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Efficacy and Safety of treatment with biologicals for severe Chronic Rhinosinusitis with Nasal Polyps

A systematic review for the EAACI Guidelines

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Abbreviations

AEs = adverse events

CI = confidence interval

CRSwNP = chronic rhinosinusitis with nasal polyps

EAACI = European Academy of Allergy and Clinical Immunology

EMA = European Medicine Agency

EURONHEED= European Network of Health Economic Evaluation Databases

FDA = Food and Drug administration

GDG = Guideline Development Group

GRADE = Grading of Recommendations Assessment, Development and Evaluation

ICERs = the incremental cost-effectiveness ratios

Ig = immunoglobulin

IL = interleukin

IRR = incidence rate ratios

Mab = monoclonal antibody

MD = mean difference

MID = minimal important difference

NPs = nasal polyps

OCS = oral corticosteroids

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis

QALY = quality adjusted life-years

QoL = quality of life

RCT = randomised controlled trial

ROB = risk of bias

RR= risk ratio

SC= subcutaneous

SNOT-22 = sino-nasal outcome test 22

SoF = summary of findings

SR = systematic review

T2 = type 2

TAE = treatment related adverse events

TPS = total nasal endoscopic score

UPSIT= University of Pennsylvania Smell Identification Test

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Key words
Chronic rhinosinusitis; dupilumab; omalizumab; mepolizumab; reslizumab

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Abstract

This systematic review evaluates the efficacy and safety of biologicals for chronic rhinosinusitis with nasal polyps (CRSwNP) compared to the standard of care.

Pubmed, EMBASE and Cochrane Library were searched for RCTs. Critical and important CRSwNP-related outcomes were considered. The risk of bias and the certainty of the evidence were assessed using GRADE.RCTs evaluated(dupilumab-2, omalizumab-4, mepolizumab-2, reslizumab-1) included 1236 adults, with follow-up 20-64 weeks.

Dupilumab reduces the need for surgery (NFS)ororal corticosteroid (OCS) use (RR 0.28; 95%CI 0.20-0.39,moderate certainty) and improves with high certainty smell evaluated with UPSIT score(mean difference (MD) +10.54; 95%CI +9.24 to +11.84) and quality of life (QoL) evaluated with SNOT-22 (MD -19.14; 95%CI -22.80 to -15.47),with fewer treatment-related adverse events (TAEs) (RR 0.95; 95%CI 0.89-1.02, moderate certainty). Omalizumab reduces NFS(RR 0.85; 95%CI 0.78 to 0.92,high certainty), decreases OCS use(RR 0.38; 95%CI 0.10-1.38, moderate certainty), improves with high certainty smell (MD +3.84; 95%CI +3.64 to +4.04) and QoL (MD -15.65; 95%CI -16.16 to -15.13), withincreasedTAE (RR 1.73; 95%CI 0.60-5.03,moderate certainty). There is low certainty for mepolizumab reducingNFS (RR 0.78; 95%CI 0.64 to 0.94) andimproving QoL (MD -13.3; 95% CI -23.93 to -2.67) and smell(MD +0.7; 95%CI -0.48 to +1.88), with increasedTAEs (RR 1.64; 95%CI 0.41-6.50). The evidence for reslizumab is very uncertain.

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Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disease of the paranasal sinuses, occurring in up to 12% of the adult population, with significant direct medical costs and severe impact on lower airway disease and general health outcomes (1,2). It is a frequent co-morbidity of patients with severe asthma (3). The diagnosis of CRS is based on clinical signs, nasal endoscopy and CT scanning (1,4). Based on the presence of nasal polyps (NP) CRS is divided into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). Patients with CRSwNPgenerally have a high symptom burden and poor health-related quality of life (QoL), often requiring recurrentoral corticosteroid (OCS) use and repeated sinus surgery (1,5).

CRSwNP is a multifactorial disease, with severaloverlappingpathomechanisms (6). According to current knowledge, there is solid evidence suggesting that CRS isprimarily a chronic inflammatory disease rather than an infectious one. Both innate and adaptive immunity contribute to the heterogeneous inflammatory pathogenesis of CRS, which is driven by genetic and environmental factors and the microbiome (6, 7,8).Mucus abnormalities and the epithelial barrier defects contribute as well (9,10,11,12,13). Current technological advances, mostly in relation to precision immunology permitting more detailed pathophysiological assessments, together with unbiased mathematical models supporting multidimensional approaches in airways diseaseshave allowed the description of several disease endotypes (14).Central to this approach are new biomarkers that are being evaluated in relation to the visible properties of CRS (15). Patients with CRS can be classified into three endotypes based on the presence of type 1, type 2, or type 3 inflammation (16). CRS endotypes can be influenced by age and geographic location (14,16). The majority of patients with CRSwNP show a type 2 (T2) inflammatory signature. However, several T2 subendotypes can be described (14,16). For example, a severe neutrophilic inflammation has been reported associated with severe eosinophilic T2 inflammatory CRSwNP (17).

CRSwNP treatment is directed at enhancing mucociliary clearance, improving sinus drainage/outflow, eradicating local infection and inflammation, and improving access for topical medications (1,4,18). First-line treatment is nasal saline irrigation and intranasal corticosteroid sprays. There may be a role for antibiotics in patients with evidence of an active, superimposed acute sinus infection. Long-term use of macrolides is currently being explored based on their immunomodulatory properties(19). If medical management fails, endoscopic sinus surgery may be effective (20,21).OCS are often used to control disease flares. Treatment success depends on

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the clarification of the underlying pathogenesis, disease-contributing factors and treatable traits. The exploration of disease endotypes and the introduction of novel agents are important advancements. T2-targeting biologicals such as anti-immunoglobulin (Ig) E, anti-interleukin (IL) 4Rα, anti-IL5, and anti-IL5Rα were investigated in phase 3 clinical trials. Dupilumab,anti-IL4Rα monoclonal antibody (Mab) and omalizumab, anti IgE Mab, have already entered the market for selected pheno/endotypes of CRSwNP patients, following European Medical Agency (EMA) and Food and Drug Administration (FDA) approval (22,23).The advent of biological agents acting directly to the endotype underlying CRSwNP pushes the scientific community to integrate clinical, surgical and immunological evaluations for each single patient.Treatable traits can serve as outcomes to evaluate the efficacy of the targeted intervention (24,25). However, due to the high cost of molecular diagnosis and biological treatment the endotype-driven treatment as part of a personalised approach in CRS is currently positioned at the tertiary level of care (26,27).

The European Academy of Allergy and Clinical Immunology (EAACI) is developing clinical practice guidelines for the use of biologicals in patients with CRSwNP. To inform key clinical recommendations, a systematic review (SR) evaluated the effectiveness and safety of currently available biologicals for patients with uncontrolled CRSwNP.

Methods

Guidelines Development Group

The EAACI Chronic Rhinosinusitis with Nasal Polyps Voting Panel and Steering Committee included clinicians and researchers with different backgrounds (the complete list of experts is available on the EAACI website), who voluntarily participate in the development of the EAACI biologicals guideline. They are referred to as the Guidelines Development Group (GDG).

Structured question and outcome prioritisation

The GDG framed the clinical question as “Is the treatment with a biological (iedupilumab, omalizumab, mepolizumab, reslizumab, and benralizumab) efficacious and safe for patients with uncontrolledCRSwNP?” (Table 1). For the purpose of this SR the population of interest was defined as patients aged 12 years or older with NPs (diagnosed by CT and/or endoscopy) and chronic symptoms of sinusitispersistent under treatment with intranasal corticosteroids.Outcomes were prioritized by the GDG group using a 1 to 9 scale (7 to 9 critical; 4 to 6 important; 1 to 3 of

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limited importance),according to the GRADE approach (28). The critical outcomes were: recurrence of NPs, need for surgery or forOCS, and safety.Only treatment related adverse events (TAE) and treatment related severe adverse events (AEs) were considered for the SR. The important outcomes were rescue medication use, topical steroid use, resource utilisation,QoL (assessed as change of the sino-nasal outcome test (SNOT-22)), and smell (assessed with University of Pennsylvania Smell Identification Test (UPSIT)) (Table 1).

The GDG also framed a cost-effectiveness question to assess the economic impact of using biological versus standard of care for patients with uncontrolled CRSwNP. The selected outcomes of interest were costs, resource use, and the incremental cost-effectiveness ratios (ICERs) per quality adjusted life-years (QALY).

Data source and search methodology

Electronic algorithms in combination with controlled vocabulary and search terms were used to identify relevant randomised controlled trials (RCTs) and economic evaluations in: i) MEDLINE (via PubMed, September 2020); ii) Cochrane Controlled Trials Register (via The Cochrane Library, September 2020), and; iii) EMBASE (via Ovid, September 2020). Search algorithms were adapted to the requirements of each database, and validated filters were used to retrieve appropriate designs (tables S1 and S2*)*. Additional studies provided by the GDG and previous SR were also evaluated.

Eligible criteria and selection of studies

The eligibility process of the original studies is summarised using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart.The SR included only RCTs comparing biologicals versus placebo added to standard of care in patients with CRSwNPand reporting one of the outcomes of interest as formulated by the GDG (figure 1). Only studies published in English were included. Abstracts or conference communications not published as full articles in peer-reviewed journals and RCTs using dose or routes not approved by EMA and/or the FDA were excluded. Two reviewers independently screened the references based on the title and abstract followed by eligibility at full text level. Discrepancies were solved by consensus or with the help of a third reviewer. All citations retrieved were imported into the bibliographic reference software (EndNote X9; Thomson Reuters) to discard duplicates and record screening decisions.

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Data extraction and risk of bias assessment

Details of the study design, patient population, setting, follow-up and results were extracted by one reviewer and confirmed by a second reviewer. If needed, additional data from the authors of the included studies were requested. The Cochrane Risk of Bias (ROB) tool for randomised trials was used to assess the risk of bias (ROB)in parallel by two reviewers (29). The ROB was judged as low, high or unclear for each domain: random sequence generation, allocation concealment, blinding of participants and personnel, blinding for outcome assessment, incomplete outcome data, and selective reporting (30,31,32).Discrepancies were solved by discussion.

For the health economic studies,the main characteristics of included studies (e.g. type of economic evaluation, perspective, time horizon, discounting, sources of information, model type) were evaluated together with the relevant outcomes, sources of funding, and conflict of interest. The methodological limitations were judged using the questionnaire to assess relevance and credibility of modeling studies for informing health care decision making (ISPOR-AMCP-NPC Good Practice Task Force) (33). The transferability to the European context was assessed using the European Network of Health Economic Evaluation Databases (EURONHEED) checklist (34,35).

Data synthesis and analysis

Main results are described narratively and included in summary of findings (SoF) tables. For dichotomous data, results are pooled as risks ratios (RR). For continuous data, results are reported as mean differences (MD), with 95% confidence intervals (CI). For each outcome, the change from baseline to the end of the treatment was assessed versus placebo. In case that the same outcome was reported using complementary definitions (i.e. “reduced need for surgery” vs “need for surgery”)the relative effect was recalculated to make them comparable.

A random-effects model was used to pool data (Review Manager v 5.3 Cochrane Collaboration, Oxford, UK). Where multiple arms were compared to a common placebo arm, standard errors were adjusted to avoid unit of analysis error (36). Statistical heterogeneity between studies was assessed with the Cochrane chi-square test, and the magnitude of heterogeneity with the I2 statistic (37). To account for heterogeneity subgroup analyses were predefined,where possible,

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by age (i.e. 12-18 years old vs18 years old and < 65 vs > 65 years old), with and without associated asthma, with and without atopy, by blood eosinophils levels(<150/mm^3, 150-30/mm^{3}0, >300/mm^3), and by ROB. The median estimate reported in the control arms of the included RCTs was used as baseline risk to estimate absolute effects for each comparison.

For the economic evidence the results (incremental cost, incremental effectiveness, ICERs and the degree of uncertainty) are summarized narratively and tabulated.

Certainty of the evidence

The certainty (quality) of the evidence of efficacy and safety was rated for each outcome as high, moderate, low or very low, following the GRADE approach and the standard GRADE domains (risk of bias, imprecision, inconsistency, indirectness, and publication bias) (38,39,40).For the evaluation of imprecision for each outcome, the minimal important difference (MID) was considered when available. For the purpose of this SR a MID of 12 points for the SNOTT-22 was considered (41).

Results

Results are presented using the GRADE informative statements (42).

Search process

The eligibility process is summarized in the PRISMA flow chart (Figure 1 A and B). For the efficacity and safety a total of 3902 unique citations were retrieved from databases searches and 15 were selected for full text assessment. An additional trial was added at the suggestion of the GDG. Sixteen articles were appraised at full text level and5 were excluded due to regulatory unapproved doseor no reporting of the outcomes of interest (Figure 1A*,* Table S3*)*.Seven publications reporting 9 RCTs were included: two RCTs for dupilumab (43), four for omalizumab (44,45,46), two for mepolizumab (47,48), and one for reslizumab (49)(Table 2, figure 1A). No study for benralizumab was identified.For the economic evidence, after screening 717 hits, one cost-utility evaluation comparing dupilumab with surgical management was included (50) (Figure 1B)

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Characteristic of included studies

The main characteristics of the studies included are detailed in Table 2. All included studies were RCTs with assigned biologicals and matching placebo. The RCTs included 1236adult patients with severe CRSwNP, inadequately controlled by standard of care. Follow up under the intervention with the biologicalranged from 20 weeks (47) to 52weeks (43). All studies included adult population(18 years or older).

Evidence of efficacy

The summary of the results and certainty of evidence per outcome is reported in Tables 3-6.The meta-analysis results are presented in the supplementary files S1-S24 and Tables S3-S11.

Reduction in the surgery for CRSwNP

This outcome was reported in two dupilumab trials (43), two omalizumab trials (44),two mepolizumab trials (48), and one reslizumab trial (49). Dupilumab reported the reduction in surgery or OCS use as a composite outcome.Omalizumab and mepolizumab studies reported the number of subjects who achieved a “reduced need for surgery” status, while dupilumab trials reported this outcome as “need for surgery”. To harmonise the interpretation all reports were adapted to the reporting style of dupilumab, thus RR<1 represents a good result of the intervention. As there is moderate certainty of evidence, dupilumab probably reduces the number of patients that needforNP surgery or OCS use (RR 0.28; 95% CI 0.20 to 0.39; 244 fewer per 1000; 95%CI from 271 fewer to 207 fewer).Omalizumab reduces the needs for NP rescue surgery with high certainty of evidence (RR 0.85; 95% CI 0.78 to 0.92; 145 fewer per 1,000 from 213 fewer to 77 fewer). As there is low certainty of evidence mepolizumab may reduce the need for rescue NP surgery (RR 0.78; 95% CI 0.64 to 0.94; 177 fewer per 1,000; 95%CI from 289 fewer to 48 fewer).Forreslizumab there is very uncertain evidence (RR 0.20; 95% CI 0.01 to 3.61, 200 fewer per 1,000; 95%CI from 248 fewer to 653 more).

