This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaid agency and public agency partners.

Gene Therapies for Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia

Systematic Review

November 2022

Table of Contents

About This Research Product

A **Systematic Review** is the most comprehensive evidence synthesis research product Drug Effectives Review Project (DERP) participants can request. The scope of the topic is generally larger (e.g., drug class review) and uses gold-standard evidence synthesis methods. Because of the scope and approach, budget and timeline are generally larger for this research product, relative to others. This product is usually the result of a topic nomination or for a research need identified through surveillance.

Overview of All Research Products Available to DERP

Research Product Type	Scoping	Budget	Synthesis of Findings	RoB and GRADE	About the Product Goal of Product
PICOS and Key Questions	Yes	No	No	No	• Outlines the scope of DERP's research interests • DERP uses this product to determine if they want a Topic Brief
Topic Brief	Yes	Yes	No	No	• Developed from PICOS and Key Questions and identifies eligible studies for the topic and proposes a budget • DERP uses this product to determine if they want to move the topic into the research work plan (e.g., Systematic Review)
Surveillance Report	No	No	No	No	• Identifies studies and FDA actions on existing topics (i.e., those completed in the last 3 years) since the previous research product was completed • DERP uses this product to determine if they want to commission an update or derivate of an existing research product
Individual Topic Request (ITR)	No	No	Yes	Yes	• A brief and succinct research product synthesizing evidence on a narrow, requested topic (e.g., a new, high-cost drug) • DERP uses this product to better understand the evidence for a narrow topic, typically on a quick timeline
Policy Brief	No	No	Yes	No	• A synthesis of management strategies, on things such therapies or payment models, for DERP participants to consider • DERP uses this product to evaluate what is or might be occurring in Medicaid at a programmatic and clinical level
Rapid Review	No	No	Yes	Yes	• An evidence synthesis product that is larger than an ITR, but less comprehensive than a Systematic Review (e.g., shorter search period) • DERP uses this product to better understand the body of evidence on a topic within a quick timeline
Systematic Review	**No**	**No**	**Yes**	**Yes**	• **The most comprehensive evidence synthesis product that uses gold-standard methods of evidence synthesis** • **DERP uses this product to understand the body of evidence for a larger topic, such as a drug class review**

Abbreviations. DERP: Drug Effectiveness Review Project; FDA: US Food and Drug Administration; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; ITR: individual topic request; PICOS: populations, interventions, comparators, outcomes, study designs; RoB: risk of bias.

Executive Summary

Background

Sickle cell disease (SCD) is a serious, inherited, multisystem, and chronic blood disorder caused by a mutation in the hemoglobin beta chain that is responsible for the transport of oxygen throughout the body. Because of this mutation, the red blood cells (RBCs) change their shape, which causes them to stick to the blood vessel walls, ultimately obstructing blood flow. These constricted and narrow blood vessels lead to a wide range of acute and chronic complications targeting nearly every organ in the body, such as vaso-occlusive crisis (VOC), chronic pain, anemia, infection, acute chest syndrome, central nervous system involvement, cardiac involvement, hand-foot syndrome, and vision loss. The available treatment options for SCD mostly target managing the symptoms and disease complications, such as hydroxyurea, which can be an effective treatment to alleviate the complications of SCD. Several other medications, such as L-glutamine oral powder, crizanlizumab, and voxelotor, are also approved by the US Food and Drug Administration (FDA) to reduce SCD complications. Alternatively, there are some curative treatment options available for SCD. One such treatment is allogeneic hematopoietic stem cell transplantation (HSCT), also known as a bone marrow transplant, which is considered a standard therapy. There are also gene therapies currently under investigation for SCD including ARU-1801, CTX001, and lovotibeglogene autotemcel.

Beta thalassemia is a genetic disorder that causes incomplete formation of RBCs, resulting in anemia. Individuals with severe forms of the disease can require regular transfusions of packed RBCs, which can result in iron overload and the need for concomitant iron chelation therapy. Treatment options for transfusion-dependent beta thalassemia (TDT) include splenectomy, HSCT, and FDA-approved drug therapies such as luspatercept. The FDA recently approved the first gene therapy for beta thalassemia in the form of betibeglogene autotemcel in August 2022. CTX001 is another gene therapy currently under investigation for use in TDT.

There are 4 different types of gene therapies available: gene addition, gene editing, gene silencing, and gene correction. ARU-1801 is a gene-addition therapy that uses modified γ-globin to produce fetal hemoglobin G16D (HbF^{G16D}) in transduced hematopoietic stem cells (HSCs). Lovotibeglogene autotemcel and betibeglogene autotemcel are one-time β-globin gene therapies that aim to correct ineffective erythropoiesis using the BB305 lentiviral vector to encode β-globin with a T87Q substitution and produce hemoglobin A T87Q (HbA^{T87Q}) in transduced HSCs. Both products are engineered with the same preparation techniques but carry different names based on the indication, with a prior product development name of lentiglobin. CTX001, also known as CRISPR-Cas9 technology, is used for site-specific genome editing to restore γ-globin synthesis by reducing BCL11A expression, which reactivates the production of fetal hemoglobin. In patients with SCD, the clinical goal is to reduce the production of sickle hemoglobin in order to reduce or eliminate VOCs as well as the associated pain and hospitalizations that occur. In patients with TDT, the clinical goal is to achieve transfusion independence, which also reduces associated complications such as iron overload.

PICOS and Key Questions

This review evaluates eligible randomized controlled trials (RCTs) and uncontrolled trials in individuals with severe SCD or TDT treated with gene therapy. Currently betibeglogene autotemcel is FDA-approved for TDT, while ARU-1801, CTX001, and lovotibeglogene autotemcel are still investigational. For all agents, comparators were another included intervention, standard of care, placebo, or no comparison. Outcomes included relevant clinical assessments for SCD such as veno-occlusive events (VOEs), hemoglobin concentrations, quality of life (QoL), and adverse events (AEs). Outcomes for TDT included transfusion independence, hemoglobin concentrations, QoL, and AEs. The key questions focus on efficacy and safety of these therapies for SCD and TDT and a summary of ongoing studies.

Interventions

Table 1. List of Brand Names and Generics for Sickle Cell Disease and Beta Thalassemia

Generic Name	Brand Name	Intended Population	FDA Approval Date
Betibeglogene autotemcel (beti-cel)	Zentyglo	• TDT	08/17/2022
ARU-1801	NA	• Severe sickle cell disease	No PDUFA date
CTX001 (CRISPR technology)	NA	• TDT • Severe SCD	No PDUFA date
Lovotibeglogene autotemcel (lovo-cel)	NA	• Severe SCD	No PDUFA date

Abbreviations. FDA: US Food and Drug Administration; NA: not applicable; PDUFA: Prescription Drug User Fee Act; SCD: sickle cell disease; TDT: transfusion-dependent beta thalassemia.

Methods

Researchers from the Center for Evidence-based Policy (Center) searched DuckDuckGo and Google Scholar and ran a literature search using Ovid MEDLINE and the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CENTRAL) for any eligible study designs analyzing a listed intervention. Searches for interventions were performed from database inception to July 26, 2022, to capture relevant studies published. We also searched ClinicalTrials.gov, International Clinical Trials Registry Platform (World Health Organization), and ScanMedicine for ongoing studies of listed interventions for SCD and TDT. We selected studies for inclusion if they met our criteria outlined in the PICOS section. Systematic reviews were not included in this report, but the reference lists contained in these reviews were used to identify additional studies. Risk of bias (RoB) assessments were conducted on all eligible studies that were published in full-text articles. We also used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to evaluate the certainty of evidence (CoE) for critical outcomes (i.e., VOEs, hemoglobin concentrations, transfusion independence, AEs) reported in full-text articles and abstracts.

Manufacturer dossiers were requested for all interventions included in the review, and bluebird bio, Inc., provided the Academy of Managed Care Pharmacy (AMCP) product dossier for betibeglogene autotemcel and lovotibeglogene autotemcel. Dossiers were not provided for ARU-1801 and CTX001.

Key Findings

Betibeglogene Autotemcel for Transfusion-Dependent Beta Thalassemia

- We identified 2 non-controlled, open-label studies with 5 total publications for participants with TDT receiving betibeglogene. The primary publications reported results for 45 total participants combined. Additional presentation abstracts provided QoL and long-term follow-up outcomes for participants enrolled in the primary studies. The study was rated as having a *high* RoB.
    - Betibeglogene improved hemoglobin levels from baseline for up to 29.5 months (*very low* CoE, based on 2 non-randomized studies [NRS]).
    - Betibeglogene reduced frequency of transfusions and helped achieve transfusion independence up to 29.5 months (*very low* CoE, based on 2 NRS).
    - A high incidence of AEs occurred with betibeglogene, most often around the time of infusion (*very low* CoE, based on 2 NRS).

ARU-1801 for Sickle Cell Disease

- We identified 1 eligible publication in participants with severe SCD. This was a summary report of early results. RoB as well as GRADE assessments were not performed.
    - 4 total participants were treated with 2 participants having extended follow-up of at least 36 months.
    - The participants with extended follow-up experienced reductions in severe VOEs of 93% and 85% compared to the annualized rate 2 years prior to treatment.
    - All 3 participants with reported results noted increases in fetal hemoglobin expression and reduced sickling hemoglobin.
    - Transient neutropenia and thrombocytopenia were reported, with each lasting a median of 7 days. Additional details and other AEs were not provided.

CTX001 for Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia

- We identified 1 study with 3 total publications in participants with severe SCD or TDT. The primary publication reported results for 1 participant each with SCD and TDT. Two additional presentation abstracts provided outcomes in 7 participants with SCD and 15 participants with TDT. The primary study was rated as having a *high* RoB with the CoE for outcomes rated as *very low*.
    - In the participant with severe SCD, total hemoglobin concentrations increased to a level considered to be just below normal at 15 months, and there were no reports of severe VOEs (*very low* CoE, based on 1 NRS).
    - In the participant with TDT, at 18 months total hemoglobin concentrations increased from baseline, with transfusion independence at month 1 (*very low* CoE, based on 1 NRS).

Lovotibeglogene Autotemcel for Sickle Cell Disease

- We identified 1 non-controlled, open-label study and 1 additional conference abstract for participants with SCD receiving lovotibeglogene. The primary publication reported results for 35 participants for some endpoints. An additional presentation abstract reported QoL and pain intensity data for participants in the primary study, but it only reported select results in a small number of participants. The study was rated as having a *high* RoB.

- Lovotibeglogene improved hemoglobin levels from baseline for up to 17.3 months (*very low* CoE, based on 1 NRS).
- Lovotibeglogene reduced the number of VOEs, including severe VOEs, from baseline for up to 17.3 months (*very low* CoE, based on 1 NRS).
- A high incidence of AEs occurred with lovotibeglogene, most often around the time of infusion (*very low* CoE, based on 1 NRS).

Discussion

Gene therapies for SCD and TDT provide potential curative options for patients with these lifelong diseases that carry significant health care burdens. Initial responses to treatment in both SCD and TDT have been positive, with nearly all individuals receiving therapy reporting positive results. Patients with TDT demonstrate transfusion independence that is sustained over the follow-up periods and SCD patients report fewer to no severe VOEs. The RoB for the studies in this review is *high* due to the lack of control groups. GRADE ratings for CoE are generally *very low* due to the small numbers of participants, *high* RoB, and lack of generalizability.

Risks of gene therapies include pre-treatment myeloablative conditioning, which can expose patients to additional complications such as infertility. Long-term durability of response is a still developing issue, and studies are ongoing up to 2039 to determine if the clinical response is maintained. Currently, long-term follow-up up to 45.6 months for betibeglogene for TDT has reported positive results. Additionally, medians of 8 months of follow-up for CTX001 and 36 months of follow-up for ARU-1801 have shown responses to treatment.

There are QoL outcomes reported in conference abstracts only for patients who received betibeglogene for TDT or lovotibeglogene for SCD in patients from the original studies up to 24 months, all reporting improved QoL. This can likely be attributed to achievement of transfusion independence in the majority of patients with TDT or decrease in number of VOEs and pain scores in patients with SCD. There are high rates of reported AEs in some participants, while other authors have not been as descriptive. For example, 1 participant receiving ARU-1801 reported 114 AEs, although a full description of these has not been published. Currently there is no data reported on QoL outcomes and patient satisfaction for CTX001 and ARU-1801. Information related to reduction in pain medications has also not been reported.

Betibeglogene autotemcel is now FDA approved, and practitioners may soon advocate for this option for their patients. The company is proposing a “pay up front, rebate over time if patients do not achieve therapeutic targets” model. This may present challenges to payers regarding the initial $2.8M proposed cost of therapy as well as associated supportive treatments such as myeloablative conditioning and hospitalization during transfusion. CTX001 and lovotibeglogene autotemcel are both on track for FDA submission in early 2023. ARU-1801 does not yet have a publicly released timeline for FDA submission. Many questions remain around the place in therapy and ability of Medicaid programs to afford broad coverage of these multimillion dollar therapies.

Background

Sickle cell disease (SCD) is a serious, inherited, multisystem, and chronic blood disorder caused by a mutation in the hemoglobin beta chain that is responsible for the transport of oxygen throughout the body.[1] Because of this mutation, the red blood cells (RBCs) change their shape, which causes them to stick to the blood vessel walls, ultimately obstructing blood flow.[1] These constricted and narrow blood vessels lead to a wide range of acute and chronic complications targeting nearly every organ in the body, such as vaso-occlusive crisis (VOC), chronic pain, anemia, infection, acute chest syndrome, central nervous system involvement, cardiac involvement, hand-foot syndrome, and vision loss.[2] Both genetic and nongenetic modifiers, such as air quality, infectious diseases, socioeconomic, climatic, and meteorologic factors, significantly contribute to the clinical variability of this disease.[3] The Centers for Disease Control and Prevention (CDC) estimated that SCD affects around 100,000 people, mostly among individuals who identify as Black or African American, and the economic burden of SCD is estimated at $2.98B per year in the United States.[4,5] People with SCD have 25 years less life expectancy at birth when compared to the general US population.[4]

The available treatment options for SCD mostly target managing the symptoms and disease complications. Hydroxyurea can be an effective treatment to alleviate the complications of SCD.[2] Several other medications, such as L-glutamine oral powder, crizanlizumab, and voxelotor, are also approved by the FDA to reduce SCD complications.[2] In addition, there are also some curative treatment options available for SCD. One such treatment is allogeneic hematopoietic stem cell transplantation (HSCT), also known as a bone marrow transplant, which is considered a standard treatment and has an outstanding 5-year overall survival rate of 93% for people with SCD.[6] Although it has a high success rate, there are considerable risks, such as finding a matching sibling or other donor, a lower survival rate for patients transplanted at 16 years or older, and patients having a higher probability of graft versus host disease (GVHD), which subsequently prompted the researchers to look for alternative treatment options.[6] Gene therapies to treat SCD are in development and offer certain advantages over HSCT, specifically avoiding the risk of GVHD because people with SCD provide the genetically modified therapeutic cells instead of a matching sibling or other matching donor.[7]

Beta thalassemia is also an inherited blood disorder where the body does not make β-hemoglobin (β+) or β-globin (β°) is absent, resulting in less production of healthy RBCs.[8] Based on the severity of phenotype, beta thalassemia can be labeled as transfusion dependent (TDT) or transfusion nondependent.[9] In general, a complete blood count is required to diagnose beta thalassemia.[10] Although it is most prevalent in Southeast Asia and the Mediterranean basin, beta thalassemia is becoming more common in the United States, with an estimated 7.5% increase over the last 50 years.[11] Migration was considered as an important factor for this higher trend in beta thalassemia prevalence.[12] Regular blood transfusions are an available treatment option, but organ damage from iron overload makes alternative therapies like luspatercept or splenectomy more desirable.[8] Similar to SCD, another standard treatment option is allogeneic HSCT. However, donor matching, reduced survival rate for adults, and risk of GVHD still exists when HSCT is used among people with beta thalassemia, which also makes gene therapies in this space an attractive option.[8]

SCD and beta thalassemia are related to hemoglobin protein, and gene therapies can directly address the inherent genetic cause and give a definitive cure.[13] There are 4 different types of gene therapies available: gene addition, gene editing, gene silencing, and gene correction.[14] ARU-1801 is a gene-addition therapy that uses modified γ-globin to produce fetal hemoglobin G16D (HbF^{G16D}) in transduced hematopoietic stem cells (HSC).[15] Because of the higher potency of this modified γ-globin, a lower dose of ARU-1801 is adequate to treat people with SCD and beta thalassemia.[16] Lovotibeglogene autotemcel and betibeglogene autotemcel are one-time β-globin gene therapies that aim to correct ineffective erythropoiesis using the BB305 lentiviral vector to encode β-globin with a T87Q substitution and produce hemoglobin A T87Q (HbA^{T87Q}) in transduced HSC.[17,18] Both products are engineered with the same preparation techniques but carry different names based on the indication, with a prior product development name of lentiglobin. CTX001, also known as CRISPR-Cas9 technology, is used for site-specific genome editing to restore γ-globin synthesis by reducing BCL11A expression, which reactivates the production of fetal hemoglobin.[19] In patients with SCD, the clinical goal is to reduce the production of sickle hemoglobin in order to reduce or eliminate VOCs as well as the associated pain and hospitalizations that occur. In patients with TDT, the clinical goal is to reduce blood transfusion burden and ultimately achieve transfusion independence, which also reduces associated complications such as iron overload. The FDA approved the gene therapy in the form of betibeglogene autotemcel for TDT in August 2022 with a manufacturer-proposed cost of $2.8M per treatment.

