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Efficacy and safety of treatment with biologicals (benralizumab, dupilumab and omalizumab) for severe allergic asthma

A systematic review for the EAACI Guidelines - recommendations on the use of biologicals in severe asthma

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Abbreviations

ACQ = asthma control questionnaire

AQLQ = asthma related quality of life questionnaire
AE = adverse events
BDP = beclomethasone dipropionate
CHEC = health economics criteria checklist
CI = confidence interval
DPP4 = Dipeptidyl peptidase-4
EAACI = European Academy of Allergy and Clinical Immunology
EMA = European Medicine Agency
ENFUMOSA = European Network for Understanding Mechanisms of Severe Asthma
EURONHEED = European Network of Health Economic Evaluation Databases
FDA = Food and Drug administration
FeNO = fractional exhaled nitric oxide
FEV1 = forced exhalation volume in one second
FP = fluticasone propionate
GDG = Guideline Development Group
GETE = global evaluation of treatment effectiveness
GINA = Global Initiative for Asthma
GRADE = Grading of Recommendations Assessment, Development and Evaluation
ICS = inhaled corticosteroids
ICER = Incremental cost-effectiveness ratio (ICERs)
Ig = immunoglobulin
IL = interleukin
IRR = incidence rate ratios
LABA = long acting beta 2 agonist
LTRA = leukotriene receptor antagonist
MID = minimal important difference
MD = mean difference
OCS = oral corticosteroids
QALY = Quality adjusted life-years
QoL = quality of life
RCT = randomised controlled trial
ROB = risk of bias
RR = risk ratio
SARP = Severe Asthma Research Program
SGRQ = St George's Respiratory Questionnaire

SR = systematic review

TASS = Total Asthma Symptoms Scores

T2 = type 2

U-BIOPRED = The Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes

Key words

benralizumab; cost-effectiveness; dupilumab; allergic asthma; exacerbations; omalizumab; severe asthma;

Abstract

Allergic asthma is a frequent asthma phenotype. Both IgE and type 2 cytokines are increased, with some degree of overlap with other phenotypes.

Systematic reviews assessed the efficacy and safety of benralizumab, dupilumab and omalizumab (alphabetical order) versus standard of care for patients with uncontrolled severe allergic asthma. Pubmed, EMBASE and Cochrane Library were searched to identify RCTs and health economic evaluations, published in English. Critical and important asthma-related outcomes were evaluated. The risk of bias and the certainty of the evidence were assessed using GRADE.

All three biologicals reduced with high certainty the annualised asthma exacerbation rate: benralizumab incidence rate ratios (IRR) 0.63 (95% CI 0.50–0.81); dupilumab IRR 0.58 (95%CI 0.47–0.73); omalizumab IRR 0.56 (95%CI 0.42–0.73). Benralizumab and dupilumab improved asthma control with high certainty and omalizumab with moderate certainty, however none reached the minimal important difference (MID). Both benralizumab and omalizumab improved QoL with high certainty, but only omalizumab reached the MID. Omalizumab enabled ICS dose reduction with high certainty. Benralizumab and omalizumab showed an increase in drug-related adverse events (AEs) with low to moderate certainty. All three biologicals had moderate certainty for an ICER/QALY value above the willingness to pay threshold. There was high certainty that in children 6-12 years old omalizumab decreased the annualised exacerbation rate [IRR 0.57 (95%CI 0.45-0.72)], improved QoL [relative risk 1.43 (95%CI 1.12 -1.83)], reduced ICS [mean difference (MD) -0.45 (95% CI -0.58 to -0.32)] and rescue medication use [MD -0.41 (95%CI -0.66 to -0.15)].

BACKGROUND

Allergic asthma is a frequent asthma phenotype. It is usually defined by the presence of sensitisation to environmental allergens, with a clinical correlation between exposure and symptoms supporting the diagnosis (1,2,3). The immunopathological distinction between allergic and “non-allergic” asthma or between eosinophilic and allergic asthma is not so clear. Total immunoglobulin (Ig) E levels, usually higher compared to “non-allergic” asthma, may overlap between the allergic and “non-allergic” asthma. The atopic background is associated with increased type 2 (T2) cytokines (interleukin (IL)-4, IL-13, IL-5) and IL-33, IL-25 and TSLP potentiate T2 inflammation (4,5,6,7,8). Abrogation of IL-4R α signalling after established allergic airway disease prevents the development of ovalbumin-induced airway hyperreactivity, eosinophilia and goblet cell metaplasia (9). Targeting the IgE pathway with omalizumab might reduce sputum and tissue eosinophils, CD3+, CD4+, and CD8+ T lymphocytes, B lymphocytes and cells staining for interleukin-4, although this was not replicated in all studies (10,11).

Allergic asthma clinical spectrum ranges from mild to severe. Atopy has been reported to be inversely associated with persistent airflow obstruction and airway remodelling (12). The true prevalence of severe allergic asthma is difficult to estimate. The proportion of asthmatics with severe disease and a negative skin prick test varies from 17 to 34% in the Severe Asthma Research Program (SARP) study to 50% in the European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) study (13,14). The Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) cohort reported a 76.6% incidence of atopy in severe asthma, including non-smokers, smokers, and ex-smokers (15). Allergic asthma was reported to be associated with greater healthcare utilisation and costs (16).

From its availability for clinical use nearly two decades ago for severe asthma, omalizumab, the first biological acknowledged by Global Initiative on Asthma (GINA) as add-on therapy against severe uncontrolled asthma, has gained strong evidence of efficacy and safety in the treatment of severe asthma not controlled by standard-of-care therapy. It is licensed for severe (and moderate in USA) IgE-mediated allergic asthma (17,18). Benralizumab, a monoclonal antibody that binds to the α subunit of IL-5 receptor (IL-5R α) was recently approved for severe eosinophilic asthma (19,20). Dupilumab, a monoclonal antibody directed against the α subunit of the IL-4 receptor (IL-4R α) acting as a dual antagonist of both IL-4 and IL-13 was approved for severe type 2 asthma (21,22).

The European Academy of Allergy and Clinical Immunology (EAACI) is developing clinical practice guidelines for the use of biologicals in patients with severe asthma. This systematic review (SR) assessed the current evidence for the efficacy, safety and the economic impact for

benralizumab, dupilumab and omalizumab (alphabetical order) as add-on treatment for patients with uncontrolled severe allergic asthma.

METHODS

Guideline Development Group

The EAACI Asthma Voting Panel and Guidelines Steering Committee include clinicians and researchers with different backgrounds (the complete list of experts is available from the EAACI website) whom voluntarily participate in the development of EAACI clinical practice guidelines for the use biologicals in severe asthma. They are referred to as the Guideline Development Group (GDG).

Structured question and outcome prioritisation

The GDG framed the clinical question as “Is treatment with benralizumab, dupilumab and omalizumab efficacious and safe for patients with allergic asthma?”. For the purpose of this systematic review the population was defined as subjects diagnosed with moderate to severe allergic asthma with asthma symptoms due to exposure to a perennial aeroallergen and serum Ig E levels of 30-1300 IU/mL not be adequately controlled on inhaled steroids (ICS) and/or other background controllers. The asthma related outcomes were prioritised by the GDG using a 1 to 9 scale (7 to 9 critical; 4 to 6 important; 1 to 3 of limited importance), as suggested by the GRADE approach. The critical outcomes were: exacerbations, asthma control measured by the asthma control questionnaire (ACQ) and asthma control test (ACT), quality of life (QoL) measured by asthma quality of life questionnaire (AQLQ) and safety. The important outcomes were: lung function measured by the force expiratory volume at first second (FEV₁), decrease in inhaled corticosteroids (ICS) and oral corticosteroids (OCS) dose, healthcare resource utilisation and rescue medication use (Table S1).

The GDG also framed a cost-effectiveness question to assess the economic impact of these biologicals versus standard of care. The outcomes of interest were costs and resources use, the incremental cost-effectiveness ratios (ICERs) per both quality adjusted life-years (QALY), and asthma-related outcomes.

Data sources and searches

MEDLINE (via PubMed, January 2019), EMBASE (via Ovid, January 2019) and CENTRAL (via The Cochrane Library, January 2019) databases were searched using pre-defined algorithms for

both SR and individual studies for the evidence of efficacy, safety and economic evaluations. Search terms were adapted to each database, and validated filters were used to retrieve appropriate designs. The references of included studies were revised as well. Members of the GDG were requested to provide additional studies.

Study selection

The SR included only randomised controlled trials (RCTs) of patients with uncontrolled severe allergic asthma that compared benralizumab, dupilumab and omalizumab as add on to the standard of care versus placebo. Separate searches were performed for each of the 3 biologicals evaluated. Only studies published in English were included. Abstracts or conference communications not published as full articles in peer reviewed journals and RCTs using doses or routes not approved by U.S. Food and Drug Administration Agency (FDA) and/or the European Medicaments Agency (EMA) were excluded. Two reviewers independently assessed the references based on title and abstract. Then, two reviewers independently assessed the eligibility of the studies according to inclusion criteria based on full text. Discrepancies were solved by consensus or with the help of a third reviewer. All citations retrieved were imported into bibliographic reference software (EndNote X5; Thomson Reuters) to discard duplicates and record screening decisions.

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 risk of bias (ROB) was assessed using the Cochrane Risk of Bias Assessment tool. Each domain (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting) was evaluated as low, high or unclear ROB (23).

