, evaluated starting 60 days after the last RBC transfusion for post-transplant support or TDT disease management.

Efficacy data are presented in Table 6 and Table 7. Table 6 shows the primary endpoint for (1) all patients enrolled in study 111 and (2) all patients infused with Casgevy in study 111. Table 7 shows secondary endpoints for patients infused with Casgevy in study 111.

Table 6: Primary efficacy outcome in patients with TDT

Primary endpoint	Casgevy Enrolled patients * (N=45) †	Casgevy Infused patients * (N=42) ‡
Proportion of patients achieving TI12 §		
n (%)	39 (86.7%)	39 (92.9%)
(95% CI)	(73.2%, 94.9%)	(80.5%, 98.5%)

* Interim analysis conducted based on April 2023 data cut.
† N represents the total number of enrolled patients who signed informed consent, and excludes patients who were waiting to receive Casgevy at the time of the analysis, or patients who were not yet evaluable for the primary efficacy endpoint.
‡ N represents the total number of patients in the primary efficacy set (PES), a subset of the full analysis set (FAS). The PES was defined as all subjects who had been infused with Casgevy and had been followed for at least 16 months after Casgevy infusion. Patients who had less than 16 months of follow-up due to death, or discontinuation due to Casgevy-related adverse events, or continuously received RBC transfusions for more than 12 months after Casgevy infusion were also included in this set.
§ TI12 is defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after Casgevy infusion. The evaluation of TI12 starts 60 days after last RBC transfusion for post-transplant support or TDT disease management.

Table 7: Secondary efficacy outcomes in patients with TDT

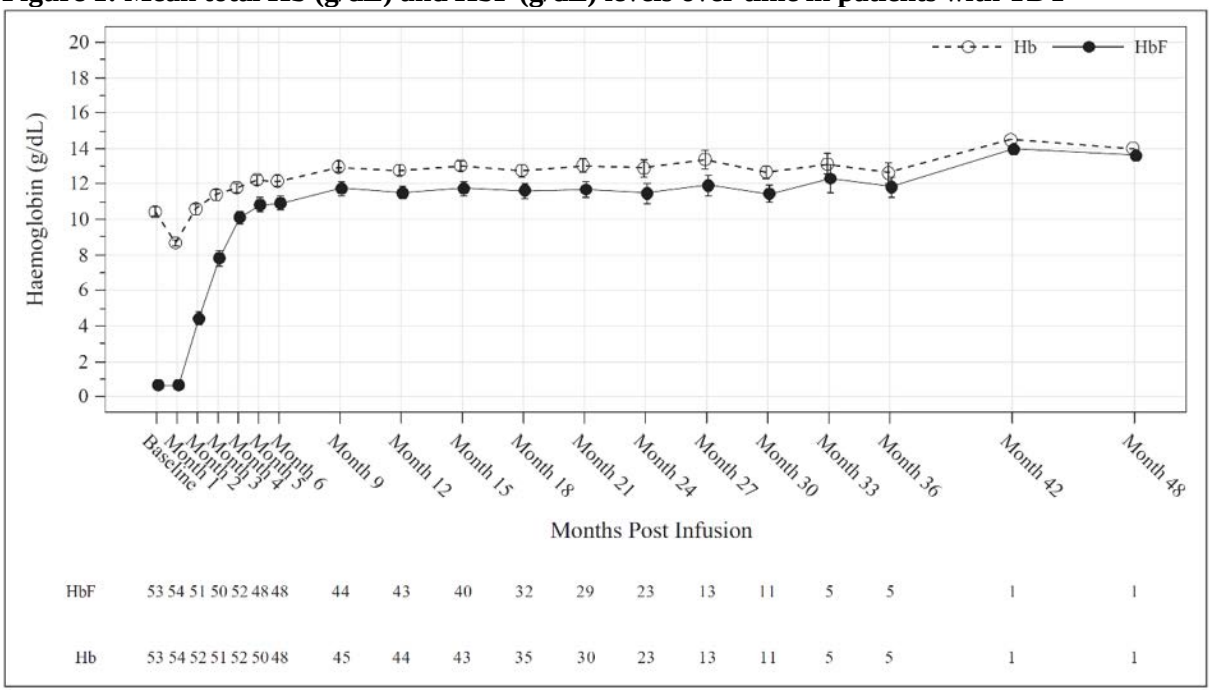
Secondary endpoints	Casgevy Infused patients * (N=42) †
Duration of transfusion-independent period in patients who have achieved TI12 (months)	
n	39
Median (min, max)	22.3 (13.5, 48.1)
Total Hb (g/dL)	
at Month 6	
n	42
Mean (SD)	12.1 (2.0)
at Month 24	
n	23
Mean (SD)	12.9 (2.4)
HbF (g/dL)	
at Month 6	
n	42
Mean (SD)	10.8 (2.8)
at Month 24	
n	23
Mean (SD)	11.5 (2.7)