PICOS

Populations

- Individuals with severe SCD
- Individuals with TDT

Interventions

Table 1. List of Brand Names and Generics for Sickle Cell Disease and Beta Thalassemia

Generic Name	Brand Name	Intended Population	FDA Approval Date
Betibeglogene autotemcel (beti-cel)	Zentyglo	• TDT	08/17/2022
ARU-1801	NA	• Severe SCD	No PDUFA date
CTX001 (CRISPR technology)	NA	• TDT • Severe SCD	No PDUFA date
Lovotibeglogene autotemcel (lovo-cel)	NA	• Severe SCD	No PDUFA date

Abbreviations. FDA: US Food and Drug Administration; NA: not applicable; PDUFA: Prescription Drug User Fee Act; SCD: sickle cell disease; TDT: transfusion-dependent beta thalassemia.

Comparators

- Another listed intervention (head-to-head comparison)
- Standard of care

- Placebo
- No comparison (single-arm trial)

Outcomes

Sickle Cell Disease

- Hemoglobin levels
- Veno-occlusive events (VOEs)
- Markers of hemolysis (e.g., bilirubin levels)
- Pain
- Quality of life (QoL)
- Mortality
- Overall adverse events (AEs)
- Specific AEs (e.g., hepatotoxicity)
- Serious adverse events (SAEs; e.g., mortality)

Beta Thalassemia

- Hemoglobin levels
- Frequency of transfusions
- Fatigue
- QoL
- Mortality
- Overall AEs (e.g., muscle pain, joint pain)
- Specific AEs (e.g., hyperuricemia)
- SAEs (e.g., mortality)

Study Designs

- RCTs
- Uncontrolled interventional trial (single-arm trial)

Key Questions

KQ1. What is the effectiveness of gene therapies for SCD?

KQ2. What are the harms of gene therapies for SCD?

KQ3. What is the effectiveness of gene therapies for beta thalassemia?

KQ4. What are the harms of gene therapies for beta thalassemia?

KQ5. What are the characteristics of ongoing studies of gene therapies for SCD and beta thalassemia?

Methods

Researchers from the Center for Evidence-based Policy (Center) searched DuckDuckGo and Google Scholar and ran a literature search using Ovid MEDLINE and the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CENTRAL) for any eligible study designs analyzing a listed intervention. Searches for interventions were performed from database inception to July 26, 2022, to capture relevant studies published. We also

searched ClinicalTrials.gov, International Clinical Trials Registry Platform (World Health Organization), and ScanMedicine for ongoing studies of listed interventions for SCD and TDT.

Manufacturer dossiers were requested for all interventions included in the review, and bluebird bio, Inc., provided the Academy of Managed Care Pharmacy (AMCP) product dossier for betibeglogene autotemcel and lovotibeglogene autotemcel. Dossiers were not provided for ARU-1801 and CTX001.

Two independent researchers conducted risk-of-bias (RoB) assessments for the published studies; conflicts were handled through discussion. We did not assess the RoB for conference abstracts because of the very limited data reported in these publications. We performed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach on select outcomes: hemoglobin expression and concentrations, transfusion independence, VOEs, and QoL. Two independent researchers assigned certainty-of-evidence (CoE) ratings from *very low* to *high*; conflicts were handled through discussion.

Only RCTs or single-arm interventional studies that evaluated a listed intervention were included. Additional eligibility criteria were studies on human participants and publication in English. A full description of our methods can be found in Appendix A.

Findings

Figure 1 shows the literature flow through the review and the associated preferred reporting items for systematics reviews and meta-analyses (PRISMA) characteristics.

Figure 1. PRISMA Diagram

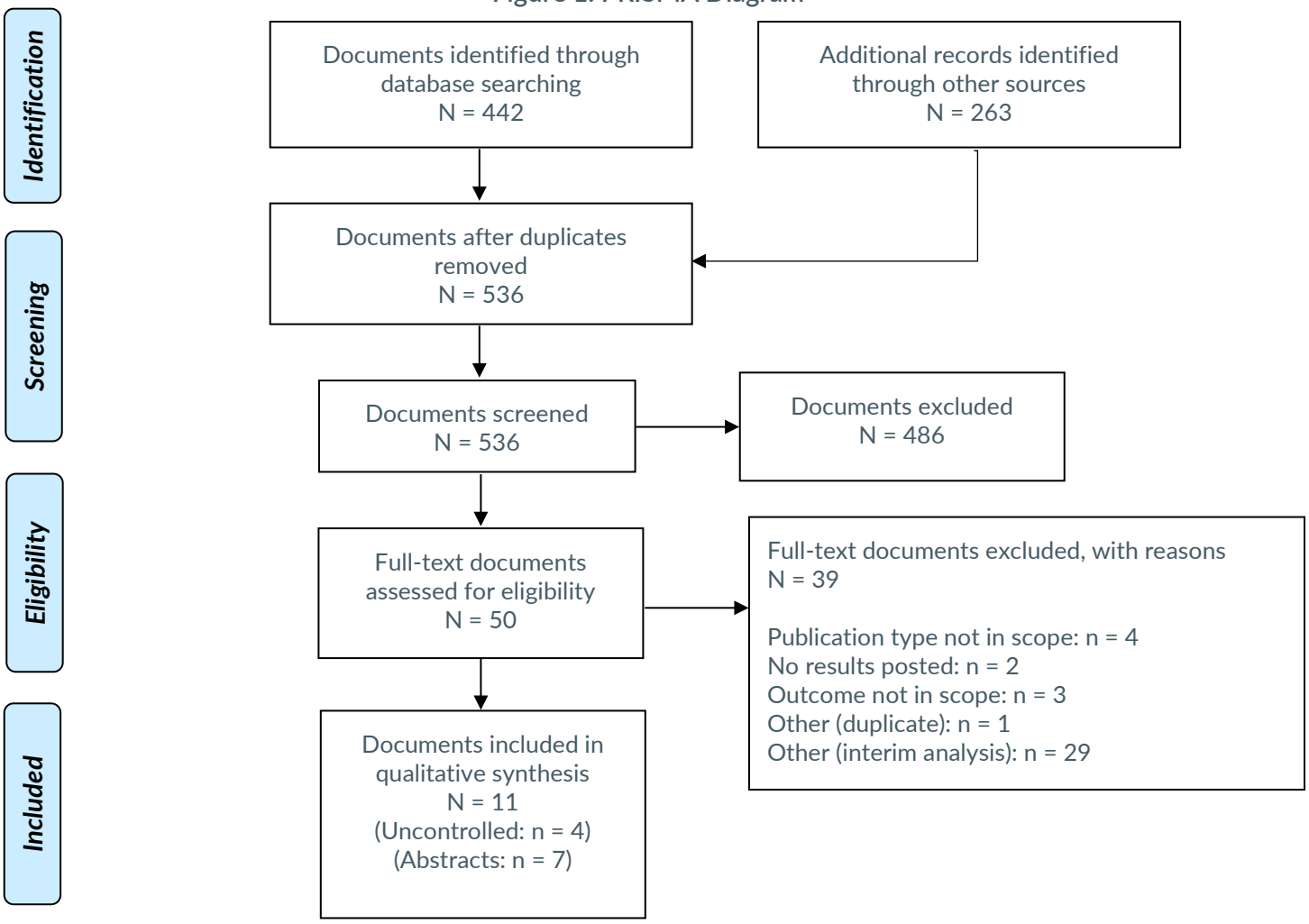

Table 2 provides a summary of findings and GRADE ratings for relevant clinical outcomes for the interventions listed in this review.

Table 2. Summary of Findings (GRADE)

Outcome Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Betibeglogene for Transfusion-Dependent Beta Thalassemia			
Hemoglobin levels 2 NRS[18,20] N = 45	●○○○ Very Low	Betibeglogene improved hemoglobin levels for up to 29.5 months	Downgraded 1 level each for RoB, imprecision, and indirectness

Outcome Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Transfusion independence 2 NRS[18,20] N = 45	●○○○ Very Low	Betibeglogene reduced frequency of transfusions and helped achieve transfusion independence up to 29.5 months	Downgraded 1 level each for RoB, imprecision, and indirectness
Overall AEs 2 NRS[18,20] N = 45	●○○○ Very Low	High incidence of AEs occurred around the time of infusion	Downgraded 1 level each for RoB, imprecision, and imprecision
CTX001 for Sickle Cell Disease			
Hemoglobin levels 1 NRS[21] N = 1	●○○○ Very low	Total hemoglobin improved from a low of 7.2 g/dL at baseline to just slightly below normal at 12 g/dL at month 15	Downgraded 1 level each for RoB, imprecision, and indirectness
VOEs 1 NRS[21] N = 1	●○○○ Very low	No VOEs reported in 16.6 months of follow-up	Downgraded 1 level each for RoB, imprecision, and indirectness
Overall AEs 1 NRS[21] N = 1	Not reported in detail		
CTX001 for Transfusion-Dependent Beta Thalassemia			
Fetal hemoglobin expression 1 NRS[21] N = 1	●○○○ Very low	At 18 months, CTX001 improved fetal hemoglobin expression from baseline	Downgraded 1 level each for RoB, imprecision, and indirectness
Transfusion independence 1 NRS[21] N = 1	●○○○ Very low	Transfusion independence reported by 1 month after infusion and through follow-up of 21.5 months	Downgraded 1 level each for RoB, imprecision, and indirectness
Overall AEs 1 NRS[21] N = 1	Not reported in detail		

Outcome Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Lovotibeglogene for Sickle Cell Disease			
Hemoglobin levels 1 NRS[22] N = 35	●○○○ Very Low	Lovotibeglogene improved hemoglobin levels from baseline up to 17.3 months	Downgraded 1 level each for RoB, imprecision, and indirectness
VOEs 1 NRS[22] N = 35	●○○○ Very Low	Lovotibeglogene reduced number of VOEs and severe VOEs experienced from baseline up to 17.3 months	Downgraded 1 level each for RoB, imprecision, and indirectness
Overall AEs 1 NRS[22] N = 35	●○○○ Very Low	High incidence of AEs occurred around the time of infusion	Downgraded 1 level each for RoB, imprecision, and imprecision

Abbreviations. AE: adverse event; CoE: certainty of evidence; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; NRS: non-randomized study; RoB: risk of bias; VOE: veno-occlusive event.

Betibeglogene Autotemcel (beti-cel) for Transfusion-Dependent Beta Thalassemia

Study Characteristics

We identified 2 eligible publications reporting results for 3 non-randomized, single-arm studies evaluating betibeglogene in TDT.[18,20] Furthermore, we identified 3 relevant conference abstracts reporting results in this patient population.[23-25] These publications document both efficacy and safety of betibeglogene. We rated the non-randomized studies (NRS) as having a *high* RoB given that studies did not include a control group. GRADE ratings for relevant outcomes were *very low* and are summarized in Table 2. Table 3 provides an overview of study characteristics for betibeglogene in TDT. Additional efficacy and harm outcomes are provided in Appendix B.

Table 3. Study Characteristics for Betibeglogene for Transfusion-Dependent Beta Thalassemia

Author, Year Trial Number Trial Name Risk of Bias	Participants	Treatment Protocol	Study Design	Follow-up
Thompson et al., 2018[20] HGB-204 NCT01745120 HGB-205 NCT02151526 NORTHSTAR High	N = 22 n = 18, HGB-204 n = 4, HGB-205	Single infusion of autologous hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, open label, phase 1/2 study	26 months

Author, Year Trial Number Trial Name Risk of Bias	Participants	Treatment Protocol	Study Design	Follow-up
Locatelli et al., 2022[18] HGB-207 NCT02906202 NORTHSTAR-2 High	N = 23	Single infusion of autologous CD34+ hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector Target Dose: at least 5.0 million CD34+ cells per kilogram of body weight	Single-arm, open label, phase 3 study	29.5 months
Kwiatkowski et al., 2021[23] Kulozik et al., 2021[25] HGB-207 NCT02906202 NORTHSTAR-2 HGB-212 NCT0320700 NORTHSTAR-3 Not performed (conference abstract)	N = 30	Single infusion of autologous hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, open label, phase 3 studies	24 months
Yannaki et al., 2021[24] LTF-303 NCT02633943 Not performed (conference abstract)	N = 44	Single infusion of autologous hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, open label, long-term follow-up study	45.6 months

Efficacy Outcomes

Thompson and colleagues reported outcomes for 22 total participants receiving a single infusion of betibeglogene in the NORTHSTAR (HGB-204) and HGB-205 studies, with a median follow-up of 26 months.[20] Twelve of 13 (92%) nonhomozygous β^0/β^0 participants achieved transfusion independence, and 3 of 9 (33%) homozygous β^0/β^0 genotype participants reported transfusion independence at follow-up.[20] The median total hemoglobin level for participants at the last study was 11.2 g/dL with a median level of 6.0 g/dL Hb^{T87Q}; however, baseline levels were not reported for comparison.[20] In patients who did not achieve transfusion independence, all were receiving a lower number of transfusions and a lower total annual RBC volume at follow-up.[20]

Locatelli and colleagues reported outcomes for 23 total participants who received betibeglogene in the NORTHSTAR 2 (HGB-207) study, with a median follow-up of 29.5 months.[18] At baseline,

patients required a median of 16 RBC transfusions per year prior to treatment. A total of 20 of 22 (91%) participants who could be evaluated for the primary endpoint achieved transfusion independence.[18] Of the 2 participants who did not achieve transfusion independence, both experienced a relative reduction in transfusion volume (67.4% and 22.7%).[18] The authors also reported transfusion independence by age category.[18] A total of 14 of 15 (93%) participants who were 12 to 50 years of age, as well as 6 of 7 (86%) participants younger than 12 years of age, achieved transfusion independence.[18] The average hemoglobin level during transfusion independence was 11.7 g/dL, which had improved from 9.6 g/dL at baseline.[18] At 12 months, the median HbA^{T87Q} level in these participants was 8.7 g/dL, and the median endogenous hemoglobin level was 3.0 g/dL.[18]

Kwiatkowski and colleagues reported health-related quality of life (HRQoL) outcomes via multiple assessment scales over a 24-month period for pediatric, adolescent, and adult participants enrolled in either the NORTHSTAR 2 (HGB-207) or NORTHSTAR 3 (HGB-212) studies.[23] Among pediatric and adolescent participants with Pediatric Quality of Life Inventory (PedsQL) data who achieved transfusion independence (n = 18), the mean (SE) PedsQL total score increased from 77.4 (3.6) at baseline to 85.3 (2.0) at month 12 and to 87.1 (1.8) at month 24.[23] Among adolescent participants with EuroQoL visual analog scale (EQ-5D-Y VAS) results who achieved transfusion independence (n = 12), the mean (SD) EQ-5D-Y VAS score increased from 81.4 (19.2) at baseline to 91.6 (4.9) at month 12 and to 92.4 (6.0) at month 24.[23] Adult participants also completed the 36-item Short Form Health Survey (SF-36), which is a widely used generic quality of life assessment tool. From the SF-36 scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were calculated. Baseline PCS and MCS scores increased from 53.8 (1.4) and 51.0 (1.7), respectively, to 55.4 (1.2) and 52.7 (2.0) at month 12 and 55.7 (1.4) and 53.4 (2.3) at month 24.[23] Participants were noted to have relatively high HRQoL scores prior to transplant and maintained or even improved those scores after treatment.

