PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}CASGEVY®

exagamglogene autotemcel

Cell suspension in patient-specific vials, 4-13 × 10^6 cells/mL, for intravenous infusion

Other hematological agents

ATC: B06AX05

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Date of Initial Authorization:
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RECENT MAJOR LABEL CHANGES

Not applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CASGEVY (exagamglogene autotemcel) is an autologous genome edited hematopoietic stem cell-based therapy indicated for the treatment of patients 12 years of age and older with:

- sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs); OR
- transfusion-dependent β-thalassemia (TDT)

1.1 Pediatrics

Pediatrics (≥ 12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of CASGEVY in adolescents (aged ≥ 12 years of age) has been established. Therefore, Health Canada has authorized an indication for pediatric use in patients 12 years of age and older (see 8.2.1 Clinical Trial Adverse Reactions – Pediatrics and 14 CLINICAL TRIALS).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): The safety and efficacy of CASGEVY has not been established in geriatric patients as clinical studies of CASGEVY were restricted to adult patients who were 35 years of age or younger.

2 CONTRAINDICATIONS

Consult the product monographs of the drugs used in mobilization (e.g., plerixafor, filgrastim) and myeloablative conditioning (e.g., busulfan).

CASGEVY is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation (e.g., DMSO, dextran 40, mannitol), including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Before mobilization, apheresis and myeloablative conditioning are initiated, confirm that hematopoietic stem cell transplantation (HSCT) is appropriate for the patient.
- CASGEVY can only be given in a treatment centre with experience in stem cell transplantation, and in the treatment of patients with SCD and TDT.
- For autologous use only. Do not infuse CASGEVY if the information on the patient specific label does not match the intended patient.
- For one--time, single -dose intravenous use only; do NOT use a leukodepleting filter.
- Do not sample, alter, or irradiate the medicinal product.
- CASGEVY must be administered between 48 hours and 7 days after the last dose of the myeloablative conditioning agent.
- Additional educational materials, including Patient Cards and Guides for Healthcare Professionals and Patients/Caregivers are available through the manufacturer.

Mobilization and Apheresis

Patients are required to undergo $CD34^+$ hematopoietic stem and progenitor cell (HSPC) mobilization followed by apheresis to isolate the $CD34^+$ cells for medicinal product manufacturing.

In clinical trials in SCD, single-agent plerixafor was administered for mobilization. Do not use granulocyte colony stimulating factor (G-CSF) products for mobilization in patients with Sickle Cell Disease.

In TDT clinical trials, both G-CSF and plerixafor were used for mobilization (see 14 CLINICAL TRIALS).

Maximize $CD34^+$ cell collection to obtain as many $CD34^+$ cells as possible for product manufacturing during each mobilization 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. An additional 2×10^6 $CD34^+$ cells/kg is required to be collected as backup for rescue therapy in an event of non-engraftment with CASGEVY. A third day of cell collection can be used to obtain backup 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 mobilization and apheresis. Each mobilization and apheresis cycle must be separated by a minimum of 14 days.

The backup 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 7 WARNINGS AND PRECAUTIONS).

See 14 CLINICAL TRIALS for descriptions of the mobilization regimen used in the clinical studies. Refer to the prescribing information for the mobilization agent(s) prior to treatment.

Disease modifying therapies (e.g., hydroxyurea for SCD and luspatercept for TDT) should be discontinued 8 weeks before the planned start of mobilization.

Sickle Cell Disease:

Prior to apheresis it is recommended that patients be transfused with a goal of maintaining HbS levels < 30% of total Hb while keeping total Hb concentration ≤ 110 g/L.

Transfusion-Dependent β-thalassemia:

Prior to apheresis procedure it is recommended that patients be transfused with a goal to maintain hemoglobin (Hb) ≥ 110 g/L.

Myeloablative Conditioning

Full myeloablative conditioning must be administered before infusion of CASGEVY. In clinical studies busulfan was administered for 4 consecutive days intravenously (IV) via a central venous catheter at a planned starting dose of 3.2 mg/kg/day once daily (qd) or 0.8 mg/kg every 6 hours (q6h). Busulfan plasma levels were measured by serial blood sampling and the dose adjusted to maintain exposure in the target range.

See 14 CLINICAL TRIALS for additional details regarding the conditioning regimen used in clinical studies. Consult prescribing information for the myeloablative conditioning agent(s) prior to treatment (see 17 SUPPORTING PRODUCT MONOGRAPHS).

Disease modifying therapies (e.g., hydroxyurea for SCD and luspatercept for TDT) should be discontinued 8 weeks before the start of myeloablative conditioning. Iron chelation therapy should be stopped at least 7 days prior to myeloablative conditioning.

In patients with sickle cell disease it is recommended to transfuse for at least the 8 weeks prior to the initiation of myeloablative conditioning, with a goal of maintaining HbS levels of < 30% of total Hb while keeping total Hb concentration ≤ 110 g/L.

In patients with TDT it is recommended to maintain hemoglobin (Hb) ≥ 110 g/L for 60 days prior to myeloablative conditioning.

Prophylaxis for seizures should be considered. Refer to the prescribing information of the conditioning agent used for information on drug interactions.

Prior to starting the myeloablative conditioning regimen, confirm availability of the complete set of vials comprising the total dose of CASGEVY and unmodified rescue cells, and inspect the vial(s) for any breaks or cracks. See the Lot Information Sheet provided with the product shipment for confirmation of the number of vials and total dose of CASGEVY.

CASGEVY must be administered between 48 hours and 7 days after the last dose of the myeloablative conditioning agent.

4.2 Recommended Dose and Dosage Adjustment

The minimum recommended dose of CASGEVY is 3×10^6 viable $CD34^+$ cells/kg.

CASGEVY is provided as a single dose for infusion containing a suspension of $CD34^+$ cells in one or more vials. See the Lot Information Sheet provided with the product shipment for additional information pertaining to dose.

4.4 Administration

Receipt and Storage of CASGEVY

- CASGEVY is shipped to the treatment centre frozen in the vapor phase of liquid nitrogen in a cryoshipper.
- **Confirm patient identifiers on the product label(s) and Lot Information Sheet.**
- If there are any concerns about the product, packaging or shipping temperatures upon receipt, contact VERTEX at 1-877-634-8789.
- Transfer CASGEVY from the vapour phase of the nitrogen cryoshipper to the vapour phase of liquid nitrogen (≤135 °C) storage located at the treatment centre.

Preparation for CASGEVY Administration

CASGEVY contains human cells. Follow universal precautions (wearing gloves, protective clothing, and eye protection) and local biosafety guidelines applicable for handling and disposal of such products to avoid potential transmission of infectious diseases. All material that has been in contact with CASGEVY (solid and liquid waste) should be handled and disposed of as potentially infectious waste in

accordance with local biosafety guidelines (see 12 SPECIAL HANDLING INSTRUCTIONS for additional details).

Before thawing a vial, confirm CASGEVY is printed on the vial label and that the patient's identity matches the unique patient information on the CASGEVY vial(s). Do not remove the CASGEVY vials from cryostorage if the information on the patient-specific label does not match the intended patient's information, and contact VERTEX at 1-877-634-8789.

Coordinate the timing of CASGEVY thaw and infusion. CASGEVY must be infused within 20 minutes of thawing the vial. Confirm the infusion time in advance and adjust the start time of the thaw so that CASGEVY is available for infusion when the patient is ready. Thaw and infuse one vial at a time.

Premedication: Administer an antipyretic (e.g., acetaminophen) and an antihistamine (e.g., diphenhydramine hydrochloride) prior to administering CASGEVY.

A dose of CASGEVY may be contained in one or more cryopreserved patient-specific vial(s). The number of vials provided is stated on the Lot Information Sheet. Ensure that each vial is accounted for and confirm that each vial is within the expiry date by comparing the product label information to the information on the accompanying Lot Information Sheet.

Inspect the vial(s) for any breaks or cracks prior to thawing. If a vial is compromised, do not infuse the contents. Call VERTEX at 1-877-634-8789.

Gather the supplies that are needed to thaw and withdraw the product from the vial(s). With the exception of the water bath, these supplies are single use. Gather 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
- 0.9% sodium chloride (saline, 5 to 10 mL needed for each vial)
- 10 mL luer-lock syringe for saline rinse

Thawing the CASGEVY Vials

- When the dose consists of multiple vials, thaw and administer one vial at a time. While thawing and administering 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 CASGEVY unattended during thaw.
- 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 cellular suspension, which may contain proteinaceous particles or cellular aggregates.
- Do not wash, spin down and/or resuspend CASGEVY in new media prior to infusion.
- Do not sample, alter, irradiate, or refreeze CASGEVY.
- Infuse within 20 minutes of thaw.

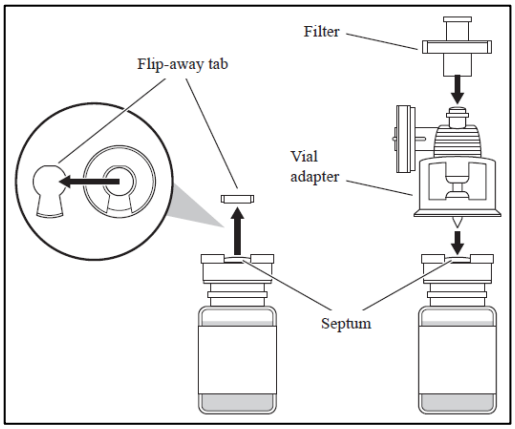
Administration of CASGEVY

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's information.