* Interim analysis conducted based on April 2023 data cut.
† N represents the total number of patients in the primary efficacy set (PES), a subset of the full analysis set (FAS). The PES was defined as all patients who had been infused with Casgevy and had been followed for at least 16 months after Casgevy infusion. Subjects who had less than 16 months follow-up due to death or discontinuation due to Casgevy-related adverse events, or continuously received RBC transfusions for more than 12 months after Casgevy infusion were also included in this set.
SD: Standard Deviation

All patients who achieved TI12 remained transfusion-independent, with a median (min, max) duration of transfusion-independence of 22.3 (13.5, 48.1) months and normal weighted average total Hb levels (mean [SD] 13.2 [1.4] g/dL). The median (min, max) time to last RBC transfusion for patients who achieved TI12 was 28 (11, 91) days following Casgevy infusion. Three patients did not achieve TI12. These patients had reductions in frequency of RBC transfusions over time, and then stopped receiving transfusions between 12.2 and 21.6 months after Casgevy infusion, consistent with an overall slower haematopoietic recovery.

Total Hb (g/dL) and HbF (g/dL) levels over time are provided in Figure 1 for all patients administered Casgevy for the treatment of β-thalassemia.

Figure 1: Mean total Hb (g/dL) and HbF (g/dL) levels over time in patients with TDT



Mean values are plotted in the line, mean +Standard Error (SE) and mean -SE values are plotted as bars at each visit. The numbers of patients with values available at the corresponding visits are shown beneath the figure.

Increases in mean (SD) total Hb and HbF levels were observed as early as month 3 after Casgevy infusion and continued to increase to 12.2 (2.0) g/dL and 10.9 (2.7) g/dL respectively at month 6. After month 6, levels of total Hb and HbF were maintained thereafter, with HbF comprising ≥ 88% of total Hb.

All patients who achieved TI12 in study 111 (n=39) had normal (28/39 patients, 71.8%) or near-normal (11/39 patients, 28.2%) weighted average total Hb levels. The patients with near-normal weighted average total Hb levels included 6 males and 5 females, with weighted average total Hb within < 0.1 to 0.7 g/dL and within < 0.4 to 1.4 g/dL of the WHO age and sex dependent reference threshold, respectively.

Subgroup analyses evaluating the effects in age, sex, race or genotype subgroups on transfusion-related endpoints and haematological parameters did not suggest differences due to these factors.

Sickle cell disease

Study 121 is an ongoing open-label, multicentre, single-arm study to evaluate the safety and efficacy of Casgevy in adult and adolescent patients with severe sickle cell disease. After completion of 24 months of follow-up in study 121, patients were invited to enrol in study 131, an ongoing long-term safety and efficacy study.

Patients were eligible for the study if they had a history of at least 2 severe vaso-occlusive crisis (VOC) events per year in the 2 years prior to screening, which were defined as:

- Acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous non-steroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions
- Acute chest syndrome
- Priapism lasting > 2 hours and requiring a visit to a medical facility
- Splenic sequestration.

Patients with $Hb^{S/S}$, Hb^{S/β^0} and Hb^{S/β^+} genotypes were eligible for inclusion. Patients were also required to have a Lansky or Karnofsky performance score of ≥ 80%.

Patients were excluded from the study if they had an available HLA-matched related HSC donor. Patients were excluded if they had advanced liver disease, history of untreated Moyamoya disease, or presence of Moyamoya disease that in the opinion of the investigator put the patient at risk of bleeding. Patients aged 12 to 16 years were required to have normal transcranial doppler (TCD) and patients aged 12 to 18 years were excluded if they had any history of abnormal TCD in the middle cerebral artery and the internal carotid artery.

