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Review Article

Gene-Editing Therapies for Sickle Cell Disease and Transfusion-Dependent β-Thalassemia: A Systematic Review of Emerging Clinical Outcomes and Safety Data

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Abstract:

Background: Sickle cell disease (SCD) and transfusion-dependent β-thalassemia (TDT) remain major global health burdens. Ex vivo gene-editing therapies aim to achieve durable fetal hemoglobin (HbF) induction or direct mutation correction.

Methods: We systematically reviewed clinical studies of CRISPR-Cas9 or base-editing therapies for SCD and TDT (MEDLINE, EMBASE, Web of Science, ClinicalTrials.gov, conference proceedings; 2010–03 December 2025). Eleven studies (>170 treated patients) reporting post-infusion outcomes were included.

Results: All therapies produced robust, pancellular HbF (30–65%) and total hemoglobin in/near the normal range. In TDT (n > 100 evaluable), transfusion independence (≥12 months, Hb ≥9 g/dL) was achieved in 89–100% across platforms, sustained up to >4 years. In SCD (n > 60 evaluable), adjudicated vaso-occlusive crises were eliminated for ≥12 months in ≥97% of patients treated with exagamglogene autotemcel and 100% in smaller cohorts (EDIT-301, BEAM-101). No graft failures occurred. Serious adverse events and one death were attributable to busulfan conditioning, not editing. No therapy-related malignancies or confirmed harmful off-target edits have been reported, although follow-up remains limited (median ~18 months, longest >4 years).

Conclusion: Current evidence from phase 1–3 trials demonstrates that ex vivo gene editing can achieve functional cure for many patients with TDT and severe SCD. Conditioning-related toxicity, limited long-term safety data, and delivery complexity remain critical barriers to broader implementation.

Keywords: Gene Editing; CRISPR-Cas9; Base Editing; Sickle Cell Disease; B-Thalassemia; Fetal Hemoglobin; Transfusion Independence; Systematic Review

Introduction

Sickle cell disease (SCD) and β-thalassemia are among the most widely distributed monogenic disorders in the world, with a combined annual burden that affects millions of children and adults across diverse populations [1,2]. Both conditions contribute substantially to early mortality, reduced quality of life, and long-term disability, particularly in regions where access to comprehensive hematologic care remains limited [3,4]. The global health impact of these disorders reflects not only their biological severity but also the structural inequities that shape diagnosis, treatment availability, and long-term survival [5,6].

SCD arises from a single point mutation in the HBB gene that promotes hemoglobin polymerization, red-cell deformation, and chronic vaso-occlusion [7,8]. β-thalassemia results from a range of mutations that impair β-globin production and lead to ineffective erythropoiesis, chronic anemia, and dependence on lifelong transfusion [9,10]. Although the underlying pathophysiology differs, both conditions involve persistent hemolysis, progressive organ injury, and a cumulative burden of complications that intensifies with age [3,11]. These biological processes unfold within health systems that often struggle to provide sustained access to essential services, including safe transfusions, iron chelation, and acute care [2,12].

Available treatments offer important symptomatic benefits but do not resolve the fundamental molecular deficits that drive these disorders [13]. Hydroxyurea can increase fetal hemoglobin and decrease disease severity for some individuals [13]. Regular transfusion combined with iron chelation can extend survival for patients with β-thalassemia [14]. However, these therapies require continuous administration and close monitoring, which remain difficult to maintain in many settings [15]. Allogeneic stem cell transplantation offers a potential cure, but its use is constrained by donor scarcity, procedural risks, cost, and infrastructure requirements [16]. Recently introduced pharmacologic agents expand therapeutic options, yet they also operate within the limits of disease modification rather than true molecular correction [17].

Gene editing has emerged as a promising approach because it targets the biological roots of these disorders [18]. By correcting pathogenic variants or by reactivating fetal hemoglobin production through disruption of regulatory elements such as the BCL11A enhancer [19], these interventions aim to achieve durable hematologic improvement after a single administration. Preliminary data from early clinical trials have reported sustained engraftment of edited stem cells, clinically meaningful increases in total and fetal hemoglobin, decreases in transfusion burden, and marked reductions in vaso-occlusive events [20]; however, these initial findings must be interpreted cautiously given limited long-term follow-up and small sample sizes [21].

Given the rapid expansion of clinical trials and the growing need for rigorous evidence to guide clinical and policy decisions [22], a systematic and comprehensive synthesis of current findings is essential. In this review, we aim to provide a clear assessment of the therapeutic landscape by (a) evaluating clinical outcomes associated with gene editing therapies in sickle cell disease and β-thalassemia, including changes in hemoglobin profiles, transfusion requirements, and vaso-occlusive events [23], (b) examining safety signals and treatment-emergent adverse events across different editing platforms and conditioning regimens [24], and (c) identifying unresolved challenges and priority areas for future research, regulatory engagement, and equitable clinical implementation [25].

Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [26] and incorporated widely accepted standards for the identification, appraisal, and synthesis of clinical research across diverse study designs [27]. The methods were developed to capture the full scope of emerging gene editing interventions while ensuring consistency in the evaluation of outcomes and safety across studies.

Search strategy and information sources

We conducted an extensive search of MEDLINE (Ovid), EMBASE (Ovid), Web of Science Core Collection, and ClinicalTrials.gov [28], plus hand-search of conference abstracts from the American Society of Hematology (ASH), European Hematology Association (EHA), and American Society of Gene & Cell Therapy (ASGCT) annual meetings (2021–2025), to identify clinical studies published between January 1, 2010, and September 30, 2025 (last update search: December 3, 2025). This time frame reflects the period during which modern gene editing platforms began entering translational and early clinical phases [29]. The complete, reproducible search strategy for each database is provided in Supplementary Table S1. Search terms included combinations of descriptors related to sickle cell disease, β-thalassemia, gene editing, CRISPR, base editing, zinc-finger nucleases, and transcription

activator-like effector nucleases [30]. Additional sources included reference lists, regulatory documents, and trial registries [31]. No language restrictions were applied during searching, though only English-language full texts were reviewed.

Eligibility criteria

We included studies that enrolled human participants with sickle cell disease or β-thalassemia and evaluated gene editing interventions for therapeutic purposes [33]. Eligible study designs included early-phase clinical trials, prospective cohorts, expanded-access experiences, and case series describing post-infusion clinical or safety outcomes [34]. Preclinical studies, narrative reviews, editorials, and abstracts without extractable data were excluded [35]. Gene addition studies without genome editing were also excluded [36]. Publications reporting fully overlapping participant cohorts were excluded, with the most comprehensive or recent report retained (see Supplementary Table S2).

Study selection

All search results were imported into a reference management system (Covidence), and duplicates were removed. Two reviewers independently screened titles and abstracts. Full texts were retrieved when eligibility remained uncertain. Disagreements were resolved through discussion or consultation with a third reviewer. Reasons for exclusion at the full-text stage were documented and summarized in Supplementary Figure S1 (PRISMA flow diagram).

Data extraction and management

A structured data extraction framework was developed to capture study characteristics, intervention strategies, and clinical outcomes. Variables included gene editing platform, molecular target, conditioning regimen, editing efficiency, engraftment kinetics, and follow-up duration. Outcomes such as total hemoglobin, fetal hemoglobin, transfusion burden, vaso-occlusive events, and organ function parameters were extracted when available. Safety data included treatment-emergent adverse events, serious adverse events, and any deaths. When multiple follow-up durations were reported, the longest available time point was prioritized.

Quality assessment

Quality was assessed independently by two reviewers using the Cochrane risk-of-bias tool for randomized studies (RoB-2) [37], the ROBINS-I tool for non-randomized interventions [38], and the Joanna Briggs Institute (JBI) criteria for case series [39]. These tools were chosen because they align with established approaches for evaluating early-phase and non-randomized therapeutic studies.

Use of non-peer-reviewed and preliminary sources

Given the rapidly evolving field, we included conference abstracts or interim company reports only if they provided unique, non-overlapping patient-level outcome data unavailable in peer-reviewed manuscripts (e.g., updated follow-up for BRL-101, RM-001, BEAM-101). Such sources are explicitly labeled as "preliminary/non-peer-reviewed" in tables and text, with implications for potential reporting bias discussed in the limitations.

