# Molina Clinical Policy
# Casgevy (exagamglogene autotemcel) for Sickle Cell Disease
# Policy No. 447

**Last Approval: 12/10/2025**
**Next Review Due By: December 2026**

## DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

## OVERVIEW

**This policy addresses the use of Casgevy for the treatment of individuals with sickle cell disease.**

Sickle cell disease (SCD) is an inherited (autosomal recessive) hemoglobinopathy characterized by chronic hemolytic anemia and intermittent, painful, vaso-occlusive crisis (VOC). A VOC is defined as pain resulting from tissue ischemia caused by vaso-occlusion most commonly in the bone(s) and bone marrow. Those with greater than 3 hospitalizations for VOC per year are at increased risk for early death.

There are about 100,000 individuals with SCD in the United States. About 20,000 are considered to have severe sickle cell disease. Specific pathogenic mutations in the beta globin gene cause sickle cell anemia. SCD is the leading cause of ischemic stroke in children. Chronic complications from sickle cell anemia shorten life span by 20 years, on average. Individuals with sickle cell disease may endure stigma and bias in attempting to get care and face additional mental health challenges as they cope with this disorder (Kavanaugh et al. 2022).

Standard therapies (hydroxyurea, L-glutamine, crizanlizumab, voxelotor) reduce symptoms but do not prevent VOCs. Allogeneic HSCT is the only established curative option but requires an HLA-matched donor, available to <20% of patients (Hayes, 2025, Vichinsky et al. 2025). Gene-cell therapy, which involves the autologous transplantation of genetically modified hematopoietic stem cells, is a new therapeutic option that is potentially curative.

Exagamglogene autotemcel (Casgevy, CTX001) is a new, first in class gene-cell therapy for the treatment of severe sickle cell disease with recurrent VOCs. Casgevy gene-cell therapy modifies a patient's own CD34+ stem cells with the CRISPR/cas9 system to turn on fetal hemoglobin production. Enhanced expression of fetal hemoglobin increases the proportion of functional hemoglobin capable of oxygen transport without the propensity of sickling.

This therapy is not only unique in that it is the first therapy to use CRISPR technology, but also in its target. Casgevy does not directly target or edit the beta globin gene mutation that causes sickle cell anemia. Instead, Casgevy indirectly promotes the expression of gamma globin to make fetal hemoglobin (HbF). Because fetal hemoglobin uses gamma globin instead of beta globin as a carrier of oxygen, the effects of the beta globin mutation are lessened. Casgevy (exa-cel) promotes the expression of gamma globin by disrupting its natural repressor. Once gamma globin expression is restored, fetal hemoglobin (HbF) is made. Real world evidence supports the clinical benefit of HbF once it reaches 20% or higher of total hemoglobin.

The mechanism of action of Casgevy is as follows: Casgevy edits / disrupts an enhancer of the BCL11-A gene. By disrupting the enhancer of BCL11-A, BCL11-A expression is reduced and subsequently repression of gamma globin is reduced allowing fetal hemoglobin production. The faulty beta globin gene and its expression are untouched and still produce some degree of hemoglobin with potential to sickle albeit at lower levels. Casgevy CRISPR/Cas9 therapy is delivered to CD34+ stem cells via electroporation; viral vectors are not used. Side effects of Casgevy were similar to those that occur with autologous stem cell transplants. There were no significant safety events attributable to Casgevy. Off-target genome editing is a risk and cannot be ruled out.

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Administration of Casgevy involves harvesting the patient's stem cells, and once outside the body, purifying and editing the patient's cells. Once enough edited cells are grown, the cells are shipped back to the treatment center in preparation for transfusion into the patient. The patient will then go through standard myeloablation procedures and remain in the hospital after receiving their edited cells while engraftment occurs.

## RELATED POLICIES

*MCP-448: Lyfgenia (lovotibeglogene autotemcel) for Sickle Cell Disease*
*MCP-449: Casgevy (exagamglogene autotemcel) for Transfusion Dependent Thalassemia*

## COVERAGE POLICY

**All Gene Therapy requests require Molina Medical Director review.**

**Casgevy** (exa-cel or exagamglogene autotemcel) for the treatment of sickle cell disease (SCD) may be **considered medically necessary** when ALL the following clinical criteria with documentation are met:

1. Member is age 12 to 35 years old

2. A diagnosis of severe SCD defined by:
    a. Genetic testing confirming severe SCD genotype (βS/βS, βS/β0, or βS/β+);
    b. History of at least two severe vaso-occlusive events per year for the previous two years, defined as at least TWO of the following while receiving appropriate supportive care (i.e., Hydroxyurea, transfusions):
        i. Acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or IV nonsteroidal anti-inflammatory drugs or RBC transfusions)
        ii. Acute chest syndrome indicated by a new pulmonary infiltrate associated with pneumonia -like symptoms, pain, or fever
        iii. Priapism lasting > 2 hours & requiring a visit to a medical facility
        iv. Splenic sequestration, defined by an enlarged spleen, left upper quadrant pain and an acute decrease in hemoglobin concentration ≥ 2g/dL