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

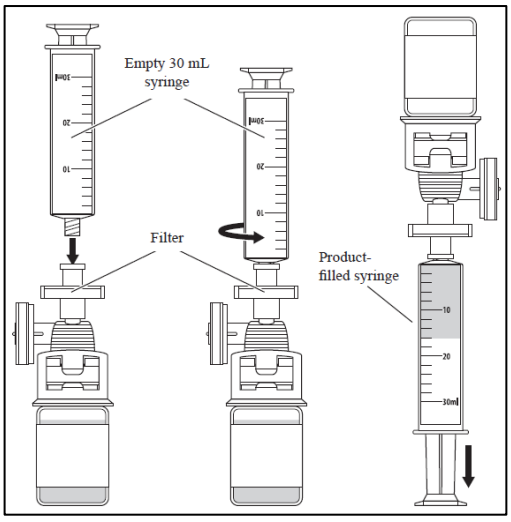
1. Attaching the vial adapter and filter

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

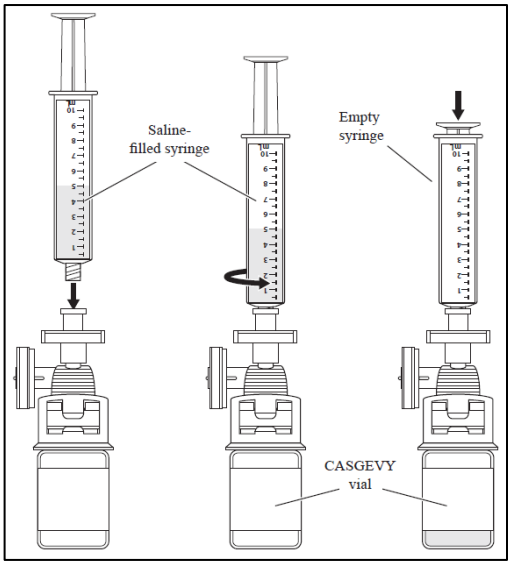


2. Withdrawing CASGEVY from the vial

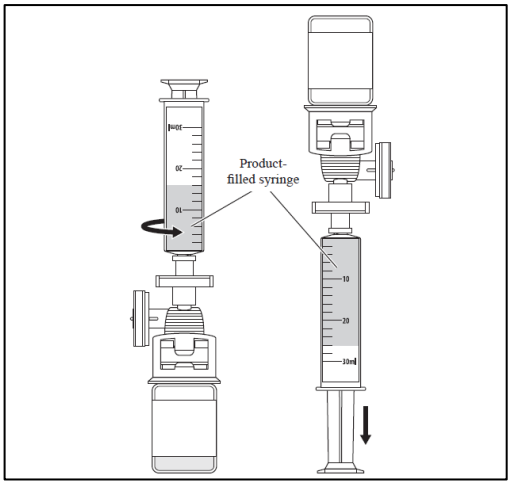
a. Attach an empty 30 mL syringe to the filter.
b. Withdraw the entire vial contents of the vial.
c. Remove the product-filled syringe from the filter and set aside.



d. Draw 5 - 10 mL of saline into the empty 10 mL syringe.
e. Attach the saline-filled syringe to the filter.
f. Inject the saline into the CASGEVY vial and remove the empty syringe from the filter. Discard the empty syringe.



g. Attach the product-filled syringe to the filter.
h. Withdraw the contents of the vial into the syringe, then remove the syringe from the filter.
i. Peel the product/patient identifier label from the Lot Information Sheet and affix to the product-filled syringe.



<u>3. Administer CASGEVY through central venous catheter</u>

a. Perform a two-person confirmation and verification of patient's identification at the bedside prior to the infusion of each vial.
b. Administer CASGEVY as an intravenous bolus (IV push) within 20 minutes of product thaw. Do not use an in-line blood filter or infusion pump when infusing CASGEVY. The total volume of CASGEVY administered within one hour must not exceed 2.6 mL/kg.
c. After administration of each vial of CASGEVY, flush the primary line with saline solution, using enough volume to flush the tubing and the length of the IV catheter.

Repeat steps 1-3 for each remaining vial. If the patient specific product was provided in more than 1 vial, administer each vial completely before proceeding to thaw and infuse the next vial. **All vials must be administered.**

After CASGEVY Administration

Follow standard procedures for monitoring and patient management after HSCT after CASGEVY infusion.

- Irradiate any blood products required within the first 3 months after CASGEVY infusion.
- Patients should not donate blood, organs, tissues, or cells at any time in the future.
- 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 9 DRUG INTERACTIONS).

Special Populations

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. Patients should be assessed for renal impairment to ensure HSCT is appropriate.

Hepatic Impairment

CASGEVY has not been studied in patients with advanced liver disease (see 14 Clinical Trials). Patients should be assessed for hepatic impairment to ensure HSCT is appropriate.

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 should not be used in patients with active HIV-1, HIV-2, HBV or HCV infections.

Patients with Prior HSCT

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

4.5 Missed Dose

Not applicable

5 OVERDOSAGE

Not applicable.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Cell suspension in	Cryostor® CS5 (contains DMSO, dextran 40,

	patient-specific vials 4-13 × 10^6 cells/mL 1.5 - 20 mL per vial 1 - 9 vials per carton A single patient may require multiple cartons for a complete dose	mannitol, multiple electrolytes for injection) see 7 WARNINGS AND PRECAUTIONS

CASGEVY is supplied in cryopreservation medium in vials made of cyclic olefin copolymer, packed in an outer paperboard carton.

Each lot of CASGEVY is shipped from the manufacturing facility to the treatment centre storage facility in a liquid nitrogen dry shipper. One shipper contains a single carton, which may contain multiple vials, all intended for a single patient. More than one Drug Product lot may be required for a single patient dose.

The actual quantitative information regarding strength and dose for CASGEVY is provided in the Lot Information Sheet. The Lot Information Sheet is included inside the lid of the liquid nitrogen dry shipper used to transport CASGEVY.

7 WARNINGS AND PRECAUTIONS

Individual patients must be considered suitable candidates for HSCT if they are to receive CASGEVY, taking into account the warnings and precautions of mobilization and myeloablative conditioning agents required as part of the overall therapy.

Carcinogenesis and Mutagenesis

Gene-Editing Related Oncogenesis

No cases of myelodysplasia, leukemia, or lymphoma have been reported in clinical studies with CASGEVY. There is a theoretical risk of hematologic oncogenesis related to gene editing. Monitor patients at least annually (including complete blood count) for 15 years after treatment with CASGEVY. If myelodysplasia, leukemia, or lymphoma are detected, contact Vertex at (1-877-634-8789) to determine how to appropriately sample for further analysis.

Off-target genome editing was not observed in studies in which the edited $CD34^+$ cells from healthy donors and patients were evaluated; however, the risk of unintended, off-target editing in an individual's $CD34^+$ cells cannot be entirely ruled out. The clinical significance of potential off-target editing is unknown.

Hematologic

Potential Neutrophil Engraftment Failure

Neutrophil engraftment failure is a potential risk in hematopoietic stem cell transplants, including after infusion with CASGEVY. In clinical trials, all patients treated with CASGEVY achieved neutrophil engraftment.

Patients should be monitored for absolute neutrophil counts (ANC) and infections should be managed

according to standard guidelines and medical judgment. In the event of neutrophil engraftment failure, patients should be infused with unmodified rescue $CD34^+$ cells (see 4.1 Dosing Considerations).

Prolonged Time to Platelet Engraftment

Longer median platelet engraftment times were observed with CASGEVY treatment than are typically observed with allogeneic HCST. There is an increased risk of bleeding until platelet engraftment is achieved. In clinical trials, there was no association observed between incidence of bleeding events and time to platelet engraftment.

Monitor patients for bleeding according to standard guidelines and medical judgement. Conduct frequent platelet counts until platelet engraftment and platelet recovery are achieved. Perform blood cell count determination and other appropriate testing whenever clinical symptoms suggestive of bleeding arise (see 8 ADVERSE REACTIONS).

Immune

Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, can occur during or following infusion of CASGEVY. Monitor patients for hypersensitivity reactions during and after infusion.

Live Vaccines

The safety of immunization with live viral vaccines during or following CASGEVY treatment has not been studied.

Reproductive Health: Female and Male Potential

Women of Childbearing Potential/Contraception in Males and Females

A negative serum pregnancy test must be confirmed prior to the start of each mobilization cycle and re-confirmed prior to myeloablative conditioning. Women of childbearing potential and men capable of fathering a child must use effective method of contraception from start of mobilization through at least 6 months after administration of CASGEVY due to the risks associated with myeloablative conditioning with busulfan. Advise patients of the risks associated with myeloablative conditioning agents. There are insufficient exposure data to provide a precise recommendation on duration of contraception following treatment with CASGEVY.