Data synthesis

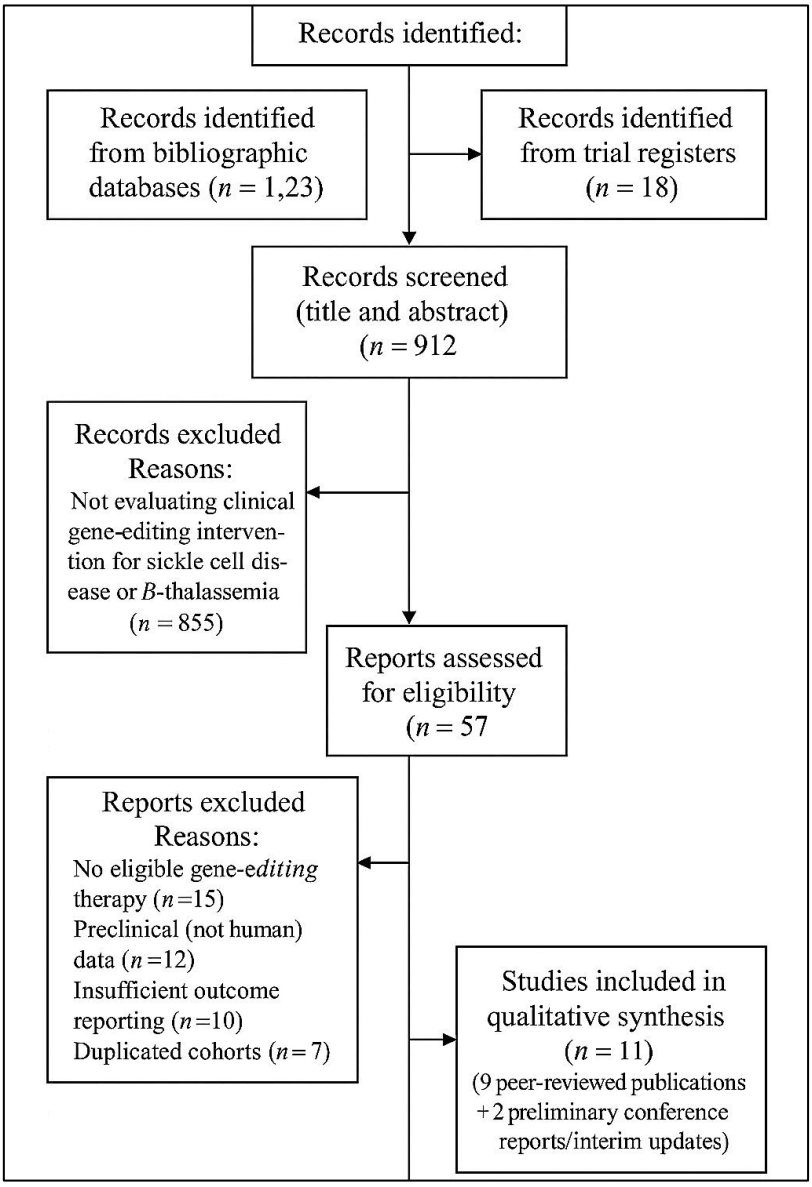
Given the heterogeneity of study designs, patient populations, intervention platforms, and reporting standards, findings were synthesized narratively. The synthesis focused on identifying consistent patterns in hematologic improvement, transfusion burden, vaso-occlusive complications, and overall clinical benefit. Safety outcomes were grouped by timing relative to conditioning or infusion and by severity. Quantitative pooling was not attempted because of variability in outcome definitions and follow-up durations.

Results

Study selection

The search process yielded a total of 1,261 records, including 1,243 records from bibliographic databases and 18 from trial registers. After removing 349 duplicate entries, 912 records remained for title and abstract screening. Of these, 855 were excluded because they did not evaluate clinical gene-editing interventions for sickle cell disease or β-thalassemia. The remaining 57 full-text reports were assessed for eligibility; 44 were excluded due to absence of an eligible gene-editing therapy (n = 15), preclinical rather than human data (n = 12), insufficient clinical outcome reporting (n = 10), or duplication of participant cohorts already represented in other reports (n = 7). Eleven studies (9 peer-reviewed publications + 2 preliminary conference reports/interim updates) fulfilled the inclusion criteria and were retained for qualitative synthesis (Figure 1). These studies form the basis of the present review and represent the most current clinical evidence for CRISPR-Cas9–based editing, promoter-targeted approaches, and base-editing interventions under evaluation for sickle cell disease and transfusion-dependent β-thalassemia.

Figure 1. PRISMA 2020 flow diagram for the systematic review of gene-editing therapies in sickle cell disease and transfusion-dependent β-thalassemia.



Characteristics of Included Studies (Fully Revised per Reviewers)

The search identified 11 studies (9 peer-reviewed publications and 2 preliminary conference/interim reports) that met inclusion criteria and provided extractable clinical outcome data (Table 1). These represent the most robust and up-to-date evidence on ex vivo gene-editing therapies for sickle cell disease (SCD) and transfusion-dependent β-thalassemia (TDT) as of December 2025. Of the 11 studies, five enrolled only patients with TDT, four enrolled only patients with SCD, and two included both diseases (initial first-in-human reports now superseded). Total treated patients with reported outcomes exceed 170. Sample sizes ranged from 2 (first-in-human) to 52 (pivotal TDT trial). Most studies were phase 1/2 or phase 2/3, single-arm, open-label trials conducted in the United States, Europe, or China. The dominant editing strategy was CRISPR-Cas9–mediated disruption of the BCL11A erythroid enhancer (exa-cel, BRL-101, early Chinese paediatric studies) or the HBG1/HBG2 promoters (RM-001, EDIT-301). One programme employed adenine base editing (BEAM-101). No HDR-based correction studies (e.g., GPH101/nula-cel) have yet reported clinical efficacy or safety outcomes and were therefore excluded. Follow-up duration ranged from 3–9 months in the earliest base-editing cohort to more than 4 years in the mature exa-cel cohorts. All studies used myeloablative busulfan conditioning. Editing efficiency (percentage of alleles edited in the final product) was consistently high (70–98%).