For the health economics analysis, two reviewers extracted the main characteristics of included studies (e.g. type of economic evaluation, perspective, time horizon, discount, sources of information, model type), relevant outcomes and costs (e.g. ICERs, sensitivity analyses results), sources of funding, and conflict of interest. Two reviewers assessed the methodological limitations of the complete economic evaluations with the consensus on health economics criteria checklist (CHEC) (24). Transferability to the European context was assessed using the European Network of Health Economic Evaluation Databases (EURONHEED) checklist (25, 26).

Data synthesis and analysis

Main results are described narratively and tabulated as summary of findings. For dichotomous data results are pooled as incidence rate ratios (IRR) and 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 versus placebo was assessed. A random-effects model was used to pool data (Review Manager v 5.3). Where multiple arms were compared to a common placebo arm standard errors were adjusted to avoid unit of analysis error (27). Statistical heterogeneity between studies was assessed with the Cochrane chi-square test, and the magnitude of heterogeneity with the I^2 statistic. To account for clinical heterogeneity, whenever possible subgroup analyses were performed for different doses, age groups, total IgE serum levels and biomarkers (FeNO, DPP4, periostin). A post hoc subgroup analysis for the rate of severe asthma exacerbation following the reduction in the OCS dose was added. 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, results are summarized narratively and tabulated, including the ICERs and the degree of uncertainty.

Certainty of evidence

The certainty (quality) of the evidence of efficacy, safety and economic impact was rated as high, moderate, low or very low, for each outcome in line with the standard GRADE domains (ROB, imprecision, inconsistency, indirectness and publication bias) (28,29). To evaluate the imprecision for each outcome the minimal important difference (MID) thresholds were considered where available (30,31,32,33). For FEV₁ the GDG panel recommended a MID of 0.20 litres (L).

RESULTS

Search results

The selection process is summarised in the PRISMA flowchart (Figure 1). From 3,441 unique citations from data base searches we selected 91 to be appraised as full text. 37 publications from 28 RCTs were included: 3 RCTs (from 3 publications) for benralizumab (34,35,36), 1 RCT (from 2 publications) for dupilumab (37,38), 21 RCTs (from 27 publications) for omalizumab for the population ≥ 12 years old (39-64) and 3 RCTs (from 5 publications) for omalizumab for 6-20 years old (65-69) (table S2). Publications excluded due to population or outcomes of interest not relevant, different comparisons, or regulatory unapproved dose or route are included in table S3.

Characteristic of included studies

The description of studies included for the evidence of efficacy and safety are detailed in table S1. All were randomized control trials, conducted between 2011 and 2018, including patients with uncontrolled severe allergic asthma receiving the biological in addition to standard of care versus placebo. The follow-up under study medication ranged from 12 to 56 weeks. The age of the patients included ranged from 12 to 75 years old, except for omalizumab that included children 6-11 years old as well. Benralizumab trials evaluated 3,208 patients (1,602 on treatment versus 1,606 on placebo), dupilumab trials 1,083 patients (721 on treatment arm versus 362 on placebo) and omalizumab, 6,847 patients (3,754 on treatment versus 3,093 on placebo). The characteristics of studies included for the economical impact are presented in table S4 (supplement).

Evidence of efficacy

The summary of the results and certainty of evidence per outcome are summarized in Tables 1,2,3, S8, figures S1 and S2.

Severe asthma exacerbation rate

Two RCTs for benralizumab (34), one RCT for dupilumab (38) and six RCTs for omalizumab (42, 44, 51, 54, 55, 68), reported annualized exacerbations rates. All three biologicals reduced asthma exacerbation rate compared to standard of care with high certainty of the evidence: benralizumab IRR 0.63; 95%CI 0.50 to 0.81; dupilumab IRR 0.58; 95%CI 0.47 to 0.73; omalizumab IRR 0.56; 95%CI 0.45 to 0.69;. No differences were found for omalizumab between children 6-11 years old and adolescent/adults ($p=0.88$).

Asthma control

Two RCTs for benralizumab (34), one RCT for dupilumab (38) and three RCTs for omalizumab (44, 56, 59) reported ACQ-6 scores. Benralizumab (MD -0.17; 95%CI -0.34 to 0.00) and dupilumab (MD -0.27; 95%CI -0.40 to -0.14) improve asthma control compared to standard of care (high certainty of evidence). Omalizumab probably improves asthma control compared to standard of care in adolescent/adults (MD -0.38; 95%CI -0.68 to -0.09; moderate certainty). ACQ was not evaluated for children 6-11 years old. None of the biologicals showed a reduction above the MID.

Global evaluation of treatment effectiveness

Global evaluation of treatment effectiveness (GETE) was evaluated for omalizumab versus standard of care. Ten RCTs reported GETE assessed by physicians/investigators (40, 43, 47,48,

54, 59, 62, 63, 66, 68,) and 8 RCTs GETE assessed by patients (40, 44, 47, 54, 59, 62,63,68). The overall effect for GETE evaluated by physicians/investigators showed an increase with high certainty of evidence in the proportion of treatment effectiveness evaluations rated as excellent or good (RR 1.50; 95%CI 1.32 to 1.70). There were no differences between children 6-11 years old (RR 1.41; 95%CI 1.25 to 1.58) and adolescent/adults (RR 1.55; 95%CI 1.31 to 1.83) (p=0.34). The overall effect for GETE evaluated by patients showed a similar significant improvement (RR 1.49; 95%CI 1.26 to 1.77). A significantly larger increase in GETE was observed in adolescent/adults (RR 1.57; 95%CI 1.3 to 1.89) compared to the 6-11 years old population (RR 1.11; 95%CI 1.01 to 1.23) (p=0.001).

Quality of life (QoL)

Asthma quality of life questionnaire (AQLQ) score were reported for benralizumab in two RCTs (34) and for omalizumab in 9 RCTs (40, 47, 51, 52, 54, 55, 62,63,67). Benralizumab improved QoL in the population who met atopy and IgE criteria (MD 0.1; 95%CI -0.08 to 0.28; high certainty), however the improvement was below the MID. Omalizumab increases with high certainty of evidence the QoL in adults and children: RR 1.32; 95%CI 1.16 to 1.51. There was no difference between adolescent/adults (RR 1.31; 95%CI 1.14 to 1.51) and children 6-11 years old (RR 1.43; 95%CI 1.12 to 1.83) (p=0.37).

Evidence for safety

Drug-related adverse events

Drug-related AE were reported for benralizumab in 1 RCT (35) and in 7 RCTs for omalizumab (41, 43, 50, 54,60,63,66). Both biologicals showed an increase in drug-related AE compared to standard of care: benralizumab RR 1.41 (95%CI 0.87 to 2.27; low certainty); omalizumab (children 6-11 years old and adolescents/adults) RR 1.27 (95% CI 0.93 to 1.72; moderate certainty of evidence). No differences were observed between adolescent/adults (RR 1.2; 95%CI 0.92 to 1.57) and children 6-11 years old (RR of 6.78; 95% CI 0.90 to 50.91) (p=0.10).

Drug-related serious adverse events

Drug-related SAE were reported for benralizumab in one RCT (36) and for omalizumab in 2 RCTs (51, 60). Benralizumab may reduce the incidence of SAE (RR 0.56; 95%CI 0.22 to 1.44) but there is low certainty of evidence. Omalizumab may increase SAE in adolescent/adults (RR 1.62; 95%CI 0.76 to 3.45; 11 more per 1,000 patients, from 4 fewer to 43 more) with low certainty of evidence. No drug-related SAE were reported for children 6-11 years old.

Corticosteroid and rescue medication

Inhaled corticosteroid dose

ICS dose reduction was evaluated only for omalizumab versus placebo in five RCTs (41, 42, 46, 52, 65). The addition of omalizumab reduced ICS dose both in children 6-11 years old and in adolescent/adults with high certainty of the evidence (overall effect MD -0.38; 95%CI -0.48 to -0.29). There were no differences between children 6-11 years old (MD -0.31; 95%CI -0.45 to -0.18) and adolescent/adults (MD -0.45; 95%CI -0.58 to -0.32) ($p=0.16$).

Oral corticosteroids dose

The reduction in OCS use from baseline was reported for omalizumab in a subpopulation of patients with severe asthma requiring OCS maintenance throughout the run-in phase (8 weeks prior to randomization) (45). Compared to standard of care omalizumab showed a significant reduction of prednisolone equivalent milligrams per day at 32 weeks (MD -6.7; 95%CI -12.93 to -0.47).

Rescue medication use (puffs/day)

The variation in rescue medication use was evaluated only for omalizumab, both in adolescent/adults (42, 46, 51, 52, 59) and in children 6-11 years old (66, 68). Omalizumab reduced with high certainty the rescue medication use in the overall population (MD -0.47; 95%CI -0.68 to -0.27). There were no differences between children 6-11 years old (MD -0.41; 95%CI -0.66 to -0.15) and adolescent/adults (MD -0.52; 95%CI -0.80 to -0.24) ($p=0.55$).

Lung function

FEV₁ variation in litres was reported in two RCT for benralizumab (34), one for dupilumab (38) and six RCTs for omalizumab (42, 43, 55, 60, 61, 62). Both dupilumab (MD 0.15; 95%CI 0.09 to 0.20) and omalizumab (MD 0.17; 95%CI 0.02 to 0.32) improve FEV₁ with low certainty of evidence. Benralizumab probably does not increase FEV₁ in the population that met atopy and IgE criteria (MD 0.055; 95%CI -0.025 to 0.136; moderate certainty of evidence).

