

Anemia-Relieving Pharmacotherapies for Thalassemia: A Cross-Sectional Study of Clinical Trials from Clinicaltrials.gov

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Abstract

Background: Thalassemia is a prevalent inherited hematologic disorder imposing substantial health burdens, with unmet clinical needs for effective anemia-relieving therapies. Despite the rapid advancement of targeted drug development, systematic characterization of the global clinical trial landscape remains insufficient.

Objective: To examine the characteristics and publication status of clinical trials involving anemia-relieving pharmacotherapies for thalassemia registered on ClinicalTrials.gov.

Methods: Data of interventional clinical trials of anemia-relieving pharmacotherapies for thalassemia, registered on ClinicalTrials.gov, were collected on July 27, 2026. Key aspects such as the general characteristics, study design features, treatment strategies, outcome measures, and publication status were analyzed.

Results: Fifty-six clinical trials were included. Of these, 29 (51.8%) were completed, while only 12 (21.4%) had posted results. Most trials targeted adults and older adults (19, 33.9%), with the majority of studies conducted in Asia (22, 39.3%). Phase 2 studies were the most common (23, 41.1%), and 25 (44.6%) employed randomization. Additionally, 30 (53.6%) used a parallel assignment intervention model, while 39 (69.6%) had no blinding. The most commonly studied drug category was fetal hemoglobin inducers (29, 51.8%). Recently, research into novel therapeutic agents has risen considerably, including erythroid maturation agents (10, 17.9%) and pyruvate kinase activators (11, 19.6%). While primary outcome measures varied across studies, hemoglobin level changes were the most commonly utilized measure (24, 42.9%).

Conclusions: Most interventional trials on anemia-relieving pharmacotherapies for thalassemia were non-randomized, non-blinded, and employed parallel assignment, primarily involving adult and older adult patients. While a significant portion of the research focused on fetal hemoglobin inducers, there has been a rising interest in erythroid maturation agents and pyruvate kinase activators. The current trial landscape is marked by low rates of registry result posting and full-text publication, highlighting the need for improved methodological rigor, standardized outcome assessment, and extended follow-up to support evidence-based drug development for this lifelong disease.

Keywords

Thalassemia, clinical trial, treatment, Clinicaltrials.gov

1. Introduction

Thalassemia comprises a group of inherited blood disorders characterized by deficient or absent synthesis of the α - or β -globin chains of hemoglobin (Hb), leading to an imbalance between α - and β -globin chains. This disruption impedes normal hemoglobin A formation, shortening erythrocyte lifespan, increasing osmotic fragility, and ultimately producing hemolytic anemia. Thalassemia shows high prevalence across specific regions, notably Southeast Asia, the Mediterranean area, and southern China. With ~1.5% of the global population carrying related mutations(1), it created substantial public health, medical, and socioeconomic burdens. Clinically, Thalassemia is stratified into transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) according to transfusion requirements(2).

Present therapeutic approaches for thalassemia encompass regular blood transfusions, iron chelation therapy to manage iron overload, hematopoietic stem cell transplantation (HSCT), and newly developing gene therapy(3, 4). Despite these advances, blood shortages and economic constraints often prevent patients from accessing consistent and adequate transfusion therapy(5, 6). Meanwhile, many patients remain ineligible for transplantation or gene therapy due to availability and cost barriers. Therefore, the development of pharmacologic agents to alleviate anemia is critically important. Historically, agents such as hydroxyurea and thalidomide have been used in patients with TDT to relieve anemia symptoms(6). Recent advances in the molecular understanding of thalassemia have facilitated the identification of new therapeutic targets, ushering in a new era of pharmacologic strategies for anemia management. Nevertheless, the rapid proliferation of drug development efforts lacks a systematic assessment, which may lead to study duplication, fragmented evidence generation, and a misalignment between research priorities and clinical needs.

As the gold standard for evaluating safety and efficacy of emerging treatments, clinical trials constitute a critical foundation for therapeutic advancement(7, 8). To enhance research transparency, the International Committee of Medical Journal Editors requires registration of all clinical trials in a public database prior to recruiting participants, which led to the establishment of Clinicaltrials.gov as a repository of clinical trial information(9).

