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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CASGEVY® safely and effectively. See full prescribing information for CASGEVY.

CASGEVY (exagamglogene autotemcel), suspension for intravenous infusion

Initial U.S. Approval: 2023

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	07/2026
Dosage and Administration (2.2)	07/2026
Warnings and Precautions, Off-Target Genome Editing Risk (5.4)	08/2025

----------INDICATIONS AND USAGE----------

CASGEVY is an autologous genome edited hematopoietic stem cell-based gene therapy indicated for the treatment of patients aged 2 years and older with:

- sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs). (1)
- transfusion-dependent β-thalassemia (TDT). (1)

----------DOSAGE AND ADMINISTRATION----------

For autologous use only. For intravenous use only.

- Patients are required to undergo hematopoietic stem cell (HSC) mobilization followed by apheresis to obtain $CD34^+$ cells for CASGEVY manufacturing. (2.2)
- Dosing of CASGEVY is based on body weight. The minimum recommended dose is 3×10^6 $CD34^+$ cells/kg. (2.1, 2.3)
- Full myeloablative conditioning must be administered between 48 hours and 7 days before infusion of CASGEVY. (2.2)
- Prophylaxis for seizures should be considered prior to initiating myeloablative conditioning. (2.2)
- Prophylaxis for hepatic veno-occlusive disease (VOD) should be considered prior to initiating myeloablative conditioning. (2.2)
- Verify that the patient's identity matches the unique patient identification information on the product labels and Lot Information Sheet prior to thaw and infusion. (2.2)
- Do not sample, alter, or irradiate CASGEVY. (2.2)
- Do not use an in-line blood filter when infusing CASGEVY. (2.3)
- Administer each vial of CASGEVY via intravenous infusion within 20 minutes of thaw. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- CASGEVY is a cell suspension for intravenous infusion. (3)
- The minimum recommended dose of CASGEVY is 3×10^6 $CD34^+$ cells per kg of body weight, which may be composed of multiple vials. (3)

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Neutrophil Engraftment Failure: Monitor absolute neutrophil counts (ANC) after CASGEVY infusion. Administer rescue cells in the event of neutrophil engraftment failure. (5.1)
- Delayed Platelet Engraftment: Monitor platelet counts until platelet engraftment and recovery are achieved. Patients should be monitored for bleeding. (5.2)
- Hypersensitivity Reactions: Monitor for hypersensitivity reactions during and after infusion. (5.3)
- Off-Target Genome Editing Risk: The risk of unintended, off-target editing in $CD34^+$cells due to genetic variants cannot be ruled out. (5.4)

----------ADVERSE REACTIONS----------

The most common Grade 3 or 4 non-laboratory adverse reactions (incidence ≥ 25%) were mucositis and febrile neutropenia in patients with SCD and TDT, and decreased appetite in patients with SCD. (6)

The most common Grade 3 or 4 laboratory abnormalities (≥ 50%) were neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Vertex Pharmaceuticals Incorporated at 1-877-634-8789 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Granulocyte Colony-Stimulating Factor: Granulocyte Colony-Stimulating Factor (G-CSF) must not be used for $CD34^+$ HSC mobilization of patients with SCD. (7.1)
- Hydroxyurea: Discontinue hydroxyurea at least 8 weeks prior to start of mobilization and conditioning. (7.2)
- Crizanlizumab: Discontinue the use of crizanlizumab at least 8 weeks prior to start of mobilization and conditioning. (7.3)
- Iron Chelators: Discontinue iron chelators at least 7 days prior to initiation of myeloablative conditioning. 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. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2026

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

CASGEVY is indicated for the treatment of patients aged 2 years and older with:

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

2 DOSAGE AND ADMINISTRATION

2.1 Dose

For autologous use only. For one-time, single dose intravenous use only.

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

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

2.2 Preparation Before CASGEVY Infusion

Confirm that autologous hematopoietic stem cell (HSC) transplantation is appropriate for the patient before mobilization, apheresis and myeloablative conditioning are initiated.

It is recommended that patients with SCD weigh at least 12 kg prior to start of mobilization since patients below this weight may experience difficulty in achieving the minimum target cell dose.

Screen patients for HIV-1, HIV-2, HBV, 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.

Discontinue disease modifying therapies (e.g., hydroxyurea, crizanlizumab) 8 weeks before the planned start of mobilization and conditioning *[see Drug Interactions (7.2, 7.3)]*.

Preparation for Mobilization and Apheresis

Sickle Cell Disease: Prior to planned start of mobilization, it is recommended to transfuse red blood cells (RBCs) (simple or exchange) as needed, for a minimum of 8 weeks and continue until initiation of myeloablation or reinitiate transfusion for a minimum of 8 weeks prior to start of myeloablation with a goal to maintain hemoglobin S (HbS) levels < 30% of total hemoglobin (Hb) while keeping total Hb concentration ≤ 11 g/dL.

Transfusion-dependent β thalassemia: Prior to planned start of mobilization, it is recommended to transfuse RBCs as needed, with a goal to maintain hemoglobin (Hb) ≥ 11 g/dL and continue until start of myeloablation or reinitiate transfusion for at least 60 days prior to start of myeloablation.

Mobilization and Apheresis

HSC mobilization followed by apheresis to isolate the $CD34^+$ cells is required to manufacture CASGEVY. Refer to the prescribing information for the mobilization agent(s) used, prior to treatment. See Clinical Studies (14) for description of the mobilization agents used in the clinical trials. Alternative mobilization regimens may be considered if clinically indicated.

Sickle Cell Disease: Administer plerixafor 0.24 mg/kg/day via subcutaneous injection 2 to 3 hours prior to planned apheresis for a maximum of 3 days. Do not use Granulocyte Colony-Stimulating Factor (G-CSF) for mobilization in patients with SCD.

Transfusion-dependent β thalassemia: Administer G-CSF for 5 to 6 days, starting 4 days prior to plerixafor administration. In non-splenectomized patients, administer 5 µg/kg G-CSF every 12 hours intravenously or subcutaneously. In splenectomized patients, administer 5 µg/kg G-CSF daily. The dose may be increased to every 12 hours in splenectomized patients if there is no increase in white blood cell (WBC) or peripheral blood $CD34^+$ counts. In all patients, administer plerixafor at 0.24 mg/kg per day for a maximum of 3 days, 4 to 6 hours prior to each planned apheresis.

Perform up to three 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, but as many collected cells as possible should be sent for product manufacture even if the total collection target is not achieved. Perform additional cycles of mobilization and apheresis if the minimum dose of CASGEVY (3×10^6 $CD34^+$ cells/kg) is not met.

Separate each mobilization and apheresis cycle by a minimum of 14 days.

Collect and cryopreserve an additional $\geq 2 \times 10^6$ $CD34^+$ cells/kg of unmodified back-up rescue cells prior to myeloablative conditioning and infusion with CASGEVY. Back-up cells may be needed for engraftment failure or product compromise after myeloablation [*see Warnings and Precautions (5.1)*].

Myeloablative Conditioning

Administer full myeloablative conditioning with busulfan or another myeloablative conditioning regimen prior to treatment with CASGEVY. Refer to the prescribing information for the myeloablative conditioning agent prior to treatment. See Clinical Studies (14) for description of the myeloablative agent used in the clinical trials.

Do the following before initiation of myeloablative conditioning:

- In patients with SCD, transfuse at least 8 weeks prior to the initiation of myeloablative conditioning, with a goal of maintaining hemoglobin S (HbS) levels of < 30% of total Hb while keeping total Hb concentration ≤ 11 g/dL. Discontinue disease modifying therapies for sickle cell disease (e.g., hydroxyurea, crizanlizumab) at initiation of red blood cell exchange or simple transfusions (simple or exchange). In patients with TDT, transfuse to maintain hemoglobin (Hb) ≥ 11 g/dL for 60 days prior to myeloablative conditioning.
- Stop iron chelation therapy for at least 7 days prior to myeloablative conditioning.
- Confirm availability of complete set of vial(s) comprising the total dose of CASGEVY has been received and stored at the treatment center. See the Lot Information Sheet(s) provided with the product shipment for confirmation of the total dose of CASGEVY.
- Confirm availability of the back-up collection of unmodified rescue cells at the treatment center.