3. Clinical documentation and recent relevant evaluation, labs, and workup establishing eligibility for autologous stem cell transplant including ALL the following:
    a. Absence of an HLA matched related donor available
    b. Member has not had a previous HSCT
    c. Absence of significant active infections or cytopenias (white blood cell count < 3 x$10^9$/L or platelet count < 50 x 10 9/L
    d. Absence of a baseline HbF concentration >15%
    e. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (ambulatory and able to carry out work of a light or sedentary nature); OR Karnofsky or Lansky performance status (KPS) of at least 80%

4. Adequate and stable renal, liver, lung, and cardiac function as evidenced by recent evaluation and laboratory workup of ALL the following:
    a. Estimated glomerular filtration rate ≥ 60ml/min/1.73 $m^2$
    b. Liver function tests < 3 x ULN
    c. Direct bilirubin < 2.5 x the Upper Limit of Normal (ULN)
    d. Prothrombin time (INR – International normalized ratio) ≤ 1.5 x ULN
    e. Carbon monoxide diffusion capacity of the lung (DLCO) ≥ 50% (corrected for Hb and or alveolar volume)
    f. Left ventricular ejection fraction ≥ 45%

5. Member has not received a previous gene therapy and is not being considered for other gene therapies or any investigational cellular therapy for sickle cell disease

6. Negative testing for Human Immunodeficiency virus-1, Human Immunodeficiency virus-2, hepatitis B, hepatitis C, syphilis, Human T-Cell lymphotropic virus-1 and Human T-Cell lymphotropic virus-2

7. Negative testing for malaria, tuberculosis, toxoplasmosis, Trypanosoma cruzi, and West Nile Virus

8. No prior or current malignancy or myeloproliferative disorder or a significant immunodeficiency disorder

9. No history of significant bleeding disorder

10. No History of untreated Moyamoya disease or presence of Moyamoya disease at screening that could put the patient at risk for bleeding

11. For Members aged 12 - 16 years of age: A screening Transcranial Doppler (TCD) Velocity study in the middle cerebral artery and the internal carotid artery does not indicate a high risk for stroke (TAMMV < 170 cm/sec for non-imaging TCD and <155 cm/sec for imaging TCD)

12. For Members aged 12 - 18 years of age: No History of abnormal TCD (TAMMV ≥ 200cm/sec for non-imaging TCD and ≥ 185 cm/sec for imaging TCD)

13. For Members of childbearing potential (male and female): Member has been counseled on the use of effective contraception during treatment (from start of mobilization through at least 6 months after administration of Casgevy) AND advised of the risks associated with conditioning agents

14. For female Members of childbearing potential: Member is not breast feeding or pregnant, as confirmed by a negative serum pregnancy test within the past 30 days
    NOTE: A negative serum pregnancy test must be confirmed prior to the start of mobilization and re-confirmed prior to conditioning procedures and before Casgevy administration.

## CONTINUATION OF THERAPY

Repeat administration is experimental and investigational since the safety and efficacy beyond one treatment has not been studied and is not indicated in the current FDA approval for Casgevy. The evidence is insufficient to determine the effects on net health outcomes.

## LIMITATIONS AND EXCLUSIONS

There are no contraindications listed in the manufacturer's labeling at this time.

The following are considered **experimental, investigational, and unproven** based on insufficient evidence:
1. Any indications other than those listed above (e.g., sickle cell disease)
2. Prior treatment with any form of HSCT, Casgevy, or other gene therapy

**DURATION OF APPROVAL:** Duration sufficient for **ONE** single course of treatment

**PRESCRIBER REQUIREMENTS:** Prescribed by, or in consultation with, a board-certified hematologist

**AGE RESTRICTIONS:** ≥ 12 years and ≤ 35 years at the time of infusion
*The age across the trials was 12 to 35 years of age.*

**DOSING CONSIDERATIONS:** Cell suspension for IV infusion. For autologous use only.
- Patients are required to undergo HSC mobilization followed by apheresis to obtain CD34+ cells for Casgevy manufacturing.
- Dosing is based on the number of CD34+ cells in the infusion bag(s) per kg of body weight. Minimum recommended dose: 3 x $10^6$ CD34+ cells/kg as a one-time IV infusion
- Myeloablative conditioning must be administered before infusion of Casgevy.

**ADMINISTRATION:**

1. Casgevy is considered a provider-administered therapy in a Qualified Treatment Center by a physician(s) with experience in HSCT and in the treatment of patients with SCD.
2. Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

**DOCUMENTATION REQUIREMENTS.** Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or rendering a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

## SUMMARY OF MEDICAL EVIDENCE

Accelerated approval for Casgevy is based on results from interim analysis of one phase 1/2/3 clinical trial. The CLIMB SCD-121 trial (NCT03745287) is an international, multicenter, open-label, single arm study of 44 patients, ages 12-35 years of age with severe SCD indicated by both genotype and phenotype. βS/βS, βS/β0, or βS/β+ are considered severe genotypes. Phenotypically, severe SCD is defined as having a clinical history of ≥ 2 VOCs per year over the previous 2 years. Thirty of the 44 patients had been followed long enough at the June 14, 2023, data cut to be included in the analysis.