Clinicaltrials.gov is the world's largest clinical trial database. It offers unique strengths including full research pipeline coverage, unbiased trial design assessment and standardized structured fields, thus delivering critical insights into current research trends and knowledge gaps(10). Several studies have examined medication strategies and trial characteristics across various domains using this registry. However, a systematic ClinicalTrials.gov-based evaluation of pharmacologic therapies for thalassemia remains absent. By analyzing trials related to anemia-relieving pharmacotherapies for thalassemia registered in ClinicalTrials.gov, this study comprehensively examines their trial characteristics, study designs, drug categories, and outcome measures. It aims to deepen understanding of the current research landscape, inform the design of future studies, and provide regulators, funding agencies and researchers with evidence on therapeutic development gaps.

2. Methods

2.1 Ethical Compliance

The Research Ethics Committee of Jiangbin Hospital of Guangxi Zhuang Autonomous Region confirmed that no ethical approval was required, as this study relies solely on publicly available data from ClinicalTrials.gov and involves no human participants or animals.

2.2 Data Collection

In this study, a cross-sectional analysis was performed to examine clinical trials related to anemia-relieving pharmacotherapies for thalassemia registered on Clinicaltrials.gov. Data were retrieved on July 27th, 2026, using an advanced search strategy with the following query: “AREA[Condition]Thalassemia,” restricted to interventional studies. Retrieved records were downloaded in CSV format and imported into Microsoft Excel for screening and extraction. Duplicate records were automatically identified in Microsoft Excel based on identical trial registration numbers (NCT numbers), with manual verification performed by comparing study titles. Incomplete records were defined as trials missing essential information required for analysis, including: NCT number, study title, study status, brief summary, study results, targeted conditions, interventions, outcome measures, participant characteristics, study phase, enrollment size, funding source, study design and geographic location. After excluding incomplete records, eligible records were screened to identify trials investigating anemia-relieving pharmacotherapies. For this study, "anemia-relieving pharmacotherapies" were defined as pharmacological agents that target the pathophysiology of anemia in thalassemia to increase Hb levels or reduce transfusion dependency. Eligible trials were identified by systematically evaluating description in the brief summary, intervention and outcome measures of the clinical trials. Trials evaluating interventions not primarily intended to correct anemia (e.g., iron chelators, HSCT, gene therapy, and medications for thalassemia-related complications) were excluded. (Figure 1)

2.3 Data Evaluation

The correlation between categorical variables was examined using Fisher's exact test. Given the exploratory nature of this registry-based study and the multiple comparisons performed across drug categories, a conservative significance threshold of $p < 0.01$ was used to reduce the risk of false-positive findings. R version 4.5.0 and Microsoft Excel served as the platforms for conducting all analytical procedures.

2.4 Search For Publications Of Trials

We searched EMBASE, MEDLINE (PubMed), and the Cochrane Central Register using NCT numbers to identify published trial results. All searches were conducted on August 20th, 2026.

2.5 Sensitivity Analysis

During data cleaning after data retrieval from ClinicalTrials.gov, we identified a subset of included trials with an “Unknown” study status. To evaluate the robustness of our primary findings against potential bias introduced by these records with uncertain status, we performed a post-hoc exploratory sensitivity analysis. In this sensitivity scenario (Scenario B), after excluding all trials with “Unknown” status, all analyses were re-performed. The primary analysis based on the full included cohort was defined as Scenario A. Given its post-hoc nature, findings from Scenario B serve only for robustness checking, and our main conclusions remain anchored to the primary analysis (Scenario A).

3. Results

3.1 Screening And Included Trials

Our preliminary search identified 336 trials. After removing incomplete records, 304 trials remained. Subsequent detailed review excluded 248 trials for the following reasons: 75 trials investigating medications for thalassemia-related complications (including bone disease, endocrine disorders, pulmonary and hepatic diseases, and thrombotic conditions), 56 trials assessing iron-chelating agents, 50 trials related to gene therapy, 44 trials evaluating HSCT or transplantation-related complications (e.g., graft-versus-host disease), 13 trials on dietary supplements, and 10 trials involving medical

devices and diagnostics. Ultimately, 56 registered trials met the inclusion criteria and were included in the final analysis.