Busulfan Myeloablative Conditioning

If busulfan is used for myeloablative conditioning, administer intravenously (IV) for 4 consecutive days via a central venous catheter. Measure busulfan plasma levels by serial blood sampling and adjust dose to maintain exposure in the 4-day cumulative target range.

For patients 12 years and older, administer busulfan at a planned starting dose of 3.2 mg/kg/day once-daily (qd) or 0.8 mg/kg every 6 hours (q6h). For the once-daily dosing, adjust busulfan dose for a four day target cumulative busulfan exposure of 82 mg*h/L (range: 74 to 90 mg*h/L), corresponding to an AUC0-24h of 5000 μM*min (range 4500 to 5500 μM*min). For the every 6-hours dosing, adjust for a four day target cumulative busulfan exposure of 74 mg*h/L (range: 59 to 89 mg*h/L), corresponding to an AUC0-6h of 1125 μM*min (range: 900 to 1350 μM*min).

For patients 2 to less than 12 years of age, every 6-hour dosing is recommended. Administer busulfan for 4 consecutive days, with the first dose according to patient weight (see Table 1).

Table 1: Busulfan weight-based starting dose for patients aged 2 years to < 12 years

Patient Weight (kg)	**Initial Busulfan Dose**
12 to < 16 kg	1.2 mg/kg/dose
16 to < 23 kg	1.1 mg/kg/dose
23 to < 34 kg	0.95 mg/kg/dose
≥ 34 kg	0.8 mg/kg/dose

In patients 2 to less than 12 years of age, adjust busulfan dose with a 4-day target cumulative busulfan exposure of 82 mg*h/L (range: 74 to 90 mg*h/L), corresponding to a per-dose AUC0-6h of 1250 μM*min (range: 1125 to 1375 μM*min).

Consider anti-seizure prophylaxis (use agents other than phenytoin) and hepatic veno occlusive disease (VOD)/hepatic sinusoidal obstruction syndrome prophylaxis prior to initiating busulfan conditioning.

As CASGEVY is an autologous therapy, immunosuppressive agents are not required after initial myeloablative conditioning.

Administer CASGEVY between 48 hours and 7 days after the last dose of the myeloablative conditioning regimen.

Receipt and Storage of CASGEVY

- CASGEVY is shipped to the treatment center frozen in a vapor phase of one or more liquid nitrogen shipper(s). A Lot Information Sheet is included in each liquid nitrogen shipper.
- Confirm patient identifiers on the product label(s) and Lot Information Sheet(s).
- If there are any concerns about the product or packaging upon receipt, contact Vertex at +1-877-634-8789.
- Transfer CASGEVY from the vapor phase of nitrogen shipper to the treatment center vapor phase of liquid nitrogen storage at ≤ -135 °C (≤ -211 °F).

Preparing 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.

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 and healthcare providers are 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.

Before thaw, confirm CASGEVY is printed on the vial label and the patient's identity matches the unique patient information located on the CASGEVY vial(s). Do not infuse CASGEVY if the information on the patient-specific label on any of the vials does not match the intended patient, and contact Vertex at +1-877-634-8789.

A dose of CASGEVY may be contained in one or more cryopreserved patient-specific vial(s). Ensure that the correct number of vials are present. Use the accompanying Lot Information Sheet to confirm the total number of vials to be administered and confirm that each vial is within the expiration date prior to preparation of CASGEVY for infusion.

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.

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 cryostorage at ≤ -135 °C (≤ -211 °F).

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 needleless 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

- Thaw each CASGEVY vial at 37 °C (98 °F) using a water bath. Thaw each vial holding the vial neck, gently agitating clockwise and counterclockwise.
- Thawing of each vial can take between 10 to 15 minutes. Thawing is complete when ice crystals are no longer visible in the vial. Ensure water bath temperature does not exceed 40 °C (104 °F) during thawing.
- Do not leave CASGEVY unattended during thaw.
- Remove vial from water bath immediately once thawed.
- The thawed product should appear as a cellular suspension, which may contain proteinaceous particles or cellular aggregates.
- Inspect the vial(s) for any breaks or cracks after thawing.

- 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.

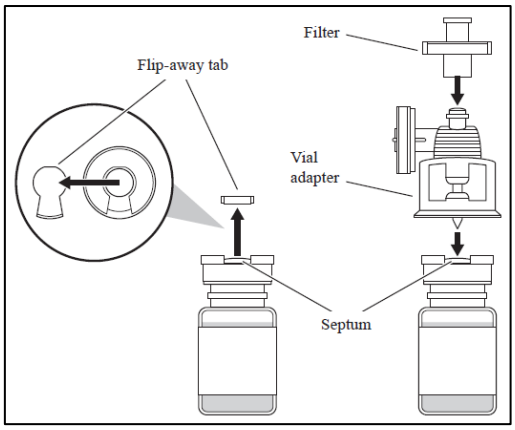
2.3 Administration

CASGEVY is for autologous use only. Before infusion, confirm that the patient's identity matches the unique 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. Use the Lot Information Sheet to confirm the total number of vials to 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.

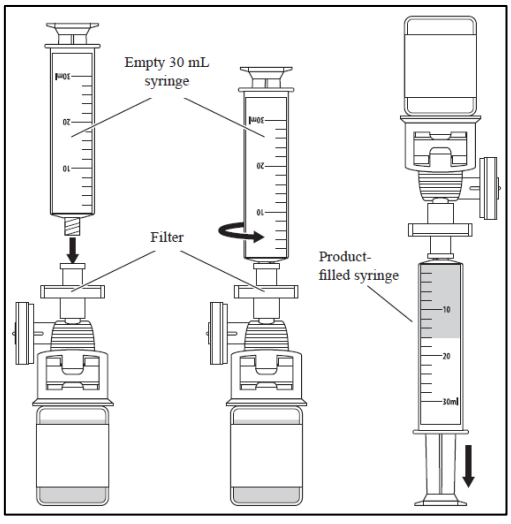
1. Attaching the vial adapter and filter

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 pop.
d. Pull up on the adapter until you feel it lock.
e. Attach the filter to the vial adapter.

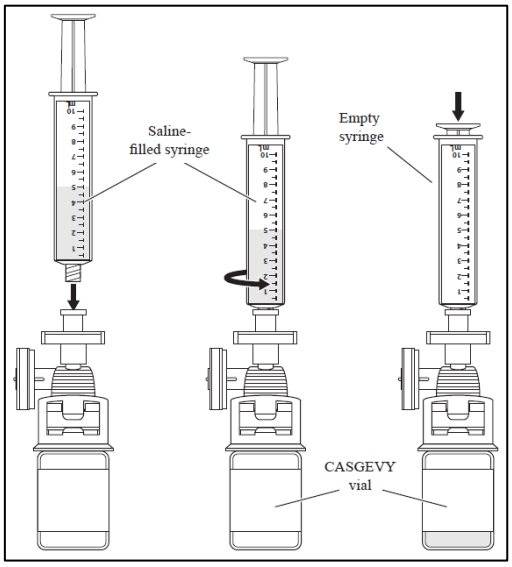


2. Withdrawing CASGEVY from the vial

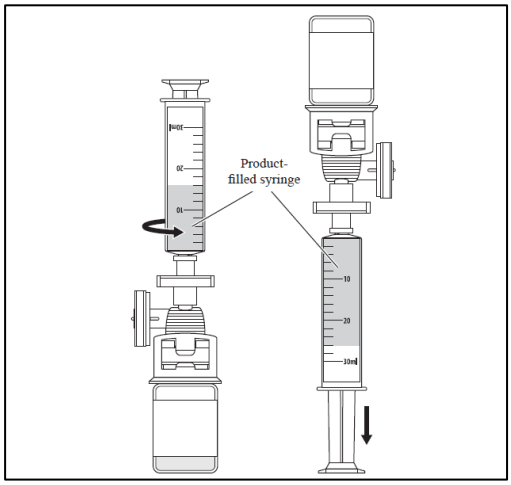
a. Attach an empty 30 mL syringe to the filter.
b. Withdraw the entire vial product volume.
c. Remove the product-filled syringe from the filter and set aside.