Evidence of cost-effectiveness

After screening 1884 hits and reviewing 36 full text articles, 22 economic evaluations were included (figure 2, table S3). Two studies evaluated benralizumab (70,71), one dupilumab (70) and twenty studies omalizumab (72-91) (table S3). Most of the studies excluded did not evaluate

patients with allergic asthma (3/14), did not report health outcomes (3/14) or were conference abstracts (3/14) (table S4).

For benralizumab there was an important variation of ICER from 39,135 £ (low certainty of the evidence) to 412,000 \$ / QALY (moderate certainty of the evidence). The key driver for this difference is unclear since there is missing information in the report (71). However, in both studies the ICER/ QALY was higher than the 30,000 € threshold for the willingness to pay (tables S5 and S6). Overall, the resources needed for adding the biologic treatment to standard therapy are mainly the cost of the drug and its administration (table S7). The potential savings are related to decreased rate of hospitalisation, emergency department care, primary care visits, and the management of a clinically significant severe exacerbation (tables S5 and S6).

For dupilumab the reported ICER was 269,000 \$ for the 'responder to treatment' scenario. The uncertainty resides in the potential ROB in the utility estimates for the biological and standard therapy for the non-exacerbation health state, for standard therapy and annual exacerbation, and costs of chronic OCS use (moderate certainty of the evidence) (table S6 and S7).

For omalizumab there is important variation across studies in terms of the cost-effectiveness results. Cost-utility Markov model studies with low ROB (high quality studies) consistently show ICER / QALY values higher than the willingness to pay threshold in most European countries with moderate certainty of the evidence. Low quality studies reported ICER values lower than 30,000 €, with very low certainty of the evidence. The difference can be explained by the fact that the low quality studies assumed a higher asthma-related mortality risk and a higher QoL improvement with omalizumab. Furthermore, these studies were limited in their time horizon to up to 1 year (table S6 and S7).

DISCUSSION

Main findings

Overall the included studies were of low concern of ROB for most of the reported asthma related outcomes. All included studies were funded by the industry and all showed positive results, which raised concerns of potential sponsorship bias. The main reasons to downgrade the certainty of evidence were ROB due to the use of not validated tools for some outcomes, imprecision (i.e. ACQ, AQLQ) and indirectness (i.e. FEV₁, FeNO as surrogate outcomes).

The current systematic review of efficacy showed with high certainty that benralizumab, dupilumab and omalizumab as add-on to standard of care reduce the exacerbation rates for

patients with allergic asthma older than 12 years (adolescent/adults). Similarly, for children 6-11 years old with allergic asthma, omalizumab as add-on treatment significantly reduces the exacerbations rates.

The improvement in asthma control with benralizumab and dupilumab did not reach the MID. Omalizumab improves asthma control if GETE is considered, however the results are inconsistent with the ACQ score analysis. There is no evidence to support a MID for GETE. However, the first three response levels of both the physician and patient versions of the GETE ("complete control of asthma," "marked improvement of asthma," and "discernible, but limited improvement of asthma") are clearly differentiated from each other and this clear differentiation is associated with clinically important differences in terms of clinical indices and some AQLQ subscales (92).

Omalizumab also improves quality of life for children and adolescents/adults. Benralizumab did not show a clinically relevant improvement.

Rescue medication use (puffs/day), inhaled and oral corticosteroid use were evaluated only for omalizumab. The current SR showed with high certainty a reduction, both for children and adolescent/adults.

Although short term safety data are reassuring there is low to very low certainty for serious adverse effects. The very low certainty derives from the fact that drug related AEs were reported combined with worsening of asthma symptoms or were not reported in detail in the main publication or in the supplementary documents.

All three biologicals evaluated had with moderate certainty of the evidence an ICER/QALY value above the willingness to pay threshold of 30,000 €.

Current results in the context of previous results

Similar to results reported by this SR, all previous systematic reviews evaluating benralizumab, dupilumab and omalizumab efficacy and safety in adolescent/adults with allergic severe asthma reported a reduction of approximately half of annualized exacerbations in the population (93-97). The reduction in the exacerbation rates reported by the previous systematic reviews that evaluated omalizumab in children 6-11 years old was also very similar (96, 97, 98). Aligned with the current results the systematic review that evaluated asthma control and quality of life (96) in adolescent/adults population for omalizumab reported an improvement on these outcomes. The

current SR highlighted with high certainty that the improvement in QoL following the addition of omalizumab is clinically relevant.

An important difference between the current SR and the previous SRs is the assessment of the certainty of evidence using the GRADE approach. With the exception of Normansell all previous SRs limited their evaluation to the risk of bias of the included trials. The current SR evaluated the heterogeneity, imprecision and the indirectness of the evidence. As an example, MID used for the assessment of imprecision, enabled us to determine the clinical relevance of the variation for each outcome.

A previous SR of 20 economic evaluations included 19 studies that assessed the cost-effectiveness of omalizumab. Ten studies concluded that omalizumab was cost-effective for base-case scenarios, four studies showed that omalizumab was not cost-effective, and the remaining studies reported that omalizumab was cost-effective only when targeted to specific severe subgroups or when given considerable price discounts. The key drivers of cost-effectiveness included day-to-day health-related QoL, asthma-related mortality, acquisition price of biological therapy, and time horizon. The SR concluded that in order to improve the value for biologicals in asthma they should target specific populations (i.e. responders) or discounted acquisition price should be granted (99). Another review of 72 studies assessing the cost-effectiveness of asthma treatment, reported that among patients with uncontrolled severe persistent allergic asthma, omalizumab could be cost-effective in patients with more severe disease. The quality among studies was uneven and the main cost-effectiveness drivers were the cost or rate of asthma exacerbations, the cost or rate of use of asthma medication, asthma mortality risk and the rate of utilization of health services for asthma (100). A third review of 53 economic evaluations, evaluating patients with asthma and COPD included nine assessments of omalizumab use. This review concluded that few economic evaluations used validated models and identified controversies among results (101).

Strengths and limitations

The current SR has several strengths. A comprehensive evaluation of both desirable and undesirable effects of the use of benralizumab, dupilumab and omalizumab for allergic asthma was conducted, including the assessment of their economic impact. This compilation of outcomes provided an improved perspective of the biologicals profile. Rigorous methods including the GRADE approach to rate the certainty of the evidence were used, leading to transparent and precise judgement of the quality of evidence. The most updated results available from the included RCTs were included and only licensed doses and/or routes of the biologicals were

considered. Results are provided in friendly tabulated summaries using optimal presentation format for patients, clinicians and policy makers, thus offering a consistent support for the decision of use biologicals for patients with uncontrolled severe allergic asthma.

There are however several limitations. The basal exacerbation rate was used to estimate the absolute benefit for each drug/analysis. However, we did not perform a subgroup or sensitivity analysis based on the basal exacerbation rate. To ensure the robustness of the results based on high quality data observational studies that could have been informative for some of the outcomes with low or very low quality evidence from RCTs (e.g. serious adverse events) were not included in the SR. Only English language articles were included, however, the risk of selection bias is probably small because previous systematic reviews were carefully screened, and the GDG included several international experts in the field, thus the possibility of missing results from non-English articles is unlikely. A 'the novo' economic analysis for the cost-effectiveness outcomes was not conducted. Instead, a global perspective on the use of biologicals in different health systems, with a rigorous and explicit critical appraisal of the available evidence was chosen, that could be useful for the decisions of using biologicals across different countries.

Implications for practice and research

Despite biologicals showing an improvement in asthma related critical and important outcomes, the observed overall effect is relatively modest (reducing exacerbations but only probably improving asthma control, quality of life or lung function). Given the high cost of these drugs their use will probably be limited to very specific circumstances (e.g. patients with severe asthma uncontrolled under standard treatment). In this context panels are likely to formulate conditional recommendations on the use of biologicals.

Although short term safety data is reassuring more accurate reporting is warranted, in combination with long-term safety evaluation, including observational studies and registries. For omalizumab there is good data available to support its efficacy and safety in the pediatric population however for benralizumab and dupilumab the data are limited highlighting the urgent unmet need for rigorous trials with biologicals in severe asthma in the pediatric population.