3.2 General Characteristics And Study Designs Of Included Trials

The characteristics of the 56 included clinical trials are presented in Table 1. With respect to trial status, 29 (51.8%) were completed, and 12 (21.4%) had reported study results. In terms of participant populations, 19 (33.9%) enrolled adults and older adults, and the vast majority (53, 94.6%) included participants of all sexes. Geographically, 22 (39.3%) were conducted in Asia. Multi-center trials accounted for 35 (62.5%). Industry funding was reported for 25 trials (44.6%), while 31 (55.4%) received non-industry support. Regarding trial phase, phase 2 trials were most common (23, 41.1%). Of the included trials, 25 (44.6%) employed randomization. A parallel-group design was used in 30 (53.6%) trials, and no masking design was applied in 39 (69.6%). Most trials enrolled ≤ 50 participants (23, 41.1%), and the majority (34, 60.7%) had an observation period of ≤ 6 months, while 7 (12.5%) followed participants for ≥ 24 months.

3.3 Characteristics Of Trials With Available Results And Publication

Among the 56 clinical trials included in the analysis, 13 had corresponding publications. Table S1 summarizes these 13 published trials, including NCT number, title, journal, impact factor, and Journal Citation Reports (JCR) quartile ranking. The impact factors of the publishing journals ranged from 1.9 to 109.

3.4 Analysis And Summarization Of Drug Categories

Investigated pharmacological agents were grouped into five categories according to their primary mechanism of action (Table 2): fetal hemoglobin (HbF) inducers (N=29), pyruvate kinase activators (N=11), erythroid maturation agents (N=10), traditional Chinese medicine (TCM, N=4), and erythropoiesis inducers (N=2). HbF inducers represented the largest group. Within this class, thalidomide (n=9) and hydroxyurea (n=7) were the most frequently studied single agents, and combination regimens were also assessed. Among pyruvate kinase activators, etavopivat (n=6) and mitapivat (n=5) were evaluated. Luspatercept accounted for 9 out of 10 trials of erythroid maturation agents. Four TCM trials mainly involved Colla Corii Asini and one herbal concoction. Two trials tested erythropoiesis-inducing compounds, including AND017 (an oral hypoxia-inducible factor stabilizer that enhances erythropoiesis) and Pegylated Erythropoietin. Drug categories differed substantially with respect to industry funding, results posting and publication status (Table 3). All pyruvate kinase activator and erythropoiesis inducer trials received industry funding, compared with only 13.9% of HbF inducer trials and zero TCM trials (overall $p < 0.01$). No statistically significant between-group differences were detected for the proportion of posted results ($p = 0.1424$) or study publication rate ($p = 0.1605$).

3.5 Outcome Measures In The Included Clinical Trials

Outcome measures are summarized in Table 4. Change in Hb level was the most frequent used outcome measure (24/56, 42.9%). Five trials applied differentiated outcome measures for TDT and NTDT. Several composite endpoints combining Hb, HbF and transfusion-related parameters were also used across smaller subsets of trials.

3.6 Sensitivity analysis

A sensitivity analysis excluding the eight trials with “Unknown” study status (Scenario B, n=48) was performed to test the robustness of primary findings (Scenario A, n=56, Supplementary Tables S2-S4). After exclusion, the proportion of completed trials increased moderately, but the overall distribution of

trial characteristics remained largely consistent with the primary analysis. The difference in industry funding across drug classes remained statistically significant, while p values for result posting and publication changed. The TCM subgroup was reduced to n=1 in Scenario B, yielding unstable estimates for this category. Change in Hb level remained the most commonly employed outcome measure. Collectively, sensitivity analysis supported the robustness of the main conclusions derived from the primary dataset.

4. Discussion

This study systematically mapped the landscape of interventional trials evaluating anemia-relieving pharmacotherapies for thalassemia registered on ClinicalTrials.gov. To date, the only published analysis related to clinical trials for thalassemia is a systematic review focused on gene therapy of β -hemoglobinopathies(11). No study has examined drug trials specifically, leaving the pharmacological pipeline entirely uncharacterized until now.

Consistent with the global epidemiological distribution, Asia dominated trial conduct (39.3%, Table 1). However, this geographic concentration may limit generalizability. Specifically, Asian cohorts predominantly harbor the α -thalassemia-associated Southeast Asian (α -SEA) deletion and distinct β -mutations (e.g., CD41-42, IVS-II-654). These profiles contrast sharply with Mediterranean populations, who primarily carry β^0 mutations, and African cohorts, where α^+ variants (e.g., $-\alpha^{3.7}$) are prevalent(12, 13). Genetic heterogeneity is known to modify transfusion requirements and drug responsiveness(14-16). Thus, geographically restricted trial recruitment may limit the applicability of evidence to global patient populations. These observations indicate the need for more cross-continental collaborations to ensure representative enrollment and robust external validity.