In the long-term follow-up of combined NORTHSTAR studies (phase 1/2 studies: HGB-204, HGB-205; phase 3 studies: HGB-207, HGB-212) presented by Yannaki and colleagues, at a median of 45.6 months, transfusion independence was maintained in 15 of 22 (68%) participants from phase 1/2 studies and 20 of 22 (91%) participants from phase 3 studies.[24] During transfusion independence, weighted average hemoglobin was 10.3 and 11.8 g/dL in participants from phase 1/2 studies and phase 3 studies, respectively.[24]

Kulozik and colleagues reported outcomes for pediatric participants participating in the NORTHSTAR-2 (HGB-207) and NORTHSTAR-3 (HGB-212) studies.[25] Transfusion independence was achieved in 9 of 11 (82%) participants younger than 12 years old and 10 of 10 (100%) participants between 12 and 18 years old.[25] Median duration of ongoing transfusion independence at the time of the report was 19.5 months.[25] Weighted average hemoglobin during transfusion in participants aged younger than 12 and 12 to 18 was 10.0 g/dL and 11.5 g/dL, respectively.[25]

The first real-world experience for use of betibeglogene outside of a clinical trial in 2 patients was reported by Kunz and colleagues.[26] Both patients were diagnosed with TDT at age 2 and began blood transfusion therapy. One patient received betibeglogene at age 14 (P1) and

1 patient received it at age 28 (P2). At 6 months follow-up, P1 remained transfusion independent with a hemoglobin level of 12.9 g/dL from a hemoglobin of 11.0 g/dL prior to betibeglogene. At 1 month follow-up, P2 has also remained transfusion independent with a hemoglobin level of 10.5 g/dL from a baseline of 9.2 g/dL.[26]

Harm Outcomes

SAEs reported in the NORTHSTAR study, with 22 participants, included 2 occurrences of veno-occlusive liver disease, 1 occurrence of cellulitis, and 2 reports of thrombosis.[20] No SAEs were considered related to the intervention.[20] Other AEs included stomatitis, febrile neutropenia, and pharyngeal inflammation, which all resolved early in the course of beti-cel therapy.[20] No deaths were reported through 24 months of follow-up; however, this data was not reported in the primary publication but on ClinicalTrials.gov.[27,28]

Of the 23 patients in the NORTHSTAR 2 study, all participants experienced at least 1 AE.[18] The most common AEs were thrombocytopenia, neutropenia, anemia, stomatitis, and leukopenia, which occurred in more than 50% of participants.[18] SAEs reported included 3 occurrences of veno-occlusive liver disease, 2 reports of thrombocytopenia, and 1 report of pyrexia.[18] No deaths were reported at the time of publication.[18]

In the ongoing LTF-303 study of 13 patients, no drug product–related AEs have been reported more than 2 years after betibeglogene infusion.[24] SAEs occurring after 2 years of follow-up included gonadotropic insufficiency, ectopic pregnancy, fetal death, gallbladder wall thickening/polyp, bacteremia with neutropenia, and major depression (n = 1 for all occurrences).[24] No deaths have been reported as of the most recent report. Additional information on harm outcomes is provided in Appendix B (Table B3).

In the report of pediatric participants by Kulozik and colleagues, grade 3 or higher AEs were reported as follows[25]:

- Stomatitis (n = 14)
- Febrile neutropenia (n = 13)
- Epistaxis (n = 6)
- Decreased appetite (n = 5)
- Increased alanine aminotransferase (n = 3)
- Hypoxia (n = 3)
- Pyrexia (n = 3)

Three incidences of veno-occlusive liver disease were reported (n = 2, grade 4; n = 1, grade 2).[25] Drug-related AEs were reported in 2 participants younger than 12 years old (thrombocytopenia and tachycardia) and in 2 participants between 12 and 18 years old (abdominal pain).[25]

Kunz and colleagues reported AEs for 2 patients treated in a real-world setting.[26] After betibeglogene, 1 patient experienced febrile neutropenia, elevated C-reactive protein, pruritus, gingivitis, mild mucositis, and vertigo.[26] The patient also experienced transient subjective hearing loss at day 23 and 26, which quickly resolved.[26] The second patient experienced febrile neutropenia and grade 3 mucositis.[26] No hepatic veno-occlusive disease events occurred in either patient.[26]

ARU-1801 for Sickle Cell Disease

Study Characteristics

We identified 1 eligible publication for ARU-1801 in severe SCD.[15] This was a summary report of early results presented to the American Society of Hematology in 2021.[15] In this report, 4 participants were treated with ARU-1801, with 3 of those participants having at least 12 months of follow-up post-transplant.[15] All participants received a pre-transplant conditioning regimen consisting of melphalan 140 mg/m^2.[15] Table 4 provides an overview of notable study characteristics.

Table 4. Study Characteristics for ARU-1801

Author, Year Trial Number Trial Name Risk of Bias	Participants	Treatment Protocol	Study Design	Follow-up
Grimley et al., 2021[15] NCT02186418 Not performed (conference abstract)	N = 4	Single infusion of autologous CD34+ hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, phase 1/2 study	15 to 36 months

Efficacy Outcomes

Grimley and colleagues reported interim results for 3 participants, with 2 of the participants having 36 months of follow-up and 1 participant having 15 months of follow-up.[15] The participants with extended follow-up (36 months) experienced reductions in severe VOEs of 93% and 85% compared with the 2 years prior to receiving therapy; however, no details on the baseline frequency of severe VOEs were reported.[15] The participant with 15 months of follow-up had not experienced any severe VOEs since transplantation; again, no baseline data were reported.[15] The authors reported that all 3 participants demonstrated increases in fetal hemoglobin expression, which reduces sickling hemoglobin; however, baseline data were not reported.[15]

Harm Outcomes

In the 3 participants treated with ARU-1801, 1 case each of transient neutropenia and thromobocytopenia were reported with each lasting a median of 7 days.[15] How many participants experienced these as well as any need for additional support for these events were not reported. No other SAEs were reported with treatment.

CTX001 for Transfusion-Dependent Beta Thalassemia and Sickle Cell Disease

Study Characteristics

We identified 1 published study with interim results for 2 participants, 1 each with TDT and SCD.[21] Additional abstracts of updated results were presented at the European Hematology Association virtual conference in June 2021 and included in this review.[29,30] Median follow-up was 8.7 months for participants with TDT and 7.6 months for participants with SCD. The results reported by Frangoul and colleagues was rated as having a *high* RoB and GRADE ratings of *very*

low due to the small numbers of participants with reported results. Table 5 provides an overview of notable study characteristics for CTX001.

Table 5. Study Characteristics for CTX001

Author, Year Trial Number Trial Name Risk of Bias	Participants	Treatment Protocol	Study Design	Follow-up
Frangoul et al., 2021[21] Locatelli et al., 2021[30] Grupp et al., 2021[29] NCT03655678 NCT03745287 CLIMB-THAL-111 CLIMB-SCD-121 High	SCD: n = 7 TDT: n = 15 N = 22	Pre-transplant myeloablative conditioning with busulfan Single infusion of autologous CD34+ hHSPCs modified with CRISPR-Cas9 at the erythroid lineage-specific enhancer of the BCL11A gene	Single-arm, phase 2/3 study	7.6 to 21.5 months

Abbreviations. SCD: sickle cell disease; TDT: transfusion-dependent beta thalassemia.

Efficacy Outcomes

Frangoul and colleagues reported outcomes for 2 participants receiving CTX001 gene therapy, 1 each with SCD and TDT.[21] The participant with SCD reported an increase in total hemoglobin concentrations from well below normal of 7.2 g/dL at baseline to just slightly below the normal range of 12.0 g/dL at month 15.[21] Percentages of fetal hemoglobin to sickle hemoglobin ratio improved from 9.1% to 74.1% at baseline to 43.2% to 52.3% at month 15.[21] Fetal hemoglobin is more resistant to sickling therefore increasing it results in fewer VOEs. No VOEs were reported in the participant with SCD, while transfusion independence was achieved by day 30 in the participant with TDT.[21]

Locatelli and colleagues reported additional interim outcomes in 15 participants with TDT with a median of 8.7 months of follow-up.[30] In these participants total hemoglobin improved to a mean of 14.7 g/dL at follow-up with all participants reporting transfusion independence by month 2.[30]

Grupp and colleagues reported interim outcomes in 7 participants with severe SCD with a median of 7.6 months of follow-up.[29] These participants experienced an increase in total hemoglobin to 12.0 g/dL at last report with no participants reporting severe VOEs after infusion.[29]

Harm Outcomes

Harm outcome reporting by Frangoul and colleagues, Locatelli and colleagues, and Grupp and colleagues was limited.[21,29,30] Frangoul and colleagues noted that the participant with TDT experienced 32 total AEs with only pneumonia and veno-occlusive liver disease listed.[21] The participant with SCD experienced 114 AEs with sepsis secondary to neutropenia, cholethiasis, and abdominal pain listed.[21] Locatelli and colleagues reported 1 participant experienced SAEs, while Grupp and colleagues reported no SAEs or additional AEs were observed.[29,30]

Lovotibeglogene Autotemcel (lovo-cel) for Sickle Cell Disease

Study Characteristics

We identified 1 eligible publication reporting results for a non-randomized, single-arm study evaluating lovotibeglogene in severe SCD with an additional 1 relevant conference abstract reporting results in this patient population.[22,31] These publications document both efficacy and safety of lovotibeglogene. We rated the NRS as having a *high* RoB given that it did not include a control group. GRADE ratings for relevant outcomes were *very low* and are summarized in Table 2. Table 6 provides an overview of study characteristics for lovotibeglogene in SCD.

Table 6. Study Characteristics for Lovotibeglogene for Severe Sickle Cell Disease

Author, Year Trial Number Trial Name Risk of Bias	Participants	Treatment protocol	Study Design	Follow-up
Kanter et al., 2022[22] HGB-206 NCT02140554 High	N = 35	Single infusion of autologous hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, open label, phase 1/2 study	17.3 months
Walters et al., 2021[31] HGB-206 NCT02140554 Not performed (conference abstract)	N = 25	Single infusion of autologous hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, open label, phase 1/2 study	24 months

Efficacy Outcomes

Kanter and colleagues reported outcomes for 35 total participants treated with lovotibeglogene for severe SCD with a median follow-up of 17.3 months.[22] The primary efficacy outcome was complete resolution of severe VOEs, assessed in 25 participants who had previously had 4 or more severe VOEs in the 24 months prior to enrollment.[22] No severe VOEs were reported in this group from 6 months to 18 months after lovotibeglogene infusion.[22] Overall VOEs occurred in 3 participants after lovotibeglogene infusion, and 2 had VOEs between infusion and last visit.[22] Other efficacy outcomes reported included hemoglobin levels and markers of hemolysis.[22] The median total hemoglobin increased from 8.5 g/dL to greater than or equal to 11.0 g/dL at 6 months.[22] This was sustained through 36 months.[22] Markers of hemolysis were also reported. Lactate dehydrogenase and indirect bilirubin levels were similar to normal levels from 6 months post-infusion through the last visit.[22] Starting at 6 months, reticulocyte counts were lower than at baseline but higher than reference range levels.[22] Haptoglobin levels were reported to be at least 0.1 g/L in all participants in the transplant population.[22]

Walters and colleagues reported QoL outcomes via the Patient-Reported Outcomes Measurement Information System (PROMIS)-57, a QoL monitoring tool validated in SCD, for participants enrolled in HGB-206.[31] Data was reported for 25 participants for up to 24 months.[31]

In participants with baseline "worse" scores than the United States population norm, improvements were reported in all domains at month 6 after infusion through month 24, though overall total scores were not reported in the abstract.[31] Notably, the authors did report a decrease from baseline of 64.2 to 44.5 in mean pain interference, pain intensity decreased from 6.5 to 1.8 (on the 0–10 Pain Intensity numeric rating scale), and fatigue decreased from 64.6 to 46.9.[31] Scores remained stable through month 24 in participants with baseline "better or near" scores than the US population norm.[31] Anxiety was the only domain of the PROMIS-57 tool that did not demonstrate meaningful change from baseline.[31]

A long-term observational follow-up (LTF-307) evaluating lovotibeglogene in SCD is ongoing.[32] To date, 1 of 3 participants evaluated has experienced a VOE, 30 months after receiving lovotibeglogene.[32] The other 2 participants have not experienced a VOE at 5.1 and 3.3 years up to the latest data cutoff date.[32]

Harm Outcomes

SAEs reported in HGB-206 included 2 occurrences each of abdominal pain, opioid withdrawal syndrome, nausea, and vomiting. Furthermore, 16 other unique SAEs occurred once during the study.[22] Other common AEs that occurred in more than 50% of the study population included stomatitis, thrombocytopenia, and neutropenia with no occurrences of veno-occlusive liver disease.[22] One death occurred 20 months after lovotibeglogene infusion.[22] An investigator determined the death to be due to cardiac fibrosis and other chronic cardiopulmonary organ injury due to patient history and autopsy.[22] Additional harm outcomes are reported in Appendix B.

In the ongoing LTF-307 study, 2 participants have reported SAEs, including increased hepatic enzymes, sickle cell anemia with crisis, acute coronary syndrome, back pain, arthralgia, patellofemoral pain syndrome, procedural pain, cholestasis, presyncope, and influenza.[32]

The FDA previously halted studies for lovotibeglogene due to 1 participant developing acute myeloid leukemia and another myelodysplastic syndrome. Both of these participants were enrolled in studies evaluating SCD. Studies were resumed in early June 2021 after the events were determined not to be related to lovotibeglogene.

Ongoing Studies

We identified a total of 14 ongoing studies eligible for this topic, which include the following:

- 4 studies with betibeglogene autotemcel in TDT[33-36]
- 1 study with ARU-1801 in SCD[37]
- 2 studies with CTX001 in SCD[38,39]
- 2 studies with CTX001 in TDT[40,41]
- 2 studies with CTX in both SCD and TDT[42,43]
- 3 studies with lovotibeglogene autotemcel in SCD[44-46]

Study sizes range from 7 to 114 participants, with many of the studies noted as long term follow-ups to previous trials. All of the studies are single-arm or observational, with long-term follow-up scheduled to continue until 2039 for CTX001. Table 7 provides a summary of ongoing studies.

