

Journal Pre-proof

Indirect Treatment Comparison of Biologics in Chronic Rhinosinusitis with Nasal Polyps

Anju T. Peters, MD, Joseph K. Han, MD, Peter Hellings, MD, PhD, Enrico Heffler, MD, PhD, Philippe Gevaert, MD, PhD, Claus Bachert, MD, PhD, Yingxin Xu, PhD, Chien-Chia Chuang, PhD, Binod Neupane, PhD, Jérôme Msihid, MSc, Leda P. Mannent, MD, Patricia Guyot, PhD, Siddhesh Kamat, MSc



PII: S2213-2198(21)00159-8

DOI: <https://doi.org/10.1016/j.jaip.2021.01.031>

Reference: JAIP 3408

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 25 September 2020

Revised Date: 9 December 2020

Accepted Date: 22 January 2021

Please cite this article as: Peters AT, Han JK, Hellings P, Heffler E, Gevaert P, Bachert C, Xu Y, Chuang CC, Neupane B, Msihid J, Mannent LP, Guyot P, Kamat S, Indirect Treatment Comparison of Biologics in Chronic Rhinosinusitis with Nasal Polyps, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2021.01.031>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

Indirect Treatment Comparison of Biologics in Chronic Rhinosinusitis with Nasal Polyps

Anju T. Peters, MD^a, Joseph K. Han, MD^b, Peter Hellings, MD, PhD^c, Enrico Heffler, MD, PhD^{d,e}, Philippe Gevaert, MD, PhD^f, Claus Bachert, MD, PhD^{f,g,h}, Yingxin Xu, PhDⁱ, Chien-Chia Chuang, PhD^j, Binod Neupane, PhD^k, Jérôme Msihid, MSc^l, Leda P. Mannent, MD^l, Patricia Guyot, PhD^l, and Siddhesh Kamat, MScⁱ

^aAllergy-Immunology Division and the Sinus and Allergy Center, Feinberg School of Medicine, Northwestern University, Chicago, Ill

^bEastern Virginia Medical School, Norfolk, VA

^cUniversity Hospitals Leuven, Leuven, Belgium

^dPersonalized Medicine, Asthma & Allergy – Humanitas Clinical and Research Center IRCCS, Rozzano (MI), Italy

^eDepartment of Biomedical Science, Humanitas University, Pieve Emanuele (MI), Italy

^fGhent University, Ghent, Belgium

^gKarolinska Institutet, Stockholm, Sweden

^hSun Yat-sen University, First Affiliated Hospital, Guangzhou, China

ⁱRegeneron Pharmaceuticals, Inc., Tarrytown, N.Y.

^jSanofi, Cambridge, Mass

^kEvidera, Montreal, QC, Canada

^lSanofi, Chilly-Mazarin, France

Corresponding author: Professor Anju Peters, MD,
Director of Clinical Research,
Division of Allergy-Immunology,
211 E. Ontario, Suite 1000,

Chicago, IL 60611,

312-695-4000.

E-mail: anjupeters@northwestern.edu

Author email addresses

Joseph K. Han: HanJK@EVMS.EDU

Peter Hellings: peter.hellings@icloud.com

Enrico Heffler: enrico.heffler@hunimed.eu

Philippe Gevaert: philippe.gevaert@UGent.be

Claus Bachert: Claus.Bachert@UGent.be

Yingxin Xu: yingxin.xu@regeneron.com

Chien-Chia Chuang: Chien-chia.Chuang@sanofi.com

Binod Neupane: Binod.Neupane@evidera.com

Jérôme Msihid: Jerome.Msihid@sanofi.com

Leda P. Mannent: Leda.Mannent@sanofi.com

Patricia Guyot: Patricia.Guyot2@sanofi.com

Siddhesh Kamat: siddhesh.kamat@regeneron.com

Funding: The SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454) were sponsored by Sanofi (Cambridge, MA) and Regeneron Pharmaceuticals, Inc. (Tarrytown, NY), who also provided funding for the indirect treatment comparison analyses and medical writing assistance for this manuscript.

Conflicts of interest: Anju T. Peters: Sanofi, Regeneron Pharmaceuticals, Inc. – advisory board member; AstraZeneca – research support and advisory board member; Optinose – consultant and research support. Joseph K. Han: Sanofi – advisory board member. Peter W. Hellings: Regeneron Pharmaceuticals, Inc., Sanofi – advisory board member. Enrico Heffler: AstraZeneca, Boehringer Ingelheim, Circassia, GlaxoSmithKline, Nestlé Purina, Novartis, Sanofi Genzyme, Teva, Valeas – research grants. Philippe Gevaert: 3NT, ALK, Argenx, Genentech, Novartis, Regeneron Pharmaceuticals, Inc., Roche, Sanofi, Stallergenes Greer – clinical trial funding, advisory board member. Claus Bachert: ALK, AstraZeneca, GlaxoSmithKline, Mylan, Novartis, Sanofi, Stallergenes Greer – advisory board member and speakers' fees. Yingxin Xu and Siddhesh Kamat: Regeneron Pharmaceuticals, Inc. – employees and shareholders. Chien-Chia Chuang, Jérôme Msihid, Leda P. Mannent, and Patricia Guyot: Sanofi – employees, may hold stock and/or stock options in the company. Binod Neupane: None to declare.

ABSTRACT

BACKGROUND: Among patients with chronic rhinosinusitis with nasal polyps (CRSwNP), randomized clinical trials (RCTs) of biologics, such as anti-IL-4/IL-13 (dupilumab) and anti-immunoglobulin E (omalizumab), have demonstrated efficacy versus intranasal corticosteroids (INCS). However, no head-to-head RCTs exist between biologics.

OBJECTIVE: To perform an indirect treatment comparison (ITC) of the efficacy of biologics plus INCS versus placebo (INCS) as a common comparator.

METHODS: Embase[®], MEDLINE[®], and Cochrane were searched for RCTs of biologics in CRSwNP. Bucher ITCs were performed for outcomes at Week 24: nasal polyp score (NPS; range 0–8), nasal congestion (NC; 0–3), loss of smell (LoS; 0–3), University of Pennsylvania Smell Identification Test (UPSIT; 0–40), total symptom score (TSS; 0–12), sino-nasal outcomes test (SNOT-22; 0–110), and responder analyses based on NPS/NC improvement ≥ 1 .

RESULTS: Assessment of trial design, baseline characteristics, and outcome measures suggested ITC was feasible with four phase 3 RCTs: dupilumab SINUS-24/-52 (NCT02912468/NCT02898454); omalizumab POLYP1/2 (NCT03280550/NCT03280537). In the intent-to-treat population, dupilumab had significantly greater improvements from baseline to Week 24 versus omalizumab across key outcomes: NPS (least squares mean difference [95% CI] $-1.04 [-1.63, -0.44]$), NC ($-0.35 [-0.60, -0.11]$), LoS ($-0.66 [-0.90, -0.42]$), UPSIT (6.70 [4.67, 8.73]), and TSS ($-1.18 [-1.95, -0.41]$). Improvement in SNOT-22 was greater in dupilumab versus omalizumab but was not statistically significant. Dupilumab patients were significantly more likely to achieve ≥ 1 -point improvement in NPS (odds ratio [95% CI] 3.85 [1.82, 7.04]) and NC (2.13 [1.12, 4.04]) versus omalizumab.

CONCLUSION: Although ITCs have limitations, these results demonstrated dupilumab had consistently greater improvements in key CRSwNP outcomes versus omalizumab at Week 24.

HIGHLIGHTS BOX

35 words per highlight box

What is already known about this topic? Add-on anti-interleukin (IL)-4/IL-13 and anti-immunoglobulin E biologics have previously demonstrated efficacy versus intranasal corticosteroids in patients with chronic rhinosinusitis with nasal polyps (CRSwNP), however, no comparative head-to-head studies are available.

What does this article add to our knowledge? This article presents results from the first Bucher indirect treatment comparison of biologics in CRSwNP, demonstrating significantly greater improvements in key symptoms and objective measures of disease with dupilumab compared with omalizumab.

How does this study impact current management guidelines? Although ITCs have limitations, results suggest that patients with CRSwNP may have greater improvements in key CRSwNP outcomes with dupilumab versus omalizumab. Nevertheless, it will be important to confirm these findings in head-to-head clinical studies.