Methodologically, the current research landscape is characterized by early-phase exploration, limited scale, and inadequate methodological rigor. Early-phase trials (early phase 1, phase 1, phase 1/2, phase 2) constituted the majority of included studies, with phase 2 studies alone constituting 41.1% (Table 1). Confirmatory-stage phase 3 and post-marketing phase 4 trials were markedly underrepresented. The relative scarcity of phase 3 registered trials in this database snapshot suggests that few candidates are currently in late-stage confirmatory development visible on ClinicalTrials.gov, while the low proportion of phase 4 post-marketing studies (10.7%) indicates inadequate real-world evidence on long-term safety and efficacy for approved agents. Non-randomized designs were common, and 69.6% of trials were conducted without blinding (Table 1). While such designs are common and often necessary in exploratory development, they increase susceptibility to performance and detection bias, thereby reducing the reliability of reported outcomes(17). Furthermore, most trials (60.7%) had an observation period of six months or less, whereas only 12.5% followed participants for ≥ 24 months (Table 1). Given that thalassemia requires lifelong treatment, data from extended follow-up on safety and efficacy are critical. Evidence suggests that prolonged thalidomide use may cause neuropathic complications(18). Similarly, prolonged hydroxyurea use has been linked to painful skin ulcers, aphthous ulcers, non-ulcerative skin toxicity with erythema, and skin infiltration(19). However, the short follow-up durations in current trials hinder comprehensive safety assessment and may obscure these delayed toxicities. Coupled with the predominance of small-scale trials, the ability to detect rare adverse events is severely limited. This highlights the necessity of long-term extension studies, standardized adverse event reporting, and real-world post-marketing surveillance to fully characterize delayed and rare toxicities and enable comprehensive pharmacovigilance. Collectively, these

methodological shortcomings highlight important gaps that should be addressed in the design of future clinical trials.

In addition to methodological limitations, the evolution of treatment strategies also reflects the current development status of the field. HbF inducers remained the most frequently studied class, led by thalidomide and hydroxyurea, yet received minimal industry sponsorship (13.8%, Table 3). Most interventions in this category were established marketed drugs or repurposed agents (e.g., benserazide), with only a minority being novel investigational compounds (e.g., IMR-687, a selective phosphodiesterase-9 inhibitor). In contrast, erythroid maturation agents and pyruvate kinase activator attracted strong commercial investment, reflecting a strategic focus on innovative mechanisms to address unmet clinical needs. The disparity in industry sponsorship across drug classes reflects patent-status economics rather than clinical promise alone. Most HbF inducers are long off-patent legacy drugs offering minimal commercial incentive, leaving their evidence base anchored in small, academically driven studies with limited regulatory reliability. In contrast, patent-protected novel agents carry strong commercial incentives for rigorous, registration-directed trials, explaining their more advanced regulatory trajectories. This creates a concerning landscape: decades-old therapies lack modern confirmatory data, while innovative agents, though methodologically superior, remain supported by a narrow real-world evidence base. Future policy should therefore incentivize independent, publicly funded comparative trials and long-term safety surveillance of generic HbF inducers to address these unmet needs. Notably, among the novel therapeutic agents investigated, luspatercept is the only drug that has received approval from the United State Food and Drug Administration (FDA) for the treatment of anemia in adult patients with TDT. It is also recommended as a treatment option in the Thalassemia International Federation Guidelines for the Management of TDT(4), indicating that high barriers exist for regulatory approval even with abundant early-phase clinical research data.

Outcome measures were heterogeneous, with Hb level change being the most common used outcome measure (42.9%, Table 4). However, regular or intermittent transfusions can alter hematologic parameters and bias efficacy assessments. To address this, ten trials used composite outcomes that combined changes in Hb levels with transfusion frequency, rather than relying on Hb alone. This approach minimized potential bias from transfusion-dependent fluctuations. Similarly, five studies differentiated outcome measures between TDT and NTDT patients, which may further reduce bias. Nevertheless, outcome measures based on transfusion metrics are subject to variability due to donor Hb concentrations and storage durations of transfused blood, both of which can influence post-transfusion Hb levels(20). Therefore, future studies should carefully select appropriate outcome measures and ensure adequate follow-up durations to reduce bias and yield reliable, meaningful data.