Rescue OCS use

The rescue OCSwas reported in three omalizumab trials (44, 46) and one reslizumab trial (49). It wasreported as the need for rescue OCS(44,49) or as OCS plus antibiotics(46). As there is

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moderate certainty of evidence,omalizumab probably reduces the need for OCSuse (RR 0.38; 95% CI 0.10 to 1.38; 38 fewer per 1000; 95%CI from 56 fewer to 24 more). For reslizumabthe evidence is very uncertain.For dupilumab the reduction in the OCS use is reported as a composite outcome, together with the reduction in surgery (see above).

Sense of smell

This outcome was measured by: a) the UPSIT score in two dupilumab trials (43) and two omalizumab trials (44); b) by the NP symptoms score including loss of smell in three omalizumab trials (44, 45); c) and by the Sniffin' Sticks Screening-12 test (SST) in one mepolizumab trial (48). Dupilumab improved with high certainty of evidence the sense of smell by increasing the score of UPSIT (MD +10.54; 95%CI +9.24 to +11.84). Similarly, omalizumab improved the sense of smell by increasing UPSIT score (MD +3.84; 95%CI +3.64 to +4.04, high certainty), and probably reduced the NP symptom score (loss of sense of smell) (MD -0.48 score; 95%CI -0.62 to -0.34, moderate certainty). There is low certainty of evidence for mepolizumab (+MD 0.7; 95%CI -0.48 lower to +1.88).

Quality of life

QoL was evaluated by SNOT-22 score in two dupilumab trials (43), two omalizumab trials (44), and one mepolizumab trial (48); dupilumab and omalizumab improve with high certainty the QoL (for dupilumab MD -19.14, 95% CI -22.80 to -15.47, for omalizumab MD -15.65, 95% CI -16.16 to -15.13). For mepolizumab there is low certainty of evidence, however there is a large effect(MD -13.3; 95% CI -23.93 to -2.67). All 3 biologicals' impact on QoL above the SNOT-22 MID of 12.

Nasal polyp score

Nasal polyp score was evaluated fordupilumab, mepolizumab, omalizumab and reslizumabusing the total nasal endoscopic polyp score (TPS) (43, 44, 45, 47, 48). Dupilumab improved TPSwith high certainty of evidence at 24 weeks (MD -1.92; 95% CI -2.18 to -1.65). For omalizumab therewasmoderate certainty of evidence (MD -1.42; 95% CI -2.53 to -0.32).For both mepolizumab and reslizumabthere is a very low certainty of evidence.

Computer tomography (CT) score

Two dupilumab trials (43) and one omalizumab trial (45) evaluated the Lund-Mackay CT score. Dupilumab reduced the CT scorewith high certainty of evidence(MD -6.26; 95%CI -8.53 to -3.99). For omalizumab there is very low certainty of evidence (MD -4.5; 95%CI -10.47 to +1.47 higher).

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Symptom score

Two omalizumab trials (44) evaluated this outcome using the total nasal symptom score. Omalizumab relieved the nasal symptoms withhigh certainty of evidence (MD -2, 95% CI -2.08 to -1.92).

Subgroup analysis

Dupilumab had a larger effect on the improvement of nasal polyp score in the subgroup patients below 65 years old (MD - 2.06, 95% CI -2.32 to -1.81) versus those above 65 years old (MD -1.04, 95% CI -1.53 to -0.55) (figure S11). Compared with the overall population(see above), in patients with asthma as a comorbidity, dupilumab produced a similar improvement of nasal polyp score and CT score (MD -1.63, 95%CI -2.64 to -0.62; and MD -6.63, 95%CI -8.88 to -4.39) (figure S12, S13). No data were identified for the other subgroups of interest (atopy, blood eosinophils, ROB) .

Evidence of safety

Treatment-related adverse eventswere reported in two trials for dupilumab (43), two trials for omalizumab (44), one for mepolizumab (48), and one for reslizumab (49). Patients treated with dupilumab had fewer TAE compared to those with placebo (RR 0.95; 95% CI 0.89 to 1.02; 45 fewer per 1000 patients; 95% CI from 100 fewer to 18 more, moderate certainty of evidence) andfewer serious TAE (RR 0.61; 95% CI 0.31 to 1.17; 39 fewer per 1.000 patients; 95% CI from 69 fewer to 17 more, moderate certainty of evidence).For omalizumab there was an increase in TAE (RR 1.73; 95% CI 0.60 to 5.03, 28 more per 1,000; 95% CI from 15 fewer to 155 more, moderate certainty).OverallTAE were increased by mepolizumab (RR 1.64; 95% CI 0.41 to 6.50, 37 more per 1,000; 95% CI from 34 fewer to 317 more, low certainty).Reslizumab did not increase TAE, but the evidence is very uncertain.

Economic evidence

The one cost-utility evaluationincluded reports a microsimulation Markov model-based assessing dupilumab versus endoscopic sinus surgery (ESS) plus postoperative medical therapy (50). The SNOT-22 score for the surgical arm was obtained from a US cohort of CRSwNP patient refractory to medical therapy(51,52). For patients receiving dupilumab 300 mg the model used data from the SINUS-24 and SINUS-25 clinical trials (53). The costs were informed by using a systematic

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review reporting a mean cost for uncomplicated ESS of $8,968 (54), a study reporting a cost of $16,877 for complicated ESS (55), and a study estimating a yearly cost for dupilumab of $31,000 in patients with biologic treatments for asthma (56). The economic evaluation suggestedfor ESS strategy a total cost of $50,437 with a total of 9.80 QALYs, while for the dupilumab the total cost was $536,420 with a total of 8.95 QALYs (Table 7). Consequently, the dupilumab treatment may be costlier and less effective than the ESS strategy.

The main reasons to downgrade the certainty of the evidence for the efficacy outcomes were ROB, indirectness, and imprecision, and for economic data were limitations and indirectness.

Discussion

Main findings

This systematic review found that dupilumab as an add-on treatment in adults with severe uncontrolled CRSwNP, reduces with moderate certainty the need for rescue NP surgery or for OCS, and improves with high certainty the sense of smell, quality of life, the nasal polyp score, and CT score,with a good safety profile. There is high certainty that omalizumab reduces the need for surgery, improves the sense of smell and quality of life, and moderate certainty that it reduces the use of rescue medications, the NPsymptoms and the NP score.However, it likelyincreasestreatment related AEs. Mepolizumab may reduce the need for surgery, improve the QoL and the sense of smell, while increasing adverse events, but there is low level of certainty. Evidence for reslizumab is very limited and uncertain.For dupilumab and omalizumab trials the overall ROB was low, but the trials included were funded by the same company for each biological, which raises a concern of a potential sponsorship bias. In addition, there is a concern regarding indirectness since dupilumab trials pooled two critical outcomes (need for surgery and OCS) into one coprimary end-point and this precludes from assessing each outcome directly. Both for dupilumab and omalizumab the overall evidence quality is moderate to high. For mepolizumab and reslizumab there are concerns of ROB probably due to the: a) imbalance between arms at baseline due to small sample size; b) imprecision due to the number of events.Therefore, the certainty of evidence is low to very low.

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The economic evaluation suggests that in patients with CRSwNP refractory to treatment, ESS may offers a better cost-effectiveness profile than dupilumab.However, patients with concomitant asthma could benefit from the treatment of both diseases, and other patients might prefer not undergoing surgical procedures.None of these scenarios were included in the economic model. In addition, the costs of OCS side effects were not factored in. There is low certainty of evidence for cost-utility. The evidence was downgraded:a) one level for the ROB due to the inclusion of input parameters of moderate certainty and due to not reporting a validation procedure for the model development; b) and one level for indirectness given that some patients might have another concomitant inflammatory disease (i.e. asthma) who could benefit from dupilumab treatment and were not captured by the model.Additionally, unitary costs were provided exclusively by studies performed in the US. These results may not apply to Europe or outside high-income countries.

Results in the context of previous research

Compared to previous SRs, the current study shows a similar effect of dupilumab regarding the improvement of quality of life and nasal polyp score, and similar limited evidence regarding mepolizumab and reslizumab (57,58). Meanwhile,the inclusion of the two newly completed RCTs of omalizumab brought sufficient evidence for the efficacy of omalizumab.Moreover, the current SRevaluated the efficacy based on GDG's predefined patient-related outcomes, which enhanced clinical impact. As an example, this SR showed high certainty both for dupilumab and omalizumab in improving the sense of smell. In addition, the predefined subgroup analysis revealed a better effect of dupilumab on the reduction of the nasal polyp score for patientsbelow 65 years old, a finding which may improveclinical decision making. Finally, the current study alsoattempted an evaluation of cost-effectiveness evidence to support the decision making by clinicians and patients.

Limitations and strengths

The current systematic review has several strengths. Both the desired and undesired effect of using biologicals in CRSwNP were evaluated exhaustively. A comprehensive systematic search of three main databasesarticles suggested by the GDGsupports the comprehensiveness of evidence selection. Moreover, the minimal important difference was consideredwhen available (e.g., SNOT-22) for grading the evidence.Results arepresented in an optimal format to improve communication to healthcare professionals,patients, regulatory and other stakeholders.

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This SR also has limitations. Only studies published in Englishwere included. However, the studies included in previous systematic reviews were hand-searched and additional studies wereadded through the GDG, which mitigated the possibility of missing studies. Although observational studies were not included per protocol, a pragmatic search of the literature was conducted instead and did not identify any relevant data. One ongoing trial (NCT04362501) looking at several potential disease endotypesmight be useful in the future to support our findings. Other limitations derive from the definition of the need for surgery and the ability to get surgery.A '*de novo*' economic analysis was not conducted. Instead, a rigorous and explicit critical appraisal and transferability assessment of cost-effectiveness existing data was performed.

Implications for practice and research

Dupilumab showed a promising impact on the need for rescue nasal polyp surgery, use of OCS,while improving quality of life and the sense of smell, with a good safety profile. However, as the results of the cost-effectiveness analysisare unclear, patients' values and preferenceswill haveto drive recommendations. Omalizumab showed also a good effect, but probably with increased treatment related AEs, which might raise a concern from the patients' perspective. Coupled with the high cost of biologicals, their use may need to be limited to particular relevant circumstances, for example for uncontrolled CRS patients. Therefore, after balancing the benefits and harms for dupilumab and omalizumabwhileconsidering the lack of cost-effectiveness data together with patient's values and preferences, panels are more likely to formulate conditional rather than strongrecommendations.

The evidence is very uncertain for the efficacy and safety of reslizumaband mepolizumab. Although mepolizumab showed a benefit in decreasing the need for surgery and improving quality of life, the quality of the evidence is low to very low. Large and rigorously conducted clinical trials, as well as real-life studies, are therefore needed.

Conflict of Interest Statement

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Table 1: PICO question and prioritisation of outcomes for the SR

P (population)	Patients aged 12 years or older with NPs (diagnosed by CT and/or endoscopy) and chronic symptoms of sinusitis persistent under treatment with intranasal corticosteroids
I (intervention)	Benralizumab, Dupilumab, Omalizumab, Mepolizumab, Reslizumab
C (comparison)	Standard of care
O (outcome)	**Critical**: Recurrence of nasal polyps, need for surgery or OCS, safety* (score 7-9) **Important:** Rescue medication use, Topical steroid, Quality of Life, Smell (score 4-6) **Low importance:** Nasal polyp score, CT score, symptom scores (score 1-3)

*Only treatment related adverse events (TAE) and treatment related severe adverse events were considered for the SR.

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Table 2. Characteristics and summary of results of the included studies for the evaluation of dupilumab efficacy, safety and economic impact

Studies evaluating clinical efficacy						
Author, Year, trial number, and name	**Study design (Number of subjects included)**	**Age (years) (intervention versus comparator)**	**Population**	**Intervention**	**Comparator**	**Follow up**
Dupilumab						
Bachert 2019 NCT02912468 LIBERTY NP SINU-24	Multicentre RCT (N=276, 2 arms)	Mean (SD) 50 (41-60) vs. 52 (39-61)	18 years or older with bilateral CRSwNP and symptoms despite intranasal corticosteroid use, receiving systemic corticosteroids in the preceding 2 years, or having had sinonasal surgery.	Dupilumab 300 mg (q2w), 24 weeks	matching placebo	24weeks
Bachert 2019 NCT02898454 LIBERTY NP SINU-52	Multicentre RCT (N=448, 3 arms)	Mean (SD) 53 (44-61) vs. 53 (42-63)		Arm1: Dupilumab 300 mg (q2w), 52 weeks; Arm2: Dupilumab 300 mg q2w (24 weeks) + 300 mg q4w (42 weeks)	matching placebo	52 weeks
Omalizumab						
Gevaert 2020 NCT03280550 POLYP 1	Multicentre RCT (N=138, 2 arms)	Mean (SD) 52.2 (11.6) vs. 50.0 (14.5)	Patients aged 18-75 years with CRSwNP with inadequate response to intranasal corticosteroids and weight and serum IgE level permitting omalizumab dosing.	Dosing of 75 to 600 mg by S.C., q2w/q4w, depending on the pretreatment serum total IgE level and body weight.	Standard of care	24 weeks
Gevaert 2020 NCT03280537 POLYP 2	Multicentre RCT (N=127, 2 arms)	Mean (SD) 51.0 (12.0) vs. 49.0 (11.9)			Standard of care	24 weeks
Gevaert 2012 (No registration)	Multicentre RCT (N=24, 2 arms)	Median (IQR) 50 (44-56) vs. 45 (42-54)	18 years or older with allergic and non-allergic CRSwNP and comorbid asthma	Omalizumab dose (mg) based on total serum IgE levels and body weight, SC.	placebo	20 weeks

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				(q2w/q4w)		
Pinto 2010 (NCT00117611)	Single centre RCT (N: 14, 2 arms)	Mean (SD) 43.1 ± 9.8 vs. 48.6 ± 9.1	Patients with 18 - 75 years with CRSwNP (symptoms >12weeks, serum total IgE between 30 - 700 IU/ml)	Omalizumab 0.016 mg/kg per IU total serum IgE/m), SC. (q4w)	placebo	24 weeks
Mepolizumab						
Gevaert 2011	Single centre RCT (N=30, 2 arms)	Mean (SD) 50.05 (8.86) vs. 45.9 (11.43)	CRSwNP with severe nasal polyposis (grade 3 or 4 or recurrent after surgery) refractory to corticosteroid therapy	Mepolizumab: 750mg IV (q4w)	matching placebo	48weeks
Bachert 2017 NCT01362244	Multicentre RCT (N=155, 2 arms)	Mean (SD) 50 (10) vs. 51 (11)	Patients aged 18 to 70 years with recurrent bilateral nasal polyposis who required surgery according to the predefined criteria of endoscopic nasal polyp score of ≥3 in one nostril and a visual analogue scale (VAS) nasal symptom score >7	Mepolizumab 750mg IV. (q4w)	matching placebo	25 weeks
Reslizumab						
Gevaert 2006	Multicentre RCT (N=24, 3 arms)	Mean (Range) 48 (21-59) vs. 43.6 (22-63) (arm1) / 48.5 (18-57) (arm2)	Patients with massive bilateral nasal polyps (grade 3 or 4) or recurrent nasal polyps after surgery	Arm1: Reslizumab, 1mg/kg, over 30 minutes, IV., single dose Arm2: Reslizumab, 2mg/kg, over 30 minutes, IV., single dose	matching placebo	36weeks

Studies evaluating the economic evidence

Author, year	Design, Country	Intervention	Control	Time horizon, perspective	Difference in cost (year value)	Difference in outcome	ICER	Credibility (ISPOR-AMCP-NPC)	Transferability score	Source of funding

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Scangas 2020	Cost-utility Markov model (microsimulation), US	Lifetime (36 years)* dupilumab	ESS plus medical therapy	Lifetime, US health system perspective	485,983 $ (2014 USD)	-0.85 QALYs	Dominated by the ESS	Validation was not described	13/16	No sources of financial funding declared

ESS: endoscopic sinus surgery; ICER: Incremental cost-effectiveness ratio; IV: Intravenous; NCT: ClinicalTrials.gov identifier; q2w: every 2 weeks; qw: every week; QALY: Quality adjusted life years. SC.: subcutaneous; SD: Standard deviation; USD: US Dollars.

