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EVIDENCE REVIEW

Safety profile of concizumab: A systematic review and meta-analysis of randomised controlled trials

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Introduction: Haemophilia, a genetic bleeding disorder caused by deficiencies in clotting factors VIII (haemophilia A) or IX (haemophilia B), impairs coagulation, requiring frequent intravenous clotting factor infusions. Concizumab, a subcutaneous monoclonal antibody targeting tissue factor pathway inhibitor (TFPI), offers a potential alternative for prophylactic treatment. **Objective:** This meta-analysis evaluates the safety of concizumab in people with haemophilia, focusing on adverse events, serious adverse events, upper respiratory tract infections, and joint bleeding episodes. **Methodology:** A systematic search of PubMed, Cochrane Library, Scopus, Google Scholar, and ClinicalTrials.gov (up to February 15, 2025) identified randomised controlled trials comparing concizumab with placebo or standard therapy. Risk ratios (RR) with 95% confidence intervals (CI) were calculated, and heterogeneity was assessed using the I^2 statistic. **Results:** Four studies (137 participants) met inclusion criteria. Concizumab showed a non-significant increase in overall adverse events (RR = 1.17; 95% CI: 0.89–1.54). Serious adverse events were lower in the concizumab group (RR = 0.46; 95% CI: 0.06–3.53) but not statistically significant. Upper respiratory tract infections were similar (RR = 0.75; 95% CI: 0.15–3.85). Joint bleeding was slightly reduced (RR = 0.66; 95% CI: 0.45–0.96). **Conclusion:** Concizumab appeared generally well tolerated in short-term randomised trials. The current evidence base is small and lacks long-term or real-world data; therefore, the comparative safety of concizumab relative to standard therapies remains uncertain. Given the challenges of

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conducting large randomised trials in rare diseases, long-term registry-based follow-up may provide the most feasible and informative data on concizumab's safety and efficacy.

Keywords: *Haemophilia, Concizumab, Tissue factor pathway inhibitor, Monoclonal antibody, Adverse events, Safety, Meta-analysis*

Haemophilia A is an inherited bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) due to F8 gene mutations, leading to impaired thrombin generation and unstable clot formation. The severity is classified by plasma FVIII activity as severe (<1%), moderate (1%–5%), or mild (5%–40%), with a reference range of 50%–150% [1]. The primary goal of treatment is to prevent bleeding episodes and long-term joint damage [2].

Current guidelines recommend prophylactic (PPX) coagulation factor replacement as the standard of care for severe haemophilia, but frequent intravenous administration poses challenges, including venous access difficulties, prolonged preparation, and patient discomfort [3,4]. Alternative therapies, such as antibodies that mimic FVIII or inhibit endogenous coagulation regulators, have emerged. Concizumab, a humanised monoclonal antibody targeting tissue factor pathway inhibitor (TFPI), is designed for subcutaneous prophylaxis in haemophilia A or B, with or without inhibitory alloantibodies to FVIII or FIX. By inhibiting TFPI, concizumab restores haemostatic balance, potentially reducing bleeding episodes and improving adherence compared to intravenous therapies.

Early-phase clinical trials have demonstrated concizumab's ability to enhance thrombin generation in a dose-dependent manner. However, its safety profile, particularly concerning thrombotic risk and immunogenicity, remains under investigation [8,9]. This systematic review and meta-analysis consolidates existing evidence on concizumab's safety, evaluating adverse events, thrombosis risk, and immunogenic responses in randomised controlled trials. The findings aim to inform clinical decision-making, optimise haemophilia care, and identify gaps for future research.

METHODOLOGY

Data sources and search strategy

A systematic search was performed across PubMed, Cochrane Library, Scopus, Google Scholar, and ClinicalTrials.gov from inception to February 15, 2025.

HIGHLIGHTS

- Concizumab's potential – A subcutaneous TFPI inhibitor for haemophilia, offering an alternative to intravenous therapy
- Safety profile – Meta-analysis of RCTs shows no significant increase in adverse events compared to standard treatments
- Serious adverse events – Lower, though not statistically significant, risk in the concizumab group
- Bleeding reduction – Potential to reduce joint bleeding episodes, enhancing haemophilia management
- Future research – Larger, long-term studies are needed to confirm safety and efficacy

The search strategy incorporated both controlled vocabulary (MeSH and Supplementary Concepts) and free-text terms to identify relevant studies on the safety of concizumab in haemophilia. The following search string was applied:

("Hemophilia A"[Mesh] OR "Hemophilia B"[Mesh] OR hemophilia[tiab]) AND ("Concizumab"[Supplementary Concept] OR Concizumab[tiab]) AND ("Adverse Events"[Mesh] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "Safety"[tiab] OR "Serious Adverse Events"[tiab] OR "Upper Respiratory Tract Infections"[Mesh] OR "Hemarthrosis"[Mesh])

This strategy ensured a comprehensive retrieval of studies assessing concizumab's safety profile, focusing on adverse events, serious complications, and trial-based evidence.

Selection criteria

Studies were included if they met the following criteria: (i) randomised controlled trials or clinical trials comparing concizumab with placebo or standard therapy, (ii) enrolled patients with haemophilia A or B, (iii) reported safety outcomes, including overall adverse events, serious adverse events, upper respiratory tract infections, or haemarthrosis, (iv) published in English, and (v) provided sufficient data for extraction. Studies were excluded if they were observational, review articles, case reports, or involved concizumab in combination with other interventions that could confound safety outcomes.

Selection process

Two reviewers independently screened titles and abstracts to identify relevant studies, followed by a full-text assessment to confirm eligibility. Any differences were settled through discussion or by consulting a third reviewer. Extracted data included study design, sample size, patient demographics, intervention details (concizumab dose and duration), comparator information, and reported safety outcomes.

Outcome measures

The primary outcomes assessed were safety-related parameters, including the incidence of adverse events, serious adverse events, upper respiratory tract infections, and joint bleeding episodes. Data was extracted according to the follow-up periods reported in each study.

Data extraction

Two reviewers independently extracted data using standardised forms, capturing study characteristics, patient demographics, intervention details, comparator information, and safety data (e.g., event counts and total participants per group). Discrepancies were resolved through consensus.