Publication venue critically affects the dissemination and influence of trial findings, with studies demonstrating that papers in prestigious journals exert stronger influence on clinical practice and future research trajectories(21, 22). Consistent with this, our findings show that an increasing number of trials on anemia-relieving pharmacotherapies for thalassemia are being published in high-quality, high-impact journals (Table S1), underscoring growing international academic recognition. Despite the trend toward publication in prestigious high-impact journals, our analysis reveals a critically low rate of trial result reporting and subsequent full publication. Among the 29 completed trials, merely 12 posted results on ClinicalTrials.gov. This low compliance rate creates a transparency gap that severely hampers real-time evidence synthesis. More concerning is the observed discordance between registry reporting and publication. We noted that while none of the TCM trials posted results on the registry,

two (50.0%) had corresponding journal publications. This pattern reflects a broader issue: under the FDA Amendments Act of 2007, applicable clinical trials are mandated to submit and post results within 12 months of the primary completion date(23). Failure to adhere to these mandates carries both academic and legal consequences: it exacerbates publication bias and compromises evidence-based medicine, while also exposing sponsors to civil monetary penalties and regulatory liability. Beyond these direct harms, the absence of timely registry reporting leads to research waste, as without access to negative or neutral results via registries, researchers may unknowingly duplicate failed experiments, resulting in inefficient resource allocation in thalassemia drug development.

Based on these findings, several key considerations may guide further investigations in this field. Enhanced methodological quality should be pursued through standardized randomization and blinding across all trial phases, including early developmental studies. Extended follow-up durations are warranted for therapeutic strategies aimed at chronic hematological disorders like thalassemia. Future investigations ought to prioritize multi-center and cross-continental collaborations to strengthen the external validity of outcomes across diverse patient cohorts and healthcare settings worldwide. Concerted efforts are also required to optimize the reporting of trial data. Complete reporting of all study findings, irrespective of endpoint outcomes, may minimize research redundancy and improve transparency in the developmental pathway of therapeutic modalities for thalassemia.

This study has several limitations. First, the analysis was limited to trials registered on ClinicalTrials.gov, which may not fully capture studies recorded on other international clinical trial registration platforms. Second, registry entries depend on submitter provided information and are susceptible to reporting errors and omissions. We only have access to registry recorded fields and cannot retrieve original trial protocols, so it is impossible to verify whether the actual trial implementation is consistent with registry submissions. Third, several drug specific subgroups have extremely small sample sizes. The observed between-group associations should therefore be regarded as exploratory rather than conclusive. Fourth, data were collected on 27 July 2026, and the findings may not reflect subsequent trial updates or newly registered studies.

5. Conclusion

This study provides the first analysis of registered interventional clinical trials evaluating anemia-relieving pharmacotherapies for thalassemia on ClinicalTrials.gov. Among 56 eligible trials, most were conducted in Asia and characterized by early-phase, small-sample, open-label designs with short observation durations, while HbF inducers remained the most investigated drug class and novel agents attracted substantial industry investment. The current trial landscape is marked by low rates of registry result posting and full-text publication, heterogeneous outcome measures, and limited long-term safety data. These findings highlight the need for improved methodological rigor, standardized outcome assessment, complete result dissemination, and extended follow-up to support evidence-based drug development for this lifelong disease.

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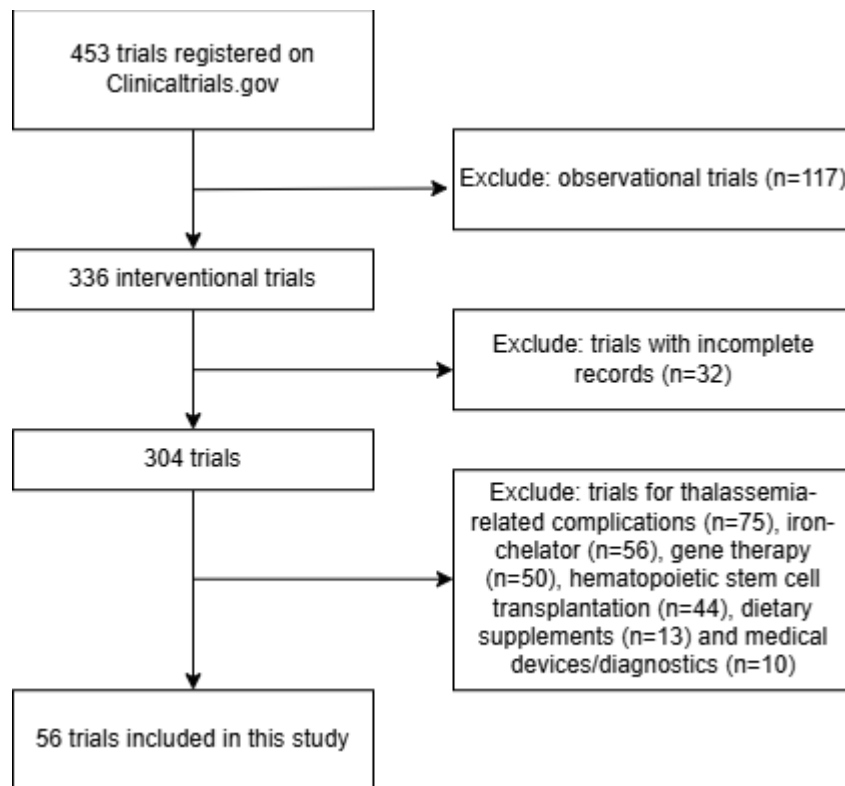
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Figure