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COI statement

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Figure 1: Study flowchart for the evaluation of evidence of efficacy and safety

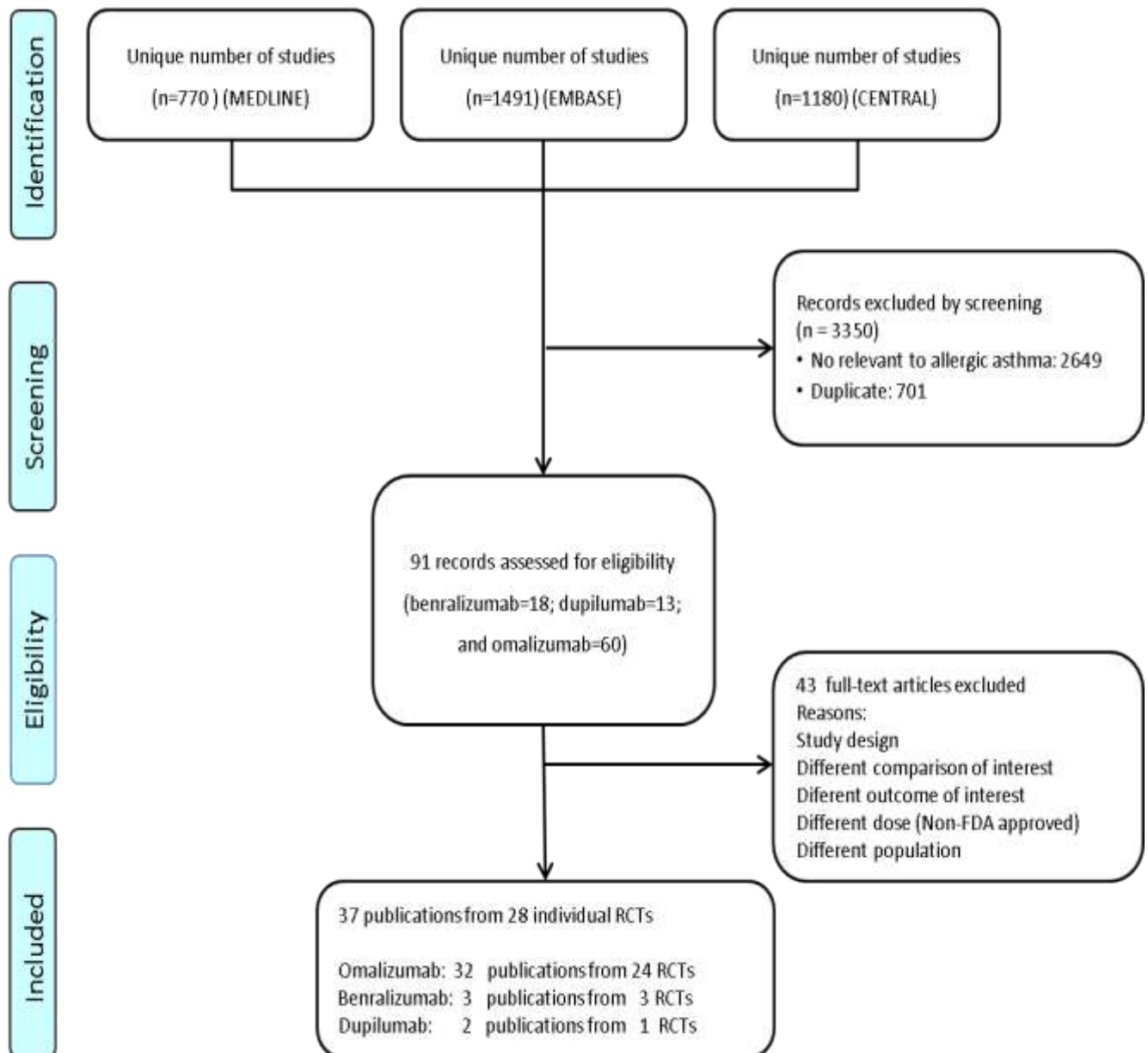


Figure 2. Study flowchart for the economic evidence

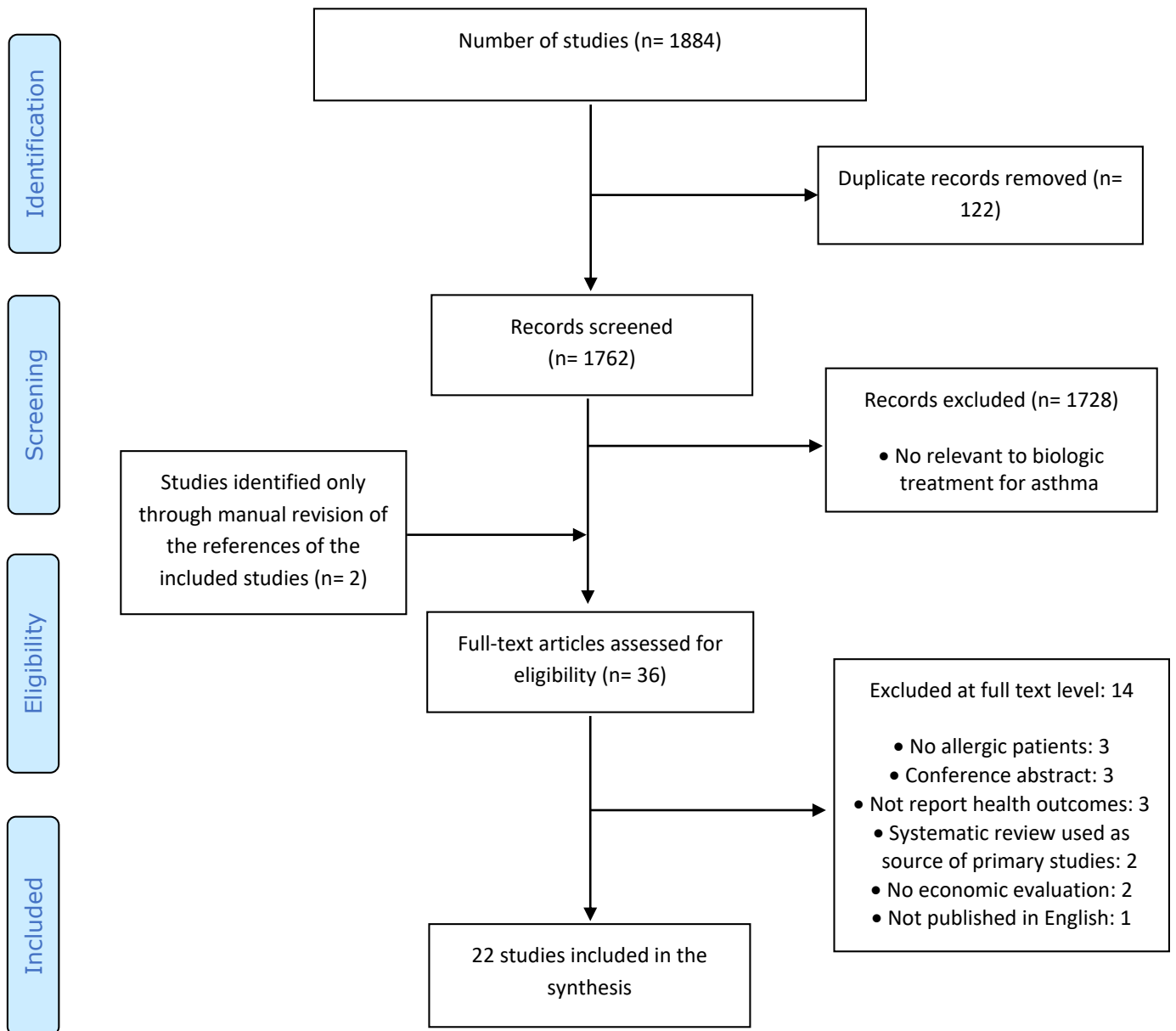


Table 1: Summary of findings for benralizumab efficacy and safety compared to standard of care for allergic asthma

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 Benralizumab
Exacerbations assessed with annual asthma exacerbation rate	297 (2 RCTs) ³⁴ 48 weeks to 56 weeks	⊕⊕⊕⊕ HIGH ^{2,a}	Rate ratio 0.63 (0.50 to 0.81)	13 per 1.000	5 fewer per 1.000 (6 fewer to 2 fewer)
Asthma Control assessed with: ACQ-6 score between-group-difference at the end of treatment	414 (2 RCTs) ³⁴ 48 weeks to 56 weeks	⊕⊕⊕⊕ HIGH ^{2,3,a,b}	-	The mean asthma Control was 0 Mean change	MD - 0.17 (-0.34 to 0)
Quality of Life assessed with: Quality of Life Questionnaire for 12 years and older [AQLQ(S)+12], between-group-difference at the end of treatment	404 (2 RCTs) ³⁴ 48 weeks to 56 weeks	⊕⊕⊕⊕ HIGH ^{2,5,a,e}	-	The mean quality of Life was 0 Mean change	MD +0.1 (-0.08 to +0.28)
Any drug related adverse event assessed with: Number of events- Urgent care visit, or admission to hospital	478 (1 RCT) ³⁵ 56 weeks	⊕⊕○○ LOW ^{2,a,f,g}	Rate ratio 1.41 (0.87 to 2.27)	105 per 1.000	43 more per 1.000 (14 fewer to 133 more)
Any drug related serious adverse event assessed with: Number of SAE unrelated to asthma exacerbation	148 (1 RCT) ³⁶ 28 weeks	⊕⊕○○ LOW ^{2,a,f,g}	Rate ratio 0.56 (0.22 to 1.44)	147 per 1.000	65 fewer per 1.000 (114 fewer to 65 more)
Lung function assessed with: Pre-bronchodilator FEV1 (mL) between-group-difference at the end of treatment)	490 (2 RCTs) ³⁴ 48 weeks to 56 weeks	⊕⊕⊕○ MODERATE ^{2,3,4,a,c,d}	-	The mean lung function was 0 L	MD + 0.055 L (-0.025 to + 0.136)

*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; MD: Mean difference; RR: Risk ratio

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 Benralizumab	

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: Moderate 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 little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Explanations

- a. Included studies were all funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to contrast the results. Therefore, evidence was downgraded for potential publication bias (102).
- b. For ACQ-6 the minimal important difference is 0.5 points (30)
- c. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms (103).
- d. The effect may both be harmful or beneficial. The minimal important difference (MID) for FEV1 is 0.20 L (Guidelines development group consensus).
- e. For AQLQ(S) + 12 the minimal important difference is 0.5 (32)
- f. Downgraded one level due to indirectness (data from severe asthma patients that may have or may have not allergic asthma)
- g. The effect may both be harmful or beneficial. Estimations are based on less than 300 events, thus there is probably important imprecision.