Of the 58 patients that initiated mobilisation in study 121, 11 patients (19.0%) discontinued after starting mobilisation and apheresis and prior to Casgevy administration. Six patients (10.3%) did not achieve the minimum dose. Five patients (8.6%) discontinued due to noncompliance, withdrawn consent, or no longer meeting eligibility requirements.

The key demographics and baseline characteristics are shown in Table 8, below, for (1) all patients enrolled in study 121 and (2) all patients infused with Casgevy in study 121.

Table 8: Study 121 demographics and baseline characteristics

Demographics and disease characteristics	Casgevy Enrolled patients (N=63) *	Casgevy Infused patients (N=43) †
Age (years), n (%)		
Adults (≥ 18 and ≤ 35 years)	50 (79.4%)	31 (72.1%)
Adolescents (≥ 12 and < 18 years)	13 (20.6%)	12 (27.9%)
All ages (≥ 12 and ≤ 35 years)		
Median (min, max)	21 (12, 35)	20 (12, 34)
Sex, n (%)		
Male	36 (57.1%)	24 (55.8%)
Female	27 (42.9%)	19 (44.2%)
Race, n (%)		
Black or African American	55 (87.3%)	37 (86.0%)
White	4 (6.3%)	3 (7.0%)
Other	4 (6.3%)	3 (7.0%)
Genotype, n (%) ‡		
β^S/β^S	58 (92.1%)	39 (90.7%)
β^S/β^0	3 (4.8%)	3 (7.0%)
β^S/β^+	2 (3.2%)	1 (2.3%)
Annualised rate of severe VOCs in the 2 years prior to enrolment (events/year)		
Median (min, max)	3.5 (2.0, 19.0)	3.5 (2.0, 18.5)
Annualised rate of hospitalisations due to severe VOCs in the 2 years prior to enrolment (events/year)		
Median (min, max)	2.5 (0.0, 11.0)	2.5 (0.5, 9.5)
Annualised duration of hospitalisation due to severe VOCs in the 2 years prior to enrolment (days/year)		
Median (min, max)	15.5 (0.0, 136.5)	13.5 (2.0, 136.5)
Annualised units of RBCs transfused for SCD-related indications in the 2 years prior to enrolment (units/year)		
Median (min, max)	5.0 (0.0, 86.1)	5.0 (0.0, 86.1)

* N represents the total number of enrolled patients who signed informed consent.
† Interim analysis conducted based on April 2023 data cut with 43 patients having been administered Casgevy and 4 patients awaiting Casgevy infusion.
‡ There is no data available for patients with other genotypes.

Mobilisation and apheresis
Patients underwent red blood cell exchange or simple transfusions for a minimum of 8 weeks before the planned start of mobilisation and continued receiving transfusions or red blood cell exchanges until the initiation of myeloablative conditioning. HbS levels were maintained at < 30% of total Hb while keeping total Hb concentration ≤ 11 g/dL.

To mobilise stem cells for apheresis, patients in study 121 were administered plerixafor at a planned dose of 0.24 mg/kg via subcutaneous injection approximately 2 to 3 hours prior to each planned apheresis. Patients underwent apheresis for up to 3 consecutive days to achieve the target collection of cells for manufacture and for the unmodified rescue $CD34^+$ cells. The median (min, max) and mean (SD) number of mobilisation and apheresis cycles required for manufacture Casgevy and for the collection of rescue $CD34^+$ cells were 2 (1, 6) and 2.21 (1.30), respectively.

Pre-treatment conditioning
All patients received full myeloablative conditioning with busulfan prior to receiving Casgevy. Busulfan was administered for 4 consecutive days intravenously via a central venous catheter at a planned starting dose of 3.2 mg/kg/day once daily or 0.8 mg/kg every 6 hours. Busulfan plasma levels were measured by serial blood sampling and the dose adjusted to maintain exposure in the target range. For once daily dosing, the four-day target cumulative busulfan exposure of 82 mg*h/L (range 74 to 90 mg*h/L), corresponding to $AUC_{0\text{-}24h}$ of 5000 μM*min (range: 4500 to 5500 μM*min). For dosing every 6 hours, the four-day target cumulative busulfan exposure of 74 mg*h/L (range 59 to 89 mg*h/L), corresponding to $AUC_{0\text{-}6h}$ of 1125 μM*min (range 900 to 1350 μM*min).

