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Research Article

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Comparative Safety of Biologic Therapies in Chronic Obstructive Pulmonary Disease: A Systematic Review and Network Meta-Analysis

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Abstract

Background: Biologic therapies targeting type 2 inflammatory pathways have emerged for eosinophilic chronic obstructive pulmonary disease (COPD), but comparative safety across different molecular targets remains unclear. This network meta-analysis evaluated and ranked the safety of biologic therapies in COPD.

Methods: We systematically searched PubMed, Cochrane CENTRAL, and ClinicalTrials.gov through September 2026 for randomized controlled trials comparing biologics with placebo in adult COPD. Network meta-analysis with SUCRA ranking, trial sequential analysis (TSA), and pre-specified subgroup analyses were performed. PROSPERO: CRD4202615024201.

Results: Ten RCTs (7,758 patients; 7 biologics, 6 targets) were included. Biologics did not increase serious adverse events (RR=0.97, 95% CI 0.86-1.08), death (RR=0.81, 0.50-1.32), or pneumonia (RR=0.97, 0.78-1.21). Treatment-related adverse events were higher (RR=1.41, 1.25-1.58), driven by injection-site reactions (RR=2.32, 1.79-3.00). SUCRA ranking identified CNTO 6785 as safest and dupilumab as highest risk. Subgroup analysis revealed IL-5 pathway agents had no excess treatment-related AE risk, while IL-4Rα pathway agents showed significantly higher risk. TSA confirmed sufficient evidence for treatment-related AEs but not for mortality.

Conclusions: Biologics in COPD have acceptable serious-event safety. IL-5 pathway agents have the most favorable tolerability profile. These findings support preferential use of IL-5-targeted biologics when multiple options are available for eosinophilic COPD.

Keywords: COPD; biologic therapy; network meta-analysis; safety; trial sequential analysis; SUCRA; eosinophilic COPD; subgroup analysis

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health burden, affecting over 250 million people and ranking as the third leading cause of death worldwide [1, 2]. Despite current guideline-based therapies including bronchodilators and inhaled corticosteroids, a substantial proportion of patients continue to experience recurrent exacerbations, driving disease progression and healthcare costs [3].

In recent years, the recognition of inflammatory heterogeneity in COPD has transformed our understanding of disease pathogenesis. A significant subset of COPD patients exhibit type 2 airway inflammation characterized by elevated blood eosinophil counts, which correlates with exacerbation risk and steroid responsiveness [4, 5]. This eosinophilic endotype has opened the door to precision medicine approaches originally developed for asthma, including biologic therapies targeting specific inflammatory mediators.

Over the past decade, multiple biologic agents have been evaluated in phase II and III randomized controlled trials (RCTs) in COPD, targeting six distinct molecular pathways: IL-4Rα (dupilumab), IL-5 (mepolizumab), IL-5Rα (benralizumab), IL-33 (tozorakimab), IL-1R1 (MEDI8968), and IL-17A (CNTO 6785) [6-10]. Pivotal phase III trials including BOREAS and NOTUS (dupilumab), GALATHEA and TERRANOVA (benralizumab), and METREX/METREO (mepolizumab) have reported efficacy in eosinophilic COPD subgroups [9, 10, 26]. However, the comparative safety profiles of these different biologic agents across molecular targets remain incompletely characterized.

While individual RCTs have generally reported favorable safety profiles for biologics in COPD, no study has comprehensively compared the safety of multiple biologics head-to-head using network meta-analysis (NMA). This is clinically important because safety considerations often guide treatment selection when multiple agents are available. Furthermore, conventional meta-analysis may produce imprecise or even misleading conclusions due to repeated testing across outcomes and sparse event data for rare but important outcomes such as mortality [11].

Trial sequential analysis (TSA) addresses these limitations by adjusting for repetitive testing and calculating the required information size to reach firm conclusions [12]. In addition, subgroup analyses by molecular target pathway and eosinophil phenotype could

provide deeper insights into safety mechanisms and help identify which biologic classes are best tolerated in specific patient populations.

This systematic review and NMA aimed to: (1) evaluate the safety of seven biologic therapies across six molecular targets in COPD; (2) rank treatments by safety using SUCRA; (3) apply TSA to assess evidence sufficiency for key outcomes; (4) explore dose-response relationships; (5) conduct pre-specified subgroup analyses by baseline eosinophil threshold and molecular target pathway; and (6) evaluate robustness through sensitivity analyses, publication bias assessment, and GRADE certainty rating.

2. Methods

This systematic review and NMA was conducted in accordance with the PRISMA 2020 statement and its extension for network meta-analyses [13, 31]. The study protocol was prospectively registered on PROSPERO (CRD4202615024201).

2.1 Search Strategy

We systematically searched PubMed, Cochrane CENTRAL, and ClinicalTrials.gov from inception to September 2026. The search strategy combined Medical Subject Heading (MeSH) terms and free-text keywords for COPD, biologic therapies, and randomized controlled trials. No language restrictions were applied. Reference lists of included studies and relevant reviews were hand-searched to identify additional eligible trials.

2.2 Eligibility Criteria

We included RCTs that: (1) enrolled adults (≥18 years) with a confirmed diagnosis of COPD per GOLD criteria; (2) compared any biologic therapy with placebo; (3) reported at least one safety outcome of interest. We excluded: observational studies, trials without a placebo comparator, conference abstracts without extractable safety data, and studies enrolling mixed asthma-COPD overlap populations unless COPD-specific data were available.

2.3 Data Extraction

Data were independently extracted by two reviewers using a standardized data collection form. Extracted information included: study characteristics (first author, publication year, trial phase, trial registration), patient demographics (mean age, proportion female, baseline

eosinophil count, GOLD stage distribution), intervention details (biologic agent, molecular target, dose, dosing frequency, treatment duration), and safety outcomes. Disagreements were resolved by consensus or third reviewer adjudication. Inter-rater agreement between the two independent extractors was good (Cohen's kappa > 0.85).

2.4 Outcomes

Eight pre-specified safety outcomes were analyzed: (1) any adverse event (AE); (2) serious adverse event (SAE); (3) death; (4) pneumonia; (5) discontinuation due to AE; (6) treatment-related AE; (7) injection-site reaction; and (8) headache.

2.5 Risk of Bias Assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [14] across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

2.6 Statistical Analysis

Pairwise meta-analysis was performed using random-effects models (DerSimonian-Laird method) [15]. Risk ratios (RR) with 95% confidence intervals (CI) were calculated for binary outcomes. Between-study heterogeneity was assessed using the I^2 statistic, with $I^2 > 50\%$ indicating substantial heterogeneity [16].

NMA was conducted using a frequentist consistency framework with placebo as the common comparator [17]. Surface under the cumulative ranking curve (SUCRA) values were calculated to rank treatments by safety [18]. The league table presented pairwise comparisons between all treatment pairs. Given the low between-study heterogeneity observed in pairwise analyses ($I^2 < 50\%$ for all outcomes), a fixed-effect model was used for NMA.

Notably, all included trials employed a star-shaped network design, with each biologic compared only to placebo and no head-to-head trials between biologics. Therefore, formal statistical testing of network consistency was not applicable [17, 31].

TSA was performed using the O'Brien-Fleming alpha-spending approach (two-sided $\alpha=0.05$, power=80%) [12]. The required information size and trial sequential monitoring

boundaries were calculated for key outcomes. These parameters were chosen per Cochrane Handbook recommendations for clinical meta-analyses.