Table 7. Summary of Ongoing Studies

NCT Number Title Study Name (If Available)	Intervention and Comparator Condition or Disease Study Design	Estimated Completion Date Enrollment	Outcomes
Betibeglogene Autotemcel for Transfusion-Dependent Beta Thalassemia			
NCT02906202[33] A study evaluating the efficacy and safety of the lentiglobin-BB305 drug product in subjects with transfusion-dependent β-thalassemia who do not have a β^0/β^0 genotype NORTHSTAR 2[a]	Betibeglogene Beta thalassemia Non-randomized	March 2022 N = 23	• Transfusion independence • Transfusion reduction • Successful engraftment • AEs • Detection of vector-derived replication competent lentivirus
NCT03207009[34] A study evaluating the efficacy and safety of the lentiGlobin-BB305 drug product in subjects with transfusion-dependent β-thalassemia NORTHSTAR 3[a]	Betibeglogene Beta thalassemia Non-randomized	November 2022 N = 18	• Transfusion independence • Transfusion reduction • Successful engraftment • AEs • Detection of vector-derived replication competent lentivirus
NCT01639690[35] β-thalassemia major with autologous CD34+ hematopoietic progenitor cells transduced with TNS9.3.55: a lentiviral vector encoding the normal human β-globin gene	Betibeglogene Beta thalassemia Non-randomized	July 2023 N = 10	• Occurrence of oncogenesis • Detection of vector-derived replication competent lentivirus • Level of engraftment • Transfusion reduction
NCT02633943[36] Long-term follow-up of subjects with hemoglobinopathies treated with ex vivo gene therapy LTF-303[a]	Betibeglogene Beta thalassemia SCD Observational	March 2031 N = 94	• Overall survival • AEs • Change in hemoglobin • Change in transfusion burden • Iron content of liver and heart
ARU-1801 for Sickle Cell Disease			
NCT02186418[37] Gene transfer for patients with SCD	ARU-1801 SCD Non-randomized	June 2035 N = 7	• AEs • SAEs • Quantity of hemoglobin subtypes • Change in proportion of anti-sickling/sickling hemoglobin

NCT Number Title Study Name (If Available)	Intervention and Comparator Condition or Disease Study Design	Estimated Completion Date Enrollment	Outcomes
CTX001 for Transfusion-Dependent Beta Thalassemia and Sickle Cell Disease			
NCT03655678[40] A phase 1/2/3 study of the safety and efficacy of a single dose of autologous CRISPR-Cas9 modified CD34+ human hematopoietic stem and progenitor cells (hHSPCs) in subjects with TDT CLIMB THAL-111[a]	CTX001 Beta thalassemia Non-randomized	August 2024 N = 45	• Transfusion independence for at 12 months • AEs • SAEs • Time to engraftment • HRQoL • Changes in liver and cardiac iron concentrations
NCT03745287[38] A phase 1/2/3 study to evaluate the safety and efficacy of a single dose of autologous CRISPR-Cas9 modified CD34+ human hematopoietic stem and progenitor cells (CTX001) in subjects with severe SCD CLIMB SCD-121[a]	CTX001 SCD Non-randomized	October 2024 N = 45	• No VOCs for at least 12 months • AEs • SAEs • Time to engraftment • Reduction in hospitalizations due to VOCs • Sustained HbF response
NCT05477563[42] Evaluation of efficacy and safety of a single dose of CTX001 in participants with TDT and severe SCD	CTX001 Beta thalassemia SCD Non-randomized	February 2025 N = 12	• AEs • SAEs • Time to engraftment • Hemoglobin changes over time • Transfusion independence (TDT) • Reduction in VOCs (SCD)
NCT05329649[39] A phase 3 study to evaluate the safety and efficacy of a single dose of CTX001 in pediatric subjects with severe SCD	CTX001 SCD Non-randomized	May 2026 N = 12	• No VOCs for at least 12 months • AEs • SAEs • Time to engraftment • Reduction in hospitalizations due to VOCs • Sustained HbF response

NCT Number Title Study Name (If Available)	Intervention and Comparator Condition or Disease Study Design	Estimated Completion Date Enrollment	Outcomes
NCT05356195[41] A phase 3 study to evaluate the safety and efficacy of a single dose of CTX001 in pediatric subjects with TDT	CTX001 Beta thalassemia Non-randomized	May 2026 N = 12	• Transfusion independence for at 12 months • AEs • SAEs • Time to engraftment • HRQoL • Change in annualized volume of RBC transfusions
NCT04208529[43] A long-term follow-up study of subjects with β-thalassemia or SCD treated with autologous CRISPR-Cas9 modified hematopoietic stem cells (CTX001)	CTX001 Beta thalassemia SCD Observational	September 2039 N = 114	• New malignancies • AEs • SAEs • Hemoglobin changes over time • Transfusion independence (TDT) • Reduction in VOCs (SCD)
Lovotibeglogene Autotemcel for Sickle Cell Disease			
NCT02140554[44] 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 SCD[a]	Lovotibeglogene SCD Non-randomized	February 2024 N = 50	• Resolution of VOEs between 6 and 18 months • HgB response • Annualized VOEs/VOCs • Frequency of transfusions • AEs • SAEs
NCT04293185[45] 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 SCD	Lovotibeglogene SCD Non-randomized	September 2025 N = 35	• Resolution of VOEs between 6 and 18 months • Hb response • Annualized VOEs/VOCs • Frequency of transfusions • AEs • SAEs
NCT04628585[46] Long-term follow-up of subjects with SCD treated with ex vivo gene therapy using autologous hematopoietic stem cells transduced with a lentiviral vector LTF-307	Lovotibeglogene SCD Observational	January 2038 N = 85	• Immune-related AEs • Malignancies • Resolution of VOEs • Annualized number of VOEs • Hb response

Note. [a] *Interim results of ongoing study presented in the respective Findings section of this report.*
Abbreviations. AE: adverse events; Hb: hemoglobin; HbB: hemoglobin B; HbF: hemoglobin F; HRQoL: health-related quality of life; RBC: red blood cell; SAE: serious adverse event; SCD: sickle cell disease; TDT: transfusion-dependent beta thalassemia; VOC: veno-occlusive crisis; VOE: veno-occlusive event.

Discussion

Gene therapies for SCD and TDT provide potential curative options for patients with these lifelong diseases that carry significant health care burdens. Initial responses to treatment in both SCD and TDT have been positive, with nearly all individuals receiving therapy reporting positive results. Patients with TDT demonstrate transfusion independence that is sustained over the follow-up periods, and SCD patients report fewer to no severe VOEs. The RoB for the studies in this review is *high* due to the lack of control groups. GRADE ratings for CoE are generally *very low* due to the small numbers of participants, *high* RoB, and lack of generalizability.

Risks of gene therapies include pre-treatment myeloablative conditioning, which can expose patients to additional complications such as infertility. Long-term durability of response is a still-developing issue, and studies are ongoing up to 2039 to determine if the positive response is maintained. Currently, long-term follow-up up to 45.6 months for betibeglogene for TDT has reported positive results. Additionally, medians of 8 months of follow-up for CTX001 and 36 months of follow-up for ARU-1801 have shown responses to treatment.

There are QoL outcomes reported for patients who received betibeglogene for TDT or lovotibeglogene for SCD in patients from the original studies up to 24 months, all reporting improved QoL. This can likely be attributed to achievement of transfusion independence in the majority of patients with TDT or decrease in number of VOEs and pain scores in patients with SCD. There are high rates of reported AEs in some participants while other authors have not been as descriptive. For example, 1 participant receiving ARU-1801 reported 114 AEs, although a full description of these has not been published. Currently there is no data reported on QoL outcomes and patient satisfaction for CTX001 and ARU-1801. Information related to reduction in pain medications has also not been reported.

Betibeglogene autotemcel is now FDA approved, and practitioners may soon advocate for this option for their patients. The company is proposing a “pay up front, rebate over time if patients do not achieve therapeutic targets” model. This may present challenges to payers regarding the proposed $2.8M initial cost of therapy as well as associated supportive treatments such as myeloablative conditioning and hospitalization during transfusion. CTX001 and lovotibeglogene autotemcel are both on track for FDA submission in early 2023. ARU-1801 does not yet have a publicly released timeline for FDA submission. Many questions remain around the place in therapy and ability for Medicaid programs ability to afford broad coverage of these multimillion-dollar therapies.

References

1. National Heart Lung and Blood Institute. Sickle cell disease. 2022; https://www.nhlbi.nih.gov/health/sickle-cell-disease. Accessed March 28, 2022.

2. Maakaron J. Sickle cell disease clinical presentation. 2021; https://emedicine.medscape.com/article/205926-clinical. Accessed March 28, 2022.

3. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. *N Engl J Med.* 2017;376(16):1561-1573. doi: 10.1056/NEJMra1510865.

4. Centers for Disease Control and Prevention. Data and statistics on sickle cell disease. 2020; https://www.cdc.gov/ncbddd/sicklecell/data.html#:~:text=In%20the%20United%20States&text=It%20is%20estimated%20that%3A,every%2016%2C300%20Hispanic%2DAmerican%20births. Accessed March 28, 2022.

5. Huo J, Xiao H, Garg M, Shah C, Wilkie D. The economic burden of sickle cell disease in the United States. 2018; https://www.valueinhealthjournal.com/article/S1098-3015(18)33183-8/fulltext. Accessed March 28, 2022.

6. Gluckman E, Cappelli B, Bernaudin F, et al. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. *Blood.* 2017;129(11):1548-1556. doi: 10.1182/blood-2016-10-745711.

7. Demirci S, Uchida N, Tisdale JF. Gene therapy for sickle cell disease: an update. *Cytotherapy.* 2018;20(7):899-910. doi: https://dx.doi.org/10.1016/j.jcyt.2018.04.003.

8. Payen E. Efficacy and safety of gene therapy for β-thalassemia. *N Engl J Med.* 2022;386:488-490.

9. Danjou F, Anni F, Galanello R. Beta-thalassemia: from genotype to phenotype. *Haematologica.* 2011;96(11):1573-1575.

10. Muncie Jr HL, Campbell J. Alpha and beta thalassemia. *Am Fam Physician.* 2009;80(4):339-344.

11. Sayani FA, Kwiatkowski JL. Increasing prevalence of thalassemia in America: implications for primary care. *Ann Med.* 2015;47(7):592-604. doi: 10.3109/07853890.2015.1091942.

12. Vichinsky EP, MacKlin EA, Waye JS, Lorey F, Olivieri NF. Changes in the epidemiology of thalassemia in North America: a new minority disease. *Pediatrics.* 2005;116(6):e818-825. doi: 10.1542/peds.2005-0843.

13. Dong AC, Rivella S. Gene addition strategies for β-thalassemia and sickle cell anemia. *Adv Exp Med Biol.* 2017(1013):155-176. doi: 10.1007/978-1-4939-7299-9_6.

14. Kanter J, Falcon C. Gene therapy for sickle cell disease: where we are now? *Hematology.* 2021;2021(1):174-180.

15. Grimley M, Asnani M, Shrestha A, et al. Safety and efficacy of ARU-1801 in patients with sickle cell disease: early results from the phase 1/2 momentum study of a modified gamma globin gene therapy and reduced intensity conditioning. *Blood.* 2021;138:3970. doi: https://doi.org/10.1182/blood-2021-147469.

16. Aruvant Sciences. One-time gene therapy for sickle cell disease. 2020; https://media.nature.com/original/magazine-assets/d43747-020-00925-4/d43747-020-00925-4.pdf. Accessed March 28, 2022.

17. Goyal S, Tisdale J, Schmidt M, et al. Acute myeloid leukemia case after gene therapy for sickle cell disease. *N Engl J Med.* 2022;386(2):138-147. doi: https://dx.doi.org/10.1056/NEJMoa2109167.

18. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene autotemcel gene therapy for non-beta^0/beta^0 genotype beta-thalassemia. *N Engl J Med.* 2022;386(5):415-427. doi: https://dx.doi.org/10.1056/NEJMoa2113206.

19. Wu Y, Zeng J, Roscoe BP, et al. Highly efficient therapeutic gene editing of human hematopoietic stem cells. *Nat Med.* 2019;25(5):776-783. doi: https://dx.doi.org/10.1038/s41591-019-0401-y.

20. Thompson AA, Walters MC, Kwiatkowski J, et al. Gene therapy in patients with transfusion-dependent beta-thalassemia. *N Engl J Med.* 2018;378(16):1479-1493. doi: https://dx.doi.org/10.1056/NEJMoa1705342.

21. Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 gene editing for sickle cell disease and beta-thalassemia. *N Engl J Med.* 2021;384(3):252-260. doi: https://dx.doi.org/10.1056/NEJMoa2031054.

22. Kanter J, Walters MC, Krishnamurti L, et al. Biologic and clinical efficacy of lentiglobin for sickle cell disease. *N Engl J Med.* 2022;386(7):617-628. doi: https://dx.doi.org/10.1056/NEJMoa2117175.

23. Kwiatkowski JL, Locatelli F, Walters MC, et al. Improvement in health-related quality of life following treatment with betibeglogene autotemcel in patients with transfusion-dependent β-thalassemia enrolled in phase 3 studies. *Blood.* 2021;138(Supplement 1):3085-3085. doi: 10.1182/blood-2021-150392.

24. Yannaki E, Locatelli F, Kwiatkowski J, et al. Betibeglogene autotemcel gene therapy for the treatment of transfusion-dependent B-thalassemia: updated long-term efficacy and safety results. *HemaSphere*. 2021;5:86-87.

25. Kulozik AE, Thuret I, Thompson AA, et al. Interim results of betibeglogene autotemcel gene-addition therapy in pediatric patients with transfusion-dependent β-thalassemia (TDT) treated in the Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies. *Oncol Res Treat*. 2021;44.

26. Kunz JB, Roth E, Mirza A, et al. The first real-world experience with betibeglogene autotemcel (beti-cel) gene therapy treatment for transfusion-dependent β-thalassemia (TDT). *Blood*. 2022;138 S1.

27. Clinicaltrials.gov. A study evaluating the safety and efficacy of the LentiGlobin BB305 drug product in β-thalassemia major participants. 2012; https://ClinicalTrials.gov/show/NCT01745120. Accessed October 4, 2022.

28. Clinicaltrials.gov. A study evaluating the safety and efficacy of LentiGlobin BB305 drug product in β-thalassemia major (also referred to as transfusion-dependent β-thalassemia [TDT]) and sickle cell disease. 2014; https://ClinicalTrials.gov/show/NCT02151526. Accessed October 4, 2022.

29. Grupp S, Bloberger N, Campbell C, et al. CTX001 for sickle cell disease: safety and efficacy results from the ongoing CLIMB SCD-121 study of autologous CRISPER-Cas9-modified CD34+ hematopoietic stem and progenitor cells. Paper presented at: European Hematology Association 2021; Virtual.

30. Locatelli F, Ailinca-Luchian S, Bobruff Y, et al. CTX001 for transfusion-dependent b-thalassemia: safety and efficacy results from the ongoing CLIMB THAL-111 study of autologous CRISPR-Cas9-Modified CD34+ hematopoietic stem and progenitor cells. Paper presented at: Eurpean Hematology Association 2021; Virtual.

31. Walters MC, Tisdale JF, Mapara MY, et al. Sustained improvements in patient-reported quality of life up to 24 months post-treatment with lentiglobin for sickle cell disease (bb1111) gene therapy. *Blood*. 2021;138:7. doi: https://doi.org/10.1182/blood-2021-146905.