SECTION/CATEGORY

Rhinitis, Sinusitis, and Upper Airway Disease

CLASSIFICATION

Rhinitis and Other Respiratory Diseases – Nasal polyposis

Key Words

CRSwNP, dupilumab, indirect treatment comparison, omalizumab

Clinical trial registration numbers

SINUS-24: NCT02912468; SINUS-52: NCT02898454; POLYP 1: NCT03280550; POLYP 2: NCT03280537

Abbreviations used

CRSwNP- Chronic rhinosinusitis with nasal polyps

CI- Confidence interval

EMA- European Medicines Agency

FDA- Food and Drug Administration

Ig- Immunoglobulin

IL- Interleukin

INCS- Intranasal corticosteroid

ITC- Indirect treatment comparison

ITT- Intention-to-treat

LMK- Lund-Mackay

LoS- Loss of smell

LS- Least squares

MA- Meta-analysis

NC- Nasal congestion

NP- Nasal polyps

NPS- Nasal polyp score

NSAID-AERD- Non-steroidal anti-inflammatory drug aspirin-exacerbated respiratory disease

NSAID-ERD- Non-steroidal anti-inflammatory drug exacerbated respiratory disease

OR- Odds ratio

q2w- Every two weeks

q4w- Every 4 weeks

- 129 RCT- Randomized clinical trial
- 130 SCS- Systemic corticosteroids
- 131 SE- Standard error
- 132 SLR- Systematic literature review
- 133 SNOT-22- 22-item sino-nasal outcomes test
- 134 TSS- Total symptom score
- 135 UPSIT- University of Pennsylvania Smell Identification Test

INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory disease predominantly driven by type 2 inflammation, which is characterized by upregulation of type 2 cytokines interleukin (IL)-4, IL-13, and IL-5, high concentrations of tissue immunoglobulin (Ig) E, and increased serum IgE.¹⁻³ CRSwNP is characterized by bilateral nasal polyps and chronic inflammation in the paranasal sinuses, with persistent and debilitating symptoms that include nasal obstruction, hyposmia or anosmia, and anterior and posterior nasal drainage. Persistent symptoms of CRSwNP have a strong negative effect on quality of life and productivity comparable with other serious chronic disease.⁴⁻¹⁰ Approximately 80% of CRSwNP is driven by type 2 inflammation,¹¹⁻¹³ and patients with severe CRSwNP commonly have other type 2 inflammatory conditions such as asthma and non-steroidal anti-inflammatory drug/aspirin-exacerbated respiratory disease (NSAID-ERD/AERD),^{14, 15} which substantially increase the overall disease burden.^{16, 17}

Nasal saline irrigation and topical intranasal corticosteroids (INCS) are standard-of-care treatments for CRSwNP used at all levels of disease severity, while short-courses of oral systemic corticosteroids (SCS) and/or sino-nasal surgeries are used for uncontrolled severe disease.^{2, 18} Although sinus surgery is effective in improving symptoms and removal of polyps, disease recurrence is common, especially among patients with comorbid type 2 inflammatory conditions who have a higher risk of recurrence of nasal polyps following surgery, and as a result revision surgeries are more frequent in these patients.¹⁹⁻²²

Given the contribution of type 2 inflammation to the pathophysiology underpinning CRSwNP, several biologic therapies targeting different aspects of type 2 inflammation have been evaluated or are currently under evaluation, including anti-IgE (omalizumab), anti-IL-4/IL-13 (dupilumab), anti-IL-5 (mepolizumab) and anti-IL-5 receptor α (benralizumab) monoclonal antibodies.²²⁻³³ There are no head-to-head randomized clinical trials (RCTs) between biologic treatments, and no criteria (eg, biomarkers) that can assist with the selection of appropriate biologics for patients with inadequately controlled CRSwNP. In the absence of such trials, an alternative approach to evaluate the relative merits of biologics in CRSwNP

is indirect treatment comparison (ITC), which examines the comparative efficacy of each treatment for selected key endpoints shared between RCTs of patients with similar well defined clinical and inflammatory phenotypes. Although data from RCTs form the strongest level of evidence, in the absence of head-to-head RCTs of biologics, ITCs can provide useful comparative evidence to inform health technology assessment agencies and policymakers.

The objective of this analysis was to conduct an ITC using data from RCTs of biologics for the treatment of patients with inadequately controlled CRSwNP.

METHODS

Search strategy and feasibility assessment

A systematic literature review (SLR) of relevant RCTs was conducted by searching the Embase[®], MEDLINE[®] and Cochrane databases, supplemented with manual reference checks and conference presentations. Search strategies were designed using a combination of index terms (Emtree in Embase[®]; Medical Subject Headings in MEDLINE[®] and Cochrane) and free-text terms to identify relevant RCTs that investigated biologic treatments in CRSwNP between January 1, 1980 to May 18, 2020. Non-English language publications, non-RCTs, review articles, case studies and case reports, and animal or in vitro studies were excluded. Studies identified in the SLR were further evaluated based on study design, population, endpoints, patient cohort size, and the timing of endpoint assessments, to systematically select studies for inclusion in the ITC (Figure 1).

ITC methodology

Although there are several statistical approaches for conducting ITCs, guidance from the European Network for Health Technology Assessment states that “preference should be given to the most transparent method available.”³⁴ Following the feasibility assessment, a Bucher ITC was employed owing to its transparency compared with other ITC methodologies.³⁵

The Bucher ITC was performed in 2 steps. First, results from trials of the same biologic treatment were meta-analyzed to derive a pooled treatment effect for the biologic treatment versus control arm. Next, the pooled treatment effect of each active biologic treatment was compared indirectly through the common control arm. As RCTs of biologics in CRSwNP compare the active treatment versus an INCS control, the INCS arm served as a common comparator in the Bucher ITC. A classical (frequentist) random-effects model was used for the meta-analysis. This model assumes that the true treatment effects are randomly distributed around a population mean effect; such modeling approaches generally provide conservative estimates by acknowledging that RCTs evaluating the same treatment may differ on the clinical characteristics of patients enrolled in the trials, or on study design (eg, duration of follow-up).

A Bucher ITC was performed for each outcome of interest presented in Table E1. For continuous outcomes, the contrast-level mean differences (ie, mean difference between the biologic and control arm reported in the trial) were used in the analyses, given the adjusted estimates were available from all studies in the analysis. For binary outcomes, the number of patients who achieved response criteria (improvement of ≥ 1 or ≥ 2 in nasal polyp score [NPS], or ≥ 1 in nasal congestion [NC] score) was derived by using the reported percentage of responders as the numerator and the number of patients in the intention-to-treat (ITT) or subgroup population as the denominator. This was utilized to derive the odds ratios (ORs).

Analyses were conducted using the metafor package in R (3.3.0). Results are presented as a point estimate of the relative effect of interest (eg, OR, mean difference) with variation shown by 95% confidence intervals (CIs).

RESULTS

Literature search and feasibility assessment

The systematic literature search identified 11,757 records, excluding duplicates (Figure 1). After title, abstract, and full text screening, 74 publications were retained, representing 32 unique RCTs, 14 of which were RCTs for 5 biologic therapies for CRSwNP: benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab. Of these 14 RCTs, 10 were excluded and 4 were retained for the ITC. Reasons for exclusion from the ITC were dissimilar study selection criteria, a sample size of ≤ 10 per treatment arm, endpoints evaluated earlier than 24 weeks, a treatment dose no longer in use, and data not adequate for ITC (Table E2). The four RCTs eligible for ITC analyses were two phase 3 dupilumab trials (SINUS-24 [NCT02912468] and SINUS-52 [NCT02898454]) and two phase 3 omalizumab trials (POLYP 1 [NCT03280550] and POLYP 2 [NCT03280537]; Figure 1).

In the SINUS-24 and SINUS-52 and POLYP 1 and POLYP 2 trials, dupilumab and omalizumab, respectively, were administered subcutaneously. The 2-arm, 24-week SINUS-24 and 3-arm, 52-week SINUS-52 trials were similar in study design up to 24 weeks and included dupilumab 300 mg administered every 2 weeks (q2w). Similarly, the 2-arm, 24-week POLYP 1 and POLYP 2 trials were alike

in design, with omalizumab administered q2w or every 4 weeks (q4w) based on baseline body weight and IgE value.

Patient inclusion criteria (Table E3) and qualitative assessment of patient baseline characteristics suggested that the patient populations were mostly comparable (Table I, Table E4). Similar rates of prior sino-nasal surgery and comorbid asthma, which may be reflective of disease severity, were observed in the SINUS and POLYP trials at baseline. The prevalence of prior SCS use within the last year was higher in patients treated in the dupilumab studies than those in the omalizumab studies. However, use of SCS was stopped prior to enrollment (4–5 weeks before randomization and treatment initiation) in both the SINUS and POLYP trials.

The SINUS and POLYP trials used bilateral NPS as the objective measure of disease, with core symptoms of CRSwNP assessed using a patient-reported diary with a daily recall period including NC score, loss of smell (LoS) score, and total symptom score (TSS; a composite score of 4 symptoms: NC, LoS, anterior rhinorrhea or runny nose, and posterior rhinorrhea or post-nasal drip), and the 40-odorant University of Pennsylvania Smell Identification Test (UPSIT). There are currently no established minimal clinically important differences for NPS, NC, LoS, TSS or UPSIT. The 22-item sino-nasal outcomes test (SNOT-22) score assessed disease-specific health-related quality of life. SNOT-22 is a multi-domain questionnaire with a 2-week recall period that assesses rhinologic, extra-nasal rhinologic, and ear/facial symptoms, along with distal effects such as emotional and social impacts, and is currently the only CRSwNP measure with a validated minimal clinically important difference (patient improvement $\geq 8.9^{36}$).

The following endpoints were available for comparison across the trials: mean change from baseline at Week 24 in NPS (range 0–8), NC score (range 0–3), LoS score (range 0–3), TSS (presented on a scale ranging from 0–12 in the POLYP trials; TSS from the SINUS trials was computed to match the scale range from the POLYP trials), UPSIT score (range 0–40), and SNOT-22 score (range 0–110); higher scores represent worse outcomes for all endpoints except UPSIT. The proportions of patients achieving response thresholds of improvement from baseline at Week 24 of NPS ≥ 1 and ≥ 2 , and NC score improvement ≥ 1 was also available as endpoints for comparison.

A qualitative assessment of baseline scores of the key outcomes of interest, NPS, NC score, LoS score, TSS, and UPSIT scores, showed all were comparable between the SINUS and POLYP trials at baseline (Table I). Baseline SNOT-22 scores in the ITT population of the POLYP trials were higher than those in the SINUS trials, given the POLYP trial inclusion criterion of SNOT-22 score ≥ 20 at baseline. A placebo (INCS) comparator arm was common across the 4 trials. A qualitative assessment showed that among patients in the placebo groups, change from baseline at Week 24 in key outcomes of interest were comparable between the SINUS and POLYP trials, with the exception of a greater reduction in NPS with placebo in the POLYP 2 trial (Table E5).

