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SYSTEMATIC REVIEW ARTICLE **OPEN ACCESS**

Safety and Tolerability of Biologic Therapies for Chronic Rhinosinusitis with Nasal Polyps: A Systematic Review of Randomized Controlled Trials

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Transparency note. The original database-specific retrieval logs and the reason-level full-text screening log were unavailable during revision. No database-specific retrieval counts or historical exclusion counts were retrospectively estimated. The search strings below document the final reproducible revision-stage search specification used to define the evidence-update scope through 28 August 2026; retrieval counts are therefore reported as unavailable (NR).

Supplementary Table S1. Complete database-specific search strategies.

Source	Coverage / last searched	Final reproducible strategy	Filters / limits	Records retrieved
MEDLINE via PubMed	Database inception to 28 Aug 2026	("Chronic Rhinosinusitis"[Mesh] OR "Nasal Polyps"[Mesh] OR "chronic rhinosinusitis with nasal polyps"[tiab] OR CRSwNP[tiab] OR "nasal polyp"[tiab] OR "nasal polyps"[tiab] OR "nasal polyposis"[tiab] OR "eosinophilic chronic rhinosinusitis"[tiab] OR ECRS[tiab]) AND ("Biological Products"[Mesh] OR "Antibodies, Monoclonal"[Mesh] OR biologic*[tiab] OR "monoclonal antibod*"[tiab] OR dupilumab[tiab] OR omalizumab[tiab] OR mepolizumab[tiab] OR benralizumab[tiab] OR reslizumab[tiab] OR depemokimab[tiab] OR tezepelumab[tiab] OR stapokibart[tiab] OR CM310[tiab] OR GR1802[tiab] OR PF-06817024[tiab] OR "interleukin-4 receptor"[tiab] OR "IL-4R"[tiab] OR "anti-IgE"[tiab] OR "interleukin-5"[tiab] OR "IL-5"[tiab] OR "IL-5 receptor"[tiab] OR "IL-5R"[tiab] OR "thymic stromal lymphopoietin"[tiab] OR TSLP[tiab] OR "interleukin-33"[tiab] OR "IL-33"[tiab]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR random*[tiab] OR placebo*[tiab] OR trial[tiab]) NOT (animals[mh] NOT humans[mh])	No date limit. No language filter in the electronic search; English-language full-text eligibility applied during screening. Safety terms were not mandatory.	NR - retrieval log unavailable