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 Syringe Label Sheet and affix to the product-filled syringe.



3. Administer CASGEVY through central venous catheter

a. Perform a two-person confirmation and verification of patient's identification at the bedside prior to the infusion of each vial(s).
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 0.9% sodium chloride solution, using enough volume to flush the tubing and the length of the IV catheter.

Repeat steps **1-3** for each remaining vial. If more than one vial is needed to achieve the patient-specific dose, administer each vial completely before proceeding to thaw and infuse the next vial.

Follow standard procedures for patient management after autologous HSC transplantation after CASGEVY infusion.

3 DOSAGE FORMS AND STRENGTHS

CASGEVY is a cell suspension for intravenous infusion.

A single dose of CASGEVY is composed of one or more vials. Each vial contains 4 to 13 × 10^6 $CD34^+$ cells/mL suspended in 1.5 to 20 mL cryopreservation medium *[see How Supplied/Storage and Handling (16)]*. The minimum recommended dose of CASGEVY is 3 × 10^6 $CD34^+$ cells per kg of body weight.

See the Lot Information Sheet(s) for actual strength and dose. The Lot Information Sheet is included inside the lid of each liquid nitrogen dry shipper used to transport CASGEVY.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Neutrophil Engraftment Failure

There is potential risk of neutrophil engraftment failure after treatment with CASGEVY. In the clinical trials, all treated patients achieved neutrophil engraftment and no patients received rescue $CD34^+$ cells.

Monitor absolute neutrophil counts (ANC) and manage infections according to standard guidelines and medical judgement. In the event of neutrophil engraftment failure, patients should be infused with rescue $CD34^+$ cells *[see Adverse Reactions (6.1)]*. Granulocyte Colony-Stimulating Factor (G-CSF) is not recommended for 21 days after CASGEVY infusion.

5.2 Delayed Platelet Engraftment

Delayed platelet engraftment has been observed with CASGEVY treatment. There is an increased risk of bleeding until platelet engraftment is achieved *[see Adverse Reactions (6.1)]*.

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.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, can occur due to dimethyl sulfoxide (DMSO) or dextran 40 in the cryopreservation solution. Monitor patients for hypersensitivity reactions during and after infusion.

5.4 Off-Target Genome Editing Risk

The risk of unintended, off-target editing in an individual's $CD34^+$ cells cannot be ruled out due to genetic variants. The clinical significance of potential off-target editing is unknown.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common Grade 3 or 4 non-laboratory adverse reactions (occurring in ≥ 25%) were mucositis and febrile neutropenia in patients with SCD and patients with TDT, and decreased appetite in patients with SCD.

All (100%) of the patients with TDT and SCD experienced Grade 3 or 4 neutropenia and thrombocytopenia. Other common Grade 3 or 4 laboratory abnormalities (≥ 50%) include leukopenia, anemia and lymphopenia.

Sickle Cell Disease

The safety of CASGEVY in patients with SCD was evaluated in two open-label, single-arm trials (Trial 1 and Trial 4) and a long-term follow-up trial that included patients with SCD and TDT (Trial 3). Trial 1 included 44 patients 12 years and older and Trial 4 included 11 patients 5 years to less than 12 years of age. Patients were treated with CASGEVY after undergoing myeloablative conditioning with busulfan.

Trial 1 (patients 12 years and older)

The median (min, max) duration of follow-up for 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 with SCD. 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.

Trial 4 (patients 5 years to less than 12 years of age)

The median (min, max) duration of follow-up after being administered CASGEVY was 16.9 (7.6, 24.3) months *[see Use in Specific Populations (8.4), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

Serious adverse reactions after myeloablative conditioning and CASGEVY infusion were observed in 46% of patients with SCD. The most common serious adverse reactions (all in 1 patient each) were enterococcal sepsis, platelet count decreased, and viral abdominal infection.

Table 2 presents the Grade 3 or 4 non-laboratory adverse reactions observed after myeloablative conditioning and CASGEVY infusion in at least 10% of patients in Trial 1 with corresponding incidences for Trial 4. Table 3 presents the Grade 3 or 4 laboratory abnormalities that occurred in at least 10% of patients with SCD.

Table 2: Grade 3 or 4 non-laboratory adverse reactions in ≥ 10% of patients with SCD who underwent busulfan myeloablative conditioning and received CASGEVY in Trial 1 with corresponding incidences in Trial 4: Day 1 to Month 24 after CASGEVY infusion [*]

System organ class, preferred term	Trial 1 (N=44) n (%)	Trial 4 (N=11) n (%)
Blood and lymphatic system disorders		
Febrile neutropenia	21 (48)	8 (73)
Gastrointestinal disorders		
Mucositis [†, ‡]	38 (86)	8 (73)
Abdominal pain [§]	5 (11)	0
Hepatobiliary disorders		
Cholelithiasis	5 (11)	0
Metabolism and nutrition disorders		
Decreased appetite	18 (41)	3 (27)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain [¶, ‡]	6 (14)	0
Skin and subcutaneous tissue disorders		
Pruritus	5 (11)	0

[*] Table includes adverse events associated with busulfan myeloablative conditioning and treatment with CASGEVY.
[†] Mucositis includes mucosal inflammation, pharyngeal inflammation, and stomatitis.
[‡] Encompasses preferred terms that belong to other system organ class.
[§] Abdominal pain includes abdominal pain and abdominal pain upper.
[¶] Musculoskeletal pain includes back pain, musculoskeletal chest pain, neck pain, non-cardiac chest pain, and pain in extremity.

In Trial 1, other clinically important adverse reactions that occurred in less than 10% of patients or were Grade 1 or Grade 2 include the following:
Hepatobiliary disorders: Veno-occlusive liver disease (1 [2%] patient).
Infusion-related reactions: 6 (14%) patients, including preferred terms of 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.

Table 3: Grade 3 or 4 laboratory abnormalities in ≥ 10% of patients with SCD who underwent busulfan myeloablative conditioning and received CASGEVY in Trial 1 with corresponding incidences in Trial 4: Day 1 to Month 24 after CASGEVY infusion [*]

Laboratory abnormality	Trial 1 N=44 [†] (%)	Trial 4 N=11 (%)
Neutropenia	100	100
Thrombocytopenia	100	100
Leukopenia	98	100
Anemia	84	100
Lymphopenia	50	64
CD4 lymphocytes decreased	23	0
Activated partial thromboplastin time prolonged	16	9
Hyperbilirubinemia	14	18

[*] Table includes laboratory abnormalities associated with busulfan myeloablative conditioning and treatment with CASGEVY.
[†] 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.

Platelet engraftment in patients with SCD (Trial 1 and Trial 4)

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.

One patient in Trial 4 received a thrombopoietin (TPO) mimetic which was initiated on Day 52 and continued through Day 151. The median time to platelet engraftment for patients with SCD by age sub-group is provided in Table 4.

Table 4: Median (min, max) time to platelet engraftment in patients with SCD

Age	Number of patients	Median (min, max) Time (days) to Platelet Engraftment
5 to < 12 years	11	47 (24, 78)
12 to < 17 years	9	40 (23, 64)
17 years and older	34	32.5 (23, 126)

In both Trials 1 and 4, there was no association observed between bleeding events and time to platelet engraftment.