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. Infertility has been observed with myeloablative conditioning; therefore, fertility preservation options should be discussed with patients

and their family before proceeding with treatment (i.e., prior to mobilization), particularly in prepubertal individuals where fertility preservation options are limited.

7.1 Special Populations

7.1.1 Pregnant Women

Pregnancy

There are no clinical data from the use of exagamglogene autotemcel in pregnant women and no animal reproductive and developmental toxicity studies have been conducted with exagamglogene autotemcel. Due to the potential for fetal harm of myeloablative conditioning regimens, including teratogenicity, CASGEVY must not be administered during pregnancy. Pregnancy after CASGEVY infusion should be discussed with the treating physician (see guidance on contraception, above).

7.1.2 Breast-feeding

Breast-feeding

Breast-feeding should be discontinued during myeloablative conditioning due to the potential for serious outcomes including the potential for tumorigenicity. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for CASGEVY and any potential adverse effects on the breastfed child from the mobilization and myeloablative conditioning agents used prior to CASGEVY administration or from the underlying maternal condition.
Breast-feeding after infusion of CASGEVY should be discussed with the treating physician.

7.1.3 Pediatrics

No data in patients less than 12 years of age are available to Health Canada; therefore, Health Canada has not authorized an indication of pediatric use in patients less than 12 years of age.

7.1.4 Geriatrics

Patients Aged 65 Years and Older

CASGEVY has not been studied in patients > 35 years of age. The safety and efficacy of CASGEVY in a geriatric population has not been established.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following serious adverse reactions are described under 7 WARNINGS and PRECAUTIONS:

- Potential Neutrophil Engraftment Failure
- Prolonged Time to Platelet Engraftment
- Hypersensitivity Reactions

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to

the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of CASGEVY was evaluated in two open-label, single-arm studies (study 121 and study 111) and one long-term follow-up study (study 131), in which 98 adolescent and adult patients with SCD or TDT were treated with CASGEVY after undergoing myeloablative conditioning with busulfan. The adverse event profile was generally consistent with that expected from busulfan myeloablative conditioning and HSCT.

Patients with SCD

Summary of the Safety Profile

The median (min, max) duration of follow-up for the 44 patients with SCD after being administered CASGEVY was 19.3 (0.8, 48.1) months.

Serious adverse reactions after myeloablative conditioning and CASGEVY infusion were observed in 45% of patients in study 121. The most common serious adverse reactions (≥ 2 patients) were cholelithiasis, pneumonia, abdominal pain, constipation, pyrexia, abdominal pain upper, non-cardiac chest pain, oropharyngeal pain, pain, and sepsis.

One (2%) patient died due to a COVID-19 infection and subsequent respiratory failure. The event was not related to CASGEVY.

Tabulated List of Adverse Reactions

Table 2 presents the non-laboratory adverse reactions observed after myeloablative conditioning and CASGEVY infusion in at least 10% of patients with SCD. Adverse reactions are listed by MedDRA body system organ class and preferred term.

Table 2: Adverse reactions in ≥ 10% of patients with SCD who underwent busulfan myeloablative conditioning and received CASGEVY in study 121: Day 1 to month 24 after CASGEVY infusion [*]

MedDRA [†] System Organ Class	**Adverse Drug Reactions (Preferred Term)**	**CASGEVY N= 44 n (%)**
Blood and Lymphatic System Disorders	Febrile neutropenia	24 (55)
Cardiac Disorders	Tachycardia [‡]	9 (20)
Eye Disorders	Vision blurred	6 (14)
Gastrointestinal Disorders	Mucositis [§, #]	43 (98)
	Nausea	31 (70)
	Abdominal pain [**]	27 (61)
	Vomiting	25 (57)
	Constipation	20 (45)
	Diarrhea	17 (39)
	Gastritis	11 (25)

	Gastroesophageal reflux disease	8 (18)
	Dyspepsia	5 (11)
	Hematochezia	5 (11)
General Disorders and Administration Site Conditions	Pyrexia	18 (41)
	Fatigue	16 (36)
	Edema peripheral	12 (27)
	Pain	11 (25)
	Drug withdrawal syndrome	9 (20)
Hepatobiliary Disorders	Cholelithiasis	8 (18)
Infections and Infestations	COVID-19 [††]	12 (27)
	Oral candidiasis	9 (20)
	Upper respiratory tract infection [‡‡]	9 (20)
	Pneumonia	5 (11)
	Viral infection [§, §§]	5 (11)
Injury, Poisoning and Procedural Complications	Procedural pain	9 (20)
	Infusion related reactions [§, ##]	6 (14)
Investigations	Weight decreased	8 (18)
Metabolism and Nutrition Disorders	Decreased appetite	21 (48)
Musculoskeletal and Connective Tissue Disorders	Musculoskeletal pain [§, ***]	29 (66)
	Arthralgia	19 (43)
Nervous System Disorders	Headache	22 (50)
	Dizziness	10 (23)
	Paraesthesia	5 (11)
Psychiatric Disorders	Anxiety	9 (20)
	Insomnia	7 (16)
Renal and Urinary Disorders	Dysuria	7 (16)
Respiratory, Thoracic and Mediastinal Disorders	Oropharyngeal pain [§, †††]	11 (25)
	Epistaxis	9 (20)
	Cough	7 (16)
Skin and Subcutaneous Tissue Disorders	Pruritus	22 (50)
	Pigmentation disorder [‡‡‡]	17 (39)

	Skin exfoliation	10 (23)
	Rash §§§	8 (18)
	Alopecia	7 (16)
	Dry skin	6 (14)
Vascular Disorders	Hypertension	7 (16)
	Hot flush	5 (11)

* Table includes non-laboratory adverse events associated with busulfan myeloablative conditioning and treatment with CASGEVY. Adverse event profile generally consistent with that expected from busulfan myeloablative conditioning and HSCT.
† MedDRA version 26.0
‡ Tachycardia includes sinus tachycardia and tachycardia.
§ Encompasses preferred terms that belong to other system organ class.
# Mucositis includes anal inflammation, mucosal inflammation, pharyngeal inflammation, and stomatitis.
** Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness.
†† COVID-19 includes COVID-19 and SARS-CoV-2 test positive.
‡‡ Upper respiratory tract infection includes upper respiratory tract infection and viral upper respiratory tract infection.
§§ Viral infection includes adenovirus infection, influenza, parvovirus B19 test positive, viral infection, and viral test positive.
Infusion related reactions includes terms on Day 1 of CASGEVY infusion that were consistent with common infusion-related signs and symptoms: abdominal pain in 3 (7%) patients; and infusion-related reaction, nausea, non-cardiac chest pain, pruritus, sinus tachycardia and vomiting in 1 (2%) patient each.
*** Musculoskeletal pain includes back pain, bone pain, chest pain, costochondritis, musculoskeletal chest pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and tendon pain.
††† Oropharyngeal pain includes oral pain, oropharyngeal pain, and pain in jaw.
‡‡‡ Pigmentation disorder includes nail pigmentation, skin hyperpigmentation, and skin hypopigmentation.
§§§ Rash includes dermatitis, rash, rash macular, rash maculo-papular, rash papular, and urticaria.

Platelet Engraftment in Patients with SCD

Platelet engraftment in patients with SCD is defined as 3 consecutive measurements of platelet counts ≥50 × 10^9/L, obtained on 3 different days after CASGEVY infusion without administration of platelet transfusions for 7 days. In study 121, the median (min, max) time to platelet engraftment for patients with SCD was 35 (23, 126) days (n=43). There was no association observed between bleeding events and time to platelet engraftment.

Neutrophil Engraftment in Patients with SCD

Neutrophil engraftment is defined as 3 consecutive measurements of ANC ≥ 0.5 × 10^9 cells/L on 3 different days after CASGEVY infusion, without use of the unmodified rescue $CD34^+$ cells. In study 121, the median (min, max) time to neutrophil engraftment was 27 (15, 40) days (n=44). There was no association observed between infections and time to neutrophil engraftment. There was no use of rescue $CD34^+$ cells in any patient.

Patients with TDT

Summary of the Safety Profile

The median (min, max) duration of follow-up for 54 patients with TDT after being administered CASGEVY was 22.8 (2.1, 51.1) months.

Serious adverse reactions after myeloablative conditioning and CASGEVY infusion were observed in 35% of patients with TDT. The most common serious adverse reactions (≥ 2 patients) were

veno-occlusive liver disease, pneumonia, COVID-19, hypoxia, thrombocytopenia, and upper respiratory tract infection.

Tabulated List of Adverse Reactions

Table 3 presents the non-laboratory adverse reactions observed after myeloablative conditioning and CASGEVY infusion in at least 10% of patients in study 111. Adverse reactions are listed by MedDRA body system organ class and preferred term.