32. Magrin E, Semeraro M, Hebert N, et al. Long-term outcomes of lentiviral gene therapy for the β-hemoglobinopathies: the HGB-205 trial. *Nat Med*. 2022;28(1):81-88. doi: 10.1038/s41591-021-01650-w.

33. Clinicaltrials.gov. A study evaluating the efficacy and safety of the LentiGlobin® BB305 drug product in participants with transfusion-dependent β-thalassemia, who do not have a β0/β0 genotype. 2016; https://ClinicalTrials.gov/show/NCT02906202. Accessed August 24, 2022.

34. Clinicaltrials.gov. A study evaluating the efficacy and safety of the LentiGlobin® BB305 drug product in participants with transfusion-dependent β-thalassemia. 2017; https://ClinicalTrials.gov/show/NCT03207009. Accessed August 24, 2022.

35. Clinicaltrials.gov. ß-thalassemia major with autologous CD34+ hematopoietic progenitor cells transduced with TNS9.3.55 a lentiviral vector encoding the normal human ß-globin gene. 2012; https://ClinicalTrials.gov/show/NCT01639690. Accessed August 24, 2022.

36. Clinicaltrials.gov. Longterm follow-up of subjects with transfusion-dependent ß-thalassemia treated with ex vivo gene therapy. 2015; https://clinicaltrials.gov/show/NCT02633943. Accessed August 24, 2022.

37. Clinicaltrials.gov. Gene transfer for patients with sickle cell disease. 2014; https://ClinicalTrials.gov/show/NCT02186418. Accessed August 24, 2022.

38. Clinicaltrials.gov. A safety and efficacy study evaluating CTX001 in subjects with severe sickle cell disease. 2018; https://ClinicalTrials.gov/show/NCT03745287. Accessed August 24, 2022.

39. Clinicaltrials.gov. Evaluation of safety and efficacy of CTX001 in pediatric participants with severe sickle cell disease (SCD). 2022; https://ClinicalTrials.gov/show/NCT05329649. Accessed August 24, 2022.

40. Clinicaltrials.gov. A safety and efficacy study evaluating CTX001 in subjects with transfusion-dependent β-thalassemia. 2018; https://ClinicalTrials.gov/show/NCT03655678. Accessed August 24, 2022.

41. Clinicaltrials.gov. Evaluation of safety and efficacy of CTX001 in pediatric participants with transfusion-dependent β-thalassemia (TDT). 2022; https://ClinicalTrials.gov/show/NCT05356195. Accessed August 24, 2022.

42. Clinicaltrials.gov. Evaluation of efficacy and safety of a single dose of CTX001 in participants with transfusion-dependent β-thalassemia and severe sickle cell disease. https://ClinicalTrials.gov/show/NCT05477563. Accessed August 24, 2022.

43. Vertex Pharmaceuticals Incorporated. A long-term follow-up study in subjects who received CTX001. 2019; https://www.scanmedicine.com/clinicaltrials/NCT04208529. Accessed August 24, 2022.

44. Clinicaltrials.gov. A study evaluating the safety and efficacy of bb1111 in severe sickle cell disease. 2014; https://ClinicalTrials.gov/show/NCT02140554. Accessed August 24, 2022.

45. Clinicaltrials.gov. A study evaluating gene therapy with BB305 lentiviral vector in sickle cell disease. 2020; https://ClinicalTrials.gov/show/NCT04293185. Accessed August 24, 2022.

46. Clinicaltrials.gov. Long-term follow-up of subjects with sickle cell disease treated with ex vivo gene therapy. 2020; https://ClinicalTrials.gov/show/NCT04628585. Accessed August 24, 2022.

47. National Heart, Lung, and Blood Institute. Quality assessment tool for before-after (pre-post) studies with no control group. 2018; https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed April 27, 2017.

48. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi: 10.1136/bmj.39489.470347.AD.

49. Schünemann H, Brozek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html. Accessed October 26, 2022.

Appendix A. Methods

Search Strategy

We searched Drug Effectiveness Review Project (DERP) bibliographic database and gray literature clinical evidence sources to identify randomized controlled trials (RCTs), uncontrolled interventional trials (single-arm studies), and systematic reviews (with and without meta-analyses) including the terms *sickle cell disease*, *transfusion-dependent beta thalassemia*, *beta thalassemia*, *ARU-1801*, *betibeglogene autotemcel*, *lovobeglogene autotemcel*, *CTX001*, and *CRISPR*. We limited records retrieved to those studies focused on human participants and published in the English language. Systematic reviews were used for reference list searching and not as evidence sources. Searches were conducted on July 27, 2022.

Manufacturer dossiers were requested for all interventions included in the review. bluebird bio, Inc., provided the Academy of Managed Care Pharmacy (AMCP) product dossier for betibeglogene autotemcel and lovotibeglogene autotemcel. Dossiers were not provided for ARU-1801 and CTX001.

Bibliographic Databases

Database	Platform	Issue/Version	Total Number of Records Retrieved
MEDLINE ALL	Ovid	1946 to July 27, 2022	162
CENTRAL and CDSR	Wiley	Searched July 27, 2022	9
Google Scholar	Google	Searched July 27, 2022	34

Abbreviations. CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials.

Gray Literature Sources

- Agency for Healthcare Research and Quality (AHRQ)
  - Effective Health Care (EHC) Program
  - Evidence-based Practice Centers (EPC) Reports
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Epistemonikos
- Health Evidence Review Commission (HERC)
- International Health Technology Assessment (HTA) Database
- US Department of Veterans Affairs Evidence-based Synthesis Program (VA-ESP)
- Washington Health Technology Assessment (WA HTA)

We searched DuckDuckGo and Google Scholar for background and gray literature searches. We also searched AHRQ, CADTH, Epistemonikos, HERC, International HTA database, VA-ESP, and WA HTA to identify systematic reviews and gray literature using the following search terms: *sickle cell disease*, *transfusion-dependent beta thalassemia*, *beta thalassemia*, *ARU-1801*, *betibeglogene autotemcel*, *lovobeglogene autotemcel*, *CTX001*, and *CRISPR*.

Ovid MEDLINE ALL Search Strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to July 26, 2022>

Search Strategy:

1 beta-Thalassemia/ (9708)

2 exp Anemia, Sickle Cell/ (24787)

3 (sickle cell or sickle-cell or beta-thalassemia or beta thalassemia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (43747)

4 1 or 2 or 3 (43852)

5 Clustered Regularly Interspaced Short Palindromic Repeats/ (4996)

6 (ARU-1801 or Betibeglogene autotemcel or Beti-cel or Zynteglo or Lovotibeglogene autotemcel or Lentiglobin or Lovo-cel or Bb1111 or CTX001 or CRISPR or Clustered Regularly Interspaced Short Palindromic Repeats).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (34640)

7 5 or 6 (34640)

8 4 and 7 (217)

9 limit 8 to (english language and humans) (162)

CDSR and CENTRAL via the Cochrane Library Search Strategy

((sickle cell OR beta thalassemia)):ti,ab,kw AND ((ARU-1801 OR Betibeglogene autotemcel OR Beti-cel OR Zynteglo OR Lovotibeglogene autotemcel OR Lentiglobin OR Lovo-cel OR Bb1111 OR CTX001 OR CRISPR OR Clustered Regularly Interspaced Short Palindromic Repeats)):ti,ab,kw (Word variations have been searched)9

Gray Literature Search Terms

Anemia, *ARU-1801*, *Bb1111*, *beta-thalassemia*, *betibeglogene autotemcel*, *Beti-cel*, *CRISPR*, *CTX001*, *Lentiglobin*, *Lovo-cel*, *lovotibeglogene autotemcel*, *severe sickle cell disease*, *sickle cell*, *transfusion-dependent beta thalassemia*, *Zynteglo*

Ongoing Studies

We searched the following DERP sources for ongoing studies using the search terms *anemia*, *ARU-1801*, *Bb1111*, *beta-thalassemia*, *betibeglogene autotemcel*, *Beti-cel*, *CRISPR*, *CTX001*, *Lentiglobin*, *Lovo-cel*, l*ovotibeglogene autotemcel*, *sickle cell*, and *Zynteglo*:

- ClinicalTrials.gov
- International Clinical Trials Registry Platform (World Health Organization)
- ScanMedicine
- Bluebirdbio.com

- Vertex pharmaceuticals
- Aruvant Sciences

Inclusion Criteria

Populations

- Individuals with severe sickle cell disease (SCD)
- Individuals with transfusion-dependent beta thalassemia (TDT)

Interventions

Table A1. List of Brand Names and Generics for Sickle Cell Disease and Beta Thalassemia

Generic Name	Brand Name	Intended Population	FDA Approval Date
Betibeglogene autotemcel (beti-cel)	Zentyglo	• TDT	08/17/2022
ARU-1801	NA	• Severe SCD	No PDUFA date
CTX001 (CRISPR technology)	NA	• TDT • Severe SCD	No PDUFA date
Lovotibeglogene autotemcel (lovo-cel)	NA	• Severe SCD	No PDUFA date

Abbreviations. FDA: US Food and Drug Administration; NA: not applicable; PDUFA: Prescription Drug User Fee Act; SCD: :sickle cell disease; TDT: transfusion-dependent beta thalassemia.

Comparators

- Another listed intervention (head-to-head comparison)
- Standard of care
- Placebo
- No comparison (single-arm trial)

Outcomes

Sickle Cell Disease

- Hemoglobin levels
- Markers of hemolysis (e.g., bilirubin levels)
- Pain
- Quality of life (QoL)
- Mortality
- Overall adverse events (AEs)
- Specific AEs (e.g., hepatotoxicity)
- Serious adverse events (SAEs; e.g., mortality)

Beta Thalassemia

- Hemoglobin levels
- Frequency of transfusions
- Fatigue
- QoL
- Mortality
- Overall AEs (e.g., muscle pain, joint pain)

- Specific AEs (e.g., hyperuricemia)
- SAEs (e.g., mortality)

Study Designs

- RCTs
- Uncontrolled interventional trial (single-arm trial)

Exclusion Criteria

We excluded studies if they were not published in English or conducted in human participants.

Screening

Two experienced researchers independently screened all titles and abstracts of identified documents. In cases in which there was disagreement about eligibility, disagreement was resolved with discussion. This method was repeated for full-text review of documents that could not be excluded by title and abstract screening.

Participant Characteristics and Association with Outcomes

When discussing risk and protective factors or variables in statistical models in DERP research products, in almost all cases, we are referring to associations of participant characteristics with outcomes, and not causation of outcomes. This is important because participant characteristics, such as race and ethnicity, serve as proxy or surrogate measures for underlying etiological factors not measured or evaluated in analyses. Etiological factors that might cause differences in outcomes for subgroups of participants could include systemic racism or other forms of systemic discrimination, stress, poverty, housing instability, or epigenetics. For example, by describing any differences in outcomes by race and ethnic groups, we are noting observed associations; these associations are not caused by biological determinants of being Black, White, or Hispanic.

Risk-of-Bias Assessment

We assessed the risk of bias of the included single-arm interventional studies using standard instruments developed and adapted by DERP that are modifications of instruments used by national and international standards for quality.[47] Two experienced researchers independently rated all included studies. In cases in which there was disagreement about the risk of bias of a study, disagreement was managed by discussion.

Quasi-experimental Studies

Low-risk-of-bias quasi-experimental studies have a control group that is unexposed to the intervention being studied; methods are in place to prevent contamination bias; pre- and post-measures are done concurrently; and participant characteristics are balanced between groups or controlled for by propensity scores, by statistical adjustment, or both. Moderate-risk-of-bias quasi-experimental studies have incomplete information about methods that might mask important limitations, a meaningful conflict of interest, or are at risk for contamination bias. High-risk-of-bias quasi-experimental studies do not have a control group (i.e., before and after studies or interrupted time series) or have other clear flaws that could introduce significant bias.

Certainty-of-Evidence Assessment

We assigned each outcome a summary judgment for the overall certainty of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[48,49] Two independent experienced researchers assigned ratings, with disagreements resolved by a third rater. The GRADE system defines the overall certainty of a body of evidence for an outcome in the following manner:

- **High:** Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are RCTs with few or no limitations, and the estimate of effect is likely stable.
- **Moderate:** Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are RCTs with some limitations or well-performed non-randomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low:** Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or non-randomized studies without special strengths.
- **Very low:** Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are non-randomized studies with serious limitations or inconsistent results across studies.
- **Not Applicable:** Researchers did not identify any eligible articles.

Appendix B. Full Evidence Tables

Table B1. Study Design, Demographics, and Quality Ratings for Listed Therapies

Author, Year Study Number Study Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Enrolled	Demographic Characteristics Key Inclusion and Exclusion Criteria
Betibeglogene Autotemcel for Transfusion-Dependent Beta Thalassemia		
Thompson et al., 2018[20] HGB-204 NCT01745120 HGB-205 NCT02151526 NORTHSTAR HGB-204 was conducted at 6 sites (4 in the United States, 1 in Australia, and 1 in Thailand) HGB-205 was conducted at Necker Children's Hospital in Paris bluebird bio, Inc. High	Two non-randomized, open-label, single-dose, phase 1/2 studies HGB-204, n = 18 HGB-205, n = 4 Total, N = 22	Median age (range), by group • HGB-204: 20 (12 to 35) years • HGB-205: 18 (16 to 19) years Median age (range) at initiation of regular transfusions, by group • HGB-204: 3.5 (0 to 26) years • HGB-205: 1.8 (0 to 14) years Female, by group • HGB-204: 72% (13 of 18) • HGB-205: 50% (2 of 4) Race (White) • HGB-204: 22% (4 of 18) • HGB-205: 50% (2 of 4) Race (Asian) • HGB-204: 78% (14 of 18) • HGB-205: 50% (2 of 4) Genotype (β^0/β^0 or IVS1-110 mutation) • HGB-204: 44% (8 of 18) • HGB-205: 25% (1 of 4) Genotype (β^E/β^0) • HGB-204: 33% (6 of 18) • HGB-205: 75% (3 of 4) Genotype (other) • HGB-204: 22% (4 of 18) • HGB-205: 0% (0 of 4)

Author, Year Study Number Study Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Enrolled	Demographic Characteristics Key Inclusion and Exclusion Criteria
		Median monthly transfusion volume for 2 years before enrollment (range) • HGB-204: 13.6 (10.4 to 21.8) mL/kg • HGB-205: 15.2 (11.6 to 15.7) mL/kg Splenectomy • HGB-204: 33% (6 of 18) • HGB-205: 75% (3 of 4) Inclusion criteria • Aged ≤ 35 years old with beta thalassemia of any genotype • Restricted to participants who were at least 12 years of age in HGB-204 and at least 5 years of age in HGB-205 Exclusion criteria • Advanced organ damage • Presence of HIV type 1 or 2 • Active hepatitis B or C infection • White blood cell counts < 3×10^9/L, and/or platelet counts < 100×10^9/L (not due to hypersplenism) • Uncorrected bleeding disorder • Prior or current malignancy or myeloproliferative or immunodeficiency disorder • Immediate family members with a known or suspected Familial Cancer Syndrome • Prior HSCT • Advanced liver disease • Kidney disease with a baseline estimated glomerular filtration rate < 70 mL/min/1.73 m^2 • Uncontrolled seizure disorder • Other evidence of severe iron overload • Clinically significant pulmonary hypertension • Prior receipt of gene therapy • Diagnosis of a significant psychiatric disorder