*Neutrophil engraftment in patients with SCD (*Trial 1 *and Trial 4)*

Neutrophil engraftment is 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 in Trials 1 and 4.

The median time to neutrophil engraftment for patients with SCD by age sub-group is provided in Table 5.

Table 5: Median (min, max) time to neutrophil engraftment in patients with SCD

Age	Number of patients	Median (min, max) Time (days) to Neutrophil Engraftment
5 to < 12 years	11	28 (20, 37)
12 to < 17 years	9	29 (26, 40)
17 years and older	35	26 (15, 38)

In Trial 1, 19 out of 44 (43%) and in Trial 4, 8 out of 11 patients (73%) received G-CSF beginning on or after Day 21, post-infusion.

Transfusion-dependent β-thalassemia

The safety of CASGEVY in patients with TDT was evaluated in two open-label, single-arm trials (Trial 2 and Trial 5) and a long-term follow-up trial that included patients with SCD and TDT (Trial 3). Trial 2 included 52 patients 12 years and older and Trial 5 included 15 patients 5 years to less than 12 years of age. Patients were treated with CASGEVY after undergoing myeloablative conditioning with busulfan.

Trial 2 (patients 12 years and older)

The median (min, max) duration of follow-up for 52 patients with TDT after being administered CASGEVY was 20.4 (2.1, 48.1) months.

Serious adverse reactions after myeloablative conditioning and CASGEVY infusion were observed in 33% of patients with TDT. The most common serious adverse reactions (≥ 2 patients) were veno-occlusive liver disease, pneumonia, hypoxia, thrombocytopenia, viral infection, and upper respiratory tract infection.

Trial 5 (patients 5 years to less than 12 years of age)

The median (min, max) duration of follow up after CASGEVY infusion was 16.0 (2.2, 24.3) months.

Serious adverse reactions after myeloablative conditioning and CASGEVY infusion were observed in 33% of patients with TDT. The most common serious adverse reaction was veno-occlusive liver disease, which occurred in two patients.

One patient who received busulfan conditioning and CASGEVY developed veno-occlusive disease (VOD) and hemophagocytic lymphohistiocytosis (HLH) and died due to pneumonia and subsequent multi-organ failure *[see Use in Specific Populations (8.4), Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

Table 6 presents the Grade 3 or 4 non-laboratory adverse reactions observed after myeloablative conditioning and CASGEVY infusion in at least 10% of patients in Trial 2 with the corresponding incidences in Trial 5. Table 7 presents the Grade 3 or 4 laboratory abnormalities that occurred in at least 10% of patients with TDT.

Table 6: Grade 3 or 4 non-laboratory adverse reactions in ≥ 10% of patients with TDT who underwent busulfan myeloablative conditioning and received CASGEVY in Trial 2 with corresponding incidences in Trial 5: Day 1 to Month 24 after CASGEVY infusion [*]

System organ class, preferred term	Trial 2 (N=52) n (%)	Trial 5 (N=15) n (%)
Blood and lymphatic system disorders		
Febrile neutropenia	28 (54)	13 (87)
Gastrointestinal disorders		
Mucositis [†,‡]	37 (71)	12 (80)
Hepatobiliary disorders		
Veno-occlusive liver disease	5 (10)	2 (13)
Metabolism and nutrition disorders		
Decreased appetite	12 (23)	2 (13)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	7 (13)	1 (7)

[*] Table includes adverse events associated with busulfan myeloablative conditioning and treatment with CASGEVY.
[†] Mucositis includes anal inflammation, mucosal inflammation, pharyngeal inflammation, and stomatitis.
[‡] Encompasses preferred terms that belong to other system organ class.

In Trial 2 or Trial 5, other clinically important adverse reactions that occurred in less than 10% of patients or were Grade 1 or Grade 2 include the following:
Immune system disorders: Hemophagocytic lymphohistiocytosis (Trial 2: 1 [2%] patient; Trial 5: 1 [7%] patient).

Nervous system disorders: Cerebellar hemorrhage (intracranial hemorrhage) (Trial 2: 1 [2%] patient).
Infusion-related reactions: In Trial 2, 12 (23%) patients, including preferred terms of abdominal pain and nausea in 4 (8%) patients each; pruritus and vomiting in 2 (4%) patients each; and abdominal pain lower, chills, sinus tachycardia, and tachycardia in 1 (2%) patient each. In Trial 5, 2 (13%) patients, with preferred term of abdominal pain.

Table 7: Grade 3 or 4 laboratory abnormalities in ≥ 10% of patients with TDT who underwent busulfan myeloablative conditioning and received CASGEVY in Trial 2 with corresponding incidences in Trial 5: Day 1 to Month 24 after CASGEVY infusion [*]

Laboratory abnormality	Trial 2 N=52 [†] (%)	Trial 5 N=15[‡] (%)
Neutropenia	100	100
Thrombocytopenia	100	100
Leukopenia	98	100
Anemia	92	93
Lymphopenia	79	67
CD4 lymphocytes decreased	23	8
Hyperbilirubinemia	23	27
Alanine aminotransferase increased	19	33
Hypokalemia	19	13
Gamma-glutamyltransferase increased	17	7
Activated partial thromboplastin time prolonged	13	27
Hypocalcemia	12	7

[*] Table includes laboratory abnormalities associated with busulfan myeloablative conditioning and treatment with CASGEVY.
[†] The denominator for CD4 lymphocytes decreased is 48 and the denominator for all other laboratory data is 52, based on evaluable data at the time of the interim analysis.
[‡] The denominator for CD4 lymphocytes decreased is 13 and the denominator for all other laboratory data is 15, based on evaluable data at the time of the interim analysis.

Platelet engraftment in patients with TDT (Trial 2 and Trial 5)

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.
The median time to platelet engraftment for patients with TDT by age sub-group is provided in Table 8.

Table 8: Median (min, max) time to platelet engraftment in patients with TDT

Age	Number of patients	Median (min, max) Time (days) to Platelet Engraftment
5 to < 12 years	14	51 (22, 82)
12 to < 17 years	13	46 (20, 199)
17 years and older	39	40 (24, 200)

In both Trials 2 and 5, there was no association observed between bleeding events and time to platelet engraftment.

In Trial 2, 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 47.5 (27, 200) days in patients with an intact spleen. 13 of the 14 patients achieving platelet engraftment in Trial 5 had an intact spleen.

While the use of TPO mimetics was not specified in the Trial 2 protocol, five patients (10%) received a TPO mimetic at the time of platelet engraftment. All 5 patients continued TPO mimetic use for thrombocytopenia beyond engraftment. The total duration of TPO mimetic use was 98-457 days.

Neutrophil engraftment in patients with TDT (Trial 2 and Trial 5)

Neutrophil engraftment is 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 in Trials 2 and 5.
The median time to neutrophil engraftment for patients with TDT by age sub-group is provided in Table 9.

Table 9: Median (min, max) time to neutrophil engraftment in patients with TDT

Age	Number of patients	Median (min, max) Time (days) to Neutrophil Engraftment
5 to < 12 years	15	30 (19, 38)
12 to < 17 years	13	31 (19, 56)
17 years and older	39	29 (12, 40)

In Trial 2, one patient had neutrophil engraftment on Day 56. In Trial 2, 33 out of 52 (63%) patients and in Trial 5, 12 out of 15 patients (80%) received G-CSF beginning on or after Day 21 post-infusion.

7 DRUG INTERACTIONS

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.

7.1 Use of Granulocyte Colony-Stimulating Factor (G-CSF)

Granulocyte-Colony Stimulating Factor (G-CSF) must not be used for $CD34^+$ HSC mobilization of patients with SCD *[see Warnings and Precautions (5.1)]*.