Table 3: Adverse reactions in ≥ 10% of patients with TDT who underwent busulfan myeloablative conditioning and received CASGEVY in study 111: Day 1 to month 24 after CASGEVY infusion [*]

MedDRA [†] System Organ Class	**Adverse Drug Reactions (Preferred Term)**	**CASGEVY N= 54 n (%)**
Blood and Lymphatic System Disorders	Febrile neutropenia	33 (61)
Cardiac Disorders	Tachycardia [‡]	11 (20)
Eye Disorders	Vision blurred	8 (15)
Gastrointestinal Disorders	Mucositis [§, #]	48 (89)
	Nausea	23 (43)
	Abdominal pain [**]	22 (41)
	Vomiting	22 (41)
	Constipation	18 (33)
	Diarrhea	15 (28)
	Gastritis	6 (11)
	Gingival bleeding	6 (11)
General Disorders and Administrative Site Conditions	Pyrexia	15 (28)
	Fatigue	8 (15)
	Asthenia	7 (13)
	Pain	6 (11)
Hepatobiliary Disorders	Veno-occlusive liver disease	7 (13)
Infections and Infestations	COVID-19 [§, ††]	20 (37)
	Upper respiratory tract infection [‡‡]	6 (11)
	Viral infection [§, §§]	6 (11)

Injury, Poisoning and Procedural Complications	Infusion related reactions [§, ##]	13 (24)
	Transfusion reactions [***]	9 (17)
	Procedural pain	8 (15)
Metabolism and Nutrition Disorders	Decreased appetite	14 (26)
Musculoskeletal and Connective Tissue Disorders	Musculoskeletal pain [§, †††]	26 (48)
	Arthralgia	19 (35)
Nervous System Disorders	Headache	30 (56)
	Dizziness	8 (15)
Psychiatric Disorders	Insomnia	9 (17)
Renal and Urinary Disorders	Hematuria	7 (13)
Respiratory, Thoracic and Mediastinal Disorders	Epistaxis	20 (37)
	Oropharyngeal pain [§, ‡‡‡]	11 (20)
	Cough	10 (19)
	Rhinitis [§, §§§]	8 (15)
Skin and Subcutaneous Tissue Disorders	Rash [###]	19 (35)
	Pruritus	15 (28)
	Petechiae	12 (22)
	Alopecia	11 (20)
	Pigmentation disorder [****]	6 (11)
Vascular Disorders	Hypertension	6 (11)

[*] Table includes non-laboratory adverse events associated with busulfan myeloablative conditioning and treatment with CASGEVY. Adverse event profile generally consistent with that expected from busulfan myeloablative conditioning and HSCT.
[†] MedDRA version 26.0
[‡] Tachycardia includes sinus tachycardia and tachycardia.
[§] Encompasses preferred terms that belong to other system organ class.
[#] Mucositis includes anal inflammation, mucosal inflammation, pharyngeal inflammation, and stomatitis.
[**] Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, and epigastric discomfort.
[††] COVID-19 includes COVID-19, COVID-19 pneumonia, and SARS-CoV-2 test positive.
[‡‡] Upper respiratory tract infection includes nasopharyngitis and upper respiratory tract infection.
[§§] Viral infection includes influenza, respiratory tract infection viral, viral infection, and viral test positive.
[##] Infusion related reactions includes terms on Day 1 of CASGEVY infusion that were consistent with common infusion-related signs and symptoms: abdominal pain and nausea in 4 (7%) patients each; vomiting in 3 (6%) patients; pruritis in 2 (4%) patients; and abdominal pain lower, chills, sinus tachycardia, and tachycardia in 1 (2%) patient each.
[***] Transfusion reactions related to transfusion of blood products, includes allergic transfusion reaction and transfusion reaction.
[†††] Musculoskeletal pain includes back pain, bone pain, chest pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and spinal pain.
[‡‡‡] Oropharyngeal pain includes oral pain, oropharyngeal pain, and pain in jaw.
[§§§] Rhinitis includes rhinitis, rhinitis allergic, and rhinorrhea.
[###] Rash includes dermatitis, dermatitis acneiform, rash, rash erythematous, rash maculo-papular, rash pruritic, and urticaria.
[****] Pigmentation disorder includes skin hyperpigmentation.

Platelet engraftment in patients with TDT

Platelet engraftment in patients with TDT is defined as 3 consecutive measurements of platelet counts ≥ 20×10^9/L, obtained on 3 different days after CASGEVY infusion without administration of platelet transfusions for 7 days. In study 111, the median (min, max) time to platelet engraftment was 44 (20, 200) days (n=53). There was no association observed between bleeding events and time to platelet engraftment. 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.

Neutrophil engraftment in patients with TDT

Neutrophil engraftment is defined as 3 consecutive measurements of ANC ≥ 0.5×10^9 cells/L on 3 different days after CASGEVY infusion, without use of the unmodified rescue $CD34^+$ cells. In study 111, the median (min, max) time to neutrophil engraftment was 29 (12, 56) days (n=54). There was no association observed between infections and time to neutrophil engraftment. There was no use of rescue $CD34^+$ cells in any patient.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The safety profile was generally consistent among adolescent and adult patients. Engraftment times were similar in adolescent and adult patients.

Patients with SCD (study 121)

The safety of CASGEVY in study 121 was evaluated in 19 patients with SCD aged 12 to less than 18 years. 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. The median (min, max) time to neutrophil engraftment was 28 (24, 40) days in adolescent patients and 25.5 (15, 38) days in adult patients.

Patients with TDT (study 111)

The safety of CASGEVY in study 111 was evaluated in 19 patients with TDT aged 12 to less than 18 years. The median (min, max) time to platelet engraftment was 45 (20, 199) days in adolescent patients and 40 (24, 200) days in adult patients. The median (min, max) time to neutrophil engraftment was 31 (19, 56) days in adolescent patients and 29 (12, 40) days in adult patients.

8.3 Less Common Clinical Trial Adverse Reactions

Other clinically important adverse reactions that occurred in less than 10% of patients with SCD include the following:

- *Hepatobiliary disorders*: Veno-occlusive liver disease (1 [2%] patient)

Other clinically important adverse reactions that occurred in less than 10% of patients with TDT include the following:

- *Immune system disorders*: Hemophagocytic lymphohistiocytosis (1 [2%] patient),
- *Injury, poisoning and procedural complications:* delayed neutrophil engraftment (1 [2%] patient)
- *Nervous system disorders*: Cerebellar hemorrhage (intracranial hemorrhage) (1 [2%] patient)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 4 presents the Grade 3 or 4 laboratory abnormalities that occurred in at least 10% of patients with SCD.

Table 4: Grade 3 or 4 laboratory abnormalities in ≥ 10% of patients with SCD who underwent busulfan myeloablative conditioning and received CASGEVY in study 121: Day 1 to month 24 After CASGEVY infusion [*]

Laboratory abnormality	**Patients with SCD (study 121) (N=44) [†] (%)**
Neutropenia	100
Thrombocytopenia	100
Leukopenia	98
Anemia	84
Lymphopenia	50
CD4 lymphocyte count decreased	23
Activated partial thromboplastin time prolonged	16
Hyperbilirubinaemia	14

[*] Table includes laboratory abnormalities associated with busulfan myeloablative conditioning and treatment with CASGEVY. Laboratory abnormalities generally consistent with that expected from busulfan myeloablative conditioning and HSCT.
[†] The denominator for CD4 lymphocytes decreased is 43 and the denominator for all other laboratory data is 44, based on evaluable data at the time of the interim analysis.

Table 5 presents the Grade 3 or 4 laboratory abnormalities that occurred in at least 10% of patients with TDT.

Table 5: Grade 3 or 4 laboratory abnormalities in ≥ 10% of patients with TDT who underwent busulfan myeloablative conditioning and received CASGEVY in study 111: Day 1 to month 24 after CASGEVY infusion [*]

Laboratory abnormality	**Patients with TDT (study 111) (N=54) [†] (%)**
Neutropenia	100
Thrombocytopenia	100
Leukopenia	98
Anemia	93
Lymphopenia	80

Hyperbilirubinemia	24
CD4 lymphocytes decreased	23
Alanine aminotransferase increased	20
Hypokalemia	19
Gamma-glutamyltransferase increased	17
Activated partial thromboplastin time prolonged	13
Hypocalcemia	13
Aspartate aminotransferase increased	11

[*] Table includes laboratory abnormalities associated with busulfan myeloablative conditioning and treatment with CASGEVY. Laboratory abnormalities generally consistent with those expected from busulfan myeloablative conditioning and HSCT.
[†] The denominator for CD4 lymphocytes decreased is 52 and the denominator for all other laboratory data is 54, based on evaluable data at the time of the interim analysis.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

The drug-drug interactions of mobilization and myeloablative conditioning agents 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.

9.4 Drug-Drug Interactions

Use of hydroxyurea should be discontinued at least 8 weeks prior to start of mobilization and at least 8 weeks prior to the start of conditioning. There is no experience on the use of hydroxyurea after CASGEVY infusion.

Discontinue the use of luspatercept at least 8 weeks prior to start of mobilization and conditioning, as the interaction potential with mobilization and myeloablative conditioning agents is not known.