Pre-specified subgroup analyses were conducted for treatment-related AEs: (1) by baseline eosinophil threshold (≥300 vs <300 cells/μL); (2) by molecular target pathway (IL-5 pathway: benralizumab and mepolizumab; IL-4Rα pathway: dupilumab; IL-33: tozorakimab; IL-1R1: MEDI8968; IL-17A: CNTO 6785). Dose-response meta-regression was performed using log-transformed biologic doses. Publication bias was assessed using Egger's regression test [19]. Sensitivity analysis was performed using the leave-one-out approach. The GRADE framework was used to assess the certainty of evidence [20].

Given the exploratory nature of multiple outcome analyses and subgroup comparisons, a two-sided $p < 0.05$ was considered statistically significant without additional multiple comparison adjustment, consistent with standard systematic review methodology.

The certainty of evidence was downgraded for several reasons: (1) the star-shaped network design precludes head-to-head comparisons between biologics, limiting indirect comparison certainty; (2) some agents are supported by only one small trial; and (3) AE reporting was not standardized across studies.

3. Results

3.1 Study Selection

A total of 1,036 records were identified through database searching (740 PubMed, 158 Cochrane CENTRAL, 141 ClinicalTrials.gov). After removing duplicates, titles and abstracts were screened, 49 full-text articles were assessed for eligibility, and 10 RCTs comprising 7,758 patients were ultimately included in the review (Fig. 1). The included trials evaluated seven biologic agents across six molecular targets: IL-4Rα (dupilumab, 2 trials), IL-5Rα (benralizumab, 3 trials), IL-5 (mepolizumab, 2 trials), IL-33 (tozorakimab, 1 trial), IL-1R1 (MEDI8968, 1 trial), and IL-17A (CNTO 6785, 1 trial). Six trials were phase III and four were phase II. Treatment duration ranged from 12 to 56 weeks. Key study characteristics are summarized in Table 1.

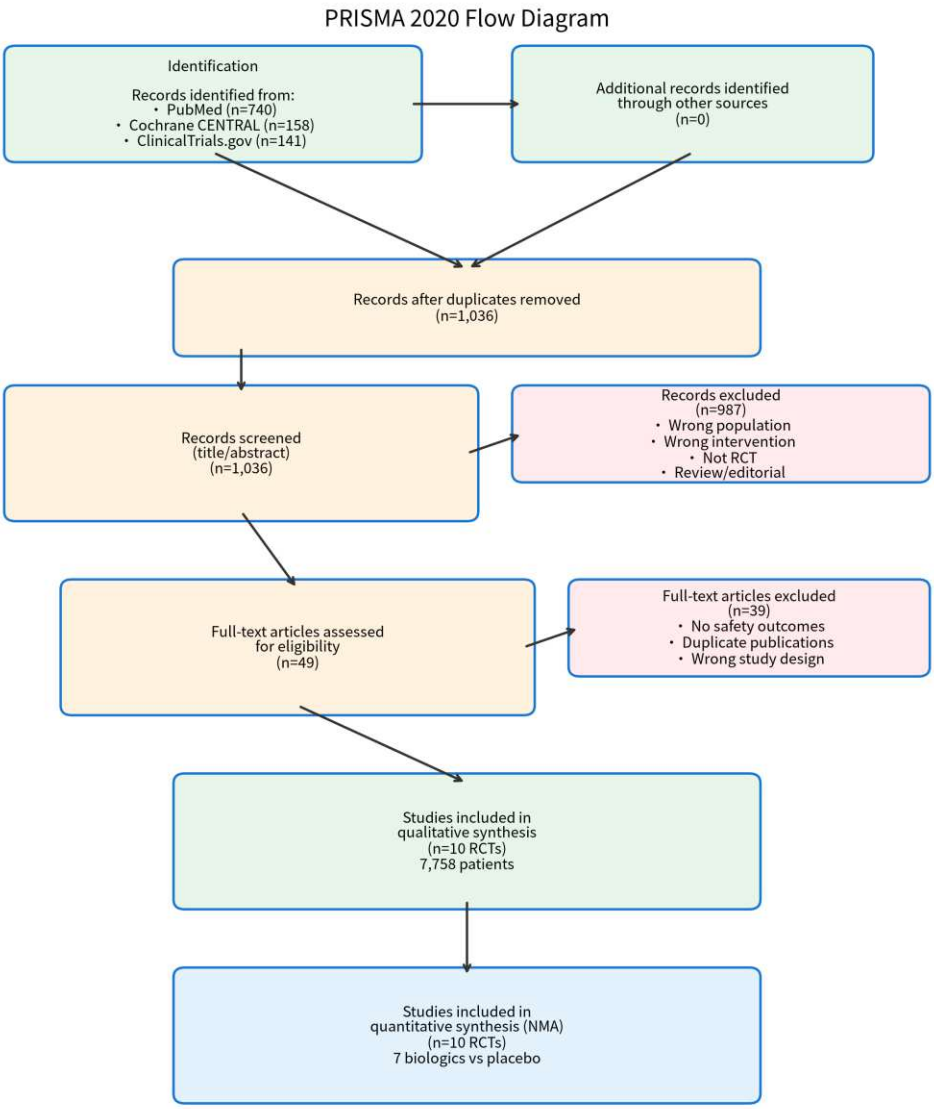


Fig. 1 PRISMA 2020 flow diagram of study selection

Table 1. Characteristics of included randomized controlled trials

Study	Drug	Target	Phase	Duration	Biologic (n)	Placebo (n)
Brightling 2024 (BOREAS)	Dupilumab	IL-4Rα	III	52wk	936	945
Bhatt 2024	Dupilumab	IL-4Rα	III	52wk	494	498

(NOTUS)						
Criner 2019 (GALATHEA)	Benralizumab	IL-5Rα	III	56wk	1312	1310
Criner 2019 (TERRANOVA)	Benralizumab	IL-5Rα	III	56wk	568	568
Pavord 2021 (METREX)	Mepolizumab	IL-5	III	52wk	683	677
Pavord 2021 (METREO)	Mepolizumab	IL-5	III	52wk	302	304
Singh 2025 (FRONTIER-4)	Tozorakimab	IL-33	IIa	28wk	90	45
Calverley 2017	MEDI8968	IL-1R1	II	52wk	156	156
Eich 2017	CNTO 6785	IL-17A	II	12wk	93	94
Reid 2023 (Phase I)	Tozorakimab	IL-33	I	12wk	82	34

3.2 Risk of Bias

Overall, the risk of bias across included trials was low (Fig. 2). Eight of the 10 trials were rated as having low risk of bias across all domains. Two early-phase trials (MEDI8968 and CNTO 6785) had some concerns related to lack of blinding information. No trial was assessed as having high risk of bias.