All patients received anti-seizure prophylaxis with agents other than phenytoin prior to initiating busulfan conditioning. Phenytoin was not used for anti-seizure prophylaxis because of its induction of cytochrome P-450 and resultant increased clearance of busulfan.

Prophylaxis for hepatic veno-occlusive disease (VOD)/hepatic sinusoidal obstruction syndrome was administered, per regional and institutional guidelines.

Casgevy administration
Patients were administered Casgevy with a median (min, max) dose of 4.0 (2.9 to 14.4) × 10^6 $CD34^+$ cells/kg as an intravenous infusion. All patients were administered an antihistamine and an antipyretic prior to Casgevy infusion.

After Casgevy administration
G-CSF was not recommended within the first 21 days after Casgevy infusion. As Casgevy is an autologous therapy, immunosuppressive agents were not required after initial myeloablative conditioning.

Efficacy results – sickle cell disease
An interim analysis was conducted with 29 patients administered Casgevy and eligible for the primary efficacy analysis. The primary efficacy set (PES) was defined as all patients who had been followed for at least 16 months after Casgevy infusion. At the time of the interim analysis 63 patients were enrolled and 43 patients had been administered Casgevy. The median (min, max) total duration of follow-up was 17.5 (1.2, 46.2) months from the time of Casgevy infusion.

The efficacy of Casgevy was based on evaluation of patients with at least 16 months of follow-up. The primary endpoint was the proportion of patients who did not experience any severe VOCs for at least 12 consecutive months any time within the first 24 months after Casgevy infusion in study 121 (VF12, primary efficacy endpoint). For this endpoint, a severe VOC was defined as either (a) an acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous non-steroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions, (b) acute chest syndrome, (c) priapism lasting > 2 hours and requiring a visit to a medical facility, or (d) splenic sequestration. The proportion of patients who did not require hospitalisation due to severe VOCs for at

least 12 consecutive months (HF12, key secondary endpoint) was also assessed. The evaluation of VF12 and HF12 began 60 days after last RBC transfusion for post-transplant support or SCD management.

Efficacy data are presented in Table 9 and Table 10. Table 9 shows the primary endpoint for (1) all patients enrolled in study 121 and (2) all patients infused with Casgevy in study 121. Table 10 shows secondary endpoints for all patients infused with Casgevy in study 121.

Table 9: Primary efficacy outcome in patients with SCD

Primary endpoint	**Casgevy Enrolled patients [*] (N=46) [†]**	**Casgevy Infused patients [*] (N=29) [‡]**
Proportion of patients achieving VF12 (%)[§]		
n (%)	28 (60.9%)	28 (96.6%)
(95% CI)	(45.4%, 74.9%)	(82.2%, 99.9%)

[*] Interim analysis conducted based on April 2023 data cut.
[†] N represents the total number of enrolled patients who signed informed consent, and excludes patients who were waiting to receive Casgevy at the time of the interim analysis, or patients who were dosed but not yet evaluable for the primary efficacy endpoint.
[‡] N represents the total number of patients in the primary efficacy set (PES), a subset of the full analysis set (FAS). The PES was defined as all patients who had been infused with Casgevy and had been followed for at least 16 months after Casgevy infusion. Subjects who had less than 16 months follow-up due to death, or discontinuation due to Casgevy-related adverse events, or continuously received RBC transfusions for more than 12 months after Casgevy were also included in this set.
[§] VF12 is defined as no severe VOCs for at least 12 consecutive months after Casgevy infusion. The evaluation of VF12 starts 60 days after last RBC transfusion for post-transplant support or SCD management.

