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GENE THERAPIES FOR SICKLE CELL DISEASE

Lovotibeglogene autotemcel (Lyfgenia)
Exagamglogene autotemcel (Casgevy)

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ABBREVIATIONS

α	Alpha
β	Beta
γ	Gamma
ACS	Acute chest syndrome
AE(s)	Adverse event(s)
ANC	Absolute neutrophil counts
ASH	American Society of Hematology
AUC	Area under the curve
COVID-19	Coronavirus disease 2019
CRISPR	Clustered regularly interspaced short palindromic repeats
DUR	Drug Utilization Review
FDA	US Food and Drug Administration
G-CSF	Granulocyte-colony stimulating factor
GVHD	Graft-versus-host disease
Hb	Hemoglobin
HbA	Hemoglobin A; adult hemoglobin
HbF	Hemoglobin F; fetal hemoglobin
HbS	Hemoglobin S; sickle hemoglobin
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSC(s)	Hematopoietic stem cell(s)
HSCT	Hematopoietic stem cell transplantation
IV	Intravenous
NHLBI	National Heart, Lung, and Blood Institute
PA	Prior authorization
PCR	Polymerase chain reaction
PK	Pharmacokinetic
PROMIS-57	Patient-Reported Outcome Measurement Information System-57
RBC	Red blood cell
RCT(s)	Randomized controlled trial(s)
SAE(s)	Serious adverse event(s)
SCD	Sickle cell disease
SR(s)	Systematic review(s)
TDT	Transfusion-dependent β-thalassemia
US	United States
VOC	Vaso-occlusive crisis
VOE(s)	Vaso-occlusive event(s)/episode(s)

1.0 INTRODUCTION

Sickle cell disease (SCD) is a rare genetic disorder that yields distorted (ie, sickle-cell) erythrocytes due to a point mutation in a gene for hemoglobin A (HbA).[1-5] Sickle-cell erythrocytes cause vaso-occlusive crises (VOCs; also referred to as vaso-occlusive events/episodes [VOEs]) that cause intense acute pain, premature hemolysis, tissue ischemia, and organ damage.[2,6] Thus, VOCs are a major contributor of SCD-related morbidity and hospitalization for serious complications (eg, acute chest syndrome [ACS], stroke).[2-4,7,8] Recurrent VOCs generally result in severe disabilities and/or premature mortality.[8]

Conventional treatment for SCD includes non-curative disease-modifying agents that often fail to completely eliminate SCD-related complications.[9-11] Although allogenic hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for SCD,[2,4,12] the scarcity of suitable donors limits its availability to patients.[3,9,11-15] However, two newly approved gene therapies circumvent donor issues because they are *autologous*.[13,14,16]

In December 2023, the United States (US) Food and Drug Administration (FDA) approved the first hematopoietic stem cell (HSC)-based gene therapies for SCD: lovotibeglogene autotemcel (Lyfgenia) and exagamglogene autotemcel (Casgevy),[8] hereafter referred to as lovo-cel and exa-cel, respectively.

Lovo-cel and exa-cel are genetically modified HSC products that express healthy hemoglobin (Hb) molecules, and thus, non-sickled erythrocytes. These products are derived from the patient's own HSCs (ie, autologous), which are genetically modified *ex vivo*, and then administered as a one-time intravenous (IV) infusion.[8,17,18] While both lovo-cel and exa-cel are composed of HSCs, each undergoes a distinct gene modification strategy to arrive at the final genetically-modified product[17,18]:

- Lovo-cel production entails *adding* a healthy beta (β)^{A}-globin gene variant into the stem cells using a lentiviral vector to produce a modified type of HbA (HbA^{T87Q}).[17]
- Exa-cel production involves *editing* the expression of *BCL11A* in the stem cells using clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 technology to increase production of endogenous fetal hemoglobin (HbF).[18]

Similar to allogeneic HSCT, these therapies require patients to undergo myeloablative conditioning before being treated to deplete existing HSCs from the bone marrow.[19,20] However, the use of therapeutic HSCs offers a continuous source of non-sickled erythrocytes throughout a patient's lifetime[16]; thus, lovo-cel and exa-cel may be considered potentially curative treatments for SCD.[9]

Both lovo-cel and exa-cel are indicated for patients with SCD who are 12 years of age and older.[8,17,18] Lovo-cel is approved for patients with a history of VOEs, and similarly, exa-cel is approved for patients who experience recurrent VOCs.[17,18] Additionally, in January 2024, exa-cel was FDA-approved for transfusion-dependent β-thalassemia (TDT) in patients 12 years of age and older, becoming the second approved gene therapy for TDT, after betibeglogene autotemcel (Zynteglo) in 2022.[21]

The objective of this report is to provide evidence on the safety and efficacy of lovo-cel and exa-cel to support the Utah Medicaid Drug Utilization Review (DUR) board in ensuring safe and appropriate use in patients with SCD.

2.0 METHODS

The scope of this report is to review the place-in-therapy for lovo-cel and exa-cel for SCD only. We briefly include details from the prescribing information regarding exa-cel and its approved indication for TDT.

The following major US-based organization websites were searched for clinical practice guidelines on the treatment of SCD, specifically regarding the use of gene therapy:

- American Society of Hematology (ASH): https://www.hematology.org/
- National Heart, Lung, and Blood Institute (NHLBI): https://www.nhlbi.nih.gov/

The website of the Institute for Clinical and Economic Review (ICER), available at https://icer.org/, was also searched for evidence-based reports related to gene therapies for SCD.

Prescribing information for lovo-cel and exa-cel, including package inserts, were obtained from the website of the respective product sponsor.

We queried two bibliographic databases (Ovid-Medline and Embase), using free-text terms and controlled vocabulary, for randomized controlled trials (RCTs) and systematic reviews (SRs) of RCTs addressing the efficacy and/or safety of lovo-cel or exa-cel. Due to the paucity of information regarding the place-in-therapy for lovo-cel and exa-cel, and gene therapy in general, we also conducted a literature search in Ovid-Medline for recent (2020–2024) expert reviews, using a modified CADTH filter.[22] Complete search strategies are provided in **Appendix A**.

3.0 BACKGROUND

Sickle cell disease (SCD) is a rare hematological, genetic disorder, inherited in an autosomal recessive pattern.[1,23,24] It originates from a singular point mutation in the gene responsible for encoding the beta (β)-globin chain, a component that, when combined with 2 alpha (α)-globins, constitutes adult hemoglobin (HbA).[1-5,25] As the name implies, HbA is the predominant hemoglobin type in adults.[25,26] Rather than functional HbA, the sickle mutation causes the formation of sickle hemoglobin (HbS), an aberrant type of hemoglobin (Hb) that polymerizes, particularly under hypoxic conditions,[27] and distorts erythrocytes into a rigid, sickle-shaped morphology, resulting in tissue ischemia, vaso-occlusion, organ damage, and premature hemolysis.[2,6] Vaso-occlusive crises (VOCs; also referred to as vaso-occlusive events/episodes [VOEs])[2,8] are the predominant clinical manifestation of SCD, and a major contributor of SCD-related morbidity and hospitalization.[3,7] Other SCD-related complications include hemolytic anemia, infections, retinopathy, pulmonary hypertension, stroke, skin ulcers, cardiovascular disease, among others.[2,11,28] Given the potential for multisystemic, severe clinical manifestations of SCD, the associated healthcare costs are substantial. The estimated annual economic burden of SCD on the United States (US) health care system is about $3 billion, mostly attributed to inpatient costs (57%).[3,12] In addition to the significant economic impact, SCD is also associated with poor quality of life, morbidity, and premature mortality.[10] On average, patients with SCD have approximately a 20-year reduction in life expectancy compared to the general population.[12,23] The estimated prevalence of SCD in the US is around 100,000 persons, mostly affecting those of African descent (1 in 365 births),[29] although the exact prevalence is unknown due to limited surveillance and reporting.[3,12]

Inter-patient variability exists regarding the severity of SCD,[3] which is influenced by the patient's inherited SCD genotype.[29] The most severe manifestations of SCD are typically observed in patients with genotypes of HbSS (βS/βS) or HbSβ^0-thalassemia (βS/β0)—both genotypes are commonly referred to as sickle cell anemia.[30] Regardless of the symptomatic genotype, symptoms of SCD are absent at birth, but tend to manifest within a couple months of birth, usually by 6 months of age as the concentration of fetal hemoglobin (HbF) naturally decreases and is replaced by HbS.[29,31,32] HbF is not affected by the sickle cell-causing mutation because its production employs a different set of genes within the *HBB* gene cluster[33]; unlike HbA, HbF consists of gamma (γ)-globin chains instead of β-globin chains.[25,33,34]

Details on the screening and diagnosis of SCD are provided in **Appendix B**.

3.1 Treatments for sickle cell disease

Conventional treatment for SCD includes hydroxyurea (the mainstay of SCD treatment),[3,35] newer disease-modifying agents (eg, L-glutamine, voxelotor, crizanlizumab)*, red blood cell (RBC) transfusions, and supportive care (eg, analgesics), primarily aimed at preventing SCD-related complications and symptom management.[11,12,16,35] Of the disease modifying agents, typically hydroxyurea is started first-line to mitigate VOCs.[36,37] L-glutamine, voxelotor, or crizanlizumab may be used as adjunct therapy to hydroxyurea, or as alternatives if the patient has an inadequate response or intolerance to hydroxyurea.[36-38] In general, most reviewed clinical studies for lovo-cel and exa-cel began prior to the approval of L-glutamine, voxelotor, and crizanlizumab[1,39-41]; date of approval spans from 2017 through 2019, depending on the agent.[1]

In addition to providing benefits when used as monotherapy, L-glutamine and crizanlizumab clinical trials showed that these treatments can be added to hydroxyurea to attain significant reductions in the number of VOCs.[42,43] The pivotal clinical trial for voxelotor showed significant improvements in Hb levels and hemolysis markers, with or without hydroxyurea.[44] Moreover, L-glutamine, crizanlizumab, and voxelotor were generally well-tolerated in clinical trials.[42-44] Nonetheless, while these treatments may improve disease status, they are not curative[45] and often fail to completely eliminate SCD-related complications, especially among patients with greater SCD severity.[9-11] Additionally, disease-modifying therapies exhibit variability in clinical response, and require indefinite use, accompanied by chronic monitoring.[9]

Prior to the approval of lovo-cel and exa-cel, allogeneic hematopoietic stem cell transplantation (HSCT) was the only potential curative option for SCD.[2,4,11,12] However, the scarcity of suitable donors, especially human leukocyte antigen (HLA)-matched sibling donors,[32,46] hinders most patients with SCD from pursuing allogeneic HSCT[3,9,12-15]; less than 15% to 20% of patients have an HLA-matched donor.[32,46] Additionally, allogeneic HSCT is associated with significant risks, such as graft-versus-host disease (GVHD), graft failure/rejection, and mortality.[3,4,9,11,12,15,32] Therefore, *autologous* HSCT using gene therapy has been explored as an alternative, potentially curative treatment for SCD to address the lack

* For additional information on disease-targeted pharmacological agents for sickle cell disease (SCD), refer to our Drug Utilization Review (DUR) report completed in July 2023, available at: https://medicaid.utah.gov/pharmacy/drug-utilization-review-board/

of a suitable donor pool, and to circumvent certain risks associated with allogenic HSCT, including GVHD.[13,14,16]

4.0 OVERVIEW OF LOVO-CEL AND EXA-CEL

Lovo-cel and exa-cel were recently approved by the US Food and Drug Administration (FDA) in December 2023 for patients with SCD, aged 12 years and older.[8,17,18] Lovo-cel is approved for patients with a history of VOEs, and similarly, exa-cel[†] is approved for patients who experience recurrent VOCs.[17,18] Although lovo-cel and exa-cel are both derived from the patient's own hematopoietic stem cells (ie, autologous), which are genetically modified *ex vivo*, the production of each product employs a distinct gene modification strategy.[8,16-18] Lovo-cel production entails *adding* a healthy β^{A}-globin gene variant ($\beta^{A\text{-}T87Q}$) into the stem cells using a replication-incompetent, self-inactivating lentiviral vector to produce a modified type of HbA (HbA^{T87Q})[17]; whereas, exa-cel production involves *editing* the expression of *BCL11A* in the stem cells using clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 technology.[18] *BCL11A* is a repressor of γ-globin gene transcription, and thus HbF production.[47] Silencing *BCL11A* using precise CRISPR/Cas9 technology, augments the production of endogenous HbF.[47] Thus, lovo-cel and exa-cel **do not** repair the genetic mutation responsible for SCD,[14] but rather aim to diminish the proportion of HbS, and thereby sickled erythrocytes, to alter the phenotype.[48]

Before lovo-cel or exa-cel administration, patient preparation procedures must be performed (see **Section 4.2**), including HSC mobilization (ie, mobilizing stem cells from bone marrow into the blood),[49] apheresis (ie, separation of HSCs from the blood for collection), and myeloablative conditioning with chemotherapy to deplete existing HSCs from the bone marrow.[19,20] Although the duration of these procedures varies, patients should expect to spend several days at the treatment center for HSC collection (mobilization and apheresis) and several weeks for myeloablative conditioning, infusion treatment, and recovery.[20] Due to the complexity of the multifaceted treatment process, lovo-cel and exa-cel are exclusively accessible and administered at treatment centers equipped with the requisite expertise and training.[50,51] Most qualified or authorized treatment centers[‡] for lovo-cel and exa-cel are located in the Eastern US, with the closest centers in relation to Utah located in California or Arizonia (lovo-cel only); currently, none are located in Utah.[50,51]

4.1 Administration of lovo-cel and exa-cel

Lovo-cel and exa-cel are administered as a one-time intravenous (IV) infusion, as a suspension of CD34+ HSCs.[8,17,18] The minimum recommended dose for both products is 3 x 10^6 CD34+ cells/kg, with the actual patient-specific dose dependent on the quantity of CD34+ cells in the cryopreserved infusion bag(s) or

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[†] As of January 2024, exa-cel is also approved for transfusion-dependent β-thalassemia (TDT) in patients 12 years of age and older.

[‡] Qualified/authorized treatment centers are approved by the manufacturers of the products; a registry of treatment centers for lovo-cel or exa-cel are available at the following websites:

- For lovo-cel: https://www.mybluebirdsupport.com/qualified-treatment-center-locator
- For exa-cel: https://www.casgevyhcp.com/authorized-treatment-centers

vial(s). Product labeling for lovo-cel and exa-cel advise healthcare providers to refer to the *Lot Information Sheet* that accompanies the product for additional details regarding the single dose, which may consist of multiple infusion bags or vials. Because lovo-cel and exa-cel are for *autologous* use only, it is crucial to confirm that the patient's identity matches the distinct patient identification details on the product before administration.[17,18] Additionally, patients receiving exa-cel should be premedicated with an antipyretic (eg, acetaminophen) and an antihistamine (eg, diphenhydramine) before the infusion is administered.[18] Each infusion bag of lovo-cel (up to 4 bags may be provided) should be infused over <30 minutes.[17] Exa-cel is given as an IV bolus (IV push) through a central venous catheter; the total volume administered in 1 hour should be ≤2.6 mL/kg.[18] To maximize the amount of cells infused into the patient, the delivery system (eg, tubing) should be flushed with 0.9% sodium chloride after each infusion.[17,18]

Lovo-cel and exa-cel are stored frozen (vapor phase of liquid nitrogen) and must be thawed prior to administration.[17,18] If administration of multiple infusion bags or vials is required, the entire contents of a single bag or vial should be administered before commencing the thawing and infusion process for the next one. Once thawed, lovo-cel must be administered within 4 hours, and exa-cel within 20 minutes.[17,18]

Following the infusion of lovo-cel or exa-cel, patients should remain in the treatment center for approximately 3−6 weeks to facilitate close monitoring.[17,18] The decision regarding the appropriate time for discharge should be made by the healthcare provider overseeing the patient's care.[17,18]

Table 1 summarizes the FDA approved indication, mechanism of action, and directions for use for lovo-cel and exa-cel, according to their respective prescribing information.