Table 2: Summary of findings of dupilumab compared to standard of care for allergic asthma

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated effects absolute	
				Risk with standard of care	Risk difference with Dupilumab
Clinically significant exacerbations rate ratio assessed with: annual asthma exacerbations	1083 (1 RCT) ³⁸ 52 weeks	⊕⊕⊕⊕ HIGH ^{2,a}	Rate ratio 0.58 (0.47 to 0.73)	Moderate 10 per 1.000	4 fewer per 1.000 (5 fewer to 3 fewer)
Asthma control assessed with: Asthma Control Questionnaire (ACQ-5) Scale from: 1 to 5	1013 (1 RCT) ³⁸ 24 weeks	⊕⊕⊕⊕ HIGH ^{2,7,a,d}	-	The mean asthma control was 0	MD - 0.27 (-0.4 to -0.14)
Lung function assessed with: Forced expiratory volume in one second (FEV1 in L) change from baseline	1055 (1 RCT) ³⁸ 12 weeks	⊕⊕○○ LOW ^{2,3,4,5,a,b,c}	-	The mean lung function change from baseline was 0 L	MD + 0.15 L (+0.09 to +0.2)

*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; 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 little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Explanations

- The study included was funded by Sanofi and Regeneron Pharmaceuticals. No industry-independent observational or randomised trials were identified to compare the results. The GDG members considered that there were no major concerns about potential publication/sponsorship bias
- Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a uncertain correlation with asthma symptoms (103).
- The minimal important difference (MID) for FEV1 is 0.20 L (GDG consensus).
- The effect of dupilumab is below the MID (0.5 points). (32)

Table 3: Summary of findings of omalizumab efficacy and safety compared to standard of care for allergic asthma

Outcomes	№ of participants (studies) Follow-up range	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with Omalizumab
Annual rate of clinically significant asthma exacerbations assessed with annualised rate	2772	⊕⊕⊕⊕ HIGH ^{b,c,d}	Rate ratio 0.56 (0.45 to 0.69) ^{e,f}	Low	
	(6 RCTs) ^{42,44,51,54,55,68} 24 weeks to 52 weeks ^a			14 per 1.000	616 fewer per 1.000 (770 fewer to 378 fewer)
Asthma control assessed with ACQ-6 score;	939 (3 RCTs) ^{44,56,59} 26 weeks to 52 weeks	⊕⊕⊕○ MODERATE ^{9,b,d,g}	-	The mean asthma Control was 0 point	MD 0.38 point lower (0.68 lower to 0.09 lower) ^{h,i}
Global evaluation of treatment effectiveness assessed with: physicians/investigators' assessment	3783 (10 RCTs) ^{68, 54,59,62,66,40,48,47,43,63} 16 weeks to 52 weeks	⊕⊕⊕⊕ HIGH ^{b,d,j}	Rate ratio 1.50 (1.32 to 1.70) ^k	418 per 1.000	209 more per 1.000 (134 more to 292 more) ^k
Clinically significant improvement of Asthma Quality of Life (≥0.5 from baseline) assessed with: AQLQ Questionnaire (S)	3540 (9 RCTs) ^{40,47,51,52,54,55,62,63,67} 12 weeks to 52 weeks	⊕⊕⊕⊕ HIGH ^{b,d,l}	Rate ratio 1.32 (1.16 to 1.51) ^m	563 per 1.000	180 more per 1.000 (90 more to 287 more) ^m
Any drug-related AE	2341 (7 RCTs) ^{68,54,66, 43, 63, 67, 50} 16 weeks to 52 weeks	⊕⊕⊕○ MODERATE ^{ab,b,d}	Rate ratio 1.27 (0.93 to 1.74)	127 per 1.000	34 more per 1.000 (9 fewer to 94 more)
Any drug-related SAE)	1163 (2 RCTs) ^{51, 60} 16 weeks to 48 weeks	⊕⊕⊕○ MODERATE ^{ab,b,d}	Rate ratio 1.62 (0.76 to 3.45)	18 per 1.000	11 more per 1.000 (4 fewer to 43 more)

Outcomes	№ of participants (studies) Follow-up range	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with Omalizumab
Lung function (FEV1) assessed with absolute FEV1 (L) change versus baseline	1209 (6 RCTs) ^{55, 42, 62, 43, 60, 61} range 12 weeks to 52 weeks ^{n, o}	⊕⊕○○ LOW 21, 22, 23, b, p, q, r	-	The mean lung function was 0 L	MD 0.17 L higher (0.02 higher to 0.32 higher) ^s
Lung function (PEF) assessed with morning PEF rate change (L/m) versus baseline	1735 (7 RCTs) ^{59, 48, 52, 60, 41, 58, 49} 12 weeks to 36 weeks ^t	⊕⊕⊕○ MODERATE 21, 22, 23, b, p, r, u	-	The mean lung function was 0	MD 10.04 higher (7.49 higher to 12.6 higher)
Decrease in inhaled corticosteroid assessed as µg/day variation versus baseline	1861 (5 RCTs) ^{41, 42, 46, 52, 65} 24 weeks to 52 weeks	⊕⊕⊕⊕ HIGH 23, b, r, v	-	-	SMD 0.38 SD lower (0.48 lower to 0.29 lower)
Rescue medication use (puffs/day) assessed with change from baseline	3367 (7 RCTs) ^{68, 54, 42, 59, 66, 52, 41} 16 weeks to 52 weeks ^{22, w}	⊕⊕⊕⊕ HIGH b, d, x	-	The mean the change from baseline of Rescue medication use (puffs/day) was 0 puff/day	MD 0.47 puff/day fewer (0.68 fewer to 0.27 fewer)
FeNO level change from baseline ^{29, y}	495 (3 RCTs) ^{51, 65, 41}	⊕⊕⊕○ MODERATE 32, 33, b, d, z	-	The mean feNO level change from baseline was 0 ppb	MD 4.65 ppb lower (7.39 lower to 1.92 lower) ^{aa}

*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; MD: Mean difference; RR: Risk ratio; SMD: Standardised 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: Moderate 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 little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Explanations

- a. Clinical significant asthma exacerbation: episodes of asthma worsening requiring treatment with systemic corticosteroids.
- b. Despite some studies being at high risk of bias for some of the domains, the effect observed in all of them is similar.
- c. Lanier included patients aged 6-12 years old, all had allergic asthma (68).
- d. Included studies were all funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to compare the results. Therefore, evidence was downgraded for potential publication bias (102).
- e. 9 studies included reported exacerbations as "patients who had ≥ 1 exacerbation", the pooled risk ratio was 0.59(95% CI 0.52-0.67). 3 studies included reported clinically significant severe asthma exacerbation, the pooled rate ration was 0.51 (95% CI 0.39-0.67)
- f. The pooled effect of risk ratio evaluated at 24-28 weeks (44, 54, 68, 63) and at 48-52 weeks (42, 51, 68, 55). Lanier 2009 included patients aged 6-12 years old.
- g. Downgraded because the effect of omalizumab is beneficial but the upper side of the CI is less than the minimal important difference (MID=0.5) (32).
- h. Asthma control using asthma control test (ACT) was assessed by three studies (65, 43, 56), the pooled mean different was 0.57(95% CI 0.17-0.97). We also included the ACQ scores assessed by 5 studies (68, 51, 52, 59, 46), the pooled standard mean difference was -0.20 (95% CI -0.26 - -0.14)
- i. The pooled effect of ACQ-6 evaluated at 16 weeks (44), 24-32 weeks (44, 59), and at 52 weeks (56).
- j. Although there were a high I² (67%), this was influenced by only one study with low number of events.
- k. The pooled data were assessed at 16 and 20 weeks (48, 62), and 52 weeks (68); Other studies evaluated at 24-28 weeks. GETE evaluated by patients show that omalizumab is more effective than placebo, the risk ratio was 1.49 (1.26-1.77), see full text report.
- l. Statistically significant (I²=83%), but probably unimportant heterogeneity.
- m. The mean change of AQLQ scores was assessed by 7 studies, the pooled standard mean difference was 0,34 (95% IC 0.18-0.49)
- n. Milgrom reported FEV1 in children (6-12 years old) for 28 weeks follow up (64). The Mean change from baseline was 93.9 mL in the omalizumab group and 28.3 mL in the placebo group. Lanier reported between group differences in FEV1 at week 48 and 52 in 40 ml (p=0.28) and 52 ml (p=0.16) (41).
- o. Lung function was also reported as ratio FEV1/FVCx100. Busse reported the ratio in 77.5 $\pm$ 0.38 in the intervention group and 77.3 $\pm$ 0.36 in the placebo group (63). Milgrom also reported mean FVC in children (6-12 years old) for 28 weeks follow up. Mean FVC change from baseline was 132.7 in the omalizumab group and 132.7 mL in the placebo group at week 28 (64). See full text report.
- p. Downgraded because FEV1 and PEF are considered surrogate outcomes for asthma control, with an inconsistent correlation with asthma symptoms (101).
- q. The minimal important difference (MID) for FEV1 is 0.20 L (Guidelines Development Group consensus).
- r. Included studies were all funded by industry, and all showed positive results. One observational study showed similar results (102), therefore, we did not downgrade for potential publication bias.
- s. The predicted value for pre-bronchodilator FEV1 was assessed by 6 studies, the pooled standard mean difference was 1.05 (95% CI 0.35-1.75), see full text report.
- t. Milgrom 2001 reported PEFR in children (6-12 years old) with 28 weeks of follow up. Mean morning PEFR change from baseline was 8.5 L/min in the omalizumab group, and 1 L/min in the placebo group at week 28)
- u. Average MID is 18.8L/min (30)
- v. High heterogeneity (91%); Not downgraded as all effects favour intervention.
- w. For rescue medication use MID is the reduction by 0.81 puffs/day (30)
- x. Statistically significant (68% (p=0.004)) but probably unimportant heterogeneity.
- y. The MID of FeNO change from baseline is more than 10ppb (33).
- z. Downgraded because FeNO is not consistently considered a good surrogate of asthmatic inflammation (105, 106)
- aa. FeNO change was reported according to IgE level by one study (64). The median percentage change was -7.2 (for IgE 30-300 IU/ml) and -16 (for IgE 700–2,000 IU/ml) in the Omalizumab group and 64 in the placebo group.
- bb. ab. The effect may both be harmful or beneficial.