Iron chelators should be discontinued at least 7 days prior to initiation of myeloablative conditioning, due to potential interaction with the conditioning agent. Some iron chelators are myelosuppressive. If iron chelation is required, 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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

CASGEVY is a cellular therapy consisting of autologous $CD34^+$ HSPCs, obtained by apheresis, which are edited by CRISPR/Cas9-technology. A specific guide RNA enables CRISPR/Cas9 to make a precise DNA double-strand break, which disrupts the critical transcription factor (GATA1) binding site in the erythroid specific enhancer region of the *BCL11A* gene. As a result of the permanent editing, GATA1 binding is disrupted and BCL11A expression reduced. Reduced BCL11A expression results in increased γ-globin expression and fetal hemoglobin (HbF) protein production in erythroid cells, addressing the underlying causes of disease. In patients with severe sickle cell disease (SCD), HbF expression is expected to reduce the intracellular hemoglobin S (HbS) concentration, preventing the red blood cells from sickling.

In patients with transfusion-dependent β-thalassemia (TDT), γ-globin production corrects the α-globin to non-α-globin imbalance thereby reducing ineffective erythropoiesis and hemolysis and increasing total hemoglobin levels, primarily in the form of HbF, eliminating the dependence on regular red blood cell (RBC) transfusions.

10.2 Pharmacodynamics

Sickle Cell Disease

Fetal Hemoglobin and Total Hemoglobin

HbF and total Hb over time are provided in Table 6 for all patients administered CASGEVY for the treatment of sickle cell disease (full analysis set). HbF and total Hb over time for the subset of patients included in the primary efficacy analysis were consistent with full analysis set.

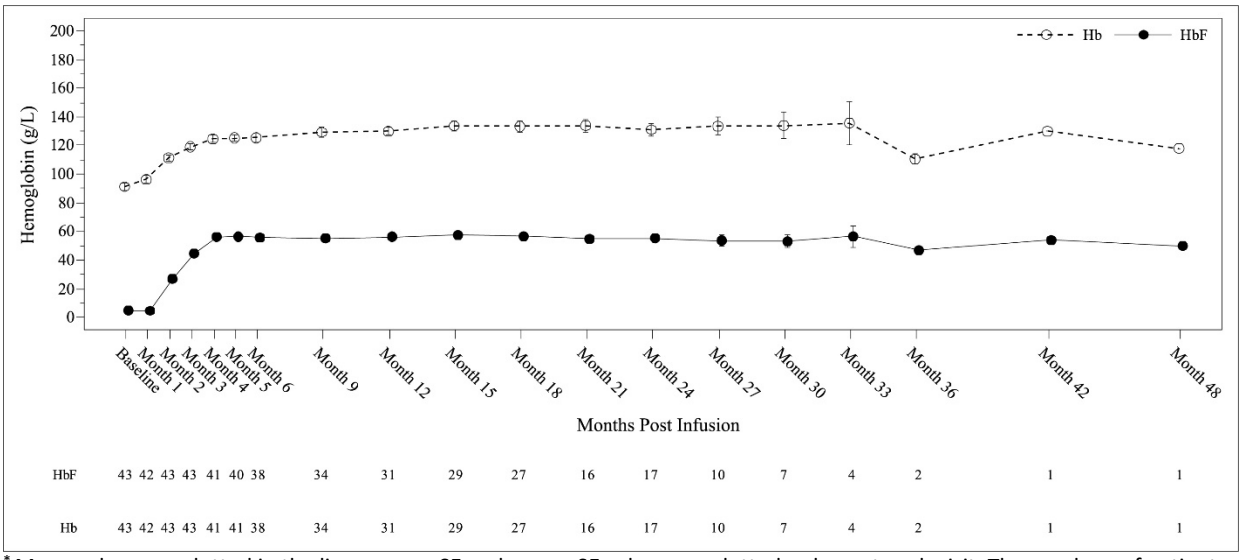
Table 6: Proportion of hemoglobin comprised of HbF (%) and total Hb (g/L) over time in patients with SCD in study 121

	CASGEVY Full Analysis Set (FAS) (N=44)	
	Proportion of total Hb comprised of HbF (%) *	Total Hb (g/L) *
Month 6		
n	38	38
Mean (SD)	43.9 (8.6)	125 (18)
Median (min, max)	44.3 (14.9, 68.4)	123 (72, 159)
Month 12		
n	32	31
Mean (SD)	43.4 (4.6)	130 (15)
Median (min, max)	42.9 (35.1, 52.1)	129 (103, 157)
Month 18		
n	27	27
Mean (SD)	42.3 (5.8)	133 (19)
Median (min, max)	43.1 (27.5, 53.3)	127 (110, 173)
Month 24		
n	17	17
Mean (SD)	42.1 (5.2)	131 (18)
Median (min, max)	42.2 (33.3, 49.1)	130 (105, 173)

* %HbF/Hb data not available for all patients at all timepoints.
SD: Standard Deviation.

Total Hb (g/L) and HbF (g/L) levels over time is provided in Figure 1 for all patients administered CASGEVY for the treatment of sickle cell disease.

Figure 1: Mean Total Hb and HbF 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.

[†] The average total Hb at month 36 is reduced due to one patient having a lower total Hb across all timepoints. This patient achieved VF12 and HF12.

Increased mean (SD) total Hb was observed by month 3 after CASGEVY infusion, which increased to approximately 125 (18) g/L at month 6 and remained relatively stable thereafter. The mean (SD) proportion of Hb comprised by HbF was 43.9% (8.6%) at Month 6 and was maintained thereafter.

Consistent with the increase in HbF levels, the mean (SD) proportion of circulating erythrocytes expressing HbF (F-cells) at month 3 was 70.1% (13.8%). At month 6, the mean (SD) proportion of F-cells was 94.0% (12.4%) with the proportion remaining stable thereafter, indicating sustained pan-cellular expression of HbF.

Transfusion-dependent β-thalassemia

Fetal Hemoglobin and Total Hemoglobin

Total Hb and HbF levels over time are provided in Table 7 for all patients administered CASGEVY for the treatment of transfusion-dependent β-thalassemia (full analysis set). HbF and total Hb over time for the subset of patients included in the primary efficacy analysis were consistent with full analysis set.

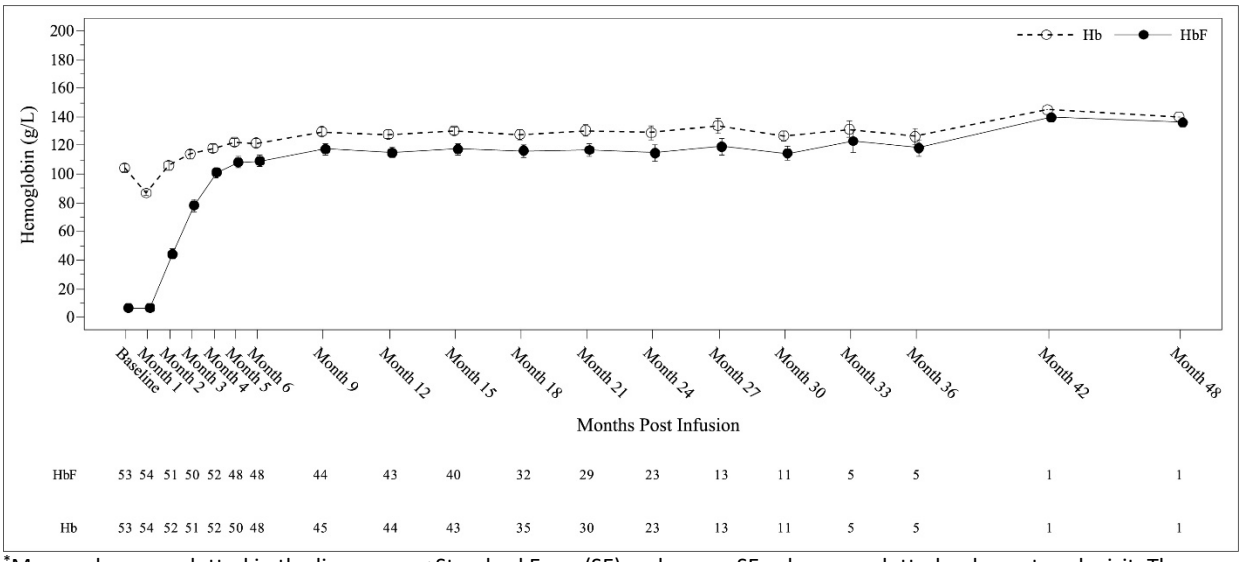
Table 7: Total Hb (g/L) and HbF levels over time in patients with TDT in study 111

	CASGEVY Full Analysis Set (FAS) (N=54)	
	Total Hb (g/L) *	Total HbF (g/L) *
Month 6		
n	48	48
Mean (SD)	122 (20)	109 (27)
Median (min, max)	125 (65, 164)	116 (11, 145)
Month 12		
n	44	43
Mean (SD)	128 (21)	115 (25)
Median (min, max)	129 (62, 172)	123 (44, 153)
Month 18		
n	35	32
Mean (SD)	128 (22)	116 (24)
Median (min, max)	129 (65, 177)	121 (43, 154)
Month 24		
n	23	23
Mean (SD)	129 (24)	115 (27)
Median (min, max)	135 (77, 169)	120 (67, 154)

* Hb/HbF data not available for all patients at all timepoints.