7.2 Use of Hydroxyurea

Discontinue the use of hydroxyurea at least 8 weeks prior to start of each mobilization cycle and conditioning. There is no experience of the use of hydroxyurea after CASGEVY infusion.

7.3 Use of Crizanlizumab

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

7.4 Use of Iron Chelators

Discontinue the use of iron chelators 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.

7.5 Live Vaccines

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

8 USE IN SPECIFIC POPULATIONS

Consider the risks of mobilization and myeloablative conditioning agents in patients with reproductive potential and patients that are pregnant or breastfeeding.

8.1 Pregnancy

Risk Summary

There are no clinical data from the use of exagamglogene autotemcel during pregnancy. No animal reproductive and developmental toxicity studies have been conducted with exagamglogene autotemcel to assess whether it can cause fetal harm when administered to a pregnant patient. CASGEVY must not be administered during pregnancy because of the risks associated with myeloablative conditioning. Pregnancy after CASGEVY infusion should be discussed with the treating physician(s).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of exagamglogene autotemcel in human or animal milk, the effects on the breastfed child, or the effects on milk production. Because of the potential risks associated with myeloablative conditioning, breastfeeding should be discontinued during conditioning. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CASGEVY and any potential adverse effects on the breastfed child from CASGEVY or from the underlying maternal condition. Breastfeeding after CASGEVY infusion should be discussed with the treating physician(s).

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

A negative serum pregnancy test must be confirmed prior to the start of each mobilization cycle and re-confirmed prior to myeloablative conditioning.

Contraception

There are insufficient exposure data to provide a precise recommendation on duration of contraception following treatment with CASGEVY. Females of childbearing potential and males capable of fathering a child should use an effective method of contraception from start of mobilization through at least 6 months after administration of CASGEVY. Advise patients of the risks associated with conditioning agents.

Infertility

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, advise patients of fertility preservation options before treatment, if appropriate.

8.4 Pediatric Use

Sickle Cell Disease

The safety and effectiveness of CASGEVY have been established in pediatric patients with SCD aged 5 years and older and are supported by 2 adequate and well-controlled clinical studies (Trials 1 and 4). Trial 1 included 12 patients aged 12 years to less than 18 years and Trial 4 included 11 patients aged 5 years to less than 12 years. The primary efficacy outcome of VF12 was 86% in patients aged 12 years to less than 18 years and 100% in patients aged 5 years to less than 12 years *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*.

CASGEVY has not been studied in patients less than 5 years of age in clinical trials. The use of CASGEVY in pediatric patients aged 2 years to less than 5 years of age with SCD is supported by extrapolation of data from 2 adequate and well-controlled studies (Trials 1 and 4).

The safety and efficacy of CASGEVY in pediatric patients aged less than 2 years have not been established.

Transfusion dependent β-thalassemia

The safety and effectiveness of CASGEVY have been established in pediatric patients with TDT aged 5 years and older and are supported by 2 adequate and well-controlled clinical studies (Trials 2 and 5). Trial 2 included 18 patients aged 12 years to less than 18 years and Trial 5 included 15 patients aged 5 years to less than 12 years. The primary efficacy outcome of TI12 was 91% in patients aged 12 years to less than 18 years and 89% in patients aged 5 years to less than 12 years *[see Adverse Reactions (6.1) and Clinical Studies (14.2)]*.

CASGEVY has not been studied in patients less than 5 years of age in clinical trials. The use of CASGEVY in pediatric patients 2 years to less than 5 years of age with TDT is supported by extrapolation of data from 2 adequate and well-controlled studies (Trials 2 and 5).

The safety and efficacy of CASGEVY in pediatric patients aged less than 2 years have not been established.

8.5 Geriatric Use

CASGEVY has not been studied in patients > 65 years of age. Autologous HSC transplantation must be appropriate for a patient to be treated with CASGEVY.

8.6 Patients with 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 autologous HSC transplantation is appropriate.

8.7 Patients with Hepatic Impairment

CASGEVY has not been studied in patients with hepatic impairment. Patients should be assessed for hepatic impairment to ensure autologous HSC transplantation is appropriate.

8.8 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.

8.9 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.

11 DESCRIPTION

CASGEVY (exagamglogene autotemcel) is a cellular gene therapy consisting of autologous $CD34^+$ HSCs edited by CRISPR/Cas9-technology at the erythroid specific enhancer region of the *BCL11A* gene to reduce BCL11A expression in erythroid lineage cells, leading to increased fetal hemoglobin (HbF) protein production.

CASGEVY is prepared from the patient's own HSCs, which are obtained via apheresis procedure(s). The autologous cells are enriched for $CD34^+$ cells, and then genome edited *ex vivo* by introducing the CRISPR/Cas9 ribonucleoprotein (RNP) complex by electroporation. The guide RNA included in the RNP complex enables CRISPR/Cas9 to make a precise DNA double-strand break at a 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 disrupted and BCL11A expression is reduced. This reduction in BCL11A expression conversely results in an increase in gamma-globin expression and downstream fetal hemoglobin formation.

The edited $CD34^+$ cells are formulated into a suspension in a sterile cryopreservation medium and cryopreserved. CASGEVY is shipped as a frozen suspension in patient-specific vial(s). The product is thawed prior to infusion and administered as an autologous HSC transplant *[see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16)]*. Due to the presence of cells, the thawed product may be clear to slightly cloudy and may contain small inherent proteinaceous particles or visible cell aggregates.

The formulation contains 5% dimethyl sulfoxide (DMSO) and dextran 40.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

After CASGEVY infusion, the edited $CD34^+$ cells engraft in the bone marrow and differentiate to erythroid lineage cells with reduced BCL11A expression. Reduced BCL11A expression results in an increase in γ-globin expression and HbF protein production in erythroid cells. In patients with severe sickle cell disease, HbF expression reduces intracellular hemoglobin S (HbS) concentration, preventing the red blood cells from sickling and addressing the underlying cause of disease, thereby eliminating VOCs. In patients with transfusion-dependent β-thalassemia, γ-globin production improves the α-globin to non-α-globin imbalance

thereby reducing ineffective erythropoiesis and hemolysis and increasing total hemoglobin levels, addressing the underlying cause of disease, and eliminating the dependence on regular red blood cell (RBC) transfusions.

12.2 Pharmacodynamics

Sickle Cell Disease

Fetal Hemoglobin and Total Hemoglobin

Trial 1 (patients 12 years and older)

HbF and total Hb over time are provided in Table 10 for all patients administered CASGEVY in Trial 1 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 10: Proportion of hemoglobin comprised by HbF (%) and total Hb (g/dL) over time in patients with SCD in Trial 1

	CASGEVY Full Analysis Set (FAS) (N=44)	
	Proportion of total Hb comprised by HbF (%) *	Total Hb (g/dL) *
Month 3		
n	43	43
Mean (SD)	36.9 (9.0)	11.9 (1.5)
Median (min, max)	36.2 (17.8, 59.6)	11.9 (8.2, 15.4)
Month 6		
n	38	38
Mean (SD)	43.9 (8.6)	12.5 (1.8)
Median (min, max)	44.3 (14.9, 68.4)	12.3 (7.2, 15.9)
Month 12		
n	32	31
Mean (SD)	43.4 (4.6)	13.0 (1.5)
Median (min, max)	42.9 (35.1, 52.1)	12.9 (10.3, 15.7)
Month 18		
n	27	27
Mean (SD)	42.3 (5.8)	13.3 (1.9)
Median (min, max)	43.1 (27.5, 53.3)	12.7 (11.0, 17.3)
Month 24		
n	17	17
Mean (SD)	42.1 (5.2)	13.1 (1.8)
Median (min, max)	42.2 (33.3, 49.1)	13.0 (10.5, 17.3)

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

The mean (SD) proportion of Hb comprised by HbF was 43.9% (8.6%) at Month 6 and was maintained thereafter. 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 was maintained thereafter. Of the 44 patients infused with CASGEVY, three male patients reached total Hb levels of at least 16.5 g/dL at one or more time points after Month 9.