Comparison of outcome measures for dupilumab versus omalizumab in the ITT population

Dupilumab and omalizumab both demonstrated superiority versus placebo (INCS) across all outcome measures assessed. Bucher ITCs were performed for the comparable endpoints available from the 4 selected studies. Dupilumab demonstrated significantly greater improvements versus omalizumab in change from baseline at Week 24 with NPS, NC score, LoS score, UPSIT score, and TSS (mean difference [95% CI] -1.04 [-1.63 , -0.44], -0.35 [-0.60 , -0.11], -0.66 [-0.90 , -0.42], 6.70 [4.67 , 8.73], and -1.18 [-1.95 , -0.41], respectively; Figures 2–5).

In terms of responder analyses at Week 24, the proportion of patients achieving a ≥ 1 -point improvement in NPS was 63.0% with dupilumab versus 13.6% with placebo in the pooled SINUS-24 and SINUS-52 trials, and 56.3% with omalizumab versus 28.7% for placebo in the pooled POLYP 1 and POLYP 2 trials. The proportion of patients achieving a ≥ 2 -point improvement in NPS was 46.1% with dupilumab versus 2.4% with placebo in the pooled SINUS trials, and 31.3% with omalizumab versus 11.6% with placebo in the pooled POLYP trials. Similarly, the proportion of patients achieving a ≥ 1 -point improvement in NC score was 64.2% with dupilumab versus 23.8% with placebo in the pooled SINUS trials, and 44.4% with omalizumab versus 21.4% with placebo in the pooled POLYP trials.^{22, 23}

Based on these data, dupilumab also demonstrated significantly greater improvements versus omalizumab in a responder analysis of patients achieving NPS improvement ≥ 1 and ≥ 2 , and NC score

improvement ≥ 1 (odds ratio [95% CI] 3.58 [1.82, 7.04], 11.18 [1.52, 82.22], and 2.13 [1.12, 4.04], respectively; Figure 2, Figure E1, Figure 3). Numerically greater improvements were observed with dupilumab versus omalizumab in change from baseline at Week 24 in SNOT-22 score, however the differences were not statistically significant (Figure 5).

Comparison of outcome measures for dupilumab versus omalizumab in patients with comorbid asthma (with or without NSAID-ERD) and comorbid asthma patients with NSAID-ERD

Subgroup analyses were performed among patients with comorbid asthma (with or without NSAID-ERD) and among comorbid asthma patients with NSAID-ERD. Data from POLYP 1 and 2 were available only on the outcomes of change from baseline to Week 24 in NPS and NC score in both subgroups; hence only these outcomes were assessed.³⁷ Despite the smaller subgroup sizes of patients with comorbid asthma with or without NSAID-ERD, 59% of the ITT population of the SINUS trials (428/724) and 57% of the ITT population of the POLYP trials (151/265), dupilumab had significantly greater improvement in NPS and NC score at Week 24 from baseline compared with omalizumab (Table II).

Comorbid asthma patients with NSAID-ERD comprised only 25% (181/724) of the ITT population of the SINUS trials and 27% (72/265) of the ITT population from POLYP trials. In these subgroups, dupilumab demonstrated significantly greater improvements versus omalizumab in change from baseline at Week 24 in NC score (mean difference [95% CI], -0.58 [-1.01, -0.15]); greater improvements were also observed in NPS (-0.73 [-1.57, 0.12]), however, the differences in NPS were not statistically significant (Table II).

Sensitivity analyses

Patient subgroups with SNOT-22 ≥ 20 at baseline. Given the POLYP trials included patients with SNOT-22 ≥ 20 at baseline, a sensitivity analysis was conducted for all outcomes of interest by selecting the subgroup of patients from the SINUS trials with baseline SNOT-22 ≥ 20 and comparing them with the omalizumab ITT population. In the SINUS trials, 681 patients (94%) had a SNOT-22 score ≥ 20 at

baseline. Results from this analysis were consistent with results from the previously shown ITT populations, with dupilumab demonstrating significantly greater improvements in all key outcome measures versus omalizumab except for SNOT-22 score, which showed greater improvement with dupilumab versus omalizumab without being statistically significant (Table E6).

Patient subgroups with IgE 30–1500 IU/mL and weight 30–150 kg at baseline. Dosing guidelines for omalizumab state eligibility criteria of total serum IgE of 30–1500 IU/mL and weight of 30–150 kg for patients receiving treatment.²³ In the SINUS trials, 599 patients (83%) met the IgE and weight criteria for omalizumab at baseline. A sensitivity analysis was conducted for all outcomes of interest for patients from the dupilumab RCTs who met omalizumab dosing guidelines versus the omalizumab ITT populations. Results from this analysis (Table E6) were consistent with those previously shown in the ITT population analysis.

Patients from SINUS-24 and -52 versus patients from POLYP 1 only. The POLYP 2 trial demonstrated a high placebo response for change in NPS, thereby reducing the magnitude of effect for omalizumab versus placebo (change from baseline to Week 24 in mean NPS for placebo in POLYP 1, 0.06 [SE, 0.16]; POLYP 2, -0.31 [SE, 0.16]).²³ A sensitivity analysis was conducted for the NPS outcome measure by comparing patients from the SINUS-24 and SINUS-52 trials with those from the POLYP 1 trial only. These results were consistent with those observed in the pooled analyses, with dupilumab demonstrating significantly greater improvements in NPS from baseline at Week 24 versus omalizumab (Figure E2).

DISCUSSION

This is the first ITC performed in patients with CRSwNP that comprehensively evaluates the evidence from RCTs of biologics for inadequately controlled CRSwNP. The RCTs selected for the ITC had similar (albeit not identical) criteria with respect to study design, trial populations, and specific outcome measures that supported the cross-study comparisons, a key requirement for minimizing bias or erroneous comparisons.

The results of this analysis demonstrated that dupilumab had significantly greater improvements compared with omalizumab in all key outcome measures assessed across the 4 RCTs, including NPS, NC, LoS, TSS, and UPSIT scores. Nasal congestion and sense of smell impairment are among the most important symptoms affecting the daily lives of patients with CRSwNP,⁵ and dupilumab showed superiority versus omalizumab in the outcome measures assessing these symptoms. For the SNOT-22 outcome, improvements were greater in the dupilumab group compared with the omalizumab group, however, these differences were not statistically significant. The SNOT-22 score is based on a multi-domain health-related quality of life questionnaire that includes distal effects (such as emotional and social impacts) of CRSwNP. Due to the multi-domain nature of the questionnaire and variability in patient experiences, relatively large variability was present in the SNOT-22 scores in the SINUS and POLYP studies (coefficient of variation in baseline SNOT-22 scores of up to 42%).^{22, 23} It is also expected that patient experiences of symptoms are more reliably reported using the daily recall periods assessed by other outcome measures such as NC, LoS, or TSS, rather than the longer 2-week recall period of the SNOT-22 questionnaire.³⁸ Additionally, in both the POLYP 1 and POLYP 2 trials, the improvement in SNOT-22 score plateaus at the Week 16 assessment, and remains unchanged through Week 24.²³ However, in the SINUS trials the magnitude of dupilumab's impact on SNOT-22 score continues to improve without plateau at Week 16 (least squares [LS] mean difference for dupilumab versus placebo [95% CI], -15.20 [-17.79, -12.62]; $P < .001$) and Week 24 (-18.86 [-21.52, -16.20]; $P < .0001$) and does not plateau even through the Week 52 assessment in the SINUS-52 trial (-20.96 [-25.03, -16.89]; $P < .0001$).²² A comparison of SNOT-22 scores at a longer time-point of assessment (such as 52 weeks) was

not feasible due to the shorter randomized treatment period duration of 24 weeks for both POLYP trials of omalizumab.

A key requirement of ITC analyses is that the study populations are sufficiently similar to permit appropriate comparisons. Although the SINUS and POLYP trials were mostly similar, there were some differences. Patients in the SINUS trials had higher SCS use at baseline compared with the POLYP trials and both POLYP trials had additional inclusion criteria of baseline SNOT-22 score ≥ 20 , and IgE 30–1500 IU/mL and weight 30–150 kg. Two sensitivity analyses were performed by selecting subgroups of dupilumab patients from the SINUS trials matching the SNOT-22 and IgE and weight criteria of the POLYP trials, respectively. These sensitivity analyses showed that dupilumab demonstrated significantly greater improvements compared with omalizumab in all outcomes except SNOT-22, demonstrating no overall effect of these additional inclusion criteria on the conclusions drawn from the ITC results in the ITT populations. A sensitivity analysis in the subgroup of patients with or without prior SCS use was not feasible, as data from these subgroups were not available in the public domain for the POLYP trials. However, in post hoc analyses of the pooled SINUS studies that evaluated patients with and without SCS use within 2 years prior to enrolment it was observed that the treatment effect of dupilumab was similar in both subgroups.³⁹ It should be noted that it was not possible to assess whether other specific patient populations had greater treatment response with omalizumab versus dupilumab as other subgroup data were not available. Further ITC analyses should be conducted when such data are available, in order to better inform treatment stratification options.

While the effect of placebo treatment was generally similar across the trials, it was observed that in the POLYP 2 trial of omalizumab, there was a higher placebo response for change in NPS at Week 24 compared with the POLYP 1 trial. This would result in a smaller magnitude of effect for omalizumab, and hence a larger effect size of dupilumab versus omalizumab on NPS when both POLYP 1 and POLYP 2 are included. In a sensitivity analysis of NPS excluding the POLYP 2 trial, dupilumab consistently and significantly outperformed omalizumab, suggesting the smaller mean difference in NPS between placebo and omalizumab in the POLYP 2 trial did not influence the conclusions drawn from the main ITC analysis.