Supplementary file

Table S1. Outcome prioritization by GDG	
O (outcome)	Critical: exacerbations, asthma control (ACQ, ACT), quality of life (AQLQ, EQ5D), safety Important: lung function (FEV1), decrease in ICS dose and OCS dose, healthcare resource utilization, rescue medication use, FeNO

Table S2: Characteristics of the studies included for evaluation of efficacy and safety

Benralizumab									
N	Author	Study Design	Age (range)	Population	Intervention	Control	Outcomes	Time-point	
1	Chipps et al 2018	Pooled results (SIROCCO and CALIMA studies)	12-75 years	Subgroup of patients that met the atopy (by Phadiatrop test) and serum IgE concentration of 30 to 700 kU/L criteria, with physician-diagnosed with severe uncontrolled asthma, that required treatment with medium- to high-dose ICS + LABA for at least 12 months before enrolment.	Benralizumab 30mg Q8W	Placebo	Annualised asthma exacerbation rate Pre-bronchodilator FEV1 Asthma control (ACQ-6) Asthma related QoL (AQLQ[S]+12)	48W (SIROCCO) 56w (CALIMA)	
2	FitzGerald 2016	RCT (CALIMA)	12-75 years	Severe asthma uncontrolled by high-dose ICS +LABA	Benralizumab 30 mg Q8W	Placebo	Included only for safety outcomes: urgent care visit, or admission to hospital	56W	

3	Nair 2017	RCT (ZONDA)	18-75 years old	Severe asthma treated with high-dose ICS+LABA plus OCS;	Benralizumab 30mg Q8W	placebo	Included only for safety outcomes:AE	28W
Dupilumab								
Omalizumab								
N	Author	Design	Age (range)	Population	Intervention	Control	Outcome	Time point
1	Busse2001, Finn 2003, Lanier2003	RCT+ extension	12-75	Allergic asthmatics; 420 to 840 µg/day of BDP or equivalent ICSs: total serum IgE 30 IU/mL - 700 IU/mL.	Omalizumab according to FDA approved product labelling	Placebo	Number of exacerbation episodes per patient Number of patients with at least 1 exacerbation Daily asthma symptoms Rescue medication use Pulmonary function GETE. Quality of life Safety: AE	16 W, 28 W
2	Milgrom 2001, Lemanske 2002	RCT	6-12 years	Stable asthmatics; ICSs equivalent to 168 to 420 mg/d of BDP; total serum IgE 30 - 1300 IU/mL.	Omalizumab according to FDA approved product labelling	Placebo	Incidence and the frequency of exacerbations GETE. Asthma symptom scores Quality of Life Questionnaire Rescue medication use Safety: AE	28 W
3	Ayres 2004	RCT	12-75	Moderate-to-severe allergic asthma. total serum IgE 30–700 IU/ml.	Omalizumab according to FDA approved product labelling	Best standard care	Annualized number of exacerbations Clinically significant exacerbations Lung function Asthma symptom scores AQLQ Rescue medication use Safety: AE	52 W
4	Bardelas 2012	RCT	≥ 12	Inadequately controlled, persistent, allergic asthma; step 4 or higher asthma maintenance therapy (medium-dose ICS plus a LABA/LTRA/ theophylline/ zileuton	Omalizumab according to FDA approved product labelling	Placebo	ACT score. Investigator's GETE Lung function Rescue medication use Safety: AE	26 W

5	Bousquet 2011, Siergiejko 2011	RCT	12–75	Severe persistent allergic asthma; ≥ 800 μ g BDP or equivalent and LABA, with total IgE level of 30–700 IU/ml.	Omalizumab according to FDA approved product labelling	Optimized asthma therapy	Investigator's GETE Lung function Asthma symptom scores ACQ score Reduction OCS Rescue medication use Safety: AE	16 W, 32 W
6	Solèr 2001, Buhl 2002a (extension to 52w), Buhl 2002b (extension to 52w).	RCT	40/39 12–75	Moderate-to-severe allergic asthma; total serum IgE 30–700 IU/mL.	Omalizumab + optimised asthma therapy	Placebo+ optimised asthma therapy	Asthma exacerbation Lung function (morning PEF) -Asthma symptom -Quality of life -Reduction in inhaled BDP. -Rescue medication use -Safety: AE	16 W, 28 W, 52w
7	Busse 2011 (NCT00377572)	RCT	10.8 6-20	Persistent allergic symptoms and uncontrolled asthma; total serum IgE 30 - 1300 IU per mL.	Omalizumab according to FDA approved product labelling	Placebo	-The number of days with symptoms. -Exacerbations -ICS dose needed to maintain asthma control; -ACT (both paediatric and adult) -Safety: AE	48 W, 52 W
8	Chanez 2010 (NCT00454051)	RCT	47.4 ≥ 18	Severe persistent allergic asthma; high ICS >1000 mg BDP+LABA; total serum IgE 30-700 IU/ml.	Omalizumab according to FDA approved product labelling	Placebo	-Change in Fc3RI expression on basophils -Exacerbations -Asthma symptoms; -Rescue SABA -Safety:AE	16 W
9	Corren 2010 (NCT00495612)	RCT	31 18-65	Allergic asthma (cat dander-induced, total serum IgE 30 - 700 IU/mL.	Omalizumab according to FDA approved product labelling	Placebo	-Lung function (FEV1%) -Asthma symptoms; - FeNO -Safety: AE	16 W
10	Cruz 2007	RCT	15/16 12-30	Allergic asthma subcutaneous allergen-immunotherapy.	Omalizumab according to FDA approved product labelling	Placebo	-Safety:AE	52 W
11	Hanania 2011 (EXTRA, NCT 00314575)	RCT	43.7/45.3 12-75	Inadequately controlled asthma, high-dose ICS plus LABAs.	Omalizumab according to FDA approved product labelling	Placebo	-Asthma exacerbations -Total asthma symptom score (TASS) -Asthma Quality of Life Questionnaire (AQLQ) -FeNO -Safety:AE	48 W

12	Holgate 2004	RCT	40.5/41.1 12-75	Severe allergic asthma; ≥ 1000 mcg/day fluticasone; total serum IgE 30–700 IU/mL.	Omalizumab according to FDA approved product labelling	Placebo	-ICS dose reduction -Lung function (morning PEF) -Asthma symptoms -Quality of life -Rescue medication use -Safety: AE	16 W, 32 W
13	Hoshino 2012	RCT	20-75	Severe allergic asthma; high-dose ICS plus LABA; total serum IgE 30 - 700 IU/ml.	Omalizumab+ conventional therapy	conventional therapy	-Lung function (FEV1, morning PEF) -Quality of life	16 W
14	Humber 2005 (INNOVATE), Niven 2008 (subgroup analysis)	RCT	59.2/51.2 12-75	Persistent allergic asthma; >1000 Ig/day BDP or equivalent and LABA.	Omalizumab according to FDA approved product labelling	Placebo	-Clinically significant asthma exacerbations -Asthma symptoms -Lung function -Reduction in reliever medication -Quality of life -Safety:AE	28 W
15	Ledford 2017	RCT	51.5 17-70	Moderate-to-severe asthma stable doses of other asthma therapies, had received long-term (5 years) treatment with omalizumab before randomization	Omalizumab according to FDA approved product labelling	Placebo	-Asthma exacerbations - ACT scores, ACQ scores -Lung function (FEV1) -Total serum IgE -Safety: AE	52 W
16	Rensen 2009	RCT	18-29	Non-smoking asthmatics using short-acting b2-agonists; total serum IgE 30 - 700 IU/ml.	Omalizumab according to FDA approved product labelling	Placebo	-Lung function: FEV1 -Total serum IgE -Safety: AE	12 W
17	Pasha 2014	RCT	39/36 ≥ 12	Allergic asthma with FeNO >13 ppb, and IgE 30–700 IU/mL.	Omalizumab according to FDA approved product labelling	Placebo	-FeNO	16 W
18	Li 2016 (NCT01202903)	RCT	46.5 18-75	Moderate-to-severe persistent allergic asthma aged, total serum IgE 30-700 IU/mL.	Omalizumab according to FDA approved product labelling	Placebo	-Lung function (morning PEF FEV1) - ACQ scores -Asthma symptom scores -Rescue medication use -AQLQ[S scores -GETE responder analysis	16 W, 24 W