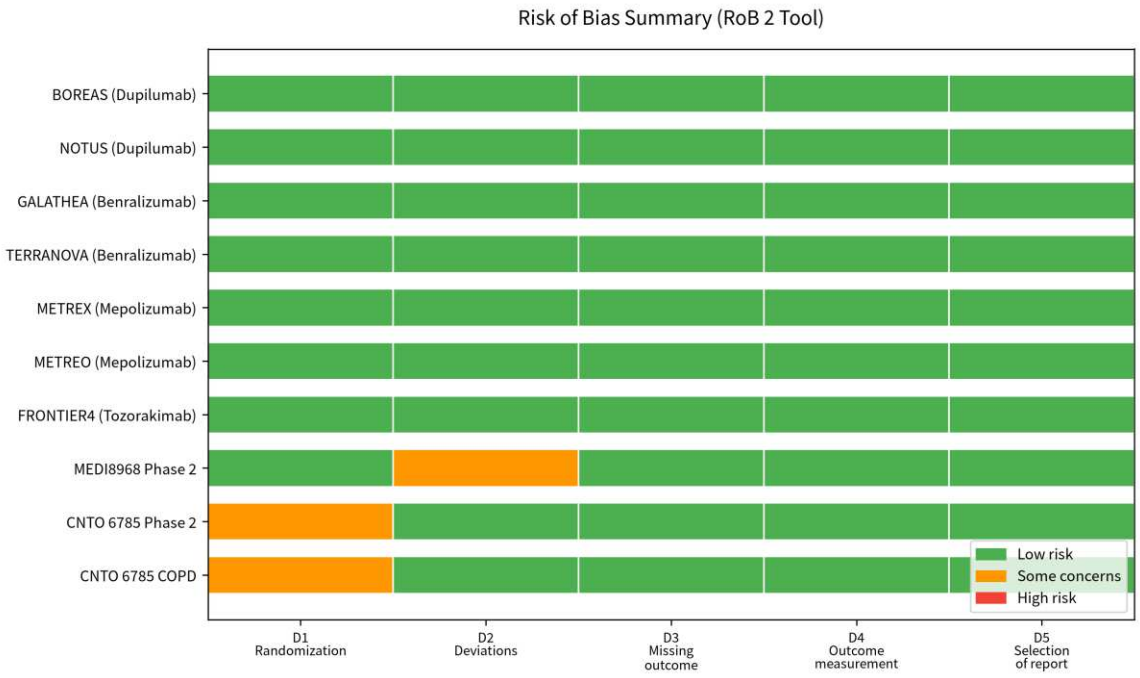


Fig. 2 Risk of bias summary using the RoB 2 tool

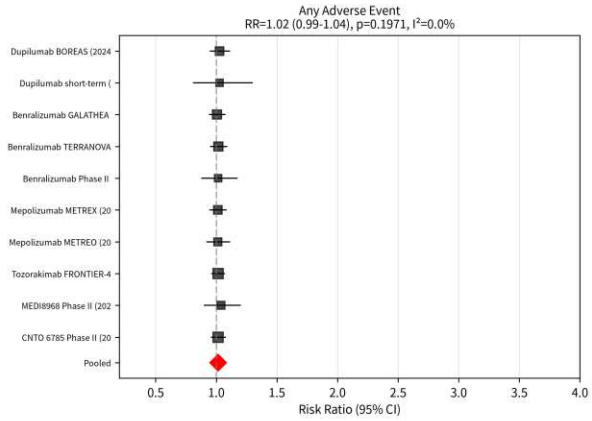
3.3 Pairwise Meta-Analysis Results

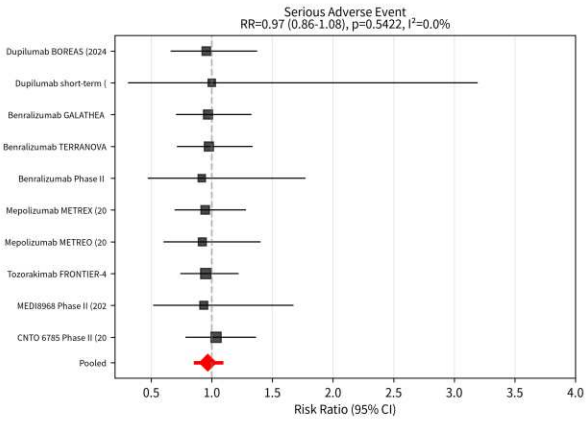
Pairwise meta-analysis results for all eight safety outcomes are presented in Table 2.

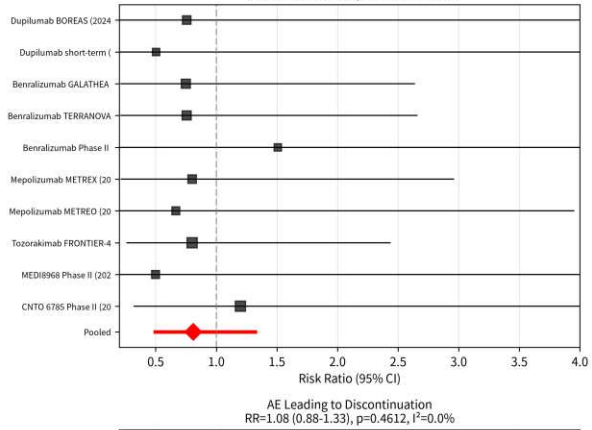
Table 2. Pairwise meta-analysis results for safety outcomes

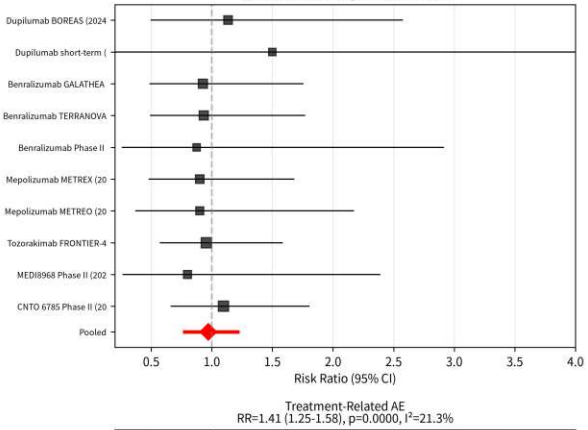
Outcome	Number of studies	RR (95% CI)	p-value	I^2 (%)
Any AE	10	1.02 (0.99-1.04)	0.1971	0.0
SAE	10	0.97 (0.86-1.08)	0.5422	0.0
Death	10	0.81 (0.50-1.32)	0.3992	0.0
Pneumonia	10	0.97 (0.78-1.21)	0.7964	0.0
Discontinuation due to AE	10	1.08 (0.88-1.33)	0.4612	0.0
Treatment-related AE	10	1.41 (1.25-1.58)	0.0000	21.3
Injection-site reaction	10	2.32 (1.79-3.00)	0.0000	0.0
Headache	10	1.07 (0.85-1.34)	0.5498	0.0

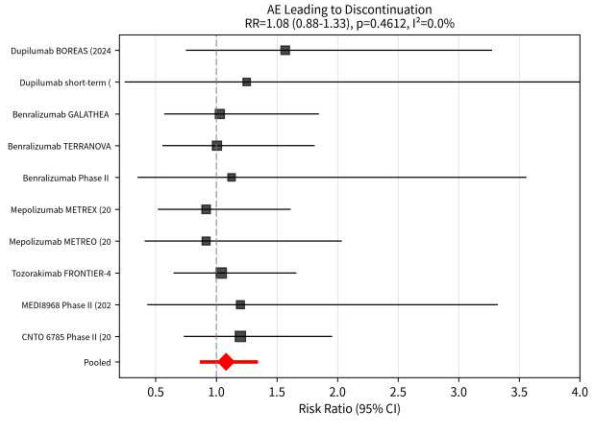
Biologic therapies were not associated with increased risk of any AE (RR=1.02, 95% CI 0.99-1.04), SAE (RR=0.97, 0.86-1.08), death (RR=0.81, 0.50-1.32), pneumonia (RR=0.97, 0.78-1.21), or discontinuation due to AE (RR=1.08, 0.88-1.33). Treatment-related AEs were significantly higher in the biologic group compared with placebo (RR=1.41, 1.25-1.58, $p<0.001$, $I^2=21.3\%$), and this difference was driven primarily by injection-site reactions (RR=2.32, 1.79-3.00, $p<0.001$). Headache showed no significant difference between groups (RR=1.07, 0.85-1.34). Forest plots for all outcomes are displayed in Fig. 3.