*Horizon time of 36 years under treatment according to life expectancy for the US.

Table 3. Summary of findings for Dupilumab compared to standard of care for CRSwNP (listed by outcome)

Dupilumab compared to Standard of care for adult Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Patient or population: Adults with uncontrolled Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Intervention: Dupilumab

Comparison: Standard of care

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard of care	Risk difference with Dupilumab
Rescue Nasal polyp surgery or OCS use Assessed with number of patients	724 (2 RCTs) [1] 24 weeks	⊕⊕⊕◯ MODERATE [a,b]	**RR 0.28** (0.20 to 0.39)	339 per 1,000	**244 fewer per 1,000** (271 fewer to 207 fewer)

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Dupilumab compared to Standard of care for adult Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Patient or population: Adults with uncontrolled Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Intervention: Dupilumab

Comparison: Standard of care

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard of care	Risk difference with Dupilumab
Safety: any treatment-related adverse events Assessed with number of patients	447 (2 RCTs) [1] 52 weeks	⊕⊕⊕◯ MODERATE [b,c,d]	**RR 0.95** (0.89 to 1.02)	907 per 1,000	**45 fewer per 1,000** (100 fewer to 18 more)
Safety: any serious treatment-related adverse events Assessed as number of patients who have undergone surgery	447 (2 RCTs) [1] 52 weeks	⊕⊕⊕◯ MODERATE [b,c,d]	**RR 0.61** (0.31 to 1.17)	100 per 1,000	**39 fewer per 1,000** (69 fewer to 17 more)
Smell Assessed with UPSIT score Range: 0 to 40	724 (2 RCTs) [1] 24 weeks	⊕⊕⊕⊕ HIGH [b]	-	-	MD +**10.54** (+9.24 to +11.84) [e]

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Dupilumab compared to Standard of care for adult Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Patient or population: Adults with uncontrolled Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Intervention: Dupilumab

Comparison: Standard of care

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard of care	Risk difference with Dupilumab
Quality of life Assessed with change in SNOT-22 score Range: 0 to 110	724 (2 RCTs) [1] 24 weeks	⊕⊕⊕⊕ HIGH [2,b,f]	-	-	MD -**19.14** (-22.8 to -15.47) [g]
Nasal polyp score Assessed with change from baseline Range: 0 to 8	724 (2 RCTs) [1] 24 weeks	⊕⊕⊕⊕ HIGH [b]	-	-	MD - **1.92** (-2.18 to - 1.65) [h]
Lund-Mackay CT score Assessed with change from baseline Range: 0 to 24	674 (2 RCTs) [1] 24 weeks	⊕⊕⊕⊕ HIGH [b]	-	-	MD - **6.26** (-8.53 to -3.99)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **CT:** computed tomography; **MD:** Mean difference; **RR:** Risk ratio; **SNOT-22**: sino-nasal outcome test 22; **UPSIT**: University of Pennsylvania smell identification test

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Dupilumab compared to Standard of care for adult Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Patient or population: Adults with uncontrolled Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Intervention: Dupilumab

Comparison: Standard of care

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard of care	Risk difference with Dupilumab

GRADE Working Group grades of evidence

High certainty: High confidence that the true effect lies close to that of the estimate of the effect

Moderate certainty: Moderately confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Limited confidence in the effect estimate : the true effect may be substantially different from the estimate of the effect

Very low certainty: Very limited confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Indirectness: the included trials reported a composite outcome (need for surgery or OCS), precluding from assessing each outcome individually.

b. Other considerations: The study included was funded by industry. The funder has participated in the whole process. No industry-independent observational or randomized studies were identified to compare the results. The GDG panel did not consider industry funded as a reson to downgrade the certainty of evidence.

c. SINUS-52 evaluated two arms with different length of intervention (one arm with q2w, 52 weeks; another arm with q2w (24 week) + q4w (28 weeks)).

d. The effect can be either beneficial or harmful.

e. The study included also evaluated smell at 24 weeks by another tool - loss of smell scale (MD - 1.5; 95%CI -1.19 to -0.91).

f. Minimal important difference for SNOTT-22 is 12 (2)

g. Evaluated at 52 weeks as well (MD - 20.96 lower; 95%CI -25.45 to -16.47).

h. Evaluated at 52 weeks as well (MD - 2.39; 95%CI -2,81 to -1.97).

References

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2. Phillips KM, Hoehle LP,Caradonna DS,Gray ST,Sedaghat AR.. Minimal clinically important difference for the 22-item Sinonasal Outcome Test in medically managed patients with chronic rhinosinusitis. Clin Otolaryngol.;2018.

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Table 4. Summary of findings of Omalizumab compared to standard of care for CRSwNP (listed by outcome)

Omalizumab compared to Placebo for Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Patient or population: Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Intervention: Omalizumab

Comparison: Placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard of care	Risk difference with Omalizumab
Reduction in need for surgery Assessed as number of patients who have undergone surgery	256 (2 RCTs) [1] 24 weeks	⊕⊕⊕⊕ HIGH [b]	**RR 0.85** (0.78 to 0.92) [c]	969 per 1,000	**145 fewer per 1,000** (213 fewer to 77 fewer) [c]
Safety: any treatment related adverse events Assessed with number of patients	265 (2 RCTs) [1] 24 weeks	⊕⊕⊕◯ MODERATE [a,b]	**RR 1.73** (0.60 to 5.03)	38 per 1,000	**28 more per 1,000** (15 fewer to 155 more)
Quality of life Assessed with SNOT-22 score Range: 0 to 110	265 (2 RCTs) [1] 24 weeks	⊕⊕⊕⊕ HIGH [b,d]	-	-	MD -**15.65** (-16.16 to- 15.13) [e]

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Omalizumab compared to Placebo for Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Patient or population: Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Intervention: Omalizumab

Comparison: Placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard of care	Risk difference with Omalizumab
Smell Assessed with UPSIT score Range: 0 to 40	265 (2 RCTs) [1] 24 weeks	⊕⊕⊕⊕ HIGH [b]	-	-	MD + **3.84** (+3.64 to +4.04) [i]
Smell Assessed with loss of sense of smell from nasal symptoms score Range 0 to 3	289 (3 RCTs) [1,2] 16 - 24 weeks	⊕⊕⊕◯ MODERATE [b,f,g,j]	-	-	MD -**0.48 score** (-0.62 to -0.34) [h]
Lund Mackay CT score Assessed with change from baseline Range 0 to 24	23 (1 RCT) [2] 16 weeks	⊕◯◯◯ VERY LOW [a,b,f,g]	-	-	MD -**4.5** (-10.47 to +1.47) [l]

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Omalizumab compared to Placebo for Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Patient or population: Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Intervention: Omalizumab

Comparison: Placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard of care	Risk difference with Omalizumab
Nasal polyp score Assessed with total nasal endoscopic polyp scorce (TPS) change from baseline Range 0 to 8	289 (3 RCTs) [1,2] 16 - 24 weeks	⊕⊕⊕◯ MODERATE [b,f,g,k]	-	-	MD -**1.42** (-2.53 to -0.32) [k]
Use of rescue medication Assessed with use of systemic steroid and antibiotic courses	258 (2 RCTs) [1] 24 weeks	⊕⊕⊕◯ MODERATE [a,b]	**RR 0.38** (0.10 to 1.38)	62 per 1,000	**38 fewer per 1,000** (56 fewer to 24 more) [l]
Total nasal symptom score Assessed with change from baseline Range 0 to 12	265 (2 RCTs) [1] 24 weeks	⊕⊕⊕⊕ HIGH [b]	-	-	MD -**2** (-2.08 to -1.92) [m]

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Omalizumab compared to Placebo for Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Patient or population: Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Intervention: Omalizumab

Comparison: Placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard of care	Risk difference with Omalizumab

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **CT:** computed tomography; **MD:** Mean difference; **RR:** Risk ratio; **SNOT-22**: sino-nasal outcome test 22; **UPSIT**: University of Pennsylvania smell identification test

GRADE Working Group grades of evidence

High certainty: High confidence that the true effect lies close to that of the estimate of the effect

Moderate certainty: Moderately confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Limited confidence in the effect estimate : the true effect may be substantially different from the estimate of the effect

Very low certainty: Very limited confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded one level for imprecision due to very small number of events, thus the effect can be either benefit or harmful.

b. Other considerations: Included studies were all funded by a same industry, and all showed positive results. No industry-independent observational or randomized studies were identified to contrast the results. The GDG panel did not consider industry funded as a reason to downgrade the certainty of evidence.

c. The RCTs included originally reported the ORs of achieving a reduced need for further surgery. To make the results comparable across biologicals, raw data were used to estimate the RR for the outcome of need for surgery.

d. For SNOT-22 a clinically important improvement is a change of at 12 (4)

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e. Pinto reported that there was no difference in the median change for the SNOT-22 score when comparing omalizumab (-1.05) versus placebo (-0.20) (P < 0.78) (3). Gevaert reported that sleep (p=0.03) and general symptoms (p =0.01) significantly improved in the omalizumab group, while no significant changes were seen in the placebo group (2)

f. One study has serious risk of bias due to potential imbalance between arms at baseline, given the small number of participants.

g. One study has serious indirectness due to the small number of doses used (small number of doses and short duration of follow-up) (2). The weight of this study in the results of the SR is 10.6%.

h. Pinto2010 reported a non-statistically significant difference for the median change of UPSIT score for omalizumab=3 versus placebo=4 (p=0.31) (3).

i. Probably not serious inconsistency (I1=95%, the direction of effects is consistent).

j. Pinto2010 reported a non-statistically significant difference for the median change of the percentage of sinus CT opacification (omalizumab=11.9%, placebo=5.9%; p<0.391) (3)

k. Pinto2010 reported a non-statistically significant difference for the median change of the nasal endoscopy score (omalizumab=0, placebo=-0.5; p<0.58) (3)

l. Pinto 2010 reported a statistically significant difference for the rescue OSC use (omalizumab=0, placebo=1; p<0.043) and a non-statistically significant difference for the rescue antibiotic used (omalizumab=0, placebo=1; p<0.32). (3)

m. Pinto2010 reported no statistically significant differences (p < 0.21) when comparing the medians of the total nasal symptom score for omalizumab (-1) versus placebo (0). (3)

References

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2. 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; 2012.

3. Pinto JM, Mehta N,DeTineo M,Wang J,Baroody FM,Naclerio RM. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. Rhinology; 2010.

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Table 5. Summary of findings of Mepolizumab compared to standard of care for CRSwNP (listed by outcome)

Mepolizumab compared to Placebo for Chronic Rhinosinusitis with Nasal Polyps (CRwNP)

Patient or population: [Chronic Rhinosinusitis with Nasal Polyps (CRwNP)]

Intervention: Mepolizumab

Comparison: Placebo

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Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with [Placebo]	Risk difference with [Mepolizumab]
Need for surgery Assessed with patient who were requiring surgery for polyposis	135 (2 RCT) [1] 25 – 48 weeks	⊕⊕◯◯ LOW [a,b]	**RR 0.78** (0.64 to 0.94) [c]	803 per 1,000	**177 fewer per 1,000** (289 fewer to 48 fewer)
Safety: treatment related adverse events	105 (1 RCT) [1] 25 weeks	⊕⊕◯◯ LOW [a,b]	**RR 1.64** (0.41 to 6.50)	58 per 1,000	**37 more per 1,000** (34 fewer to 317 more)
Quality of life Assessed with SNOT-22 score Range: 0 to 110	105 (1 RCT) [1] 25 weeks	⊕⊕◯◯ LOW [2,a,b,d]	-	-	MD -**13.3** (-23.93 to -2.67) [d]
Smell Assessed with Sniffin' Sticks Screening-12 test Range 0 to 12	105 (1 RCT) [1] 25 weeks	⊕⊕◯◯ LOW [a,b,f]	-	-	MD **0.7 Score higher** (0.48 lower to 1.88 higher)
Nasal polyp score Assessed with change from baseline Range 0 to 8	137 (2 RCTs) [1,2] 8 - 25 weeks	⊕◯◯◯ VERY LOW [a,b]	-	-	MD **1.23 score lower** (1.79 lower to 0.68 lower)

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Mepolizumab compared to Placebo for Chronic Rhinosinusitis with Nasal Polyps (CRwNP)

Patient or population: [Chronic Rhinosinusitis with Nasal Polyps (CRwNP)]

Intervention: Mepolizumab

Comparison: Placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with [Placebo]	Risk difference with [Mepolizumab]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: High confidence that the true effect lies close to that of the estimate of the effect

Moderate certainty: Moderately confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Limited confidence in the effect estimate : the true effect may be substantially different from the estimate of the effect

Very low certainty: Very limited confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded one level due to potential imbalance between arms at baseline, given small number of participants, and high risk of attrition bias.

b. Downgraded one level due to very small sample size and/or number of events.

c. The RCTs included originally reported the ORs of achieving a reduced need for further surgery. To make the results comparable across biologicals, raw data were used to estimate the RR for the outcome of need for surgery

d. The effect may be either harmful or beneficial (minimal important difference ≥ 12) (3).

e. Bachert2017 reported no difference in the EQ-5D Index score (0.00, 95% CI -0.06 to 0.07) and an increased difference with EQ-5D VAS score (5.7, 95%CI -1.3 to 12.7) (1)

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f. The effect may be either harmful or beneficial

References

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2. . Gevaert 2011, et.al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol; 2011
3. Phillips KM, et.al. Minimal clinically important difference for the 22-item Sinonasal Outcome Test in medically managed patients with chronic rhinosinusitis. Clin Otolaryngol; 2018.