Figure 1



Tables

Table 1: Characteristics of all included clinical trials

Characteristics		n (%)
Status		
	Completed	29 (51.8)
	Recruiting	10 (17.9)
	Unknown	8 (14.3)
	Active not recruiting	5 (8.9)
	Terminated	3 (5.4)
	Enrolling by invitation	1 (1.8)
Study Results Posted		
	No	44 (78.6)
	Yes	12 (21.4)
Participant Age		
	Adult, older adult	19 (33.9)
	Child, adult	13 (23.2)
	Adult	10 (17.9)
	Child, adult, older adult	8 (14.3)
	Child	6 (10.7)
Sex		
	All	53 (94.6)
	Female	3 (5.4)
Locations		
	Asia	22 (39.3)
	Multi continents	15 (26.8)
	North America	13 (23.2)
	Europe	6 (10.7)
Centers		
	Multi centers	35 (62.5)
	Single center	21 (37.5)
Industry Funded		
	No	31 (55.4)
	Yes	25 (44.6)
Phases		
	Phase 2	23 (41.1)
	Phase 3	8 (14.3)
	Phase 1	7 (12.5)
	Phase 4	6 (10.7)
	Phase 1/2	4 (7.1)
	Phase 2/3	4 (7.1)
	N/A	3 (5.4)
	Early phase 1	1 (1.8)

Randomization	No	31 (55.4)
	Yes	25 (44.6)
Intervention Model	Parallel	30 (53.6)
	Single group	20 (35.7)
	Crossover	2 (3.6)
	Factorial	2 (3.6)
	Sequential	2 (3.6)
Masking	No	39 (69.6)
	Yes	17 (30.4)
Enrollment Size	≤ 50	23 (41.1)
	51 ~ 100	18 (32.1)
	>200	8 (14.3)
	101 ~ 200	7 (12.5)
Observation Time	≤ 6 months	34 (60.7)
	6months-12months	12 (21.4)
	≥ 24 months	7 (12.5)
	12 months-24months	3 (5.4)

Table 2: Categories and names of drugs

Category of drugs	Name of drugs	n (%)
Fetal hemoglobin inducers (N=29)		
	Thalidomide	9 (31.0)
	Hydroxyurea	7 (24.1)
	Thalidomide + Hydroxyurea	5 (17.2)
	sodium 2,2-dimethylbutyrate	3 (10.3)
	IMR-687	2 (6.9)
	Benserazide	1 (3.4)
	Decitabine	1 (3.4)
	Hydroxyurea + Erythropoietin	1 (3.4)
Pyruvate kinase activator (N=11)		
	Etavopivat	6 (54.5)
	Mitapivat	5 (45.5)
Erythroid maturation agent (N=10)		
	Luspatercept	9 (90.0)
	Sotatercept	1 (10.0)
Traditional Chinese medicine (N=4)		
	Colla Corii Asini	3 (75.0)
	Chinese herbal concoction	1 (25.0)
Erythropoiesis inducer (N=2)		
	AND017	1 (50.0)
	Pegylated Erythropoietin	1 (50.0)

Table 3 Association between drug categories and trial funding or dissemination status