Total Hb (g/L) and HbF (g/L) levels over time are provided in Figure 2 for all patients administered CASGEVY for the treatment of β-thalassemia.

Figure 2: Mean Total Hb (g/L) and HbF (g/L) 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.

Increased mean (SD) total Hb and HbF were observed by month 3 after CASGEVY infusion, which increased to 122 (20) g/L and 109 (27) g/L, respectively, at month 6. After month 6, levels of total Hb and HbF were maintained thereafter, with HbF comprising ≥ 88% of total Hb.

10.3 Pharmacokinetics

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

11 STORAGE, STABILITY AND DISPOSAL

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.
- If there are any concerns about the product, packaging or shipping temperatures upon receipt, contact Vertex at 1-877-634-8789.
- Transfer CASGEVY from the vapor phase nitrogen shipper to the treatment center vapor phase of liquid nitrogen storage at ≤ -135 °C until ready for thaw and administration.
- Keep the vial(s) in the carton until ready to thaw.
- Thaw one vial at a time. Do not thaw until ready to infuse. Do not refreeze after thawing.

Stability

- CASGEVY is stable for 24 months when stored frozen in the vapor phase of liquid nitrogen.
- A vial of CASGEVY must be infused within 20 minutes after thawing.

Disposal

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

12 SPECIAL HANDLING INSTRUCTIONS

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 should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

Precautions to be Taken for Handling

Keep the vial(s) in the carton until ready to thaw.

Thaw and infuse one vial at a time. Do not refreeze after thawing (see 4 DOSAGE AND ADMINISTRATION for full thawing instructions).

Accidental Exposure

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: exagamglogene autotemcel

Physicochemical properties: Translucent cell suspension, which may contain small inherent proteinaceous particles or visible cell aggregates

Product Characteristics:

CASGEVY is prepared from the patient's own HSPCs, which are obtained via apheresis. The autologous cells are enriched for $CD34^+$ cells, and the CRISPR/Cas9 editing component is introduced *ex-vivo* by electroporation. The edited $CD34^+$ cells are suspended in a sterile cryopreservation medium and shipped as a frozen suspension in patient-specific vial(s). The product is thawed prior to infusion. The thawed product is a translucent cellular suspension, which may contain small inherent proteinaceous particles or visible cell aggregates.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Sickle Cell Disease

Study Design and Demographics

Study 121 is an ongoing multicentre, single-arm study to evaluate the safety and efficacy of single-dose CASGEVY in adult and adolescent patients, aged 12 to 35 years old, with severe sickle cell disease. Upon completion of 24 months of follow-up in study 121, patients are invited to enroll in study 131, an ongoing long-term follow-up study to collect safety and efficacy outcomes for up to 15 years after CASGEVY infusion.

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

- Acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous [IV] nonsteroidal 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 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. Patients with an available 10/10 human leukocyte antigen matched related hematopoietic stem cell donor were excluded. In addition, patients were ineligible if they had 10 unplanned hospitalizations or emergency department visits related to chronic pain, rather than SCD-related acute pain crises, in the year before screening.

Other exclusions included having an LVEF less than 45% by echocardiogram; positivity for various infectious disease markers such as HIV-1 or HIV-2, HBV, syphilis, or HCV.

As of the data cutoff, 63 SCD patients had enrolled in the study, 58 had undergone mobilization, and 44 had received CASGEVY forming the full analysis set (FAS). Of the 44 patients in the FAS, 30 were followed for a sufficient length of time (16 months) to be included in analyses of primary and key secondary outcomes. These 30 patients were included in the primary efficacy set (PES). The key demographics and baseline characteristics for the FAS and the PES are shown in Table 8.

Table 8: Study 121 Demographics and Baseline Characteristics *

Demographics and disease characteristics	CASGEVY Full Analysis Set (FAS) (N=44)	CASGEVY Primary Efficacy Set (PES) (N=30) †
Age (years), n (%)		
Adults (≥ 18 and ≤ 35 years)	32 (72.7%)	24 (80.0%)
Adolescents (≥ 12 and < 18 years)	12 (27.3%)	6 (20.0%)
All ages (≥ 12 and ≤ 35 years)		
Median (min, max)	20 (12, 34)	21 (12, 34)
Sex, n (%)		
Male	24 (54.5%)	16 (53.3%)
Female	20 (45.5%)	14 (46.7%)
Race, n (%)		
Black or African American	38 (86.4%)	26 (86.7%)
White	3 (6.8%)	1 (3.3%)
Other	3 (6.8%)	3 (10.0%)
Genotype, n (%)		
β^S/β^S	40 (90.9%)	29 (96.7%)
β^S/β^0	3 (6.8%)	1 (3.3%)
β^S/β^+	1 (2.3%)	0
Annualized rate of severe VOCs in the 2 years prior to enrolment (events/year)		
Median (min, max)	3.5 (2.0, 18.5)	3.3 (2.0, 9.5)
Annualized rate of hospitalizations due to severe VOCs in the 2 years prior to enrolment (events/year)		
Median (min, max)	2.5 (0.5, 9.5)	2.0 (0.5, 8.5)
Annualized duration of hospitalization due to severe VOCs in the 2 years prior to enrolment (days/year)		
Median (min, max)	14.0 (2.0, 136.5)	12.3 (2.0, 64.6)
Annualized units of RBCs transfused for SCD-related indications in the 2 years prior to enrolment (units/year)		
Median (min, max)	5.0 (0, 86.1)	3.3 (0, 75.5)

* Analysis conducted based on June 2023 data cut.

† The primary efficacy set (PES), is a subset of the full analysis set (FAS). The PES was defined as all patients who had been followed for at least 16 months after CASGEVY infusion. Patients 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 10 months after CASGEVY were also included in this set.

Mobilization and Apheresis

Patients underwent red blood cell exchange or simple transfusions for a minimum of 8 weeks before the planned start of mobilization and continued receiving transfusions or red blood cell exchanges until the initiation of myeloablative conditioning. Hemoglobin S (HbS) levels were maintained at < 30% of total Hb while keeping total Hb concentration ≤ 110 g/L.

To mobilize 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 mobilization and apheresis cycles required for manufacture CASGEVY and for the collection of rescue $CD34^+$ cells were 2 (1, 6) and 2.30 (1.41), respectively. Six out of 58 patients (10%) who started mobilization did not receive CASGEVY therapy due to not achieving the minimum dose.

Pre-Treatment Conditioning

All patients received full myeloablative conditioning with busulfan prior to receiving CASGEVY. Busulfan was administered for 4 consecutive days intravenously (IV) via a central venous catheter at a planned starting dose of 3.2 mg/kg/day once daily (qd) or 0.8 mg/kg every 6 hours (q6h). 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 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 regional and institutional guidelines.

CASGEVY Administration

Patients were administered CASGEVY with a median (min, max) dose of 4.0 (2.9, 14.4) × 10^6 $CD34^+$ cells/kg as an IV 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.

Study Results

An interim analysis (IA) was conducted with 30 patients eligible for the primary efficacy analysis (i.e., the primary efficacy set [PES]). At the time of the interim analysis 44 patients had been administered CASGEVY. The median (min, max) total duration of follow-up for the FAS was 19.3 (0.8, 48.1) months from the time of CASGEVY infusion, and the median (min, max) total duration of follow-up for the PES was 26.0 (17.8, 48.1) months.

The efficacy of CASGEVY was based on evaluation of 30 patients. 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 [IV] nonsteroidal 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. All patients had at least 16 months of follow-up after CASGEVY infusion. The proportion of patients who did not require hospitalization due to severe VOCs for at least 12 consecutive months (HF12, key secondary endpoint) was also assessed. The evaluations of VF12 and HF12 began 60 days after the last RBC transfusion for post-transplant support or SCD management. After CASGEVY infusion, patients in the PES had a median time to last RBC transfusion of 19.0 days (range: 11, 52).

Efficacy data for the 30 patients in the primary efficacy analysis (PES) are presented in Table 9, below.

Table 9: Efficacy Outcomes in patients with SCD – Primary Efficacy Set (PES)

Endpoint	CASGEVY Interim Analysis * (N=30) †
Proportion of patients achieving VF12 ‡ (%) n (%) (95% CI)	 29 (96.7%) (82.8%, 99.9%)
Proportion of patients free from hospitalization due to severe VOCs for at least 12 months (HF12) # (%) n (%) (95% CI)	 30 (100%) (88.4%, 100%)
Duration of severe VOC-free period in patients who have achieved VF12 (months) n Median (min, max)	 29 22.2 (14.8, 45.5)

* Analysis conducted based on June 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 followed for at least 16 months after CASGEVY infusion. Patients 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 10 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.

HF12 defined as: no severe VOC-related inpatient hospitalizations 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.

Transfusion-dependent β-thalassemia

Study Design and Demographics

Study 111 is an ongoing, multicentre, single-arm study to evaluate the safety and efficacy of single-dose CASGEVY in adult and adolescent patients aged 12 to 35 years of age with transfusion-dependent β-thalassemia (TDT). Upon completion of 24 months of follow-up in study 111, patients are invited to enroll in study 131, an ongoing long-term follow-up study to collect safety and efficacy outcomes for up to 15 years after CASGEVY infusion.