Table 6. Summary of findings of Reslizumab compared to standard of care for CRSwNP (listed by outcome)

Reslizumab compared to Placebo for Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Patient or population: Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Intervention: Reslizumab

Comparison: Placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Reslizumab
Need for Surgery Assessed with number of patients who have undergone surgery	16 (1 RCT) [1] 2 - 11 weeks	⊕◯◯◯ VERY LOW a,b,c,d,e	**RR 0.20** (0.01 to 3.61)	250 per 1,000	**200 fewer per 1,000** (248 fewer to 653 more)

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Reslizumab compared to Placebo for Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Patient or population: Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Intervention: Reslizumab

Comparison: Placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Reslizumab
Safety: AEs Assessed with number of patients Range 0 to 8	(1 RCT) [1] 36 weeks	⊕◯◯◯ VERY LOW a,b,c,e	No-drug related adverse data was reported. According to the authors administration of a single dose of reslizumab was well tolerated, and no clinically meaningful changes were observed in laboratory parameters, vital signs, or physical examinations in any of the treatment groups.		
Rescue medication used Systemic and nasal corticosteroids	(1 RCT) [1] 12 - 36 weeks	⊕◯◯◯ VERY LOW a,b,c,e	No differences in use of systemic nasal corticosteroids were observed (from 12 to 36 weeks).		

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Reslizumab compared to Placebo for Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Patient or population: Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Intervention: Reslizumab

Comparison: Placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Reslizumab
Nasal polyp score Assessed with change from baseline	(1 RCT) [1] 8 weeks	⊕◯◯◯ VERY LOW a,b,c,d,e	Gevaert 2006 reported the median of change from baseline (Reslizumab 1mg/kg =-1.0; Placebo=0; Reslizumab 3 mg/kg =0.5; Placebo = 0), “significant” and non”significant” respectively.		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: High confidence that the true effect lies close to that of the estimate of the effect

Moderate certainty: Moderately confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Limited confidence in the effect estimate : the true effect may be substantially different from the estimate of the effect

Very low certainty: Very limited confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded due to small number of participants, potential imbalance between arms at baseline, and high risk of attrition and reporting bias

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b. Only a single dose was used.

c. Downgraded by two levels due to very small sample size and number of events.

d. The effect may both be harmful or beneficial.

e. Other considerations: Included study was funded by industry. No industry-independent observational or randomized studies were identified to contrast the results. The GDG panel did not consider industry funded was an issue to downgrade the certainty of evidence.

References

1. Gevaert P, et.al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. J Allergy Clin Immunol; 2006.

Table 7. Summary of available evidence on economic impact.

7.B Cost-utility

Comparison: Dupilumab vs. endoscopic sinus surgery (ESS) plus postoperative medical therapy

Quality assessment							Summary of resources and costs			Quality
Nº. of studies	**Study design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Incremental cost per patient***	**Incremental effect per patient***	**ICER**	
ICER per QALY										
1[1]	Cost-utility, Markov model	serious[a,b]	Not serious	serious[c,d]	not serious	not serious	From 50,437$ to 536,420 $ (lifetime horizon)	From 9.80 to 8.95 QALYs (lifetime horizon)	Dominated by the ESS	⊕⊕◯◯ LOW

EES: endoscpoc nasal surgery; **ICER:** Incremental cost-effectiveness ratio. **QALY:** Quality adjusted life years. **$:** US Dollar.

Explanations

a. The study did not describe the validation/calibration procedures during Markov model development

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b. Input parameters that informed the model were of moderate certainty of evidence

c. The studies were performed in the USA. The results may not be applicable to other countries.

d. Some patients might have benefit from treatment of concomitant asthma or might not willing to undergo surgical procedures. These scenarios were not included in the model.

References

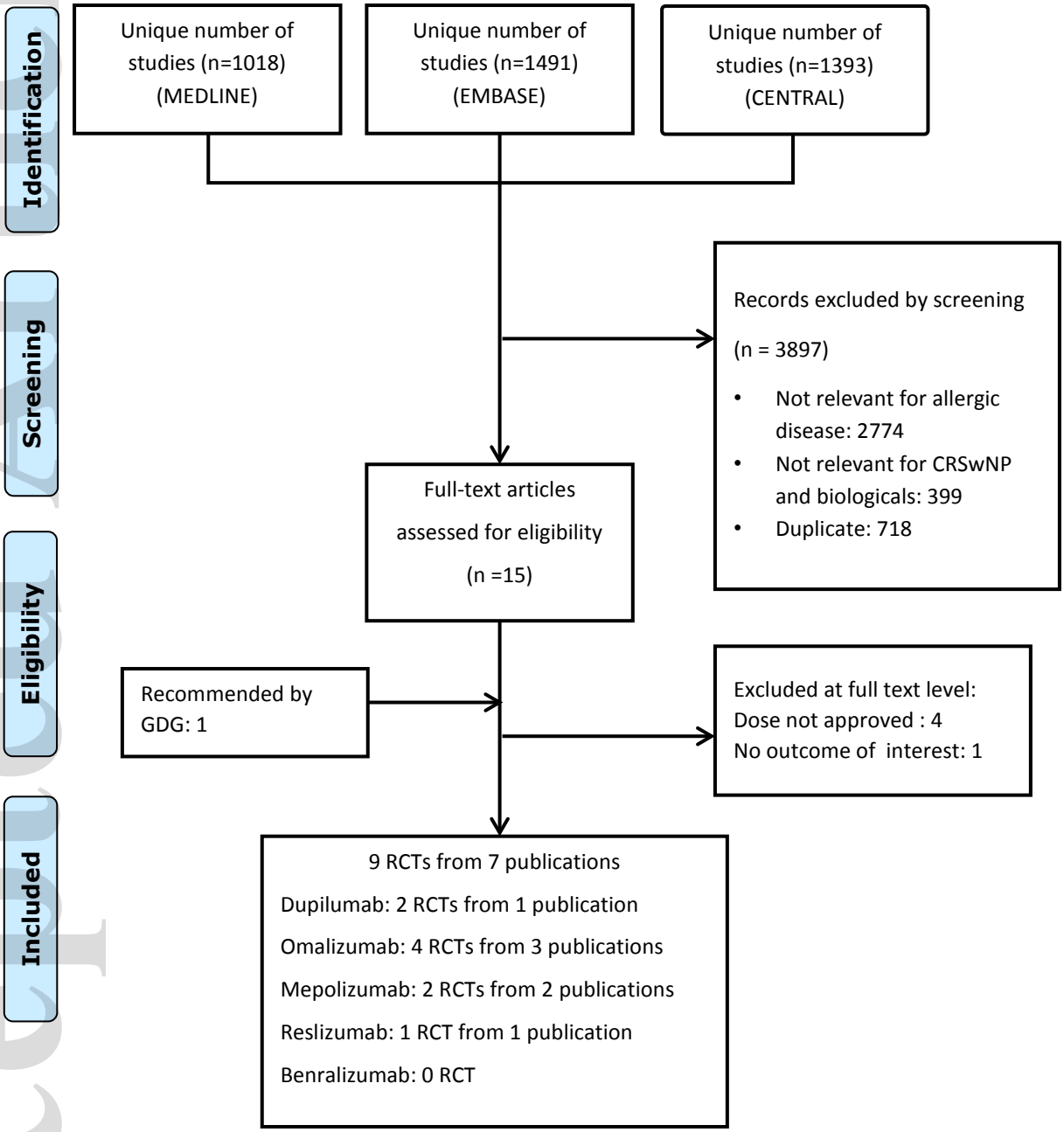
1. Scangas GA, Wu AW, Ting JY, Metson R, Walgama E, Shrime MG, Higgins TS. Cost Utility Analysis of Dupilumab Versus Endoscopic Sinus Surgery for Chronic Rhinosinusitis With Nasal Polyps. Laryngoscope. 2020 Apr 3. Epub ahead of print.

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Figure 1. Study flowchart

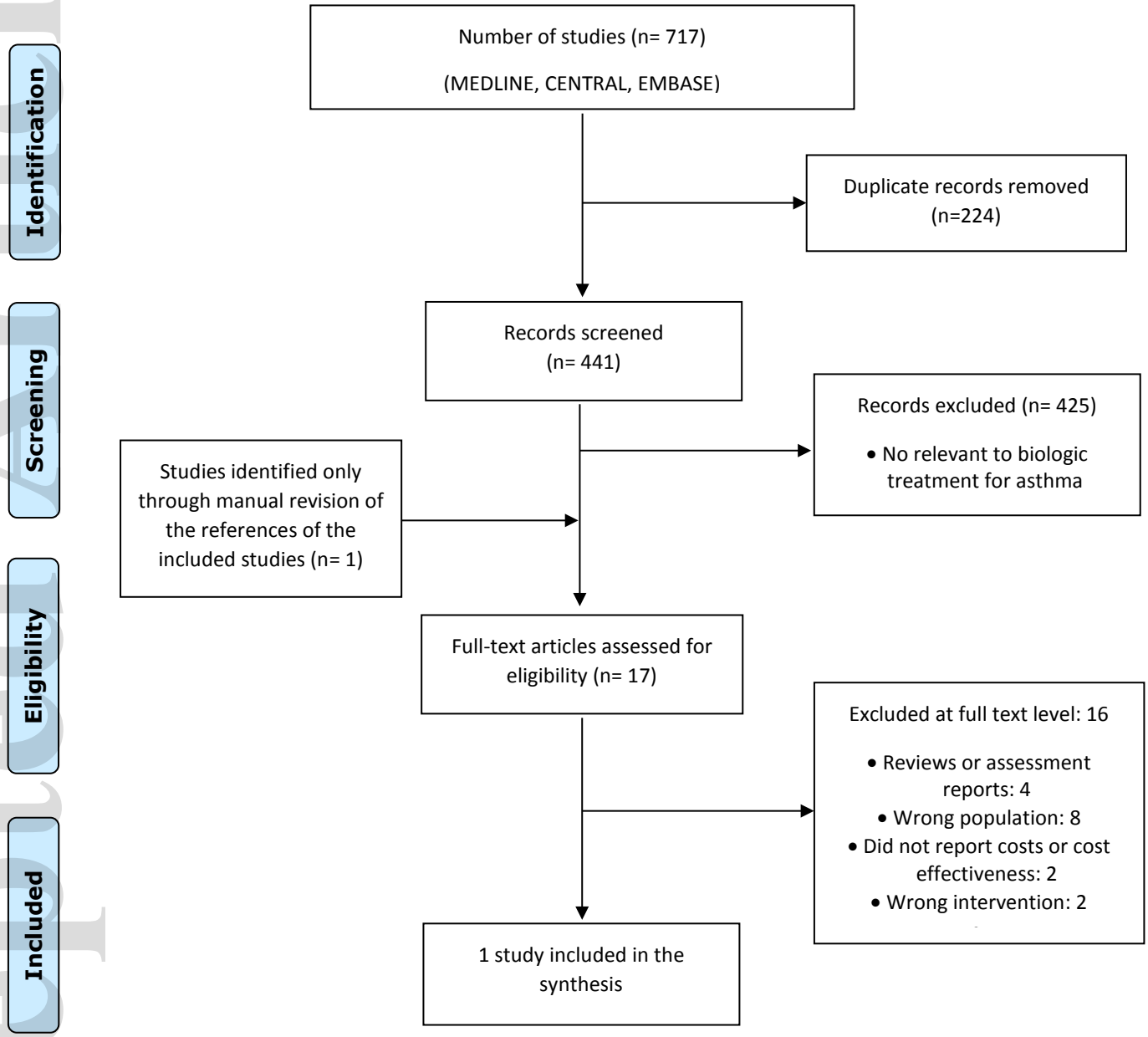
A. Studies evaluating the clinical efficacy



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B. Studies evaluating the economic impact of dupilumab



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Table S1: Search strategy for the efficacy and safety

CLINICAL QUESTION Is the treatment with biological efficacious and safe for patients with CRSwNP?	
MEDLINE PubMed 01/02/2020	#12 Add Search #5 OR #8 OR #11 #11 Add Search #9 AND #10 #10 Add Search "Vaccines"[Mesh] OR vaccin*[ti] #9 Add Search #6 NOT #8 #8 Add Search #6 AND #7 #7 Add Search ("clinical trials as topic"[mesh: noexp] OR "randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[ti]) NOT ("animals"[Mesh] NOT "humans"[Mesh]) #6 Add Search #3 NOT #5 #5 Add Search #3 AND #4 #4 Add Search systematic[sb] #3 Add Search #1 AND #2 #2 Add Search "Antibodies, Monoclonal, Humanized"[Mesh] OR "Omalizumab"[Mesh] OR "mepolizumab"[Supplementary Concept] OR "reslizumab"[Supplementary Concept] OR "benralizumab"[Supplementary Concept] OR "SAR231893"[Supplementary Concept] OR "tezepelumab"[Supplementary Concept] OR "lebrikizumab"[Supplementary Concept] OR "tralokinumab"[Supplementary Concept] OR "brodalumab"[Supplementary Concept] OR "ligelizumab"[Supplementary Concept] OR mepolizumab [tiab] OR reslizumab[tiab] OR benralizumab[tiab] OR dupilumab[tiab] OR omalizumab[tiab] OR lebrikizumab[tiab] OR tralokinumab[tiab] OR tezepelumab[tiab] OR brodalumab[tiab] OR ligelizumab[tiab] #1 Add Search "Hypersensitivity, Immediate"[Mesh] OR "Asthma"[Mesh] OR "Rhinitis, Allergic"[Mesh] OR "Rhinitis"[Majr] OR "Sinusitis"[Mesh] OR "Nasal Polyps"[Majr] OR "Dermatitis, Atopic"[Mesh] OR "Dermatitis"[Majr] OR "Urticaria"[Mesh] OR "Eosinophilic Esophagitis"[Mesh] OR "Food Hypersensitivity"[Mesh] OR allergy[tiab] OR allergic[tiab] OR asthma*[tiab] OR atopic dermatitis[tiab] OR dermatitis[ti] OR urticaria[tiab] OR erythema[ti] OR rhinosinusitis[tiab] OR allergic rhinitis[tiab] OR (food[ti] AND allerg*[ti]) OR (food[ti] AND react*[ti]) OR food allerg*[tiab] OR food reaction*[tiab] OR eosinophilic esophagitis[tiab] OR esophagitis[ti] OR eosinophil*[ti]
EMBASE Ovid Embase <1974 to 2019 January 29> 01/02/2020	**Ovid Embase** 1 exp asthma/ 2 exp allergic rhinitis/ 3 *rhinitis/ 4 exp sinusitis/ 5 *nose polyp/ 6 exp atopic dermatitis/ 7 *dermatitis/ 8 exp urticaria/ 9 exp eosinophilic esophagitis/ 10 exp food allergy/ 11 allergy.ti,ab. 12 allergic.ti,ab. 13 asthma*.ti,ab. 14 atopic dermatitis.ti,ab. 15 dermatitis.ti. 16 urticaria.ti. 17 erythema.ti. 18 rhinosinusitis.ti. 19 allergic rhinitis.ti,ab. 20 (food adj5 (allerg* or react*)).ti,ab. 21 eosinophilic esophagitis.ti,ab. 22 esophagitis.ti. 23 eosinophil*.ti. 24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