Table 10: Secondary efficacy outcomes in patients with SCD

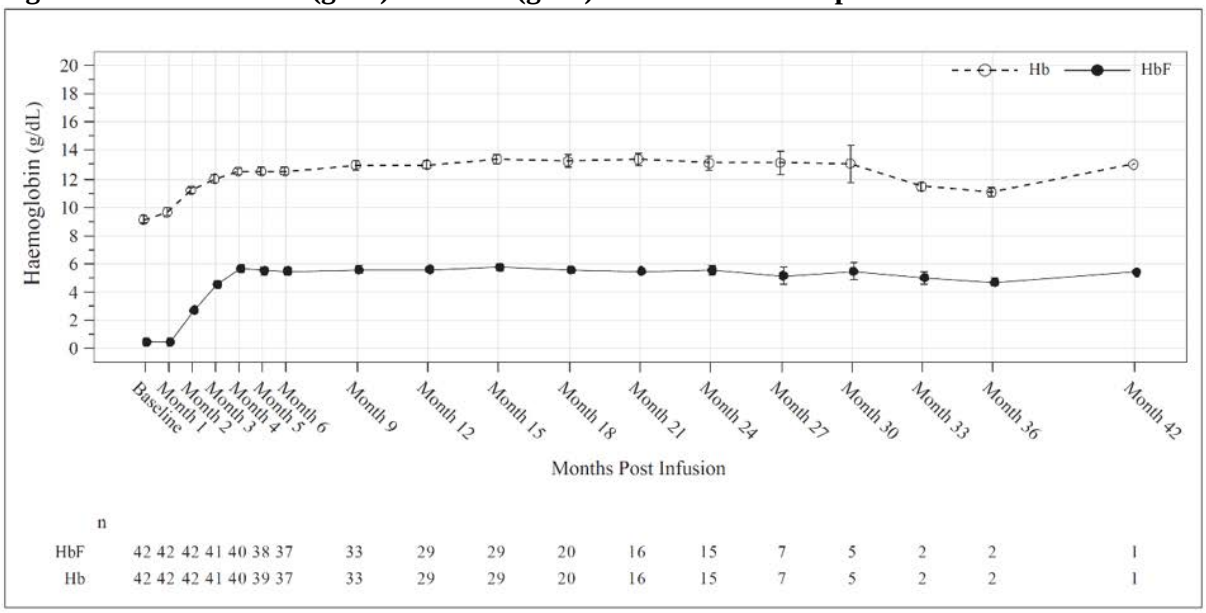
Secondary endpoints	**Casgevy Infused patients [*] (N=29) [†]**
Proportion of patients free from hospitalisation due to severe VOCs for at least 12 months (HF12) (%) [‡]	
n (%)	29 (100%)
(95% CI)	(88.1%, 100.0%)
Duration of severe VOC-free period in patients who have achieved VF12 (months)	
n	28
Median (min, max)	20.5 (13.5, 43.6)
Proportion of patients with HbF ≥ 20% at the time of analysis sustained for at least 3, 6 and 12 months (%)	
n	29
% (95% CI)	100% (88.1%, 100.0%)
Total Hb (g/dL)	
at Month 6	
n	27
Mean (SD)	12.7 (1.7)
at Month 24	
n	15
Mean (SD)	13.1 (1.9)
Proportion of total Hb comprised by HbF (%)	
at Month 6	
n	27
Mean (SD)	43.1 (6.0)
at Month 24	
n	15
Mean (SD)	42.2 (5.5)

[*] Interim analysis conducted based on April 2023 data cut.

† N represents the total number of patients in the primary efficacy set (PES), a subset of the full analysis set (FAS). The PES was defined as all patients who had been infused with Casgevy and had been followed for at least 16 months after Casgevy infusion. Subjects who had less than 16 months follow-up due to death, or discontinuation due to Casgevy-related adverse events, or continuously received RBC transfusions for more than 12 months after Casgevy were also included in this set.
‡ HF12 is defined as no severe VOC-related inpatient hospitalisations sustained for at least 12 months after Casgevy infusion. The evaluation of HF12 starts 60 days after last RBC transfusion for post-transplant support or SCD management.

Total Hb (g/dL) and HbF (g/dL) levels over time is provided in Figure 2 for all patients administered Casgevy for the treatment of sickle cell disease.

Figure 2: Mean total Hb (g/dL) and HbF (g/dL) levels over time in patients with SCD



Mean values are plotted in the line, mean +SE and mean -SE values are plotted as bars at each visit. The numbers of patients with values available at the corresponding visits are shown beneath the figure.

Increases in mean (SD) total Hb levels were observed as early as month 3 after Casgevy infusion, continued to increase to 12.5 (1.8) g/dL at month 6 and were maintained thereafter.

The mean (SD) proportion of Hb comprised by HbF was 43.2% (7.6%) at month 6 and was maintained thereafter.

Consistent with the increase in HbF levels, for all patients dosed the mean (SD) proportion of circulating erythrocytes expressing HbF (F-cells) at month 3 was 70.4% (14.0%) and continued to increase over time to 93.9% (12.6%) at month 6, with levels remaining stable thereafter, indicating sustained pan-cellular expression of HbF.