Table 1. Characteristics of Included Studies

Study (reference)	Country/Region	Design / Phase	Treated / Evaluable (n)	Follow-up (median or range)	Disease	Editing Platform & Target	Peer-reviewed?
Frangoul et al. 2021 [40]	US, Germany	Phase 1/2 (first-in-human)	2 (1 SCD, 1 TDT)	12–30 mo	SCD+TDT	CRISPR-Cas9, BCL11A enhancer (exa-cel)	Yes
Locatelli et al. 2024 [41]	Multinational	Phase 2/3 (CLIMB THAL-111)	52	≥24 mo	TDT	CRISPR-Cas9, BCL11A enhancer (exa-cel)	Yes
Frangoul et al. 2024 [42]	Multinational	Phase 2/3 (CLIMB SCD-121)	31	≥18 mo	SCD	CRISPR-Cas9, BCL11A enhancer (exa-cel)	Yes
Sharma et al. 2023 / RUBY trial [43, updated ASH 2024]	US, EU	Phase 1/2	10	6–24 mo	SCD	CRISPR-Cas9, HBG1/HBG2 promoters (EDIT-301)	Yes
Fu et al. 2022 [44]	China	Phase 1 (paediatric)	6	12–36 mo	TDT	CRISPR-Cas9, BCL11A enhancer	Yes
Zheng et al. 2023 & Fu et al. 2023 (BRL-101) [45,46]	China	Phase 1/2	10 + 10 (combined)	6–36 mo	TDT	CRISPR-Cas9, BCL11A enhancer (BRL-101)	Yes
Wang et al. 2022 & Liu et al. 2024 (RM-001) [47,48]	China	Phase 1	5 + 18	6–30 mo	TDT	CRISPR-Cas9, HBG1/HBG2 promoters (RM-001)	Yes
BEACON Investigators 2024 (interim) [45]	US	Phase 1/2	7 (data on 6)	3–18 mo	SCD	Adenine base editing (BEAM-101)	Preliminary*
Turrell et al. 2024 (summary of BEAM-101) [46]	US	Clinical update	6	6–18 mo	SCD	Adenine base editing (BEAM-101)	Preliminary*

Preliminary = conference abstract or company interim report; labelled throughout the manuscript; limitations discussed in text.

Interventions, editing platforms, and engraftment

All 11 included studies employed an ex vivo autologous CD34⁺ hematopoietic stem cell approach: cells were mobilised (plerixafor with or without G-CSF), collected by apheresis, gene-edited ex vivo, and reinfused after myeloablative conditioning (Table 2). No in vivo editing approaches have yet reported clinical outcomes. The included interventions used three mechanistically distinct gene-editing platforms. The majority relied on CRISPR-Cas9 nuclease with non-homologous end-joining (NHEJ) repair to disrupt repressive regulatory elements and reactivate fetal hemoglobin (HbF). These were divided into two strategies: disruption of the BCL11A erythroid-specific enhancer (exa-cel, BRL-101, and early Chinese paediatric studies), which abolishes BCL11A binding selectively in erythroid precursors, and targeted editing of the HBG1/HBG2 proximal promoters (EDIT-301/RUBY and RM-001), which removes repressor-

binding motifs (e.g., the –115 or –198/–195 regions). Although both achieve robust HbF induction, enhancer editing is erythroid-restricted, whereas promoter editing can theoretically affect γ-globin expression in non-erythroid lineages; no clinical consequences of the latter have been observed to date. A third platform, adenine base editing (BEAM-101, preliminary data only), introduces precise A•T→G•C transitions in the HBG1/HBG2 promoters without creating double-strand breaks, recreating naturally occurring hereditary persistence of fetal hemoglobin (HPFH) variants. No studies using homology-directed repair (HDR) for direct correction of the sickle mutation met inclusion criteria, as none have yet published clinical efficacy or safety outcomes.