Quality assessment

Two reviewers independently assessed the methodological quality of included studies using Version 2 of the Cochrane Risk of Bias tool (RoB 2) for randomised trials [6]. This evaluation covered biases related to randomization, allocation concealment, blinding, incomplete outcome data, and selective reporting. Any disagreements were addressed through discussion or, if needed, consultation with a third reviewer.

Statistical analysis

The meta-analysis followed the Cochrane Handbook for Systematic Reviews of Interventions and adhered to PRISMA guidelines [7]. Statistical analyses were performed using RevMan 5.4 (Cochrane Management System). Risk ratios (RR) with 95% confidence intervals (CI) were used to analyse dichotomous outcomes [8]. Heterogeneity was assessed using the I^2 statistic, with values over 50% indicating significant heterogeneity. A p-value of <0.05 was considered statistically significant unless specified otherwise. Analyses were conducted based on intention-to-treat populations whenever possible.

RESULTS

Literature search

Our comprehensive electronic database search yielded a total of 50 records. After subsequent screening of abstract, titles and full-text evaluation, four studies [9-12] were included in our analysis. The PRISMA flowchart for inclusion process is shown in Figure 1.

Characteristics of selected studies

Table 1 summarises the characteristics of the included studies.

Quality assessment and publication bias

The quality of the included studies was assessed using the Cochrane Risk of Bias 2.0 Tool [6], which evaluates key aspects such as how participants were randomly assigned, whether outcome data were complete, and whether all planned results were fully reported. The assessment revealed varying levels of bias across studies. Matushita 2023 [10] and Chowdary 2024 [11] (phase III trials) were classified as high risk of bias, mainly due to missing outcome data and selective reporting of results. Missing data and selective reporting can potentially skew the study findings, leading to overestimation or underestimation of the true effect. In contrast, Chowdary 2015 [12] and Shapiro 2019 [9] were deemed low risk, reflecting a more robust study design with minimal bias concerns. These findings highlight potential limitations in some studies that may affect the overall reliability of the evidence. A detailed summary of the risk of bias assessment is presented in Figure 2.Inverted funnel plots for the primary outcomes were obtained, as illustrated in Figure 3. The assessment of these plots, along with Egger's regression tests, found no significant indication of publication bias.

Certainty of evidence

The evaluation of evidence was conducted using GRADEpro Guideline Development Tool [software] [13] A detailed summary of the evidence certainty for each outcome is shown in Table 2.

Result of synthesis

Efficacy outcomes

Mean annualised bleeding ratio

For the outcome of mean annualised bleeding ratio, three studies involving 105 participants were included. Treatment with concizumab significantly reduced

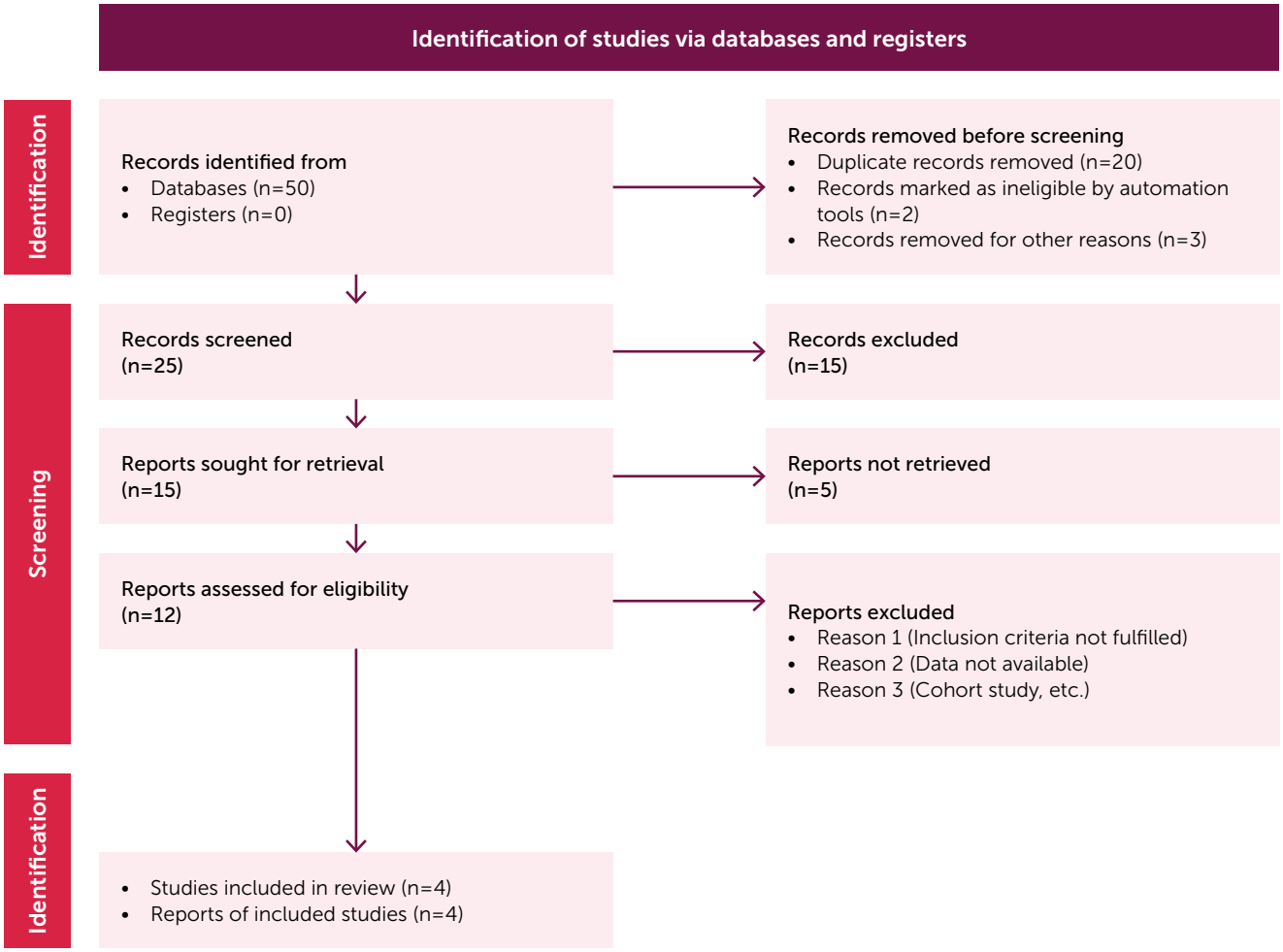
Table 1. Characteristics of studies included in the systematic review and meta-analysis