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%) and continued to increase over time to 94.0% (12.4%) at Month 6, with levels remaining stable thereafter, indicating sustained pan-cellular expression of HbF.

Trial 4 (patients 5 years to less than 12 years of age)

Of the 11 patients with SCD treated with CASGEVY in Trial 4, the median (min, max) duration of follow up after infusions was 16.9 (7.6, 24.3) months. Increases in mean (SD) total Hb and HbF levels were observed by Month 3 after CASGEVY infusion. Mean total Hb (SD) continued to increase to 12.2 (1.4) g/dL at Month 6 and was maintained at normal values for age (≥ 11.5 g/dL)

through the duration of follow-up. The mean (SD) proportion of Hb comprised by HbF was 49.5% (6.4%) at Month 6 and was maintained at ≥ 40% through the duration of follow-up.

Consistent with the increase in HbF levels, the mean (SD) proportion of circulating erythrocytes expressing HbF (F-cells) at Month 6 was 98.8% (0.9%) with levels remaining stable through the duration of follow-up, indicating sustained pan-cellular expression of HbF.

Proportion of Alleles with Intended Genetic Modification

Trial 1 (patients 12 years and older)

The mean (SD) proportion of alleles with intended genetic modification in the bone marrow and in peripheral blood is shown in Table 11 for all patients administered CASGEVY for the treatment of sickle cell disease in Trial 1.

Table 11: Proportion of alleles with intended genetic modification over time in patients with SCD in Trial 1

	CASGEVY Full Analysis Set (FAS) (N=44)	
	Proportion of Alleles with Intended Genetic Modification in $CD34^+$ Cells in Bone Marrow *	Proportion of Alleles with Intended Genetic Modification in Peripheral Blood
Month 1 n Mean (SD)	---	 42 53.5 (18.2)
Month 3 n Mean (SD)	---	 42 70.8 (10.6)
Month 6 n Mean (SD)	 37 86.1 (7.5)	 38 73.4 (8.1)
Month 12 n Mean (SD)	 31 86.1 (8.6)	 31 74.2 (8.7)
Month 24 n Mean (SD)	 16 88.5 (4.6)	 17 79.2 (5.6)

* Allelic editing data not available for all patients at all timepoints. Allelic editing in bone marrow was first assessed at Month 6.

Subgroup analyses evaluating the effects of age (adolescent versus adult) and sex (male versus female) showed consistent results on total hemoglobin, fetal hemoglobin and allelic editing in patients with SCD.

Trial 4 (patients 5 years to less than 12 years of age)

The mean (SD) percentage of $CD34^+$ cells of the bone marrow with the intended genetic modification after CASGEVY infusion was 84.5% (4.9%) at Month 6 (the first evaluation) and remained stable through the duration of follow-up.

The intended genetic modification was detectable in peripheral blood 1 month after CASGEVY infusion. The mean (SD) percentage of alleles with the intended genetic modification in peripheral blood was 67.9% (7.3%) at Month 3 and remained stable through the duration of follow-up.

Transfusion-dependent β-thalassemia

Fetal Hemoglobin and Total Hemoglobin

Trial 2 (patients 12 years and older)

Total Hb and HbF levels over time are provided in Table 12 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 12: Total Hb (g/dL) and HbF levels over time in patients with TDT in Trial 2

	CASGEVY Full Analysis Set (FAS) (N=52)	
	Total Hb (g/dL) *	Total HbF (g/dL) *
Month 3		
n	47	46
Mean (SD)	11.4 (2.2)	7.7 (2.9)
Median (min, max)	11.5 (7.1, 17.6)	8.4 (0.3, 13.0)
Month 6		
n	45	45
Mean (SD)	12.2 (2.0)	10.9 (2.8)
Median (min, max)	12.5 (6.5, 16.4)	11.6 (1.1, 14.5)
Month 12		
n	43	42
Mean (SD)	12.8 (2.1)	11.5 (2.5)
Median (min, max)	12.9 (6.2, 17.2)	12.3 (4.4, 15.3)
Month 18		
n	30	27
Mean (SD)	12.9 (2.1)	11.5 (2.4)
Median (min, max)	13.1 (6.5, 17.7)	12.0 (4.3, 15.0)
Month 24		
n	15	15
Mean (SD)	13.2 (2.1)	11.9 (2.5)
Median (min, max)	13.5 (10.1, 16.9)	12.1 (6.7, 15.4)

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

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 (2.8) 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.

Consistent with the increase in HbF levels, the mean (SD) proportion of circulating erythrocytes expressing HbF (F-cells) at Month 3 was 73.8% (19.7%) and continued to increase over time to 95.9% (15.2%) at Month 6, with levels remaining stable thereafter, indicating sustained pan-cellular expression of HbF.

Trial 5 (patients 5 years to less than 12 years of age)

Of the 15 patients with TDT treated with CASGEVY in Trial 5, the median (min, max) duration of follow up after CASGEVY infusion was 16.0 (2.2, 24.3) months. Increases in HbF were observed by Month 3 resulting in mean (SD) total Hb and HbF at Month 6, of 11.9 (1.3) g/dL and 10.8 (1.7) g/dL, respectively, and were maintained through the duration of follow-up, with mean total Hb maintained at normal values for age (≥ 11.5 g/dL).

Consistent with the increase in HbF levels, the mean (SD) proportion of circulating erythrocytes expressing HbF (F-cells) at Month 6 was 99.8% (0.2%) with levels remaining stable through the duration of follow-up, indicating sustained pan-cellular expression of HbF.

Proportion of Alleles with Intended Genetic Modification

Trial 2 (patients 12 years and older)

The mean (SD) proportion of alleles with intended genetic modification in the bone marrow and in peripheral blood is shown in Table 13 for all patients administered CASGEVY for the treatment of transfusion-dependent β-thalassemia in Trial 2.

Table 13: Proportion of alleles with intended genetic modification over time in patients with TDT in Trial 2

	CASGEVY Full Analysis Set (FAS) (N=52)	
	Proportion of Alleles with Intended Genetic Modification in $CD34^+$ Cells in Bone Marrow *	Proportion of Alleles with Intended Genetic Modification in Peripheral Blood
Month 1 n Mean (SD)	--	46 50.2 (20.6)
Month 3 n Mean (SD)	--	46 66.2 (11.4)
Month 6 n Mean (SD)	41 78.0 (82.3)	44 66.7 (11.3)
Month 12 n Mean (SD)	41 78.7 (12.6)	43 67.7 (10.2)
Month 24 n Mean (SD)	13 75.4 (16.4)	15 65.3 (12.6)

* Allelic editing data not available for all patients at all timepoints. Allelic editing in bone marrow was first assessed at Month 6.

Subgroup analyses evaluating the effects of age (adolescent versus adult), sex (male versus female), race, and genotype showed consistent results on total hemoglobin, fetal hemoglobin, and allelic editing in patients with TDT.

Trial 5 (patients 5 years to less than 12 years of age)

The mean (SD) percentage of CD34+ cells in the bone marrow with the intended genetic modification after CASGEVY infusion was 77.4% (8.5%) at Month 6 (the first evaluation) and remained stable through the duration of follow-up.

The intended genetic modification was detectable in peripheral blood 1 month after CASGEVY infusion. The mean (SD) percentage of alleles with the intended genetic modification in peripheral blood was 61.7% (8.9%) at Month 3 and remained stable through the duration of follow-up.

12.3 Pharmacokinetics

CASGEVY is an autologous cellular therapy which includes $CD34^+$ 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Conventional mutagenicity and carcinogenicity studies have not been conducted for CASGEVY. No studies on the effects of CASGEVY on fertility have been conducted.