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 enrollment and did not have a 10/10 human leukocyte antigen (HLA) matched related hematopoietic stem cell 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 left ventricular ejection fraction [LVEF], 45% by echocardiogram), advanced liver disease, or renal impairment (glomerular filtration rate <60 mL/min/1.73 m^2) 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. In addition, patients who were positive for human immunodeficiency virus-1 (HIV-1) or human immunodeficiency virus-2 (HIV-2), hepatitis B virus (HBV), syphilis or hepatitis C (HCV) were excluded.

The key demographics and baseline characteristics for all patients administered CASGEVY in study 111 are shown in Table 10, below.

Table 10: Study 111 Demographics and Baseline Characteristics *

Demographics and Disease Characteristics	CASGEVY Full Analysis Set (FAS) (N=54)	CASGEVY Primary Efficacy Set (PES) † (N=42)
Age, n (%)		
Adults (≥ 18 and ≤ 35 years)	35 (64.8%)	29 (69%)
Adolescents (≥ 12 and < 18 years)	19 (35.2%)	13 (31%)
All ages (≥ 12 and ≤ 35 years) Median (min, max)	20 (12, 35)	20 (12, 35)
Sex, n (%)		
Female	25 (46.3%)	21 (50%)
Male	29 (53.7%)	21 (50%)
Race, n (%)		
Asian	23 (42.6%)	16 (38.1%)
White	18 (33.3%)	17 (40.5%)
Multiracial	3 (5.6%)	3 (7.1%)
Other	2 (3.7%)	1 (2.4%)
Not collected	8 (14.8%)	5 (11.9%)
Genotype, n (%)		
β^0/β^0-like ‡	33 (61.1%)	25 (59.5%)
Non-β^0/β^0-like	21 (38.9%)	17 (40.5%)
Baseline annualized RBC transfusion volume (mL/kg) Median (min, max)	205.7 (48.3, 330.9)	201.0 (115.2, 330.9)
Baseline annualized RBC transfusion episodes Median (min, max)	16.5 (5.0, 34.5)	16.5 (10.5, 34.5)
Spleen intact, n (%)	38 (70.4)	30 (71.4%)
Baseline liver iron concentration (mg/g) Median (min, max)	3.5 (1.2, 14.0)	3.8 (1.2, 14.0)
Baseline cardiac iron T2* (msec) Median (min, max)	34.4 (12.4, 61.1)	34.8 (12.4, 61.1)
Baseline serum ferritin (pmol/L) Median (min, max)	3115.5 (584.2, 10837.3)	3157.0 (584.2, 10837.3)

* Analysis conducted based on April 2023 data cut

[†] The primary efficacy set (PES), is a subset of the full analysis set (FAS). The PES was defined as all patients who had been followed for at least 16 months after CASGEVY infusion. Patients 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 10 months after CASGEVY were also included in this set.
[‡] Low to no endogenous β-globin production (β^0/β^0, β^0/IVS-I-110 and IVS-I-110/IVS-I-110)

Mobilization and Apheresis

To maintain a total Hb concentration ≥ 110 g/L patients underwent RBC transfusions prior to mobilization and apheresis and continued receiving transfusions until the initiation of myeloablative conditioning.

To mobilize 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 µg/kg G-CSF approximately every 12 hours via intravenous or subcutaneous injection for 5 to 6 days. Splenectomized patients were administered a planned dose of 5 µg/kg G-CSF once daily for 5 to 6 days. The dose was increased to every 12 hours in splenectomized 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 mobilization and apheresis cycles required for manufacture of CASGEVY and for the collection of rescue $CD34^+$ cells were 1.3 (0.6) 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 (IV) via a central venous catheter at a planned starting dose of 3.2 mg/kg/day once daily (qd) or 0.8 mg/kg every 6 hours (q6h). 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 regional and institutional guidelines.

CASGEVY Administration

Patients were administered CASGEVY with a median (min, max) dose of 8.0 (3.0, 19.7) x 10^6 $CD34^+$ cells/kg as an IV 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.

Study Results

An interim analysis (IA) was conducted with 42 patients eligible for the primary efficacy analysis. At the time of the interim analysis 54 patients had been administered CASGEVY. The median (min, max) total duration of follow-up for the FAS was 22.8 (2.1, 51.1) months from the time of CASGEVY infusion, and the median (min, max) total duration of follow-up for the PES was 26.2 (16.1, 51.1).

The efficacy of CASGEVY was established based on evaluation of 42 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 a weighted average Hb ≥ 90 g/L 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.

At the time of the interim analysis, 42 patients were evaluable for TI12. Of these, 39/42 (92.9%, 95% CI: 80.5%, 98.5%) had achieved TI12. The median (min, max) time to last RBC transfusion for patients who achieved TI12 was 28 (11, 91) days following CASGEVY infusion. The three patients who did not achieve TI12 had reductions in annualized RBC transfusion volume requirements of 83.4%, 86.9% and 98.5%, and reductions in annualized transfusion frequency of 82.4%, 73.4% and 96.0%, respectively, compared to baseline requirements.

Efficacy data for the 42 patients in the primary efficacy analysis are presented in Table 11, below.

Table 11: Efficacy outcomes in patients with TDT - Primary Efficacy Set (PES)

Endpoint	CASGEVY Interim Analysis [*] (N=42) [†]
Proportion of patients achieving TI12 [‡, §] n (%) (95% CI)	 39 (92.9%) (80.5%, 98.5%)
Duration of transfusion-independent period in patients who have achieved TI12 (months) n Median (min, max)	 39 22.3 (13.5, 48.1)

[*] 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 followed for at least 16 months after CASGEVY infusion. Patients 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 10 months after CASGEVY infusion were also included in this set.

[‡] TI12 defined as maintaining weighted average Hb ≥90 g/L 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.

[§] Normal mean weighted average total Hb levels (mean [SD] 132 [14] g/L) were observed in all patients who achieved TI12.

SD: Standard Deviation

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Conventional mutagenicity, carcinogenicity and reproductive and developmental toxicity studies have not been conducted. No studies on the effects of CASGEVY on fertility have been conducted.

The toxicity and tumorigenicity of CASGEVY were evaluated in sub-lethally irradiated, immunodeficient (NSG) mice. No evidence of target organ toxicity or tumorigenicity was observed in a 20-week study.

In vitro studies with exagamglogene autotemcel manufactured from healthy donors and patients showed no evidence of off-target editing. In studies with edited $CD34^+$ cells obtained from healthy donors, no translocations were detected by either karyotyping or sequencing methods.

In vitro studies showed $CD34^+$ cells edited with exagamglogene autotemcel had impaired growth for the first few days following electroporation while long-term growth kinetics, reported by a fold-change in cell numbers, were similar to control $CD34^+$ cells that were not electroporated.

17 SUPPORTING PRODUCT MONOGRAPHS

BUSULFEX (busulfan for injection, 6 mg/mL vials) Submission Control No. 02240602, Product Monograph. Otsuka Pharmaceutical Co LTD.

MOZOBIL (plerixafor for injection, 20 mg/mL vials) Submission Control No. 02377225, Product Monograph. Sanofi-Aventis Canada Inc.

NEUPOGEN (filgrastim injection, 300 mcg/mL and 600 mcg/mL vials) Submission Control No. 270479, Product Monograph. Amgen Canada Inc.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

CASGEVY (cass-JEH-vee)

Exagamglogene autotemcel infusion

Read this carefully before you receive CASGEVY. This leaflet is a summary and will not tell you everything about this therapy. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about CASGEVY.

What is CASGEVY used for?

CASGEVY is used to treat:

- **People aged 12 years and older with sickle cell disease** who have frequent painful crises (called vaso-occlusive crises). Patients with sickle cell disease have an abnormal form of hemoglobin called sickle cell hemoglobin. Sickle cell hemoglobin causes red blood cells to have a sickle-shape, which can lead to blood vessel blockages, causing painful crises.
- **People aged 12 years and older with beta thalassemia** who need regular blood transfusions because they do not have enough hemoglobin, a protein in the blood that carries oxygen throughout the body. This causes low amounts of red blood cells, and regular blood transfusions are needed.

Children under 12 years of age

CASGEVY is not to be given to children under 12 years of age because it is not yet known if CASGEVY is safe and effective in this age group.

How does CASGEVY work?

CASGEVY is a cell therapy made from your own blood stem cells. These cells are taken from your body and are modified to make CASGEVY. CASGEVY is a one-time therapy, administered in a hospital, that works by increasing the production of a type of hemoglobin called fetal hemoglobin. Having more fetal hemoglobin improves the production and function of red blood cells. This can mean that people with beta thalassemia may not need blood transfusions. For people with sickle cell disease, CASGEVY can help stop blood vessel blockages and prevent painful crises.

What are the ingredients in CASGEVY?