Subgroup analyses evaluating the effects in age, sex, race or genotype subgroups on VOC-related endpoints and haematological parameters did not suggest differences due to these factors.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Casgevy in one or more subsets of the paediatric population in β-thalassemia and sickle cell disease (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Casgevy is an autologous cellular therapy medicinal product consisting of $CD34^+$ cells that have been edited *ex vivo* by CRISPR/Cas9. The nature of Casgevy is such that conventional studies on pharmacokinetics, absorption, distribution, metabolism, and elimination are not applicable.

5.3 Preclinical safety data

Casgevy is a $CD34^+$ cell product edited with CRISPR/Cas9 technology; therefore, conventional mutagenicity, carcinogenicity and fertility, reproductive and developmental toxicity studies have not been conducted.

Toxicological characteristics were assessed in sub-lethally irradiated, immunodeficient NSG mice treated with a dose of 3.33×10^7 edited $CD34^+$ cells/kg of body weight. There was no evidence of target organ toxicity or tumorigenicity in the 20-week study.

During preclinical development, the potential for off-target editing was assessed at over 5000 sites, including those nominated based on human genetic variation. No off-target editing was observed in edited $CD34^+$ cells from healthy donors and patients. A post-marketing non-clinical study (Study U270) evaluated 33 additional candidate off-target editing sites nominated based on the presence of genetic variations. No off-target editing was observed at 32 of these sites in edited $CD34^+$ cells from patients. One site had off-target editing due to a minor variant allele present in 3 of 91 patient samples (3.3%). This variant leads to a binding motif for Cas9 ribonucleoprotein complex in the intronic region of the gene encoding for carbamoyl-phosphate synthetase 1 (CPS1).The off-target editing was observed at a low fraction of alleles (≤ 1%) and included a balanced inversion (<0.25%). Gene editing in this minor allele is not expected to have any adverse effects in patients as the off-target site is within an intron and CPS1 is not expressed in haematopoietic cells.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CryoStor CS5 (contains dimethyl sulfoxide and dextran 40)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years at ≤ -135 °C.

Once thawed

20 minutes at room temperature (20 °C – 25 °C).

6.4 Special precautions for storage

Casgevy must be stored and transported in the vapour phase of liquid nitrogen at ≤ -135 °C and must remain frozen until the patient is ready for treatment to ensure viable cells are available for patient administration.

Thawed medicinal product must not be refrozen.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Casgevy is supplied in cryopreservation vials made of cyclic olefin copolymer. Each vial contains 1.5 mL to 20 mL of Casgevy.

Vials are packed in a paperboard carton box. Each carton may contain up to 9 vials. The final outer carton contains a variable number of vials according to the patient specific dose required.

Casgevy is shipped from the manufacturing facility to the treatment centre storage facility in a cryoshipper. One cryoshipper may contain multiple cartons, which may contain multiple vials, all intended for a single patient.

6.6 Special precautions for disposal and other handling

Precautions to be taken before handling or administering the medicinal product

Do not sample, alter, or irradiate the medicinal product. Irradiation could lead to inactivation of the product.

This medicinal product contains human blood cells. Healthcare professionals handling Casgevy must take appropriate precautions (wearing gloves, protective clothing, and eye protection) to avoid potential transmission of infectious diseases.

Receipt and storage of Casgevy

- Casgevy is shipped to the treatment centre frozen in the vapor phase of liquid nitrogen.
- Confirm patient identifiers on the product label(s) and Lot information sheet (LIS).
- Store in the vapor phase of liquid nitrogen at ≤ -135 °C until ready for thaw and administration.