Drug Categories	Industry Funded, n (%)	Results posted, n (%)	Study Published, n (%)
Fetal hemoglobin inducers (N=29)	4 (13.9)	4 (13.8)	4 (13.8)
Pyruvate kinase activator (N=11)	11 (100.0)	3 (27.3)	2 (18.2)
Erythroid maturation agent (N=10)	8 (80.0)	5 (50.0)	4 (40.0)
Traditional Chinese medicine (N=4)	0 (0.0)	0 (0.0)	2 (50.0)
Erythropoiesis inducer (N=2)	2 (100.0)	0 (0.0)	1 (50.0)
Overall P-value	< 0.01	0.1424	0.1605

Table 4: Outcome measures of the clinical trials

Outcome Measures	N (%)
Change in hemoglobin level	24 (42.9)
Change in number of red blood cell units transfused or transfusion frequency	10 (17.9)
Change in number of red blood cell units transfused (in TDT) or change in hemoglobin level (in NTDT)	5 (8.9)
Change in hemoglobin + change in fetal hemoglobin level	4 (7.1)
Pharmacokinetic parameter	4 (7.1)
Change in fetal hemoglobin level + change in transfusion frequency	3 (5.4)
Change in hemoglobin level + change in transfusion frequency	3 (5.4)
Safety and tolerability	3 (5.4)
* NTDT, non-transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia.	

Supplementary Table S1: The details of trials with publications

NCT Number	Title	Journal	IF	JCR Q
NCT00661726	A pilot study of subcutaneous decitabine in β -thalassemia intermedia.	Blood	23.9	Q1
NCT01224496	Traditional Chinese herbal medicine in the supportive management of patients with chronic cytopaenic marrow diseases -- a phase I/II clinical study.	Complementary Therapies in Clinical Practice	3.4	Q2
NCT01571635	Sotatercept, a novel transforming growth factor β ligand trap, improves anemia in β -thalassemia: a phase II, open-label, dose-finding study.	Haematologica	8.2	Q1
NCT01624038	Therapeutic superiority and safety of combined hydroxyurea with recombinant human erythropoietin over hydroxyurea in young β -thalassemia intermedia patients.	European Journal of Haematology	2.6	Q2
NCT02604433	A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent β -Thalassemia.	New England Journal of Medicine	84.5	Q1
NCT02995707	Clinical trial on the effects of thalidomide on hemoglobin synthesis in patients with moderate thalassemia intermedia.	Annals of Hematology	2.3	Q3
NCT03271541	Haematological effects of oral administration of bitopertin, a glycine transport inhibitor, in patients with non-transfusion-dependent β -thalassaemia.	British Journal of Haematology	3.6	Q2
NCT03342404	Luspatercept for the treatment of anaemia in non-transfusion-dependent β -thalassaemia (BEYOND): a phase 2, randomised, double-blind, multicentre, placebo-controlled trial.	The Lancet Haematology	20.4	Q1
NCT03374111	Therapeutic effect of Colla corii asini on improving anemia and hemoglobin compositions in pregnant women with thalassemia.	International Journal of Hematology	1.9	Q3
NCT03692052	Safety and efficacy of mitapivat, an oral pyruvate kinase activator, in adults with non-transfusion dependent	Lancet	109	Q1

NCT04064060	α-thalassaemia or β-thalassaemia: an open-label, multicentre, phase 2 study. Patient-Reported Outcomes With Luspatercept Through 5 Years of Treatment in Patients With Non-Transfusion-Dependent β-Thalassemia Treated in the BEYOND Trial. Mitapivat in adults with non-transfusion-dependent α-thalassaemia or β-thalassaemia (ENERGIZE): a phase 3, international, randomised, double-blind, placebo-controlled trial.	European Journal of Haematology	2.6	Q2
NCT04770753	Evaluation of the combination therapy of hydroxyurea and thalidomide in β-thalassemia.	Lancet	109	Q1
NCT05132270		Blood Advances	7.7	Q1

* IF, Impact Factor; JCR Q, Journal Citation Reports Quartile

Supplementary Table S2 Sensitivity Analysis of Characteristics of Included Trials