Patients with CRSwNP and comorbid asthma are difficult to treat, as evidenced by higher rates of symptom and polyp recurrence and the need for repeat surgeries.^{16, 17} Results from the ITC of dupilumab and omalizumab in the comorbid asthma population are consistent with results from the ITT population analyses. In the subgroup of patients with both comorbid asthma and NSAID-ERD, dupilumab continued to have greater improvement in NPS and NC score compared with omalizumab. The difference was statistically significant for NC score, but not for NPS, possibly due to markedly smaller subgroup sizes from the SINUS and POLYP trials.

To contextualize the results from the absolute change in NPS and NC score analysis, responder analyses were conducted by using treatment-arm level data from the ITT populations of both the SINUS and POLYP trials for the calculation of ORs and 95% CIs. Results from these responder analyses continued to remain statistically significant in favor of dupilumab compared with omalizumab, with the odds of achieving a reduction in NPS or NC score of ≥ 1 with dupilumab more than double the odds with omalizumab.

Currently no baseline biomarker parameters have been identified to select appropriate biologic treatments for individual CRSwNP patients.⁴⁰ In the absence of such biomarkers, treatment effect size and responder analysis results may guide the choice of treatment with the greatest improvements in both objective and subjective measures. The higher treatment effect size of dupilumab may be due to a broader mechanism of action on type 2 inflammation compared with omalizumab, as dupilumab targets IL-4 and IL-13, which have been shown to decrease IgE production, as well as reduce other aspects of type 2 inflammation such as eotaxin-3, IL-5, tissue eosinophilia, and mast cell production of inflammatory mediators.^{41, 42}

In routine clinical practice, patients with severe CRSwNP may need rescue treatment with SCS or sinus surgery if their symptoms worsen while on maintenance INCS. The trial design of the SINUS study enabled an assessment of the endpoint of need for rescue treatments. In the pooled SINUS trials, rescue treatment with SCS was required in 88/286 (30.8%) of placebo-treated patients and 41/438 (9.4%) of dupilumab-treated patients, and rescue treatment with nasal polyp surgery was required in 22/286 (7.7%) of placebo-treated patients and 5/438 (1.1%) of dupilumab-treated patients, up to 52 weeks, and the

proportion of subjects who required SCS or surgery was reduced by 74% and 83%, respectively.²² In the POLYP trials, the 24-week randomized, double-blind treatment period was followed by an open-label extension period, during which all patients received omalizumab. This aspect of trial design may complicate the assessment of rescue SCS or sinus surgery. In the POLYP trials, the rates for rescue SCS and surgery observed during the treatment period (over 24 weeks) were lower than those observed in the SINUS studies. Rescue SCS therapy in the POLYP studies was assessed based on the use of SCS for NP for at least 3 days; rescue SCS therapy in the SINUS studies was defined as short course SCS use, of up to 2 weeks. Rescue SCS was required in 8/129 (6.2%) placebo-treated patients and 3/129 (2.3%) omalizumab-treated patients from the pooled POLYP studies, and no sinus surgeries/polypectomies were recorded. Hence, an ITC between dupilumab and omalizumab on the endpoint of rescue SCS and sinus surgery was not feasible due to differences in the open-label portion of the trials.

Finally, it should be noted that the data used in the Bucher ITC analyses were informed by results from RCTs. These data may not fully represent real-world situations and, as a result, may not be generalizable to real-life clinical practice. Further research is required in order to analyze any differences among treatments in real-world situations.⁴³ As results of RCTs of other biologic treatments in CRSwNP become available, additional ITC analyses will be important to understand the relative efficacy of these biologics in CRSwNP.

The results of the ITC suggest that among comparable CRSwNP patient populations, dupilumab was associated with significantly greater improvements in all the key symptoms and objective measures of the disease compared with omalizumab. In the absence of head-to-head clinical trials comparing biologics in patients with CRSwNP, this analysis may provide evidence for clinicians, health technology assessments, and policymakers considering biologic treatments in CRSwNP. It will be important to confirm these findings in head-to-head comparison studies. Long-term real-world data are necessary to evaluate outcomes such as reduced need for rescue treatments including SCS and/or sino-nasal surgery in these biologics.

ACKNOWLEDGMENTS

Medical writing assistance was provided under the direction of the authors by Joseph Hodgson, PhD (Adelphi Group) in accordance with Good Publication Practice (GPP3) guidelines, funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.

The authors would like to thank Kyle Fahrbach (Evidera, Waltham, MA, USA) for assistance with data analyses, and Loubna Haddy (Hays Life Sciences, London, UK) for systematic review of the literature that informed the ITC analysis (both funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.).

REFERENCES

1. Stevens WW, Ocampo CJ, Berdnikovs S, Sakashita M, Mahdavinia M, Suh L, et al. Cytokines in chronic rhinosinusitis. Role in eosinophilia and aspirin-exacerbated respiratory disease. *Am J Respir Crit Care Med*. 2015;192:682–94.
2. Tomassen P, Vandeplas G, Van Zele T, Cardell LO, Arebro J, Olze H, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol*. 2016;137:1449–56.e4.
3. Bachert C, Marple B, Hosemann W, Cavaliere C, Wen W, Zhang N. Endotypes of chronic rhinosinusitis with nasal polyps: Pathology and possible therapeutic implications. *J Allergy Clin Immunol Pract*. 2020;8:1514–9.
4. Schenkel EJ, Messina JC, Jr., Bodine A, McGinley JS, Wirth RJ, Mahmoud RA. Disease burden of chronic rhinosinusitis (CRS) is as severe as other serious chronic diseases. *J Allergy Clin Immunol*. 2018;141:AB165.
5. Abdalla S, Alreefy H, Hopkins C. Prevalence of sinonasal outcome test (SNOT-22) symptoms in patients undergoing surgery for chronic rhinosinusitis in the England and Wales National prospective audit. *Clin Otolaryngol*. 2012;37:276–82.
6. Thompson CF, Price CP, Huang JH, Min JY, Suh LA, Shintani-Smith S, et al. A pilot study of symptom profiles from a polyp vs an eosinophilic-based classification of chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6:500–7.
7. Chung JH, Lee YJ, Kang TW, Kim KR, Jang DP, Kim IY, et al. Altered quality of life and psychological health (SCL-90-R) in patients with chronic rhinosinusitis with nasal polyps. *Ann Otol Rhinol Laryngol*. 2015;124:663–70.

- 455 8. Serrano E, Neukirch F, Pribil C, Jankowski R, Klossek JM, Chanal I, et al. Nasal polyposis in
456 France: impact on sleep and quality of life. *J Laryngol Otol.* 2005;119:543–9.
- 457 9. Craig TJ, Ferguson BJ, Krouse JH. Sleep impairment in allergic rhinitis, rhinosinusitis, and nasal
458 polyposis. *Am J Otolaryngol.* 2008;29:209–17.
- 459 10. Värendh M, Johannisson A, Hrubos-Strøm H, Andersson M. Sleep quality improves with
460 endoscopic sinus surgery in patients with chronic rhinosinusitis and nasal polyposis. *Rhinology.*
461 2017;55:45–52.
- 462 11. Kato A, Klingler AI, Stevens WW, Peters AT, Poposki JA, Suh L, et al. Heterogenous
463 inflammation in chronic rhinosinusitis without nasal polyps. *J Allergy Clin Immunol.* 2016;137:AB285.
- 464 12. Kim DW, Cho SH. Emerging endotypes of chronic rhinosinusitis and its application to precision
465 medicine. *Allergy Asthma Immunol Res.* 2017;9:299–306.
- 466 13. Bachert C, Pawankar R, Zhang L, Bunnag C, Fokkens WJ, Hamilos DL, et al. ICON: chronic
467 rhinosinusitis. *World Allergy Organ J.* 2014;7:25.
- 468 14. Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key
469 proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov.* 2016;15:35–50.
- 470 15. Khan A, Vandeplas G, Huynh TMT, Joish VN, Mannent L, Tomassen P, et al. The global allergy
471 and asthma European network (GALEN) rhinosinusitis cohort: A large European cross-sectional study of
472 chronic rhinosinusitis patients with and without nasal polyps. *Rhinology.* 2019;57:32–42.
- 473 16. Bassiouni A, Wormald PJ. Role of frontal sinus surgery in nasal polyp recurrence. *Laryngoscope.*
474 2013;123:36–41.
- 475 17. Stevens WW, Peters AT, Hirsch AG, Nordberg CM, Schwartz BS, Mercer DG, et al. Clinical
476 characteristics of patients with chronic rhinosinusitis with nasal polyps, asthma, and aspirin-exacerbated
477 respiratory disease. *J Allergy Clin Immunol Pract.* 2017;5:1061–70.e3.