	25 mepolizumab.ti,ab. 26 reslizumab.ti,ab. 27 benralizumab.ti,ab. 28 dupilumab.ti,ab. 29 omalizumab.ti,ab. 30 lebrikizumab.ti,ab. 31 tralokinumab.ti,ab. 32 tezepelumab.ti,ab. 33 brodalumab.ti,ab. 34 ligelizumab.ti,ab. 35 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 36 limit 35 to "systematic review" 37 35 not 36 38 limit 37 to "therapy (best balance of sensitivity and specificity)"
The Cochrane Library 01/02/2020 Cochrane Central	#1 MeSH descriptor: [Asthma] explode all trees #2 MeSH descriptor: [Rhinitis, Allergic] explode all trees #3 MeSH descriptor: [Rhinitis] explode all trees #4 MeSH descriptor: [Sinusitis] explode all trees #5 MeSH descriptor: [Nasal Polyps] explode all trees #6 MeSH descriptor: [Dermatitis, Atopic] explode all trees #7 MeSH descriptor: [Dermatitis] explode all trees #8 MeSH descriptor: [Urticaria] explode all trees #9 MeSH descriptor: [Eosinophilic Esophagitis] explode all trees #10 MeSH descriptor: [Food Hypersensitivity] explode all trees #11 allerg*:ti,ab #12 asthma*:ti,ab #13 (atopic NEXT dermatitis):ti,ab #14 dermatitis:ti,ab #15 urticaria:ti,ab #16 erythema:ti,ab #17 rhinosinusitis:ti,ab #18 (allergic NEXT rhinitis):ti,ab #19 (food NEAR5 react*):ti,ab #20 (eosinophilic NEXT esophagitis):ti,ab #21 esophagitis:ti #22 eosinophil*:ti #23 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 #24 MeSH descriptor: [Antibodies, Monoclonal, Humanized] explode all trees #25 mepolizumab:ti,ab #26 reslizumab:ti,ab #27 benralizumab:ti,ab #28 dupilumab:ti,ab #29 omalizumab:ti,ab #30 lebrikizumab:ti,ab #31 tralokinumab:ti,ab #32 tezepelumab:ti,ab #33 brodalumab:ti,ab #34 ligelizumab:ti,ab #35 #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 #36 #23 AND #25

Table S2: Search strategy for the economic evidence

CLINICAL QUESTIONS Is the treatment with biologicals cost-effective for patients with chronic rhinosinusitis with nasal polyps?	
MEDLINE PubMed 22/02/2020	#1 Add Search ((((((((((((((((((((((((((“Hypersensitivity, Immediate”[Mesh]) OR “Asthma”[Mesh]) OR “Rhinitis, Allergic”[Mesh]) OR “Rhinitis”[Majr]) OR “Sinusitis”[Mesh]) OR “Nasal Polyps”[Majr]) OR “Dermatitis, Atopic”[Mesh]) OR “Dermatitis”[Majr]) OR “Urticaria”[Mesh]) OR “Eosinophilic Esophagitis”[Mesh]) OR “Food Hypersensitivity”[Mesh]) OR allergy[tiab]) OR allergic[tiab]) OR asthma*[tiab]) OR atopic dermatitis[tiab]) OR dermatitis[ti]) OR urticaria[tiab]) OR erythema[ti]) OR rhinosinusitis[tiab]) OR allergic rhinitis[tiab])) OR ((food[ti]) AND AND allerg*[ti])) OR ((food[ti]) AND react*[ti])) OR food allerg*[tiab]) OR food reaction*[tiab]) OR eosinophilic esophagitis[tiab]) OR esophagitis[ti]) OR OR eosinophil*[ti] 465782 #2 Add Search (“Antibodies, Monoclonal, Humanized”[Mesh] OR “Omalizumab”[Mesh] OR "mepolizumab"[Supplementary Concept] OR "reslizumab"[Supplementary Concept] OR “benralizumab”[Supplementary Concept] OR “SAR231893”[Supplementary Concept] OR "tezepelumab"[Supplementary Concept] OR “lebrikizumab”[Supplementary Concept] OR “tralokinumab”[Supplementary Concept] OR “brodalumab”[Supplementary Concept] OR “ligelizumab”[Supplementary Concept] OR mepolizumab [tiab] OR reslizumab[tiab] OR benralizumab[tiab] OR dupilumab[tiab] OR omalizumab[tiab] OR lebrikizumab[tiab] OR tralokinumab[tiab] OR tezepelumab[tiab] OR brodalumab[tiab] OR ligelizumab[tiab]) 58423 #3 Add Search #1 AND #2 4362 #4 Add Search ((((((((((“Costs and Cost Analysis”[Mesh])) OR “Health Care Costs”[Mesh]) OR economic*[tiab]) OR ((cost*[ti] OR cost[tiab] OR costs[tiab] OR cost effect*[tiab] OR cost utility*[tiab]))) OR ((price[tiab] OR prices[tiab] OR pricing[tiab]))) OR pharmacoeconomic*[tiab]) OR budget*[tiab]))) 882360 #5 Add Search #3 AND #4 295
EMBASE Ovid Embase <1974 to 2019 January 29> 17/04/2020	**Ovid Embase** 1 asthma/exp (267,928) 2 allergic rhinitis/exp (47,520) 3 rhinitis/mj (6,696) 4 sinusitis/exp (45,426) 5 nose polyp/exp (11,691) 6 allergy.ti,ab (106,574) 7 allergic.ti,ab (163,997) 8 asthma:ti,ab (216,149) 9 rhinosinusitis:ti,ab (11,425) 10 rhinitis:ti,ab (40,174) 11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (508,141) 12 mepolizumab:ti,ab (1,068) 13 reslizumab:ti,ab (343) 14 benralizumab:ti,ab (392) 15 dupilumab:ti,ab (957) 16 omalizumab:ti,ab (4,629) 17 lebrikizumab:ti,ab (119) 18 tralokinumab:ti,ab (90) 19 tezepelumab:ti,ab (32) 20 brodalumab:ti,ab (413) 21 ligelizumab:ti,ab (34) 22 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (7,195) 23 economic evaluation/exp (301,725) 24 price:ti.ab (38,487) 25 pricing:ti.ab (8,111) 26 cost: ti.ab (563,322) 27 pharmaeconomics:ti.ab (3,451)

	28 budget:ti.ab (27,247) 29 23 or 24 or 25 or 26 or 27 or 28 (741,021) 30 11 or 22 or 29 (341)
The Cochrane Library 22/02/2020 Cochrane Central Register of Controlled Trials Issue 2 of 12, February 2020	#1 MeSH descriptor: [Asthma] explode all trees 11554 #2 MeSH descriptor: [Rhinitis, Allergic] explode all trees 3020 #3 MeSH descriptor: [Rhinitis] explode all trees 3835 #4 MeSH descriptor: [Sinusitis] explode all trees 987 #5 MeSH descriptor: [Nasal Polyps] explode all trees 356 #6 MeSH descriptor: [Dermatitis, Atopic] explode all trees 1719 #7 MeSH descriptor: [Dermatitis] explode all trees 3979 #8 MeSH descriptor: [Urticaria] explode all trees 761 #9 MeSH descriptor: [Eosinophilic Esophagitis] explode all trees 79 #10 MeSH descriptor: [Food Hypersensitivity] explode all trees 922 #11 allerg*:ti,ab 24298 #12 asthma*:ti,ab 31703 #13 (atopic NEXT dermatitis):ti,ab 3685 #14 dermatitis:ti,ab 6070 #15 urticaria:ti,ab 1699 #16 erythema:ti,ab 5396 #17 rhinosinusitis:ti,ab 1241 #18 (allergic NEXT rhinitis):ti,ab 6114 #19 (food NEAR5 react*):ti,ab 107134 #20 (eosinophilic NEXT esophagitis):ti,ab 243 #21 esophagitis:ti 1186 #22 eosinophil*:ti 1305 #23 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 162656 #24 MeSH descriptor: [Antibodies, Monoclonal, Humanized] explode all trees 8172 #25 mepolizumab:ti,ab 266 #26 reslizumab:ti,ab 111 #27 benralizumab:ti,ab 162 #28 dupilumab:ti,ab 300 #29 omalizumab:ti,ab 860 #30 lebrikizumab:ti,ab 74 #31 tralokinumab:ti,ab 75 #32 tezepelumab:ti,ab 23 #33 brodalumab:ti,ab 131 #34 ligelizumab:ti,ab 26 #35 #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 9755 #36 #23 AND #35 2407 #37 MeSH descriptor: [Costs and Cost Analysis] explode all trees 10196 #38 MeSH descriptor: [Health Care Costs] explode all trees 3364 #39 economic*:ti,ab 18053 #40 cost*:ti 12873 #41 cost:ti,ab 50265 #42 costs:ti,ab 27945 #43 cost effect*:ti,ab 44927 #44 cost utility:ti,ab 3111 #45 #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 76856 #46 #36 AND #45 81

Table S3: Excluded studies (efficacy and safety)

Excluded for efficacy and safety evidences			
N	**Author/Year**	**Design**	**Reasons for exclusion**
1	Bachert2016	RCT	Dose not approved by EMA/FDA
2	Bachert2019a	Pooled analysis of RCT	Dose not approved by EMA/FDA
3	Bachert2020	Pooled analysis of RCT	Dose not approved by EMA/FDA
4	Jonstam2018	Pooled analysis of RCT	Dose not approved by EMA/FDA
5	NCT01066104	Unpublished RCT	Dose not approved by EMA/FDA

Table S4: Excluded studies (economic evidence)

No.	Author	Reason for exclusion
1	Boyle 2019	Review used as source of primary studies
2	Codispoti 2019	Review used as source of primary studies
3	Ferguson 2009	Review used as source of primary studies
4	Klimek 2016	Did not evaluate patients with chronic rhinosinusitis with nasal polyps
5	Menzella 2015	Did not evaluate patients with chronic rhinosinusitis with
6	Morjaria 2007	Did not evaluate patients with chronic rhinosinusitis with nasal polyps
7	Morjaria 2009	Did not evaluate patients with chronic rhinosinusitis with nasal polyps
8	Mostafa 2019	Did not report resources, costs, or cost-effectiveness results
9	Nasta 2019	Review used as source of primary studies
10	Okayama 2020	Did not evaluate patients with chronic rhinosinusitis with nasal polyps
11	Stock 2007	Did not evaluate patients with chronic rhinosinusitis with nasal polyps
12	Vashisht 2013	Did not evaluate patients with chronic rhinosinusitis with nasal polyps
13	Wagenmann 2017	Did not report resources, costs, or cost-effectiveness results
14.	Hunter 2018	Evaluated only a subgroup of patients with CRS that received endoscopic sinus surgery

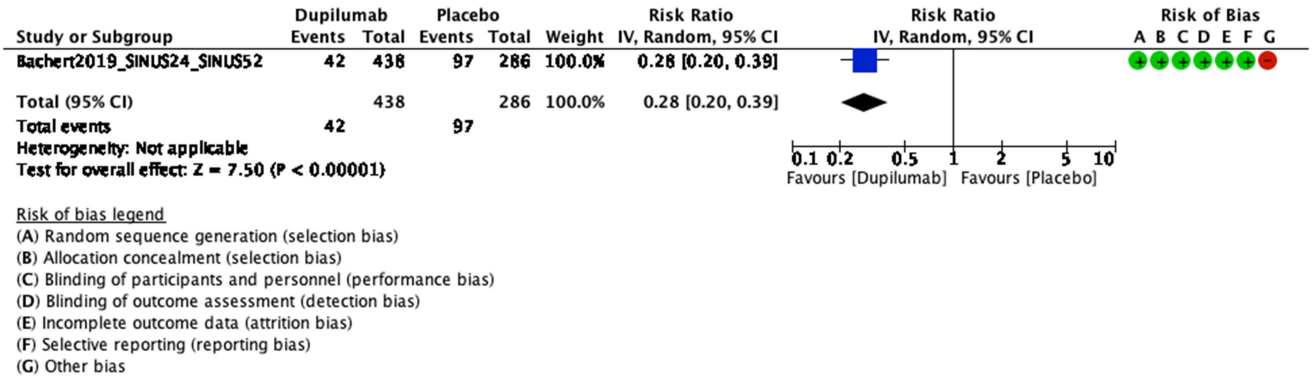
15.	Scangas	Cost effectiveness of sinus surgery in patients with CRSwNP and asthma

References

1. 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(5):469-79.
2. Bachert C, Hellings PW, Mullol J, Hamilos DL, Gevaert P, Naclerio RM, et.al. Dupilumab improves health-related quality of life in patients with chronic rhinosinusitis with nasal polyposis. Allergy. 2020;75(1):148-157.
3. Bachert C, Zinreich SJ, Hellings PW, Mullol J, Hamilos DL, Gevaert P, et.al. Dupilumab reduces opacification across all sinuses and related symptoms in patients with CRSwNP. Rhinology. 2020 Feb 1;58(1):10-17.
4. Jonstam K, Swanson BN, Mannent LP, Cardell LO, Tian N, Wang Y, et.al. Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis. Allergy. 2019 Apr;74(4):743-752.
5. NCT01066104. Subcutaneous Omalizumab for Treatment of Chronic Rhinosinusitis With Nasal Polyposis.