Source	Coverage / last searched	Final reproducible strategy	Filters / limits	Records retrieved
Embase (Elsevier)	Database inception to 28 Aug 2026	('chronic rhinosinusitis'/exp OR 'nasal polyp'/exp OR 'chronic rhinosinusitis with nasal polyps':ti,ab,kw OR crswnp:ti,ab,kw OR 'nasal polyp':ti,ab,kw OR 'nasal polyps':ti,ab,kw OR 'nasal polyposis':ti,ab,kw OR 'eosinophilic chronic rhinosinusitis':ti,ab,kw OR ecrs:ti,ab,kw) AND ('biological product'/exp OR 'monoclonal antibody'/exp OR 'dupilumab'/exp OR 'omalizumab'/exp OR 'mepolizumab'/exp OR 'benralizumab'/exp OR 'reslizumab'/exp OR depemokimab:ti,ab,kw OR 'tezepelumab'/exp OR stapokibart:ti,ab,kw OR cm310:ti,ab,kw OR gr1802:ti,ab,kw OR 'pf-06817024':ti,ab,kw OR biologic*:ti,ab,kw OR 'monoclonal antibod*':ti,ab,kw OR 'interleukin 4 receptor':ti,ab,kw OR 'il 4r':ti,ab,kw OR 'anti ige':ti,ab,kw OR 'interleukin 5':ti,ab,kw OR 'il 5':ti,ab,kw OR 'il 5 receptor':ti,ab,kw OR 'il 5r':ti,ab,kw OR 'thymic stromal lymphopoietin':ti,ab,kw OR tslp:ti,ab,kw OR 'interleukin 33':ti,ab,kw OR 'il 33':ti,ab,kw) AND ('randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR random*:ti,ab,kw OR placebo*:ti,ab,kw OR trial:ti,ab,kw) AND [humans]/lim	No date limit. No language filter in the electronic search; English-language full-text eligibility applied during screening. Safety terms were not mandatory.	NR - retrieval log unavailable
Web of Science Core Collection	Database inception to 28 Aug 2026	TS=("chronic rhinosinusitis with nasal polyps" OR CRSwNP OR "nasal polyp*" OR "nasal polyposis" OR "eosinophilic chronic rhinosinusitis" OR ECRS) AND TS=(biologic* OR "monoclonal antibod*" OR dupilumab OR omalizumab OR mepolizumab OR benralizumab OR reslizumab OR depemokimab OR tezepelumab OR stapokibart OR CM310 OR GR1802 OR PF-06817024 OR "interleukin-4 receptor" OR "IL-4R" OR "anti-IgE" OR "interleukin-5" OR "IL-5" OR "IL-5 receptor" OR "IL-5R" OR "thymic stromal lymphopoietin" OR TSLP OR "interleukin-33" OR "IL-33") AND TS=(random* OR placebo* OR trial)	No date limit. No document-type or language restriction in the search; eligibility restrictions applied during screening. Safety terms were not mandatory.	NR - retrieval log unavailable
CENTRAL (Cochrane Central Register of Controlled Trials)	Database inception to 28 Aug 2026	#1 MeSH descriptor: [Chronic Rhinosinusitis] explode all trees #2 MeSH descriptor: [Nasal Polyps] explode all trees #3 ("chronic rhinosinusitis with nasal polyps" OR CRSwNP OR "nasal polyp*" OR "nasal polyposis" OR "eosinophilic chronic rhinosinusitis" OR ECRS):ti,ab,kw #4 #1 OR #2 OR #3 #5 MeSH descriptor: [Biological Products] explode all trees #6 MeSH descriptor: [Antibodies, Monoclonal] explode all trees #7 (biologic* OR "monoclonal antibod*" OR dupilumab OR omalizumab OR mepolizumab OR benralizumab OR reslizumab OR depemokimab OR tezepelumab OR stapokibart OR CM310 OR GR1802 OR PF-06817024 OR "interleukin-4 receptor" OR "IL-4R" OR "anti-IgE" OR "interleukin-5" OR "IL-5" OR "IL-5 receptor" OR "IL-5R" OR "thymic stromal lymphopoietin" OR TSLP OR "interleukin-33" OR "IL-33"):ti,ab,kw #8 #5 OR #6 OR #7 #9 (random* OR placebo* OR trial):ti,ab,kw #10 #4 AND #8 AND #9	No date or language limit. CENTRAL trial indexing supplemented by explicit trial terminology. Safety terms were not mandatory.	NR - retrieval log unavailable

Additional identification methods: reference lists of eligible randomized trials and relevant systematic reviews were checked during the revision-stage evidence reconciliation. No separate count was available for citation-chasing records.

Supplementary Table S2. Apparently eligible reports excluded after full-text reassessment and primary exclusion reason.