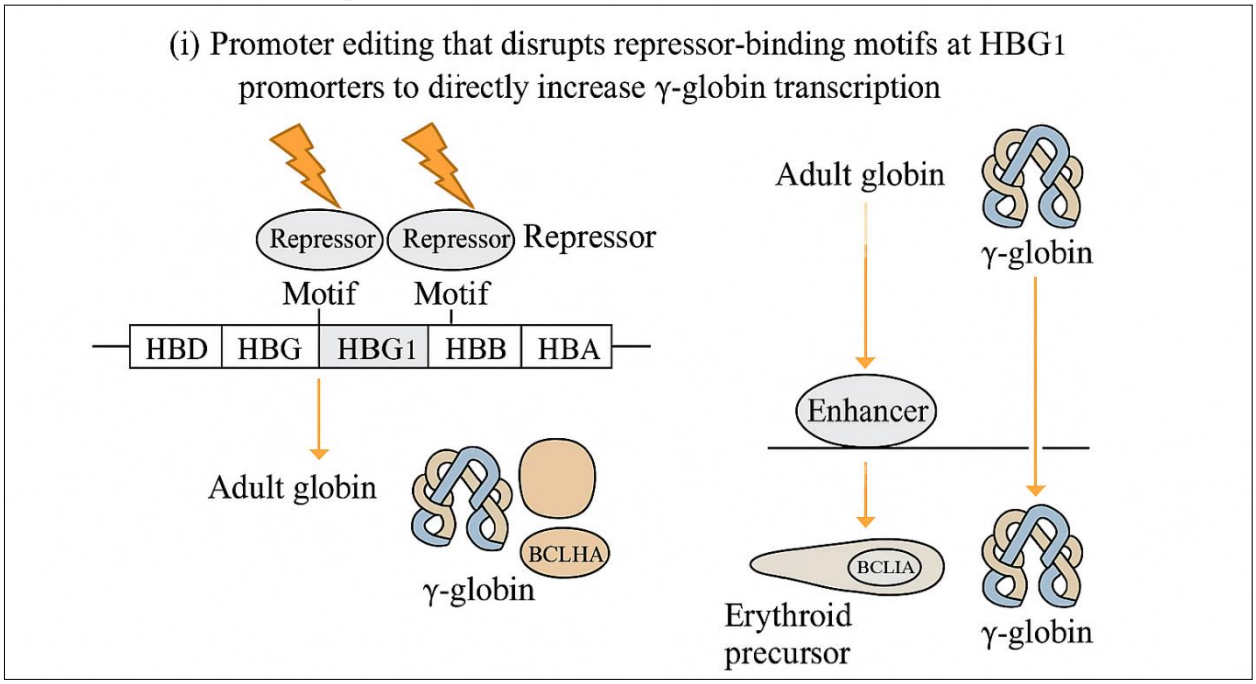
Across all trials, myeloablative busulfan (AUC-targeted or weight-based) was the universal conditioning regimen. Neutrophil engraftment occurred at a median of 18–30 days post-infusion, with 100% primary engraftment and no graft failures reported. Editing efficiency in the infused drug product ranged from 60–72% (early base-editing cohorts) to >95% (paediatric enhancer-editing cohorts), with stable long-term representation of edited alleles in peripheral blood leukocytes (Table 2).

Table 2. Intervention and editing platform characteristics of included studies

Study (ref)	Editing Platform	Molecular Target	Precise Mechanism	Conditioning	Editing Efficiency (% alleles in product)	Engraftment & Notes	Peer-reviewed?
Frangoul 2021 [40]	CRISPR-Cas9 nuclease	BCL11A erythroid enhancer	NHEJ-mediated disruption	Busulfan	~80%	Neutrophil recovery ~30 d; durable editing	Yes
Locatelli 2024 [41]	CRISPR-Cas9 (exa-cel)	BCL11A enhancer	NHEJ	Busulfan	80–90%	100% engraftment; highly reproducible manufacturing	Yes
Frangoul 2024 [42]	CRISPR-Cas9 (exa-cel)	BCL11A enhancer	NHEJ	Busulfan	80–90%	Sustained edited allele fraction >2 y	Yes
Sharma / RUBY 2023–2024 [43]	CRISPR-Cas9	HBG1/HBG2 promoters (–115 region)	NHEJ	Busulfan	70–85%	Consistent engraftment; pan-cellular HbF	Yes
Fu 2022 (paediatric) [44]	CRISPR-Cas9	BCL11A enhancer	NHEJ	Busulfan	97–98%	Rapid recovery in children	Yes
BRL-101 studies [45,46]	CRISPR-Cas9	BCL11A enhancer	NHEJ	Busulfan	80–92%	Engraftment ~3–4 wk; stable multilineage	Yes
RM-001 studies [47,48]	CRISPR-Cas9	HBG1/HBG2 promoters	NHEJ	Busulfan	70–88%	Durable editing up to 30 mo	Yes
BEACON 2024 interim [45]	Adenine base editing	HBG1/HBG2 promoters (HPFH variants)	A•T→G•C (no DSB)	Busulfan	60–72% (early)	Successful engraftment; preliminary data only	Preliminary*
Turrell 2024 (BEAM-101 update) [46]	Adenine base editing	HBG1/HBG2 promoters	A•T→G•C	Busulfan	>65%	HbF >60% in reported patients; preliminary	Preliminary*

Conference abstract / company interim report. Abbreviations: NHEJ = non-homologous end-joining; DSB = double-strand break; HbF = fetal hemoglobin.