14 CLINICAL STUDIES

14.1 Sickle Cell Disease

The efficacy and safety of CASGEVY in patients with sickle cell disease (SCD) were evaluated in two multicenter, open label, single arm trials. Trial 1 (NCT03745287) included 44 patients aged 12 years and older and Trial 4 (NCT05329649) included 11 patients 5 years to less than 12 years of age. Patients were then followed for 24 months after CASGEVY infusion. Patients from Trial 1 or Trial 4 are eligible to enroll in an ongoing trial for long-term follow up for a total of 15 years after CASGEVY infusion.

Patients were eligible for the trials if they were ≥ 12 kg (Trial 4 only) and had a history of at least 2 protocol-defined severe vaso-occlusive crisis (VOC) events during each of the 2 years prior to screening. In these trials severe VOC is defined as an occurrence of at least one of the following events:

- Acute pain event (including dactylitis for Trial 4) requiring a visit to a medical facility and administration of pain medications (opioids or intravenous [IV] 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 were excluded if they had an available 10/10 human leukocyte antigen (HLA) matched related hematopoietic stem cell donor, advanced liver disease, history of untreated Moyamoya disease or Moyamoya disease at risk of bleeding, and more than 10 unplanned hospitalizations or emergency department visits related to chronic pain in the year prior to screening. Patients aged 5 to 18 years were excluded if they had any history of abnormal transcranial doppler.

All patients received pre-treatment RBC transfusion, mobilization with plerixafor, apheresis to collect $CD34^+$ stem cells for CASGEVY manufacture and myeloablative conditioning with busulfan prior to treatment with CASGEVY *[see Dosage and Administration (2)]*.

The primary efficacy outcome was the proportion of VF12 responders, defined as patients who did not experience any protocol defined severe VOCs for at least 12 consecutive months within the first 24 months after CASGEVY infusion. The proportion of patients who did not require hospitalization due to severe VOCs for at least 12 consecutive months within the 24-month evaluation period (HF12) was also assessed. The evaluation of VF12 and HF12 began 60 days after the last RBC transfusion for post transplant support or SCD management.

Trial 1 (patients 12 years of age and older)

Sixty-three patients enrolled in the trial, of whom 58 (92%) started mobilization, 44 of 58 (76%) received CASGEVY infusion. Thirty of 44 (68%) with at least 16 months of follow-up post CASGEVY infusion constituted the primary efficacy population. One patient who had less than 16 months of follow-up was determined to be a non-responder and was included in the efficacy analysis. Of the 31 efficacy-evaluable patients which included 24 adults and 7 adolescents (aged 12 to less than 18 years), the median (range) age was 21 (12, 34) years, 17 (55%) were male, the majority 27 (87%) were Black, and most (30, 97%) had β^S/β^S genotype. The median (min, max) annualized rate of severe VOCs and hospitalizations due to severe VOCs in the 2 years prior to enrollment were 3.5 (2.0, 18.5) and 2.0 (0.5, 8.5) events per year, respectively.

The mean (SD) and median (min, max) number of mobilization and apheresis cycles required for the manufacture of CASGEVY and for the back-up collection of rescue $CD34^+$ cells were 2.3 (1.41) and 2 (1, 6), respectively. Six (10%) patients were unable to receive CASGEVY therapy due to inadequate cell collection.

The median (min, max) CASGEVY dose was 4.0 (2.9, 14.4) × 10^6 $CD34^+$ cells/kg. The median (min, max) duration of follow-up was 26.0 (17.8, 48.1) months from the time of CASGEVY infusion and the median (min, max) time to the last RBC transfusion was 19 (11, 52) days following CASGEVY infusion. There were no cases of graft failure or graft rejection.

Of the 31 efficacy-evaluable patients, the primary efficacy outcome of VF12 response was achieved in 29 of 31 (93.5%, 98% one sided CI: 77.9%, 100.0%) patients with a median duration VOC-free of 22.2 months. One VF12 responder experienced a severe VOC at Month 22.8 during a parvovirus B19 infection. Of the 31 patients evaluable for VF12 response, one patient was not evaluable for HF12 response. All 30 (100%, 98% one sided CI: 87.8%, 100.0%) evaluable patients achieved the secondary endpoint of HF12.

Trial 4 (patients 5 years to less than 12 years of age)

Thirteen patients enrolled in the trial, of whom all 13 (100%) started mobilization, and 11 of 13 (85%) patients received CASGEVY infusion. Eight of the 11 patients (73%) had at least 16 months of follow-up post CASGEVY infusion and constituted

the primary efficacy population. Of these 8 efficacy-evaluable pediatric patients, the median (range) age was 7 (5, 11) years, 5 (63%) were female, all 8 (100%) were Black and had a β^S/β^S genotype. The median (min, max) annualized rate of severe VOCs and hospitalizations due to severe VOCs in the 2 years prior to enrollment were 2.5 (2.0, 5.0) and 2.0 (1.0,4.5) events per year, respectively.

The mean (SD) and median (min, max) number of apheresis cycles required for the manufacture of CASGEVY and for the back-up collection of rescue $CD34^+$ cells were 1.9 (0.8) and 2 (1, 3), respectively. One patient did not receive CASGEVY due to inadequate cell collection. All 11 patients received busulfan every 6-hour dosing regimen. Four (36%) patients were within the protocol-specified busulfan target cAUC range and 7 patients had an exposure below the target cAUC range.

The median (min, max) CASGEVY dose was 5.4 (3.0, 8.3) × 10^6 $CD34^+$ cells/kg. The median (min, max) duration of follow-up was 20.2 (16.2, 24.3) months from the time of CASGEVY infusion and the median (min, max) time to the last RBC transfusion was 30 (15, 33) days following CASGEVY infusion. There were no cases of graft failure or graft rejection.

Of the 8 efficacy-evaluable patients, the primary efficacy outcome of VF12 was achieved in all 8 patients (100%), with a median (min, max) duration VOC free of 17.5 (13.2, 21.3) months. All 8 patients achieved the secondary endpoint of HF12.

14.2 Transfusion-dependent β-thalassemia

The efficacy and safety of CASGEVY in patients with transfusion-dependent β thalassemia (TDT) were evaluated in two multicenter, open-label, single arm trials. Trial 2 (NCT03655678) included 52 patients aged 12 years and older and Trial 5 (NCT05356195) included 15 patients 5 years to less than 12 years of age. Patients were followed for 24 months after CASGEVY infusion. Patients from Trial 2 or Trial 5 are eligible to enroll in an ongoing trial for long-term follow-up for a total of 15 years after CASGEVY infusion.
Patients were eligible for the trials if they were ≥ 12 kg (Trial 5 only) and 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.

Patients were excluded if they had an available 10/10 HLA matched related hematopoietic stem cell donor, 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) or advanced liver disease (aspartate transaminase [AST] or alanine transaminase [ALT] > 3 × the upper limit of normal [ULN], or direct bilirubin value > 2.5 × ULN, or if a liver biopsy demonstrated bridging fibrosis or cirrhosis [liver biopsy was performed if liver iron content was ≥ 15 mg/g by MRI]).

All patients received pre-treatment RBC transfusions, mobilization with G-CSF and plerixafor, apheresis to collect CD34+ stem cells for CASGEVY manufacture and myeloablative conditioning with busulfan prior to administration of CASGEVY *[see Dosage and Administration (2)]*.

The primary efficacy outcome 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, evaluated starting 60 days after the last RBC transfusion for post-transplant support or TDT disease management.