Study/report	Population/design	Why it appeared potentially eligible	Primary exclusion reason under revised criteria	Identifier
Harrison et al., 2021 - ANDHI	Phase 3b randomized placebo-controlled trial in severe eosinophilic asthma; nasal-polyposis subgroup	Benralizumab; randomized; nasal-polyposis outcomes reported	Other-indication trial: the safety data used in the earlier manuscript were from the overall asthma safety population and were not separately extractable for the randomized CRSwNP/nasal-polyp subgroup.	Lancet Respir Med. 2021;9:260-274. doi:10.1016/S2213-2600(20)30414-8
Castro et al., 2011	Randomized placebo-controlled reslizumab trial in poorly controlled eosinophilic asthma; some participants had nasal polyps	Biologic RCT with a nasal-polyp subgroup	Other-indication trial: CRSwNP/nasal-polyp-specific randomized safety data were not separately extractable.	Am J Respir Crit Care Med. 2011;184:1125-1132. doi:10.1164/rccm.201103-0396OC
Hayashi et al., 2020	Double-blind randomized crossover omalizumab trial in aspirin-exacerbated respiratory disease with nasal polyposis	Randomized biologic trial in a population with nasal polyposis	Crossover design; the final eligibility criteria were restricted to parallel-group or multi-arm controlled RCTs.	Am J Respir Crit Care Med. 2020;201:1488-1498. doi:10.1164/rccm.201906-1215OC
Pinto et al., 2010	Double-blind parallel-group omalizumab trial in chronic rhinosinusitis (n=14)	Randomized placebo-controlled anti-IgE trial; most participants had nasal polyps	Mixed CRS population without a fully separable CRSwNP randomized safety population (7/7 active and 5/7 placebo participants had nasal polyposis).	Rhinology. 2010;48:318-324. doi:10.4193/Rhino09.144

Study/report	Population/design	Why it appeared potentially eligible	Primary exclusion reason under revised criteria	Identifier
Danto et al., 2024 - PF-06817024	Phase 1 randomized double-blind placebo-controlled study; CRSwNP part included 20 participants	CRSwNP randomized safety data were available	Phase 1/single-dose development study; excluded by the prespecified phase/design eligibility criterion for the therapeutic RCT synthesis.	J Clin Pharmacol. 2024;64:529-543. doi:10.1002/jcph.2360; NCT02743871
ORCHID (NCT04157335)	Phase 3 randomized placebo-controlled benralizumab trial in eosinophilic CRSwNP; terminated early	Directly relevant CRSwNP RCT with registry results	No eligible peer-reviewed full-text primary publication was available under the review publication criterion at the revision cutoff.	ClinicalTrials.gov NCT04157335
EVEREST - De Corso et al., 2025	Phase 4 randomized double-blind head-to-head dupilumab versus omalizumab trial in severe CRSwNP with asthma	Direct CRSwNP randomized safety comparison	Active biologic comparator rather than placebo or standard care; outside the prespecified comparator criterion for the primary synthesis.	Lancet Respir Med. 2025;13:1067-1077. doi:10.1016/S2213-2600(25)00287-5; NCT04998604
NCT01066104	Randomized placebo-controlled omalizumab study in nasal polyposis/CRSwNP	Direct randomized CRSwNP biologic trial	Registry results without an eligible peer-reviewed full-text primary publication under the review publication criterion.	ClinicalTrials.gov NCT01066104

Supplementary Table S3. Trial-level Cochrane RoB 2 judgments and domain-level justifications.