18. Orlandi RR, Kingdom TT, Hwang PH, Smith TL, Alt JA, Baroody FM, et al. International consensus statement on allergy and rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6 Suppl 1:S22–209.
19. Vlamincx S, Vauterin T, Hellings PW, Jorissen M, Acke F, Van Cauwenberge P, et al. The importance of local eosinophilia in the surgical outcome of chronic rhinosinusitis: A 3-year prospective observational study. *Am J Rhinol Allergy*. 2014;28:260–4.
20. Lou H, Zhang N, Bachert C, Zhang L. Highlights of eosinophilic chronic rhinosinusitis with nasal polyps in definition, prognosis, and advancement. *Int Forum Allergy Rhinol*. 2018;8:1218–25.
21. Calus L, Van Bruaene N, Bosteels C, Dejonckheere S, Van Zele T, Holtappels G, et al. Twelve-year follow-up study after endoscopic sinus surgery in patients with chronic rhinosinusitis with nasal polyposis. *Clin Transl Allergy*. 2019;9:30.
22. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. 2019;394:1638–50.
23. Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol*. 2020;146:595–605.
24. Bachert C, Sousa AR, Lund VJ, Scadding GK, Gevaert P, Nasser S, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial. *J Allergy Clin Immunol*. 2017;140:1024–31.e14.
25. Gevaert P, Lang-Loidolt D, Lackner A, Stammberger H, Staudinger H, Van Zele T, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. *J Allergy Clin Immunol*. 2006;118:1133–41.

26. Zangrilli JG, Maspero J, Harrison T, Werkstrom V, Wu Y. Clinical efficacy of benralizumab in patients with severe, uncontrolled eosinophilic asthma and nasal polyposis: Pooled analysis of the SIROCCO and CALIMA trials. *Pneumologie*. 2019;73:P254.
27. GlaxoSmithKline. Clinical trial: effect of mepolizumab in severe bilateral nasal polyps. *ClinicalTrials.gov*; 2020. Report No.: NCT03085797. Available from: <https://clinicaltrials.gov/ct2/show/study/NCT03085797>. Accessed 14 September 2020.
28. Weinstein SF, Katial RK, Bardin P, Korn S, McDonald M, Garin M, et al. Effects of reslizumab on asthma outcomes in a subgroup of eosinophilic asthma patients with self-reported chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol Pract*. 2019;7:589–96.e3.
29. Nelsen L, Bradford ES, Bratton DJ, Albers FC, Brusselle G. Improvement in rhinosinusitis health related quality of life in patients with severe eosinophilic asthma. *Eur Respir J*. 2017;50(Suppl. 61):PA3583.
30. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2013;131:110–6.e1.
31. Gevaert P, Van Bruaene N, Cattaert T, Van Steen K, Van Zele T, Acke F, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol*. 2011;128:989-95.e1–8.
32. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA*. 2016;315:469–79.
33. Pinto JM, Mehta N, DiTineo M, Wang J, Baroody FM, Naclerio RM. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. *Rhinology*. 2010;48:318–24.

34. European Network for Health Technology Assessment. HTA Core Model® for rapid relative effectiveness assessment of pharmaceuticals In: Assessment ENfHT, editor. Version 3.0 ed: European Network for Health Technology Assessment; 2013.
35. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol*. 1997;50:683–91.
36. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol*. 2009;34:447–54.
37. Bachert C, Gevaert P, Corren J, Mullol J, Han J, Ow R, et al. Omalizumab improves outcomes in patients with chronic rhinosinusitis with nasal polyps irrespective of asthma status. American Academy of Allergy, Asthma & Immunology (AAAAI) Annual Meeting; 13–16 March; Philadelphia, PA, USA 2020.
38. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Health CfDaR. Guidance for industry patient-reported outcome measures: Use in medical product development to support labeling claims: Silver Spring, MD: Office of Communications, Division of Drug Information. 2009. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims>. Accessed November 10, 2020
39. Desrosiers M, Bachert C, Hellings P, Hopkins C, Olze H, Han JK, et al., editors. Dupilumab reduces need for systemic corticosteroid use, sinonasal surgery in patients with severe chronic rhinosinusitis with nasal polyps: Pooled results from the SINUS-24, SINUS-52 phase 3 studies. Poster presentation at the Annual Congress of the European Academy of Allergy and Clinical Immunology (EAACI); 01–05 June 2019; Lisbon, Portugal.
40. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl*. 2012;23:3 p preceding table of contents, 1–298.

41. Hahn C, Teufel M, Herz U, Renz H, Erb KJ, Wohlleben G, et al. Inhibition of the IL-4/IL-13 receptor system prevents allergic sensitization without affecting established allergy in a mouse model for allergic asthma. *J Allergy Clin Immunol*. 2003;111:1361–9.
42. Allinne J, Scott G, Lim WK, Birchard D, Erjefält JS, Sandén C, et al. IL-33 blockade affects mediators of persistence and exacerbation in a model of chronic airway inflammation. *J Allergy Clin Immunol*. 2019;144:1624–37.e10.
43. Naclerio R, Baroody F, Bachert C, Bleier B, Borish L, Brittain E, et al. Clinical research needs for the management of chronic rhinosinusitis with nasal polyps in the new era of biologics: A national institute of allergy and infectious diseases workshop. *J Allergy Clin Immunol Pract*. 2020;8:1532–49.e1.

Figures

FIGURE 1. Publication screening strategy

FIGURE 2. Dupilumab versus omalizumab comparison: NPS

FIGURE 3. Dupilumab versus omalizumab comparison: NC score

FIGURE 4. Dupilumab versus omalizumab comparison: mean difference in change in loss of smell score (A) and UPSIT score (B) from baseline to Week 24

FIGURE 5. Dupilumab versus omalizumab comparison: mean difference in change in TSS (A) and SNOT-22 (B) from baseline to Week 24

TABLE I. Patient characteristics

Characteristics, mean	SINUS-24* (n = 276)	SINUS-52* (n = 448)	POLYP 1 [†] (n = 138)	POLYP 2 [†] (n = 127)
Age, years	50.5	52.0	51.0	50.1
Male, %	57.2	62.3	63.7	65.3
Prior surgery,%	71.7	58.3	57.2	62.2
Prior surgery, pooled ITT, % [‡]		64.3		59.6
Prior SCS within 1 year, %	53.6	64.5	18.8	26.0
NPS, 0–8	5.8	6.1	6.2	6.3
NC score, 0–3	2.4	2.4	2.4	2.3
SNOT-22 total score, 0–110	49.4	51.9	60.1	59.5
UPSIT score, 0–40	14.6	13.6	13.3	13.0
LMK score, 0–24	19.0	18.0	—	—
Loss of smell score, 0–3	2.7	2.8	2.7	2.7
TSS, 0–12 [§]	9.0	9.3	8.9	8.6
Comorbid asthma, %	58.3	59.6	53.6	60.6
Comorbid asthma and NSAID- ERD, %	26.8	23.6	19.6	35.4
Mean blood eosinophil count, 10 ⁹ cells/L	0.44	0.43	0.35	0.33
Serum total IgE, IU/mL	212.0	239.8	160.9	190.2

*Mean of all randomized patients.

[†]Weighted mean of all randomized patients from mean reported by treatment arms.

[‡]Data presented for pooled ITT cohorts of 2 SINUS trials per data available for 2 POLYP trials.

[§]TSS presented on a 0–12 scale, calculated from the sum of the weekly average daily self-reported scores of 4 symptoms (NC, loss of smell, and anterior/posterior rhinorrhea [each 0–3]) in both SINUS and POLYP trials for the Bucher ITC. Data from the SINUS trials were used to generate TSS on a 0–12 scale for patients treated with dupilumab.

IgE, immunoglobulin E; *ITC*, indirect treatment comparison; *ITT*, intention-to-treat; *LMK*, Lund-Mackay; *NC*, nasal congestion; *NP*, nasal polyps; *NPS*, nasal polyp score; *NSAID-ERD*, non-steroidal anti-inflammatory drug-exacerbated respiratory tract disease; *SCS*, systemic corticosteroids; *SNOT-22*, 22-item sino-nasal outcome test; *UPSIT*, University of Pennsylvania Smell Identification Test; *TSS*, total symptom score.

Note: data for the POLYP 1 and POLYP 2 trials came from either ClinicalTrials.gov or Gevaert et al. 2020 J Allergy Clin Immunol.²³

TABLE II. Subgroup analysis for patients with CRSwNP with comorbid asthma (with or without NSAID-ERD) and comorbid asthma with NSAID-ERD

Change from baseline to Week 24, mean difference for dupilumab versus omalizumab (95% CI)			
		NPS, 0–8	NC score, 0–3
Asthma subgroup (with or without NSAID-ERD) (n = drug/placebo)	SINUS-24, n = 82/79		
	SINUS-52, n = 176/91	–1.09	–0.52
	Pooled POLYP 1/2, n = 80/71*	(–1.60, –0.57)	(–0.84, –0.20)
Asthma with NSAID-ERD subgroup (n = drug/placebo)	SINUS-24, n = 33/39		
	SINUS-52, n = 40/64	–0.73	–0.58
	POLYP 1, n = 16/11	(–1.57, 0.12)	(–1.01, –0.15)
	POLYP 2, n = 24/21		

Data from the SINUS trials were used to generate patient subgroups of asthma, and asthma with or without NSAID-ERD for patients treated with dupilumab.

*Sample size available only for pooled POLYP trial patients.

CRSwNP, chronic rhinosinusitis with nasal polyps; NC, nasal congestion; NPS, nasal polyp score; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory tract disease.

Significant results are presented in bold.

FIGURE 1. Publication screening strategy

The literature search was conducted specifically for the ITC analysis with a goal of identifying all clinical evidence of biologic and conventional treatments including surgery and other pharmacotherapies used in CRSwNP. At the full text publication screening stage, evidence was categorized by the class of treatment intervention, for example biologic, surgery, and others (corticosteroids and anti-leukotrienes), and from this point onwards focused on evidence for biologic treatments.

CRSwNP, chronic rhinosinusitis with nasal polyps; *ITC*, indirect treatment comparison; *RCT*, randomized clinical trials.