Author, Year Study Number Study Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Enrolled	Demographic Characteristics Key Inclusion and Exclusion Criteria
		• Pregnancy or breastfeeding or absence of contraception for fertile subjects • Contraindication to the conditioning regimen
Locatelli et al., 2022[18] HGB-207 NCT02906202 NORTHSTAR-2 United States (3 locations), France, Germany, Italy, Thailand, United Kingdom bluebird bio, Inc. High	Non-randomized, open-label, single-dose, phase 3 study N = 23	Genotype • β^0/β^+: 52% (12 of 23) • β^E/β^0: 26% (6 of 23) • β^+/β^+: 22% (5 of 23) Sex • Female: 52% (12 of 23) • Male: 48% (11 of 23) Race • Asian: 57% (13 of 23) • White: 35% (8 of 23) • Other: 9% (2 of 23) Age (median: 15, range: 4-34) • < 12 years: 35% (8 of 23) • 12 to < 18 years: 26% (6 of 23) • ≥ 18 years: 39% (9 of 23) Median transfusion volume for 2 years before enrollment (range) • 207.9 mL/kg/year (142.1-274.4) Median number of transfusions for 2 years before enrollment (range) • 16 transfusions/year (11.5-37.0) Average nadir Hb levels (range): • 9.6 g/dL (7.5-11.0) Prior splenectomy • 17% (4 of 23) Iron status • Median liver iron concentration (range): 5.3 mg/g (1.0-41.0) • Median myocardial iron (range): 36.7 msec (21.0-57.0) • Median serum ferritin (range): 1975.2 ng/mL (349.0-10,021)

Author, Year Study Number Study Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Enrolled	Demographic Characteristics Key Inclusion and Exclusion Criteria
		Number of mobilization and apheresis cycle • 1 cycle: 78% (18 of 23) • 2 cycles: 22% (5 of 23) Inclusion criteria • 50 years of age or less at the time of consent (participants younger than 5 years of age may be enrolled if they weigh a minimum of kg) • Diagnosis of transfusion-dependent thalassemia with a history of at least 100 milliliter per kilogram per year (mL/kg/year) of PRBCs in the 2 years preceding enrollment (all participants) or be managed with 8 transfusions of PRBCs per year or more in the 2 years preceding enrollment • Clinically stable and eligible to undergo HSCT • Treated and followed for at least the past 2 years in a specialized center that maintained detailed medical records, including transfusion history Exclusion criteria • β0 mutation at both alleles of the β-globin gene • HIV-1, HIV-2, HBV, or HCV positive • WBC count less than $3\times10^{\wedge9}$/L, and/or platelet count less than $100\times10^{\wedge9}$/L not related to hypersplenism • Uncorrected bleeding disorder • Any prior or current malignancy • Immediate family member with a known Familial Cancer Syndrome • Prior HSCT • Advanced liver disease • A cardiac T2* less than 10 msec by MRI • Evidence of severe iron overload • Participation in another clinical study with an investigational drug within 30 days of screening • Other conditions rendering the participant ineligible for HSCT • Prior receipt of gene therapy

Author, Year Study Number Study Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Enrolled	Demographic Characteristics Key Inclusion and Exclusion Criteria
		• Pregnancy or breastfeeding in a postpartum female or absence of adequate contraception for fertile participant • A known and available Human leukocyte antigen (HLA) matched family donor • Any contraindications to the use of granulocyte colony stimulating factor (G-CSF) and plerixafor during the mobilization of hematopoietic stem cells and any contraindications to the use of busulfan and any other medicinal products required during the myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients
Kwiatkowski et al., 2021[23] Kulozik et al., 2021[25] HGB-207 NCT02906202 NORTHSTAR-2 HGB-212 NCT0320700 NORTHSTAR-3 bluebird bio, Inc. conference abstract	Non-randomized, open-label, single-dose, phase 3 studies N = 30 total	Age • Range: 4 to 34 years • Age < 18 years: 66% Duration of hospitalization from conditioning through discharge • Median: 44 days • Range: 29 to 92 days See Locatelli et al., 2021 for detailed inclusion/exclusion criteria for HGB-207 (same for HGB-212)
Yannaki et al., 2021[24] LTF-303 NCT02633943	Non-randomized, open-label, single-dose, phase 3 studies	Age at enrollment of parent study • Median: 19.5 years • Range: 7 to 35 years Inclusion criteria

Author, Year Study Number Study Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Enrolled	Demographic Characteristics Key Inclusion and Exclusion Criteria
bluebird bio, Inc. conference abstract	Long-term follow-up of participants from HGB-204, HGB-205, HGB-207, and HGB-212) N = 44 total n = 22 from HGB-204, HGB-205 n = 22 from HGB-207, HGB-212	• Written informed consent by subjects or subject's parent/legal guardian if applicable • Treated with drug product for therapy of a hemoglobinopathy in a bluebird bio, Inc.-sponsored clinical study (HGB-204, HGB-205, HGB-207, HGB-212) Exclusion criteria • None
ARU-1801		
Grimley et al., 2021[15] NCT02186418 USA and Jamaica Aruvant Sciences conference abstract	Single-arm, phase 1/2 study ARU-1801 N = 4	Age: mean 26 years Inclusion criteria • 18 to 45 years old • Severe SCD • Failed or was unable to tolerate hydroxyurea therapy Exclusion criteria • Hepatitis B, hepatitis C, or HIV • Females who are pregnant or lactating/breastfeeding • Active malignancy or receiving treatment for any type of cancer
CTX001		
Frangoul et al., 2021[21] NCT03655678 NCT03745287 CLIMB-THAL-111 CLIMB-SCD-121 USA, Italy, Germany, France, Canada, UK	Single-arm, phase 2/3 study CTX001 N = 2	Patient 1 (TDT) • 19 year old female • Received average of 34 units of PRBCs in the previous 2 years Patient 2 (SCD) • 33 year old female • Averaged 7 severe VOEs annually in previous 2 years Inclusion criteria • 18 to 35 years of age

Author, Year Study Number Study Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Enrolled	Demographic Characteristics Key Inclusion and Exclusion Criteria
CRISPR Therapeutics Vertex Pharmaceuticals High		• (TDT) Received at least an average of 10 units of PRBCs per year the previous 2 years • (SCD) Two or more severe VOEs per year in the previous 2 years
Locatelli et al., 2021[30] NCT03655678 CLIMB-THAL-111 conference abstract	Single-arm, phase 2/3 study CTX001 N = 15	Female: 9 of 15 (60%) Age (median), years: 23 Pre-study units of PRBCs per year, median (range): 34 (20.5 to 61)
Grupp et al., 2021[29] NCT03745287 CLIMB-SCD-121 conference abstract	Single-arm, phase 2/3 study CTX001 N = 7	Female: 3 of 7 (43%) Age (median), years: 22 Pre-study severe VOEs per year, median (range): 5.5 (2.5 to 9.5)
Lovotibeglogene Autotemcel for Sickle Cell Disease		
Kanter et al., 2022[22] HGB-206 NCT02140554 United States (10 sites) bluebird bio, Inc. High	Non-randomized, open-label, single-dose, phase 1/2 study N = 35	Age (median: 24, range: 12 to 38) • 18 to 50 years: 77% (27 of 35) • 12 to 17 years: 23% (8 of 23) Sex • Female: 37% (13 of 35) • Male: 63% (22 of 23) Race • Black: 97% (34 of 35) • Not provided: 3% (1 of 35) Genotype • β^S/β^S: 100% (35 of 35)

Author, Year Study Number Study Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Enrolled	Demographic Characteristics Key Inclusion and Exclusion Criteria
		History of SCD • Annual severe VOE in prior 24 months, median (range): 3.0 (0-13.5) events/year • History of stroke: 14% (5 of 35) • Tricuspid regurgitant velocity ≥ 2.5 m/s: 17% (6 of 35) • Hydroxyurea treatment ≤ 3 months prior: 66% (23 of 35) Inclusion criteria • Age ≥12 and ≤50 of age at time of consent • Diagnosis of SCD, with either βS/βS or βS/β0 or βS/β+ genotype • Severe SCD having experienced at least 4 severe VOEs in the 24 months prior to informed consent • Karnofsky performance status of ≥ 60 (≥16 years of age) or a Lansky performance status of ≥60 (<16 years of age). • Intolerance or failure of hydroxyurea in the past • Treated and followed at medical center with detailed records for SCD history for at least the past 24 months prior Exclusion criteria • HIV-1, HIV-2, HBV, or HCV positive • Clinically significant and active bacterial, viral, fungal, or parasitic infection • ANC < 1000/mcL or < 500/mcL on hydroxyurea • Platelets < 100,000/mcL • History of cerebral vasculopathy • Advanced liver disease • Any contraindications to the use of plerixafor during the mobilization of hematopoietic stem cells and any contraindications to the use of busulfan and any other medicinal products required during the myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients

Author, Year Study Number Study Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Enrolled	Demographic Characteristics Key Inclusion and Exclusion Criteria
		• Prior or current malignancy or immunodeficiency disorder • Prior receipt of allogenic transplant • Family history of Familial Cancer Syndrome • Diagnosis of psychiatric disorder that may impede ability to participate in the study • Pregnancy or breastfeeding • Participation in another clinical study with investigational drug within 30 days of screening • Prior receipt of gene therapy • Patients needing treatment doses of anticoagulation during period of conditioning through platelet engraftment • Unable to receive RBC transfusions
Walters et al., 2021[31] HGB-206 NCT02140554 United States (10 sites) bluebird bio, Inc. conference abstract	Non-randomized, open-label, single-dose, phase 1/2 study N = 25	Age • Median: 25 years • Interquartile Range: 19-38 years Sex • Female: 40% • Male: 60% See Kanter et al., 2022 for detailed inclusion/exclusion criteria

Abbreviations: AE: adverse events; G-CSF: granulocyte colony stimulating factor; Hb: hemoglobin: HbB: hemoglobin B; HbF: hemoglobin F; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; HRQoL: health-related quality of life; HSCT: hematopoietic stem cell transplant; MRI: magnetic resonance imaging; PRBC: packed red blood cell; RBC: red blood cell; SAE: serious adverse event; SCD: sickle cell disease; TDT: transfusion-dependent beta thalassemia; VOC: veno-occlusive crisis; VOE: veno-occlusive event; WBC: white blood cell.

Table B2. Primary Outcomes, Secondary Outcomes, Additional Outcomes, and Follow-up

Author, Year Study Number Study Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome (Mean + SD or %)	Follow-up
Betibeglogene Autotemcel for Transfusion-Dependent Beta Thalassemia				
Thompson et al. 2018[20] HGB-204 NCT01745120 HGB-205 NCT02151526 NORTHSTAR	HGB-204 primary efficacy measures: • Sustained production of ≥ 2.0 g/dL of Hb containing βA^{T87Q}-globin for 6 month period between month 18 and month 24 post-drug product infusion HGB-205 primary efficacy measures: • Success of engraftment with autologous CD34+ hematopoietic stem cells transduced with LentiGlobin BB305 lentiviral vector in severe sickle cell disease and transfusion-dependent thalassemia • Production of Hb^{T87Q} without specifying a threshold limit HGB-204 primary safety measures: • Transplant related mortality through 100 days post treatment • Overall survival • Detection of vector derived RCL in any subject • Insertional mutagenesis leading to clonal dominance or leukemia • Monitoring of lab parameters and frequency and severity of clinical AEs	Average VCN in cell populations from peripheral blood RBC transfusion requirements (measured in mL/kg) per month and per year post-transplant Degree of reduction in transfusion requirements compared to pre-transplant needs Length of time any subject was free of transfusions Length of time from drug product infusion to last RBC transfusion	• HGB-204 – Median time to neutrophil engraftment (range): 18.5 (14 to 30) days • HGB-205 – Median time to neutrophil engraftment (range): 16.5 (14 to 29) days • HGB-204 – Median time to platelet engraftment (range): 39.5 (19 to 191) days • HGB-205 – Median time to platelet engraftment (range): 23 (20 to 26) days • HGB-204 – Median VCN at 15 months: 0.3 copies per diploid genome (range 0.1 to 0.9) • HGB-205 – Median VCN at 15 months: 2 copies per diploid genome (range 0.3 to 4.2) • Pooled analysis – Correlation between the VCN in peripheral blood mononuclear cells at 6 months and the initial VCN in the drug product: $r^2 = .69$, $P < .01$) • Median Hb^{T87Q}(range): 6.0 (3.4 to 10) g/dL • Median total Hb (range): 11.2 (8.2 to 13.7) g/dL • Median Hb^{T87Q} for 6 participants who had β^0/β^0 genotype or homozygosity for IVS1-110 mutation: 4.2 (0.4 to 8.7) g/dL	HGB-204 ranged from 15 to 38 months HGB-205 ranged from 20 to more than 36 months

Author, Year Study Number Study Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome (Mean + SD or %)	Follow-up
	HGB-204 primary safety measures: • Incidence of transplant related mortality through 100 days post treatment • Overall survival • Detection of vector derived RCL in any subject • Characterization of events of insertional mutagenesis leading to clonal dominance or leukemia • Monitoring of laboratory parameters and frequency and severity of clinical AEs		• Median reduction in the annual number of transfusions for β^0/β^0 genotype or homozygosity for IVS1-110 mutation (range): 74% (7% to 100%) • Median reduction in annual transfusion volume for β^0/β^0 genotype or homozygosity for IVS1-110 mutation (range): 73% (19% to 100%) • Hb^{T87Q} for the 3 participants who had β°/β° genotype or two copies of IVS1-110 mutation and did not receive transfusion for 14 to 20 months: 6.6 to 8.2 g/dL • Total Hb level for these 3 participants who had β^0/β^0 genotype or two copies of IVS1-110 mutation: 8.3 to 10.2 g/dL	
Locatelli et al., 2022[18] HGB-207 NCT02906202 NORTHSTAR-2	• Transfusion independence (average Hb level of at least 9 g/dL starting 60 days after the last transfusion in patients who had not received red-cell transfusions for 12 months or longer)	Efficacy • Duration of transfusion independence • Total hemoglobin and gene therapy– derived HbA^{T87Q} levels over time • Decrease in the number of transfusions Safety • Engraftment survival	• Transfusion independence: 91% (20 of 22) • Median duration of transfusion independence: 20.4 months (range, 15.7 to 21.6) • Average Hb levels during transfusion independence: 11.7 g/dL (range, 9.5 to 12.8) • Median HbA^{T87Q} levels at 12 months: 8.7 g/dL (range, 5.2 to 10.6) • Median endogenous Hb levels at 12 months: 3.0 g/dL (range, 0.9 to 5.0) • Median reduction in annual transfusion volume for 2 patients	29.5 months (range, 13.0 to 48.2)

Author, Year Study Number Study Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome (Mean + SD or %)	Follow-up
		• AEs • Overall Survival	that did not achieve transfusion independence: 67.4% and 22.7%	
Kwiatkowski et al., 2021[23] Kulozik et al., 2021[25] HGB-207 NCT02906202 NORTHSTAR-2 HGB-212 NCT0320700 NORTHSTAR-3	Health-related QoL • PedsQL • EQ-5D-Y VAS • SF-36 (Physical Component Summary [PCS] and Mental Component Summary [MCS]) • FACT-BMT • FACT-G • EQ-5D-3L	N/A	PedsQL (< 18 years achieving transfusion independence): mean (SD) • Baseline: 77.4 (3.6) • 12 months: 85.3 (2.0) • 24 months: 87.1 (1.8) EQ-5D-Y VAS (11 to 17 years achieving transfusion independence): mean (SD) • Baseline: 81.4 (19.2) • 12 months: 91.6 (4.9) • 24 months: 92.4 (6.0) SF-36 PCS (≥ 18 years achieving transfusion independence): mean (SD) • Baseline: 53.8 (1.4) • 12 months: 55.4 (1.2) • 24 months: 55.7 (1.4) SF-36 MCS (≥ 18 years achieving transfusion independence): mean (SD) • Baseline: 51.0 (1.7) • 12 months: 52.7 (2.0) • 24 months: 53.4 (2.3)	24 months

Author, Year Study Number Study Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome (Mean + SD or %)	Follow-up
			FACT-BMT (≥ 18 years achieving transfusion independence): mean (SD) • Baseline: 125.8 (3.4) • 12 months: 128.4 (3.3) • 24 months: 128.9 (3.0) FACT-G (≥ 18 years achieving transfusion independence): mean (SD) • Baseline: 94.2 (2.6) • 12 months: 96.1 (2.5) • 24 months: 95.8 (2.1) EQ-5D-3L Composite (≥ 18 years achieving transfusion independence): mean (SD) • Baseline: 0.92 (0.08) • 12 months: 0.96 (0.07) • 24 months: 0.95 (0.08) EQ-5D-3L VAS (≥ 18 years achieving transfusion independence): mean (SD) • Baseline: 85.2 (10.5) • 12 months: 90.9 (4.5) • 24 months: 94.2 (4.8)	
Yannaki et al., 2021[24] LTF-303 NCT02633943	• Transfusion independence (average Hb ≥ 9 g/dL without PRBC transfusions for 12 months)	• Average Hb levels during transfusion independence • Hb levels over time • HbA^{T87Q} levels over time • Drug-related AEs	Transfusion independence • HGB-204/HGB-205: 68.2% (15 of 22) • HGB-207/HGB-212: 90.9% (20 of 22) Average Hb levels during transfusion independence • HGB-204/HGB-205: 10.3 g/dL	45.6 months (range, 22.9 to 76.4)

Author, Year Study Number Study Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome (Mean + SD or %)	Follow-up
		• SAEs • Mortality	• HGB-207/HGB-212: 11.8 g/dL • Hb levels at 24 months of those achieving transfusion independence • HGB-204/HGB-205: 10.3 g/dL • HGB-207/HGB-212: 12.5 g/dL • Hb levels at 36 months of those achieving transfusion independence • HGB-204/HGB-205: 10.5 g/dL • HGB-207/HGB-212: 12.3 g/dL • HbAT87Q levels at 24 months • HGB-204/HGB-205: 7.3 g/dL • HGB-207/HGB-212: 9.4 g/dL • HbAT87Q levels at 36 months • HGB-204/HGB-205: 7.6 g/dL • HGB-207/HGB-212: 10.6 g/dL	
ARU-1801				
Grimley et al., 2021[15] NCT02186418	• Incidence of grade 3 allergic reaction • Incidence of grade 4 infection, neutropenia, or organ toxicity • AEs • SAEs	• Hemoglobin subtypes • Change in proportion of anti-sickling/sickling hemoglobin • QoL • Annualized VOEs • Frequency of opioid use pre-transplant vs. post-transplant	Patient 1 • HbF expression stable at 27% at 36 months post-transplant Patient 2 • HbF expression 14% at 36 months Patient 3 • HbF expression 36% at 15 months All patients noted reductions in VOEs	15 to 36 months

Author, Year Study Number Study Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome (Mean + SD or %)	Follow-up
CTX001				

Frangoul et al., 2021[21]
 	
NCT03655678
NCT03745287
 	
CLIMB-THAL-111
CLIMB-SCD-121
	• Engraftment
	• TDT: Reduction in transfusions of RBCs at 6 months
	• SCD: Sustained HgF ≥ 20% for at least 3 months starting 6 months after infusion
		• Total Hb
		• Hb fractions
		• AEs
		• SCD
		  ○ Change in annualized rate of hospitalizations of VOEs
		  ○ Absence of severe VOEs
		  ○ Reduction of PRBC infusions
		• TDT
		  ○ Transfusion independence
		  ○ HRQoL
		• Reduction in iron overload
			Patient 1 (TDT)
			• HbF expression
			  ○ Baseline: 0.3 g/dL
			  ○ Month 3: 8.4 g/dL
			  ○ Month 12: 12.4 g/dL
			  ○ Month 18: 13.1 g/dL
			• Transfusion independent by day 30 after infusion
			
			Patient 2 (SCD)
			• Total hemoglobin
			  ○ Baseline: 7.2 g/dL
			  ○ Month 3: 10.1 g/dL
			  ○ Month 15: 12 g/dL
			• HbF to sickle hemoglobin ratio
			  ○ Baseline: 9.1% to 74.1%
			  ○ Month 3: 37.2% to 32.6%
			  ○ Month 15: 43.2% to 52.3%
			
			No VOEs reported
				Patient 1: 21.5 months
				
				Patient 2: 16.6 months

Locatelli et al., 2021[30] NCT03655678 CLIMB-THAL-111	• Engraftment • Reduction in transfusions of RBCs at 6 months	• Total hemoglobin • Hemoglobin fractions • AEs • Transfusion independence • HRQoL • Reduction in iron overload	Platelet engraftment (median), study day: 40 Neutrophil engraftment (median), study day: 29 Total hemoglobin • Baseline (mean): 10.1 g/dL • Month 6 (mean): 11.6 g/dL • Month 24 (n = 1): 14.7 g/dL HgF • Baseline (mean): 0.5 g/dL	8.7 months (median)

Author, Year Study Number Study Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome (Mean + SD or %)	Follow-up
			• Month 6 (mean): 10.3 g/dL • Month 24 (n = 1): 14.1 g/dL All participants report transfusion independence by 2 months after infusion and through follow-up	
Grupp et al., 2021[29] NCT03745287 CLIMB-SCD-121	• Engraftment • Sustained HgF ≥ 20% for at least 3 months starting 6 months after infusion	• Total hemoglobin • Hemoglobin fractions • AEs • Change in annualized rate of hospitalizations of VOEs • Absence of severe VOEs • Reduction of PRBC infusions	Platelet engraftment (median), study day: 33 Neutrophil engraftment (median), study day: 25 Total hemoglobin • Baseline (mean): 7.7 g/dL • Month 6 (mean): 13.5 g/dL • Month 21 (n = 1): 12.0 g/dL HgF • Baseline (mean): 4.0% • Month 6 (mean): 45.9% • Month 24 (n = 1): 42% All participants report no recurrence of severe VOEs after infusion	7.6 months (median)
Lovotibeglogene Autotemcel for Sickle Cell Disease				
Kanter et al., 2022[22] HGB-206 NCT02140554	• Complete resolution of severe VOEs between 6 months and 18 months post-infusion	Efficacy • All VOEs • Hb levels • HbA^{T87Q} levels • Markers of hemolysis Safety • AEs	Complete Resolution of Severe VOEs: 100% (25 of 25 evaluable cases) Median VOEs per year (range) • Baseline: 3.5 (2.0 to 13.5) events/year in 24 months prior • 6-36 months: 0 (0 to 5.9) events/year	17.3 months

Author, Year Study Number Study Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome (Mean + SD or %)	Follow-up
		• Mortality	• 3 total participants had VOEs after infusion Median Hb levels • Baseline: 8.5 g/dL • 6 months (all): 11.0 g/dL • 6 months (adolescents, n = 8): 13.4 g/dL (HbA^{T87Q} levels: 5.9 g/dL)	
Walters et al., 2021[31] HGB-206 NCT02140554 Not performed	• PROMIS-57 score (QoL tool)	• Pain Intensity Score (0–10)	PROMIS-57 scores (Pain Interference Subscale) • Baseline: 64.2 (n = 16) • 24 months: 44.5 (n = 5) PROMIS-57 scores (Fatigue Subscale) • Baseline: 64.6 (n = 8) • 24 months: 46.9 (n = 1) Pain Intensity • Baseline: 6.5 (n = 15) • 24 months: 1.8 (n = 5)	24 months

Abbreviations. AE: adverse events; ANC: absolute neutrophil count; EQ-5D-3L: Euro Quality of Life; EQ-5D-Y VAS: Euro Quality of Life Visual Analog Scale; FACT-BMT: Functional Assessment of Cancer Therapy – Bone Marrow Transplantation; FACT-G: Functional Assessment of Cancer Therapy – General; Hb: hemoglobin; HbF: hemoglobin F; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HRQoL: health related quality of life; HSCT: hematopoietic stem cell transplant; MCS: mental component summary; MRI: magnetic resonance imaging; PCS: physical component summary; PedsQL: Pediatric Quality of Life Inventory; PRBC: packed red blood cell; PROMIS-57: Patient Reported Outcomes Measurement Information System-57; QoL: quality of life; RBC: red blood cell; RCL: replication-competent Lentivirus; SAE: serious adverse event; SCD: sickle cell disease; SF-36: Short Form 36; TDT: transfusion-dependent beta thalassemia; US: United States; VCN: vector copy number; VOE: veno-occlusive event.

Table B3. Adverse Events

Author, Year Study Number Study Name	Adverse Events
Betibeglogene Autotemcel for Transfusion-Dependent Beta Thalassemia	
Thompson et al. 2018[20] HGB-204 NCT01745120 HGB-205 NCT02151526 NORTHSTAR	HGB-204 Nonlaboratory grade 3 to 5 AEs in ≥ 2 participants (days 1 to 43 vs. days > 43) • Total: 34 vs. 1 • Stomatitis: 12 vs. 0 • Febrile neutropenia: 10 vs. 0 • Pharyngeal inflammation: 5 vs. 0 • Epistaxis: 2 vs. 0 • Fever: 2 vs. 0 • Veno-occlusive liver disease: 2 vs. 0 • Menstruation irregular: 1 vs. 1 All SAEs (days 1 to 43 vs. days > 43) • Total: 34 vs. 1 • Veno-occlusive liver disease grade 3: 2 vs. 0 • Klebsiella infection grade 3: 1 vs. 0 • Cardiac ventricular thrombosis grade 3: 0 vs. 1 • Cellulitis grade 3: 0 vs. 1 • Device related thrombosis grade 2: 0 vs. 1 • Hyperglycemia grade 3: 0 vs. 1 • Gastroenteritis grade 3: 0 vs. 1 • Diarrhea infectious grade 2: 0 vs. 1 All AEs related or possibly related to drug product (days 1 to 43 vs. days > 43) • Total: 5 vs. 0 • Abdominal pains grade 1: 2 vs. 0 • Dyspnea grade 1: 1 vs. 0 • Hot flush grade 1: 1 vs. 0 • Chest pain noncardiac grade 3: 1 vs. 0 HGB-205 Nonlaboratory grade 3 to 5 AEs in ≥ 2 participants (days 1 to 43 vs. days > 43) • Total: 7 vs. 5

Author, Year Study Number Study Name	Adverse Events
	• Stomatitis: 3 vs. 0 • Aspartate aminotransferase increased: 1 vs. 1 • Alanine aminotransferase increased: 1 vs. 0 • Premature menopause: 0 vs. 1 • Tooth infection: 0 vs. 1 • Oral herpes: 0 vs. 1 • Major depression: 0 vs. 1 All SAEs (days 1 to 43 vs. days > 43) • Total: 0 vs. 3 • Tooth infection grade 3: 0 vs. 1 • Pneumonia grade 2: 0 vs. 1 • Major depression grade 3: 0 vs. 1 All AEs related or possibly related to drug product (days 1 to 43 vs. days > 43) Total: 0 vs. 0 Overall survival: 100%
Locatelli et al., 2022[18] HGB-207 NCT02906202 NORTHSTAR-2	Grade 3 ≥ AEs in ≥ 2 participants through 2 years of follow-up • Thrombocytopenia: 96% • Neutropenia: 78% • Anemia: 61% • Stomatitis: 61% • Leukopenia: 57% • Febrile Neutropenia: 35% • Epistaxis: 22% • Pyrexia: 17% • Decreased appetite: 13% • Veno-occlusive liver disease: 13% • Increased alanine aminotransferase: 9% • Increased bilirubin: 9% • Hypoxia: 9% • Lymphopenia: 9% • Neutropenic sepsis: 9% • Pharyngeal inflammation: 9%

Author, Year Study Number Study Name	Adverse Events
	SAEs in ≥ 2 participants through last follow-up • Veno-occlusive liver disease: 13% • Thrombocytopenia: 9% • Pyrexia: 9% Overall survival: 100%
Yannaki et al., 2021[24] LTF-303 NCT02633943	Drug-related AEs > 2 years post-betibeglogene infusion • None SAEs > 2 years post-betibeglogene infusion • Gonadotropic insufficiency: 2% (1 of 44) • Ectopic pregnancy: 2% (1 of 44) • Fetal death: 2% (1 of 44) • Gallbladder wall thickening/polyp: 2% (1 of 44) • Bacteremia with neutropenia: 2% (1 of 44) • Major depression: 2% (1 of 44) Overall survival: 100%
ARU-1801	
Grimley et al., 2021[15] NCT02186418	Transient neutropenia and thrombocytopenia lasting a median of 7 days.
CTX001	
Frangoul et al., 2021[21] NCT03655678 NCT03745287 CLIMB-THAL-111 CLIMB-SCD-121	Patient 1 (TDT) • 32 total AEs reported • 2 SAEs reported were pneumonia and veno-occlusive liver disease. Both resolved Patient 2 (SCD) • 114 total AEs reported 3 SAEs reported were sepsis secondary to neutropenia, cholethiasis, and abdominal pain. All 3 resolved with treatment
Locatelli et al., 2021[30]	1 participant reported 4 SAEs likely related to CTX001: headache, haemophagocytic lymphohistiocytosis, acute respiratory distress syndrome, and idiopathic pneumonia

Author, Year Study Number Study Name	Adverse Events
NCT03655678 CLIMB-THAL-111	
Grupp et al., 2021[29] NCT03745287 CLIMB-SCD-121	No additional SAEs reported
Lovotibeglogene Autotemcel for Sickle Cell Disease	
Kanter et al., 2022[22] HGB-206 NCT02140554	Grade 3 ≥ AEs in ≥ 2 participants • Stomatitis: 69% • Thrombocytopenia: 66% • Neutropenia: 54% • Febrile Neutropenia: 43% • Anemia: 37% • Leukopenia: 31% • Increase in aspartate aminotransferase: 17% • Increase in ɣ-glutamyltransferase: 14% • Decrease in appetite: 9% • Abdominal pain: 6% • Upper abdominal pain: 6% • Increase in bilirubin: 6% • Lymphopenia: 6% • Pharyngeal inflammation: 6% • Premature menopause: 6% SAEs in ≥ 1 participants • Abdominal pain: 6% • Drug withdrawal (opioid): 6% • Nausea: 6% • Vomiting: 6% • Upper abdominal pain: 3% • Asthma: 3% • Colitis: 3%

Author, Year Study Number Study Name	Adverse Events
	• Constipation: 3% • Dehydration: 3% • Depression: 3% • Epiglottitis: 3% • Mucosal inflammation: 3% • Non-cardiac chest pain: 3% • Obstructive pancreatitis: 3% • Splenic hematoma: 3% • Substance-induced psychotic disorder: 3% • Sudden death: 3% • Suicidal ideation: 3% Note: 1 death occurred 20 months post-infusion not attributed to study drug

Abbreviations. AE: adverse event; SAE: serious adverse event; SCD: sickle cell disease; TDT: transfusion-dependent beta thalassemia.

Appendix C. Bibliography of Included Studies

Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 gene editing for sickle cell disease and beta-thalassemia. *N Engl J Med*. 2021;384(3):252-260. doi: https://dx.doi.org/10.1056/NEJMoa2031054.

Grimley M, Asnani M, Shrestha A, et al. Safety and efficacy of ARU-1801 in patients with sickle cell disease: early results from the phase 1/2 momentum study of a modified gamma globin gene therapy and reduced intensity conditioning. *Blood*. 2021;138:3970. doi: https://doi.org/10.1182/blood-2021-147469.

Grupp S, Bloberger N, Campbell C, et al. CTX001 for sickle cell disease: safety and efficacy results from the ongoing CLIMB SCD-121 study of autologous CRISPER-Cas9-Modified CD34+ hematopoietic stem and progenitor cells. European Hematology Association. 2021;Virtual.