Meta-analysis of the Efficacy of dupilumab for adult CRSwNP patients

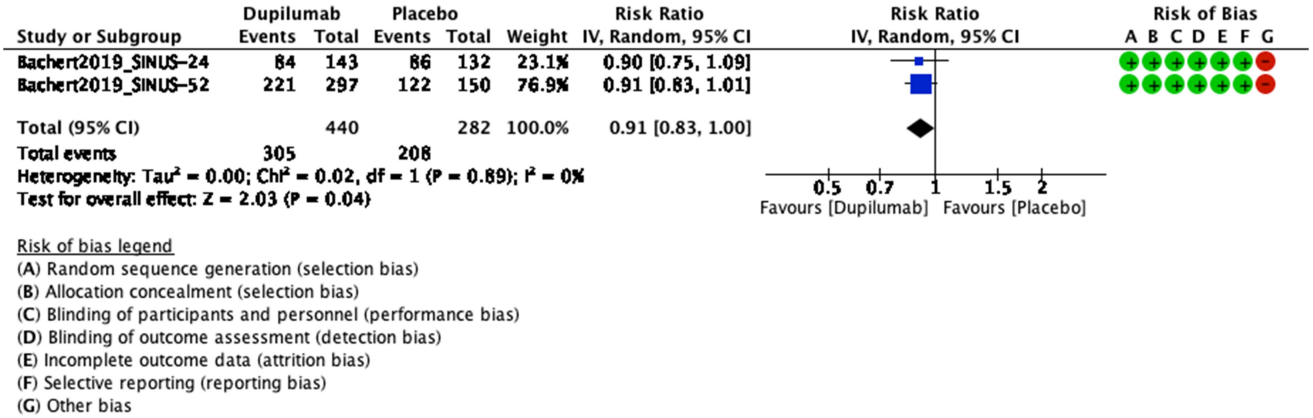
Figure S1: Number of patients took nasal polyp surgery or rescue oral systemic corticosteroid (OCS)*



* Bachert 2019 reported this outcome by pooling three arms of two trials of the dupilumab 300mg at 24 weeks: the arm with q2w to 24weeks (SINUS-24), the arm with q2w to 52 weeks (SINUS-52), and the arm of q2w (24w) to 24+ q4w (28w) (SINUS-52);

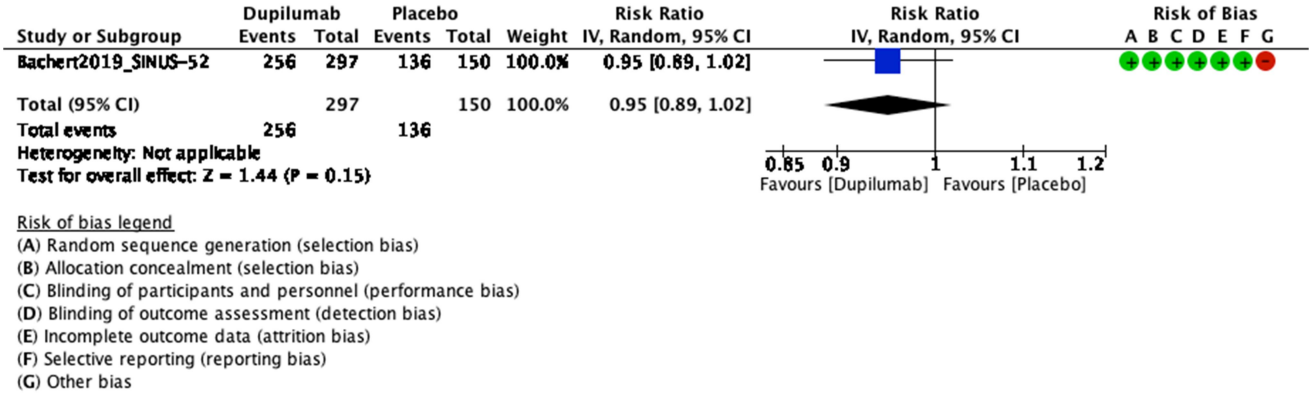
Time for the first nasal polyp surgery/systemic corticosteroid use was evaluated at 52 weeks, the Hazard ratio compare to placebo is 0.243 (95%CI 0.169 to 0.351).

Figure S2: Any treatment-emergent AE (TEAE) at 24 weeks*



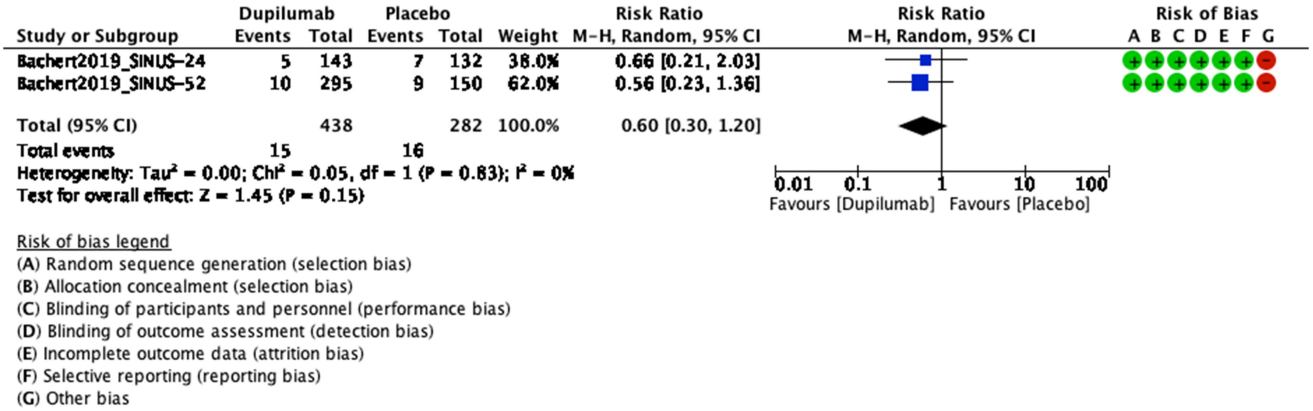
*SINUS-52 has a forced censor at week 24; and included two arms of q2w to 24 weeks.

Figure S3. Any treatment-emergent AE (TEAE) at 48-64 weeks*



*SINUS-52 evaluated two arms of intervention (one arm with q2w, 52 weeks; another arm with q2w (24 week) + q4w (28 weeks)). SINUS-24 evaluated TEAE at 48 weeks, the risk ratio is 0.92 (0.78 to 1.09).

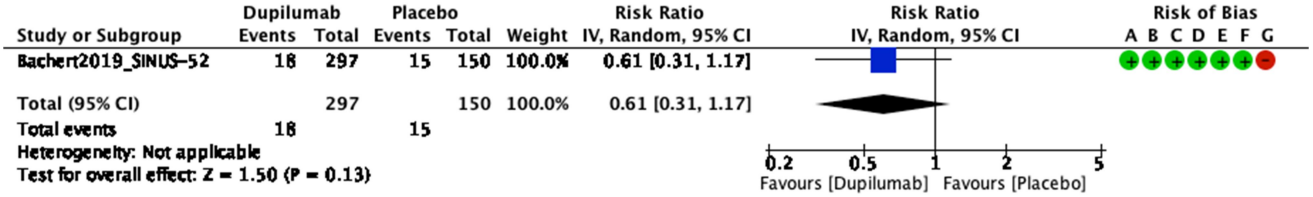
Figure S4. Any serious TEAE at 24 weeks*



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

*SINUS-52 has a forced cernsor at week 24; and included two arms of q2w to 24 weeks.

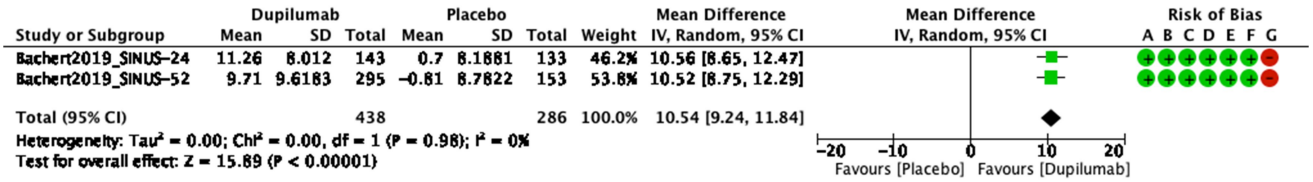
Figure S5. Any serious TEAE at 64 weeks*



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

*SINUS-52 evaluated two arms of intervention (one arm with q2w, 52 weeks; another arm with q2w (24 week) + q4w (28 weeks)). SINUS-24 evaluated serious TEAE at 48 weeks, the risk ratio is 0.29 (0.12 to 0.71).

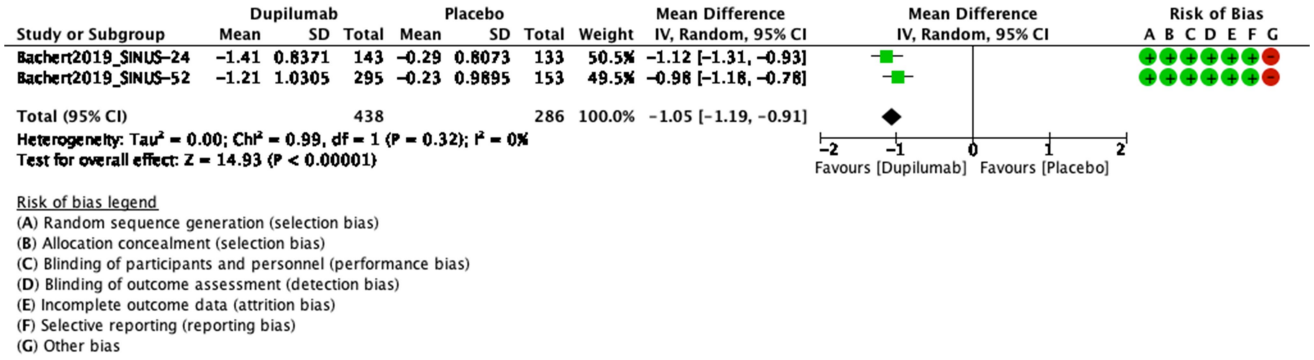
Figure S6: University of Pennsylvania Smell Identification Test – UPSIT at 24 weeks*



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

*SINUS-52 has a forced censor at week 24; and included two arms of q2w to 24 weeks; Higher scores of UPSIT corresponding to a better sense of smell.

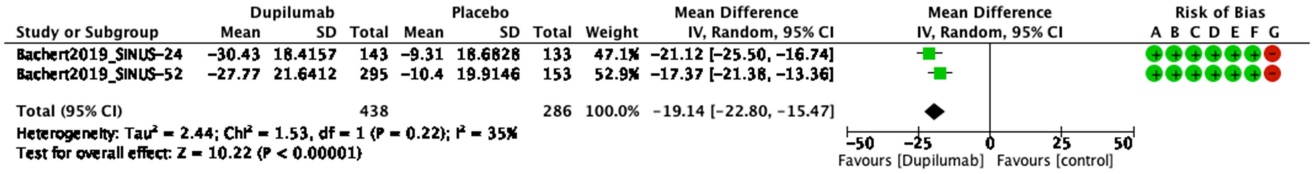
Figure S7: Loss of smell (categorical scale) at 24 weeks*



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

*SINUS-52 evaluated this outcome at week 24; and pooled two arms of q2w to 24 weeks together; Loss of smell ranged from 0 to 3 (0=absent, 1=mild, 2=moderate, 3=severe).

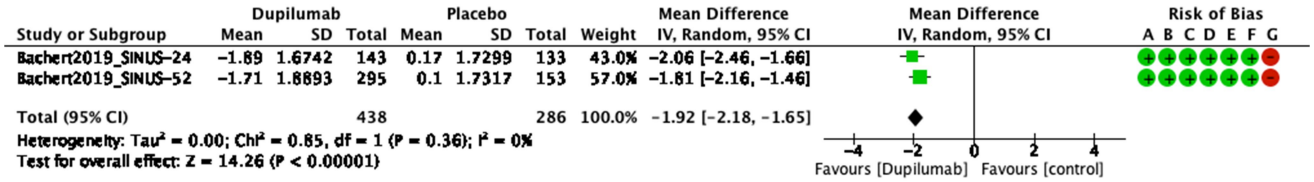
Figure S8: The change from baseline of SNOT-22 at 24 weeks*



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

*SINUS-52 evaluated this outcome at week 24; and pooled two arms of q2w to 24 weeks together; higher total scores of SNOTT-22 imply greater impact on quality of life, MID = 12 (undergoing medical management) (Phillips 2018)

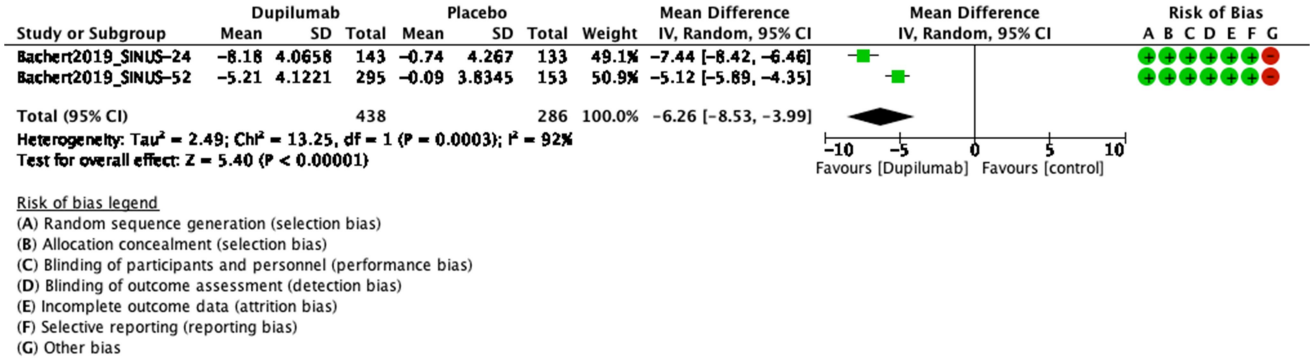
Figure S9. The change from baseline of the Nasal polyp score at 24 weeks*



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

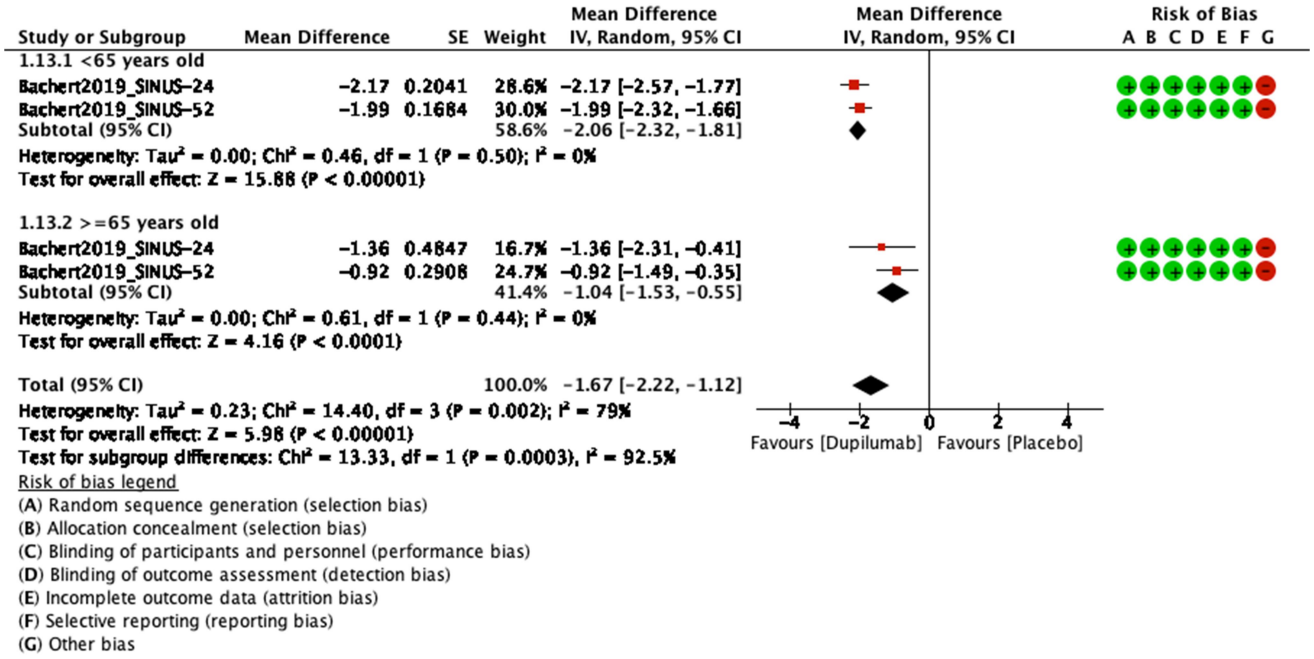
*SINUS-52 evaluated this outcome at week 24; and pooled two arms of q2w to 24 weeks together.