FIGURE 2. Dupilumab versus omalizumab comparison: NPS

A, Random-effects mean difference in change in NPS from baseline to Week 24. B, Responder analysis for patients with NPS improvement ≥ 1 from baseline to Week 24, random-effects odds ratio.

CI, confidence interval; *NPS*, nasal polyp score; *PBO*, placebo; *q2w*, every 2 weeks; *q4w*, every 4 weeks;

Tx, treatment.

610 **FIGURE 3.** Dupilumab versus omalizumab comparison: NC score

611 A, Random-effects mean difference in change in NC score from baseline to Week 24. B, Responder

612 analysis for patients with NC score improvement ≥ 1 from baseline to Week 24, random-effects odds ratio.

613 *CI*, confidence interval; *NC*, nasal congestion; *PBO*, placebo; *q2w*, every 2 weeks; *q4w*, every 4 weeks;

614 *Tx*, treatment.

615 **FIGURE 4.** Dupilumab versus omalizumab comparison: mean difference in change in loss of
616 smell score (A) and UPSIT score (B) from baseline to Week 24

617 Panels show random-effects mean difference.

618 *CI*, confidence interval; *LoS*, loss of smell; *PBO*, placebo; *q2w*, every 2 weeks; *q4w*, every 4 weeks; *Tx*,
619 treatment.

620 *UPSIT*, University of Pennsylvania Smell Identification Test.

FIGURE 5. Dupilumab versus omalizumab comparison: mean difference in change in TSS* (A) and SNOT-22 (B) from baseline to Week 24

*TSS presented on a 0–12 scale, calculated from the sum of the weekly average of daily self-reported scores of 4 symptoms (nasal congestion, loss of smell, and anterior/posterior rhinorrhea [each 0–3]) in both SINUS and POLYP trials for the Bucher indirect treatment comparison. Data from the SINUS trials were used to generate TSS on a 0–12 scale for patients treated with dupilumab.

Panels show random-effects mean difference.

CI, confidence interval; *PBO*, placebo; *q2w*, every 2 weeks; *q4w*, every 4 weeks; *SNOT-22*, 22-item Sino-Nasal Outcome Test; *TSS*, total symptom score; *Tx*, treatment.

1 **TABLE E1.** ITC analyses performed for dupilumab versus omalizumab

CRSwNP population	Scenario	Continuous outcomes (mean difference in change from baseline)	Binary outcomes at Week 24 (number of persons evaluated/events, odds ratio)
Primary	ITT population	Change from baseline at Week 24 in:	
		• NPS • NC score • LoS • TSS* • UPSIT • SNOT-22	• NPS responders (improvement ≥ 1) • NPS responders (improvement ≥ 2) • NC score responders (improvement ≥ 1)
Subgroup analysis	Asthma (with or without NSAID-ERD)	Change from baseline at Week 24 in:	Not feasible due to lack of data
		• NPS • NC score	
	Asthma and NSAID-ERD	Change from baseline at Week 24 in:	Not feasible due to lack of data
		• NPS • NC score	
Sensitivity	Subgroup with baseline SNOT-22 ≥ 20 (Table E6)	• All outcomes from ITT population	• NPS responders (improvement ≥ 1) • NC score responders

(improvement ≥ 1)

Subgroup with		
baseline IgE		• NPS responders
30–1500 IU/mL and	• All outcomes	(improvement ≥ 1)
body weight	from ITT	
30–150 kg (per	population	• NC score responders
omalizumab dosing)		(improvement ≥ 1)
SINUS-24/-52	• Change from	
versus POLYP 1 [†]	baseline at	Not feasible due to lack of data
	Week 24 in NPS	

*TSS presented on a 0–12 scale, calculated from the sum of the weekly average of daily self-reported scores of 4 symptoms (nasal congestion, loss of smell, and anterior/posterior rhinorrhea [each 0–3]) in both SINUS and POLYP trials for the Bucher indirect treatment comparison. Data from the SINUS trials were used to generate TSS on a 0–12 scale for patients treated with dupilumab.

[†]This sensitivity analysis excluded the POLYP 2 trial.

CRSwNP, chronic rhinosinusitis with nasal polyps; *ITC*, indirect treatment comparison; *LoS*, loss of smell; *NSAID-ERD*, non-steroidal anti-inflammatory drug-exacerbated respiratory tract disease; *NC*, nasal congestion; *NPS*, nasal polyp score; *SNOT-22*, 22-item Sino-Nasal Outcome Test; *TSS*, total symptom score; *UPSIT*, University of Pennsylvania Smell Identification Test.

Note: only pooled data from POLYP 1 and POLYP 2 trials were available at the time of analyses.

1 **TABLE E2.** Feasibility assessment

Study name	N	Primary population	Included in ITC	Reason for exclusion
Dupilumab, SINUS-24 ^{E1}	276	CRSwNP	✓	NA
Dupilumab, SINUS-52 ^{E1}	448	CRSwNP	✓	NA
Omalizumab, POLYP 1 ^{E2}	138	CRSwNP	✓	NA
Omalizumab, POLYP 2 ^{E2}	127	CRSwNP	✓	NA
Mepolizumab, SYNAPSE ^{E3,E4*}	413	CRSwNP	✗	No data were available in the literature sources searched during the SLR
Mepolizumab ^{E5}	105	CRSwNP	✗	Dose not used in CRSwNP phase 3 program (IV 750 mg q4w)
Dupilumab ^{E6}	60	Bilateral nasal polyposis with chronic symptoms of sinusitis	✗	Evaluation time earlier than 24 weeks
Reslizumab ^{E7}	150	Asthma (with self- reported CRSwNP)	✗	CRSwNP was not a primary indication included in the trial

Mepolizumab ^{E8}	105	Asthma (with NP)	✖	CRSwNP was not a primary indication included in the trial
Benralizumab ^{E9}	NR	Asthma (with NP)	✖	CRSwNP was not a primary indication included in the trial
Mepolizumab ^{E10}	30	CRSwNP	✖	Sample size ≤10 in either arm
Omalizumab ^{E11}	14	CRSwNP	✖	Sample size ≤10 in either arm
Mepolizumab ^{E12}	24	Bilateral or recurrent nasal polyps	✖	Sample size ≤10 in either arm
Omalizumab ^{E13}	24	CRSwNP	✖	Sample size ≤10 in either arm; evaluation time earlier than 24 weeks

2

3 *Two data points were presented in a press release at the time of the SLR. Data from this study were
4 published in a conference presentation after the SLR cut-off date, and are not included in the present
5 manuscript.

6 *CRSwNP*, chronic rhinosinusitis with nasal polyps; *ITC*, indirect treatment comparison; *IV*, intravenous;
7 *NA*, not applicable; *NP*, nasal polyps; *NR*, not reported; *q4w*, every 4 weeks; *SLR*, systemic literature
8 review.

TABLE E5. Change from baseline to Week 24 in key endpoints for the placebo (INCS) groups of the SINUS and POLYP trials

Outcome measure, LS mean change from baseline to Week 24 (SE)	SINUS-24 (n = 133)	SINUS-52 (n = 153)	POLYP 1 (n = 66)	POLYP 2 (n = 65)
NPS, 0–8	0.17 (0.15)	0.10 (0.14)	0.06 (0.16)	–0.31 (0.16)
NC score, 0–3	–0.45 (0.07)	–0.38 (0.07)	–0.35 (0.11)	–0.20 (0.11)
SNOT-22 total score, 0–110	–9.31 (1.62)	–10.40 (1.61)	–8.58 (2.08)	–6.55 (2.19)
UPSIT score, 0–40	0.70 (0.71)	–0.81 (0.71)	0.63 (0.90)	0.44 (0.81)
LMK score, 0–24	–0.74 (0.37)	–0.09 (0.31)	—	—
Loss of smell score, 0–3	–0.29 (0.07)	–0.23 (0.08)	–0.23 (0.10)	–0.13 (0.10)
TSS, 0–12*	–1.67 (0.23)	–1.37 (0.26)	–1.06 (0.34)	–0.44 (0.32)

*TSS presented on a 0–12 scale, calculated from the sum of the weekly average daily self-reported scores of 4 symptoms (NC, loss of smell, and anterior/posterior rhinorrhea [each 0–3]) in both SINUS and POLYP trials for the Bucher ITC. Data from the SINUS trials were used to generate TSS on a 0–12 scale for patients treated with dupilumab.

LMK, Lund-Mackay; LS, least squares; NC, nasal congestion; NPS, nasal polyp score; SE, standard error; SNOT-22, 22-item sino-nasal outcome test; UPSIT, University of Pennsylvania Smell Identification Test; TSS, total symptom score.

Note: data for the POLYP 1 and POLYP 2 trials came from Gevaert et al. 2020 J Allergy Clin Immunol.

TABLE E6. Sensitivity analysis for dupilumab subgroups: baseline SNOT-22 ≥ 20 ; baseline serum total IgE 30–1500 IU/mL and body weight 30–150 kg

Dupilumab versus omalizumab		
	Baseline SNOT-22 ≥ 20 ($n_{\text{SINUS}} = 681/n_{\text{POLYP}} = 265$)*	Baseline IgE 30–1500 IU/mL and body weight 30–150 kg ($n_{\text{SINUS}} = 599/n_{\text{POLYP}} = 265$) [†]
Change from baseline to Week 24, mean difference (95% CI)		
NPS	-1.05 (-1.65, -0.45)	-1.16 (-1.76, -0.56)
NC score	-0.36 (-0.60, -0.11)	-0.40 (-0.65, -0.16)
LoS	-0.65 (-0.88, -0.42)	-0.69 (-0.95, -0.43)
UPSIT	6.54 (4.49, 8.60)	7.02 (4.94, 9.10)
TSS [‡]	-1.23 (-2.01, -0.45)	-1.31 (-2.10, -0.52)
SNOT-22	-4.09 (-9.87, 1.69)	-3.76 (-8.97, 1.45)
Responders with improvement from baseline, odds ratio (95% CI)		
NPS improvement ≥ 1	3.56 (1.73, 7.33)	4.49 (1.98, 10.14)
NC score improvement ≥ 1	2.11 (1.11, 4.02)	2.30 (1.19, 4.45)

*Data from the SINUS trials were used to generate the subgroup with baseline SNOT-22 ≥ 20 for patients treated with dupilumab.

[†]Data from the SINUS trials were used to generate the subgroup with baseline IgE 30–1500 IU/mL and body weight 30–150 kg (per omalizumab dosing table)² for patients treated with dupilumab.

[‡]TSS presented on a 0–12 scale, calculated from the sum of the weekly average of daily self-reported scores of 4 symptoms (nasal congestion, loss of smell, and anterior/posterior rhinorrhea [each 0–3]) in both SINUS and POLYP trials for the Bucher indirect treatment comparison. Data from the SINUS trials were used to generate TSS on a 0–12 scale for patients treated with dupilumab.

- 12 *CI*, confidence interval; *IgE*, immunoglobulin E; *LoS*, loss of smell; *NC*, nasal congestion; *NPS*, nasal
13 polyp score; *SNOT-22*, 22-item Sino-Nasal Outcome Test; *TSS*, total symptom score; *UPSIT*, University
14 of Pennsylvania Smell Identification Test.
- 15 Significant results are presented in bold.

TABLE E4. Distribution of clinical study sites for the SINUS and POLYP studies

Regions of study sites, n (%)	SINUS-24 (n = 276)	SINUS-52 (n = 448)	POLYP 1 (n = 138)	POLYP 2 (n = 127)
Asia	0	49 (10.9)	0	0
Latin America	0	137 (30.6)	0	0
East Europe	173 (62.7)	43 (9.6)	71 (51.4)	68 (53.5)
Western countries	103 (37.3)	219 (48.9)	67 (48.6)	59 (46.5)

1 **TABLE E3.** Patient selection criteria for trials included in the ITC

Trial selection criteria	SINUS-24 and -52	POLYP 1 and 2
NPS ≥ 5 , with score of ≥ 2 for each nostril at both the first screening visit and end of run-in period	✓	✓
NC score ≥ 2 (with presence of nasal discharge and/or reduced smell) at first screening visit and weekly average NC > 1 at randomization	✓	✓
Adult patients (SINUS excluded patients < 18 , POLYP included 18–75)	✓	✓
Exclusion: History of nasal surgery (including polypectomy) within 6 months prior to screening	✓	✓
Prior treatment with systemic glucocorticoids within the last 2 years (or a medical contraindication or intolerance to systemic glucocorticoids), prior surgery for nasal polyps, or both	✓	No
Stratified recruitment approach	• Asthma/NSAI • D-ERD • Prior surgery • Country	• Asthma/NSAI • D-ERD • Geographic region
SNOT-22 ≥ 20	No	✓

Background treatment (INCS with mometasone furoate)

✓

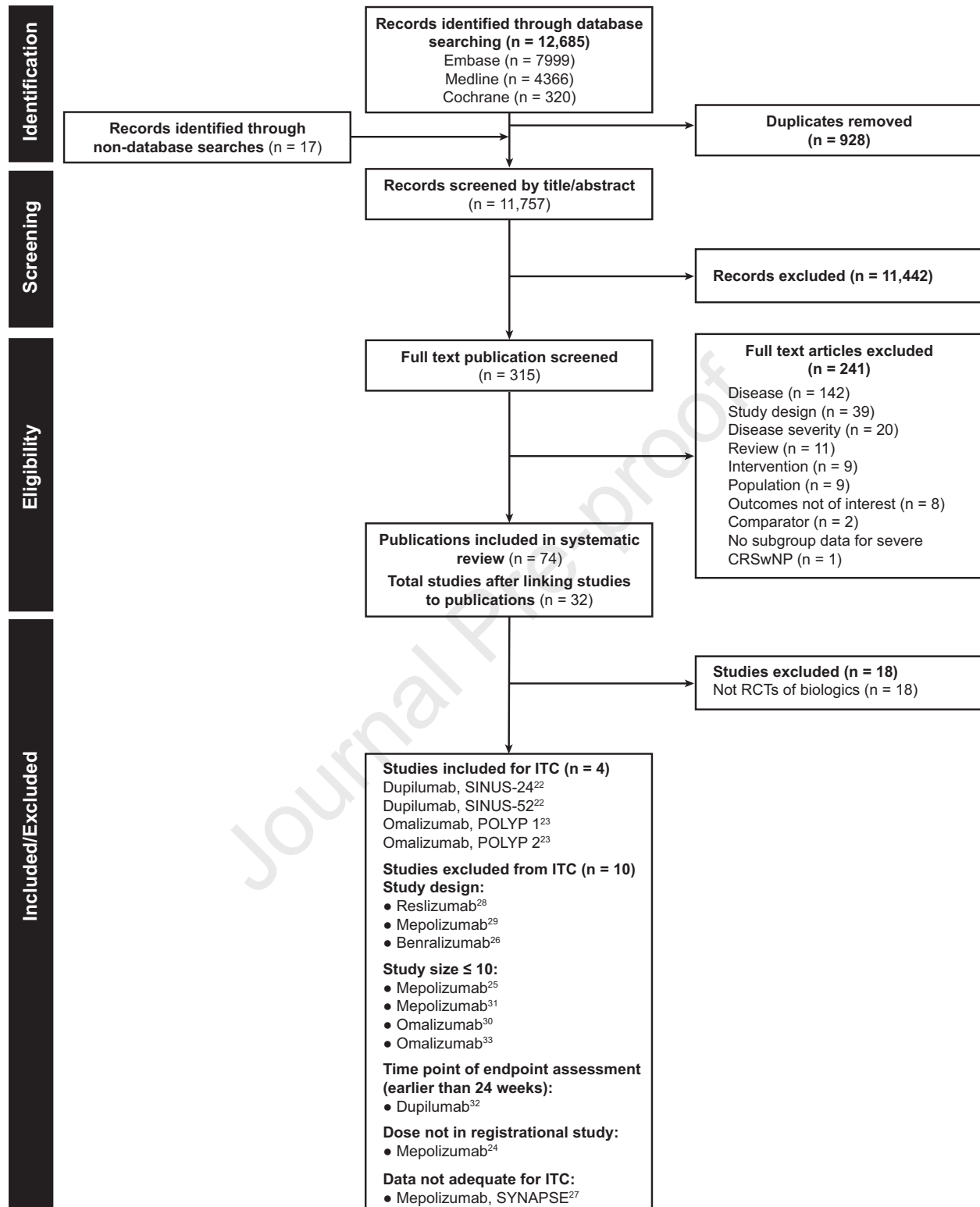
✓

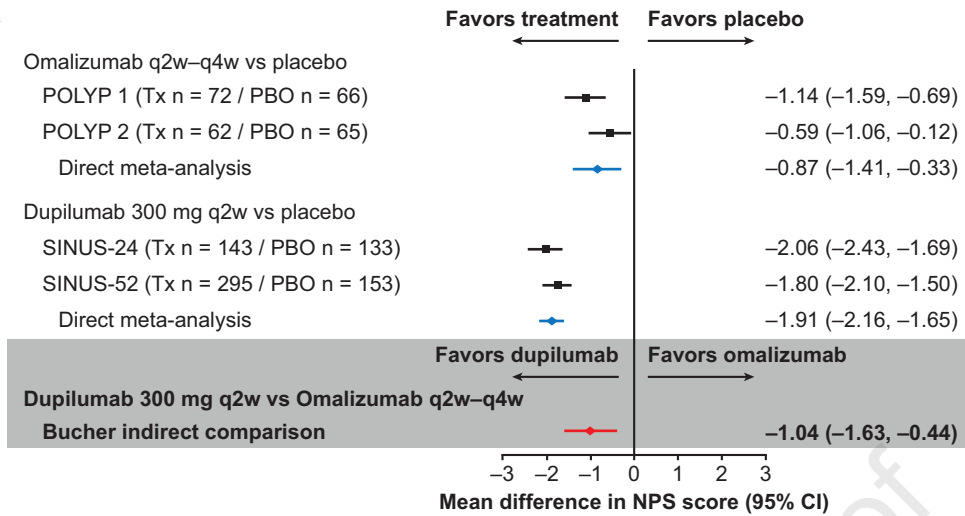
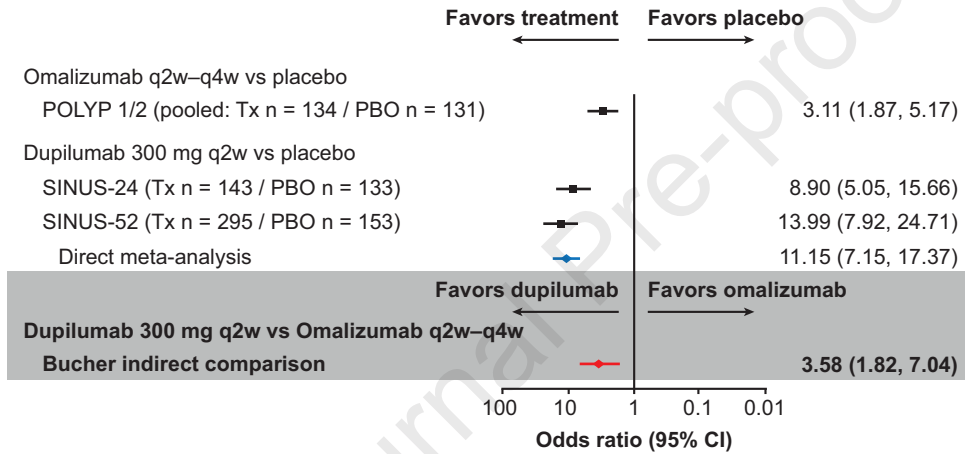
IgE criteria of 30–1500 IU/mL and weight 30–150 kg (per omalizumab dosing)