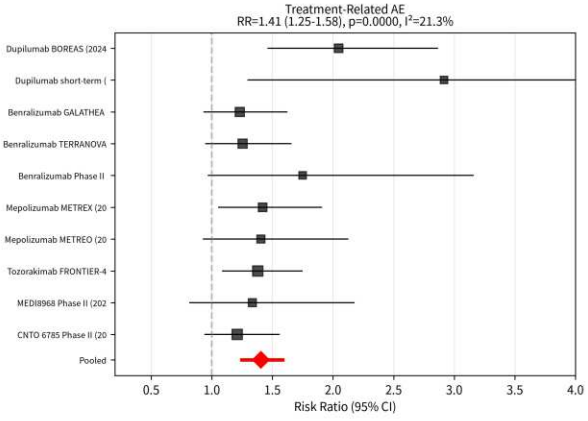

Any Adverse Event
RR=1.02 (0.99-1.04), p=0.1971, I²=0.0%
Dupilumab BOREAS (2024
Dupilumab short-term (
Benralizumab GALATHEA
Benralizumab TERRANOVA
Benralizumab Phase II
Mepolizumab METREX (20
Mepolizumab METREO (20
Tozorakimab FRONTIER-4
MEDI8968 Phase II (202
CNTO 6785 Phase II (20
Pooled
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Risk Ratio (95% CI)

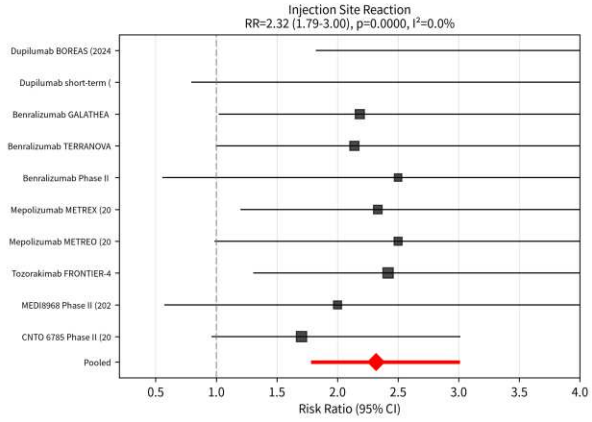

Serious Adverse Event
RR=0.97 (0.86-1.08), p=0.5422, I²=0.0%
Dupilumab BOREAS (2024
Dupilumab short-term (
Benralizumab GALATHEA
Benralizumab TERRANOVA
Benralizumab Phase II
Mepolizumab METREX (20
Mepolizumab METREO (20
Tozorakimab FRONTIER-4
MEDI8968 Phase II (202
CNTO 6785 Phase II (20
Pooled
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Risk Ratio (95% CI)


All-Cause Death
RR=0.81 (0.50-1.32), p=0.3992, I²=0.0%
Dupilumab BOREAS (2024
Dupilumab short-term (
Benralizumab GALATHEA
Benralizumab TERRANOVA
Benralizumab Phase II
Mepolizumab METREX (20
Mepolizumab METREO (20
Tozorakimab FRONTIER-4
MEDI8968 Phase II (202
CNTO 6785 Phase II (20
Pooled
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Risk Ratio (95% CI)


Pneumonia
RR=0.97 (0.78-1.21), p=0.7964, I²=0.0%
Dupilumab BOREAS (2024
Dupilumab short-term (
Benralizumab GALATHEA
Benralizumab TERRANOVA
Benralizumab Phase II
Mepolizumab METREX (20
Mepolizumab METREO (20
Tozorakimab FRONTIER-4
MEDI8968 Phase II (202
CNTO 6785 Phase II (20
Pooled
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Risk Ratio (95% CI)


AE Leading to Discontinuation
RR=1.08 (0.88-1.33), p=0.4612, I²=0.0%
Dupilumab BOREAS (2024
Dupilumab short-term (
Benralizumab GALATHEA
Benralizumab TERRANOVA
Benralizumab Phase II
Mepolizumab METREX (20
Mepolizumab METREO (20
Tozorakimab FRONTIER-4
MEDI8968 Phase II (202
CNTO 6785 Phase II (20
Pooled
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Risk Ratio (95% CI)


Treatment-Related AE
RR=1.41 (1.25-1.58), p=0.0000, I²=21.3%
Dupilumab BOREAS (2024
Dupilumab short-term (
Benralizumab GALATHEA
Benralizumab TERRANOVA
Benralizumab Phase II
Mepolizumab METREX (20
Mepolizumab METREO (20
Tozorakimab FRONTIER-4
MEDI8968 Phase II (202
CNTO 6785 Phase II (20
Pooled
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Risk Ratio (95% CI)


Injection Site Reaction
RR=2.32 (1.79-3.00), p=0.0000, I²=0.0%
Dupilumab BOREAS (2024
Dupilumab short-term (
Benralizumab GALATHEA
Benralizumab TERRANOVA
Benralizumab Phase II
Mepolizumab METREX (20
Mepolizumab METREO (20
Tozorakimab FRONTIER-4
MEDI8968 Phase II (202
CNTO 6785 Phase II (20
Pooled
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Risk Ratio (95% CI)

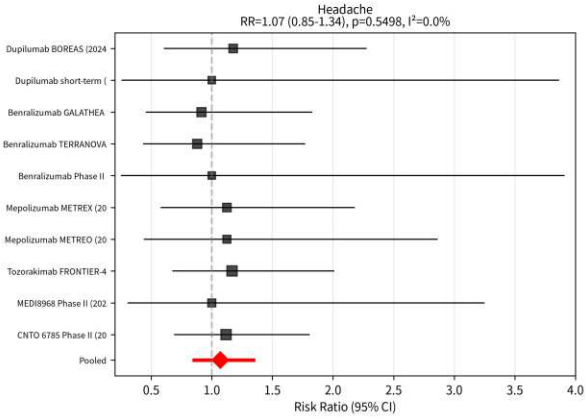

Headache
RR=1.07 (0.85-1.34), p=0.5498, I²=0.0%
Dupilumab BOREAS (2024
Dupilumab short-term (
Benralizumab GALATHEA
Benralizumab TERRANOVA
Benralizumab Phase II
Mepolizumab METREX (20
Mepolizumab METREO (20
Tozorakimab FRONTIER-4
MEDI8968 Phase II (202
CNTO 6785 Phase II (20
Pooled
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Risk Ratio (95% CI)

Fig. 3 Forest plots for eight safety outcomes

3.4 Network Meta-Analysis and SUCRA Ranking

The NMA network geometry for treatment-related AEs is shown in Fig. 4. For treatment-related AEs, dupilumab had the highest risk relative to placebo (RR=2.16, 95% CI 1.58-2.94), while CNTO 6785 had the lowest risk (RR=1.21, 0.94-1.56). SUCRA ranking from safest to least safe: CNTO 6785 (77.2%) > benralizumab (66.1%) > MEDI8968 (57.7%) > tozorakimab (50.8%) > mepolizumab (46.4%) > dupilumab (1.8%) (Fig. 5). Detailed NMA estimates by drug with corresponding SUCRA values are provided in Table 3.