STUDY	STUDY DESIGN	STUDY LOCATION	TREATMENT DURATION	INCLUSION CRITERIA	MEAN AGE	INTERVENTION GROUP	CONTROL GROUP	OUTCOMES MEASURED
Chowdary 2015 [12]	Prospective, multi-centre, open-label, randomised phase 3a trial	69 investigational sites in 31 countries	• 24 weeks for group 1 (no prophylaxis) • 32 weeks for group 2 (concizumab prophylaxis) • 38 weeks on the previous prophylaxis regimen (in the intra-patient analysis set) • 24 weeks on the concizumab maintenance dose (in the intra-patient analysis set)	• Male • Aged 12 years or older • Congenital severe haemophilia A or moderate/severe haemophilia B without inhibitors • Documented treatment with clotting factor concentrate in the 24 weeks prior to screening • Participation in the prior phase 2 concizumab trial (explorer5) allowed	25.3 ± 3.1	Group 2, who received concizumab prophylaxis	Group 1, who received no prophylaxis and continued on-demand clotting factor treatment	1. Treated spontaneous and traumatic bleeding episodes, assessed at confirmatory analysis cutoff (N) 2. Treated spontaneous and traumatic bleeding episodes during concizumab prophylaxis vs. previous prophylaxis, in intra-patient comparison (N) 3. Secondary outcomes: • Treated spontaneous bleeding episodes (N) • Treated spontaneous and traumatic joint bleeds (N) • Treated spontaneous and traumatic target joint bleeds (N) • Safety measures (e.g., thromboembolic events, hypersensitivity reactions, anti-drug antibodies)

STUDY	STUDY DESIGN	STUDY LOCATION	TREATMENT DURATION	INCLUSION CRITERIA	MEAN AGE	INTERVENTION GROUP	CONTROL GROUP	OUTCOMES MEASURED
Shapiro 2019 [9]	explorer4 (inhibitor trial): multi-centre, open-label, randomised controlled trial explorer5 (non-inhibitor trial): multi-centre, single-arm, open label phase 2 trial	explorer4 (inhibitor trial): multiple sites across 12 countries explorer5 (non-inhibitor trial): multiple sites across 11 countries	At least 24 weeks for those receiving concizumab (in both trials)	• Male patients • Aged 12 years or older • Congenital severe haemophilia A or moderate/severe haemophilia B without inhibitors • Documented treatment with clotting factor concentrate in the 24 weeks prior to screening • Participation in the prior phase 2 concizumab trial (explorer5) allowed	N/A	Participants who received concizumab prophylaxis (both trials)	explorer4 (inhibitor trial): participants with haemophilia A or B with inhibitors, who received on-demand treatment with eptacog alfa activated (rFVIIa) instead of concizumab prophylaxis	1. Bleeding episodes during at least 24 weeks of treatment with subcutaneous concizumab (N) 2. Secondary outcomes: • assessment of concizumab safety and immunogenicity • safety of administering rFVIIa when exposed to concizumab • supportive PK and PD endpoints
Chowdary 2024 [11]	First human dose, phase 1, multi-centre, randomised, double-blind, placebo-controlled, single-dose, dose-escalation trial	Multiple sites in 9 countries: Austria, Denmark, Germany, Malaysia, South Africa, Spain, Switzerland, Thailand, UK	43 days	• Age 18-65 years • Body weight 50-100 kg • Body mass index 18-30 kg/m^2	30-36 years	Participants who received concizumab	Participants who received placebo, with 1:3 ratio of placebo to concizumab within each dose cohort	1. Safety, including adverse events, local tolerability, and various clinical laboratory assessments 2. Pharmacokinetics of concizumab, including plasma concentrations 3. Pharmacodynamics of concizumab, including free TFPI levels, TFPI functionality, and markers of procoagulant effect (D-dimer and prothrombin F1+2)

STUDY	STUDY DESIGN	STUDY LOCATION	TREATMENT DURATION	INCLUSION CRITERIA	MEAN AGE	INTERVENTION GROUP	CONTROL GROUP	OUTCOMES MEASURED
Matsushita 2023 [10]	Prospective, multi-centre, open-label, phase 3a trial, comparing concizumab prophylaxis with no prophylaxis	N/A	• At least 24 weeks for the no prophylaxis group (Group 1) • At least 32 weeks for the concizumab prophylaxis group (Group 2), including a 5-8 week dose-adjustment period • Extension period of 128-136 weeks after the main part of the trial (Groups 3 and 4)	• Congenital haemophilia A or B with inhibitors (of any severity) • Aged 12 years or older when providing written informed consent • Body weight ≥25 kg at screening • Previously treated with bypassing agents in the 24 weeks before screening (if not transferring from explorer4)	N/A	Group 2, who received concizumab prophylaxis Groups 3 and 4 also received concizumab prophylaxis	Group 1, who received no prophylaxis (on-demand treatment with bypassing agents).	1. Treated spontaneous and traumatic bleeding episodes (N), comparing the concizumab prophylaxis group vs. no prophylaxis group 2. Key secondary outcomes: • changes in bodily pain and physical functioning scores on SF-36v2 3. Additional secondary and exploratory endpoints, including safety outcomes

Figure 1. PRISMA flow diagram for the systematic review



The PRISMA flow diagram illustrates the study selection process for this systematic review and meta-analysis, showing the identification, screening, eligibility, and inclusion phases. Numbers at each step represent studies identified through database and other sources, duplicates removed, studies screened, full-text articles assessed for eligibility, and studies included in the final analysis, providing an overview of how studies were selected and reasons for exclusion.

Figure 2. Risk of bias summary for included studies using Cocharane Risk of Bias 2.0 tool

ID	STUDY	EXPERIMENTAL	COMPARATOR	OUTCOME	WEIGHT	D1	D2	D3	D4	D5	OVERALL
1	Chowdary 2015 [12]	Concizumab	Placebo	Adverse events	10.2	🟢	🟢	🟢	🟢	🟢	🟢
2	Chowdary 2024 [11]	Concizumab	Placebo	Adverse events	14.8	🟢	🟡	🟢	🟢	🔴	🔴
3	Matushita 2023 [10]	Concizumab	Placebo	Adverse events	52.9	🟢	🔴	🟢	🔴	🔴	🔴
4	Shapiro 2019 [9]	Concizumab	Placebo	Adverse events	22.1	🟢	🟢	🟢	🟢	🟢	🟢

Key
D1 Randomisation process
D2 Deviations from intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

🟢 Low risk
🟡 Some concerns
🔴 High risk

Table 4. Product comparison data for three patients who received a SHL FIX product for a prior surgery

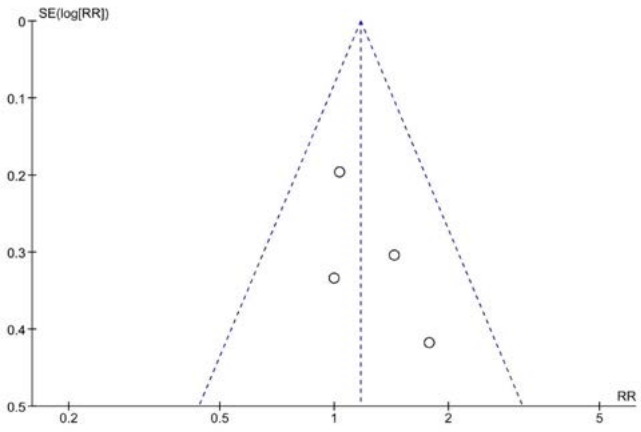
CERTAINTY ASSESSMENT							PATIENTS (N;%)		EFFECT			
STUDIES (N)	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	CONCIZUMAB	STANDARD	RELATIVE (95% CI)	ABSOLUTE (95% CI)	CERTAINTY	IMPORTANCE
Bleeding joint												
2	RCT	NS	NS	NS	NS	publication bias strongly suspecteda	15/30 (50.0%)	10/13 (76.9%)	**RR 0.66** (0.45 to 0.96)	**262 fewer per 1,000** (from 423 fewer to 31 fewer)	⊕⊕⊕◯ Moderate[a]	
Adverse events												
4	RCT	S	NS	NS	NS	none	74/99 (74.7%)	21/38 (55.3%)	**RR 1.17** (0.89 to 1.54)	**94 more per 1,000** (from 61 fewer to 298 more)	⊕⊕⊕◯ Moderate[b]	
Upper respiratory tract infection												
2	RCT	S	NS	NS	NS	publication bias strongly suspecteda	4/69 (5.8%)	2/28 (7.1%)	**RR 0.75** (0.15 to 3.85)	**18 fewer per 1,000** (from 61 fewer to 204 more)	⊕⊕◯◯ Low[a]	
Serious adverse events												
3	RCT	S	NS	NS	NS	none	7/81 (8.6%)	6/32 (18.8%)	**RR 0.46** (0.06 to 3.53)	**101 fewer per 1,000** (from 176 fewer to 474 more)	⊕⊕⊕◯ Moderate[b]	

RCT: Randomised controlled trial
NS: Not serious
S: Serious

CI: Confidence interval
RR: Risk ratio

[a] Since a funnel plot could not be generated for the outcome, publication bias is expected
[b] Since the analysis included a study with a high risk of bias, a strong bias is expected

Figure 3. Funnel plot for outcome 'adverse events'



The funnel plot shows evaluation of potential publication bias for the outcome 'adverse events'. The X-axis represents the risk ratios (RR) between concizumab and placebo; the Y-axis represents the standard error of log risk ratios (SE(log[RR])). Each open circle corresponds with an individual study. The vertical line indicates the null hypothesis (RR=1). The triangle represents the expected 95% confidence interval in the absence of publication bias. Symmetry around the vertical line suggests a low likelihood of publication bias, while asymmetry may indicate potential reporting or small-study effects.

annualised bleeding rates compared with placebo, with an overall mean difference (MD) of -15.79 (95% CI, -21.28 to -10.31; p<0.00001). Heterogeneity across studies was low (I^2 = 0%). Subgroup analysis showed a similar effect in patients with inhibitors (two studies; MD=-15.52, 95% CI, -21.87 to -9.18) and in those without inhibitors (1 study; MD=-16.60, 95% CI, -27.55 to -5.65), indicating consistent benefit across both groups. (Figure 4a).

Patients with bleeding episodes

For the outcome of number of patients experiencing bleeding episodes (defined as the number of participants with at least one bleeding episode during follow-up), four studies were included, with two studies each in the inhibitor and non-inhibitor subgroups. Overall, concizumab was associated with a lower, but not statistically significant, risk of experiencing a bleeding episode compared with placebo (RR=0.69, 95% CI, 0.38 to 1.28), although substantial heterogeneity was observed (I^2=79%,

p=0.24). Subgroup analysis showed a non-significant reduction in patients with inhibitors (RR=0.62, 95% CI, 0.28 to 1.37), while results in patients without inhibitors were inconclusive due to wide confidence intervals (RR=2.03, 95% CI, 0.10 to 42.74). Sensitivity analysis identified Shapiro 2019 [9] and Chowdary 2024 [11] as main contributors to heterogeneity. Excluding these studies revealed a consistent and statistically significant effect, with fewer patients experiencing bleeding episodes in the concizumab group compared with placebo (RR=0.46, 95% CI, 0.31 to 0.67; I^2=0%, p<0.0001) (Figure 4b).

Joint bleeding

For the outcome of joint bleeding (defined as the number of patients experiencing joint bleeding), two studies including 43 participants were analysed. Overall, treatment with concizumab significantly reduced the risk of bleeding joints compared with placebo (RR=0.66, 95% CI, 0.45 to 0.96; I^2=0%, p=0.03). Subgroup analysis showed a significant reduction in patients with inhibitors (one study; RR=0.64, 95% CI, 0.43 to 0.94), whereas in patients without inhibitors (one study), the effect was uncertain due to a wide confidence interval (RR=1.33, 95% CI, 0.20 to 8.71) (Figure 4c).

Safety outcomes

Adverse events

For the outcome of adverse events (defined as the number of patients experiencing any adverse event), four studies including 137 participants were analysed. The pooled analysis showed no significant difference between concizumab and placebo (RR=1.17, 95% CI, 0.89 to 1.54; I^2=0%, p=0.25). Subgroup analysis revealed similar findings in patients with inhibitors (two studies; RR=1.14, 95% CI, 0.83 to 1.58) and in those without inhibitors (two studies; RR=1.25, 95% CI, 0.75 to 2.08), indicating no clear subgroup effect (Figure 4d).

Serious adverse events

For the outcome of serious adverse events, three studies including 113 participants were analysed. Overall, there was no significant difference between concizumab and placebo (RR=0.46, 95% CI, 0.06 to 3.53), with moderate heterogeneity (I^2=56%, p=0.46). Subgroup analysis showed a non-significant reduction in patients with inhibitors (two studies; RR=0.27, 95% CI, 0.01 to 7.31), whereas the single study in patients without inhibitors reported no clear effect (RR=1.15, 95% CI, 0.06 to 23.88). Sensitivity analysis identified Shapiro 2019 [9] as the main contributor to heterogeneity. Excluding this study resulted in more consistent findings, showing no significant difference between groups (RR=1.15, 95% CI, 0.36 to 3.70; I^2=0%, p=0.81). (Figure 4e).

Other outcomes

Upper respiratory tract infections

For the outcome of upper respiratory tract infections, two studies including 97 participants were analysed. The pooled results showed no significant difference between concizumab and placebo (RR=0.75, 95% CI, 0.15 to 3.85). No subgroup analysis was performed for this outcome.

DISCUSSION:

Our meta-analysis demonstrates that concizumab consistently reduces annualised bleeding rates and joint bleeding events in people with haemophilia A and B, both with and without inhibitors. These efficacy findings are directly aligned with the pharmacologic mechanism of concizumab as a TFPI blocker. By inhibiting TFPI, concizumab enhances thrombin generation, thereby improving hemostasis without directly replacing deficient clotting factors [14]. This mechanism helps explain the observed reductions in bleeding episodes across trials [10].

Safety outcomes in the included RCTs showed no statistically significant increase in overall or serious adverse events compared with placebo. While this suggests that short-term TFPI modulation is generally well tolerated [10], it is important to contextualise these findings with the limitations of small sample sizes, short follow-up durations, and the lack of real-world pharmacovigilance data. Rare but clinically important events, including thrombotic complications, may not be captured in these controlled trial populations [15].

These results are consistent with prior non-randomised and early-phase studies, which also reported favourable safety and efficacy profiles, though with similar limitations regarding sample size and follow-up [14,15]. Mechanistically, TFPI inhibition carries a theoretical risk of hypercoagulability, highlighting the importance of ongoing monitoring in larger patient populations. Moreover, immunogenicity trends remain incompletely characterised beyond the short-term follow-up reported in most trials.

Integrating mechanistic understanding with clinical outcomes provides valuable insight for clinicians considering non-factor prophylactic therapies. While

Figure 4. Forest plots highlighting aspects of the included studies

Figure 4a. Mean annualised bleeding rates (ABR) across the included studies

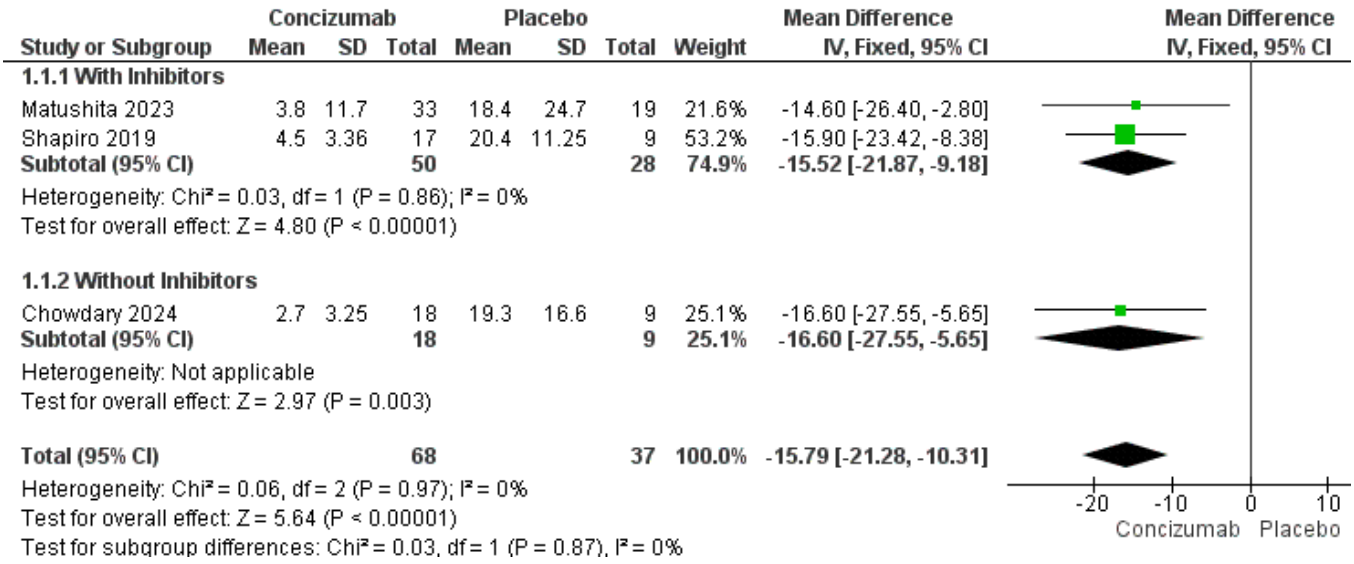


Figure 4b. Proportion of patients experiencing one or more bleeding episodes

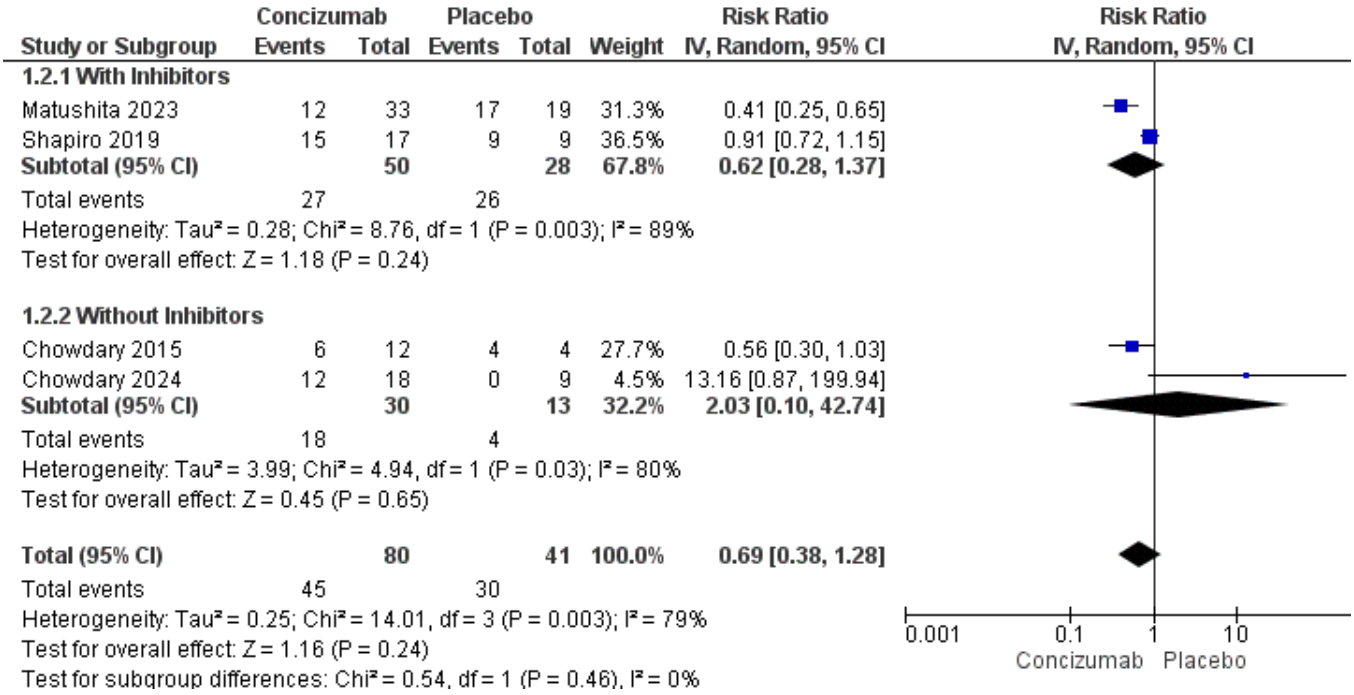


Figure 4c. Frequency of bleeding events involving joints

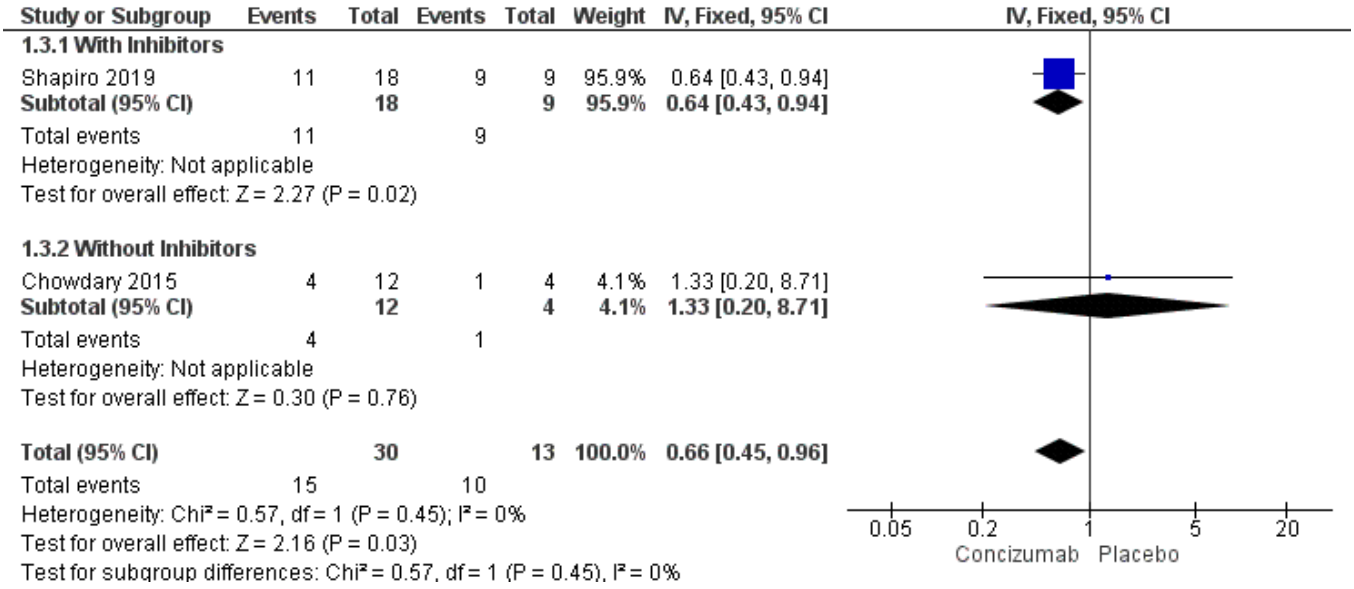


Figure 4d. Incidence of all reported adverse events

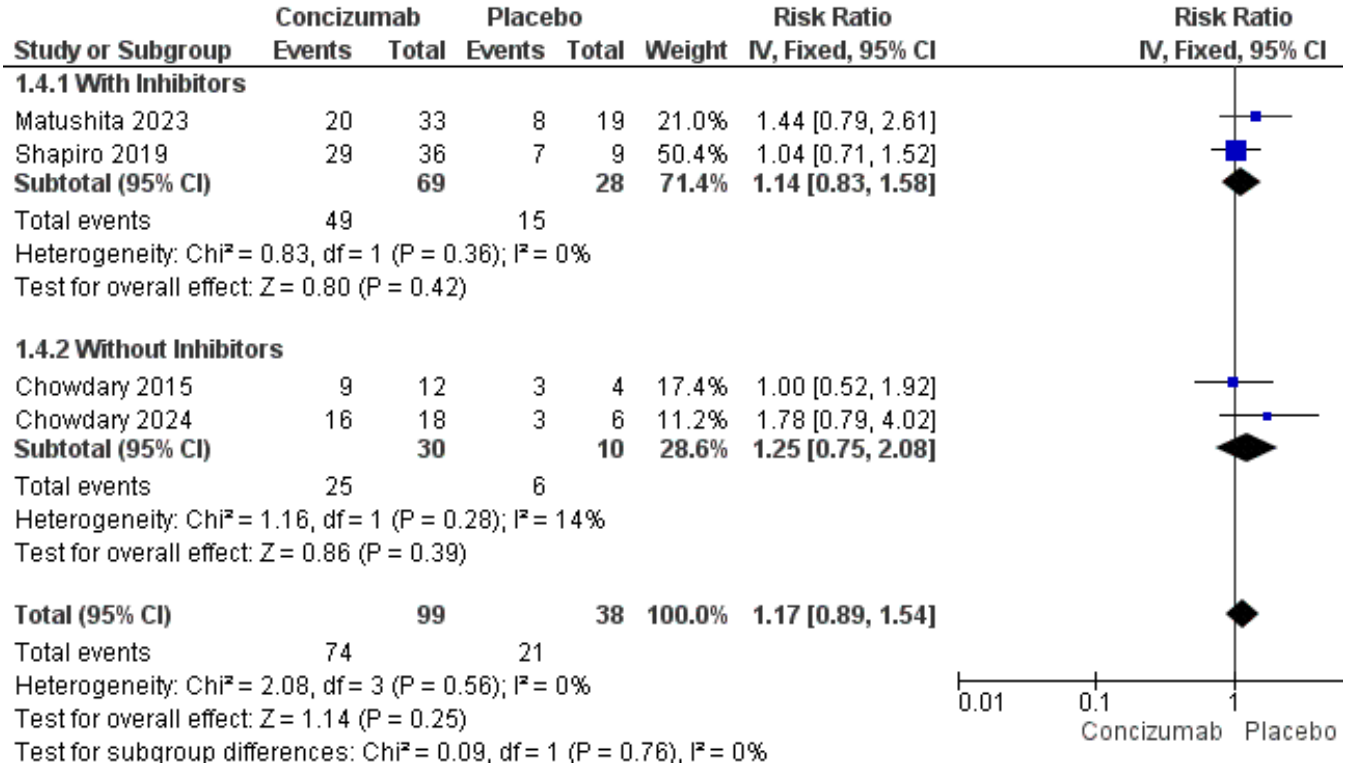
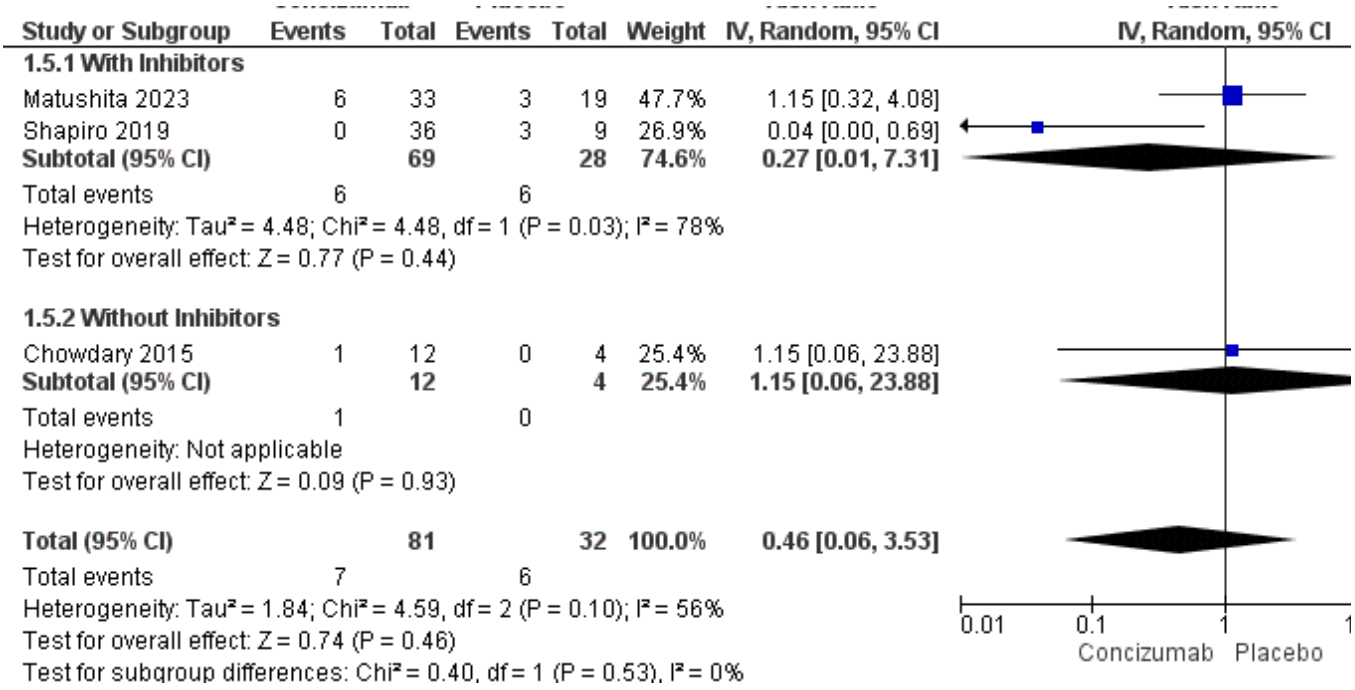


Figure 4e. Occurrence of serious adverse events



concizumab shows promising efficacy and short-term tolerability, caution is warranted regarding rare or delayed adverse events, and these findings should inform careful patient selection and monitoring strategies. Future studies incorporating larger populations, longer follow-up, and real-world data are essential to fully define the safety profile and guide clinical use [16].

Immunogenicity is an important consideration for therapeutic antibodies such as concizumab, as the development of anti-drug antibodies (ADAs) could theoretically reduce efficacy or alter safety profiles. None of the included randomised trials systematically reported ADA incidence or its potential impact. Furthermore, all trials had relatively short follow-up durations, which limits the ability to detect delayed immunogenicity or long-term effects on efficacy and safety [10,15]. Future studies and post-marketing surveillance are therefore needed to evaluate whether immunogenicity may influence clinical outcomes during extended treatment.