Kanter J, Walters MC, Krishnamurti L, et al. Biologic and clinical efficacy of lentiglobin for sickle cell disease. *N Engl J Med*. 2022. 386:617-628.

Kulozik AE, Thuret I, Thompson AA, et al. Interim results of betibeglogene autotemcel gene-addition therapy in pediatric patients with transfusion-dependent β-thalassemia (TDT) treated in the phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies. *Oncol Res Treat*. 2021;44.

Kwiatkowski JL, Locatelli F, Walters MC, et al. Improvement in health-related quality of life following treatment with betibeglogene autotemcel in patients with transfusion-dependent β-thalassemia enrolled in phase 3 studies. *Blood*. 2021;138(Supplement 1):3085-3085. doi: 10.1182/blood-2021-150392.

Locatelli F, Ailinca-Luchian S, Bobruff Y, et al. CTX001 for transfusion-dependent b-thalassemia: safety and efficacy results from the ongoing CLIMB THAL-111 study of autologous CRISPR-Cas9-modified CD34+ hematopoietic stem and progenitor cells. European Hematology Association. 2021;Virtual.

Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene autotemcel gene therapy for non-beta^0/beta^0 genotype beta-thalassemia. *N Engl J Med*. 2022. 386:415-427.

Thompson AA, Walters MC, Kwiatkowski J, et al. Gene therapy in patients with transfusion-dependent beta-thalassemia. *N Engl J Med*. 2018;378(16):1479-1493. doi: https://dx.doi.org/10.1056/NEJMoa1705342.

Walters MC, Tisdale JF, Mapara MY, et al. Sustained improvements in patient-reported quality of life up to 24 months post-treatment with lentiglobin for sickle cell disease (bb1111) gene therapy. *Blood*. 2021;138:7. doi: https://doi.org/10.1182/blood-2021-146905.

Yannaki E, Locatelli F, Kwiatkowski J, et al. Betibeglogene autotemcel gene therapy for the treatment of transfusion-dependent β-Thalassemia: Updated long-term efficacy and safety results. *HemaSphere*. 2021;5:86-87.

Appendix D. Bibliography of Excluded Studies With Reasons

Bank A. On the road to gene therapy for beta-thalassemia and sickle cell anemia. *Pediatr Hematol Oncol*. 2008;25(1):1-4. doi: https://dx.doi.org/10.1080/08880010701773829. Exclusion criteria: Publication type not in scope.

Bluebird bio, Inc. A study evaluating the efficacy and safety of the lentiglobin BB305 drug product in participants with transfusion-dependent β-thalassemia. https://ClinicalTrials.gov/show/NCT03207009; 2017. Exclusion criteria: Publication type not in scope.

Cavazzana M, Ribeil J-A, Payen E, et al. Clinical outcomes of gene therapy with BB305 lentiviral vector for sickle cell disease and β-thalassemia. *Mol Ther*. 2016;24:S111-S112. doi: https://doi.org/10.1016/S1525-0016(16)33088-X. Exclusion criteria: Interim analysis.

Cavazzana M, Ribeil J-A, Payen E, et al. Outcomes of gene therapy for severe sickle disease and beta-thalassemia major via transplantation of autologous hematopoietic stem cells transduced ex vivo with a lentiviral beta AT87Q-Globin Vector. *Blood*. 2015;126(23):202. doi: https://doi.org/10.1182/blood.V126.23.202.202. Exclusion criteria: Interim analysis.

Hongeng S, Thompson AA, Kwiatkowski JL, et al. Efficacy and safety of betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia) gene therapy in 60 patients with transfusion-dependent β-thalassemia (TDT) followed for up to 6 years post-infusion. *Transplant Cell Ther*. 2021;27(3). doi: 10.1016/s2666-6367(21)00027-0. Exclusion criteria: Interim analysis.

Kanter J, Tisdale JF, Mapara MY, et al. Resolution of sickle cell disease manifestations in patients treated with lentiglobin gene therapy: updated results from the phase 1/2 Hgb-206 group C study. *Blood*. 2019;134:990. doi: https://doi.org/10.1182/blood-2019-128894. Exclusion criteria: Interim analysis.

Kanter J, Walters MC, Hsieh MM, et al. Interim results from a phase 1/2 clinical study of lentiglobin gene therapy for severe sickle cell disease. *Blood*. 2017;130:527. doi: http://doi.org/10.1182/blood.V130.Suppl_1.527.527. Exclusion criteria: Interim analysis.

Kanter J, Walters MC, Hsieh MM, et al. Interim results from a phase 1/2 clinical study of lentiglobin gene therapy for severe sickle cell disease. *Blood*. 2017;130:527. doi: http://doi.org/10.1182/blood.V130.Suppl_1.527.527. Exclusion criteria: Interim analysis.

Kulozik AE, Thuret I, Thompson AA, et al. Betibeglogene autotemcel (beti-cel) gene therapy for the treatment of transfusion-dependent β-thalassemia (TDT): updated long-term efficacy and safety results. *Oncol Res Treat*. 2021;44:8. Exclusion criteria: Other (duplicate).

Kwiatkowski J, Walters M, Locatelli F, et al. Lentiglobin gene therapy in pediatrics, adolescents, adults with transfusion-dependent B-thalassemia. *Pediatr Blood Cancer*. 2020;67. Exclusion criteria: Interim analysis.

Kwiatkowski JL, Thompson AA, Rasko JEJ, et al. Long-term clinical outcomes of lentiglobin gene therapy for transfusion-dependent β-thalassemia in the Northstar (HGB-204) study. *Blood*. 2019;134:4628. doi: https://doi.org/10.1182/blood-2019-125807. Exclusion criteria: Interim analysis.

Kwiatkowski JL, Walters MC, Hongeng S, et al. Long-term efficacy and safety of betibeglogene autotemcel gene therapy for the treatment of transfusion-dependent β-thalassemia: results in patients with up to 6 years of follow-up. *Blood*. 2020;136:51-52. doi: https://doi.org/10.1182/blood-2020-135850. Exclusion criteria: Interim analysis.

Lal A, Locatelli F, Kwiatkowski JL, et al. Northstar-3: interim results from a phase 3 study evaluating lentiglobin gene therapy in patients with transfusion-dependent β-thalassemia and either a β0 or IVS-I-110 mutation at both alleles of the HBB gene. *Blood*. 2019;134:815. doi: https://doi.org/10.1182/blood-2019-128482. Exclusion criteria: Interim analysis.

Lattanzi A, Meneghini V, Pavani G, et al. Optimization of CRISPR/Cas9 Delivery to human hematopoietic stem and progenitor cells for therapeutic genomic rearrangements. *Mol Ther*. 2019;27(1):137-150. doi: https://dx.doi.org/10.1016/j.ymthe.2018.10.008. Exclusion criteria: Outcomes not in scope.

Locatelli F, Kwiatkowski J, Thompson A, et al. Clinical outcomes following autologous hematopoietic stem cell transplantation with lentiglobin gene therapy in the phase 3 Northstar-2 and Northstar-3 studies for transfusion-dependent β-thalassemia. *Bone Marrow Transplant*. 2020;55:71-72. Exclusion criteria: Interim analysis.

Locatelli F, Kwiatkowski J, Thompson A, et al. Clinical outcomes following autologous hematopoietic stem cell transplantation with betibeglogene autotemcel gene therapy in the phase 3 NORTHSTAR-2 and NORTHSTAR-3 studies for transfusion dependent β-thalassemia (TDT). *Haematologica*. 2020;105. Exclusion criteria: Interim analysis.

Locatelli F, Kwiatkowski J, Walters M, et al. Betibeglogene autotemcel in patients with transfusion-dependent β-thalassemia: updated results from HGB-207 (NORTHSTAR-2) and HGB-212 (NORTHSTAR-3). *HemaSphere*. 2021;5. Exclusion criteria: Interim analysis

Locatelli F, Kwiatkowski J, Walters M, et al. Durable clinical outcomes following betibeglogene autotemcel (Beti-cel) gene therapy with up to 6 years of follow-up in patients with transfusion dependent β-thalassemia (TDT). *Bone Marrow Transplant*. 2021;56:69-70. Exclusion criteria: Interim analysis.

Magrin E, Semeraro M, Hebert N, et al. Long-term outcomes of lentiviral gene therapy for the β-hemoglobinopathies: the HGB-205 trial. *Nat Med*. 2022;28(1):81-88. doi: 10.1038/s41591-021-01650-w. Exclusion criteria: Interim analysis.

Magrin E, Semeraro M, Hebert N, et al. Red blood cells properties in patients with sickle cell disease treated with lentiglobin gene therapy in the HGB-205 trial. *HemaSphere*. 2019;3(S1):173-174. doi: 10.1097/01.Hs9.0000559976.13796.07. Exclusion criteria: Interim analysis.

Modarai SR, Kanda S, Bloh K, Opdenaker LM, Kmiec EB. Precise and error-prone CRISPR-directed gene editing activity in human CD34+ cells varies widely among patient samples. *Gene Ther*. 2021;28(1-2):105-113. doi: https://dx.doi.org/10.1038/s41434-020-00192-z. Exclusion criteria: Outcomes not in scope.

Patsali P, Turchiano G, Papasavva P, et al. Correction of IVS I-110(G>A) beta-thalassemia by CRISPR/Cas-and TALEN-mediated disruption of aberrant regulatory elements in human hematopoietic stem and progenitor cells. *Haematologica*. 2019;104(11):e497-e501. doi: https://dx.doi.org/10.3324/haematol.2018.215178. Exclusion criteria: Outcomes not in scope.

Payen E, Leboulch P. Advances in stem cell transplantation and gene therapy in the β-hemoglobinopathies. *Hematology*. 2012;2012(1):276-283. doi: 10.1182/asheducation.V2012.1.276.3807841. Exclusion criteria: Publication type not in scope.

Porter J, Locatelli F, Kwiatkowski J, et al. Clinical outcomes following autologous haematopoietic stem cell transplantation with LentiGlobin gene therapy in the phase 3 Northstar-2 and Northstar-3 studies for transfusion-dependent β-thalassaemia. *Br J Haematol*. 2020;189:39-40. Exclusion criteria: Interim analysis.

Porter J, Thompson A, Walters M, et al. Improvement in erythropoiesis in patients with transfusion-dependent β-thalassemia following. *HemaSphere*. 2020;4. Exclusion criteria: Interim analysis.

Ribeil JA, Hacein-Bey-Abina S, Payen E, et al. Update from the Hgb-205 phase 1/2 clinical study of lentiglobin gene therapy: sustained clinical benefit in severe hemoglobinopathies. Blood Conference: 58th Annual Meeting of the American Society of Hematology. 2016;128(22). Exclusion criteria: Interim analysis.

Schneiderman J, Thompson AA, Walters MC, et al. Interim results from the phase 3 HGB-207 (Northstar-2) and HGB-212 (Northstar-3) studies of betibeglogene autotemcel gene therapy (lentiglobin) for the treatment of transfusion-dependent β-thalassemia. *Biol Blood Marrow Transplant*. 2020;26(3):S87-S88. doi: 10.1016/j.bbmt.2019.12.588. Exclusion criteria: Interim analysis.

Thompson AA, Kwiatkowski J, Rasko J, et al. Lentiglobin gene therapy for transfusion-dependent beta-thalassemia: update from the Northstar Hgb-204 phase 1/2 clinical study. Blood Conference: 58th Annual Meeting of the American Society of Hematology. 2016;128(22). Exclusion criteria: Interim analysis.

Thompson AA, Kwiatkowski JL, Porter JB, et al. Favorable outcomes in pediatric patients in the phase 3 Hgb-207 (Northstar-2) and Hgb-212 (Northstar-3) studies of betibeglogene autotemcel gene therapy for the treatment of transfusion-dependent β-thalassemia. *Blood*. 2020;136(Supplement 1):52-54. doi: 10.1182/blood-2020-135857. Exclusion criteria: Interim analysis.

Thompson AA, Walters MC, Mapara MY, et al. Resolution of serious vaso-occlusive pain crises and reduction in patient-reported pain intensity: results from the ongoing phase 1/2 HGB-206 group C study of lentiglobin for sickle cell disease (bb1111) gene therapy. *Blood*. 2020;136:16-17. doi: https://doi.org/10.1182/blood-2020-134940. Exclusion criteria: Interim analysis.

Thuret I, Thompson A, Kwiatkowski J, et al. Interim results of betibeglogene autotemcel gene therapy in pediatric patients with transfusion-dependent t β-thalassemia (TDT) treated in the Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies. *Bone Marrow Transplant*. 2021;56:64-65. Exclusion criteria: Interim analysis.

Vertex Pharmaceuticals Incorporated, CRISPR Therapeutics. A safety and efficacy study evaluating ctx001 in subjects with transfusion-dependent β-thalassemia. https://ClinicalTrials.gov/show/NCT03655678; 2018. Exclusion criteria: No results posted.

Walters M, Thompson A, Hongeng S, et al. A phase 3 study to evaluate safety and efficacy of lentiglobin gene therapy for transfusion-dependent beta-thalassemia in patients with non-beta^0/beta^0 genotypes: the Northstar-2 (HGB-207) trial. Haematologica Conference: 22nd Congress of the European Hematology Association Spain. 2017;102:335. Exclusion criteria: Publication type not in scope.

Walters M. Transplantation of clustered regularly interspaced short palindromic repeats modified hematopoietic progenitor stem cells (CRISPR_SCD001) in patients with severe sickle cell disease. https://ClinicalTrials.gov/show/NCT04774536; 2022. Exclusion criteria: No results posted.

Walters MC, Chui DHK, Farrell JJ, et al. Response of patients with transfusion-dependent β-thalassemia (TDT) to betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia) gene therapy based on HBB genotype and disease genetic modifiers. *Blood*. 2020;136(S1):1-3. doi: 10.1182/blood-2020-137642. Exclusion criteria: Interim analysis.

Walters MC, Kwiatkowski JL, Porter JB, et al. Safety and efficacy outcomes in pediatric patients with transfusion-dependent β-thalassemia (TDT) receiving betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia) gene therapy in the phase 3 Hgb-207 (Northstar-2) and Hgb-212 (Northstar-3) studies. *Transplant Cell Ther*. 2021;27(3):S112-S114. doi: 10.1016/s2666-6367(21)00148-2. Exclusion criteria: Interim analysis.

Walters MC, Locatelli F, Thrasher AJ, et al. Safety of autologous hematopoietic stem cell transplantation with gene addition therapy for transfusion-dependent β-thalassemia, sickle cell disease, and cerebral adrenoleukodystrophy. *Biol Blood Marrow Transplant*. 2020;26(3):S38-S39. doi: 10.1016/j.bbmt.2019.12.104. Exclusion criteria: Interim analysis.

Yannaki E, Locatelli F, Kulozik AE, et al. Betibeglogene autotemcel (lentiglobin) in patients with transfusion-dependent β-thalassemia and B0/B0, B+IVS-I-110/B+IVS-I-110, or B0/B+IVS-I-110 genotypes: updated results from the HGB-212 study. *HemaSphere*. 2020:691-692. Exclusion criteria: Interim analysis.

Yannaki E, Locatelli F, Thrasher A, et al. Safety of autologous hematopoietic stem cell transplantation with gene addition therapy for transfusion-dependent β-thalassemia, sickle cell disease, and cerebral adrenoleukodystrophy. *Bone Marrow Transplant*. 2020;55:75-76. Exclusion criteria: Interim analysis.

Lindsey WT, Steuber TD, Grabowsky AB. *Gene therapies for sickle cell disease and transfusion-dependent beta thalassemia.* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2022.

Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.