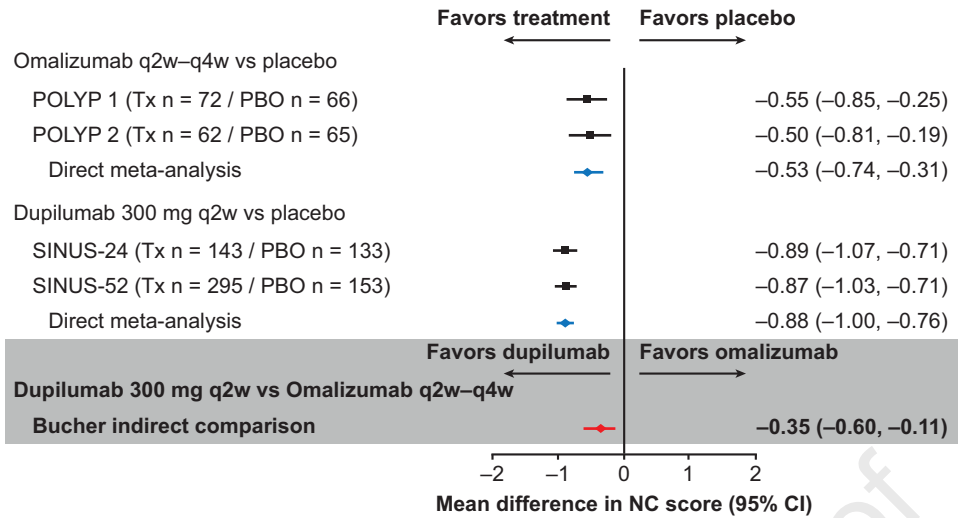
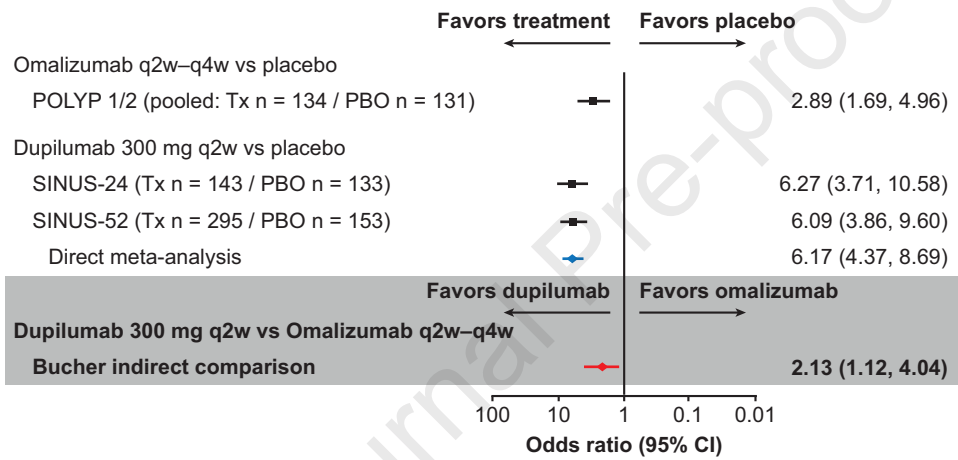
No

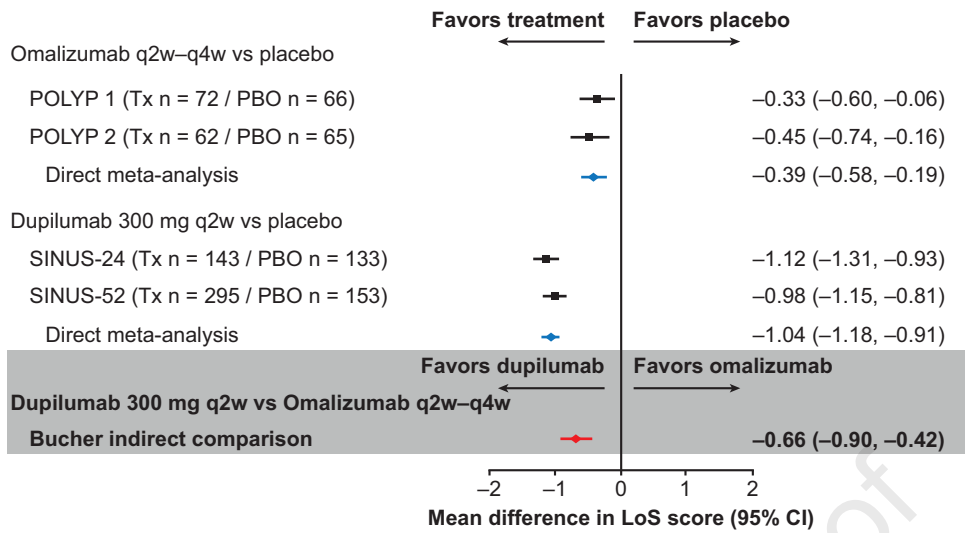
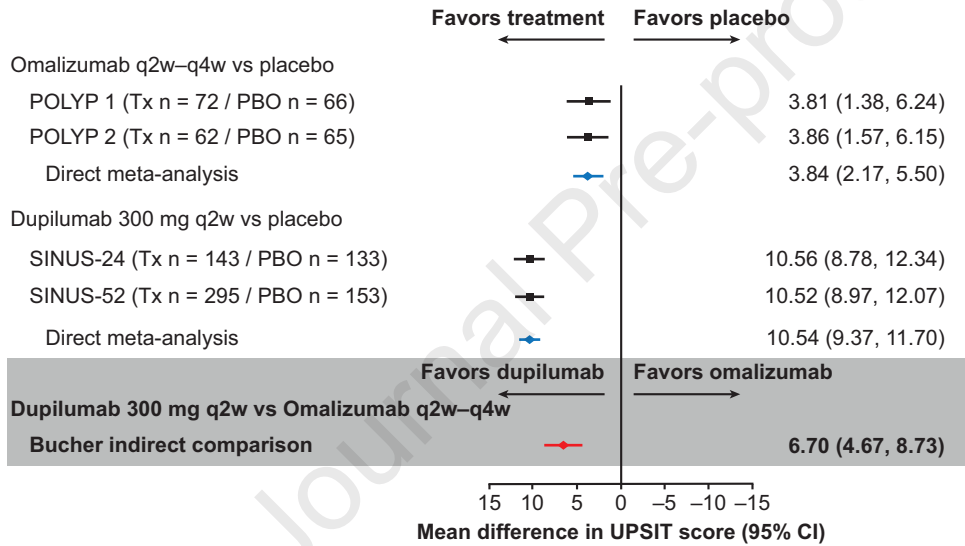
✓

-
- 2 *IgE*, immunoglobulin E; *INCS*, intranasal corticosteroids; *NC*, nasal congestion; *NSAID-ERD*, non-
 3 steroidal anti-inflammatory drug-exacerbated respiratory tract disease; *NP*, nasal polyps; *NPS*, nasal
 4 polyp score; *SNOT-22*, 22-item Sino-Nasal Outcome Test.

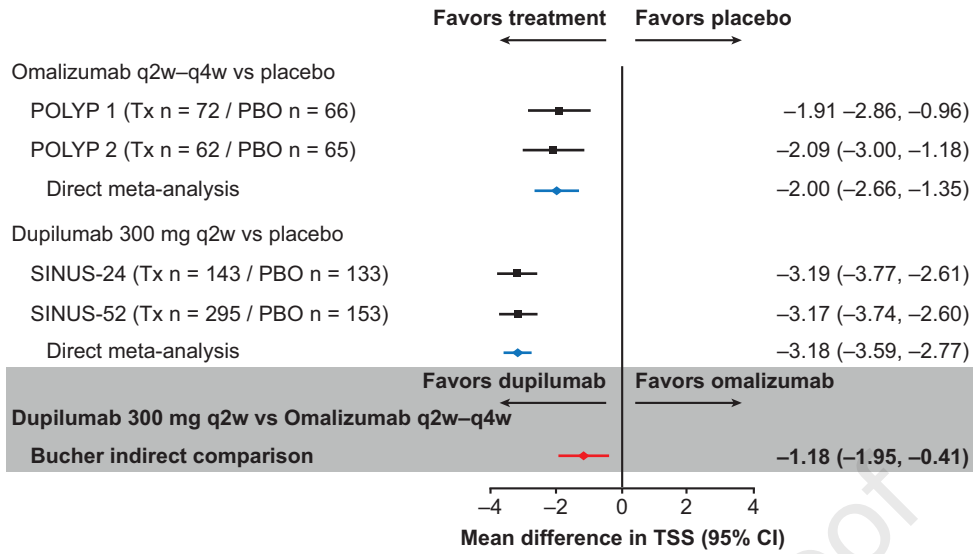


A**B**

A**B**

A**B**

A



B