							-Rate and seasonal effect of protocol-defined asthma exacerbations -Safety: AE, SAE	
19	Ohta 2009 (NCT00232050)	RCT	48.8/49.2 20-75	Moderate-to-severe insufficient controlled asthma; ≥ 800 mg/day of BDP(or equivalent) and one or additional controller medications recommended in GINA step 3 or 4; total serum IgE of 30–700 IU/mL.	Omalizumab according to FDA approved product labelling	Placebo	-Lung function (morning PEF) -Asthma symptoms -Daily activity status -Sleep status -Use of asthma medications -Anti-omalizumab antibody -Clinically significant asthma exacerbations event leading to withdrawal from the study -Safety: AE, SAE.	16 W
20	Prieto 2006	RCT	32/30 18-65	Stable, mild to moderate persistent allergic asthma aged 18-65; ICS 200–1000 μ g, ; total serum IgE 30–700 IU/mL.	Omalizumab according to FDA approved product labelling	Placebo	- PC 20 for AMP -FEV1	12 W
21	Rubin 2012	RCT	43.8/45.2 12-75	Severe, uncontrolled, persistent; 500 μ g/day of fluticasone equivalent) and LABA, total serum IgE 30–700 IU/mL.	Omalizumab according to FDA approved product labelling	Placebo	-Asthma exacerbation frequency -Rescue medication use - Symptoms scores -GETE -Pulmonary function (FEV1) -AQLQ -Safety: AE, SAE.	12 W, 20 W
22	Vignola 2004	RCT open-label	38.3/38.5 12-75	Allergic asthma; ≥ 400 μ g/day ICS; total serum IgE 30–1300 IU/mL.	Omalizumab according to FDA approved product labelling	Placebo	-Asthma exacerbations during the treatment period - AQLQ and RQLQ scores -Rescue-medication use -Patient and investigator GETE -Lung function (FEV1, FVC, morning PEF) -ICS use -Safety: AE, SAE	28 W

23	Zielen 2012	RCT	18-65	Allergic asthma	Omalizumab according to FDA approved product labelling	Placebo	-Lung function: -Early/Late-phase allergic response -FeNO -Safety	16 W
24	Lanier 2009, Kulus 2010	RCT	6-12	Moderate-to-severe allergic asthma; medium doses of ICS ($\geq 200\mu\text{g/d}$ FP); total serum IgE 30 - 1300 IU/mL	Omalizumab according to FDA approved product labelling	Placebo	-Clinically significant asthma exacerbations - Nocturnal clinical symptom score - Rescue medication use - QOL score - GETE -Safety	24 W, 52 W

Table S3: Studies excluded from the efficacy and safety evaluation

No.	Author	Design
1	Baena-Cagnani CE, Teijeiro A, Canonica GW. Four-year follow-up in children with moderate/severe uncontrolled asthma after withdrawal of a 1-year omalizumab treatment. Curr Opin Allergy Clin Immunol 2015;15(3):267-71.	Not RCT
2	Bang LM, Plosker GL. Spotlight on omalizumab in allergic asthma. BioDrugs. 2004;18(6):415-8.	Not RCT
3	Brodlie M, McKean MC, Moss S, Spencer DA. The oral corticosteroid-sparing effect of omalizumab in children with severe asthma. Arch Dis Child. 2012;97(7):604-9.	Not RCT
4	Bousquet J, Siergiejko Z, Swiebocka E, et al. Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. Allergy. 2011;66(5):671-678.	Open-label
5	Corren J, Shapiro G, Reimann J, Deniz Y, Wong D, Adelman D, et al. Allergen skin tests and free IgE levels during reduction and cessation of omalizumab therapy. J Allergy Clin Immunol. 2008;121(2):506-11.	No comparison and different disease.
6	Garcia G, Magnan A, Chiron R, Contin-Bordes C, Berger P, Taille C, et al. A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma. Chest. 2013;144(2):411-9.	Different disease
7	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(1):110-6e1.	Different disease
8	Johansson SG, Nopp A, Oman H, Ankerst J, Cardell LO, Gronneberg R, et al. The size of the disease relevant IgE antibody fraction in relation to 'total-IgE' predicts the efficacy of anti-IgE (Xolair) treatment. Allergy. 2009;64(10):1472-7.	No outcome of interest. Different disease.
9	Kopp MV, Hamelmann E, Zielen S, Kamin W, Bergmann KC, Sieder C, et al. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. Clinical and experimental	No outcome of interest.

	allergy. 2009;39(2):271-9.	
10	Lupinek C, Derfler K, Lee S, Prikoszovich T, Movadat O, Wollmann E, et al. Extracorporeal IgE Immunoabsorption in Allergic Asthma: Safety and Efficacy. EBioMedicine. 2017;17:119-33.	Different intervention
11	Luskin AT, Kosinski M, Bresnahan BW, Ashby M, Wong DA. Symptom control and improved functioning: the effect of omalizumab on asthma-related quality of life (ARQL). J Asthma. 2005;42(10):823-7.	Pooled data, original RCTs already included
12	Massanari M, Nelson H, Casale T, Busse W, Kianifard F, Geba GP, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. J Allergy Clin Immunol. 2010;125(2):383-9.	No outcome of interest.
13	Ohta, K., Miyamoto, T., Amagasaki, T., Yamamoto, M., Study, Group. Efficacy and safety of omalizumab in an Asian population with moderate-to-severe persistent asthma. Respirology; Nov 2009.	No comparison
14	Pillai P, Chan YC, Wu SY, Ohm-Laursen L, Thomas C, Durham SR, et al. Omalizumab reduces bronchial mucosal IgE and improves lung function in non-atopic asthma. Eur Respir J. 2016;48(6):1593-601.	Different disease
14	Silkoff PE, Romero FA, Gupta N, Townley RG, Milgrom H. Exhaled nitric oxide in children with asthma receiving Xolair (omalizumab), a monoclonal anti-immunoglobulin E antibody. Pediatrics. 2004;113(4):e308-12.	No outcome of interest.
15	Sorkness CA, Wildfire JJ, Calatroni A, Mitchell HE, Busse WW, O'Connor GT, et al. Reassessment of omalizumab-dosing strategies and pharmacodynamics in inner-city children and adolescents. J Allergy Clin Immunol Pract. 2013;1(2):163-71.	No outcome of interest.
16	Zhu R, Zheng Y, Putnam WS, Visich J, Eisner MD, Matthews JG, et al. Population-based efficacy modeling of omalizumab in patients with severe allergic asthma inadequately controlled with standard therapy. AAPS Journal. 2013;15(2):559-70.	Pooled analysis, original RCT have already been included
17	Nct. Omalizumab to Mepolizumab Switch Study in Severe Eosinophilic Asthma Patients. https://clinicaltrials.gov/show/nct02654145 . 2016.	Different intervention
18	O Casale TB, Chipps BE, Rosen K, Trzaskoma B, Haselkorn T, Omachi TA, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. Allergy 2018;73(2):490-7.	Different disease
19	Berger WE, Gupta N, McAlary M, Fowler-Taylor A. Evaluation of long-term safety of the anti-IgE antibody, omalizumab, in children with allergic asthma. Annals of Allergy, Asthma and Immunology. 2003;91(2):182-8.	No comparison
20	Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: An analysis of biomarkers in the EXTRA study. American journal of respiratory and critical care medicine. 2013;187(8):804-11.	No outcome of interest.
21	Hendeles L, Khan YR, Shuster JJ, Chesrown SE, Abu-Hasan M. Omalizumab therapy for asthma patients with poor adherence to inhaled corticosteroid therapy. Annals of Allergy, Asthma and Immunology. 2015;114(1):58.	No outcome of interest.
22	Noga O, Hanf G, Kunkel G. Immunological and clinical changes in allergic asthmatics following treatment with omalizumab. International archives of allergy and immunology. 2003;131(1):46-52.	No outcome of interest.
23	Noga O, Hanf G, Brachmann I, Klucken AC, Kleine-Tebbe J, Rosseau S, et al. Effect of omalizumab treatment on peripheral eosinophil and T-lymphocyte function in patients with allergic asthma. J Allergy Clin Immunol. 2006;117(6):1493-9.	No outcome of interest.
24	Stoeger ZM, Eliraz A, Asher I, Berkman N, Elbirt D. The beneficial effects of Xolair (omalizumab)	Pooled analysis,