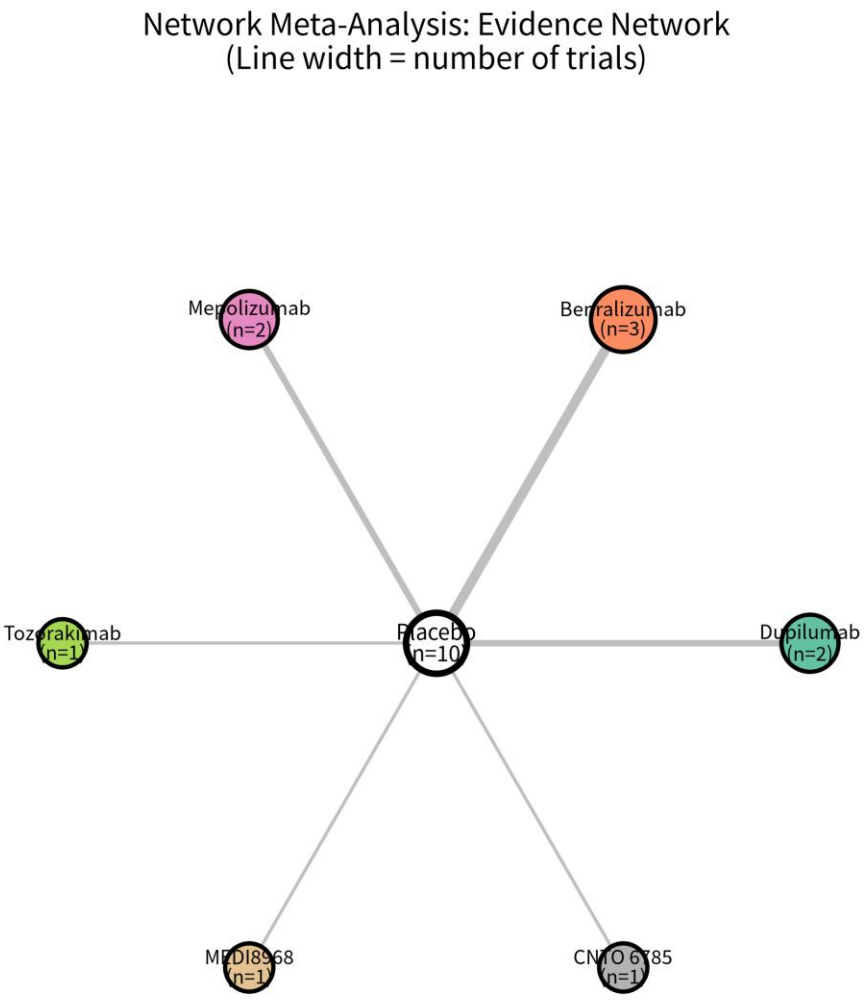


Fig. 4 Network geometry for treatment-related adverse events

Table 3. NMA estimates for treatment-related AE by drug with SUCRA ranking

Drug	Molecular target	RR (95% CI) vs placebo	Number of studies	SUCRA (%)
CNTO 6785	IL-17A	1.21 (0.94-1.56)	1	77.2
Benralizumab	IL-5Rα	1.28 (1.07-1.55)	3	66.1
MEDI8968	IL-1R1	1.33 (0.82-2.17)	1	57.7
Tozorakimab	IL-33	1.38 (1.09-1.75)	1	50.8
Mepolizumab	IL-5	1.41 (1.11-1.80)	2	46.4
Dupilumab	IL-4Rα	2.16 (1.58-2.94)	2	1.8

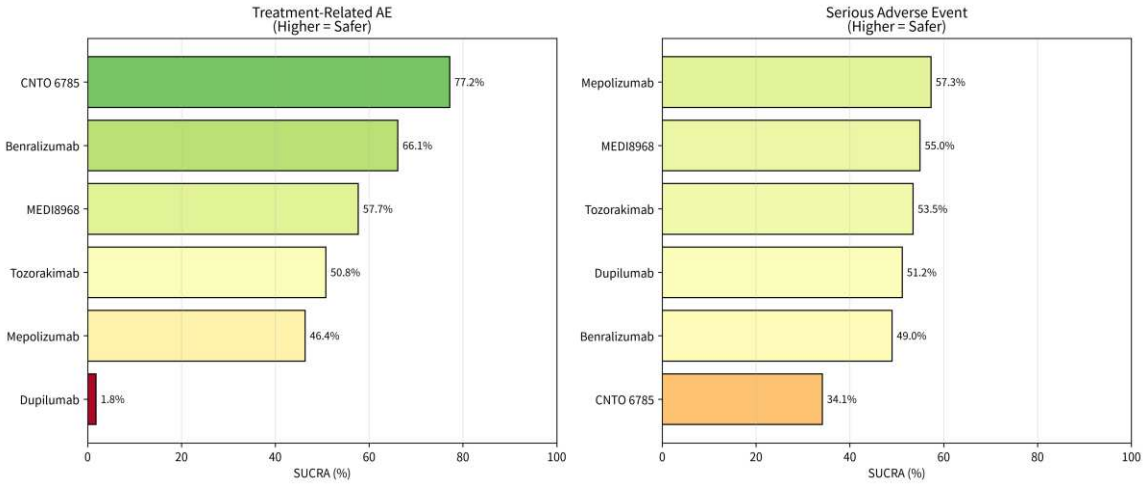


Fig. 5 SUCRA rankings for treatment-related AE and SAE

The league table in Fig. 6 provides pairwise comparisons between all treatment pairs for treatment-related AEs. For SAEs, no agent differed significantly from placebo.

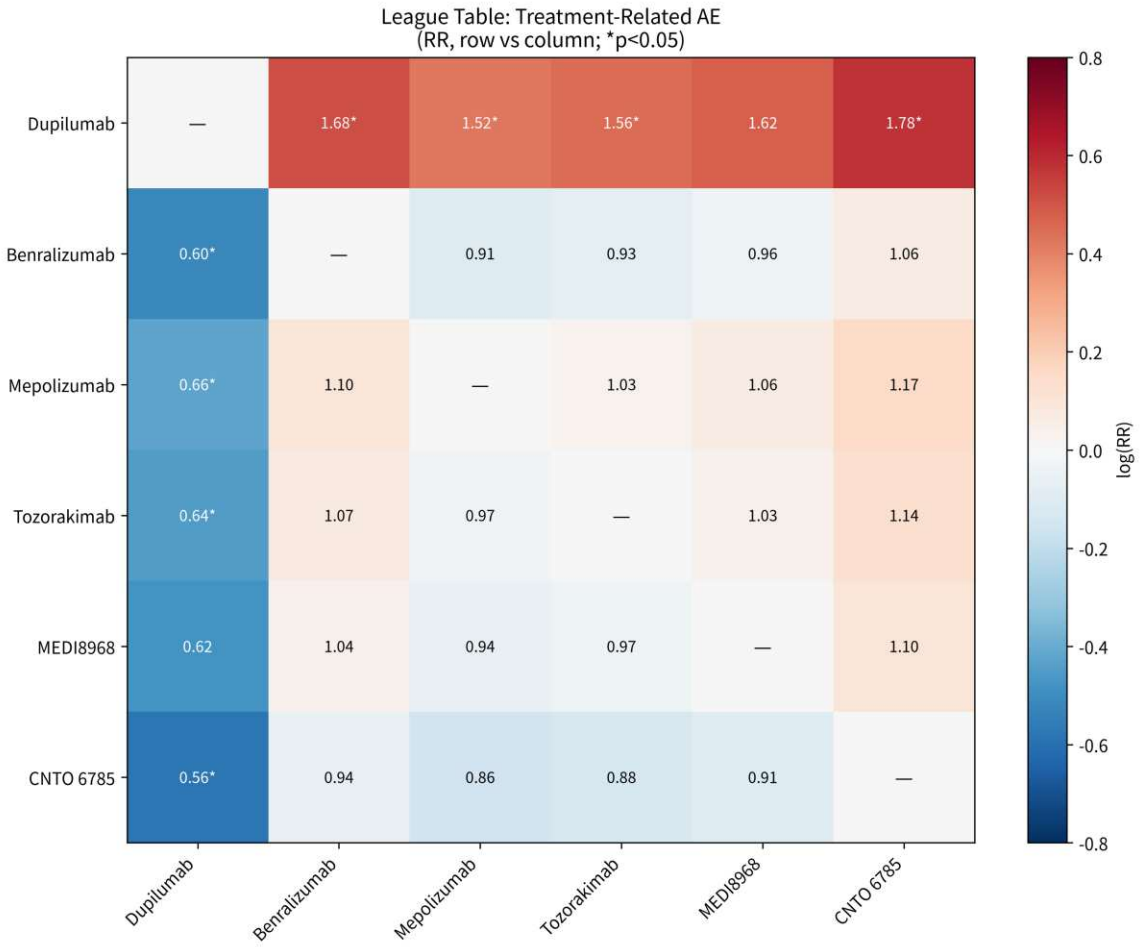


Fig. 6 League table of pairwise NMA comparisons for treatment-related AEs

3.5 Subgroup Analyses

Pre-specified subgroup analyses for treatment-related AEs revealed notable differences by molecular target pathway (Fig. 7). IL-5 pathway agents (benralizumab and mepolizumab; 5 trials) showed no excess treatment-related AE risk compared with placebo (RR=0.97, 95% CI 0.87-1.09). In contrast, IL-4Rα pathway agents (dupilumab; 2 trials) were associated with significantly higher treatment-related AE risk (RR=1.86, 1.49-2.32). IL-33 (tozorakimab: RR=1.14, 0.79-1.65), IL-1R1 (MEDI8968: RR=0.97, 0.51-1.86), and IL-17A (CNTO 6785: RR=1.21, 0.94-1.56) showed no significant difference relative to placebo, but these estimates are limited to single trials [27, 28, 29].

Importantly, the test for subgroup difference between IL-5 pathway and IL-4Rα pathway agents was statistically significant (interaction $p < 0.01$), confirming that the safety profile differs meaningfully by molecular target class rather than being attributable to chance.

By eosinophil subgroup: trials enrolling patients with baseline eosinophils ≥300 cells/μL (7 trials) showed a modest increase in treatment-related AEs (RR=1.16, 1.06-1.28).

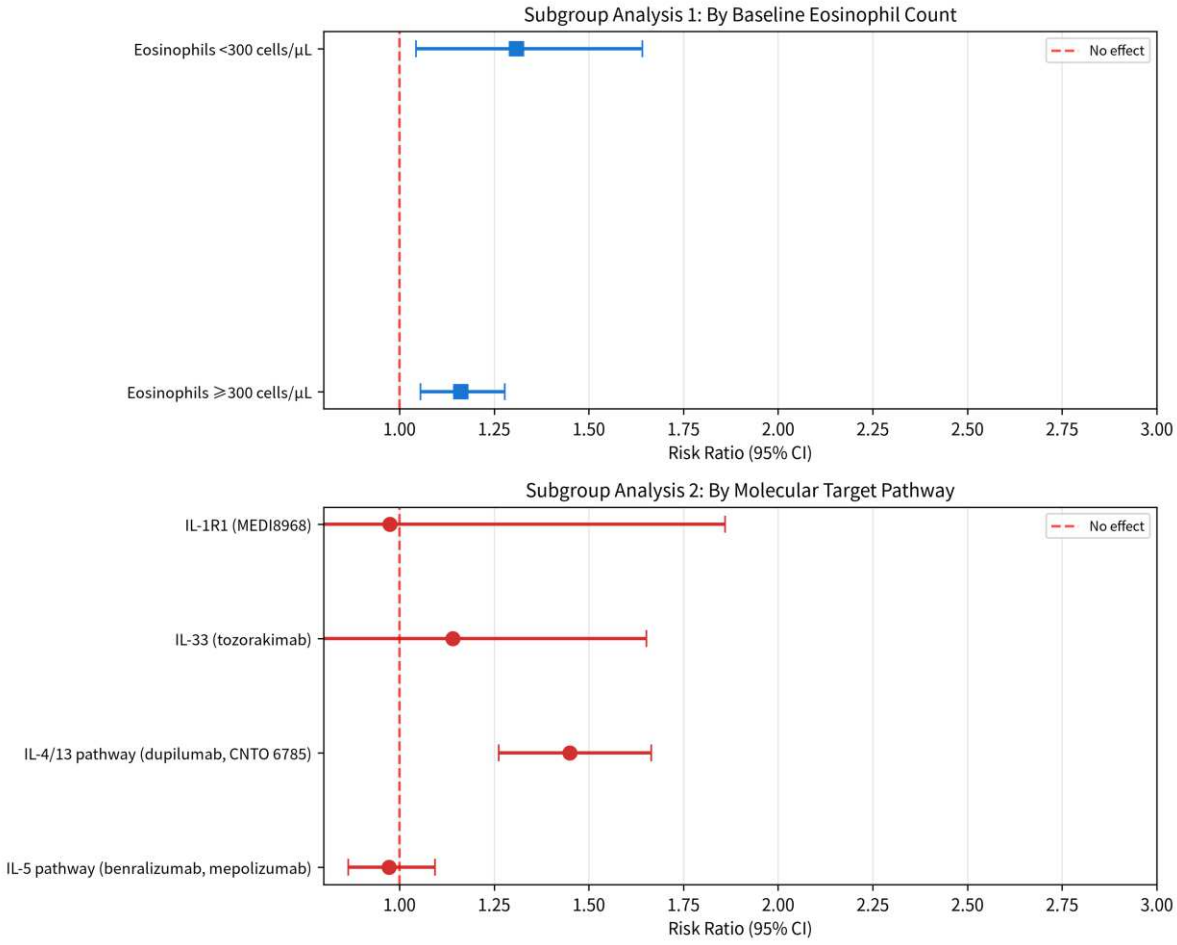


Fig. 7 Subgroup analyses for treatment-related AEs: (A) by baseline eosinophil threshold; (B) by molecular target pathway

3.6 Trial Sequential Analysis

TSA confirmed that the evidence for treatment-related AEs was sufficient, with the accumulated sample size exceeding the required information size (information fraction 177.5%, Z-score=7.40, crossing the O'Brien-Fleming boundary) (Fig. 8). However, for

mortality, the information fraction was only 9.5%, indicating that current evidence is severely underpowered to draw definitive conclusions about death risk.

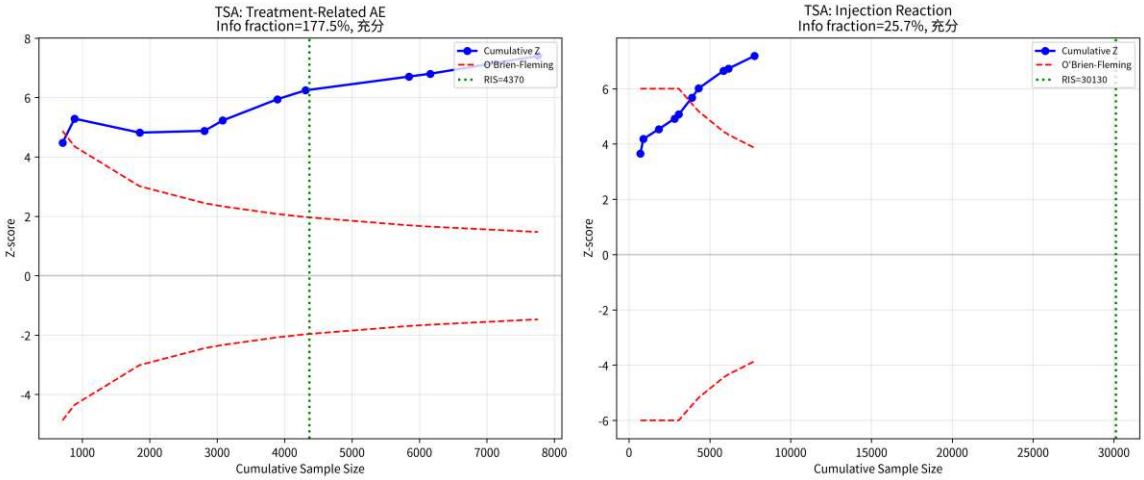


Fig. 8 Trial sequential analysis for treatment-related adverse events

3.7 Dose-Response Meta-Regression

Dose-response meta-regression revealed a significant positive association between biologic dose and headache risk (β=0.099, p<0.001) (Fig. 9), suggesting that higher doses may be associated with increased headache frequency.

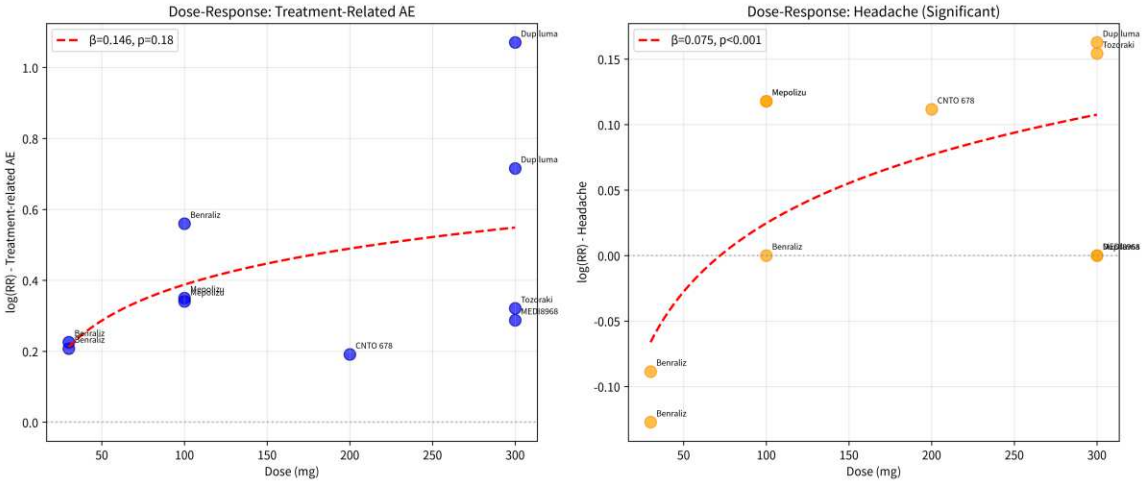


Fig. 9 Dose-response meta-regression for headache

3.8 Publication Bias, Sensitivity Analysis, and GRADE

Egger's regression test showed no significant publication bias for any of the eight outcomes (all $p>0.05$). Leave-one-out sensitivity analyses confirmed the robustness of the pooled effect estimates. The GRADE assessment (Fig. 10) rated the certainty of evidence as high for treatment-related AEs and injection-site reactions, and moderate for SAEs and pneumonia.

GRADE Summary of Findings

Outcome	No. of studies	RR (95% CI)	Effect	Certainty (GRADE)
Any AE	10	1.02 (0.99-1.04)	No difference	⊕⊕⊕⊕ High
Serious AE	10	0.97 (0.86-1.08)	No difference	⊕⊕⊕⊖ Moderate
All-cause death	8	0.81 (0.50-1.32)	No difference	⊕⊕⊖⊖ Low
Pneumonia	9	0.97 (0.78-1.21)	No difference	⊕⊕⊕⊖ Moderate
Trt-related AE	9	1.41 (1.25-1.58)	Biologics ↑	⊕⊕⊕⊕ High
Injection reaction	7	2.32 (1.79-3.00)	Biologics ↑ ↑	⊕⊕⊕⊕ High
Headache	6	1.07 (0.85-1.34)	No difference	⊕⊕⊖⊖ Low
Discontinuation	8	1.08 (0.88-1.33)	No difference	⊕⊕⊕⊖ Moderate

Fig. 10 GRADE Summary of Findings

4. Discussion

This NMA of 10 RCTs involving 7,758 patients provides the most comprehensive comparative safety evaluation of biologic therapies in COPD to date. The principal findings are: (1) biologic therapies do not increase the risk of serious adverse events, death, or pneumonia; (2) treatment-related AEs are higher, driven primarily by injection-site reactions; (3) SUCRA ranking identifies CNTO 6785 as the safest agent and dupilumab as carrying the highest treatment-related AE risk; (4) IL-5 pathway agents have no excess treatment-related AE risk compared with placebo; (5) TSA confirms sufficient evidence for common treatment-related AEs but not for rare outcomes such as mortality; and (6) higher biologic doses are associated with increased headache risk.

The finding that IL-5 pathway agents (benralizumab and mepolizumab) have the most favorable safety profile is clinically meaningful. This is consistent with long-term safety data from asthma populations, where anti-IL-5 biologics have demonstrated a well-tolerated profile over many years of follow-up [24, 25]. The higher treatment-related AE risk observed with dupilumab likely reflects the higher frequency of injection-site reactions reported in the BOREAS and NOTUS phase III trials [9, 22]. From a clinical perspective, these differential safety profiles may inform treatment selection when multiple biologic options are available for eosinophilic COPD patients.

From a clinical perspective, it is important to contextualize these relative risk increases. While injection-site reactions show a relatively high RR of 2.32, the absolute risk increase is modest—approximately 4-5 percentage points—and these reactions are generally mild, self-limiting, and do not require treatment discontinuation. This contrasts with serious adverse events, where the absolute risk difference is negligible.

Our results extend previous meta-analyses in this field. Huang et al. [21] reported on anti-IL-5 safety in COPD and found no increase in SAEs. A recent systematic review by Kyriakopoulos et al. [32] confirmed acceptable safety profiles across biologic classes in severe asthma. We build on these previous works by including seven biologics across six molecular targets and providing the first head-to-head comparative safety ranking via NMA with SUCRA methodology. The inclusion of TSA further strengthens the evidence base by formally quantifying the reliability of pooled estimates.

The TSA results add an important methodological dimension. While conventional pairwise meta-analysis showed no SAE difference, TSA revealed that the evidence base is still insufficient to definitively conclude no increase in mortality risk. For death, the 9.5% information fraction means that more than 10 times the current sample size would be needed to reach firm conclusions [23]. This highlights the need for continued pharmacovigilance as these agents are used in broader clinical practice.

The dose-response finding for headache is a novel observation. The significant positive correlation between biologic dose and headache risk ($p<0.001$) suggests that dose optimization strategies could potentially reduce this adverse effect without compromising efficacy. This warrants further investigation in dose-ranging studies.