Trial	D1	D2	D3	D4	D5	Overall	Concise justification
Gevaert 2011 [11]	SC	L	L	L	SC	SC	Randomized/double-blind trial, but sequence generation/concealment were incompletely described and an accessible prospective protocol/SAP was insufficient for complete selective-reporting verification.
Gevaert 2013 [12]	SC	L	L	L	SC	SC	Randomized/double-blind trial; allocation-concealment detail and prospective safety-reporting documentation were insufficient for unequivocal low-risk judgments.
Bachert 2016 [13]	L	L	L	L	L	L	Randomized, double-blind placebo-controlled procedures and safety reporting were sufficiently documented; no material safety-outcome missingness or selective reporting identified.
Bachert 2017 [14]	L	SC	L	L	L	SC	Randomization was adequately documented. One participant randomized to mepolizumab received placebo and was classified according to treatment received for safety analysis, raising some concern for the effect-of-assignment estimand.
SINUS-24 [15]	L	L	L	L	L	L	Large phase 3 randomized double-blind program with adequate allocation/masking and complete safety reporting for the outcomes used in this review.
SINUS-52 [15]	L	L	L	L	L	L	Large phase 3 randomized double-blind program with adequate allocation/masking and complete safety reporting for the outcomes used in this review.
POLYP 1 [16]	L	L	L	L	L	L	Randomized, double-blind, placebo-controlled phase 3 trial with prospectively defined safety monitoring and adequate reporting.
POLYP 2 [16]	L	L	L	L	L	L	Randomized, double-blind, placebo-controlled phase 3 trial with prospectively defined safety monitoring and adequate reporting.
SYNAPSE [17]	L	L	L	L	L	L	Centralized randomized double-blind phase 3 design; safety population and adverse-event reporting were sufficiently complete for the prespecified outcomes.
Tversky 2021 [18]	SC	L	L	L	SC	SC	Small randomized double-blind study; public reporting did not fully establish sequence/concealment procedures, and prospective safety-reporting verification was limited.
Takabayashi 2021 [19]	SC	L	L	L	L	SC	Prospectively registered randomized double-blind study, but sequence-generation/allocation-concealment detail was insufficient for an unequivocal low-risk D1 judgment.
OSTRO [20]	L	L	L	L	L	L	Large multicenter phase 3 randomized double-blind trial with adequate masking, safety follow-up, and reporting.
CROWNS-1 [21]	L	L	L	L	L	L	Random sequence, interactive response allocation, masking, and safety reporting were adequately documented.
MERIT [22]	L	L	L	SC	L	SC	Randomized phase 3 trial. Sponsor-identified suspected GCP violations at two sites affecting six participants introduced residual uncertainty regarding safety-data integrity/measurement.
CROWNS-2 [23]	L	L	L	L	L	L	Prospectively registered randomized double-blind phase 3 trial with adequate safety ascertainment and reporting.
WAYPOINT [24]	L	L	L	L	L	L	Randomized double-blind placebo-controlled phase 3 trial with prospectively documented protocol and safety monitoring.
ANCHOR-1 [25]	L	L	L	L	L	L	Computer-generated allocation, masking, prospective adverse-event monitoring, and sufficiently complete safety reporting.
ANCHOR-2 [25]	L	L	L	L	L	L	Computer-generated allocation, masking, prospective adverse-event monitoring, and sufficiently complete safety reporting.
GR1802 phase II [26]	SC	L	L	L	L	SC	Randomized double-blind placebo-controlled design; sequence-generation/concealment detail available in the primary reporting was insufficient for an unequivocal low-risk D1 judgment.

Trial	D1	D2	D3	D4	D5	Overall	Concise justification
Chinese dupilumab 2026 [27]	L	L	L	L	L	L	Prospectively registered, masked randomized phase 3 trial with protocol/SAP availability and adequate safety-outcome reporting.

Abbreviations: D1, bias arising from the randomization process; D2, bias due to deviations from intended interventions; D3, bias due to missing outcome data; D4, bias in measurement of the outcome; D5, bias in selection of the reported result; L, low risk; SC, some concerns. No trial was judged at high overall risk for the safety outcomes.

Supplementary Table S4. Participant-level safety extraction dataset for quantitative synthesis.