		Scenario A Primary, N=56 (%)	Scenario B Excl. Unknown, N=48 (%)
Status	Completed	29 (51.8)	29 (60.4)
	Recruiting	10 (17.9)	10 (20.8)
	Unknown	8 (14.3)	-
	Active not recruiting	5 (8.9)	5 (10.4)
	Terminated	3 (5.4)	3 (6.3)
	Enrolling by invitation	1 (1.8)	1 (2.1)
Study Results Posted	No	44 (78.6)	36 (75.0)
	Yes	12 (21.4)	12 (25.0)
Participant Age	Adult, older adult	19 (33.9)	16 (33.3)
	Child, adult	13 (23.2)	12 (25.0)
	Adult	10 (17.9)	7 (14.6)
	Child, adult, older adult	8 (14.3)	7 (14.6)
	Child	6 (10.7)	6 (12.5)
Sex	All	53 (94.6)	48 (100.0)
	Female	3 (5.4)	0 (0.0)
Locations	Asia	22 (39.3)	18 (37.5)
	Multi continents	15 (26.8)	13 (27.1)
	North America	13 (23.2)	12 (25.0)
	Europe	6 (10.7)	5 (10.4)
Centers	Multi centers	35 (62.5)	30 (62.5)
	Single center	21 (37.5)	18 (37.5)
Industry Funded	No	31 (55.4)	25 (52.1)
	Yes	25 (44.6)	23 (47.9)
Phases	Phase2	23 (41.1)	20 (41.7)
	Phase3	8 (14.3)	8 (16.7)
	Phase1	7 (12.5)	7 (14.6)
	Phase4	6 (10.7)	3 (6.3)
	Phase 1/2	4 (7.1)	4 (8.3)
	Phase 2/3	4 (7.1)	3 (6.3)
	NA	3 (5.4)	3 (6.3)
	Early phase1	1 (1.8)	-

Randomization	No	31 (55.4)	27 (56.3)
	Yes	25 (44.6)	21 (43.8)
Intervention Model	Parallel	30 (53.6)	25 (52.1)
	Single group	20 (35.7)	17 (35.4)
	Crossover	2 (3.6)	2 (4.2)
	Factorial	2 (3.6)	2 (4.2)
	Sequential	2 (3.6)	2 (4.2)
Masking	No	39 (69.6)	33 (68.8)
	Yes	17 (30.4)	15 (31.3)
Enrollment Size	≤50	23 (41.1)	20 (41.7)
	51~100	18 (32.1)	14 (29.2)
	>200	8 (14.3)	7 (14.6)
	101~200	7 (12.5)	7 (14.6)
Observation Time	≤6months	34 (60.7)	28 (58.3)
	6months-12months	12 (21.4)	12 (25.0)
	≥24 months	7 (12.5)	6 (12.5)
	12 months-24months	3 (5.4)	2 (4.2)
* Scenario A: Primary analysis (n=56), Scenario B: Excluding 8 Unknown-status trials (n=48)			

Supplementary Table S3 Association between drug categories and trial funding or dissemination status (Excluding 8 Unknown-status trials)

Drug Categories	Industry Funded, n (%)	Results posted, n (%)	Study Published, n (%)
Fetal Hemoglobin Inducers (N=25)	4 (16.0)	4 (16.0)	2 (8.0)
Pyruvate kinase activator (N=11)	11 (100.0)	3 (27.3)	2 (18.2)
Erythroid maturation agent (N=9)	8 (88.9)	5 (55.6)	4 (44.4)
Erythropoiesis inducer (N=2)	2 (100.0)	0 (0.0)	1 (50.0)
Traditional Chinese Medicine (N=1)	0 (0.0)	0 (0.0)	1 (100.0)
Overall P value	< 0.01	0.1825	0.0181
* p values: Fisher's exact test (two-sided) for each drug class vs. all others			

Supplementary Table S4 Sensitivity Analysis of Outcome Measures

Outcome Measures	Scenario A Primary, N=56 (%)	Scenario B Excl. Unknown, N=48 (%)
Change in hemoglobin level	24 (42.9)	20 (41.7)
Change in number of red blood cell units transfused or transfusion frequency	10 (17.9)	9 (18.8)
Change in number of red blood cell units transfused (in TDT) or change in hemoglobin level(in NTDT)	5 (8.9)	5 (10.4)
Change in hemoglobin level + change in fetal hemoglobin level	4 (7.1)	3 (6.3)
Pharmacokinetic parameter	4 (7.1)	4 (8.3)
Change in fetal hemoglobin level + change in transfusion frequency	3 (5.4)	3 (6.3)
Change in hemoglobin level + change in transfusion frequency	3 (5.4)	1 (2.1)
Safety and tolerability	3 (5.4)	3 (6.3)
* Scenario A: Primary analysis (n=56), Scenario B: Excluding 8 Unknown-status trials (n=48) ;		
* NTDT, non-transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia		