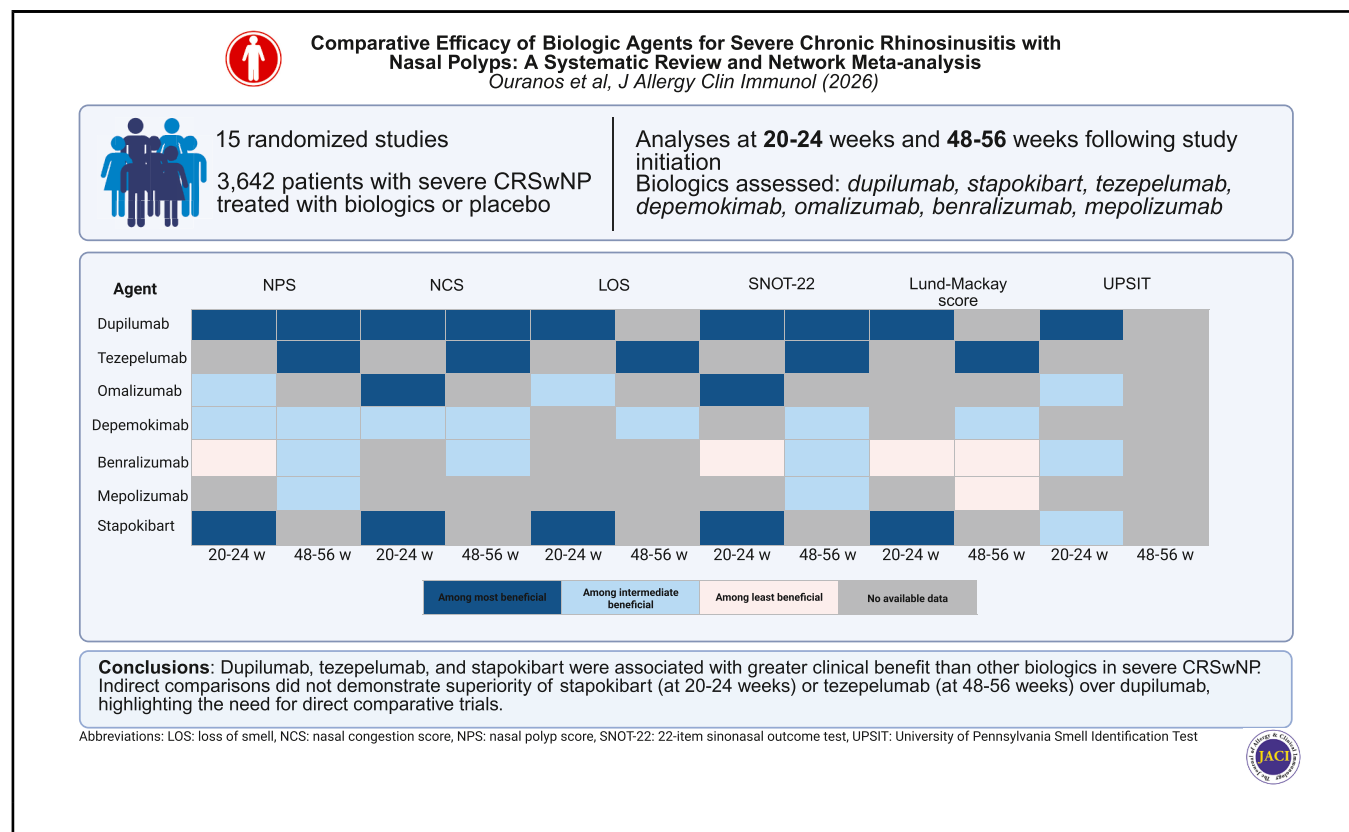


Comparative efficacy of biologic agents for severe chronic rhinosinusitis with nasal polyps: Systematic review and network meta-analysis



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GRAPHICAL ABSTRACT



Capsule summary: In this network meta-analysis of 15 randomized trials including 3,642 patients with severe chronic rhinosinusitis with nasal polyps, dupilumab, tezepelumab, and stapokibart produced greater improvements in nasal polyp and congestion scores than other biologics, without clear superiority of tezepelumab (at 48-56 weeks) or stapokibart (at 20-24 weeks) over dupilumab.

Comparative efficacy of biologic agents for severe chronic rhinosinusitis with nasal polyps: Systematic review and network meta-analysis



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Background: Biologic therapies improve outcomes in severe chronic rhinosinusitis with nasal polyps (CRSwNP), but their comparative efficacy remains uncertain.

Objective: We compared the efficacy and safety of 7 biologic agents (dupilumab, omalizumab, mepolizumab, benralizumab, depemokimab, tezepelumab, and stapokibart) for the treatment of severe CRSwNP.

Methods: We systematically reviewed randomized trials in PubMed and EMBASE evaluating biologic agents for severe CRSwNP. Primary outcomes were changes in nasal polyp score (NPS) and nasal congestion score (NCS) at 20-24 and 48-56 weeks. Secondary outcomes included changes in loss-of-smell test, 22-item Sinonasal Outcome Test, University of Pennsylvania Smell Identification Test, Lund-Mackay scores, need for nasal polyp surgery or systemic corticosteroids, and safety. We used mean differences and odds ratios with 95% confidence intervals for analysis.

Results: Fifteen randomized trials involving 3,642 patients were included. At 20-24 weeks, dupilumab and stapokibart produced greater reductions in NPS and NCS compared to depemokimab, omalizumab, and benralizumab, with no significant differences between dupilumab and stapokibart for NPS (mean difference [95% confidence interval]: 0.29 [−0.97, 0.40]) and NCS (0.19 [−0.03, 0.42]). At 48-56 weeks, dupilumab and tezepelumab produced greater reductions in NPS and NCS than depemokimab, mepolizumab, or benralizumab; no significant differences were observed between dupilumab and tezepelumab for NPS (0.32 [−0.17, 0.81]) and NCS (0.06 [−0.19, 0.31]). Dupilumab, tezepelumab (at 48-56 weeks only), and stapokibart (at 20-24 weeks only) showed superior outcomes for secondary end points against other tested biologics. Safety profiles were comparable across agents.

Conclusion: Dupilumab, tezepelumab, and stapokibart were associated with greater clinical benefit than other biologics in

severe CRSwNP. Indirect comparisons did not demonstrate superiority of stapokibart (at 20-24 weeks) or tezepelumab (at 48-56 weeks) over dupilumab, highlighting the need for direct comparative trials. (*J Allergy Clin Immunol* 2026;158:1047-57.)

Key words: CRSwNP, chronic rhinosinusitis with nasal polyps, tezepelumab, dupilumab, stapokibart

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory disease of the upper airways that can significantly impair quality of life.^{1,2} Associated symptoms include loss of smell (LOS), nasal congestion, impaired sleep, fatigue, facial pressure, and rhinorrhea.³ CRSwNP exhibits significant heterogeneity in disease pathogenesis, and different inflammatory endotypes have been identified.⁴ The classification of inflammatory endotypes has shifted from a tissue pathology-based framework to one defined by key inflammatory mediators, broadly categorized as type 1, 2, and 3. Type 1 inflammation is associated with increased IFN- γ , whereas type 2 inflammation is characterized by elevated IL-4, IL-5, and IL-13. Type 3 inflammation is marked by increased IL-17 and IL-22. CRSwNP is predominantly associated with type 2 inflammation, characterized by eosinophilia and elevated IL-4, IL-5, and IL-13, although mixed endotypes have been reported. This heterogeneity underscores the complex, dysregulated immune mechanisms underlying chronic rhinosinusitis.⁵

Conventional management of CRSwNP typically involves intranasal corticosteroids, systemic corticosteroids, and/or surgical intervention, with functional endoscopic sinus surgery being the most frequently used surgical approach.⁶ While corticosteroids can alleviate symptoms and reduce the risk of disease recurrence after surgery, the disease of a subset of patients experiences insufficient response, necessitating escalation of therapy.^{7,8} Functional endoscopic sinus surgery aims to excise polypoid tissue and inflammatory debris while preserving the mucosa, thereby optimizing sinus ventilation and drainage and promoting gradual resolution of mucosal disease. Nevertheless, polyp recurrence may occur even after endoscopic surgery.⁹⁻¹² As such, treatment interventions aimed at targeting key inflammatory pathways seen in CRSwNP are needed. Over the past few years, multiple biologic agents have been studied in phase 2 and 3 clinical trials, showing superiority over placebo in reducing polyp size and improving patient symptoms and quality of life.¹³ At present, biologic therapies approved by the US Food and Drug Administration for the treatment of CRSwNP include dupilumab (anti-IL-4 receptor alpha [IL-4R α] monoclonal antibody [mAb]), omalizumab (anti-IgE mAb), mepolizumab (anti-IL-5 mAb), and tezepelumab (mAb that acts by blocking of anti-thymic stromal

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Abbreviations used

AERD:	Aspirin-exacerbated respiratory disease
CI:	Confidence interval
CRSwNP:	Chronic rhinosinusitis with NPs
IL-4R α :	IL-4 receptor alpha
LOS:	Loss of smell
mAb:	Monoclonal antibody
MD:	Mean difference
NCS:	Nasal congestion score
NP:	Nasal polyp
NPS:	NP score
OR:	Odds ratio
RoB-2:	Revised Cochrane risk-of-bias assessment tool
SNOT-22:	22-item Sinonasal Outcome Test
SUCRA:	Surface under the cumulative ranking
TSLP:	Thymic stromal lymphopoietin
UPSIT:	University of Pennsylvania Smell Identification Test

lymphopoietin [TSLP] from receptor binding). In addition, other agents, such as depemokimab (anti-IL-5 mAb), benralizumab (anti-IL-5 receptor alpha mAb), and stapokibart (anti-IL-4R α mAb; approved for use in China¹⁴), have demonstrated encouraging efficacy in recently published clinical trials,¹⁵ although a recent unpublished study comparing benralizumab to placebo in patients with CRSwNP failed to meet its primary end points.¹⁶

Despite the presence of multiple monoclonal antibodies for CRSwNP, head-to-head trials between different biologics are lacking. Recently, the EVEREST trial was the first to directly compare dupilumab and omalizumab and showed that dupilumab was superior to omalizumab in patients with severe CRSwNP and coexisting asthma.¹⁷ Previously published meta-analyses were conducted before major clinical trials of newer biologics for CRSwNP were published, included patients with CRSwNP of any severity, or performed analyses without considering duration of study interventions as a variable that could affect comparison outcomes.¹⁸⁻²³ Currently, it is still unclear which biologic agent is superior for the management of patients with severe CRSwNP, the subgroup of patients most likely to benefit from such treatment.

The aim of this systematic review and network meta-analysis was to compare the efficacy of different biologic agents for the management of patients with severe CRSwNP by pooling data from randomized clinical trials. A network meta-analysis is an advanced meta-analytic approach that compares multiple treatments simultaneously by synthesizing evidence from a network of studies. It integrates both direct comparisons and indirect evidence to estimate the relative effectiveness among all interventions included in the network.²⁴

METHODS

Study methodology

For this systematic review and meta-analysis, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for network meta-analyses 2015 checklist.²⁵ The study protocol was submitted to the International Prospective Register of Systematic Reviews (PROSPERO; CRD420251179693).

Databases and search string

The PubMed and EMBASE databases were queried for literature in English (from database inception to October 1, 2025), using the following search string: ((“chronic rhinosinusitis with nasal polyps” OR CRSwNP OR rhinosinusitis OR “nasal polyps” or “nasal polyposis”) AND (“monoclonal antibody” OR benralizumab OR mepolizumab OR omalizumab OR dupilumab OR depemokimab OR tezepelumab OR “biological therapy” OR “biological agent*” OR interleukin-5 OR IL-5 OR “interleukin-5 receptor” OR IL-5R OR interleukin-4 OR IL-4 OR “interleukin-4 receptor” OR IL-4R OR interleukin-13 OR IL-13 OR “interleukin-13 receptor” OR IL-13R OR anti-IgE or “thymic stromal lymphopoietin” OR TLSP)). Non-English-language studies were not considered for inclusion in the study. To identify additional eligible articles, we manually checked the reference lists of the articles retrieved by our automatic database search.

Study eligibility criteria

We considered randomized studies eligible for inclusion in our analysis if they met the following criteria: (1) patients were 18 years of age or older; (2) patients had physician-diagnosed severe CRSwNP, which was defined as CRSwNP that was consistent with a need for surgery: a total endoscopic nasal polyp score (NPS) of at least 5, with a minimum of at least 2 for each nostril; (3) patients needed to have symptoms of CRSwNP for more than 8 weeks before study entry; (4) patients were required to have evidence of treatment with systemic glucocorticoids in the previous 12 months before study initiation (or a medical contraindication or intolerance to systemic corticosteroids) or have had previous nasal polyp (NP) surgery of any type (any procedure involving incision and removal of tissue from the nasal cavity, such as polypectomy or endoscopic sinus surgery); (5) patients were randomized to receive either a biologic agent or placebo; (6) outcomes of interest were reported at predefined time periods after study initiation, specifically during weeks 20-24 or weeks 48-56, in alignment with the reporting of major clinical trials of biologic agents in CRSwNP; and (7) at least one outcome of interest was reported in the study under consideration. Studies with patient-reported diagnosis of CRSwNP, diagnosis of CRSwNP of any severity other than severe, and CRSwNP with no mention of disease severity were not included in the analysis. Randomized studies that reported outcomes before week 20 after study initiation were excluded to ensure greater homogeneity in the timing of outcome reporting. We excluded observational studies, review articles, and case reports. We included abstract presentations only if there was no corresponding full-text publication on the same study. When multiple publications reported results from the same trial, we selected the study that provided the most comprehensive data suitable for our analysis. If separate reports from the same trial presented outcomes at different time points relevant to our analysis, both reports were included.

Primary and secondary study outcomes

The coprimary end points were the changes from baseline in endoscopic total NPS (range, 0 to 8, with higher scores indicating greater severity) and patient-reported nasal congestion score (NCS; range, 0 to 3, with higher scores indicating higher severity) during weeks 20-24 and weeks 48-56.

Secondary end points were the change from baseline in the mean LOS score (range, 0 to 3, with higher scores indicating greater severity); the 22-item Sinonasal Outcome Test (SNOT-22) total score (range, 0 to 110, with higher scores indicating greater severity); the Lund-Mackay score (range, 0 to 24, with higher scores indicating greater severity), which evaluates sinus opacification on computed tomographic scans; the University of Pennsylvania Smell Identification Test (UPSIT) total score (range, 0 to 40, with higher scores indicating less severity); and the first decision to treat with NP surgery or systemic glucocorticoids for CRSwNP during weeks 20-24 and weeks 48-56. We also calculated the number of patients who experienced clinically significant NPS (≥ 1 -point decrease compared to baseline) and NCS (≥ 1 -point decrease compared to baseline) responses. Finally, we assessed the safety of biologic agents by reporting the number of any-grade, severe adverse events and events leading to treatment discontinuation. Additional information regarding primary and secondary outcome data are available in [Table E1](#) in this article's Online Repository available at www.jacionline.org.

Data collection and quality evaluation

Two reviewers (K.O. and M.M.) conducted an independent evaluation of study eligibility by reviewing titles and abstracts and then conducted a full text review of the chosen studies. Disagreements were resolved by a third reviewer (S.C.M.). Extractable data from each study included biologic agent under consideration, duration of treatment, dosing regimen, number of participants entering the study, demographics, time since diagnosis of CRSwNP, previous NP surgery, previous systemic glucocorticoid receipt, underlying diagnosis of asthma or aspirin-exacerbated respiratory disease (AERD), IgE levels, absolute peripheral eosinophil count at baseline, the NPS, NCS, LOS, SNOT-22, UPSIT, and Lund-Mackay scores, and number and type of adverse events.

Study quality was assessed by 2 reviewers (K.O. and M.M.) using the revised Cochrane risk-of-bias assessment tool (RoB-2)²⁶ for randomized trials. The RoB-2 tool consists of 5 sections: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. Each individual study and all outcomes within those studies were categorized as having low risk, intermediate risk, or high risk of bias.

Statistical analysis

We conducted a random-effects network meta-analysis²⁷ estimating mean differences (MDs) in change from baseline with 95% confidence intervals (CIs) to compare biologic agents based on NCS, NPS, LOS, SNOT-22, UPSIT, and Lund-Mackay scores during weeks 20-24 and weeks 48-56. For adverse event assessment, clinically significant NPS and NCS responses, and need for surgery or systemic steroids, we estimated the odds ratios (ORs) with 95% CIs for different biologic agents. The network meta-analysis was performed with the restricted maximum likelihood method to estimate the heterogeneity variance.²⁸ To identify the superior treatment, we estimated the surface under the cumulative ranking (SUCRA) curve, which quantifies the probability that each treatment is among the most effective, with values ranging from 0 (least effective) to 1 (most effective).²⁹ Analyses

were performed by the 'meta' (cran.r-project.org/web/packages/meta/index.html)³⁰ and 'netmeta' (cran.r-project.org/package=netmeta)³¹ packages in R v4.3.3 (www.r-project.org). Consistency between direct and indirect evidence was assessed by the design-by-treatment interaction model within a random-effects framework, as implemented in 'netmeta.' $P < .05$ was considered indicative of statistically significant inconsistency. Statistical heterogeneity was evaluated by the I^2 statistic and between-study variance τ^2 within the random-effects model. I^2 values of approximately 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively. Transitivity was assessed by comparing key study characteristics across treatment comparisons, including age, sex, CRSwNP duration, prior surgical interventions, and relevant comorbidities (asthma and AERD). For all data analysis, we used an intention-to-treat approach by including in the analysis all patients entering each individual study.

Subgroup analyses assessed treatment efficacy for the primary and secondary outcomes according to coexisting asthma or AERD, baseline peripheral eosinophil count (≥ 300 IU/mL), and prior NP surgery.

RESULTS

Search results

Our literature search identified 9,609 studies. We removed 1,823 duplicates and assessed 7,786 studies against our inclusion criteria. A total of 7,719 studies were excluded after careful review of their title and abstract, so we reviewed 67 publications in full text. For the analysis of our outcomes, we retrieved 15 randomized studies from 12 publications.^{17,32-42}

The study schema is detailed in [Fig 1](#).

Baseline study characteristics

[Table E2](#) (in this article's Online Repository at www.jacionline.org) provides an overview of the characteristics of the studies included in the analysis. Overall, 3,642 patients with severe CRSwNP were analyzed: 2,091 (57.4%) received a biologic agent, specifically tezepelumab (203 [5.8%]), mepolizumab (344 [9.4%]), depemokimab (272 [7.5%]), stapokibart (90 [2.5%]), dupilumab (650 [17.8%]), benralizumab (219 [6.0%]), or omalizumab (313 [8.6%]), and 1,551 (42.6%) received placebo. The weighted mean age at baseline was 50.4 ± 13.0 years in biologic-treated patients and 50.0 ± 13.1 years in placebo-treated patients.

Among those with available data, 1,140 (63.5%) of 1,796 biologic-treated patients and 992 (64.0%) of 1,551 placebo-treated patients were male. Weighted mean time since diagnosis of severe CRSwNP was 12.36 ± 9.39 years for patients treated with biologic agents and 11.6 ± 9.4 years for patients receiving placebo. A total of 1,169 (75%) of 1,559 patients receiving biologic agents and 947 (72%) of 1,316 patients receiving placebo with available data had at least one NP surgery before study entry.

Previous systemic corticosteroid receipt was reported in 1,001 (58.5%) of 1,711 patients receiving biologic agents and 877 (59.7%) of 1,468 patients receiving placebo who had available data. Underlying asthma was reported in 1,241 (70.3%) of 1,765 and 955 (62.9%) of 1,519 patients treated with biologic agents and placebo, respectively. A diagnosis of AERD was reported in 449 (27.7%) of 1,621 and 317 (24.5%) of 1,294 patients treated with biologic agents and placebo, respectively. Across the

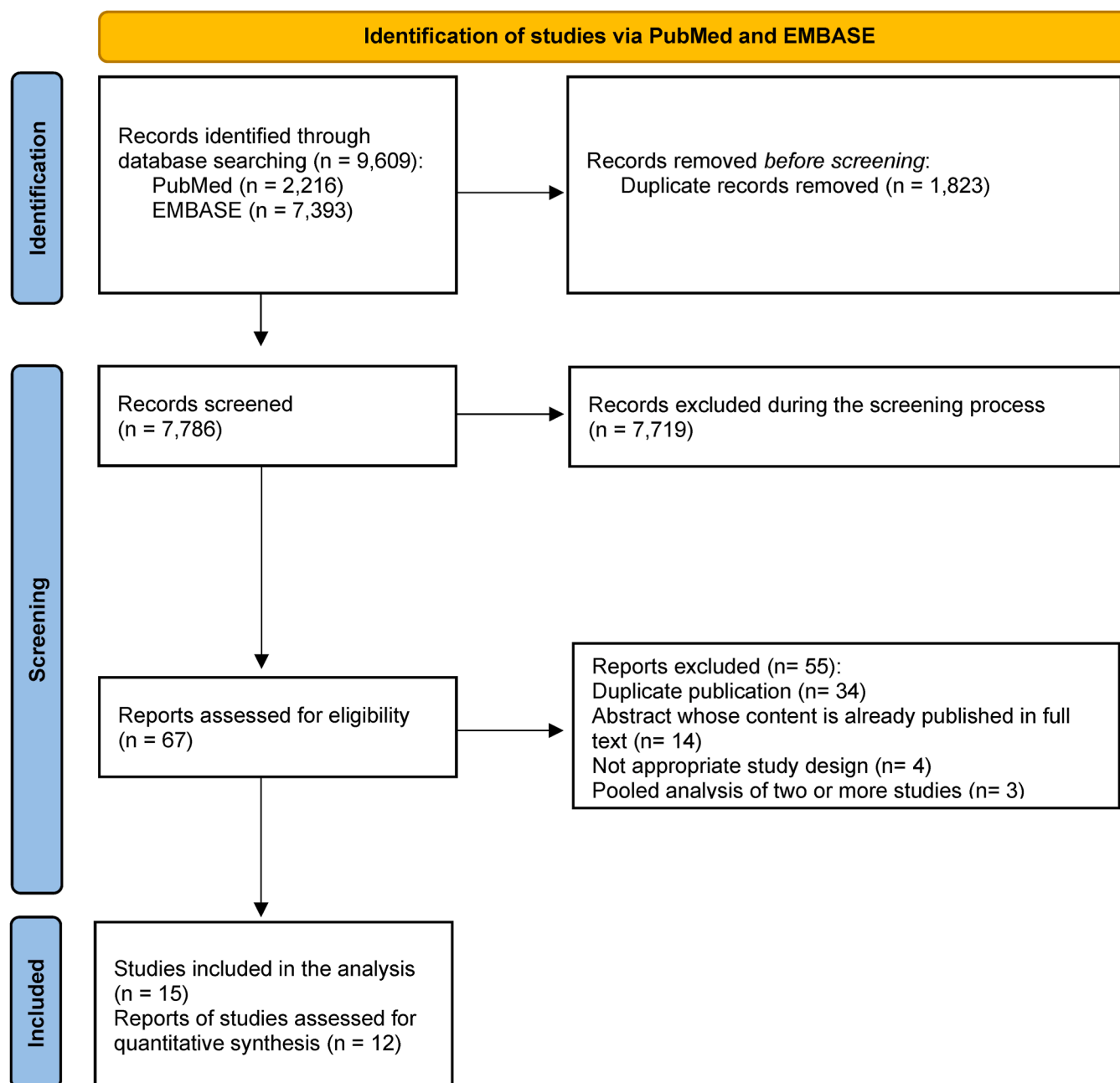


FIG 1. Flowchart for study selection.

included studies, the ranges for participant age (45.1-53.5 years) and the proportion of male participants (55-71.4%) were relatively narrow. In contrast, the range of prior endoscopic sinus surgery (18.8-100%), underlying asthma (49.7-100%), and underlying AERD (15.9-45.8%) was broader across studies. Although this broader range is less ideal, it likely reflects differences in study-specific inclusion and exclusion criteria (see Fig E1 in the Online Repository available at www.jacionline.org).

Weighted mean baseline endoscopic NPS and NCS for patients receiving biologic agents was 5.9 ± 1.21 and 2.5 ± 0.53 , respectively, whereas weighted mean baseline endoscopic NPS and NCS for patients receiving placebo was 6.12 ± 1.26 and

2.31 ± 0.56 , respectively. Weighted mean baseline LOS score, SNOT-22 score, Lund-Mackay score, and UPSIT score for patients receiving biologic agents was 2.77 ± 0.53 , 60.42 ± 22.08 , 18.95 ± 3.97 , and 12.85 ± 7.19 , respectively. Accordingly, weighted mean baseline LOS score, SNOT-22 score, Lund-Mackay score, and UPSIT score for patients receiving placebo was 2.78 ± 0.47 , 59.33 ± 21.07 , 18.74 ± 4.06 , and 12.65 ± 7.01 , respectively.

End of treatment was set at 20 weeks in 1 study,⁴⁰ 21 weeks in 1 study,³⁴ 24 weeks in 6 studies,^{17,32,37,39,42} 48 weeks in 4 studies,^{33,35,38,41} and 52 weeks in 3 studies.^{32,36} Outcomes of interest were reported during weeks 20-24 in 10 studies^{17,32,34,36,37,39,40} and during weeks 48-56 in 7

Agent	Outcomes											
	NPS ^a		NCS ^a		LOS ^a		SNOT-22 ^b		Lund-Mackay score ^c		UPSIT ^d	
	20-24 weeks	48-56 weeks	20-24 weeks	48-56 weeks	20-24 weeks	48-56 weeks	20-24 weeks	48-56 weeks	20-24 weeks	48-56 weeks	20-24 weeks	48-56 weeks
Placebo	Reference group											
Dupilumab	-2.01 [-2.35, -1.68]	-2.40 [-2.77, -2.03]	-0.89 [-1.00, -0.79]	-0.98 [-1.17, -0.79]	-1.04 [-1.16, -0.92]		-18.73 [-24.61, -12.86]	-20.96 [-25.03, -16.89]	-6.26 [-8.53, -4.00]		10.54 [9.37, 11.70]	
Tezepelumab		-2.08 [-2.40, -1.76]		-1.04 [-1.21, -0.87]		-1.01 [-1.18, -0.84]		-27.44 [-32.51, -22.37]		-5.70 [-7.01, -4.39]		
Stapokibart	-2.30 [-2.90, -1.70]		-0.70 [-0.90, -0.50]		-1.00 [-1.21, -0.79]		-12.10 [-22.99, -1.21]		-8.00 [-11.31, -4.69]		7.50 [5.85, 9.15]	
Depemokimab	-0.55 [-0.97, -0.13]	-0.65 [-0.93, -0.37]	-0.21 [-0.35, -0.07]	-0.24 [-0.40, -0.08]		-0.23 [-0.36, -0.09]		-8.44 [-14.21, -2.66]		-2.61 [-3.79, -1.44]		
Mepolizumab		-0.63 [-0.92, -0.33]						-14.19 [-19.43, -8.95]		-1.67 [-3.36, 0.02]		
Omalizumab	-0.70 [-1.09, -0.30]		-0.39 [-0.54, -0.25]		-0.31 [-0.47, -0.16]		-12.06 [-19.00, -5.12]				3.84 [2.17, 5.50]	
Benralizumab	-0.50 [-1.07, 0.07]	-0.48 [-0.81, -0.14]		-0.29 [-0.48, -0.10]			-2.58 [-13.99, 8.83]	-7.49 [-13.74, -1.24]	-2.60 [-5.92, 0.72]	-0.86 [-2.27, 0.56]	2.25 [0.05, 4.45]	
Classification of intervention (color)												
Among most beneficial; no difference in terms of response for agents in this category for a given outcome												
Among intermediate beneficial; no difference in terms of response for agents in this category for a given outcome												
Among least beneficial/not clearly different from placebo												
No data available for this agent for a given outcome												

Notes: numbers in the colored cells are the estimated mean differences (95%CI) for NPS, NCS, LOS, SNOT-22, Lund-Mackay score, and UPSIT, among the different biologic agents versus placebo. Statistically significant associations are presented in bold.

^aTotal scores for both nostrils range from 0 to 8, with higher scores indicating greater severity.

^bScores range from 0 to 3, with higher scores indicating greater severity.

^cScores range from 0 to 3, with higher scores indicating greater severity.

^dSNOT-22 score ranges from 0 to 110, with higher scores indicating greater severity.

^eScores on the Lund-Mackay scale range from 0 to 24, with higher scores indicating greater severity.

^fScores on the UPSIT range from 0 to 40, with higher scores indicating less severity.

Abbreviations: CI: confidence interval; LOS: loss of smell; NCS: nasal congestion score; NPS: nasal polyp score; SNOT-22: 22-item Sinusoidal Outcome Test; UPSIT: University of Pennsylvania Smell Identification Test

FIG 2. Summary of main findings.

studies^{32,33,35,36,38,41} (Fig E2 in the Online Repository available at www.jacionline.org). There were no studies that assessed outcome responses for tezepelumab at 20-24 weeks and stapokibart at 48-56 weeks.

Quality control of studies

Quality assessment of the included studies using the RoB-2 tool identified 13 studies^{17,32-39,41} as having low risk of bias, 1 study⁴⁰ as having intermediate risk of bias, and 1 study⁴² as having high risk of bias. Fig E3 in the Online Repository available at www.jacionline.org provides a detailed assessment of bias determination for each study included in the analysis.

Primary outcome data

NPS. In Fig 2, we present an overview of our main study results. At 20-24 weeks, among different monoclonal antibodies, stapokibart showed greater reductions in NPS compared to omalizumab (MD [95% CI]: -1.60 [-2.32, -0.89]), depemokimab (-1.75 [-2.48, -1.02]) and benralizumab (-1.80 [-2.63, -0.97]) but not compared to dupilumab (0.29 [-0.97, 0.40]) (Table I). Dupilumab also showed greater reductions in NPS compared to omalizumab (-1.32 [-1.74, -0.89]), depemokimab (-1.46 [-2.00, -0.92]) and benralizumab (-1.51 [-2.18, -0.85]). On the basis of probability ranking, the most effective interventions for achieving reduction in NPS by 20-24 weeks were the following: stapokibart (95.92%), dupilumab (84.08%), omalizumab (47.68%), depemokimab (37.58%) and benralizumab (33.86%) (see Fig E4 in the Online Repository available at www.jacionline.org).

At 20-24 weeks, subgroup analysis in patients with asthma showed that stapokibart was more likely to result in greater reductions in NPS compared to omalizumab (MD [95% CI]: -1.91 [-3.49, -0.32]) but not dupilumab (-0.67 [-2.14, 0.80]). In patients with AERD, dupilumab was more likely to result in significant NPS reduction compared to omalizumab (-1.34 [-2.09, -0.59]). Results in patients with prior NP surgery showed that stapokibart was more likely to achieve significant NPS reduction compared to omalizumab (-1.98 [-2.70, -1.26]) and benralizumab (-1.90 [-2.40, -1.40]), but not dupilumab (-0.40 [-1.01, 0.21]). Full comparison outcomes between biologic agents and probability ranking results

for NPS among the different subgroups are available in Tables E3-E5 in the Online Repository available at www.jacionline.org.

At 48-56 weeks, among different monoclonal antibodies, dupilumab showed significantly greater reductions in NPS compared to depemokimab (MD [95% CI]: -1.75 [-2.22, -1.28]), mepolizumab (-1.77 [-2.25, -1.30]) and benralizumab (-1.92 [-2.43, -1.42]) (Table I). Tezepelumab also showed significantly greater reductions in NPS compared to depemokimab (-1.43 [-1.86, -1.00]), mepolizumab (-1.45 [-1.89, -1.02]), and benralizumab (-1.60 [-2.07, -1.14]). Dupilumab did not significantly lead to lower NPS compared to tezepelumab (0.32 [-0.17, 0.81]). On the basis of probability ranking, the most effective interventions for achieving reduction in NPS by 48-56 weeks were the following: dupilumab (98.30%), tezepelumab (81.70%), depemokimab (46.40%), mepolizumab (44.74%), and benralizumab (28.80%) (Fig E4).

Subgroup analyses at 48-56 weeks showed that in patients with CRSwNP and asthma, tezepelumab was associated with significantly lower NPS compared to depemokimab (MD [95% CI]: -1.44 [-1.98, -0.89]) and mepolizumab (-1.24 [-1.81, -0.66]) (Table E3). In the subgroup of patients with AERD, tezepelumab was also linked to significantly lower NPS compared to depemokimab (-1.51 [-2.59, -0.43]) and placebo (-2.01 [-2.79, -1.24]). Subgroup analyses in patients with prior NP surgery or baseline blood eosinophil count of ≥ 300 IU/mL showed that tezepelumab was superior in achieving greater NPS reductions compared to depemokimab and mepolizumab but not dupilumab (Table E3).

At 20-24 weeks, dupilumab was more likely to achieve clinically significant NPS responses compared to omalizumab (OR [95% CI]: 3.43 [1.56, 7.54]) and mepolizumab (4.15 [1.52, 11.37]). At 48-56 weeks, tezepelumab was more likely to achieve clinically significant NPS responses compared to depemokimab (3.64 [2.03, 6.53]) and mepolizumab (3.70 [2.11, 6.52]).

NCS. At 20-24 weeks, among different monoclonal antibodies, stapokibart showed greater reductions in NCS compared to omalizumab (MD [95% CI]: -0.31 [-0.56, -0.06]) and depemokimab (-0.49 [-0.74, -0.25]), but not dupilumab (0.19 [-0.03, 0.42]) (Table I). Dupilumab also showed greater reductions in NCS compared to omalizumab (-0.50 [-0.64, -0.37]) and depemokimab (-0.69 [-0.86, -0.51]). On the basis of probability ranking, the most effective interventions for achieving reduction in NCS by 20-24 weeks were the following: dupilumab

TABLE I. NPS and NCS assessments at 48-56 and 20-24 weeks for biologic agents included in analysis

NPS, 48-56 weeks					
Dupilumab					
0.32 [−0.17, 0.81]	Tezepelumab				
−1.75 [−2.22, −1.28]*	−1.43 [−1.86, −1.00]*	Depemokimab			
−1.77 [−2.25, −1.30]*	−1.45 [−1.89, −1.02]*	−0.02 [−0.44, 0.39]	Mepolizumab		
−1.92 [−2.43, −1.42]*	−1.60 [−2.07, −1.14]*	−0.17 [−0.61, 0.26]	−0.15 [−0.60, 0.30]	Benralizumab	
−2.40 [−2.77, −2.03]*	−2.08 [−2.40, −1.76]*	−0.65 [−0.93, −0.37]*	−0.63 [−0.92, −0.33]*	−0.48 [−0.81, −0.14]*	Placebo
NCS, 48-56 weeks					
Dupilumab					
0.06 [−0.19, 0.31]	Tezepelumab				
−0.74 [−0.99, −0.49]*	−0.80 [−1.03, −0.57]*	Depemokimab			
NA	NA	NA	Mepolizumab		
−0.69 [−0.96, −0.42]*	−0.75 [−1.01, −0.50]*	0.05 [−0.20, 0.29]	NA	Benralizumab	
−0.98 [−1.17, −0.79]*	−1.04 [−1.21, −0.87]*	−0.24 [−0.40, −0.08]*	NA	−0.29 [−0.48, −0.10]*	Placebo
NPS, 20-24 weeks					
Stapokibart					
−0.29 [−0.97, 0.40]	Dupilumab				
−1.60 [−2.32, −0.89]*	−1.32 [−1.74, −0.89]*	Omalizumab			
−1.75 [−2.48, −1.02]*	−1.46 [−2.00, −0.92]*	−0.15 [−0.72, 0.43]	Depemokimab		
−1.80 [−2.63, −0.97]*	−1.51 [−2.18, −0.85]*	−0.20 [−0.89, 0.50]	−0.05 [−0.76, 0.66]	Benralizumab	
−2.30 [−2.90, −1.70]*	−2.01 [−2.35, −1.68]*	−0.70 [−1.09, −0.30]*	−0.55 [−0.97, −0.13]*	−0.50 [−1.07, 0.07]	Placebo
NCS, 20-24 weeks					
Stapokibart					
0.19 [−0.03, 0.42]	Dupilumab				
−0.31 [−0.56, −0.06]*	−0.50 [−0.64, −0.37]*	Omalizumab			
−0.49 [−0.74, −0.25]*	−0.69 [−0.86, −0.51]*	−0.18 [−0.39, 0.02]	Depemokimab		
NA	NA	NA	NA	Benralizumab	
−0.70 [−0.90, −0.50]*	−0.89 [−1.00, −0.79]*	−0.39 [−0.54, −0.25]*	−0.21 [−0.35, −0.07]*	NA	Placebo

Both direct and indirect comparisons of treatment regimens are included. Results are presented as MDs [95% CIs] between biologic agents. If MD between 2 biologic agents is negative, this suggests greater score reduction from intervention in column over intervention in row. If MD between 2 biologic agents is positive, this suggests greater score reduction from intervention in row over intervention in column. If 95% CI for MD between 2 biologic agents includes 0, association is not considered statistically significant. NA, Not available.

*Statistically significant associations.

(98.90%), stapokibart (75.88%), omalizumab (49.22%), and depemokimab (25.75%) (Fig E4).

At 20-24 weeks, subgroup analysis in patients with asthma showed that dupilumab was more likely to result in greater reductions in NCS compared to placebo (MD [95% CI]: −1.44 [−2.19, −0.69]) (Table E4). In patients with AERD, dupilumab was more likely to result in significant NCS reduction compared to omalizumab (−0.61 [−1.04, −0.19]). Results in patients with prior NP surgery showed that stapokibart (−0.80 [−1.05, −0.55]) and dupilumab (−0.89 [−1.11, −0.67]) were more likely to achieve significant NCS reduction compared to placebo, but stapokibart did not lead to significantly greater NCS reduction compared to dupilumab (0.09 [−0.24, 0.42]). Full comparison outcomes between biologic agents and probability ranking results for NCS among the different subgroups are available in Tables E3-E5.

At 48-56 weeks, among different monoclonal antibodies, dupilumab showed significantly greater reductions in NCS compared to depemokimab (MD [95% CI]: −0.74 [−0.99, −0.49]) and benralizumab (−0.69 [−0.96, −0.42]), but not tezepelumab (0.06 [−0.19, 0.31]) (Table I). Tezepelumab also showed significantly greater reductions in NCS compared to depemokimab (−0.80 [−1.03, −0.57]) and benralizumab (−0.75 [−1.01, −0.50]). On the basis of probability ranking, the most effective interventions for achieving reduction in NCS by 48-56 weeks were the following: tezepelumab (91.30%), dupilumab

(83.70%), benralizumab (41.78%), and depemokimab (33.10%) (Fig E4).

Subgroup analyses at 48-56 weeks showed that in patients with CRSwNP and asthma, tezepelumab was associated with significantly lower NCS compared to depemokimab (MD [95% CI]: −0.79 [−1.10, −0.49]) (Table E3). In the subgroup of patients with AERD, tezepelumab was also linked to significantly lower NCS compared to depemokimab (−0.95 [−1.40, −0.49]). Subgroup analyses in patients with prior NP surgery showed that dupilumab (−1.03 [−1.24, −0.82]) and tezepelumab (−1.16 [−1.37, −0.96]) achieved greater NCS reductions compared to placebo.

Secondary outcome data

LOS score. At 48-56 weeks, tezepelumab led to significantly lower LOS scores compared to depemokimab (MD [95% CI]: −0.78 [−1.01, −0.56]) (see Table E6 in the Online Repository available at www.jacionline.org). At 20-24 weeks, stapokibart led to significantly greater reductions in LOS scores compared to omalizumab (−0.69 [−0.95, −0.42]), but not dupilumab (0.04 [−0.20, 0.28]) (see Table E7 in the Online Repository). Dupilumab led to greater reductions in LOS scores compared to omalizumab (−0.73 [−0.89, −0.57]). Full comparison outcomes between biologic agents and probability ranking results for LOS

at 48-56 weeks and 20-24 weeks are available in Fig E4, Table E6, and Table E7.

SNOT-22 score. At 20-24 weeks, stapokibart did not lead to significantly greater reductions in SNOT-22 compared to dupilumab (MD [95% CI]: 6.63 [−5.74, 19.01]) (Table E7). At 48-56 weeks, among different biologic agents, dupilumab showed greater reductions in SNOT-22 compared to mepolizumab (−6.77 [−13.41, −0.14]), depemokimab (−12.52 [−19.59, −5.46]), and benralizumab (−13.47 [−20.93, −6.01]), but not tezepelumab (6.48 [−0.02, 12.98]) (Table E6). Tezepelumab showed greater reductions in SNOT-22 compared to mepolizumab (−13.25 [−20.54, −5.96]), depemokimab (−19.00 [−26.69, −11.32]), and benralizumab (−19.95 [−28.00, −11.90]). Full comparison outcomes between biologic agents and probability ranking results for SNOT-22 at 48-56 weeks and 20-24 weeks are available in Fig E4, Table E6, and Table E7.

Lund-Mackay score. At 20-24 weeks, stapokibart led to significantly greater reduction in Lund-Mackay score compared to benralizumab (MD [95% CI]: −5.40 [−10.09, −0.71]) but not dupilumab (−1.74 [−5.74, 2.27]) (Table E7). At 48-56 weeks, tezepelumab led to significantly greater reductions in Lund-Mackay score compared to depemokimab (−3.09 [−4.85, −1.33]) and benralizumab (−4.84 [−6.77, −2.92]) (Table E6). Full comparison outcomes between biologic agents and probability ranking results for Lund-Mackay score at 48-56 weeks and 20-24 weeks are available in Fig E4, Table E6, and Table E7.

UPSIT score. At 20-24 weeks, stapokibart led to greater increases in UPSIT score compared to omalizumab (MD [95% CI]: 3.66 [1.32, 6.01]) and benralizumab (5.25 [2.50, 8.00]) (Table E7). Dupilumab led to greater increases in UPSIT scores compared to stapokibart (3.04 [1.02, 5.06]), omalizumab (6.70 [4.67, 8.73]) and benralizumab (8.29 [5.80, 10.78]). Week 48-56 data were not available for the biologic agents under consideration. Full comparison outcomes between biologic agents and probability ranking results for UPSIT score at 20-24 weeks are available in Fig E4 and Table E7.

Decision to treat with systemic corticosteroids. At 48-56 weeks, the odds of treatment with systemic steroids were significantly lower with tezepelumab compared to depemokimab (OR [95% CI]: 0.37 [0.17, 0.81]), mepolizumab (0.41 [0.18, 0.92]), and benralizumab (0.34 [0.15, 0.77]) (see Table E8 in the Online Repository available at www.jacionline.org). At 20-24 weeks, dupilumab was associated with lower odds of required systemic steroid receipt compared to omalizumab (0.03 [0, 0.53]) (see Table E9 in the Online Repository). Table E10, available in the Online Repository, provides probability ranking results among biologic agents for need for systemic steroid receipt.

Decision to treat with NP surgery. At 48-56 weeks, the odds of proceeding with NP surgery were significantly lower with tezepelumab compared to depemokimab (ORs [95% CI]: 0.03 [0.00, 0.25]) and mepolizumab (0.06 [0.01, 0.49]) (Table E8). Data regarding decision to treat with NP surgery at 20-24 weeks were not available.

Safety profile of biologic agents. Safety analyses for any-grade and severe-grade adverse events or adverse events requiring treatment discontinuation did not show any significant association between the studied biologic agents at 48-56 and 20-24 weeks. Tables E8 and E9 provide more information regarding the odds of safety events between biologic agents, and Table E10 provides the probability ranking results among biologic agents for safety outcomes.

Heterogeneity and inconsistency

Testing for heterogeneity showed significant heterogeneity with regards to response analysis for SNOT-22 at 48-56 weeks, Lund-Mackay score at 20-24 weeks, and NPS and NCS assessments for the asthma subgroups at 20-24 weeks. Testing for inconsistency showed significant inconsistency with regards to NPS assessments at 20-24 weeks, SNOT-22 score at 20-24 weeks, and NPS assessment in the asthma and AERD subgroups at 20-24 weeks. Table E11 in the Online Repository available at www.jacionline.org provides the results of heterogeneity and inconsistency among the different analyses conducted in the study.

Sensitivity analysis

We conducted a sensitivity analysis by excluding a study included in the analysis that has not yet been published in full text.⁴² We excluded this study from the following analyses: NPS and NCS assessments at 20-24 weeks, LOS assessment at 20-24 weeks, and SNOT-22 assessment at 20-24 weeks.

With regards to NPS assessment at 20-24 weeks, after excluding the unpublished study, stapokibart still showed significantly greater reductions in NPS compared to depemokimab (MD [95% CI]: −1.75 [−2.53, −0.97]), omalizumab (−1.59 [−2.35, −0.82]), and benralizumab (−1.80 [−2.69, −0.91]). Dupilumab was not associated with greater reductions in NPS compared to stapokibart (0.25 [−0.50, 1.00]) (see Table E12 in the Online Repository available at www.jacionline.org). At 20-24 weeks, stapokibart showed significantly greater reductions in NCS compared to depemokimab (−0.49 [−0.74, −0.25]) and omalizumab (−0.29 [−0.54, −0.05]). Dupilumab was not associated with greater reductions in NCS compared to stapokibart (−0.22 [−0.44, 0.01]) (Table E12). LOS assessment at 20-24 weeks showed that stapokibart produced greater reductions in LOS than omalizumab (−0.68 [−0.93, −0.43]). Dupilumab was not superior to stapokibart with regards to LOS assessment (−0.07 [−0.30, 0.16]) (Table E12). Finally, stapokibart did not produce significantly greater reductions in SNOT-22 compared to omalizumab (0.70 [−8.92, 10.32]) and benralizumab (−9.52 [−21.32, −2.28]) (Table E12).

DISCUSSION

In this network meta-analysis, we compared the efficacy of biologic agents for the treatment of severe CRSwNP. At 20-24 weeks, stapokibart and dupilumab demonstrated greater efficacy than other biologic agents, with no significant difference between stapokibart and dupilumab. At 48-56 weeks, dupilumab and tezepelumab were associated with greater improvements in NPS and NCS than depemokimab, mepolizumab, and benralizumab; no significant differences in NPS or NCS were observed between dupilumab and tezepelumab. Subgroup analyses yielded consistent findings, with dupilumab, tezepelumab, and stapokibart showing greater efficacy than other agents, with neither stapokibart nor tezepelumab demonstrating superiority over dupilumab. No analyzable data were available for stapokibart at 48-56 weeks and tezepelumab at 20-24 weeks, so no data could be provided about their comparative efficacy at the given time points.

Dupilumab was associated with greater improvements in NPS and NCS at 48-56 weeks than other evaluated biologic agents, except for tezepelumab, for which no significant difference was

observed. Analyzable data were not available for stapokibart at 48-56 weeks, precluding any analyses of this agent with other biologics at this time point. These findings are consistent with prior indirect comparisons and meta-analyses, which identified dupilumab as more effective than other tested biologics.^{18,19,21-23} More recently, the EVEREST trial¹⁷ demonstrated the superiority of dupilumab over omalizumab in patients with CRSwNP and co-existing asthma, as assessed by NPS, NCS, LOS, UPSIT, and SNOT-22 scores. We note that UPSIT was a co-primary end point in the EVEREST trial, unlike other studies, in which UPSIT is usually a secondary outcome. Although the mechanisms underlying the apparent superiority of dupilumab have not been fully elucidated, dual blockade of the IL-4 and IL-13 pathways may confer broader modulation of type 2 inflammation compared to biologics that target more restricted pathways.⁴³ The lack of a significant difference between dupilumab and tezepelumab warrants further evaluation in adequately powered, head-to-head clinical trials.

In our analysis, tezepelumab also demonstrated superior improvements in NPS and NCS compared to other biologic agents, with the exception of dupilumab, at 48-56 weeks. Analyzable data were not available for tezepelumab at 20-24 weeks, precluding any analyses of this agent with other biologics at this time point. Tezepelumab also showed consistently favorable effects across secondary outcome measures. To date, the WAYPOINT trial⁴¹ is the only phase 3 study evaluating tezepelumab in patients with CRSwNP and demonstrated superior responses over placebo. Tezepelumab is a humanized mAb that targets TSLP, an epithelial-derived cytokine that functions as an upstream regulator of type 2 inflammation. TSLP promotes activation of T_H2 cells, basophils, and mast cells, thereby contributing to airway eosinophilia and amplification of downstream cytokine signaling pathways.^{44,45} In addition, TSLP activates group 2 innate lymphoid cells, which further drive eosinophilic inflammation through production of IL-5 and IL-13. Beyond immune cell activation, TSLP has been implicated in structural mechanisms that contribute to airway remodeling, including effects on airway smooth muscle cells and fibroblasts.⁴⁶ Compared to IL-4 receptor antagonists, which primarily block signaling mediated by IL-4 and IL-13, TSLP inhibition may provide broader suppression of upstream inflammatory cascades involved in CRSwNP.⁴⁷ Direct comparative studies of tezepelumab with other biologic agents, and particularly dupilumab, are needed, given that both agents have consistently demonstrated superior efficacy relative to other tested biologics.

At 20-24 weeks, stapokibart showed superior NPS and NCS responses compared to other tested biologic agents, except for dupilumab. The CROWNS-1⁴⁸ and CROWNS-2³⁹ studies showed superior responses with regards to polyp size and quality-of-life indicators in patients with eosinophilic and noneosinophilic CRSwNP treated with stapokibart versus placebo. Studies with longer treatment duration and direct comparisons with dupilumab are needed to ascertain the comparative efficacy of stapokibart in patients with CRSwNP.

In subgroup analyses of patients with asthma, AERD, and baseline eosinophilia, tezepelumab was associated with greater reductions in NPS and NCS than other evaluated biologic agents. In the PATHWAY⁴⁹ and NAVIGATOR⁵⁰ trials in patients with asthma and the WAYPOINT⁴¹ trial in patients with CRSwNP, tezepelumab demonstrated superiority over placebo in patients with both high and low eosinophil counts and across type 2

inflammatory endotypes. In a *post hoc* analysis of the NAVIGATOR and PATHWAY trials, tezepelumab resulted in clinically meaningful improvements in sinonasal symptoms versus placebo in the subgroup of patients with concomitant AERD^{50,51} and NPs,⁵² respectively. In the present analysis, data on subgroup-specific efficacy of dupilumab were not available; therefore, comparative assessments between tezepelumab and dupilumab within these subgroups could not be performed. Future head-to-head trials should incorporate prespecified subgroup analyses on the basis of baseline type 2 inflammatory signatures to determine whether the observed superiority of dupilumab and tezepelumab over other biologic agents is consistent across clinically relevant inflammatory subgroups.

Strengths of this study include the evaluation of both Food and Drug Administration–approved and investigational biologic agents in a cohort of more than 3,600 patients, assessment of treatment effects at both 20-24 and 48-56 weeks, and comparison of efficacy across established objective and patient-reported outcomes. We also ran subgroup analyses in patients with asthma, AERD, baseline eosinophilia, and prior NP surgery to account for the effect of these variables on effect estimates.

This study has several limitations. Most trials compared biologic agents with placebo rather than with each other, resulting in reliance on indirect comparisons, with the exception of the EVEREST trial.¹⁷ Reporting of secondary end points (LOS, Lund-Mackay, and UPSIT scores) was limited, reducing sample sizes for these analyses. Baseline type 2 inflammatory characteristics and type 2 phenotype distribution varied across trials and may have influenced treatment effects; although subgroup analyses were performed, they were underpowered, and some agents could not be evaluated because of insufficient data. Also, network metaregression was not feasible because study-level covariates were collinear with treatment identity as a result of the star-shaped network structure (ie, all studies, except for the EVEREST trial, compared an agent to placebo), where most treatments appeared in a single study for each outcome. Under these conditions, regression coefficients could not be validly estimated because the model cannot separate covariate effects from treatment effects. Variability in the inclusion of patients with underlying asthma or AERD is likely to influence response to therapy, as type 2 inflammation–predominant comorbidities are associated with improved treatment responsiveness, particularly for agents targeting cytokine signaling within type 2 pathways, such as dupilumab or tezepelumab. Among these, AERD may represent a more pronounced type 2 phenotype than asthma, potentially further augmenting treatment response. Conversely, inclusion of fewer patients with prior surgery may also contribute to more favorable outcomes, given that prior (especially recurrent) surgery is associated with reduced responsiveness to biologic therapy. Use of an intention-to-treat approach may have underestimated treatment effects, and trials with treatment durations shorter than 20-24 weeks were excluded to improve homogeneity of outcome timing. Finally, while SUCRA values were calculated to provide a relative hierarchy of treatments, some of the results should be interpreted with caution. When no direct comparison between a given treatment A and treatment B exists, the relative effect estimates and SUCRA rankings are derived solely from indirect evidence.

In conclusion, at 20-24 weeks, stapokibart and dupilumab demonstrated greater efficacy than the other biologic agents evaluated, with no significant difference between stapokibart and

dupilumab. At 48-56 weeks, dupilumab and tezepelumab were associated with greater improvements in NPS and NCS than other tested biologics; no significant differences in these outcomes were observed between dupilumab and tezepelumab. Notably, lack of analyzable data at 20-24 weeks for tezepelumab and 48-56 weeks for stapokibart precluded analyses of these agents with other biologics at the prespecified time points. Prespecified subgroup analyses based on type 2 inflammatory endotypes yielded similar results, with stapokibart (at 20-24 weeks) and tezepelumab (at 48-56 weeks) maintaining superior outcomes relative to other biologic agents, except for dupilumab. Given the indirect comparisons in this study, adequately powered head-to-head trials, particularly those comparing tezepelumab and stapokibart with dupilumab, are needed to define comparative efficacy across clinical trial end points and inflammatory endotypes.

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Clinical implication: In severe CRSwNP, dupilumab, tezepelumab, and stapokibart provide greater clinical benefit than other biologics, without clear superiority among them, supporting individualized biologic selection pending head-to-head trials.

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