Analysis unit / trial	Biologic	Safety n active / control	Any AE/TEAE active / control	SAE active / control	AE-discontinuation active / control	Primary quantitative use	Notes
Gevaert 2011 [11]	Mepolizumab	20 / 10	NR	1 / 0	NR	Narrative; SAE sensitivity only	Published safety reporting did not provide a directly comparable patient-level any-AE count for the primary synthesis.
Gevaert 2013 [12]	Omalizumab	15 / 8 treated	NR	0 / 0 reported	NR	Narrative	Any-AE reporting was not sufficiently extractable as participant counts for primary pooling.
Bachert 2016 [13]	Dupilumab	30 / 30	30 / 25	2 / 4	2 / 5	Any AE; SAE; discontinuation	Direct participant counts.
Bachert 2017 [14]	Mepolizumab	53 / 52	40 / 42	0 / 0	NR	Any AE	Double-zero SAE contributes no conventional RR information; discontinuation definition/count not sufficiently stable for primary pooling.
SINUS-24 + SINUS-52 pooled [15]	Dupilumab	440 / 282	305 / 208	15 / 16	11 / 15	Any AE; SAE; discontinuation	Pooled safety program entered once; component trials not simultaneously entered for these outcomes.
POLYP 1 + POLYP 2 pooled [16]	Omalizumab	135 / 130	68 / 76	3 / 2	0 / 1	Any AE; SAE; discontinuation	Pooled safety program entered once. Single-zero discontinuation cell handled with continuity correction in RR model.
SYNAPSE [17]	Mepolizumab	206 / 201	169 / 168	12 / 14	4 / 4	Any AE; SAE; discontinuation	Direct participant counts.
Tversky 2021 [18]	Benralizumab	12 / 12	NR	NR	NR	Narrative	Aggregate participant-level counts for the prespecified pooled outcomes were not sufficiently extractable.
Takabayashi 2021 [19]	Benralizumab	45 active / 11 placebo	NR	NR	NR	Narrative	Two active schedules; aggregate participant-level counts for pooled outcomes were not sufficiently extractable.
OSTRO [20]	Benralizumab	207 / 203	160 / NR	23 / 17 (secondary extraction)	NR	Narrative / sensitivity only	Placebo any-AE result was available as a percentage rather than a primary-verified integer count; no reverse-engineering from rounded percentages was used.
CROWNS-1 [21]	Stapokibart/CM310	28 / 28	21 / 22	0 / 3	0 / 0	Any AE; SAE	Double-zero discontinuation retained descriptively but does not inform conventional RR.
MERIT [22]	Mepolizumab	84 / 85	68 / 65	0 / 4	NR	Any AE; SAE	Single-zero SAE handled with continuity correction.
CROWNS-2 [23]	Stapokibart	90 / 89	70 / 62	2 / 1	2 / 1	Any AE; SAE; discontinuation	Direct participant counts.
WAYPOINT [24]	Tezepelumab	203 / 205	159 / 158	10 / 12	1 / 3	Any AE; SAE; discontinuation	408 participants contributed to the principal safety analysis although 410 were randomized.
ANCHOR-1 [25]	Depemokimab	143 / 128	106 / 101	NR	See pooled ANCHOR row	Any AE	Trial-level any-AE counts; discontinuation reported at pooled program level.

Analysis unit / trial	Biologic	Safety n active / control	Any AE/TEAE active / control	SAE active / control	AE-discontinuation active / control	Primary quantitative use	Notes
ANCHOR-2 [25]	Depemokimab	129 / 128	98 / 102	NR	See pooled ANCHOR row	Any AE	Trial-level any-AE counts; discontinuation reported at pooled program level.
ANCHOR-1 + ANCHOR-2 pooled [25]	Depemokimab	272 / 256	Not used - trial-specific counts used	NR	2 / 3	Discontinuation only	Pooled program used only for discontinuation; not combined with trial-level discontinuation rows.
GR1802 phase II [26]	GR1802	NR	NR	NR	NR	Narrative	Reported treatment-related AE percentages were not treated as equivalent to any-AE/TEAE counts and were not reverse-calculated.
Chinese dupilumab 2026 [27]	Dupilumab	31 / 32	23 / 20	4 / 0	0 / 0	Any AE; SAE	Single-zero SAE handled with continuity correction; double-zero discontinuation descriptive only.

NR = not reported or not sufficiently extractable for the specified pooled outcome. The primary meta-analysis of any AE/TEAE used 12 independent analysis units (2,962 participants); SAE used 9 units (2,329 participants); AE-related discontinuation used 7 units (2,569 participants).

Supplementary Table S5. Sensitivity analyses.

Outcome	Analysis	Units	Participants	RR (95% CI)	I^2	Interpretation
Any AE/TEAE	Primary: Paule-Mandel random effects + modified Hartung-Knapp CI	12	2,962	0.995 (0.944-1.049)	18.0%	Little or no difference.
Any AE/TEAE	Fixed-effect inverse-variance	12	2,962	0.992 (0.953-1.032)	—	Essentially identical to primary analysis.
Any AE/TEAE	Restricted to overall low-RoB trials	10	2,688	1.00 (0.93-1.06)	27.5%	Conclusion unchanged.
Any AE/TEAE	Leave-one-out analysis	11 per iteration	Varied	Pooled RR range 0.979-1.006	—	No single analysis unit materially changed the conclusion; all modified Hartung-Knapp 95% CIs included 1.
Serious adverse events	Primary: Paule-Mandel random effects + modified Hartung-Knapp CI	9	2,329	0.751 (0.476-1.186)	0%	No statistically demonstrable difference; estimate imprecise.
Serious adverse events	Fixed-effect inverse-variance	9	2,329	0.751 (0.509-1.107)	—	Conclusion unchanged.
Serious adverse events	Exclude trials with a zero-event arm	6	Varied	0.765 (0.453-1.291)	—	Conclusion unchanged after removing continuity-corrected studies.
Serious adverse events	Restricted to overall low-RoB trials	8	2,160	0.78 (0.48-1.25)	0%	Conclusion unchanged.
Serious adverse events	Leave-one-out analysis	8 per iteration	Varied	Pooled RR range 0.717-0.833	—	No single unit materially changed the conclusion; all modified Hartung-Knapp 95% CIs included 1.
AE-related discontinuation	Primary: Paule-Mandel random effects + modified Hartung-Knapp CI	7	2,569	0.553 (0.282-1.085)	0%	Numerically favors biologics but not statistically significant under conservative primary model.
AE-related discontinuation	Fixed-effect inverse-variance	7	2,569	0.553 (0.323-0.949)	—	Statistically significant under fixed effect; treated as a sensitivity result because events are sparse and only seven units contribute.
AE-related discontinuation	Exclude single-zero POLYP program	6	Varied	0.562 (0.275-1.152)	—	Direction unchanged; no statistically demonstrable difference.
AE-related discontinuation	Exclude pooled ANCHOR discontinuation report	6	Varied	0.546 (0.260-1.147)	—	Direction unchanged; no statistically demonstrable difference.
AE-related discontinuation	Restricted to overall low-RoB trials	7	2,569	0.553 (0.282-1.085)	0%	All contributing primary units were low risk; identical to primary analysis.
AE-related discontinuation	Leave-one-out analysis	6 per iteration	Varied	Pooled RR range 0.499-0.651	—	No single unit materially changed the direction; all modified Hartung-Knapp 95% CIs included 1.

Supplementary Table S6. Revision-stage methodological amendments.

Amendment	Original submitted approach	Revision-stage approach	Reason for amendment	Stage	Impact on review
Evidence update and biologic scope	Original evidence base focused on five agents and did not capture several newer CRSwNP RCTs.	Evidence base updated through 28 Aug 2026; search concepts expanded to newer agents and pathway terms.	Reviewers requested complete, current, reproducible identification of randomized evidence.	Post-peer-review revision	Expanded the eligible evidence base and updated the intervention landscape.
Trial-family reconciliation	Publications were effectively treated as independent studies, creating overlap risk.	Reports grouped by registration ID, acronym, sample size, intervention, recruitment period, and parent-substudy relationships.	Reviewer identified potential double counting.	Post-peer-review revision	20 unique RCTs identified in 17 primary publications; companion reports contribute no extra participants.
Eligibility of other-indication trials	Asthma RCTs with nasal-polyp subgroups contributed whole-asthma safety data.	Other-indication trials excluded unless randomized CRSwNP safety data were separately extractable.	To align the evidence set with the stated CRSwNP eligibility criteria.	Post-peer-review revision	Removed ANDHI and Castro/reslizumab from the primary synthesis; reslizumab no longer an included CRSwNP biologic.
Study/report and participant accounting	Original manuscript reported 10 studies and approximately 2,000 participants.	Unique-trial accounting yielded 20 RCTs and 3,598 randomized participants; outcome-specific safety denominators reported separately.	Original totals were not reproducible and included overlapping/noneligible populations.	Post-peer-review revision	All totals in Abstract, Results, tables, Discussion, and Conclusion were reconciled.
Safety data unit and missing values	Safety reporting mixed percentages, event episodes, and participant counts.	Unit defined as participants with at least one event; rounded percentages not reverse-engineered; non-separable values coded NR.	To avoid invalid conversions and incompatible denominators.	Post-peer-review revision	Created auditable outcome-specific datasets and reduced analytic misclassification.
Quantitative synthesis	Original approach was primarily descriptive and did not prioritize meta-analysis.	Paule-Mandel random-effects RR meta-analysis with modified Hartung-Knapp CIs; Q, tau^2, and I^2 reported.	Compatible participant-level data were available after reconstruction, addressing reviewer request for quantitative synthesis.	Post-peer-review revision	Meta-analysis performed for any AE/TEAE, SAE, and AE-related discontinuation.
Sparse-event handling and sensitivity analyses	Not prespecified/reported in submitted version.	0.5 continuity correction for single-zero arms; double-zero trials descriptive for conventional RR; fixed-effect, sparse-event, pooled-program, leave-one-out, and low-RoB sensitivity analyses.	To ensure robustness for rare safety outcomes.	Post-peer-review revision	Primary conclusions were stable; discontinuation significance was model-sensitive and interpreted cautiously.
Risk of bias	Generic older Cochrane-domain description without presented results.	Outcome-specific Cochrane RoB 2 assessment for effect of assignment; domain-level judgments and low-RoB sensitivity analysis.	Reviewers requested transparent contemporary RoB assessment and plots.	Post-peer-review revision	13 trials low risk, 7 some concerns, 0 high risk; low-RoB analyses did not materially change results.
Reporting-bias assessment	Absent.	Study/synthesis-level assessment; funnel inspection and Egger regression only for meta-analysis with >=10 units; qualitative assessment for smaller syntheses.	Required by PRISMA 2020 and reviewer concerns about missing safety results.	Post-peer-review revision	No clear small-study effect for any AE/TEAE; reporting bias cannot be excluded for SAE/discontinuation.
Certainty of evidence	Absent.	GRADE applied to three principal safety outcomes.	Required for transparent interpretation of strength of evidence.	Post-peer-review revision	Any AE/TEAE: high certainty; SAE: moderate; discontinuation: moderate, both downgraded for imprecision.
PRISMA historical flow transparency	Submitted reason-level full-text exclusion counts were mathematically inconsistent.	Verifiable historical top-line counts retained; unavailable reason-level log explicitly disclosed; no counts invented or redistributed.	Original screening log unavailable and retrospective estimates would be unreliable.	Post-peer-review revision	PRISMA reporting now distinguishes documented historical flow from trial-level evidence reconciliation.
Software and reproducibility	Submitted version cited R descriptive analyses.	Revision-stage calculations and figures performed in Python 3.13.5 with NumPy, pandas, SciPy, statsmodels, and Matplotlib; analysis data and code supplied in the revision package.	Final methods must reflect the analyses actually performed.	Post-peer-review revision	Software reporting now matches the reconstructed meta-analysis.

Supplementary notes

Reference numbering [11-27] corresponds to the final revised main-manuscript bibliography. Supplementary Table S2 contains additional excluded-study citations that are not included in the main numbered reference list unless otherwise stated. The reconstructed event-count dataset is aggregate study-level data and contains no individual participant information.

PRISMA 2009 Checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**1**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**1-2**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**2**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**2**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**2**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**2-3**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**2-3; Supp. Table S1**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**3**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**3**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**3**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**3**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**3**
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**3-4**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**4**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**4**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**4-5**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**6-7**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**7-8**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**8-11**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**8-11**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**11-12**

Section/topic	#	Checklist item	Reported on page #
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**11**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**13-14**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**14-15**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**15**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**15**

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Note: The journal-provided PRISMA 2009 checklist has been completed in the supplied format. The manuscript reports adherence to PRISMA 2020; a completed PRISMA 2020 flow diagram is provided separately.

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