While this meta-analysis focused on concizumab, it is important to contextualise its safety profile relative to other emerging non-factor therapies, including emicizumab and fitusiran. Emicizumab, a bispecific antibody bridging factors IXa and X, has demonstrated a low incidence of thrombotic events in clinical trials, although rare thrombotic microangiopathy has been reported in combination with activated prothrombin complex concentrate [16,17]. Fitusiran, an RNA interference (RNAi) therapeutic targeting antithrombin, carries theoretical and observed risks of thrombosis, prompting careful monitoring in ongoing studies [16]. Direct comparisons with concizumab are not available; however, differences in mechanism of action may influence both efficacy and safety profiles. These considerations underscore the need for continued pharmacovigilance and real-world studies to better understand the comparative safety of novel non-factor therapies [16,17].

Regulatory agencies, including the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA), conduct post-marketing and post-trial safety reviews that can provide additional insights beyond published clinical trials. While concizumab has demonstrated short-term tolerability in the included RCTs, these regulatory assessments can capture rare adverse events and emerging safety signals, including thrombotic events, immunogenicity, and effects of concomitant therapies. Incorporating regulatory safety data into future reviews will be important for a comprehensive understanding of concizumab's risk–benefit profile [18].

Limitations

A key limitation of this meta-analysis is the combination of studies including people with haemophilia both with inhibitors and without inhibitors, which may have introduced clinical heterogeneity and limited the ability to draw definitive subgroup-specific conclusions. Another limitation is the relatively small number of participants included in the analysed studies, which may reduce the statistical power and the generalisability of the findings.

This meta-analysis included only four RCTs encompassing 137 participants. The small number of studies and limited sample size reduce the statistical power of pooled analyses and restrict the ability to detect infrequent but clinically relevant adverse events such as thrombosis or immunogenicity. As a result, while the available data suggest that concizumab is generally well tolerated in the short term, larger phase 3 studies and post-marketing surveillance data are needed to validate the safety profile and assess long-term risks.

Another key limitation is the absence of real-world data. Randomised controlled trials, while methodologically rigorous, typically include small, highly selected populations and relatively short follow-up durations. As a result, rare but clinically important safety events such as thrombosis or immunogenicity may not be captured, increasing the risk of a type II error. Incorporating real-world evidence and post-marketing pharmacovigilance data will therefore be essential to validate these findings and better define the true incidence of infrequent adverse events associated with concizumab.

Subgroup analyses by inhibitor status (patients with vs. without inhibitors) were performed for both efficacy and safety outcomes. These analyses indicate that the treatment effect on annualised bleeding rates and adverse events was generally consistent across subgroups. However, due to limited data, further subgroup analyses by trial phase or follow-up duration were not possible, which remains a limitation.

Publication bias assessment was limited by the small number of included trials, and for two outcomes, formal evaluation was not possible. Consequently, these analyses may not reliably detect reporting bias, and the possibility of unreported adverse events cannot be excluded. The interpretation of pooled estimates should therefore be considered cautiously.

The included trials provided limited information on concomitant therapies administered alongside concizumab, such as factor replacement or bypassing agents. The use of these therapies could influence the incidence and severity of adverse events, including thrombotic events or bleeding episodes. Due to insufficient reporting, we were unable to perform analyses accounting for concomitant treatments, which represents a limitation. Future studies should systematically report concomitant therapy use to allow a more precise assessment of concizumab's safety profile in real-world clinical practice.

Adverse events of special interest (AESI), including thrombosis, transaminitis, and injection site reactions, are important considerations for concizumab therapy. The included randomised trials did not systematically report these specific outcomes, limiting the ability to assess their incidence in this review. Mechanistically, concizumab enhances thrombin generation through TFPI inhibition, which could theoretically increase thrombotic risk. Injection site reactions and transient liver enzyme elevations have been reported with other non-factor therapies, although comprehensive data for concizumab are lacking. Future studies and post-marketing surveillance are needed to characterise the incidence and clinical significance of these AESI during long-term therapy.

CONCLUSION

This review places the observed efficacy and safety of concizumab into mechanistic and clinical context. Concizumab acts by inhibiting TFPI, thereby enhancing thrombin generation and improving haemostasis without replacing missing clotting factors. The reduction in annualised bleeding rates and joint bleeding aligns with this mechanism. Safety outcomes suggest short-term tolerability; however, the limited number of trials, small sample sizes, and short follow-up periods restrict insights into rare or delayed adverse events, including thrombotic events and potential immunogenicity. Comparative insights from other non-factor therapies, such as emicizumab and fitusiran, indicate that differences in mechanism can influence both efficacy and risk, highlighting the importance of individualised treatment strategies. Taken together, integrating mechanistic understanding with trial data and early observational evidence provides a more nuanced interpretation of concizumab's safety profile and helps inform clinical decision-making while identifying key gaps for future research.

In conclusion, concizumab demonstrates promising efficacy in reducing bleeding, particularly joint bleeds, with a favourable safety profile. The modest sample sizes and limited long-term data highlight the need for larger, well-designed trials to confirm these findings and establish its role in haemophilia prophylaxis. Long-

term, closely monitored follow-up using national or international registries may provide more feasible and informative data on the long-term safety and efficacy of concizumab, given the challenges of conducting large RCTs in rare diseases.

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Conflict of interest

The authors have advised no interests that might be perceived as posing a conflict or bias.

Consent

This paper reports a retrospective study in which no human participants or animals are directly involved.

Author contributions

Laiba Masood conceptualised the study and was involved in full-text screening and data extraction. Muhammad Bilal Akram contributed to data extraction and analysis. Noor Ashfaq and Ramsha Javed participated in screening and data extraction. Abdul Wasay conducted the risk of bias assessment. All remaining authors contributed equally to manuscript writing.

Declaration of generative AI and AI-assisted technologies in the writing process

In preparing this manuscript, the authors utilised generative AI tools to assist with language refinement and content structuring. Following this assistance, the authors thoroughly reviewed and edited the content, taking full responsibility for the final version of the publication.

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