Table 1. FDA-approved Indication, Mechanism of Action, and Directions for Use for Lovo-cel and Exa-cel, According to Product Labeling[17,18]

Biologic product Brand name (initial approval year)	**FDA-approved labeled indication and indicated population for use**	**Mechanism of action**	**Dosing and administration information**[a]
Lovotibeglogene autotemcel (ie, lovo-cel) Lyfgenia (2023)	Treatment of pediatric (**age ≥12 years**) and adult patients with SCD and a history of vaso-occlusive events/episodes Limitations of use: • After undergoing treatment with lovo-cel, patients with α-globin gene deletions (ie, α-thalassemia trait; −α3.7/−α3.7)[52] may experience anemia accompanied by erythroid dysplasia, potentially necessitating ongoing red blood cell transfusions ○ Insufficient evidence in patients with >2 α-globin gene deletions	Autologous hematopoietic stem cell-based (CD34+) β^{A-T87Q}-globin gene therapy that produces HbA^{T87Q} once transplanted into the patient Product production uses a replication-incompetent, self-inactivating lentiviral vector for genetic modification (*ex vivo*) of the patient's own hemopoietic stem cells	• Before administering the lovo-cel infusion, confirm that the patient's identity matches the distinct patient identification details on the infusion bag(s) and cassette(s); if information does not match, lovo-cel should not be infused • Administered as a one-time IV infusion, over <30 minutes (per bag) ○ Do not use an infusion pump or in-line blood filter ○ Flush the infusion bag and any related tubing with at least 50 mL of 0.9% sodium chloride after administering the lovo-cel infusion • Minimum recommended dose: 3 x 10^6 CD34+ cells/kg (contained in 1 to 4 infusion bags) ○ Each bag is about 20 mL, and contains 1.7 to 20 x 10^6 cells/mL suspended in a cryopreservation solution ○ Actual dosing is dependent on the quantity of CD34+ cells in the infusion bag(s) relative to the patient's body weight[b] • Must be infused within 4 hours after thawing (stored at temperatures ≤ −140°C [−220°F]) ○ Do not refreeze after thawing, irradiate, alter, or sample ○ If multiple infusion bags are needed, administer the entire contents of a single bag before initiating the thawing and infusion process for the next bag
Exagamglogene autotemcel (ie, exa-cel) Casgevy (2023)	• Treatment of pediatric (**age ≥12 years**) and adult patients with SCD and recurrent vaso-occlusive crises • Treatment of pediatric (**age ≥12 years**) and adult patients with transfusion-dependent β-thalassemia	Autologous, genome-edited, hematopoietic stem cell-based (CD34+) gene therapy that produces HbF[c] once transplanted into the patient Product production uses CRISPR/Cas9-technology for genetic modification (*ex vivo*) of the patient's own hemopoietic stem cells	• Before administering the exa-cel infusion, confirm that the patient's identity matches the distinct patient identification details on the exa-cel vials and lot information sheet; if information does not match, exa-cel should not be infused • Premedicate the patient with an antipyretic and an antihistamine before administering the infusion • Administered as a one-time IV bolus infusion via a central venous catheter ○ Do not use an infusion pump or in-line blood filter ○ Total volume given in 1 hour must be ≤2.6 mL/kg ○ Flush the primary line with an adequate volume of 0.9% sodium chloride for both the tubing and the length of the IV catheter after administering each exa-cel vial • Minimum recommended dose: 3 x 10^6 CD34+ cells/kg (a singular dose may include ≥1 vial) ○ Each vial is 1.5 to 20 mL, and contains 4 to 13 x10^6 CD34+ cells/mL suspended in sterile cryo-preservative medium ○ Actual dosing is dependent on the quantity of CD34+ cells in the vial(s) relative to the patient's body weight[b] • Must be infused within 20 minutes after thawing (stored at temperatures ≤ −135°C [−211°F]) ○ Do not refreeze after thawing, irradiate, alter, or sample ○ If multiple vials are needed, administer the entire contents of a single vial before initiating the thawing and infusion process for the next vial; all supplied vials must be administered

[a] *Before patients are able to be treated with lovo-cel or exa-cel, they must undergo CD34+ hematopoietic stem cell mobilization, apheresis, and myeloablative conditioning (see* ***Section 4.2*** *for additional details).*

[b] *Additional dosage information is provided on the 'Lot Information Sheet'.*

[c] *HbF is a hemoglobin type that is naturally at highest levels near birth and provides a protective, anti-sickling effect by disrupting HbS polymerization in persons with SCD.* [13,23,32]

Abbreviations: α, alpha; β, beta; CRISPR, clustered regularly interspaced short palindromic repeats; FDA, US Food and Drug Administration; HbA, hemoglobin A; HbF, hemoglobin F or fetal hemoglobin; HbS, hemoglobin S or sickle hemoglobin; IV, intravenous; kg, kilogram; mL, milliliter; SCD, sickle cell disease; US, United States

4.2 HSC mobilization, apheresis, and myeloablative conditioning

Before a patient can be treated with lovo-cel or exa-cel, a multi-step process, including CD34+ HSC collection and myeloablative conditioning (with chemotherapy) must be performed to prepare for the infusion.[17,18] Before starting CD34+ HSC collection (mobilization and apheresis) for product manufacturing and myeloablative conditioning, the healthcare provider should confirm the patient is a suitable candidate for autologous HSCT, and screen for human immunodeficiency virus (HIV)-1 and HIV-2, among other infectious diseases.[17,18] To mitigate the risk of SCD-related complications, prior to HSC mobilization (at least 60 days)[17] or apheresis,[18] and before or during myeloablative conditioning, patients should receive RBC transfusions to maintain an HbS proportion of <30%, and a total Hb of ≤11−12 g/dL (depending on the product).[17,18]

To isolate CD34+ HSCs for product manufacturing, patients must undergo HSC mobilization using plerixafor followed by apheresis a couple of hours later.[17,18] Patients may need to undergo several mobilization and apheresis cycles, separated by at least 14 days, to acquire the minimum quantity of HSCs needed for genetic modification and/or dosage. A reserve (back-up) harvest of HSCs is also collected and kept unmodified as a contingency in the event the manufactured product is compromised or engraftment failure occurs. The recommended minimum collection target for lovo-cel is ≥16.5 x 10^6 CD34+ cells/kg (manufacturing process + reserve), and for exa-cel is ≥20 x 10^6 CD34+ cells/kg (manufacturing process, in addition to ≥2 x 10^6 CD34+ cells/kg for reserve). In general, it can take up to about 4 or 6 months after the cells have been collected to manufacture lovo-cel or exa-cel, respecitively.[17,18]

Myeloablative conditioning should not be started until it is confirmed that either lovo-cel or exa-cel has been received at the treatment center, and the reserve is available if needed.[17,18] Prior to being treated with lovo-cel or exa-cel, patients are required to undergo myeloablative conditioning, usually with a regimen of busulfan administered IV via a central venous line or catheter for 4 consecutive days. In general, the initial starting dose of busulfan is either 0.8 mg/kg or 3.2 mg/kg depending on the patient's weight and the treatment interval (ie, every 6 hours or daily); dosage adjustments are based on pharmacokinetic (PK) monitoring to maintain the desired drug exposure. Prophylactic administration of an anti-seizure agent, other than phenytoin, should be given before starting busulfan. Additionally, prophylaxis for hepatic veno-occlusive disease/hepatic sinusoidal obstruction syndrome can also be considered before starting busulfan. After completing myeloablative conditioning, a minimum 48-hour washout period is required before initiating the lovo-cel or exa-cel infusion.[17,18]

Table 2 summarizes the HSC mobilization, apheresis, and myeloablative conditioning process for lovo-cel and exa-cel, according to their respective prescribing information.

Table 2. CD34+ Stem Cell Mobilization, Apheresis, and Myeloablative Conditioning in Preparation for Lovo-cel or Exa-cel Infusion in Patients with Sickle Cell Disease

Lovotibeglogene autotemcel (Lyfgenia), or lovo-cel[17]	Exagamglogene autotemcel (Casgevy), or exa-cel[18]

Mobilization and apheresis[a] (Step 1):
• Confirm the patient is a candidate for autologous HSC transplantation (*also performed before starting myeloablative conditioning*)
• Screen for HIV-1 and HIV-2, and other infectious diseases prior to collecting CD34+ HSCs for lovo-cel manufacturing
  ○ There is insufficient evidence for the use of lovo-cel in patients with a positive HIV status
• Patients should be prepared for HSC mobilization using at least 2 cycles (given once a month) of scheduled RBC transfusions (preferably with automated RBC exchange transfusions; recommended to be performed 4 days before mobilization)
• **To obtain CD34+ HSCs, patients are required to receive mobilization (using plerixafor 0.24 mg/kg/day), and then apheresis 4 to 6 hours afterwards**
  ○ Minimum target for collection (for the manufacturing process + reserve): ≥16.5 x 10^6 CD34+ cells/kg
  ▪ For reserve[c]: ≥1.5 x 10^6 CD34+ cells/kg; cryopreserved before myeloablative conditioning
  ○ Subsequent apheresis sessions (>1): platelet counts must be ≥75 x 10^9/L within 24 hours of the apheresis session before giving plerixafor; if not, delay mobilization and apheresis until platelets meet this criterion
  ○ Subsequent mobilization cycle (>1): each cycle must be separated by ≥14 days
Myeloablative conditioning[a] (Step 2):
• **Before receiving lovo-cel, the patient must receive myeloablative conditioning with busulfan** (started once it is confirmed that the lovo-cel infusion bag(s) have been received at the treatment center, and the reserve is available if needed)
  ○ For patients <35 kg:
  ▪ Recommended initial busulfan dose: 0.8 mg/kg/dose every 6 hours (2-hour infusion via a central venous line), for a total of 16 consecutive doses over 4 days; adjust dose based on PK monitoring to target AUC
  ▪ Target AUC: 1250 µM x minute, for every 6-hour dosing
  ○ For patients ≥35 kg:
  ▪ Recommended initial busulfan dose: 3.2 mg/kg once daily (3-hour infusion via a central venous line), for a total of 4 doses over 4 consecutive days; adjust dose based on PK monitoring to target AUC
  ▪ Target AUC: 5000 µM x minute, for once daily dosing
• **Seizure prophylaxis should be given at least 12 hours before starting busulfan**
  ○ Avoid phenytoin due to the potential for drug interactions with busulfan
• Hepatic veno-occlusive disease/hepatic sinusoidal obstruction syndrome prophylaxis can be considered, with either defibrotide or ursodeoxycholic acid
• **After completing myeloablative conditioning, ensure a minimum 48-hour washout period before administering the lovo-cel infusion**
	Mobilization and apheresis[b] (Step 1):
	• Confirm the patient is a candidate for autologous HSC transplantation (*also performed before starting myeloablative conditioning*)
	• Screen for HIV-1, HIV-2, HBV, HCV, among others (according to local guideline) prior to collecting CD34+ HSCs for exa-cel manufacturing
	  ○ Exa-cel should not be used in patients with active HIV-1, HIV-2, HBV, or HCV
	• **To obtain CD34+ HSCs, patients are required to receive mobilization (using plerixafor 0.24 mg/kg), and then apheresis 2 to 3 hours afterwards**
	  ○ Minimum target for collection for the manufacturing process: ≥20 x 10^6 CD34+ cells/kg (should send cells for manufacturing, irrespective of whether the total collection target is attained)
	  ▪ For reserve[c]: ≥2 x 10^6 CD34+ cells/kg; cryopreserved before myeloablative conditioning
	  ○ Conduct cell collection for manufacturing on 2 consecutive days per cycle, provided it is clinically tolerated
	  ○ Should the initial manufacturing process fail to meet the minimum dose of 3 x 10^6 CD34+ cells/kg, the patient must undergo additional cycles of mobilization and apheresis
	  ▪ A minimum 14-day interval is recommended between each mobilization and apheresis cycle
	Myeloablative conditioning[b] (Step 2):
	• **Before receiving exa-cel, the patient must receive myeloablative conditioning with busulfan** (started once it is confirmed that the exa-cel vial(s) have been received at the treatment center, and the reserve is available if needed)
	  ○ Exa-cel prescribing information does not outline a specific regimen for myeloablative conditioning but refers to the regimen used in the clinical studies.
	  ▪ Busulfan was administered intravenously (via central venous catheter) for 4 consecutive days, at an initial dose of 3.2 mg/kg once daily or 0.8 mg/kg every 6 hours; the dosage was adjusted based on PK monitoring
	  ▪ Target AUC: 1125 µM x minute for every 6-hour dosing; 5000 µM x minute for once daily dosing
	• **Seizure prophylaxis should be given before starting busulfan**
	  ○ Avoid phenytoin due to the potential for drug interactions with busulfan
	• Hepatic veno-occlusive disease/hepatic sinusoidal obstruction syndrome prophylaxis can be considered before starting busulfan
	• **After completing myeloablative conditioning, exa-cel must be administered within 2 to 7 days**

[a] *To mitigate the risk of SCD-related complications, patients should receive RBC transfusions (simple or exchange)[10] for a minimum of 60 days leading up to HSC mobilization and throughout the myeloablative conditioning process; patients should achieve a target hemoglobin level of 8 to 10 g/dL (upper limit not exceeding 12 g/dL), and a sickle hemoglobin percentage below 30.*

[b] *Patients should receive RBC transfusions (simple or exchange) before starting apheresis (and at least 8 weeks before starting myeloablative conditioning) to maintain an HbS percentage below 30, and a total Hb ≤11 g/dL.*

[c] *A reserve harvest may be necessary for rescue therapy in cases of the following: manufactured product is compromised or engraftment failure occurs.*

*See **Table 3** for the management of concomitant medications, including hydroxyurea, L-glutamine, crizanlizumab, and voxelotor, in the setting of hematopoietic stem cell mobilization, apheresis, and myeloablative conditioning.*

Abbreviations: AUC, area under the curve; dL, deciliter; g, gram; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSC(s), hematopoietic stem cell(s); kg, kilogram; L, liter; mg, milligram; PK, pharmacokinetic; RBC, red blood cell; SCD, sickle cell disease; µM, micromolar

4.2.1 Management of concomitant medications

Due to the potential for interactions, prescribing information for lovo-cel and exa-cel recommend to discontinue hydroxyurea and other medications for SCD (eg, voxelotor, crizanlizumab, L-glutamine) at least 2 months before starting CD34+ HSC mobilization[§].[17,18] Similarly, L-glutamine, voxelotor, and crizanlizumab should be discontinued at least 2 months before starting myeloablative conditioning for lovo-cel or exa-cel. Hydroxyurea discontinuation should occur at least 2 months before myeloablative conditioning for exa-cel or at least 2 days before for lovo-cel. Additionally, for either lovo-cel or exa-cel, iron chelators should be discontinued at least 7 days before myeloablative conditioning. Of importance, patients should continue routine RBC transfusions leading up to apheresis and myeloablative conditioning to maintain Hb levels within the target range (eg, 8 to 10 g/dL).[17,18]

There is insufficient evidence on the use of hydroxyurea after receiving lovo-cel or exa-cel[17,18]; this also applies to disease-modifying agents for SCD (eg, voxelotor, crizanlizumab) for lovo-cel.[17] Prescribing information for exa-cel does not address the use of disease-modifying therapies after receiving the infusion, but it is likely that limited evidence exists.[18]

After the lovo-cel or exa-cel infusion, the use of myelosuppressive iron chelators should be avoided for 6 months or longer.[17,18] While the lovo-cel prescribing information recommends the use of non-myelosuppressive alternatives if iron chelation becomes necessary, exa-cel prescribing information advises avoiding non-myelosuppressive iron chelators for ≥3 months[17,18]; yet, prescribing information for exa-cel hints that resuming iron chelation after the infusion may be required and should be guided by clinical practice considerations.[18] As an alternative to iron chelation, phlebotomy may be considered after lovo-cel or exa-cel treatment, if clinically appropriate.[17,18] Additional considerations after receiving lovo-cel or exa-cel include irradiating any necessary blood products for the initial 3 months or longer, and avoiding blood, organ, cell, or tissue donation at any given time in the future.[17,18]

Table 3 highlights the management of concomitant medications, including those used for the management of SCD, in the setting of HSC mobilization, apheresis, and myeloablative conditioning.

[§] Other agents that should be discontinued before starting mobilization for lovo-cel include erythropoietin, iron chelation, and prophylactic HIV anti-retroviral medications.

Table 3. Management of Concomitant Medications Surrounding the Lovo-cel or Exa-cel Infusion, in the Setting of Stem Cell Mobilization, Apheresis, and Myeloablative Conditioning

Lovotibeglogene autotemcel (Lyfgenia), or lovo-cel[17]	**Exagamglogene autotemcel (Casgevy), or exa-cel[18]**
Therapies recommended to be *discontinued* before starting HSC mobilization:	**Therapies recommended to be discontinued before starting HSC mobilization:**
• At least **2 months** before mobilization: ○ Hydroxyurea: withhold resuming until all apheresis cycles are concluded ○ SCD disease-modifying agents (eg, L-glutamine, voxelotor, crizanlizumab) ○ Erythropoietin • At least **1 month** before mobilization: ○ Prophylactic HIV anti-retroviral medications: withhold resuming until all apheresis cycles are concluded ○ *Note:* certain long-acting anti-retroviral agents may necessitate an extended discontinuation period for adequate elimination • At least **7 days** before mobilization: ○ Iron chelation • G-CSFs should be avoided (a) before or in combination with mobilization agents, and (b) during the interval between mobilization and myeloablative conditioning	• At least **2 months** before mobilization: ○ Hydroxyurea and SCD disease-modifying therapies (eg, voxelotor, crizanlizumab) • G-CSFs should be not be given for mobilization (use plerixafor) in patients with SCD
Therapies recommended to be *discontinued* before starting myeloablative conditioning:	**Therapies recommended to be *discontinued* before starting myeloablative conditioning:**
• At least **2 months** before myeloablative conditioning: ○ SCD disease-modifying agents (eg, L-glutamine, voxelotor, crizanlizumab) • At least **7 days** before myeloablative conditioning (if received after apheresis): ○ Iron chelation • At least **2 days** before myeloablative conditioning (if received after apheresis): ○ Hydroxyurea • There is insufficient evidence on the utilization of erythropoietin or anti-retroviral medications during the interval between apheresis and myeloablative conditioning	• At least **2 months** before myeloablative conditioning: ○ Hydroxyurea and SCD disease-modifying therapies (eg, voxelotor, crizanlizumab) • At least **7 days** before myeloablative conditioning: ○ Iron chelation
Therapies recommended to be *continued* between apheresis and myeloablative conditioning:	**Therapies recommended to be *continued* before starting apheresis and myeloablative conditioning:**
• Routine RBC transfusions may be continued between apheresis and myeloablative conditioning ○ Prescribing information recommends patients maintain total Hb levels within the range of 8–10 g/dL, avoiding levels exceeding 12 g/dL ○ **Patients should receive a RBC transfusion within 2 days before the myeloablative conditioning process**	• **Patients should receive a RBC transfusion before apheresis and at least 2 months before starting myeloablative conditioning** ○ Prescribing information recommends patients maintain an HbS percentage below 30, and a total Hb ≤11 g/dL ○ Hydroxyurea and SCD disease-modifying therapies (eg, voxelotor, crizanlizumab) should be discontinued upon starting a RBC transfusion (simple or exchange) in the setting of myeloablative conditioning
Therapy considerations after receiving the lovo-cel infusion:	**Therapy considerations after receiving the exa-cel infusion:**
• There is insufficient evidence on the use of SCD disease-modifying agents (eg, voxelotor, crizanlizumab), hydroxyurea, anti-retroviral agents, or erythropoietin • The use of myelosuppressive iron chelators should be avoided for 6 months. If iron chelation becomes necessary, consider the use of non-myelosuppressive alternatives; in some cases, phlebotomy can be utilized as an alternative to iron chelation if clinically appropriate • G-CSFs should be avoided for 21 days • For a minimum of 3 months after the lovo-cel infusion, and as advised by the treating transplant physician, any necessary blood products should be irradiated • Treated patients should avoid donating blood products (ie, organs, blood, tissues, or cells) at any given time in the future	• There is insufficient evidence on the use of hydroxyurea ○ Prescribing information does not address the use of SCD disease-modifying agents (eg, voxelotor, crizanlizumab) following the exa-cel infusion • Avoid using myelosuppressive iron chelators for a minimum of 6 months, and non-myelosuppressive iron chelators for a minimum of 3 months; phlebotomy can be utilized as an alternative to iron chelation if clinically appropriate • For 3 months after the exa-cel infusion, any necessary blood products should be irradiated • Treated patients should avoid donating blood products (ie, organs, blood, tissues, or cells) at any given time in the future

FDA-approved pharmacologic agents for the treatment of SCD are in blue color.

Abbreviations: dL, deciliter; FDA, US Food and Drug Administration; g, gram; G-CSF(s), granulocyte-colony stimulating factor(s); Hb, hemoglobin; HIV, human immunodeficiency virus; HSC(s), hematopoietic stem cell(s); RBC, red blood cell; SCD, sickle cell disease; US, United States

5.0 GUIDELINE RECOMMENDATIONS FOR GENE THERAPY IN SCD

Reviewed clinical practice guidelines predate FDA-approval of lovo-cel and exa-cel; therefore, they do not provide recommendations regarding their use or the use of gene therapies in general: this includes the guideline by the National Heart, Lung, and Blood Institute (NHLBI; 2014) and 5 guidelines recently published by the American Society of Hematology (ASH; 2019–2021).[30,53-57] Nonetheless, the 2021 ASH guideline described that patients with SCD should generally be optimized on the standard of care "(eg, HU [hydroxyurea], L-glutamine, crizanlizumab, and chronic transfusion therapy)" before considering matched related allogeneic HSCT.[56] However, an exception may be for patients who a) have frequent pain; b) have recurrent episodes of acute chest syndrome (ACS); or c) have an abnormal transcranial Doppler ultrasound or history of overt stroke.[56] Given the paucity of information on gene therapies from reviewed US-based guidelines for the treatment of SCD, the place-in-therapy for gene therapies was deferred to expert opinion.

Experts tend to reserve gene therapy as a potential curative option for patients who are eligible for allogeneic HSCT but lack a matched sibling donor.[9,13] Some experts consider patients who lack a matched donor eligible for gene therapy if they experience severe disease, including chronic SCD-related complications or recurrent VOEs.[13] Because sibling-matched HSCT has robust, long-standing supportive evidence within the SCD population, most clinicians would consider it first-line before gene therapy, which at present, has relatively limited evidence, especially regarding long-term toxicities and durability.[12,45] Notably, gene therapy was not yet approved at the time of the expert opinion publications[17,18]; approvals may influence future expert opinion on gene therapy eligibility. Based on evidence from matched-sibling HSCT, the 2021 ASH guideline suggests eligible patients should undergo transplantation at an earlier age before irreversible SCD-related complications occur, and to maximize the benefit of preserving organ function.[56] Theoretically, this may also be applicable to gene therapy.

Prior to referral, it is crucial that patients understand the requirements of gene therapy, and for their healthcare provider to use shared decision making to appropriately weigh the risks and benefits.[13,15] The NHLBI's Cure Sickle Cell Initiative (CureSCi) Patient Readiness and Resilience Working Group developed consensus-based, best practice recommendations to guide clinicians in evaluating patient psychosocial readiness and resilience before starting gene therapy for SCD.[58] Recommendations focus on education and assessment of other factors, such as knowledge and understanding, interest and motivation for gene therapy, and psychosocial risk and resilience.[58] For patients who undergo gene therapy, a long-term hospitalization (lasting several weeks) is typically required, similar to the hospital course for those undergoing allogeneic HSCT.[15]

6.0 CLINICAL TRIALS FOR LOVO-CEL AND EXA-CEL

Lovo-cel and exa-cel, as a one-time infusion, have been or are currently being evaluated among patients with SCD across 4 clinical trials that have results; of these, 3 trials pertain to lovo-cel (HGB-205, HGB-206, and HGB-210), and 1 trial is for exa-cel (CLIMB-121).[3] Each trial design was a single-arm, open-label study, with a follow-up duration of 2 years for the primary outcome. To date, all of these trials are ongoing except for HGB-205,[3,39,40,59] which is completed with published results in a peered reviewed journal.[60] Interim results for HGB-206 have also been published in a peered reviewed journal.[61] Additionally, there are ongoing long-term follow-up studies for these therapies: LTF-307 for lovo-cel-

treated patients and CLIMB-131 for exa-cel-treated patients.[3,10,60,62,63] Result data for ongoing and/or unpublished studies (HGB-206, HGB-210, CLIMB-121, and long-term follow-up) have been extracted from a variety of meeting abstracts, sponsor press releases, and FDA-review documents.

Table 4 provides an overview of select characteristics from each study.

Table 4. Overview of Lovo-cel and Exa-cel Clinical Trials

	Lovo-cel clinical trial(s)			Exa-cel clinical trial(s)
	HGB-205[39,60]	HGB-206[17,40]	HGB-210[59,64]	CLIMB-121[18,41]
Study design	Single-arm, open-label trial			
Study phase	Phase I/II	Phase I/II	Phase III	Phase I/II/III
Study status	Completed	Ongoing; has interim results	Ongoing; has interim results	Ongoing; has interim results
Estimated study completion date	—	February 2024	April 2027	October 2024
Study follow-up[a]	24 months			
Number of participants with reportable data	3	36	2	44
Longest median duration of follow-up available[b]	54 months[c]	38 months	35.8 months	Up to 24 months

[a] *Upon completion of HGB-205, HGB-206, HGB-210, or CLIMB-121, participants are eligible for a long-term observational extension study (either LTF-307 for lovo-cel or CLIMB-131 for exa-cel), to obtain a total of 15 years of follow-up.*[3,10,60,62,63]

[b] *Accounts not only for the original trial, but also for long-term follow-up observations, if available*

[c] *Includes participants with sickle cell disease (n=3) and transfusion-dependent β-thalassemia (n=4)*

Additional details for each trial, including the study population, are described below in **Section 6.1** for lovo-cel and **Section 6.2** for exa-cel.

6.1 Lovo-cel

FDA approval of lovo-cel for patients with SCD was primarily based on the HGB-206 trial, supported by evidence from HGB-205 and HGB-210[65,66]; the efficacy analysis for each trial, as of the latest data cut-off, included 36 participants from HGB-206 (Group C), 3 participants from HGB-205, and 2 participants from HGB-210.[64] Group C in the HGB-206 trial consisted of a subgroup of participants who mostly experienced ≥4 severe VOEs in the 2 years preceding enrollment, which was a more stringent eligibility criterion added after study enrollment began; therefore, not all participants in Group C met this criterion at baseline.[61] **Table 5** summarizes key inclusion criteria from each of these studies; refer to **Appendix C** for complete inclusion and exclusion criteria.

Table 5. Key Inclusion Criteria for Lovo-cel Clinical Trials (HGB-205, HGB-206, and HGB-210)

Key inclusion criteria	HGB-205[39,67] NCT02151526	HGB-206[40,68] NCT02140554	HGB-210[59,64] NCT04293185
Age	5–35 years	≥12 to ≤50 years	≥2 to ≤50 years (weighing ≥6 kg)
Diagnosis (genotype)	Severe SCD (undefined; any genotype), or TDT	Severe SCD (ie, HbSS [βS/βS], HbSβ^0-thalassemia [βS/β0], or HbSβ$^+$-thalassemia [βS/β+])	
HSCT status	Candidate for allogeneic HSCT but lack a matched related donor	Excluded patients <18 years of age if an HLA-matched sibling allogeneic HSCT donor was available	Candidate for allogeneic HSCT but lack a matched related donor
		No prior allogenic transplant	
Prior treatment failure, if not intolerant	Failed hydroxyurea, after a trial for ≥4 months at an adequate dosage (for patients with SCD)	Failed hydroxyurea (at any point in time) after using for ≥6 months and experiencing ≥1 ACS or >1 VOE	
VOCs/VOEs or poor prognostic risk factors	For patients with SCD: • ≥2 VOCs in the past year or in the year before starting a regular blood transfusion program, OR • another poor prognostic risk factor (eg, ≥2 episodes of ACS, sickle cell cardiomyopathy, significant cerebral abnormality such as stenosis)	≥4 *severe* VOEs[a] in the 24 months preceding enrollment despite appropriate supportive management (eg, pain plan)[b]	≥4 protocol-defined VOEs[c] in the 24 months preceding informed consent despite appropriate supportive management (eg, pain plan)

[a] *Severe VOEs were defined as an event (eg, ACS) lacking any medically determined cause other than vaso-occlusion, necessitating either a hospital or emergency room/urgent care visit lasting ≥24 hours; or at least 2 visits to either a hospital or emergency room within a 72-hour period, with both visits requiring intravenous treatment; or a priapism episode that required care at a medical center (± hospitalization).*

[b] *This inclusion criterion was added after HGB-206 study enrollment began (applied to Group C participants only), and therefore not all participants met this criterion at baseline for this study.*

[c] *Because the study protocol for HGB-210 was unable to be found, it is unclear what qualified as a "protocol-defined VOE".*

Abbreviations: ACS, acute chest syndrome; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; kg, kilogram; SCD, sickle cell disease; TDT, transfusion-dependent β-thalassemia; VOCs, vaso-occlusive crises; VOE(s), vaso-occlusive episode(s) or event(s)

6.1.1 HGB-205

Lovo-cel infusion was initially evaluated for the treatment of SCD in a phase I/II, single-arm, open-label, proof-of-concept study: HGB-205 (NCT02151526).[3,9,60] To be eligible for HGB-205, participants had to be between 5 to 35 years of age; have a confirmed diagnosis of SCD or transfusion-dependent β-thalassemia (TDT) by Hb analysis (irrespective of the genotype); and be a candidate for allogeneic HSCT but lack a matched related donor.[67] In addition, participants with SCD had to fail to attain adequate clinical improvement with hydroxyurea at an appropriate dosage for a minimum of 4 months (unless it was not indicated or poorly tolerated), and have at least 1 poor prognostic risk factor (eg, ≥2 episodes of ACS, ≥2 episodes of VOCs in the past year or in the year before starting a regular blood transfusion program).[67]

Overall, 3 patients (aged 13, 16, and 21 years)[64,69] with severe SCD[**] were treated with lovo-cel (at various time points), after undergoing CD34+ bone marrow harvesting and busulfan myeloablative conditioning.[60] Of the treated participants, 2 had HbSS (βS/βS) genotype, and the other had HbSβ^0-thalassemia (βS/β0).[60] Across treated participants, the lovo-cel dosage ranged from 3.0−5.6 x 10^6 CD34+ cells/kg,[69] with a minimum target of ≥2.0 x 10^6 CD34+ cells/kg,[64] which is below the recommended minimum dosage in the product labeling.[17] All patients achieved successful engraftment, with neutrophil and platelet engraftment occurring at a median of 32 days and 51 days, respecitvely.[60]

6.1.1.1 Efficacy/safety outcomes

Published results from a comprehensive analysis, which included data from HGB-205 and the long-term follow-up study (LTF-307) as of August 2020, showed that after 4.3 years from receiving lovo-cel, 1 of the 3 participants (33.3%) with SCD had not experienced any SCD-related symptoms, including VOCs or ACS, nor required pain medications, RBC transfusions, or hydroxyurea for SCD-related complications after engraftment (3.3 years of follow-up).[60] Another participant was VOC-free until an event was precipitated by gastroenteritis at 30 months after receiving lovo-cel.[60] The VOC event resolved after symptomatic management and hospitalization.[60,70] Since then, the participant has remained symptom-free as of August 2020, with a total of 5.1 years of follow-up.[60] Overall, these 2 participants showed stable HbA^{T87Q} levels up to 36 months after receiving the lovo-cel infusion, with concentrations ranging from 28% to 48% of total Hb (it is suggested that a proportion of ≥30% HbA^{T87Q} may provide clinically meaningful benefit),[71] and decreased hemolysis markers (eg, reticulocyte counts) without receiving chronic RBC transfusions.[60] On the contrary, the remaining participant experienced recurrent episodes of VOCs and ACS, and as a result, restarted RBC transfusions at month 6 and hydroxyurea at month 13 following the lovo-cel infusion.[60] Total Hb levels for participants at the latest follow-up time point (either 36, 42, or 60 months) ranged from 9.5−12.6 g/dL, with HbA^{T87Q} ranging from approximately 9% to 60%.[60]

No adverse events (AEs) were deemed to be directly related to lovo-cel, but all 3 participants experienced at least 1 AE and serious adverse event (SAE) related to pre-treatment procedures.[60,67] The most common SAEs that occurred after neutrophil engraftment up to the last follow-up were sickle cell

[**] We were unable to find an explicit definition delineating the criteria for "severe" sickle cell disease (SCD) in published documents for HGB-205, including the study protocol.

anemia with VOC (total of 4 events, in 2 of 3 participants), ACS (total of 3 events, in 1 of 3 participants), and increased hepatic enzymes (total of 2 events, in 2 of 3 participants).[67]

6.1.2 HGB-206

HGB-206 (NCT02140554) is an ongoing, single-arm, open-label, multi-center, phase I/II study evaluating lovo-cel among patients with severe SCD (defined as genotypes HbSS [βS/βS], HbSβ^0-thalassemia [βS/β0], or HbSβ$^+$-thalassemia [βS/β+]).[3,9,40,61] Modifications to the study protocol and enrollment criteria to optimize the lovo-cel treatment process led to the establishment of 3 study cohorts: Group A (n=7), Group B (n=2), and Group C (n=36).[3,17,61,64] Group A exhibited a durable but suboptimal expression of HbA^{T87Q} after lovo-cel treatment.[61] Subsequently, for Group B, modifications were made to the treatment process, including increasing the target area under the curve (AUC) for busulfan and the pre-collection RBC transfusion time (changed from ≤7 days to ≥60 days)[3], and increasing the minimum target dose of lovo-cel to ≥2.0 x 10^6 CD34+ cells/kg from ≥1.5 x 10^6 CD34+ cells/kg.[3,61] For Group C, the HSC collection method was refined to use plerixafor mobilization and apheresis instead of bone marrow harvesting, and the target lovo-cel dose was further increased to ≥3.0 x 10^6 CD34+ cells/kg.[3,61] The clinical data from the Group C cohort was the primary basis for lovo-cel FDA approval.[3,65]

To be eligible for the study, participants had to be between 12 and 50 years of age; be diagnosed with an SCD genotype of HbSS (βS/βS), HbSβ^0-thalassemia (βS/β0), or HbSβ$^+$-thalassemia (βS/β+); have prior failure or intolerance to hydroxyurea; and be able to perform activities of daily living with minimal to some assistance, if any.[61,68] Initial eligibility criteria was revised after some participants were enrolled, to require a minimum of 4 *severe* VOEs in the 24 months preceding enrollment.[40,61] This enabled evaluation of the primary efficacy outcome, complete VOE[††] resolution between 6–18 months after the lovo-cel infusion, and complete resolution of severe VOEs between 6–18 months as a secondary outcome.[40,61] Participants were excluded if they had previously received an allogenic transplant or gene therapy; in addition, participants <18 years of age with an HLA-matched sibling allogeneic HSCT donor were also excluded.[68]

6.1.2.1 Efficacy/safety outcomes in Group C

In total, 36 participants (Group C), including 8 adolescents, were treated with lovo-cel at a median dose of 6.4 x 10^6 CD34+ cells/kg, with a median follow-up duration of 38 months after the lovo-cel infusion.[17] All Group C participants had a genotype of HbSS (βS/βS), and none experienced graft failure or rejection (platelet and neutrophil engraftment was achieved at a median of 37 days and 20 days after the infusion, respectively). Notably, 2 participants experienced delayed platelet engraftment (after day 100); of these participants, 1 required eltrombopag until day 234.[17]

[††] VOEs were defined as an acute pain episode lacking any medically determined cause other than vaso-occlusion, lasting longer than 2 hours and requiring medical care. Events included ACS, and acute hepatic or splenic sequestration. Severe VOEs were defined as an VOE necessitating either a hospital or emergency room/urgent care visit lasting ≥24 hours; or at least 2 visits to either a hospital or emergency room within a 72-hour period, with both visits requiring intravenous treatment; or a priapism episode (painful, sustained, undesired erection lasting >2 hours) that required care at a medical center (± hospitalization).

Of the 32 participants who met the eligibility criteria of ≥4 severe VOEs in the 24 months preceding enrollment, 30 (94%) experienced complete resolution of severe VOEs and 28 (88%) were VOE-free between 6−18 months of follow-up.[17,65] After 18 months to the last follow-up assessment at a median of 38 months, 4 of 28 participants (14%) who had been VOE-free eventually experienced an event.[17]

Among all 36 treated participants, 31 achieved and maintained (≥6 months) a globin response, defined as having an HbA^{T87Q} of ≥30% of non-transfused total Hb, and an increase from baseline in non-transfused total Hb of ≥3 g/dL or a non-transfused total Hb value ≥10 g/dL.[17] An earlier interim analysis (among 25 adult participants) on patient-reported quality of life (using Patient-Reported Outcome Measurement Information System-57 [PROMIS-57][‡‡ 72]) showed mean value improvements from baseline across all domains (except anxiety) including pain, especially for patients with baseline scores "worse" than the population norm, up to 24 months after lovo-cel treatment.[73] Another earlier interim analysis (data cut-off of February 2021) reported improvements in hemolysis markers (eg, lactate dehydrogenase, reticulocytes, indirect bilirubin) from baseline up to 36 months after the lovo-cel infusion, which generally trended towards normalization.[61]

Five participants (all adults) with a history of overt stroke or vasculopathy received lovo-cel before the protocol was amended to have the condition listed as an exclusion.[3,17] All of these participants have not had recurrent stroke and continue to be transfusion independent at 44−60 months after being treated with lovo-cel.[17]

6.1.2.2 Additional safety outcomes in Groups A−C

Most treated participants (33 out of 45; 73%) experienced at least one SAE, with most events attributed to myeloablative conditioning or SCD.[17] Conditioning-related events tended to be non-serious and generally consistent with the recognized effects of alkylating agents. The most common AEs Grade 3 or higher (incidence ≥20%) from day 1 up to month 24 after receiving lovo-cel (N=45) were thrombocytopenia, anemia, neutropenia, stomatitis, febrile neutropenia, and leukopenia.[17] Three deaths have occurred[17]: 1 participant died from sudden cardiac death as a result of underlying conditions (in Group C)[61]; and 2 participants died from acute myeloid leukemia (both in Group A).[17] All deaths were deemed to not be attributed to, or highly unlikely to be caused by, the lovo-cel treatment itself.[74-76] However, **lovo-cel carries a black box warning for hematologic malignancies**, which patients with SCD are at a higher risk of developing compared to the general population.[17] Additionally, the heightened hematopoietic stress linked to the treatment process (mobilization and myeloablative conditioning) and infusion procedure may potentially increase the risk of developing a hematologic malignancy.[17]

6.1.3 HGB-210

HGB-210 (NCT04293185) is an ongoing, single-arm, open-label, multi-center, phase III study evaluating lovo-cel in participants aged 2−50 years with severe SCD (defined as genotypes HbSS [βS/βS], $HbS\beta^0$-

‡‡ PROMIS-57 is a self-reported questionnaire for adults to assess physical, social, and mental health across seven domains, along with an additional question on pain intensity. Domains include anxiety, depression, physical function, fatigue, sleep disturbances, pain interference, and ability to engage in social roles and activities.

thalassemia [βS/β0], or HbSβ$^+$-thalassemia [βS/β+]).[59] Currently, this study is ongoing, with a planned enrollment of 35 participants. Participants are required to experience ≥4 protocol-defined VOEs in the 24 months before informed consent, have prior failure or intolerance to hydroxyurea, and be able to perform activities of daily living with minimal to some assistance, if any. In addition, participants of reproductive potential must consent to using an appropriate method of contraception from screening up to ≥6 months after receiving lovo-cel.[59]

Although exclusion criteria for HGB-206 and HGB-210 are generally similar, HGB-210 has a unique exclusion criterion of chromosomal or genetic abnormalities, as determined by the investigator, that could increase the participant's risk of developing myelodysplastic syndrome or acute myeloid leukemia.[59] Additionally, those with genetic mutations causing ≥2 α-globin genes to be inactivated were excluded[§§].[52,59] At the time of the biologic license application submission, 2 enrolled participants had been treated with lovo-cel, each with 18 months of follow-up.[48]

The primary outcome was the proportion of participants with complete resolution of VOEs between 6−18 months following the lovo-cel infusion (same as HGB-206).[40,59]

6.1.3.1 Efficacy/safety outcomes

Interim results as of August 2022 among 2 participants showed a clinical benefit of complete resolution of VOEs, including severe VOEs, up to 15 months (last observed timepoint) after receiving the lovo-cel infusion.[64] Additionally, HbA^{T87Q} levels stabilized from around 6 months up to 15 months following the infusion in both treated participants; at 6 months, 1 participant had 5.62 g/dL HbA^{T87Q}, and the other had 7.53 g/dL HbA^{T87Q}.[64]

Most recent interim results as of February 2023, *also including individuals in Group C from HGB-206*, showed that 94% of participants (32 out of 34 participants who had ≥4 VOEs in the prior 2 years before treatment) had severe VOEs completely eliminated between 6−18 months after lovo-cel treatment, and approximately 88% of participants (30 out of 34) remained VOE-free for a median of 35.8 months.[74] Participants who had VOEs at any point post-treatment through long-term follow-up (n=8) demonstrated a substantial decrease in both the frequency (≥50% reduction) and severity of VOEs compared to pre-treatment with lovo-cel; annualized median hospital days reduced by 85.5% (pre-treatment, 16 days; post-treatment, about 2 days). Findings among the adolescent subgroup (n=10) showed all experienced complete resolution of severe VOEs and VOEs during the 6−18 month follow-up period. Overall, results among all evaluable participants also demonstrated sustained improvements in hematologic outcomes and hemolysis markers (except for participants with α-thalassemia trait), and showed all participants had a stable percentage of HbA^{T87Q} production (median >40%) through last follow-up at a median of 35.5 months after lovo-cel.[74]

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§§ After treatment with lovo-cel in study HGB-206, 2 participants who had 2 α-globin gene deletions (ie α-thalassemia trait; −α3.7/−α3.7) developed persistent anemia. It was determined that the α-thalassemia trait was likely attributable to the anemia (no evidence of hematologic malignancy); therefore, genetic mutations causing ≥2 α-globin genes to be inactivated was added as exclusion criterion in subsequent, ongoing studies, such as HGB-210.

Safety data indicates that lovo-cel treatment tends to be well-tolerated,[64] with most AEs ascribed to either SCD or the busulfan conditioning procedure.[74] Among the 47 participants from *HGB-206 Group C* and HGB-210 studies with a median follow-up of 35.5 months as of February 2023, lovo-cel-related SAEs occurred in 2 participants, who also had α-thalassemia trait: 2 events of anemia (4.3% of participants) and 1 event of myelodysplastic syndrome (2.1% of participants).[74] Non-SAEs associated with lovo-cel comprised infusion reactions, such as reduced diastolic blood pressure, abdominal discomfort, and nasal congestion, each occurring in one participant.[74]

6.2 Exa-cel

There are several ongoing trials assessing exa-cel for patients with SCD or TDT. Exa-cel is being evaluated in a 24-month, phase III pediatric-only study, CLIMB-151, among participants aged 5−11 years with severe SCD and recurrent VOCs.[63] Currently, the CLIMB-151 study is recruiting, with an enrollment goal of around 15 participants and an expected study completion date of May 2026.[77] Additionally, CLIMB-161 is an ongoing, phase IIIb trial, enrolling around 12 participants aged 12−35 years with either SCD or TDT.[63] Exa-cel is also being assessed in several other ongoing trials exclusively among participants with TDT: CLIMB-111 and CLIMB-141.[63]

Participants from CLIMB-121, CLIMB-151, and CLIMB-161 are eligible for the long-term extension study, CLIMB-131, which follows participants for up to 15 years after receiving the exa-cel infusion.[18,63]

Exa-cel approval for the indication of SCD is based on the pivotal clinical trial, CLIMB-121[3,78]; results from this trial are discussed below.

6.2.1 CLIMB-121

CLIMB-121 (NCT03745287) is an ongoing, single-arm, open-label, multi-center, phase I/II/III study evaluating exa-cel among participants aged 12−35 years with severe SCD, following HSC collection and myeloablative conditioning with busulfan.[18,78] To be eligible for the study, participants must be diagnosed with an SCD genotype of HbSS (βS/βS), HbSβ^0-thalassemia (βS/β0), or HbSβ$^+$-thalassemia (βS/β+), and experience a minimum of 2 severe VOC events[***] annually during the prior 2 years to screening, despite appropriate supportive management. Participants were excluded if they previously received an allogeneic HSCT or had an HLA-matched related donor (see **Appendix C** for complete inclusion and exclusion criteria).[18,78]

The primary outcome was the proportion of participants who achieved complete resolution of severe VOCs for ≥12 consecutive months after the exa-cel infusion, starting 60 days after the most recent RBC transfusion for SCD management or post-transplant support.[18,79]

[***] Severe VOC events were defined as an acute pain episode necessitating a visit to a medical facility and pain medications or red blood cell (RBC) transfusions; ACS; episodes of acute priapism (painful, sustained, undesired erection lasting >2 hours) that required care at a medical center; or splenic sequestration

6.2.1.1 Efficacy/safety outcomes

As of the latest interim analysis (June 2023), 44 participants, including 12 adolescents, with SCD (most with genotype HbSS [βS/βS]) have been treated with exa-cel.[18] At baseline, participants had a median annualized severe VOC rate of 3.5. All participants achieved platelet and neutrophil engraftment, at a median of 35 days and 27 days after the infusion, respectively. After the exa-cel infusion, 29 of the 31 evaluable participants[†††] (93.5%) had complete resolution of severe VOCs for ≥12 months, with a mean duration of 22.2 months; the median duration to the last RBC transfusion was 19 days after exa-cel treatment. One participant, who had initially achieved the primary outcome, eventually experienced a severe VOC in the context of parvovirus infection at month 22.8[18]; the participant has fully recovered and has been VOC-free since the precipitating event (as of February 2023).[79] None of the evaluable participants (a total of 30) were hospitalized for a severe VOC within ≥12 months after receiving exa-cel (key secondary outcome).[18] Additionally, improvements in patient-reported quality of life measures (eg, numerical rating scale for pain) have been observed at 6 months after the exa-cel infusion, with continual improvements observed for up to 24 months of follow-up.[78] Hemolysis markers (eg, indirect bilirubin, haptoglobin) have generally trended towards normalized values throughout the follow-up period.[78] Among all treated participants (N=44), increases in HbF levels were observed by month 6, with mean HbF proportions above 40% maintained up to month 24 (last measured timepoint),[18] which is considered to be above the clinically meaningful threshold of 30%.[12]

The safety profile of exa-cel was generally consistent with AEs related to HSCT or myeloablative conditioning.[18] Of the 44 participants with SCD included in the safety analysis, with a median of 19.3 months of follow-up, approximately 20 (45%) reported a SAE. The most common Grade 3 or 4 non-laboratory AEs (incidence ≥20% of participants), occurring after myeloablative conditioning and the exa-cel infusion up to month 24, were febrile neutropenia, mucositis, and decreased appetite. The most common Grade 3 or 4 laboratory abnormalities (incidence ≥50% of participants), occurring after myeloablative conditioning and the exa-cel infusion up to month 24, were neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia.[18] Earlier interim results as of February 2023 showed no malignancies had been reported.[79] One death, deemed unrelated to exa-cel treatment, occurred due to coronavirus disease 2019 (COVID-19) infection and secondary respiratory failure.[18]

7.0 SPECIAL POPULATIONS

Both lovo-cel and exa-cel have demonstrated safety and efficacy in the pediatric population (≥12 years of age).[17,18] In clinical trials, no significant disparities in efficacy or safety were observed between adult and pediatric (ie, aged 12 to <18 years) participants who received lovo-cel or exa-cel. The safety and efficacy of lovo-cel and exa-cel have not yet been established in pediatric patients younger than 12 years of age. Additionally, lovo-cel and exa-cel have not been studied in older adults (≥65 years of age), or in those with renal or hepatic impairment. In general, renal and hepatic function should be evaluated to determine eligibility for HSCT.[17,18]

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††† Evaluable participants for the primary efficacy outcome had ≥16 months of follow-up. However, participants with <16 months of follow-up were also included if: a) death occurred; b) exa-cel-related adverse events resulted in discontinuation; c) consistently received red blood cell (RBC) transfusions for >10 months after exa-cel treatment; or d) determined to be a non-responder.

Although there is a lack of human or animal data on the use of lovo-cel or exa-cel during pregnancy, both treatments should be avoided during pregnancy due to the risks associated with myeloablative conditioning.[17,18] Before starting HSC mobilization for either lovo-cel or exa-cel, a negative serum pregnancy test must be confirmed. A negative pregnancy status should be re-confirmed before myeloablative conditioning. Persons of reproductive potential should use effective contraception from the initiation of HSC mobilization up to ≥6 months post-infusion.

Furthermore, although there is no data on the effects of lovo-cel or exa-cel on human fertility, it is advised that providers discuss fertility preservation options with patients before treatment, if appropriate, due to the known associated risks of infertility with myeloablative conditioning.[17,18]

According to product labeling, lovo-cel should be avoided in patients who are breastfeeding,[17] whereas for exa-cel, the package insert advises that the clinical necessity should be taken into consideration with respect to the benefits and risks of breastfeeding.[18] Nonetheless, breastfeeding should be stopped during myeloablative conditioning due to potential risks.[18] Patients who are considering breastfeeding after undergoing treatment with either lovo-cel or exa-cel should discuss it with their healthcare provider.[17,18]

Before collecting CD34+ HSCs for lovo-cel or exa-cel manufacturing, patients should be screened for HIV-1 and HIV-2[17,18]; additionally patients undergoing treatment with exa-cel should be screened for hepatitis B and C.[18] Although not listed as a contraindication, prescribing information recommends to avoid administering lovo-cel or exa-cel in patients who test seropositive for HIV-1 or HIV-2.[17,18] Additionally, for exa-cel, it is recommended to avoid use in persons with active hepatitis B or C infections, or those who have previously undergone an allogeneic or autologous HSCT.[18]

Table 6 provides an overview of lovo-cel or exa-cel use in special populations, as described in the prescribing information.

Table 6. Recommendations for Lovo-cel or Exa-cel Use in Special Populations, According to Product Labeling

Special population	Key considerations	
	Lovotibeglogene autotemcel (Lyfgenia), or lovo-cel[17]	**Exagamglogene autotemcel (Casgevy), or exa-cel[18]**
Pediatric patients	• Lovo-cel has demonstrated safety and efficacy in the pediatric population (age ≥12 to <18 years) ○ As of February 2023, 10 adolescents had been evaluated for the primary outcome (proportion of participants achieving complete resolution of VOEs between 6–18 months of follow-up)[74] ○ No significant disparities in efficacy or safety were observed between adult and pediatric participants in clinical trials • Safety and efficacy of lovo-cel has not been established in pediatric patients younger than 12 years of age	• Exa-cel has demonstrated safety and efficacy in the pediatric population (age ≥12 to <18 years) ○ As of June 2023, a total of 12 adolescents have been enrolled in CLIMB-121, with 7 evaluated for the primary outcome (proportion of participants who achieved complete resolution of severe VOCs for ≥12 consecutive months of follow-up)[18] ○ No significant disparities in efficacy or safety were observed between adult and pediatric participants in clinical trials • Safety and efficacy of exa-cel has not been established in pediatric patients younger than 12 years of age
Older adults	• Lovo-cel has not been studied in older adults (aged ≥65 years)	• Exa-cel has not been studied in older adults (aged ≥65 years)
Patients with renal or hepatic impairment	• Lovo-cel has not been studied in patients with renal impairment (CrCl <70 mL/min/1.73 m^2) or advanced hepatic disease ○ No dosage adjustments for renal or hepatic impairment are provided in the prescribing information	• Exa-cel has not been studied in patients with renal impairment (eGFR <60 mL/min/1.73 m^2) or hepatic impairment ○ No dosage adjustments for renal or hepatic impairment are provided in the prescribing information
Pregnant patients	• No human or animal data on the use of lovo-cel during pregnancy ○ Most clinical trials explicitly excluded pregnant patients (HGB-206 and HGB-210)[40,59] • Prescribing information recommends to avoid using lovo-cel in pregnant patients, and to consider the known associated risks of myeloablative conditioning ○ Before starting HSC mobilization, a negative serum pregnancy test should be confirmed ○ A negative pregnancy status should be re-confirmed before myeloablative conditioning and lovo-cel administration ○ Persons of reproductive potential should use effective contraception from the initiation of HSC mobilization up to ≥6 months post-infusion • Although there is no data on the effects of lovo-cel on human fertility, fertility preservation options should be discussed with patients, if appropriate, before treatment • Patients planning to become pregnant after undergoing treatment with lovo-cel should consult their healthcare provider	• No human or animal data on the use of exa-cel during pregnancy • Prescribing information recommends to avoid using exa-cel in pregnant patients due to known risks of myeloablative conditioning ○ Before starting HSC mobilization (each cycle), a negative serum pregnancy test should be confirmed ○ A negative pregnancy status should be re-confirmed before myeloablative conditioning ○ Persons of reproductive potential should use effective contraception from the initiation of HSC mobilization up to ≥6 months post-infusion • Although there is no data on the effects of exa-cel on human fertility, fertility preservation options should be discussed with patients, if appropriate, before treatment • Patients planning to become pregnant after undergoing treatment with exa-cel should consult their healthcare provider
Patients who are breastfeeding	• Effects of lovo-cel on a breastfeed infant and maternal milk production are unknown • Unknown if lovo-cel is excreted in breast milk • Prescribing information recommends to avoid using lovo-cel in patients who are breastfeeding • Patients who are considering breastfeeding after undergoing treatment with lovo-cel should discuss it with their healthcare provider	• Effects of exa-cel on a breastfeed infant and maternal milk production are unknown • Unknown if exa-cel is excreted in breast milk • Prescribing information recommends considering the risks and benefits of breastfeeding, including the clinical necessity of exa-cel; breastfeeding must be stopped during myeloablative conditioning • Patients who are considering breastfeeding after undergoing treatment with exa-cel should discuss it with their healthcare provider
Patients seropositive for HIV	• Before collecting CD34+ HSCs for lovo-cel manufacturing, patients should be screened for HIV-1 and HIV-2 • Patients should test negative for HIV before apheresis is performed; if a patient is HIV-positive, they should not receive lovo-cel ○ Lovo-cel has not been studied in HIV-positive patients (HIV-1 or HIV-2)	• Before collecting CD34+ HSCs for exa-cel manufacturing, patients should be screened for HIV-1, HIV-2, HBV, and HCV, among others (according to local guidelines) • Exa-cel should not be used in patients with active HIV-1, HIV-2, HBV, or HCV ○ Exa-cel has not been studied in patients with HIV-1, HIV-2, HBV, or HCV

Abbreviations: CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSC(s), hematopoietic stem cell(s); HSCT, hematopoietic stem cell transplantation; m, meter; min, minute; mL, milliliter; VOE(s), vaso-occlusive episode(s) or event(s)

8.0 SAFETY

Below is a summary of reported AEs, and warnings and precautions, as reported in the lovo-cel or exa-cel prescribing information. Notably, both lovo-cel and exa-cel do not carry any labeled contraindications for use.[17,18]

8.1 Adverse events

Lovo-cel and exa-cel AEs were generally consistent with anticipated side effects associated with HSC collection, and myeloablative conditioning or SCD.[17,18] A total of 45 participants treated with lovo-cel and 44 participants treated with exa-cel were evaluated for AEs, with the follow-up duration starting from the first day after the infusion up to 24 months. Overall, 33 lov-cel-treated participants (73%) and 20 exa-cel-treated participants (45%) experienced ≥1 SAE.[17,18] For lovo-cel, the most common AEs (incidence ≥25%) Grade 3 or higher, were stomatitis (71%), thrombocytopenia (69%), neutropenia (60%), febrile neutropenia (44%), anemia (33%), and leukopenia (33%).[17] For exa-cel, the most common AEs (incidence ≥25%; Grade 3 or Grade 4), were neutropenia (100%), thrombocytopenia (100%), leukopenia (98%), mucositis (86%), anemia (84%), lymphopenia (50%), febrile neutropenia (48%), and decreased appetite (41%).[18]

Hematologic malignancies have occurred in lovo-cel clinical trials: 2 participants (both in Group A from the HGB-206 trial) developed acute myeloid leukemia, and 1 participant (who also had α-thalassemia trait) developed myelodysplastic syndrome (in Group C).[17] Information on the occurrence of malignancies is not provided in the exa-cel prescribing information,[18] but no malignancies had been reported at an interim assessment (data cut-off of February 2023).[79]

Infusion-related reactions (eg, decreased diastolic blood pressure) occurred with both lovo-cel and exa-cel treatment, but generally were mild (Grade 1 or Grade 2) and occurred in a small number of participants (<6).[17,18] Notably, all participants who received exa-cel were pre-treated with an antihistamine and an antipyretic before the infusion.[18] All participants who received lovo-cel or exa-cel achieved platelet and neutrophil engraftment,[17,18] but 2 participants treated with lovo-cel experienced delayed platelet engraftment (after day 100); of these participants, 1 required eltrombopag until day 234.[17]

Overall, 4 participants have died across lovo-cel and exa-cel clinical trials; of these, 3 participants received lovo-cel and the remaining participant received exa-cel.[17,18] In all cases, the cause of death was deemed, or highly likely, to be unrelated to lovo-cel or exa-cel.[18,74-76]

Table 7 provides an overview of select AEs for lovo-cel and exa-cel, according to prescribing information.

Table 7. Select Adverse Events and Other Safety Outcomes for Lovo-cel and Exa-cel, According to Product Labeling

	Lovotibeglogene autotemcel (Lyfgenia), or lovo-cel[17] (N=45)[a]	**Exagamglogene autotemcel (Casgevy), or exa-cel[18] (N=44)[a]**
≥1 SAE	33 participants (73%)	20 participants (45%)
Most common (incidence ≥25%) ≥ Grade 3 AEs (non-laboratory)[b]	• Stomatitis: 32 participants (71%) • Febrile neutropenia: 20 participants (44%)	• Mucositis (includes pharyngeal and mucosal inflammation, and stomatitis): 38 participants (86%) • Febrile neutropenia: 21 participants (48%) • Decreased appetite: 18 participants (41%)
Most common (incidence ≥25%) ≥ Grade 3 AEs (laboratory)[b]	• Neutropenia: 27 participants (60%) • Thrombocytopenia: 31 participants (69%) • Leukopenia: 15 participants (33%) • Anemia: 15 participants (33%)	• Neutropenia: 44 participants (100%) • Thrombocytopenia: 44 participants (100%) • Leukopenia: 43 participants (98%) • Anemia: 37 participants (84%) • Lymphopenia: 22 participants (50%)
Hematologic malignancies	• Total: 3 participants (7%) ○ Acute myeloid leukemia: 2 participants (both in Group A)[c] ○ Myelodysplastic syndrome (also has α-thalassemia trait): 1 participant (in Group C)	• Not reported in prescribing information, but 0 participants had reported any malignancies as of February 2023 (earlier interim results)[79]
Successful platelet engraftment following infusion[d]	• 45 participants (100%); achieved at a median of 37 days post-infusion ○ Delayed platelet engraftment: 2 participants (4%; after day 100)	• 43 participants (100%; N=43); achieved at a median of 35 days post-infusion ○ Delayed platelet engraftment: a specific number of participants is not reported in the prescribing information, but it has been observed in clinical trials
Successful neutrophil engraftment following infusion[e]	• 45 participants (100%); achieved at a median of 20 days post-infusion	• 44 participants (100%); achieved at median of 27 days post-infusion
Deaths	• Total: 3 participants (7%) ○ Sudden cardiac death as a result of underlying conditions: 1 participant (in Group C)[61] ○ Acute myeloid leukemia: 2 participants (in Group A)[c]	• Total: 1 participant (2%) ○ COVID-19 infection and secondary respiratory failure: 1 participant

[a] Unless otherwise noted, the total number of participants is 45 or 44 for lovo-cel and exa-cel, respectively.

[b] Follow-up was from the first day after receiving either lovo-cel or exa-cel infusion up to month 24

[c] Acute myeloid leukemia occurred in a cohort of participants that received an earlier iteration of lovo-cel (Group A), derived from a different manufacturing and treatment process than subsequent participants

[d] Successful platelet engraftment was generally defined as platelet values ≥50 x 10^9/L, for 3 consecutive measurements obtained on different days following either the lovo-cel or exa-cel infusion, in the absence of platelet transfusions for 7 days

[e] Successful neutrophil engraftment was generally defined as ANC ≥500 cells/μL, for 3 consecutive measurements obtained on 3 different days; definition for exa-cel also included in the absence of rescue (unmodified) CD34+ cells

Abbreviations: α, alpha; AE(s), adverse event(s); ANC, absolute neutrophil count; COVID-19, coronavirus disease 2019; L, liter; SAE(s), serious adverse event(s); μL, microliter

8.2 Warnings and precautions

Both lovo-cel and exa-cel carry warnings for the potential of hypersensitivity reactions, delayed platelet engraftment, and neutrophil engraftment failure.[17,18] In addition, **lovo-cel also has a black box warning for hematologic malignancy**, along with a unique warning for insertional oncogenesis.[17] Exa-cel carries a warning for the potential risk of off-target genome editing.[18] Furthermore, exa-cel prescribing information advises avoiding use in patients who have received either an allogeneic or autologous HSCT, as it has not been studied in this population[18]; prescribing information for lovo-cel does not address its use among patients who have already received an HSCT.[17] **Table 8** provides an overview of the labeled warnings/precautions for lovo-cel and exa-cel; additional details for each of these warnings/precautions are summarized in the bullet points after the table.

Table 8. Labeled Warnings and Precautions for Lovo-cel and Exa-cel

	Lovotibeglogene autotemcel (Lyfgenia), or lovo-cel[17]	Exagamglogene autotemcel (Casgevy), or exa-cel[18]
Hematologic malignancy	✓ (black box warning)	
Hypersensitivity reactions	✓	✓
Delayed platelet engraftment	✓	✓
Neutrophil engraftment failure	✓	✓
Off-target genome editing risk		✓
Insertional oncogenesis	✓	

Shared warnings and precautions for lovo-cel and exa-cel, as outlined in product labeling, are as follows[17,18]:

- **Hypersensitivity reactions**: Due to the dimethyl sulfoxide or dextran 40 in the cryo-preservative solution, patients may experience hypersensitivity reactions (eg, anaphylaxis). Therefore, patients should be monitored for such reactions during and after the lovo-cel or exa-cel infusion.
- **Delayed platelet engraftment**: Because the potential for bleeding is increased before platelet engraftment, and may persist even after engraftment in patients experiencing prolonged thrombocytopenia, patients should be monitored for bleeding and thrombocytopenia post-infusion. Regular assessments of platelet counts should be performed until the attainment of platelet engraftment and recovery. Blood cell count assessments and other relevant testing should be performed when clinical symptoms emerge that suggest the possibility of bleeding.
- **Neutrophil engraftment failure:** Absolute neutrophil counts (ANC) should be monitored after the lovo-cel or exa-cel infusion, due to the potential of neutrophil engraftment failure. Patients who experience neutrophil engraftment failure should receive their rescue CD34+ HSCs (back-up, unmodified collection of CD34+ HSCs).

Unique warnings for lovo-cel and exa-cel, as outlined in product labeling, are as follows:

- **Hematologic malignancy (black box warning for lovo-cel)**[17]: Treated patients may develop hematologic malignancies, necessitating life-long monitoring. Regular complete blood counts (with

differential) should be performed at least every 6 months for a minimum of 15 years after the lovo-cel infusion. Additionally, integration site analysis should be performed at 6 and 12 months post-infusion, and as appropriate thereafter. If malignancy occurs, the drug sponsor should be contacted.

- **Insertional oncogenesis (lovo-cel)**[17]: After treatment with lovo-cel, there is a theoretical risk of lentiviral vector-mediated insertional oncogenesis. However, this risk is likely low, if any, as the lentiviral vector is designed to be replication-incompetent and self-inactivating.
- **Risk of off-target genome editing (exa-cel)**[18]: While off-target genome editing was not detected in the examined CD34+ HSCs from healthy donors and patients, the possibility of unintentional off-target editing, due to genetic variations, cannot be dismissed. The clinical implications of potential off-target editing remains uncertain.

9.0 DRUG INTERACTIONS

Formal studies evaluating drug interactions have not been conducted for lovo-cel or exa-cel.[17,18] Nonetheless, lovo-cel and exa-cel are not anticipated to have any interactions with cytochrome P-450 hepatic enzymes or drug transporters.[17,18] However, patients who have undergone treatment with lovo-cel may have false-positive results for HIV, tested by polymerase chain reaction (PCR) assay.[17] Consequently, PCR-based assays for HIV screening should not be used in patients who have received lovo-cel.[17]

Prescribing information for lovo-cel and exa-cel recommend discontinuing certain agents (eg, hydroxyurea) in the setting of HSC mobilization and/or myeloablative conditioning; see **Section 4.2.1** for details. The safety of administering live viral vaccines during or after the lovo-cel or exa-cel infusion has not been evaluated[17,18]; lovo-cel prescribing information advises to adhere to institutional guidelines and vaccination schedules in accordance with post-autologous HSCT and functional asplenia.[17]

10.0 UTAH MEDICAID UTILIZATION DATA

Among the Utah Medicaid fee-for-service population, we found no medical claims for lovo-cel or exa-cel from December 2023 (month of FDA approval) through January 2024 (personal communication [email] with Jacob Crook, MS, Data Manager/Analyst, February 13, 2024).

11.0 CONSIDERATIONS FOR PRIOR AUTHORIZATION CRITERIA

The Drug Utilization Review (DUR) board may consider implementing the following drug-specific prior authorization (PA) criteria for lovotibeglogene autotemcel (Lyfgenia), or lovo-cel, and exagamglogene autotemcel (Casgevy), or exa-cel, to guide appropriate prescribing:

Considerations regarding patient eligibility for lovo-cel or exa-cel therapy:

- Based on provider attestation or clinical documentation, a patient meets the FDA indication for lovo-cel or exa-cel, as follows:
    - Patient is at least 12 years of age and has a confirmed diagnosis of SCD.
        - Both lovo-cel and exa-cel are FDA-approved for patients with SCD who are ≥12 years of age.[17,18] Pediatric use (≥12 to <18 years of age) is supported by the HGB-206 trial

(which treated 8 adolescents) for lovo-cel, and CLIMB-121 trial (which treated 12 adolescents) for exa-cel.

- The safety and efficacy of lovo-cel and exa-cel have not been established in patients younger than 12 years of age.[17,18] Ongoing clinical trials for lovo-cel (HGB-210) and exa-cel (CLIMB-151) are enrolling patients younger than 12 years of age,[59,63] which could potentially allow expansion of the approved age for use.

- May consider requiring an SCD genotype that corresponds to a severe phenotype.[80] For example, most clinical trials for lovo-cel and exa-cel enrolled participants with genotypes typically associated with severe disease: HbSS (βS/βS), HbSβ0-thalassemia (βS/β0), or HbSβ+-thalassemia (βS/β+).[64,78]
  - Such criterion would be more specific and perhaps more restrictive than the labeled indication.
- For lovo-cel, it may be reasonable to also require that patients do not have co-occurring α-thalassemia trait (ie, 2 α-globin gene deletions; −α3.7/−α3.7)[52] due to the potential risk of anemia with erythroid dysplasia, potentially necessitating ongoing RBC transfusions.[17,80] Notably, lovo-cel has not been studied in patients with >2 α-globin gene deletions.[17]
  - In study HGB-206, 2 participants with comorbid α-thalassemia trait developed persistent anemia after receiving lovo-cel; resultant anemia was deemed likely attributable to α-thalassemia trait.[52] Additionally, interim results (as of February 2023) reported that patients with α-thalassemia trait did not experience sustained improvements in hematologic outcomes and hemolysis markers after lovo-cel treatment.[74]

- Patient must have a history of VOEs (for lovo-cel), or experience recurrent VOCs (for exa-cel).
  - Although lovo-cel and exa-cel prescribing information does not provide specific thresholds or timeframes regarding VOEs or VOCs to indicate severity,[17] eligibility criteria for most of the lovo-cel clinical trials (HGB-206 and HGB-210) required participants to experience ≥4 VOEs within the past 2 years before enrollment or informed consent,[40,59] and the pivotal exa-cel clinical trial (CLIMB-121) required participants to have a history of ≥2 VOCs annually during the prior 2 years to screening.[18]
  - In general, VOEs/VOCs were defined in clinical trials as events lacking any medically determined cause other than vaso-occlusion, such as acute pain episodes or ACS necessitating medical evaluation at a hospital or emergency department.[17,18] However, these criteria may be arbitrary, therefore it may be reasonable to not include any specific severity thresholds or an explicit definition of VOEs/VOCs, and instead rely on provider discretion.[80] For example, some patients may opt to self-manage their VOEs/VOCs at home, despite experiencing significant pain, and under stricter criteria might not appear to meet the required frequency or severity of VOEs/VOCs from clinical trials. Likewise, patients experiencing a fewer number or

frequency of recent VOEs/VOCs, potentially due to other SCD management, may still be good candidates for lovo-cel or exa-cel.[80]

- May consider requiring provider attestation that the patient is eligible for HSCT but does not have an HLA-matched sibling allogeneic HSCT donor.
    - For patients seeking a potential cure of SCD, experts tend to prefer considering sibling-matched HSCT before gene therapies due to the more robust, long-standing evidence within the SCD population.[9,13] Therefore, gene therapies, such as lovo-cel and exa-cel, may be reserved for patients who are eligible for HSCT but lack an HLA-matched sibling allogeneic HSCT donor[9,13]; this is consistent with lovo-cel and exa-cel clinical trial eligibility criteria (see **Appendix C**).[64,78]
- May consider requiring provider attestation that the patient does not have a history of or active hematologic malignancy
    - Compared to the general population, patients with SCD are at a higher risk of developing hematologic malignancies.[17] Additionally, the heightened hematopoietic stress linked to the treatment process (mobilization and myeloablative conditioning) and infusion procedure may potentially increase the risk of developing a hematologic malignancy. Specifically for lovo-cel, prescribing information recommends life-long monitoring for the development of hematologic malignancies (a black box warning).[17]
    - For lovo-cel, may consider requiring provider attestation that the patient does not have known genetic mutations that increase the risk of developing myelodysplastic syndrome or acute myeloid leukemia.
        - Unlike previous lovo-cel clinical trials (HGB-205 and HGB-206), HGB-210 has a unique exclusion criterion of chromosomal or genetic abnormalities, as determined by the investigator, that may increase the participant's susceptibility to myelodysplastic syndrome or acute myeloid leukemia.[59] This criterion was possibly added because 2 participants from the HGB-206 study died from acute myeloid leukemia after lovo-cel treatment.[17]

Considerations related to SCD medications:

- May consider requiring provider attestation or clinical documentation that the patient has tried and failed, is intolerant, or has a contraindication to hydroxyurea, and/or at least one other disease-modifying pharmacologic agent (eg, L-glutamine, voxelotor, crizanlizumab).
    - Because hydroxyurea is the mainstay of SCD treatment,[3,35] it seems reasonable to require patients to have experienced insufficient control of VOEs/VOCs while taking hydroxyurea.[80] Notably, clinical trials for lovo-cel required participants to previously experience hydroxyurea failure or have an intolerance.[64] The exa-cel clinical trial, CLIMB-121, did not specify such criterion for study inclusion, but nonetheless required participants to experience recurrent VOEs despite "appropriate supportive care".[78]
        - L-glutamine, voxelotor, and crizanlizumab became available after most of the reviewed clinical trials for lovo-cel and exa-cel were started.[1,39-41]
    - Newer disease-modifying pharmacologic agents can provide additional benefit as adjunct therapy to hydroxyurea in the event that a patient fails hydroxyurea monotherapy. L-glutamine and crizanlizumab significantly reduced the number of VOCs with or without

hydroxyurea in pivotal clinical trials,[42,43] whereas voxelotor significantly improved Hb levels and hemolysis markers, with or without hydroxyurea.[44] Nonetheless, even with these add-on therapies (or use as monotherapy) and reduction in VOC frequency, these therapies may not completely eliminate VOCs.[9-11] If residual VOCs invoke severe complications, pursuance of an HSCT could be warranted.[56]

- May consider providing an educational note to providers that patients should avoid using disease modifying agents (eg, crizanlizumab, voxelotor, hydroxyurea) and iron chelators *before* receiving lovo-cel or exa-cel (in the setting of HSC mobilization and/or myeloablative conditioning) and immediately after the infusion (see **Table 3** for specific details regarding discontinuation of agents).
- May consider requiring provider attestation that the patient understands that **not all patients may have an adequate response (ie, disease remission) to these gene therapies**, and thus may need traditional SCD management (including trial of other disease-modifying agents) if the gene therapy is not successful.
    - Clinical trial data did not address the management of patients with newer SCD disease-modifying agents who were treated with but failed gene therapy.

Considerations related to provider eligibility prescribe:

- Consider requiring that lovo-cel or exa-cel be prescribed by a hematologist
    - Because of the complexity and invasiveness of the treatment process, lovo-cel and exa-cel are restricted to qualified or authorized treatment centers only (ie, centers approved by the drug sponsor).[50,51] At least for lovo-cel, authorized treatment centers have undergone training to carry out HSCT with the gene-therapy product.[50] See **Section 4.0** for further information.

Considerations related to lovo-cel and exa-cel dosing as a one-time treatment:

- In accordance with the FDA-approved labeling, the minimum recommended dose of lovo-cel and exa-cel is 3 x 10^6 CD34+ cells/kg, administered as a one-time IV infusion.[17,18] Patients should be aware that additional HSC collection (mobilization and apheresis cycles) may be necessary if the minimum dose is not achieved during the initial manufacturing of the product.[17,18]

Additional considerations:

- Consider requiring provider attestation that the provider will monitor the patient's pregnancy status throughout the treatment process.
    - Prescribing information for lovo-cel and exa-cel advise patients of reproductive potential to use effective contraception from the start of HSC mobilization through ≥6 months after receiving the infusion, especially given the potential pregnancy risks associated with myeloablative conditioning agents, such as busulfan.[17,18]
- Consider requiring attestation that the provider has discussed with the patient the risks of neutrophil and platelet engraftment failure after receiving the lovo-cel or exa-cel infusion, and the potential adverse effects from necessary preparation procedures (ie, HSC mobilization, apheresis, and myeloablative conditioning).
    - Patients who experience neutrophil engraftment failure, based on ANC monitoring, should receive their rescue CD34+ HSCs (ie, back-up, unmodified collection of CD34+ HSCs).[17,18]

- Patients should be monitored for bleeding and thrombocytopenia post-infusion by having regular assessments of platelet counts until the attainment of platelet engraftment and recovery.[17,18]
- Most participants (≥60%) treated with lovo-cel experienced stomatitis, thrombocytopenia, and neutropenia.[17] Similarly, ≥60% of participants treated with exa-cel reported mucositis, neutropenia, thrombocytopenia, leukopenia, and anemia.[18]

- May consider requiring provider attestation that the patient does not have any of the following:
  - Positive for HIV-1, HIV-2 (for lovo-cel and exa-cel), or hepatitis B or C (for exa-cel)
  - Inadequate bone marrow function (defined in lovo-cel clinical trials as an ANC of $<1 \times 10^9$/L [$<0.5 \times 10^9$/L if taking hydroxyurea] or a platelet count $<100 \times 10^9$/L)
  - Prior HSCT (for exa-cel, and perhaps lovo-cel)
    - Exa-cel prescribing information advises that it should not be used in patients who have received an allogeneic or autologous HSCT, given this patient population was excluded from CLIMB-121.[18,41]
    - Although patients with a prior HSCT were also excluded from lovo-cel clinical trials HGB-206 and HGB-210,[40,59] prescribing information does not explicitly recommend against its use among patients who have received an HSCT.[17]

12.0 SUMMARY

Lovotibeglogene autotemcel (Lyfgenia) and exagamglogene autotemcel (Casgevy), or lovo-cel and exa-cel, respectively, were approved by the United States (US) Food and Drug Administration (FDA) in December 2023 as the first hematopoietic stem cell (HSC)-based gene therapies for patients with SCD aged 12 years and older with a history of VOEs (for lovo-cel) or recurrent VOCs (for exa-cel).[8,17,18] Prior to the approval of lovo-cel and exa-cel, allogeneic hematopoietic stem cell transplantation (HSCT) was the only potential curative option for SCD,[2,4,12] but was generally limited by the scarcity of suitable donors[3,9,11-15] and substantial risks (eg, graft-versus-host disease [GVHD]).[3,4,9,12,15,32] Lovo-cel and exa-cel are potentially curative therapies that circumvent certain risks associated with allogenic HSCT, such as GVHD, and donor issues because they are *autologous*.[13,14,16] However, like allogeneic HSCT, both gene therapies require patients to undergo myeloablative conditioning before being treated to deplete existing HSCs from the bone marrow.[19,20]

The technologies for the production of lovo-cel and exa-cel are distinct, but entail genetic modification of HSCs (*ex vivo*) to ultimately increase the production of healthy hemoglobin (Hb) and thus non-sickled erythrocytes.[16] Ultimately, the final genetically-modified product of lovo-cel produces a modified type of hemoglobin A (HbA^{T87Q}),[17] whereas exa-cel increases the production of endogenous fetal hemoglobin (HbF).[18]

Reviewed clinical practice guidelines predate FDA-approval of lovo-cel and exa-cel and therefore do not provide recommendations regarding their use or the use of gene therapies in general.[30,53-57] **According to expert opinion, gene therapy generally tends to be reserved for patients who are eligible for allogeneic HSCT but who lack a matched sibling donor.**[9,13] Given that sibling-matched HSCT has robust, long-standing supportive evidence within the SCD population, most clinicians would consider it first-line

before gene therapy, which at present, has relatively limited evidence, especially regarding long-term toxicities and durability.[12,45]

Three open-label, single-arm studies (HGB-205, HGB-206, and HGB-210) support the use/approval of lovo-cel among patients (12−50 years of age) with severe SCD; of these trials, HGB-206 and HGB-210 are ongoing.[3,39,40,59] The majority of enrolled participants in these trials were required to have SCD genotypes associated with severe disease (HbSS [βS/βS], HbSβ^0-thalassemia [βS/β0], or HbSβ$^+$-thalassemia [βS/β+]), and experience ≥4 protocol-defined VOEs in the prior 24 months, despite appropriate supportive management.[40,59,64] Across all lovo-cel clinical trials, participants were required to have previously failed hydroxyurea, unless intolerant.[39,40,59] According to the most recent interim results (as of February 2023) from HGB-206 and HGB-210, approximately 88% (30 out of 34) of participants were VOE-free (primary outcome in both trials), and 94% (32 out of 34) of participants had severe VOEs completely eliminated (both outcomes maintained for a median of 35.8 months after lovo-cel).[74] Participants who had VOEs at any point post-treatment through long-term follow-up (n=8) demonstrated a substantial decrease in both the frequency (≥50% reduction) and severity of VOEs compared to before lovo-cel treatment. Findings among the adolescent subgroup (n=10) showed all experienced complete resolution of severe VOEs and VOEs of any severity during the 6−18 month follow-up period.[74]

Exa-cel approval for SCD was based on the open-label, single-arm clinical trial, CLIMB-121,[3,78] which is currently ongoing.[41,78] Included participants were 12 to 35 years of age; diagnosed with an SCD genotype of HbSS (βS/βS), HbSβ^0-thalassemia (βS/β0), or HbSβ$^+$-thalassemia (βS/β+); and experienced a minimum of 2 severe VOC events annually during the prior 2 years to screening, despite appropriate supportive management.[18,78] As of the latest interim analysis (June 2023), 29 (93.5%) of the 31 evaluable participants had complete resolution of severe VOCs for ≥12 consecutive months after the exa-cel infusion (primary outcome), with a mean follow-up of 22.2 months.[18] However, 1 participant, who initially achieved the primary outcome, eventually experienced a severe VOC in the context of parvovirus infection at 22.8 months[18]; this participant fully recovered and has been VOC-free since the precipitating event (as of February 2023).[79]

Adverse events (AEs) associated with HSC collection and myeloablative conditioning or SCD-breakthrough symptoms were typical of treatment with lovo-cel or exa-cel.[17,18] The most common AEs (incidence >40%) for both lovo-cel and exa-cel were neutropenia, thrombocytopenia, stomatitis or mucositis, and febrile neutropenia. Both lovo-cel and exa-cel carry warnings for the potential of hypersensitivity reactions, delayed platelet engraftment, and neutrophil engraftment failure.[17,18] Unique warnings for lovo-cel are the potentially increased risk of hematologic malignancy (a black box warning) as well as theoretical risk for insertional oncogenesis due the lentiviral vector,[17] while exa-cel carries a unique warning for the theoretical risk of off-target genome editing.[18]

Potential patients for treatment should understand that while these gene therapies have eradicated SCD vaso-occlusive symptoms and drastically changed the treatment course for the majority of treated patients, not all patients may experience a complete remission. Moreover, the preparation of HSC gene-modification and transplant is intensive and associated with serious AEs. Prior authorization (PA) criteria may be developed to help ensure appropriate use of these gene therapies. Based on the prescribing information and the respective clinical trials, considerations for developing PA criteria for lovo-cel and exa-cel are outlined in **Section 11.0**.

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APPENDIX A: LITERATURE SEARCH STRATEGIES

Embase Search, Conducted January 12, 2024

#	Searches	Results
1	'lovotibeglogene autotemcel'/exp	18
2	'lovotibeglogene':ti,ab,kw OR 'Lyfgenia':ti,ab,kw	2
3	'lovo-cel':ti,ab,kw OR 'lovocel':ti,ab,kw OR 'BB1111':ti,ab,kw OR 'BB-1111':ti,ab,kw	17
4	('LentiGlobin' NEAR/2 ('sickle-cell' OR 'SCD' OR 'SCA')):ti,ab,kw	43
5	'LentiGlobin':ti,ab,kw AND 'sickle cell anemia'/exp	64
6	#1 OR #2 OR #3 OR #4 OR #5	72
7	'exagamglogene autotemcel'/exp	50
8	'exagamglogene':ti,ab,kw OR 'Casgevy':ti,ab,kw	11
9	'exa-cel':ti,ab,kw OR 'exacel':ti,ab,kw OR 'CTX001':ti,ab,kw OR 'CTX-001':ti,ab,kw	27
10	#7 OR #8 OR #9	54
11	#6 OR #10	**121**

Ovid-Medline Search, Conducted January 12, 2024

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to January 11, 2024>

#	Searches	Results
1	(lovotibeglogene or Lyfgenia).ti,ab,kw,kf.	2
2	(lovo-cel or lovocel or BB1111 or BB-1111).ti,ab,kw,kf.	3
3	(LentiGlobin adj2 (sickle-cell or SCD or SCA)).ti,ab,kw,kf.	3
4	LentiGlobin.ti,ab,kw,kf. and (exp Anemia, Sickle Cell/ or exp Hemoglobin, Sickle/)	8
5	1 or 2 or 3 or 4	8
6	(exagamglogene or Casgevy).ti,ab,kw,kf.	0
7	(exa-cel or exacel or CTX001 or CTX-001).ti,ab,kw,kf.	4
8	6 or 7	4
9	5 or 8	**12**

Ovid-Medline Gene Therapies for Sickle Cell Disease Review Search, Conducted January 12, 2024

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to January 11, 2024>

#	Searches	Results
1	exp Anemia, Sickle Cell/ or exp Hemoglobin, Sickle/	27360
2	(sickle-cell or SCD or SCA).ti	22384
3	((hemoglobin or haemoglobin) adj2 (disease* or dysfunc* or disorder*)).ti	1036
4	1 or 2 or 3	31650
5	exp Genetic Therapy/	54276
6	(Gene* and (treatment* or therap*)).ti	54898
7	5 or 6	90423
8	"review".pt or (expert adj2 opinion*).ti,ab or (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab or algorithms/	3629232
9	exp clinical pathway/ or exp clinical protocol/ or clinical protocols/ or exp consensus/ or exp consensus development conference/ or exp consensus development conferences as topic/ or critical pathways/ or exp guideline/ or guidelines as topic/ or exp practice guideline/ or practice guidelines as topic/ or health planning guidelines/ or exp treatment guidelines/ or Clinical Decision Rules/	432645
10	(guideline or practice guideline or consensus development conference).pt.	47705
11	(position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf.	48722
12	(standards or guideline or guidelines).ti,kf. or ((practice or treatment* or clinical) adj guideline*).ab. or (CPG or CPGs).ti. or consensus*.ti,kf. or consensus*.ab. /freq=2	240499
13	(guideline* or standards or consensus* or recommendat*).au.	9
14	8 or 9 or 10 or 11 or 12 or 13	4107319
15	4 and 7 and 14	142
16	limit 15 to yr="2020 -Current"	**40**

APPENDIX B: DIAGNOSIS OF SICKLE CELL DISEASE

To effectively manage sickle cell disease (SCD) and to mitigate the risk of mortality, early detection of a patient's sickle cell status‡‡‡ is essential.[81] All 50 states, including Utah,[82] routinely perform newborn screening on all infants, typically within 24 to 48 hours after birth, to identify SCD via a blood sample.[6,15,23,29,83] To confirm the diagnosis of SCD, specific tests that can detect hemoglobin variants should be used, such as hemoglobin electrophoresis, DNA analysis, high-performance liquid chromatography, or isoelectric focusing, in conjunction with the primary test (complete blood count with a mean corpuscular volume).[23,81,83] Notably, solubility tests may provide inaccurate results and therefore should not be relied upon to ascertain an individual's sickle cell status.[83] A second test should be performed in infants with a positive screening before 2 months of age to confirm the diagnosis.[29]

Sickle cell status screening may also be conducted during adulthood, especially for individuals planning to become or currently pregnant, or after pregnancy.[83] SCD can be diagnosed during the prenatal period using pre-birth diagnostic tests (eg, chorionic villus sampling, amniocentesis), which identify genetic or chromosomal abnormalities in the developing fetus.[1,6]

‡‡‡ Sickle cell status refers to those with sickle cell disease (SCD), and those who are carriers for the trait; individuals with sickle cell trait typically do not exhibit symptoms, but can pass the abnormal gene for SCD to their children.

APPENDIX C: INCLUSION AND EXCLUSION CRITERIA IN LOVO-CEL AND EXA-CEL CLINICAL TRIALS

Table C1. Inclusion and Exclusion Criteria from Clinical Trials for Lovo-cel or Exa-cel

Study identification number, trial name, study phase and design	Inclusion criteria	Exclusion criteria
Lovotibeglogene autotemcel (Lyfgenia), or lovo-cel		
HGB-205 (NCT02151526)[39,60,67 a] Long-term outcomes of lentiviral gene therapy for the β-hemoglobinopathies: the HGB-205 trial Phase I/II, non-randomized, single-arm, single-center, open-label study	***Inclusion criteria for all cohorts:*** • All sexes aged 5 to 35 years • Confirmed diagnosis by Hb analysis of severe SCD or TDT major (defined as needing at least 100 mL/kg/year of packed erythrocytes), irrespective of genotype • Candidate for allogeneic HSCT, but lacks a matched related donor • Based on the investigator's judgement, the participant is able to adhere to the study protocol • Undergone treatment and followed for a minimum of 2 years at a specialized center that maintained comprehensive medical records, including details regarding transfusion history ***Participants with SCD must also meet all of the following criteria:*** • Fail to attain adequate clinical improvement with hydroxyurea at an appropriate dose for a minimum of 4 months (*exception: hydroxyurea was not indicated or poorly tolerated*) • Have at least one of the following poor prognostic risk factors: ○ Recurrent VOCs (≥2 episodes in the past year or in the year before starting a regular transfusion program) ○ Any significant cerebral abnormality, as detected by MRI (eg, occlusions, stenosis) ○ Stroke without significant cognitive impairment ○ Presence of osteonecrosis in ≥2 joints ○ Anti-erythrocyte alloimmunization (>2 antibodies) ○ Sickle cell cardiomyopathy, as detected by Doppler echocardiography ○ ACS (≥2 episodes), defined as an acute event with pneumonia-like symptoms (eg, wheezing, fever, cough) + the detection of previously unidentified pulmonary infiltrate	• Participants with a HLA-matched (10/10) sibling allogeneic HSCT donor (*exception: enrollment was granted by the surveillance committee based on a case-by-case basis*) • Active parasitic, fungal, bacterial, or viral infection • Previous history of, or current malignancies, or myeloproliferative or immunodeficiency disorder • Contraindicated to receive anesthesia • White blood cell count <3 x 10^9/L and/or platelet count <120 x 10^9/L • History of major organ damage, as indicated by the following: ○ Evidence of significant bridging fibrosis, acute hepatitis, or cirrhosis ○ Liver disease, and transaminase levels >3 times ULN ▪ In order to be exclusionary, evidence of significant bridging fibrosis, acute hepatitis, or cirrhosis must be present ○ Cardiovascular disease, with a left ventricular ejection fraction <25% ○ Cardiac T2* value <10 milliseconds, as determined by MRI ○ Kidney disease, with a CrCl <30% of normal ○ Iron overload, as determined by the investigator's judgement ○ Clinically significant pulmonary hypertension that necessitates medical intervention • *Although not explicitly classified as exclusion criteria, it is noted that participants who exhibit chronic oxygen saturation levels <90% (excluding periods of SCD-related crisis) or a carbon monoxide diffusing capacity <60% without an active infection should be excluded*
HGB-206 (NCT02140554)[40] *(currently ongoing; only interim results are published in peer-reviewed medical journals)*[10,61,68] A phase 1/2 study evaluating gene therapy by transplantation of autologous CD34+ stem cells transduced ex vivo with the LentiGlobin BB305 lentiviral vector in subjects with severe sickle cell disease Phase I/II, non-randomized, single-arm, multi-center, open-label study	***Inclusion criteria for all cohorts:*** • All sexes aged ≥12 to ≤50 years • Diagnosed with SCD, genotype of HbSS (βS/βS), HbSβ^0-thalassemia (βS/β0), or HbSβ$^+$-thalassemia (βS/β+) • Received treatment and follow-up for ≥2 years (24 months) before providing informed consent at a center that maintained comprehensive medical records • Lansky (participants aged <16 years) or Karnofsky (participants aged ≥16 years) performance status of at least 60 (both scales assess a patient's functional status in activities of daily living, and range from 0 to 100, with lower scores indicating greater disability) • Previously failed treatment with hydroxyurea at any point in time (defined as having ≥1 ACS or >1 VOE following hydroxyurea use for a minimum of 6 months), or have an intolerance to hydroxyurea (defined as the patient's inability to continue taking the medication, as determined by the investigator's judgement) ***Inclusion criteria added after the start of study enrollment:***	• For participants <18 years of age only, those with a HLA-matched sibling allogeneic HSCT donor • Participants who previously received an allogenic transplant or gene therapy • Seropositive for HIV-1, HIV-2, HBV, HCV, human T-lymphotrophic virus-1 or -2, or active syphilis • Active parasitic, fungal, bacterial, or viral infection • Insufficient bone marrow function (defined as an absolute neutrophil count of <1 x 10^9/L [<0.5 x 10^9/L if taking hydroxyurea] or a platelet count <100 x 10^9/L) • History of severe cerebral vasculopathy, defined as any past occurrence of overt ischemic or hemorrhagic stroke, abnormal transcranial Doppler results (>200 cm/sec) necessitating chronic transfusion, occlusion or stenosis in the circle of Willis, or Moyamoya disease. • Participants who exhibit baseline oxygen saturation levels <90% without supplemental oxygen (excluding periods of SCD-related crisis, infection, or severe anemia), or a baseline carbon monoxide diffusing capacity <50% without an infection

[a] ***HGB-205*** *also allowed the enrollment of participants with severe SCD + cerebral vasculopathy, including those with overt stroke, stenosis or occlusion in the polygon of Willis, abnormal transcranial Doppler results (>170 cm/sec), or Moyamoya disease, contingent upon approval by the surveillance committee.*[39,67] *Notably, no participants meeting this criterion were enrolled in the study.*[64]

Abbreviations: α, alpha; ACS, acute chest syndrome; cm, centimeter; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; g, gram; Hb, hemoglobin; HbF, fetal hemoglobin; HBV, hepatitis B; HCV, hepatitis C; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; kg, kilogram; L, liter; m, meter; mg, milligram; min, minute; mL, milliliter; MRI, magnetic resonance imaging; ng, nanogram; NSAID(s), non-steroidal anti-inflammatory drug(s); SCD, sickle cell disease; sec, second; TDT, transfusion-dependent β-thalassemia; ULN, upper limit of normal; VOCs, vaso-occlusive crises; VOE(s), vaso-occlusive episode(s) or event(s)

Table C1. Inclusion and Exclusion Criteria from Clinical Trials for Lovo-cel or Exa-cel

Study identification number, trial name, study phase and design	Inclusion criteria	Exclusion criteria
	• History of ≥4 *severe* VOEs in the previous 24 months before enrollment despite appropriate supportive management (Group C cohort only)[61,68] ○ Severe VOEs were defined as an event (eg, ACS, acute hepatic or splenic sequestration) lacking any medically determined cause other than vaso-occlusion, necessitating either a hospital or emergency room visit lasting ≥24 hours; or at least 2 visits to either a hospital or emergency room within a 72-hour period, with both visits requiring intravenous treatment; or episodes of acute priapism (painful, sustained, undesired erection lasting >2 hours) that required care at a medical center (± hospitalization).[68]	• Participants with a baseline left ventricular ejection fraction <45% or eGFR <70 mL/min/1.73 m^2, or clinically significant pulmonary hypertension at baseline that necessitates medical intervention (eg, pharmacologic treatment, supplemental oxygen) • Cardiac T2* value <10 milliseconds, as determined by MRI (required for participants with serum ferritin levels >1000 ng/mL or a history of iron overload) • Contraindicated to receive anesthesia, plerixafor, busulfan, or any other products required during the mobilization or myeloablative conditioning process • Any condition that would make the participant ineligible for HSCT, as determined by the transplant provider • Requirement of anticoagulation therapy from the myeloablative conditioning period through platelet engraftment (*exception: participants taking anticoagulants using prophylactic dosing*) • Unable to receive red blood cell transfusion(s) • Advanced liver disease (eg, liver enzymes or direct bilirubin >3 times ULN, evidence of liver cirrhosis based on MRI findings), or previous history of, or current malignancies or immunodeficiency disorder (*exception: treated, non-life threatening cured tumors*) • Direct family member with suspected or known Familial Cancer Syndrome (eg, hereditary breast and ovarian cancer syndrome, familial adenomatous polyposis) • Participants who are pregnant, may become pregnant, or breastfeeding • Participants with a psychiatric disorder that could hinder the capability of the participant to engage in the study, as determined by the investigator's judgement • Unable to comply with study procedures, as determined by the investigator • Participation in a clinical study using an investigational drug within 30 days of screening
HGB-210 (NCT04293185)[59] *(currently ongoing; results are not yet published in peer-reviewed medical journals)* A phase 3 study evaluating gene therapy by transplantation of autologous CD34+ stem cells transduced ex vivo with the BB305 lentiviral vector in subjects with sickle cell disease Phase III, non-randomized, single-arm, multi-center, open-label study	• All sexes aged ≥2 to ≤50 years • Weigh ≥6 kg • Diagnosed with SCD, genotype of HbSS (βS/βS), HbSβ^0-thalassemia (βS/β0), or HbSβ$^+$-thalassemia (βS/β+) • Received treatment and follow-up for ≥2 years (24 months) before providing informed consent at a center that maintained comprehensive medical records • Lansky (participants aged <16 years) or Karnofsky (participants aged ≥16 years) performance status of at least 60 (both scales assess a patient's functional status in activities of daily living, and range from 0 to 100, with lower scores indicating greater disability) • Previously failed treatment with hydroxyurea at any point in time (defined as having ≥1 ACS or >1 VOE following hydroxyurea use for a minimum of 6 months), or have an intolerance to hydroxyurea (defined as the patient's inability to continue taking the medication, as determined by the investigator's judgement)[64] • History of ≥4 protocol-defined VOEs in the previous 24 months before informed consent despite appropriate supportive management • Participants of reproductive potential consent to using an appropriate method of contraception from screening to ≥6 months after receiving the lovo-cel infusion • Written informed consent is obtained by the participant or the participant's legal guardian	• Participants who are able to undergo allogeneic HSTC and who have a HLA-matched related donor • Participants who previously received an allogenic transplant or gene therapy • Seropositive for HIV-1, HIV-2, HBV, HCV, human T-lymphotrophic virus-1, or active syphilis • Active parasitic, fungal, bacterial, or viral infection • Insufficient bone marrow function (defined as an absolute neutrophil count of <1 x 10^9/L [<0.5 x 10^9/L if taking hydroxyurea] or a platelet count <100 x 10^9/L) • History of severe cerebral vasculopathy, defined as any past occurrence of overt ischemic or hemorrhagic stroke, abnormal transcranial Doppler results (eg, >200 cm/sec) or imaging (for participants ≤16 years of age) necessitating chronic transfusion, occlusion or stenosis (>50%) in the circle of Willis, or Moyamoya disease • History of iron overload or Cardiac T2* value <10 milliseconds, as determined by MRI[64] • Contraindicated to receive anesthesia,[64] plerixafor, busulfan, or any other products required during the mobilization or myeloablative conditioning process • Any condition that would make the participant ineligible for HSCT, as determined by the transplant provider • Requirement of anticoagulation therapy from the myeloablative conditioning period through platelet engraftment

[a] ***HGB-205*** *also allowed the enrollment of participants with severe SCD + cerebral vasculopathy, including those with overt stroke, stenosis or occlusion in the polygon of Willis, abnormal transcranial Doppler results (>170 cm/sec), or Moyamoya disease, contingent upon approval by the surveillance committee.[39,67] Notably, no participants meeting this criterion were enrolled in the study.[64]*

Abbreviations: α, alpha; ACS, acute chest syndrome; cm, centimeter; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; g, gram; Hb, hemoglobin; HbF, fetal hemoglobin; HBV, hepatitis B; HCV, hepatitis C; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; kg, kilogram; L, liter; m, meter; mg, milligram; min, minute; mL, milliliter; MRI, magnetic resonance imaging; ng, nanogram; NSAID(s), non-steroidal anti-inflammatory drug(s); SCD, sickle cell disease; sec, second; TDT, transfusion-dependent β-thalassemia; ULN, upper limit of normal; VOCs, vaso-occlusive crises; VOE(s), vaso-occlusive episode(s) or event(s)

Table C1. Inclusion and Exclusion Criteria from Clinical Trials for Lovo-cel or Exa-cel

Study identification number, trial name, study phase and design	Inclusion criteria	Exclusion criteria
		• Unable to receive red blood cell transfusion(s) • Advanced liver disease (eg, evidence of liver cirrhosis, substantial fibrosis, or active hepatitis [based on MRI or liver biopsy], liver iron concentration ≥15 mg/g, unless a liver biopsy indicates the absence of cirrhosis, active hepatitis, or substantial fibrosis), or previous history of, or current malignancies or immunodeficiency disorder (*exception: treated, non-life threatening cured tumors*) • Direct family member with suspected or known Familial Cancer Syndrome (eg, hereditary breast and ovarian cancer syndrome, familial adenomatous polyposis) • Participants who are pregnant, may become pregnant (from screening to ≥6 months after the lovo-cel infusion), or breastfeeding • Participation in a clinical study using an investigational drug within 30 days of screening • Existence of a chromosomal abnormality or genetic mutation, as determined by the investigator, that could increase the participant's risk of developing myelodysplastic syndrome or acute myeloid leukemia • Participants with genetic mutations that cause ≥2 α-globin genes to be inactivated
Exagamglogene autotemcel (Casgevy), or exa-cel		
CLIMB-121 (NCT03745287)[41,78] *(currently ongoing; results are not yet published in peer-reviewed medical journals)* A phase 1/2/3 study to evaluate the safety and efficacy of a single dose of autologous CRISPR-Cas 9 CD34+ human hematopoietic stem and progenitor cells (CTX001) in subjects with severe sickle cell disease Phase I/II/III, non-randomized, single-arm, multi-center, open-label study	• All sexes aged 12 to 35 years • Diagnosed with severe SCD defined by: ○ Genotype of HbSS (βS/βS), HbSβ^0-thalassemia (βS/β0), or HbSβ$^+$-thalassemia (βS/β+), **AND** ○ History of ≥2 severe VOC events annually during the 2-year period prior to screening despite appropriate supportive management ▪ Events included an acute pain episode necessitating a visit to a medical facility and pain medications (eg, intravenous NSAIDs, opioids) or red blood cell transfusions; ACS (defined as an acute event with pneumonia-like symptoms, pain, or fever + the detection of previously unidentified pulmonary infiltrate); episodes of acute priapism (painful, sustained, undesired erection lasting >2 hours) that required care at a medical center; or splenic sequestration (characterized by spleen enlargement, left upper quadrant pain, and a sudden decrease in hemoglobin concentration of ≥2 g/dL)[18,78] • Eligible for autologous HSCT • Lansky (participants aged <16 years) or Karnofsky (participants aged ≥16 years) performance status of at least 80[78] (both scales assess a patient's functional status in activities of daily living, and range from 0 to 100, with lower scores indicating greater disability) • For participants 12–16 years, normal transcranial Doppler results (<170 cm/sec for non-imaging and <155 cm/second for imaging) in the middle cerebral artery and internal carotid artery[78]	• Participants who previously received an allogenic transplant, or have a HLA-matched related donor • White blood cell count <3 x 10^9/L or platelet count <50 x 10^9/L (unrelated to hypersplenism) • Active parasitic, fungal, bacterial, or viral infection[41] • Participants with advanced liver disease, or a carbon monoxide diffusing capacity <50% of predicted value • History of untreated Moyamoya disease, or current Moyamoya disease that contributed to bleeding risk, based on the investigator's opinion[18] • Participants with a baseline left ventricular ejection fraction <45% or eGFR <60 mL/min/1.73 m^2 • >10 unscheduled SCD-related hospitalizations or emergency department visits in the year preceding study screening that indicates substantial chronic pain rather than acute pain crises, as determined by the investigator's judgement • HbF level >15%, regardless of concomitant treatment • Any history of abnormal transcranial Doppler results in the middle cerebral artery and the internal carotid artery (participants 12–18 years only)[18]

[a] ***HGB-205*** *also allowed the enrollment of participants with severe SCD + cerebral vasculopathy, including those with overt stroke, stenosis or occlusion in the polygon of Willis, abnormal transcranial Doppler results (>170 cm/sec), or Moyamoya disease, contingent upon approval by the surveillance committee.*[39,67] *Notably, no participants meeting this criterion were enrolled in the study.*[64]

Abbreviations: α, alpha; ACS, acute chest syndrome; cm, centimeter; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; g, gram; Hb, hemoglobin; HbF, fetal hemoglobin; HBV, hepatitis B; HCV, hepatitis C; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; kg, kilogram; L, liter; m, meter; mg, milligram; min, minute; mL, milliliter; MRI, magnetic resonance imaging; ng, nanogram; NSAID(s), non-steroidal anti-inflammatory drug(s); SCD, sickle cell disease; sec, second; TDT, transfusion-dependent β-thalassemia; ULN, upper limit of normal; VOCs, vaso-occlusive crises; VOE(s), vaso-occlusive episode(s) or event(s)