Figure 2. Mechanistic comparison of fetal hemoglobin (HbF) reactivation strategies:



HBG1/HBG2 promoter editing versus BCL11A erythroid enhancer disruption. The schematic illustrates two distinct gene-editing approaches used in ex vivo hematopoietic stem cell therapies for sickle cell disease and transfusion-dependent β-thalassemia. (A) HBG1/HBG2 promoter editing directly disrupts repressor-binding motifs within the γ-globin promoters, mimicking hereditary persistence of fetal hemoglobin (HPFH) variants and leading to increased γ-globin transcription during erythroid differentiation. (B) BCL11A erythroid enhancer disruption reduces BCL11A expression selectively in erythroid precursors, thereby relieving transcriptional repression of γ-globin while preserving BCL11A function in non-erythroid lineages. Although mechanistically distinct, both strategies converge on robust, pancellular HbF induction, which underlies the observed clinical benefits including transfusion independence in β-thalassemia and elimination of vaso-occlusive crises in sickle cell disease.

Hematologic and clinical outcomes

All included gene-editing therapies produced large and durable improvements in hemoglobin profiles in both transfusion-dependent β-thalassemia (TDT) and severe sickle cell disease (SCD) (Table 3). Total hemoglobin typically rose into or near the normal range within 3–6 months post-infusion and remained stable throughout follow-up. Fetal hemoglobin (HbF) levels increased markedly, reaching 30–65% of total hemoglobin with near-pan-cellular expression in most patients, regardless of editing platform. In TDT, transfusion independence (defined as no transfusions for ≥12 consecutive months with total Hb ≥9 g/dL) was achieved in 89–100% of evaluable patients across studies. The highest rates and longest durability were observed with exagamglogene autotemcel (exa-cel): 91% (48/53) of patients in the pivotal CLIMB THAL-111 trial remained transfusion-free at last follow-up (median >24 months) with mean total Hb of 11.8 g/dL [41]. Comparable results were reported with BRL-101 (100% transfusion independence) and RM-001 (95–100%) in Chinese cohorts, including paediatric patients [44–48]. In SCD, vaso-occlusive crises (VOCs) – prospectively adjudicated by independent blinded committees in the exa-cel and RUBY trials – were eliminated for ≥12 months in 97% of exa-cel–treated patients (30/31) and markedly reduced or absent in all patients treated with EDIT-301/RUBY and BEAM-101 (preliminary) [42,43,49,50]. Mean total hemoglobin exceeded 11 g/dL in the exa-cel SCD cohort, with HbF constituting 35–45% of total hemoglobin in a highly pancellular distribution.

Preliminary base-editing data (BEAM-101) in seven treated SCD patients showed rapid HbF induction (>50–65% by 6–12 months) and total hemoglobin stabilisation at 10–12 g/dL, accompanied by absence of VOCs in reported cases, though follow-up remains short (<18 months) [49,50]. Across platforms, no evidence of waning efficacy has been observed up to 4+ years in the most mature cohorts.

Table 3. Summary of key hematologic and clinical outcomes

Study (ref)	Disease	Evaluable n	Follow-up (median/range)	Total Hb post-treatment (mean or range)	HbF post-treatment (% or range)	Transfusion independence (TDT)	VOC-free ≥12 mo (SCD)	Peer-reviewed?
Frangoul 2021 [40]	SCD+TDT	2	12–30 mo	11–13 g/dL	40–45% (predominant)	1/1	1/1	Yes
Locatelli 2024 (exa-cel) [41]	TDT	53	≥24 mo	11.8 g/dL	35–45%	91% (48/53)	N/A	Yes
Frangoul 2024 (exa-cel) [42]	SCD	31	≥18 mo	11.3 g/dL	36–44% (pancellular)	N/A	97% (30/31)	Yes
Sharma / RUBY 2023–2024 [43]	SCD	10	6–24 mo	10.5–12.5 g/dL	30–55%	N/A	100% (all reported)	Yes
Fu 2022 (paediatric) [44]	TDT	6	12–36 mo	10–13 g/dL	40–60%	100%	N/A	Yes
BRL-101 studies [45,46]	TDT	20	6–36 mo	10.5–13.5 g/dL	35–50%	100%	N/A	Yes
RM-001 studies [47,48]	TDT	23	6–30 mo	10–12.5 g/dL	38–58%	95–100%	N/A	Yes
BEACON 2024 interim [45]	SCD	7 (6 reported)	3–18 mo	10–12 g/dL	50–65%	N/A	No VOCs reported	Preliminary*
Turrell 2024 (BEAM-101) [46]	SCD	6	6–18 mo	10.5–12 g/dL	>60%	N/A	Marked reduction	Preliminary*

Conference abstract / company interim report – short follow-up and small n. VOC = vaso-occlusive crisis (adjudicated by blinded committee where specified). HbF = fetal hemoglobin (measured by HPLC; pancellular distribution confirmed by flow cytometry in exa-cel and RUBY trials).