Figure S10. The change from baseline of the Lund-Mackay CT score at 24 weeks*



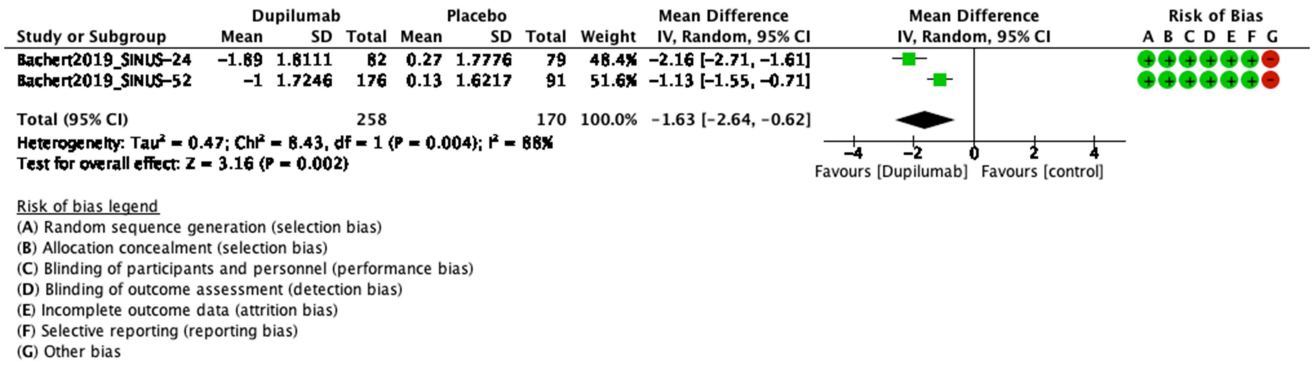
*SINUS-52 evaluated this outcome at week 24; and pooled two arms of q2w to 24 weeks together; Higher scores indicate greater disease severity.

Figure S11. The change from baseline of the Nasal polyp score at 24 weeks (Age Subgroup)*



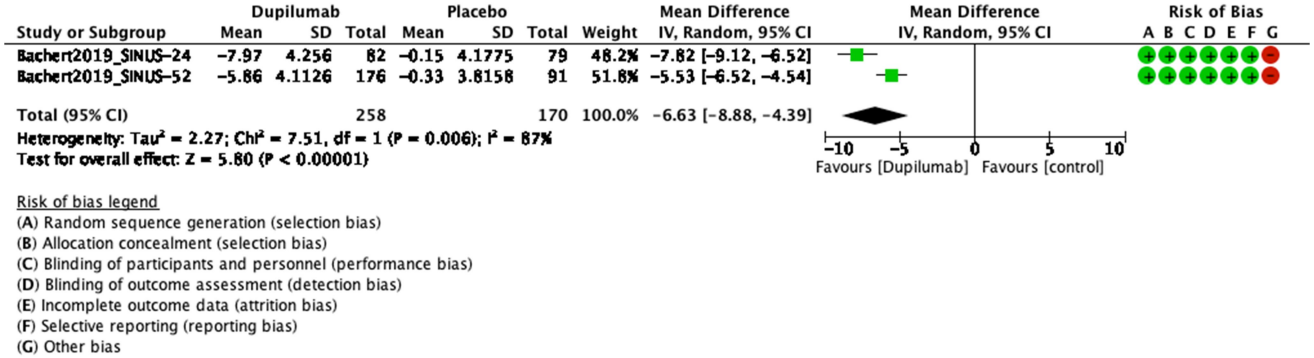
*SINUS-52 evaluated this outcome at week 24; and pooled two arms of q2w to 24 weeks together.

Figure S12. The change from baseline of the Nasal polyp score at 24 weeks (With asthma comorbility)*



*SINUS-52 evaluated this outcome at week 24; and pooled two arms of q2w to 24 weeks together.

Figure S13. The change from baseline of the Lund-Mackay CT score at 24 weeks (with asthma comorbility)*

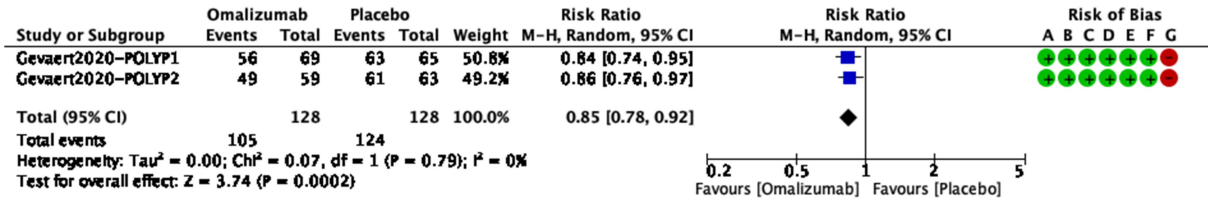


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

*SINUS-52 evaluated this outcome at week 24; and pooled two arms of q2w to 24 weeks together; Higher scores indicate greater disease severity.

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Figure S14: Number of patients who underwent nasal polyp surgery (24 weeks)*

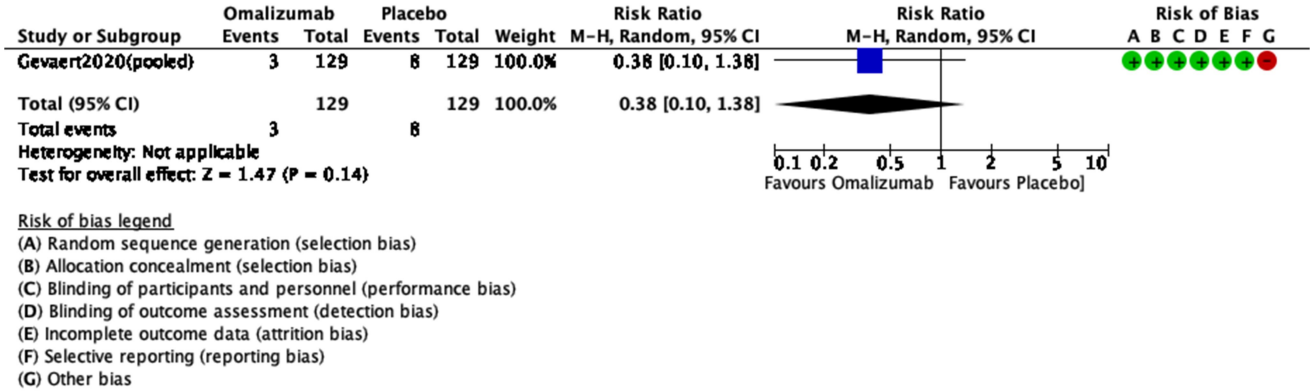


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

* The RCTs included originally reported the ORs of achieving a reduced need for further surgery. To make the results comparable across biologicals, raw data were used to estimate the RR for the outcome of need for surgery.

Geveart 2020 also adjusted for geographic region and asthma/aspirin sensitivity comorbidity status, the OR (95%CI) POLYP 1 is 6.3 [95% CI: 1.3-29.6; P=.0209]; the OR (95%CI) POLYP 2 is 6.2 [95% CI: 1.2-60.2; P = .0139])

Figure S15: Rescue OCS at 24 weeks



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Table S5: Rescue medication

Measure (Pinto2010)	Omalizumab q2w/q4w* (n=7)	Placebo (n=7)	p-value**
Systemic steroid (median nº of courses)	0	1	< 0.043
Antibiotic courses (median nº of courses)	0	1	<0.32

*q2w=every 2 weeks, q4w=every 4 weeks
** Between group comparison (Wilcoxon signed-rank test)

Pinto2010 measured this outcome at 24 weeks. Courses and time frame of systemic steroids and antibiotics are not clearly defined.

Health related quality of Life

Short-Form Health Questionnaire (SF-36) (change from baseline)

Gevaert2012 measured this outcome at 16 weeks. SF-36 physical health component significantly improved in the omalizumab group (P=.02), but not in the placebo group (P =0 .75). There was no statistically significant improvement for the mental health component in either group. No 95%CI was reported for any of the results.

Pinto2010 measured this outcome at 24 weeks. No statistically significant difference found (p > 0.05, all comparisons), except for one domain, vitality (mean 9.8 and 12.5, p<0.05 for omalizumab and placebo groups respectively). No 95%CI was reported for any of the results.

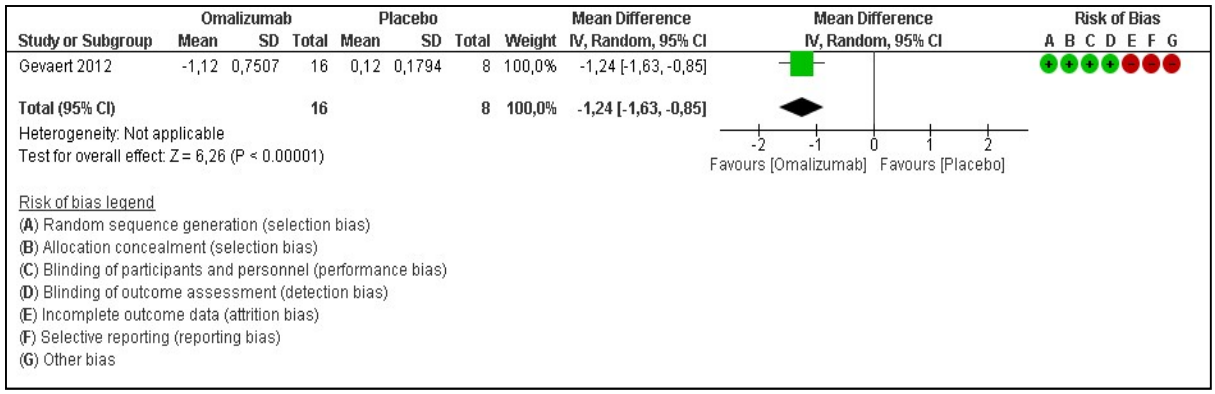
SinoNasal Outcome Test-20 (SNOT-20) (change from baseline)

Pinto2010 measured this outcome at 24 weeks. Net magnitude of the change between groups showed no difference (p < 0.78) (clinically significant improvement is a change of at least 0.8 points).

31-item Rhinosinusitis Outcome Measuring Instrument (RSOM-31) (change from baseline)

Gevaert2012 measured this outcome at 16 weeks. Sleep (p=0.03) and general symptoms (p =0.01) showed a significant improvement in the omalizumab group, whereas in the placebo group no statistically significant changes were seen.

Figure S16: Smell component of the Nasal symptom score (change from baseline)



Gevaert 2012 measured loss of sense of smell at 16 weeks using nasal symptom score (subjects scored their nasal symptoms daily, including loss of sense of smell as absent=0, mild=1, moderate=2, or severe=3). Lower score=better. Data was extracted from a figure using a plot digitalizer (Jelicic 2016).

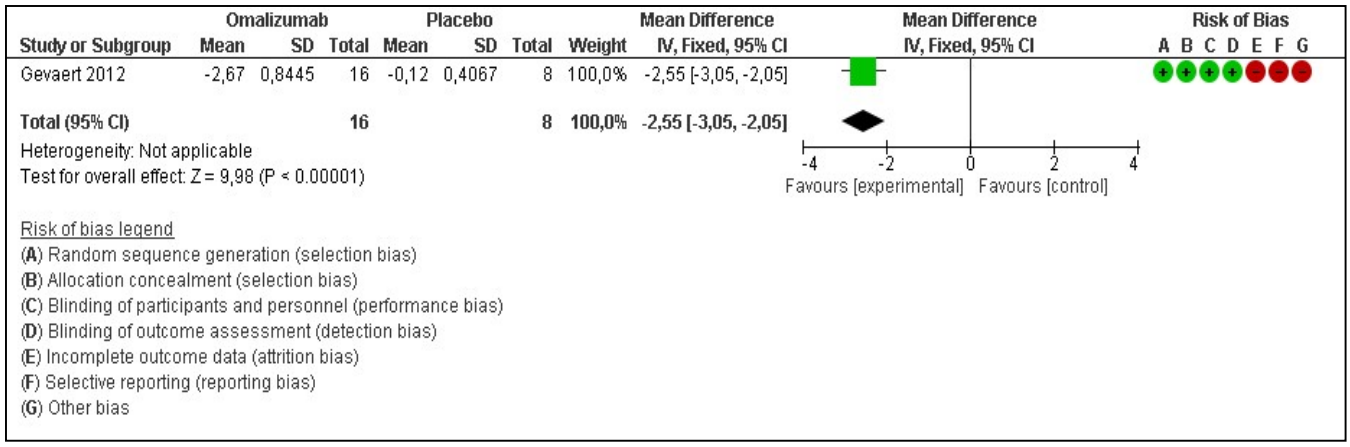
Table S6: Olfactory testing - University of Pennsylvania Smell Identification Test (UPSIT) (change from baseline)

Measure (Pinto2010)	Omalizumab q2w/q4w* (n=7)	Placebo (n=7)	p-value**
Net change (median)	3	4	<0.31

*q2w=every 2 weeks, q4w every 4 weeks
**Between group comparison (Wilcoxon signed-rank test)

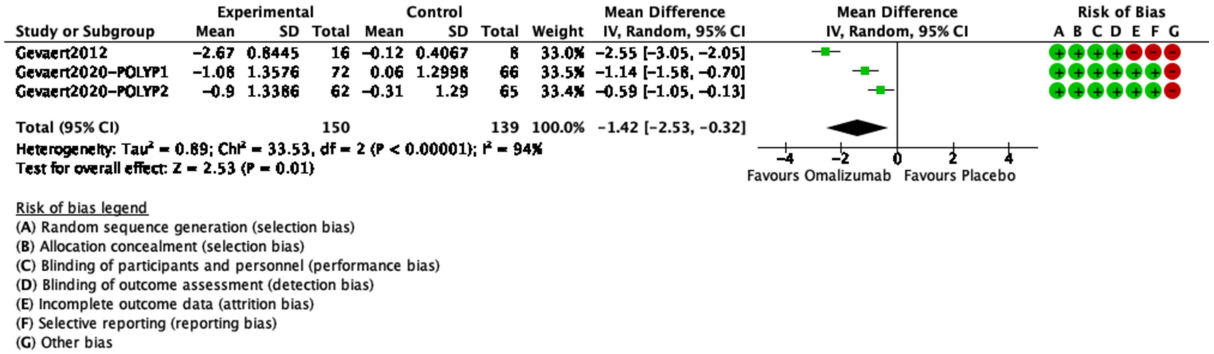
Pinto2010 measured this outcome at 24 weeks. Higher score=better sense of smell.