Medicinal ingredients: exagamglogene autotemcel

Non-medicinal ingredients: Cryostor CS5 (contains dimethyl sulfoxide (DMSO), dextran 40, mannitol, multiple electrolytes for injection)

CASGEVY comes in the following dosage forms:

CASGEVY is supplied in one or more glass vials. When thawed, CASGEVY is a colourless liquid.

You must not be given CASGEVY if:

- **you are allergic to exagamglogene autotemcel** or any of the other ingredients in this medicine.
- **you are allergic to any of the ingredients** in the mobilization or conditioning medicines you will be given before treatment with CASGEVY.

Tell your healthcare professional straight away if either of these applies to you. The treatment will not be given to you.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you are given CASGEVY. Talk about any health conditions or problems you may have, including if you:

- have an ongoing infection (low neutrophil counts).
- bruise easily, have unexplained bleeding or bleeding that takes a long time to stop.
- have a known allergy to any of the ingredients in CASGEVY such as dimethyl sulfoxide (DMSO), dextran-40 or mannitol.

Your healthcare professional will explain the treatment process and the benefits and risks of each step.

Before treatment with CASGEVY:

- You will have **two other types of medicine** before you are given CASGEVY.
    - **Mobilization medicine** that moves the blood stem cells into the blood stream, allowing them to be collected to make CASGEVY. This step will take 2-6 days.
    - **Conditioning medicine** to remove cells from the bone marrow that would prevent CASGEVY from working properly. Most side effects that make you feel sick are due to the conditioning medicine before you receive CASGEVY.
- Your healthcare professional will discuss the **possible impact of the conditioning medicine on fertility**. See below under "*Pregnancy, breastfeeding and fertility*".

After treatment with CASGEVY:

- You will have fewer blood cells for a while, until your blood cells treated with CASGEVY increase in your bone marrow. This includes:
    - Low levels of platelets (cells that help the blood to clot); low platelets may cause bleeding.
        - **Tell your healthcare professional right away** if you have any of these signs of low platelet levels: severe headache, abnormal bruising, prolonged bleeding, or bleeding without injury such as nosebleeds, bleeding from gums, blood in your urine, stool, or vomit, or coughing up blood.
    - Low levels of white blood cells (cells that prevent infections); low white blood cells may make infections more likely.
        - **Tell your healthcare professional right away** if you have any of these signs of low white blood cell levels: fever, chills, or infections.
- Your healthcare professional will monitor blood cell levels and give you treatment as required. Your healthcare professional will tell you when your blood cells return to safe levels.

- Your healthcare professional will continue to monitor your blood cell levels and overall health.

If CASGEVY treatment cannot be completed or fails

- If CASGEVY cannot be given after the conditioning medicine, or if the modified blood stem cells do not take hold in the body, your healthcare professional may decide to return your own original blood stem cells (rescue cells) that are collected and stored before treatment starts. If you are given rescue cells, you will not have any treatment benefit from CASGEVY and you will need to return to your previous treatment or start a new treatment for your disease.

Other warnings you should know about:

- **You will never be able to donate** blood, organs, tissues, or cells.
- **CASGEVY contains** ingredients that can result in allergic reactions. The medical team will monitor you closely for any allergic reactions during and after the infusion of CASGEVY.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CASGEVY:

- **Do not take medicines that remove iron from your body** (chelating agents) for at least 7 days before you are given the conditioning medicine. Your healthcare professional will advise you if and when you can start taking these medicines after CASGEVY treatment.
- **Do not take other medicines for sickle cell disease or beta thalassemia** (such as hydroxyurea and luspatercept) for at least 8 weeks before you are given the mobilization and at least 8 weeks before you are given the conditioning medicines. Your healthcare professional will advise if and when you should start taking these medicines after CASGEVY treatment.
- Talk to your healthcare professional if you need to have any **vaccinations**.

Pregnancy, breast-feeding and fertility

- **Pregnancy**
    - **This treatment is not to be given during pregnancy** because of the possibility of birth defects that can be caused by the conditioning medicine. The effects of CASGEVY in pregnant women are not known. Talk to your healthcare professional about pregnancy after receiving CASGEVY.
    - If you are pregnant or think you may be pregnant after treatment with CASGEVY, **talk to your healthcare professional immediately.**
    - If you are a woman who can get pregnant, **you will be given a pregnancy test** before starting mobilization and conditioning medicines to make sure you are not pregnant.
- **Contraception in men and women**
    - If you are a woman who can get pregnant, or a man capable of getting a partner pregnant, **you must use an effective method of contraception** from the start of mobilization and **for at least 6 months** after receiving CASGEVY. Talk to your healthcare professional about which methods of contraception are suitable.

- **Breast-feeding**
    - **Breast-feeding must be stopped before receiving conditioning medicine** because the medicine may get into your breast milk and harm your child. Your healthcare professional will advise you if the benefits of breast-feeding your child after CASGEVY treatment outweighs the risks.
- **Fertility in men and women**
    - It may not be possible for you to become pregnant or to get your partner pregnant after you have had the conditioning medicine. **You should discuss your options with your healthcare professional before treatment.** This may include collecting and storing reproductive material (e.g., eggs, sperm) to use at a later time.

How CASGEVY is made and given

CASGEVY is given as an infusion into a vein only once. You will not be given CASGEVY again.

CASGEVY can only be given in a treatment centre (specialized hospital) by healthcare professionals with experience in stem cell transplants, and in the treatment of patients with blood disorders such as beta thalassemia and sickle cell disease.

STEP 1: Before CASGEVY treatment, your healthcare professional will give you **mobilization medicine(s)**. This medicine moves blood stem cells from your bone marrow into the blood stream. The cells are then collected in a machine that separates the different blood cells. The entire step may happen more than once. Each time, it takes about one week.

'Rescue cells' are also collected and stored at the hospital. These are your existing blood stem cells and are kept untreated just in case there is a problem in the treatment process. See above in "*If CASGEVY treatment cannot be completed or fails*".

STEP 2: Your blood stem cells will be sent to the manufacturing site where they are **used to make CASGEVY**. It may take up to 6 months from the time your cells are collected to manufacture and test CASGEVY before it is sent back to your healthcare professional.

STEP 3: Shortly before you are given CASGEVY, your healthcare professional will first give you a **conditioning medicine** for a few days in hospital. This will prepare you for treatment by removing cells from the bone marrow that would prevent CASGEVY from working properly. After you are given this medicine, your blood cells will fall to very low levels. You will stay in the hospital at this point until after the CASGEVY infusion.

STEP 4: More than one vial of CASGEVY may be required. The contents of each vial is injected directly into your vein. The time it takes to be treated with CASGEVY depends on the number of vials required. Each vial is thawed for injection only after the contents of the previous vial is administered. It could take a few hours for you to receive the full dose of CASGEVY. After administration of CASGEVY, you will stay in hospital so that your healthcare team can closely monitor your recovery. Times can vary but you

may need to stay for approximately 2 months to allow your blood cells treated with CASGEVY to increase to normal levels. A healthcare professional on the team will decide when you can go home.

Usual dose:

CASGEVY is a one-time treatment. The dose is made for specifically for you.

What are possible side effects from using CASGEVY?

These are not all the possible side effects you may have during treatment with CASGEVY. If you experience any side effects not listed here, tell your healthcare professional.

Very common side effects (may affect more than 1 in 10 people)

- low levels of white blood cells, sometimes with a fever, which may make you more susceptible to infection
- infections
- increased heart rate
- increased blood pressure
- swelling or irritation of the stomach or colon
- stomach pain
- difficulty or discomfort when urinating
- symptoms of drug withdrawal (agitation, anxiety, muscle aches, insomnia, sweating)
- anxiety
- insomnia
- headache
- dizziness
- fever
- feeling tired or weak
- tingling or prickling sensations
- blurred vision
- hot flashes
- cough
- nosebleeds
- nasal congestion
- swelling or irritation of mucous membranes (e.g., gums)
- nausea or vomiting
- decreased appetite
- weight loss
- heartburn or acid reflux
- indigestion
- constipation
- diarrhea
- gallstones
- toothache
- muscle or joint pain, general pain
- swelling of the hands or feet
- itchy, dry, or flaky skin

- sunspots, pimples, or freckles
- hair loss
- rash

Serious side effects and what to do about them		
Symptom / effect	**Talk to your healthcare professional**	
	Only if severe	**In all cases**
VERY COMMON		
Pain in the right upper abdomen under the ribs, yellowing of eyes or skin, rapid weight gain, swelling of arms, legs and abdomen, and trouble breathing. These may be signs of a serious liver condition called veno-occlusive disease.		✓
Severe headache, abnormal bruising, prolonged bleeding, or bleeding without injury such as nosebleeds, bleeding from gums, blood in your urine, stool, or vomit, or coughing up blood. These may be signs of bleeding caused by lower levels of platelet cells in your blood, reducing the ability of blood to clot.		✓
Fever, chills or infections. These may be signs of lower levels of white bloods cells, reducing the ability to fight infections.		✓

Tell your healthcare professional immediately if you get any of the side effects listed above.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

CASGEVY will be stored by the healthcare professionals at your healthcare facility. You will not store CASGEVY yourself.

If you want more information about CASGEVY:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website: (https://www.vrtx.ca/), or by calling 877-634-8789.

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