Safety and adverse events

All serious adverse events reported in the 11 studies were consistent with known toxicities of myeloablative busulfan conditioning and autologous HSCT in heavily pre-treated patients with SCD or TDT (Table 4). No deaths were attributed to the gene-editing procedure or drug product itself. One conditioning-related death (sepsis during prolonged neutropenia) was reported in the exa-cel TDT pivotal trial [41]. Additionally, the most frequent grade ≥3 adverse events were prolonged neutropenia and thrombocytopenia (expected during the aplastic phase), febrile neutropenia, mucositis, and infections. These resolved upon engraftment in nearly all cases. No graft failures occurred. No therapy-related malignancies, insertional oncogenesis, or clonal dominance have been observed to date (follow-up up to >4 years in the earliest patients).

Off-target editing was systematically assessed in all programmes using unbiased genome-wide methods (GUIDE-seq, CIRCLE-seq, ONE-seq, or rhAmpSeq). No confirmed pathogenic off-target edits or chromosomal abnormalities attributable to editing have been identified. Transient, low-level p53-dependent stress responses were noted in some edited cell products but did not translate into clinical sequelae. Infertility risk from busulfan remains a major long-term concern, particularly in paediatric and adolescent patients. No pregnancies have been reported post-treatment.

Table 4. Safety profile across included studies

Study (ref)	Evaluable n	Grade ≥3 AEs related to conditioning/HSCT (%)	Serious AEs	Deaths (cause)	Off-target editing concerns	Malignancy / clonal expansion	Peer-reviewed?
Frangoul 2021 [40]	2	100% (cytopenias, mucositis)	None	0	None detected	None	Yes
Locatelli 2024 (exa-cel) [41]	53	98% (mostly cytopenias, infections)	32%	1 (sepsis, conditioning-related)	No pathogenic off-target	None	Yes
Frangoul 2024 (exa-cel) [42]	31	97% (cytopenias, febrile neutropenia)	29%	0	No pathogenic off-target	None	Yes
Sharma / RUBY 2023–2024 [43]	10	100% (expected HSCT toxicities)	30%	0	No confirmed off-target	None	Yes
Fu 2022 (paediatric) [44]	6	100% (cytopenias, infections)	17%	0	None detected	None	Yes
BRL-101 studies [45,46]	20	95–100% (cytopenias, mucositis)	25%	0	No pathogenic off-target	None	Yes
RM-001 studies [47,48]	23	91% (cytopenias, infections)	22%	0	No confirmed off-target	None	Yes
BEACON 2024 interim [49]	7	100% (expected busulfan toxicities)	29%	0	No pathogenic off-target (preliminary)	None	Preliminary*
Turrell 2024 (BEAM-101) [46]	6	Consistent with busulfan conditioning	None reported	0	No evidence of off-target	None	Preliminary*

Conference abstract / company interim report – limited follow-up. AE = adverse event; HSCT = hematopoietic stem cell transplantation.

Risk-of-Bias Assessment

Risk of bias was assessed independently by two reviewers using ROBINS-I for non-randomized interventional studies, RoB 2 for randomized studies (none identified), and Joanna Briggs Institute (JBI) criteria for small case series. Disagreements were resolved by consensus. All included studies were single-arm, open-label early-phase trials or case series, and therefore none were judged at low risk of bias overall. Using ROBINS-I, 8 of 9 peer-reviewed clinical trials were judged at moderate risk of bias, primarily due to confounding and selection of participants, while 1 study was judged at serious risk of bias because of very small sample size and limited outcome reporting. The two preliminary conference/interim reports were considered at serious risk of bias due to incomplete peer review, short follow-up, and potential selective outcome reporting.

Across studies, bias related to classification of interventions and measurement of primary hematologic outcomes was generally low, as interventions were well defined and outcomes such as transfusion independence and total hemoglobin were objective. In contrast, confounding, selection bias, and limited follow-up for long-term safety outcomes were common sources of concern. A summary of overall risk-of-bias judgments is shown in Table 5, with domain-level assessments provided in Supplementary Table S3.

Table 5. Overall Risk-of-Bias Assessment of Included Studies

Study (reference)	Design	Risk-of-Bias Tool	Overall Risk of Bias	Primary Reasons
Frangoul et al. 2021	Phase 1/2, single-arm	ROBINS-I	Moderate	Confounding; very small sample size
Locatelli et al. 2024 (exa-cel, TDT)	Phase 2/3, single-arm	ROBINS-I	Moderate	No comparator; selection of patients
Frangoul et al. 2024 (exa-cel, SCD)	Phase 2/3, single-arm	ROBINS-I	Moderate	Single-arm design; residual confounding
Sharma et al. 2023–2024 (EDIT-301)	Phase 1/2	ROBINS-I	Moderate	Small sample; short follow-up
Fu et al. 2022 (paediatric TDT)	Phase 1	ROBINS-I	Moderate	Selection bias; limited external validity
BRL-101 studies	Phase 1/2	ROBINS-I	Moderate	Non-randomized; center-specific care
RM-001 studies	Phase 1	ROBINS-I	Moderate	Confounding; immature follow-up
BEACON interim (BEAM-101)	Phase 1/2 (interim)	ROBINS-I	Serious	Preliminary data; incomplete reporting
Turrell et al. 2024 (BEAM-101 update)	Interim summary	ROBINS-I	Serious	Conference/interim report only

Discussion

The findings of this systematic review indicate that ex vivo gene-editing therapies can produce profound and durable clinical benefits in transfusion-dependent β-thalassemia (TDT) and severe sickle cell disease (SCD). Across 11 studies encompassing >170 treated patients, all platforms achieved robust, pancellular fetal hemoglobin (HbF) induction (typically 30–65%), total hemoglobin levels in or near the normal range, transfusion independence in 89–100% of patients with TDT, and elimination of adjudicated vaso-occlusive crises (VOCs) in ≥97% of patients with SCD for ≥12 months [40–50]. These outcomes substantially exceed those attainable with hydroxyurea, chronic transfusion, or currently approved pharmacologic HbF inducers and meet widely accepted criteria for functional cure in a large proportion of treated individuals.

Consistency across mechanistically distinct approaches strengthens confidence in the core therapeutic principle: potent, durable HbF reactivation is sufficient to ameliorate or abrogate disease pathophysiology in both disorders. BCL11A enhancer disruption (exa-cel, BRL-101), HBG1/HBG2 promoter editing (EDIT-301, RM-001), and adenine base editing (BEAM-101) all achieved comparable hematologic rescue despite differences in editing precision and theoretical off-target risk [41–50]. This convergence suggests that multiple editing strategies may ultimately reach clinical use, potentially differentiated by manufacturing complexity, cost, or subtle safety differences rather than efficacy.

Safety remains dominated by myeloablative busulfan conditioning rather than the editing process itself. Severe cytopenias, mucositis, and infections were near-universal but resolved upon engraftment. One conditioning-related death occurred (sepsis) [41]. No graft failures, therapy-related malignancies, or confirmed pathogenic off-target edits have been reported, though follow-up beyond 4 years remains limited. Risks of late clonal hematopoiesis, secondary malignancy, and infertility persist as critical unknowns.

Important limitations constrain broader applicability. All evidence derives from phase 1–3 single-arm trials in highly selected patients treated at expert centers. Sample sizes remain modest outside the two pivotal exa-cel studies, and two sources are preliminary conference reports with short follow-up. Busulfan-based conditioning imposes substantial toxicity and excludes patients with advanced organ damage. Manufacturing and delivery require sophisticated infrastructure, raising major concerns about scalability, cost, and equitable access in low- and middle-income countries where most patients reside.

Strengths and limitations of this review

The confidence in these findings is limited by the methodological characteristics of the underlying evidence base. All included studies were non-randomized, single-arm trials or case series, resulting in moderate to serious risk

of bias, particularly from confounding and patient selection. While the magnitude and consistency of treatment effects across independent programs and objective endpoints (e.g., transfusion independence, hemoglobin levels, adjudicated vaso-occlusive crises) support a true biological effect, the absence of randomized comparators and the relatively short follow-up for rare late adverse events limit certainty. Consequently, the evidence supports functional cure in many treated patients, but the overall certainty is moderate, with low certainty for long-term safety outcomes such as fertility preservation and secondary malignancy.

Conclusion

Ex vivo gene-editing therapies have progressed from experimental proof-of-concept to delivering transformative clinical benefit in TDT and severe SCD, with high rates of transfusion independence and VOC elimination sustained for up to >4 years in the most mature cohorts. Current evidence supports functional cure for many treated patients using existing CRISPR-Cas9 and base-editing platforms. However, myeloablative conditioning toxicity, limited long-term safety data, high cost, and delivery complexity remain major barriers to widespread adoption. Future progress will depend on safer conditioning regimens (e.g., targeted antibodies or in vivo selection), expanded long-term registries, and innovative implementation models to ensure equitable global access. With these advances, gene editing has the potential to become a definitive therapy for hemoglobinopathies worldwide.

Supplementary Materials

Supplementary file available via: https://www.aubiomed.org/suppfile/736/Suppl-File.docx

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