The primary efficacy endpoint was the proportion of subjects without VOCs for a period of 12 months post infusion. A key secondary endpoint was HF12 (proportion of patients free from inpatient hospitalization for severe VOC for at least 12 months). Twenty-nine of 30 (96.7%) patients in the primary efficacy set were free of VOCs for 12 months as of June 14, 2023. Thirty of 30 (100%) patients in the primary efficacy set achieved HF12 (Hospitalization free for 12 months). Forty of 40 patients (100%) achieved the surrogate efficacy biomarker goal of HbF ≥ 20% by month 6. Markers of hemolysis improved with mean LDH normalizing by 9 months. One patient death was attributed to covid infection potentially complicated by busulfan conditioning. That individual was 33 years old with pre-existing lung disease. Frangoul et al. (2024) published follow-up data in 2024 showing that the 29 individuals reaching the primary endpoint have continued to do so and have been free of VOCs for 22.4 months now. Final data for study 121 was expected in the second half of 2025 however to date this data has not been published.

Side effects from Casgevy were similar to those that occur with autologous stem cell transplants. These included nausea, stomatitis, vomiting and febrile neutropenia. There were no significant safety events attributable to Casgevy. All patients were successful in neutrophil and platelet engraftment.

Additional molecular safety analyses of Casgevy relied on both in-silico and cell-based assays to assess the potential off-target editing sites throughout the genome. Roughly 5000 potential off target sites were identified by in-silico methods when allowing for imperfect crisper targeting along the genome sequence. Of these, no significant off target cutting or editing could be identified in the cell-based assay. The FDA has noted that the size and quality of the cell samples used in the confirmation analyses was very small (n= 3) and may not have fully represented opportunities for off target editing to be seen.

The 15-year long term extension study, CLIMB -131, is an on-going, global, multi-site, rollover study designed to evaluate the safety and efficacy of Casgevy in subjects who previously received Casgevy in study 121 or study 111 (for treatment of transfusion dependent thalassemia). Study 151 (NCT05329649) has started and is aimed at pediatric patients aged 2-11 years of age with SCD. Study VX21-CTX001-171 is aimed at evaluating Casgevy in patients with sickle cell disease and mixed genotype βS and βC.

A standard of care comparison study determined the proportion of VOC-free patients without gene therapy, but with standard of care for SCD. The cohort of patients in the standard of care trial population had the same baseline characteristics as those in the CLIMB SCD 121 trial. This study was conducted using Medicaid claims data from 2000-2018. The study found that only one in 12 patients with severe SCD achieved VOC free status within 1 year with standard of care therapy alone (Mahesri et al. 2024). In contrast, Sharma et al. (2025) reported that 97% of participants with SCD receiving Casgevy therapy within the phase 3 SCD-121 trial had no vaso-occlusive crises. Additionally, participants had improvements on patient reported outcomes scales and reduced pain experienced.

## National and Specialty Organizations

The **Institute for Clinical and Economic Review (ICER)** published a final evidence report supporting the value of Casgevy for the treatment of sickle cell disease (July 2023). The report focused on the clinical benefits of Casgevy but noted cost-effectiveness comparisons to standard clinical management for severe sickle cell disease, could not be completed without the actual prices of therapies. The systematic review suggests Casgevy is likely to "substantially" improve quality and length of life for patients with severe SCD. The magnitude of this superiority is still uncertain due to known risks with myeloablative conditioning and unknown durability.

The **National Heart, Lung and Blood Institute** management guidelines (2014) notes, "The clinical benefit of HSCT or gene therapy vs regular blood transfusion therapy for secondary prevention of cerebral infarcts in children and adults with preexisting silent cerebral infarct should be determined."

The **National Institute for Health and Care Excellence (NICE)** guidance for exagamglogene in the treatment of sickle cell disease recommends its use in the following circumstances: those who have a confirmed sickle cell disease genotype and a severe phenotype. Individuals with sickle cell disease who have at least 2 vaso-occlusive crises per year over the last 2 years would be eligible. NICE also stipulates exagamglogene use when a suitable HLA matched donor is not available for HSCT (NICE 2025).

## CODING & BILLING INFORMATION

**CPT (Current Procedural Terminology)**

| Code | Description |
|---|---|
| **96413** | Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug |
| **96415** | Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure) |

**HCPCS (Healthcare Common Procedure Coding System)**

| Code | Description |
|---|---|
| **J3392** | Injection, exagamglogene autotemcel, per treatment |

**CODING DISCLAIMER.** Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

## APPROVAL HISTORY

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| **12/10/2025** | Policy reviewed. No changes to coverage criteria. |
| **12/11/2024** | Policy revised. Added requirement of Molina Medical Director review. No Changes to criteria. References and medical summary updated. |
| **02/14/2024** | Name modified to include "for Sickle Cell Disease." |
| **12/21/2023** | New policy. IRO review completed December 2023. |

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