Preparation prior to administration

Preparation for the infusion

- Coordinate the timing of Casgevy thaw and infusion. Confirm the infusion time in advance and adjust the start time for thaw so that Casgevy is available for infusion when the patient is ready, as Casgevy must be administered within 20 minutes of thawing the vial. Thaw and infuse the content of one vial at a time.
- Before thaw, confirm the patient's identity matches the patient information on the Casgevy vial(s). Do not remove the Casgevy vials from cryo-storage if the information on the patient-specific label does not match the intended patient.
- A dose of Casgevy may be contained in one or more cryopreserved patient-specific vial(s). Account for all vials and confirm each vial is within the expiry date using the accompanying Lot information sheet (LIS).
- Inspect the vial(s) for any breaks or cracks prior to thawing. If a vial is compromised, do not infuse the contents.
- Assemble supplies needed to thaw and withdraw the product from the vial(s). With the exception of the water bath, these supplies are single use. Assemble sufficient supplies for each vial to be administered:
    - Water bath
    - Alcohol swabs
    - Vial adapter (to allow for needle-less extraction)
    - 18 micron stainless steel filter
    - 30 mL luer-lock syringe
    - Sodium chloride 9 mg/mL (0.9%) solution for injection (5 to 10 mL needed for each vial)
    - 10 mL luer-lock syringe for sodium chloride 9 mg/mL (0.9%) solution for injection rinse

Thawing the Casgevy vials

- When the dose consists of multiple vials, thaw and administer one vial at a time. While thawing a vial, remaining vials must remain in cryo-storage at ≤ -135 °C.
- Thaw each vial at 37 °C using a water bath. Ensure water bath temperature does not exceed 40 °C.
- Thaw each vial holding the vial neck, gently agitating clockwise and counterclockwise. This can take between 10 to 15 minutes.
- Do not leave vial unattended during thawing.
- Thawing is complete when ice crystals are no longer visible in the vial.
- Remove vial from water bath immediately once thawed.
- The thawed product should appear as a translucent cell dispersion free from foreign particles.
- Infuse within 20 minutes of thaw.
- Thawed medicinal product must not be refrozen.

Administration of Casgevy

Casgevy is for autologous use only. The patient's identity must match the patient identifiers on the Casgevy vial(s). Do not infuse Casgevy if the information on the patient-specific label does not match the intended patient.

A patient's dose may consist of multiple vials. All vials must be administered. The entire volume of each vial provided must be infused. If more than one vial is provided, administer each vial completely before proceeding to thaw and infuse the next vial.

Attaching the vial adapter and filter

- Remove the flip-away tab of the vial cap; clean the septum with an alcohol swab.
- Remove the cap on the adapter spike.
- With the thumb and forefinger of both hands, push the adapter into the vial septum, applying equal pressure until you hear a single pop.
- Pull up on the adapter until you feel it lock.
- Attach the filter to the vial adapter.

Withdrawing Casgevy from the vial

- Attach an empty 30 mL syringe to the filter.
- Withdraw the entire vial product volume.
- Remove the product-filled syringe from the filter and set aside.
- Draw 5 – 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection into the empty 10 mL syringe.
- Attach the sodium chloride solution-filled syringe to the filter.
- Inject the sodium chloride solution into the Casgevy vial and remove the empty syringe from the filter. Discard the empty syringe.
- Attach the product-filled syringe to the filter.
- Withdraw the contents of the vial into the product syringe, then remove the syringe from the filter.
- The optional product/patient identifier label can be peeled from the Lot information sheet (LIS) and affixed to the syringe.

Administration of Casgevy through a central venous catheter

- Casgevy must be administered within 20 minutes of product thaw.
- Perform a two-person confirmation and verification of patient's identification at the bedside prior to the infusion of each vial(s).
- Casgevy is administered as an intravenous bolus (intravenous push).

- The total volume of Casgevy administered within one hour must not exceed 2.6 mL/kg.
- Do not use an inline filter when infusing Casgevy.
- After administration of each vial of Casgevy, flush the primary line with sodium chloride 9 mg/mL (0.9%) solution for injection.

Repeat the steps listed above for each remaining vial.

After administration of Casgevy

- Monitor vital signs every 30 minutes from when the first vial of Casgevy is infused until 2 hours after the last vial of Casgevy is infused.
- Standard procedures for patient management after HSC transplantation should be followed after Casgevy infusion.
- Irradiate any blood products required within the first 3 months after Casgevy infusion.
- Patients must not donate blood, organs, tissues, or cells at any time in the future.

Measures to take in case of accidental exposure

In case of accidental exposure local guidelines on handling of human-derived material must be followed. Work surfaces and materials which have potentially been in contact with Casgevy must be decontaminated with appropriate disinfectant.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Casgevy (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling human-derived material.

7. MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
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Dublin 9, D09 T665,
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1787/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 February 2024
Date of latest renewal: 12 February 2025

10. DATE OF REVISION OF THE TEXT

10/2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.