Figure S17: Total nasal endoscopic polyp score (TPS) (change from baseline)



Gevaert 2012 measured TPS at 16 weeks. TPS has been scored in each side by means of nasal endoscopy at each visit and graded as no polyps=0 and complete obstruction=4. Lower scores=better. TPS is the sum of the left and right nostril scores. Data was extracted from a figure using a plot digitalizer (Jelicic 2016).

Figure S18. Nasal polyp score (change from baseline)



* Geveart 2020 adjusted the data. Geveart 2020 measured at 24 weeks and Gevaert 2012 measured at 16 weeks. NPS has been scored in each side by means of nasal endoscopy at each visit and graded as no polyps=0 and complete obstruction=4. Lower scores=better. NPS is the sum of the left and right nostril scores. Data was extracted from a figure using a plot digitalizer (Jelicic 2016).

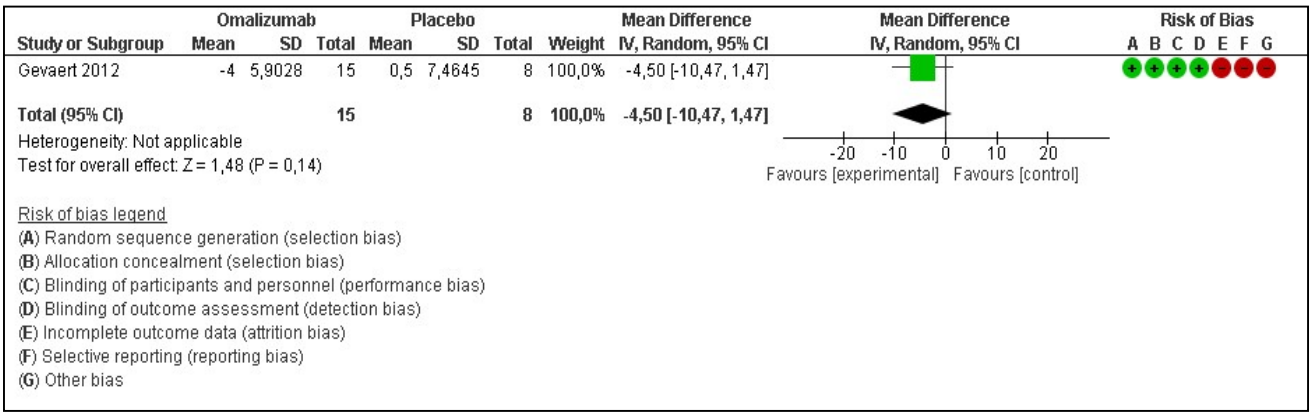
Table S7: Nasal endoscopy score (change from baseline)

Measure (Pinto2010)	Omalizumab q2w/q4w* (n=7)	Placebo (n=7)	p-value**
Net change (median)	0	-0.5	<0.58

**q2w=every 2 weeks, q4w every 4 weeks
**Between group comparison (Wilcoxon signed-rank test)

Pinto2010 measured this outcome at 24 weeks. Scores were measured using polyp size on a scale of 0 to 4 (no further information was given regarding the measurements of the outcome nor the score direction).

Figure S19: Lund-Mackay score (change from baseline)



Gevaert 2012 measured computer tomography score at 16 weeks by using the Lund-Mackay score (scale of sinus opacification from normality=0 to complete opacification=2). Lower score=better.

Table S8: Sinus CT opacification (%) (change from baseline)

Measure	Omalizumab q2w/q4w* (n=7)	Placebo (n=6)	p-value**
Net change (median)	11,9%	5.9%	<0.391

*q2w=every 2 weeks, q4w every 4 weeks
**Between group comparison (Wilcoxon signed-rank test)

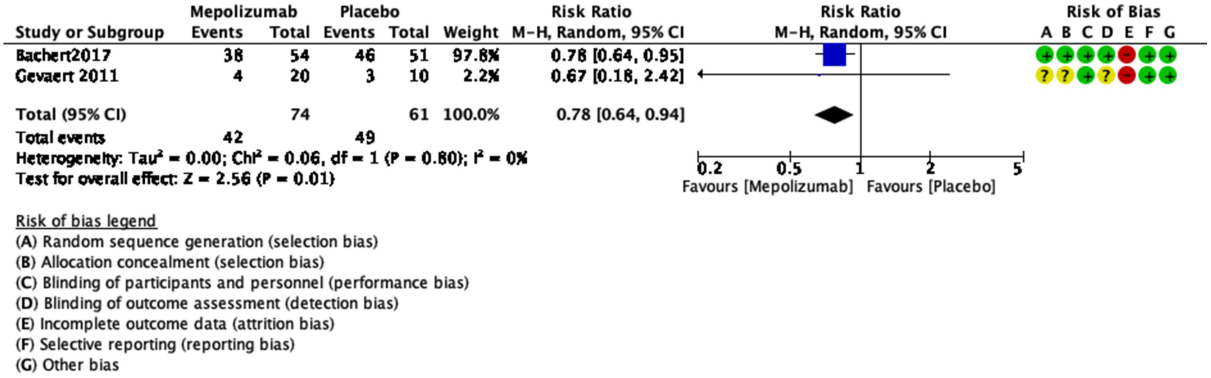
Pinto2010 measured this outcome at 24weeks. CT scan measured percentage of inflammation by percent opacification. Pre and post treatment coronal CT images at the osteomeatal unit (OMU) were matched. Improvement in sinus opacification

Symptom Score

Pinto2010 measured change from baseline in total nasal symptom score (TNSS) (nasal obstruction, nasal discharge, facial pain, and hyposmia) at 24 weeks (4 point scale: 0=none, 3=severe). There were no significant net differences across groups (omalizumab (median= –1), placebo (median= 0), p < 0.21 [Wilcoxon signed-rank test])

Meta-analysis of the Efficacy of mepolizumab for adult CRSwNP patients

Figure S20: Number of patients needing surgery (at 25 weeks)*



* Gevaert2011 reported patients requiring surgery at the end of the study (48 weeks)

Figure S21: Safety – drug related adverse events (at 25 weeks)

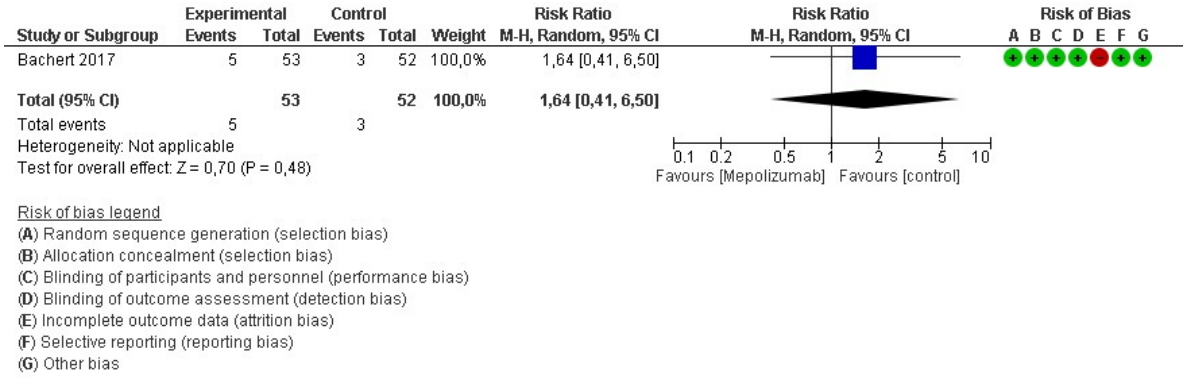
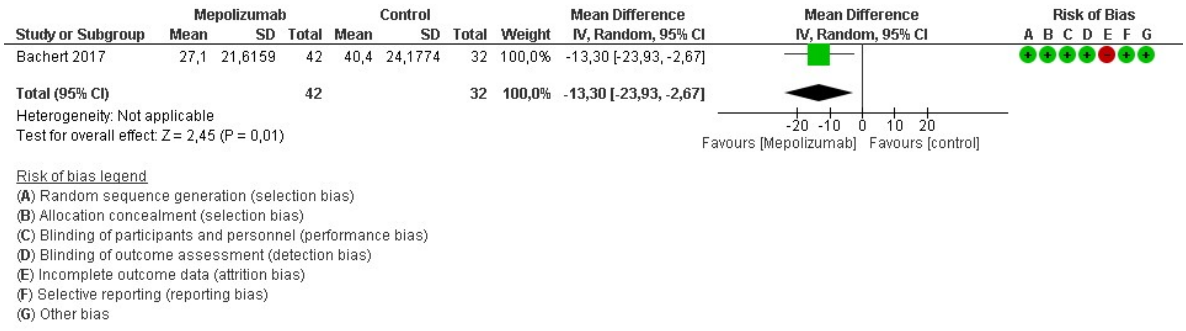


Figure S22: SNOT-22 Questionnaire (at 25 weeks) *



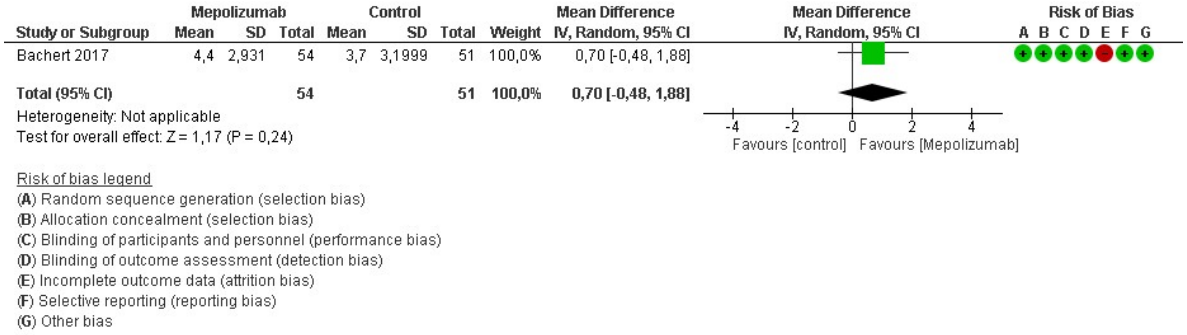
* Range from 1 to 100 (lower score=better)

Table S9: EQ-5D score (at 25 weeks) *

Measurements	Treatment Difference (95% CI)
EQ-5D Index score [1]	0.00 (95% CI -0.06 to 0.07)
EQ-5D VAS score [2]	5.7 (-1.3 to 12.7)

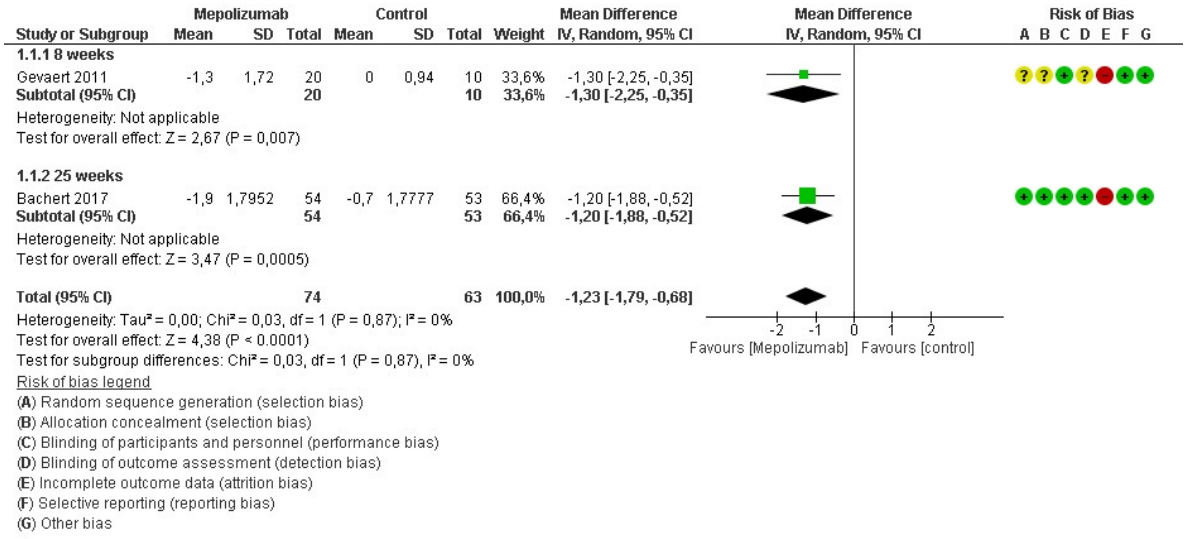
[1]Weighted mean score of 5 questions, a score of 1 indicates full health (Higher=better)
[2]VAS scale range from 0 to 100 mm (Higher score=better)

Figure S23: Smell – Olfaction testing (Sniffin' Sticks Screening-12 scores)*



*range from 0 to 12 (Higher score=better)

Figure S24: Change from baseline of total endoscopic nasal polyp score*



Bachert2017 assessed the endoscopic nasal polyposis score by means of endoscopy for each nostril separately and by using the highest unilateral score. Each nostril was scored from 0 to 4 (0= no polyps and 4= large polyps causing almost complete nasal obstruction). Gavaert2011 assessed total polyp score (TPS) is the sum of the right and left nostril scores, as evaluated by means of nasal endoscopy.

* Bachert2017 also evaluated this outcome by Nasal polyposis severity VAS score (higher score means worse), the reported difference in favor of mepolizumab is: -1.8 (95CI%-2.9 to -0.8)

Meta-analysis of the Efficacy of reslizumab for adult CRSwNP patients

Table S10: Need for surgery

Dose	Reslizumab (patients receiving surgery/all	Placebo (patients receiving surgery/all	RR (95% CI)

	patients)	patients)*	
3 mg/kg	0/8	2/8	0.20 (0.01 to 3.61)
1 mg/kg	0/8	2/8	0.20 (0.01 to 3.61)

***Reported as Safety data at 2 and 11 weeks.**

Safety

Gevaert 2006 reported this outcome narratively, with limited information (no statistical tests or confidence intervals provided): **"***Examination of other adverse events did not reveal any major differences between treatment groups. Administration of a single dose of reslizumab was well tolerated, and no clinically meaningful changes were observed in laboratory parameters, vital signs, or physical examinations in any of the treatment groups.*"

Table S11: Total nasal polyp score - Change from baseline at 8 weeks*

Dose	Reslizuman (median)	Placebo (median)
3 mg/kg	0.5	0
1 mg/kg	-1.0ι	0

* Higher score means more severe nasal polyps; This period without rescue medication used; Results were extracted by Plot Digitizer from figure 1.
ι significantly decreased.

Rescue medication used

Geveart 2006 reported this outcome narratively, with limited information (no statistical tests or confidence intervals provided): *"Systemic and nasal corticosteroids were used in 7 and 20 of 24 patients, respectively, with an equal distribution over the 3 groups and follow-up visits (from 12 to 36 weeks)".*