Trial 2 (patients 12 years of age and older)

Fifty-nine patients were enrolled in the trial, of which all 59 (100%) started mobilization, and 52 of 59 (88%) patients received CASGEVY infusion. Thirty five of 52 (67%) patients had at least 16 months of follow-up post CASGEVY infusion and constituted the primary efficacy population. Of these 35 efficacy-evaluable patients, which included 24 adults and 11 adolescents (aged 12 to less than 18 years), the median (range) age was 20 (12, 33) years, 18 (51%) were male, and the distribution was almost equal between White and Asians (43% White and 37% Asians, rest-multiracial or not collected), 20 (57%) had β^0/β^0 like genotype, and 26 (74%) had an intact spleen. The median (min, max) annualized transfusion volume and number of transfusion episodes were 205 (115, 331) mL/kg and 17 (11, 35) respectively. The baseline median (min, max) serum ferritin was 2654 (674, 10741) pmol/L with a baseline median (min, max) liver iron concentration and cardiac iron T2* of 4 (1.4, 14.0) mg/g and 34.8 (19.6, 61.1) msec respectively.

The mean (SD) and median (min, max) number of mobilization and apheresis cycles required for the manufacture of CASGEVY and for the back-up collection of rescue $CD34^+$ cells were 1.3 (0.7) and 1 (1, 4), respectively.

Patients were administered CASGEVY with a median (min, max) dose of 7.5 (3.0, 19.7) × 106 $CD34^+$ cells/kg as an IV infusion. The median (min, max) total duration of follow up was 23.8 (16.1, 48.1) months from the time of CASGEVY infusion and the median (min, max) time to last RBC transfusion for patients who achieved TI12 was 30 (11, 91) days following CASGEVY infusion. There were no cases of graft failure or graft rejection.

Of the 35 efficacy-evaluable patients, the primary efficacy outcome of TI12 was achieved in 32 of 35 (91.4%, 98.3% one sided CI: 75.7%, 100%) patients. All patients who achieved TI12 remained transfusion-independent, with a median (min, max) duration of transfusion independence of 20.8 (13.3, 45.1) months and normal mean weighted average total Hb levels (mean [SD] 13.1 [1.4] g/dL). Three patients did not achieve TI12. These patients had reductions in annualized RBC transfusion volume requirements of 79.8%, 83.9% and 97.9%, and reductions in annualized transfusion frequency of 78.6%, 67.4% and 94.6%, respectively, compared to baseline requirements.

Trial 5 (patients 5 years to less than 12 years of age)

Sixteen patients enrolled in the trial, of which 15 (94%) started mobilization, all of whom (100%) received CASGEVY infusion. Eight of 15 (53%) patients had at least 16 months of follow-up post CASGEVY infusion and constituted the primary efficacy population. One additional patient who died of VOD following treatment was included in the efficacy evaluation. Of the 9 efficacy-evaluable patients, the median (range) age was 7 (5, 11) years, 7 (78%) were male, 5 (56%) had non-β^0/β^0 like genotype, 4 (44%) were White, 2 (22%) Asian and race was not collected for 3 (33%), and 8 (89%) had an intact spleen. The median (min, max) annualized transfusion volume and number of transfusion episodes were 232.3 (173.5, 352.3) mL/kg and 14 (13.0, 17.5) respectively. The baseline median (min, max) serum ferritin was 2638.0 (896.6, 5991.9) pmol/L with a baseline median (min, max) liver iron concentration and cardiac iron T2* of 4.1 (1.2, 7.8) mg/g and 33.7 (20.9, 39.6) msec, respectively.

The mean (SD) and median (min, max) number of mobilization and apheresis cycles required for the manufacture of CASGEVY and for the back-up collection of rescue $CD34^+$ cells were 1.2 (0.4) and 1 (1, 2) respectively. Fifteen patients received busulfan. Of the 12 patients who received every 6-hour dosing regimen, 7 (58%) patients were within the protocol-specified busulfan target cAUC range. Four (33%) patients had exposure below, and 1 (8%) patient had an exposure above the target cAUC range.

Patients were administered CASGEVY with a median (min, max) dose of 11.9 (3.9, 18.8) $\times 10^6$ $CD34^+$ cells/kg as an IV infusion. The median (min, max) duration of follow-up was 23.9 (4.4, 24.3) months from the time of CASGEVY infusion and the median (min, max) time to last RBC transfusion for patients who achieved TI12 was 44.5 (16, 73) days following CASGEVY infusion. There were no cases of graft failure or graft rejection.

Of the 9 efficacy evaluable patients, including one who died prior to Month 16, 8 (89%) patients achieved the primary efficacy outcome of TI12. Among the patients who achieved TI12, the median (min, max) duration of transfusion independence was 20.1 (13.3, 21.4) months, and the mean (SD) of the patients' mean weighted average total Hb levels was 11.7 (1.2) g/dL.

16 HOW SUPPLIED/STORAGE AND HANDLING

CASGEVY is supplied in one or more vials containing a frozen suspension of genome edited autologous $CD34^+$ cells in a cryopreservation medium containing 5% DMSO and dextran 40.

CASGEVY is stored in the vapor phase of liquid nitrogen and is shipped from the manufacturing facility to the treatment center storage facility in one or more cryoshipper(s). CASGEVY is supplied in vial(s) packaged in carton(s). One carton contains a single lot of CASGEVY consisting of 1 to 9 vials. A single dose of CASGEVY may consist of multiple CASGEVY lots, and therefore may consist of multiple cartons. A Lot Information Sheet listing the total dose of CASGEVY is affixed inside each shipper.

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- Match the identity of the patient with the patient identifiers on each carton, vial, and Lot Information Sheet upon receipt.
- Store the vial(s) in the vapor phase of liquid nitrogen at ≤ -135 °C (≤ -211 °F) until ready for thaw and administration.
- Thaw CASGEVY prior to administration. Thaw and infuse one vial of CASGEVY at a time *[see Dosage and Administration (2.2, 2.3)]*.
- Once thawed, CASGEVY must be administered within 20 minutes *[see Dosage and Administration (2.2, 2.3)]*.
- Do not re-freeze CASGEVY after thawing.
- Do not irradiate CASGEVY.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Patient Information).

Prior to treatment, advise patients or caregivers of the following:

- *Risks of mobilization and conditioning agents* - Advise patients of the risks associated with mobilization and myeloablative conditioning agents and to read the FDA-approved patient labeling (Patient Information) for these agents.

- *Potential need for additional cell collection -* Ensure patients understand that if the minimum dose of CASGEVY is not met after initial product manufacturing, additional cycles of mobilization and apheresis will be needed to collect additional cells for product manufacture *[see Dosage and Administration (2.2)]*.

- *Concomitant medications -* Advise patients of the need to avoid the following medications:
  - Disease modifying therapies (e.g., hydroxyurea, crizanlizumab) should be discontinued 8 weeks before the planned start of mobilization and conditioning *[see Drug Interactions (7.2, 7.3)]*.
  - Iron chelation should be stopped at least 7 days prior to myeloablative conditioning. If iron chelation is required, the use of non-myelosuppressive iron chelators should be avoided for at least 3 months after CASGEVY administration and use of myelosuppressive iron chelators should be avoided for at least 6 months after CASGEVY administration. Phlebotomy can be used in lieu of iron chelation, when appropriate *[see Drug Interactions (7.4)]*.

After treatment, advise patients or caregivers of the following:

- *Risk of neutrophil engraftment failure -* Advise patients they will need to receive rescue treatment with their collection of unmodified $CD34^+$ cells if they do not achieve neutrophil engraftment after CASGEVY administration *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

- *Risk of bleeding -* There is an increased risk of bleeding from initiation of myeloablative conditioning until platelet engraftment is achieved. Advise patients to monitor for signs and symptoms of new or worsening bleeding or bruising and have frequent blood draws for platelet counts, until platelet recovery has been achieved *[see Warnings and Precautions (5.2)]*.

- *Donation of blood products -* Advise patients that they should not donate blood, organs, tissues, or cells at any time in the future.



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