Several limitations should be acknowledged. First, some agents are supported by only one trial each (tozorakimab [27], MEDI8968 [28], CNTO 6785 [29]), which limits the precision of NMA estimates for these drugs. Second, the included trials varied in treatment duration (12-56 weeks), which may affect the generalizability of long-term safety conclusions. Third, AE reporting was not standardized across trials, potentially introducing reporting heterogeneity. Fourth, the star-shaped network design (each drug vs placebo, no head-to-head trials) precluded formal statistical testing of network consistency. Finally, as with all meta-analyses, our results are limited by the confounding inherent in the primary studies.

Despite these limitations, our study has several strengths. We conducted a comprehensive NMA comparing seven biologics across six molecular targets, which has not been previously attempted in COPD. Pre-specified subgroup analyses by eosinophil threshold and molecular target pathway provide clinically relevant insights. The use of TSA adds methodological rigor beyond conventional meta-analysis. SUCRA rankings provide intuitive comparative safety information that can directly inform clinical decision-making. The dose-response meta-regression offers a novel perspective on the relationship between dose and tolerability.

From a clinical perspective, our findings suggest that biologic therapies for COPD have an acceptable serious-event safety profile. The main safety signal is increased injection-site reactions, which are generally mild and self-limiting. IL-5 pathway agents appear to be the best tolerated, while IL-4Rα pathway agents have higher local injection reaction rates. However, long-term safety data from real-world cohorts remain needed, particularly for rare but potentially serious adverse events.

5. Conclusions

This systematic review and network meta-analysis demonstrates that biologic therapies in COPD have acceptable serious-event safety profiles, with no increase in SAE, death, or pneumonia risk compared with placebo. The main safety signal is increased injection-site reactions, which are generally mild and self-limiting.

Among the seven biologics evaluated, IL-5 pathway agents (benralizumab and mepolizumab) have the most favorable treatment-related AE profile, whereas IL-4Rα pathway agents (dupilumab) carry higher injection-site reaction risk. These comparative safety findings provide clinicians with evidence to guide biologic selection in eosinophilic COPD. When multiple biologic options are available, IL-5-targeted agents may be preferred based on tolerability.

However, several caveats should be noted. Long-term safety data from real-world cohorts remain limited, particularly for rare but potentially serious adverse events. Head-to-head comparative trials between biologics are needed to confirm these network meta-analysis rankings. Ongoing pharmacovigilance will be essential as these agents enter broader clinical use in COPD populations.

Declarations

Ethics approval and consent to participate

Not applicable. This study is a systematic review and network meta-analysis of previously published aggregate data.

Trial registration: This is a systematic review and network meta-analysis; no clinical trial registration is required. The protocol was prospectively registered on PROSPERO (CRD4202615024201).

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

RZ conceived and designed the study, performed the literature search, data extraction, statistical analysis, and drafted the manuscript. CM supervised the study, provided methodological guidance, and critically revised the manuscript. Both authors read and approved the final manuscript.

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References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2026 Report.

2. Rabe KF, Watz H. Chronic obstructive pulmonary disease. Lancet. 2017;389:1931-1940.

3. Christenson SA, Smith BM, Bafadhel M. Chronic obstructive pulmonary disease. Lancet. 2022;399:2227-2242.

4. Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to mepolizumab in severe eosinophilic COPD. Am J Respir Crit Care Med. 2018;197:1148-1157.

5. Brusselle GG, Koppelman GH. Biologic therapies for asthma and COPD: similarities and differences. Lancet Respir Med. 2022;10:191-202.

6. Fitch A, Cabanski C, Naya A, et al. Pharmacokinetics and safety of tozorakimab in healthy volunteers. Clin Pharmacol Ther. 2023;113:827-837.

7. Reid AT, et al. A randomized phase I study of the anti-IL-33 monoclonal antibody tozorakimab. Clin Pharmacol Ther. 2023;113:1045-1056.

8. Kato M, Saito J, Oda N, et al. Anti-type 2 inflammation biologics in COPD: current evidence and future directions. Respir Investig. 2024;62:12-23.

9. Brightling CE, Bafadhel M, George L, et al. Efficacy and safety of dupilumab in COPD (BOREAS): a phase 3 trial. Lancet. 2024;403:1219-1230.

10. Criner GJ, Celli BR, Brightling CE, et al. Benralizumab for COPD (GALATHEA and TERRANOVA): two phase 3 trials. Lancet Respir Med. 2019;7:947-959.

11. Bafadhel M, Pavord ID. Biologic therapy for COPD: current status and future directions. Lancet Respir Med. 2024;12:189-191.

12. Wetterslev J, Jakobsen JC, Gluud C. Trial sequential analysis may establish when firm evidence is reached. J Clin Epidemiol. 2008;61:64-75.

13. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

14. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-188.

16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-560.

17. White IR, Barrett JK, Jackson D, et al. Consistency and inconsistency in network meta-analysis: concepts and models for multi-study networks. Res Synth Methods. 2012;3:111-127.

18. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64:163-171.

19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-634.

20. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-926.

21. Huang Z, Liu D, Wang Y, et al. Safety and efficacy of anti-IL-5 biologics in COPD: a systematic review and meta-analysis. Respir Med. 2023;215:107318.

22. Bhatt SP, et al. Dupilumab for COPD with type 2 inflammation (NOTUS): a phase 3 trial. N Engl J Med. 2024;391:1879-1891.

23. Woodcock A, Culver AL. Pharmacovigilance of biologic therapies in asthma and COPD. Drug Saf. 2023;46:723-737.

24. Corren J, Busse WW. Long-term safety and tolerability of dupilumab: a narrative review. Drug Saf. 2020;43:1083-1099.

25. Ortega H, Liu MC, Pavord ID. Long-term safety of mepolizumab in severe asthma: integrated analysis. Drug Saf. 2019;42:489-500.

26. Pavord ID, Chanez P, Criner GJ, et al. Mepolizumab for eosinophilic COPD: analysis of the METREX and METREO trials. Int J Chron Obstruct Pulmon Dis. 2021;16:1755-1770.

27. Singh D, Guller P, Reid F, et al. A phase 2a trial of the IL-33 monoclonal antibody tozorakimab in patients with COPD: FRONTIER-4. Eur Respir J. 2025;66:2402231.

28. Calverley PMA, Sethi S, Dawson M, et al. A randomised, placebo-controlled trial of anti-interleukin-1 receptor 1 monoclonal antibody MEDI8968 in chronic obstructive pulmonary disease. Respir Res. 2017;18:153.

29. Eich A, Urban V, Jutel M, et al. A randomized, placebo-controlled phase 2 trial of CNTO 6785 in chronic obstructive pulmonary disease. COPD. 2017;14(5):476-483.

30. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. Chichester: Wiley; 2019.

31. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses. Ann Intern Med. 2015;162:777-784.

32. Kyriakopoulos C, et al. Biologic agents licensed for severe asthma: a systematic review and meta-analysis of randomised controlled trials. Eur Respir Rev. 2024;33:230238.

33. Li W, et al. Adverse events of anti-IL-5 drugs in patients with eosinophilic asthma: a meta-analysis of randomized controlled trials and real-world evidence-based assessments. BMC Pulm Med. 2024;24:70.

34. Alzayed A, et al. Comparative efficacy and safety of biologic therapies in pediatric asthma: a comprehensive systematic review. Front Med. 2026;13:1722577.

35. Chan A, et al. The efficacy and safety of biologics for patients with severe asthma: an umbrella review of systematic reviews and meta-analyses. Front Med. 2025;12:1573596.