	as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available treatment (GINA 2002 step IV)--the Israeli arm of the INNOVATE study. <i>Isr Med Assoc J.</i> 2007;9(6):472-5.	original RCT have already been included
25	Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ, Calatroni A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. <i>J Allergy Clin Immunol.</i> 2015;136(6):1476-85.	Different objective.
26	Wahn U, Martin C, Freeman P, Blogg M, Jimenez P. Relationship between pretreatment specific IgE and the response to omalizumab therapy. <i>Allergy</i> 2009;64(12):1780-7.	N No outcome of interest.
27	Hanf G, Brachmann I, Kleine-Tebbe J, et al. Omalizumab decreased IgE-release and induced changes in cellular immunity in patients with allergic asthma. <i>Allergy.</i> 2006;61(9):1141–1144.	No outcome of interest.
28	Schroeder2009	Different disease and objective.
29	Baker DL, Peng K, Cheu M, Fischer SK. Evaluation of two commercial omalizumab/free IgE immunoassays: implications of use during therapy. <i>Curr Med Res Opin.</i> 2014;30(5):913–922.	Different objective
30	Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. <i>Allergy.</i> 2005;60(3):302–308	Pooled analysis, original RCT already included
31	Bousquet J, Rabe K, Humbert M, et al. Predicting and evaluating response to omalizumab in patients with severe allergic asthma. <i>Respir Med.</i> 2007;101(7):1483–1492.	Pooled analysis, original RCT already included
32	Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. <i>Chest.</i> 2004;125(4):1378–1386	Pooled analysis, original RCT already included
33	Busse WW, Massanari M, Kianifard F, Geba GP. Effect of omalizumab on the need for rescue systemic corticosteroid treatment in patients with moderate-to-severe persistent IgE-mediated allergic asthma: a pooled analysis. <i>Curr Med Res Opin.</i> 2007;23(10):2379–2386	Meeting abstract
34	Corren J, Casale T, Deniz Y, Ashby M. Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. <i>J Allergy Clin Immunol.</i> 2003;111(1):87–90	Pooled analysis, original RCT already included
35	Harris JM, Wong DA, Kapp AV. Development of the Asthma Control Composite outcome measure to predict omalizumab response. <i>Ann Allergy Asthma Immunol.</i> 2011;107(3):273–80	Different objective.
37	Humbert M, Boulet LP, Niven RM, Panahloo Z, Blogg M, Ayre G. Omalizumab therapy: patients who achieve greatest benefit for their asthma experience greatest benefit for rhinitis. <i>Allergy.</i> 2009;64(1):81–84.	Different objective
38	Iribarren C, Rahmaoui A, Long AA, et al. Cardiovascular and cerebrovascular events among patients receiving omalizumab: Results from EXCELS, a prospective cohort study in moderate to severe asthma. <i>J Allergy Clin Immunol.</i> 2017;139(5):1489–1495	Observational study
39	Karpel J, Massanari M, Geba GP, Kianifard F, Inhaber N, Zeldin RK. Effectiveness of omalizumab in reducing corticosteroid burden in patients with moderate to severe persistent allergic asthma. <i>Ann Allergy Asthma Immunol.</i> 2010;105(6):465–470	Meeting abstract
40	Lowe PJ, Renard D. Omalizumab decreases IgE production in patients with allergic (IgE-mediated) asthma; PKPD analysis of a biomarker, total IgE. <i>Br J Clin Pharmacol.</i> 2011;72(2):306–320	No outcome of interest
41	Massanari M, Holgate ST, Busse WW, Jimenez P, Kianifard F, Zeldin R. Effect of omalizumab on	Different outcome

	peripheral blood eosinophilia in allergic asthma. Respir Med. 2010;104(2):188–196	
44	Maykut RJ, Kianifard F, Geba GP. Response of older patients with IgE-mediated asthma to omalizumab: a pooled analysis. J Asthma. 2008;45(3):173–181.	Pooled analysis, original RCT already included
45	Milgrom H, Fowler-Taylor A, Vidaurre CF, Jayawardene S. Safety and tolerability of omalizumab in children with allergic (IgE-mediated) asthma. Curr Med Res Opin. 2011;27(1):163–169	Pooled analysis, original RCT already included
46	Boulet LP, Turcotte H, Laprise C, et al. Comparative degree and type of sensitization to common indoor and outdoor allergens in subjects with allergic rhinitis and/or asthma. Clin Exp Allergy. 1997;27(1):52–59.	Different objective
47	Boulay ME, Lemieux MC, Deschesnes F, Boulet LP. Relationship between cutaneous allergen response and airway allergen-induced eosinophilia. Allergy. 2003;58(9):945–949.	Full text not available.
48	Busse W, Spector S, Rosén K, Wang Y, Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. J Allergy Clin Immunol. 2013;132(2):485–6.	Different disease

Table S4: Summary of the characteristics of the included economic studies

Author, year	Design, Country	Intervention	Control	Time horizon, perspective	Difference in cost (year value)	Difference in outcome	ICER	Risk of bias (CH EC score)	Transferability score	Source of funding
Benralizumab										
ICER 2019	Cost-utility Markov model, US	Lifetime Benralizumab in addition to ST	Lifetime ST	Lifetime, US health care perspective. Societal in the sensitivity analysis.	581,000 \$ (2018 US Dollars)	1.41 QALY	412,000 \$ / QALY	17.5/20	13.5/16	Government grants and non-profit foundations
Tikhonova 2018	Cost-utility Markov model, UK	Lifetime Benralizumab in addition to ST	Lifetime ST	Lifetime, UK NHS perspective. Societal in the sensitivity analysis.	NR £ (2018 US Dollars)	NR QALY	39,135 £ / QALY	15.5/20	12.5/16	AstraZeneca financed the original model critiqued by the University of Exeter
Dupilumab										
ICER 2019	Cost-utility Markov model, US	Lifetime Dupilumab in addition to ST	Lifetime ST	Lifetime, US health care perspective. Societal in the sensitivity analysis.	704,000 \$ (2018 US Dollars)	1.51 QALY	464,000 \$ / QALY	17.5/20	13.5/16	Government grants and non-profit foundations
Omalizumab										
Brown 2007	Cost-utility Markov model, Canada	5-year omalizumab in addition to ST followed by ST	Lifetime ST	Lifetime, health system	33,854 € (NR)	1.08 QALY	31,209 € / QALY	14/20	11/16	Novartis
Campbell 2010	Cost-utility Markov model, US	5-year omalizumab in addition to ST followed by ST	Lifetime ST	Lifetime, health system	91,100 \$ (2008 US Dollar)	0.32 QALY	287,200 \$ / QALY	15.5/20	13.5/16	Novartis

Author, year	Design, Country	Intervention	Control	Time horizon, perspective	Difference in cost (year value)	Difference in outcome	ICER	Risk of bias (CH EC score)	Transferability score	Source of funding
Dal Negro 2011	Cost-utility pre-post study, Italy	1-year omalizumab in addition to ST	1-year ST	1-year, health system	Not clearly reported*	Not clearly reported*	25,983 € / QALY	8.5/18	12/16	Centro Nazionale Studi Farmacoeconomici e Farmacoepidemiologici Respiratori
Dal Negro 2012	Cost-utility pre-post study, Italy	Annual estimation based on 3-year omalizumab treatment in addition to ST	1-year ST	1-year, health system	5,169 € (2011 Euro)	0.22 QALY	23,880 € / QALY	10/19	13/16	Novartis
Dewilde 2006	Cost-utility Markov model, Sweden	5-year omalizumab in addition to ST followed by ST	Lifetime ST	Lifetime, societal	42,754 € (2001-2006 Euro)	0.76 QALY	56,091 € / QALY	17/20	13.5/16	Novartis
Entrenas 2019	Cost-effectiveness pre-post study, Spain	1-year omalizumab in addition to ST	1-year ST	1-year, societal	9,979 € (2016 Euro)	8.4 (mean) increase in ACT score; 6 avoided exacerbations	3,555 € / 3 points increase in ACT score; 1,607 € / avoided exacerbation	11/18	13/16	Novartis
Faria 2014	Cost-utility Markov model, UK	10-year omalizumab in addition to ST followed by ST	Lifetime ST	Lifetime, health system	Not clearly reported (2010 Pounds sterling)	Not clearly reported QALY	≥ <u>12 years</u> 57,557 £ / QALY <u>6 to 11 years</u> 53,348 £ /	16/20	13/16	NIHR HTA-NICE

Author, year	Design, Country	Intervention	Control	Time horizon, perspective	Difference in cost (year value)	Difference in outcome	ICER	Risk of bias (CH EC score)	Transferability score	Source of funding
							QALY			
Jahnz - Rózyk 2018	Cost-effectiveness pre-post study, Poland	1-year omalizumab in addition to ST	1-year ST	1-year, health system	Not reported clearly (2016 Euros)	Not clearly reported	17,721 € / avoided exacerbation	8/18	10/16	Military Institute of Medicine
Levy 2014	Cost-utility pre-post study, Spain	10-month omalizumab in addition to ST	10-month ST	10-month, societal	3,581 € (2012 Euro)	0.1333 QALY	26,865 € / QALY	10/18	13.5/16	Novartis
Menzella 2012	Cost-effectiveness pre-post study, Italy	Annual estimation of 4-year treatment with omalizumab in addition to ST	1-year ST	1-year, health system	Not reported clearly (2010 Euro)	Not clearly reported	2,273 € / avoided exacerbation	8/19	11/16	Novartis (partly)
Morisima 2013	Cost-utility Markov model, Japan	5-year omalizumab in addition to ST followed by ST	Lifetime ST	Lifetime, societal	71,100 (2010 US Dollar)	0.1 QALY	755,200 \$ / QALY	18/20	13.5/16	Ministry of Health, Labour and Welfare of Japan
Norman 2013	Cost-utility Markov model, UK	10-year omalizumab in addition to ST followed by ST	Lifetime ST	Lifetime, health system	<u>≥ 12 years</u> 39,720 <u>6 to 11 years</u> 52,279 (2009-2010 Pounds sterling)	<u>≥ 12 years</u> 0.47 QALY <u>6 to 11 years</u> 0.67 QALY	<u>≥ 12 years</u> 83,822 £ / QALY <u>6 to 11 years</u> 78,009 £ / QALY	17.5/20	15.5/16	NIHR HTA-NICE

Author, year	Design, Country	Intervention	Control	Time horizon, perspective	Difference in cost (year value)	Difference in outcome	ICER	Risk of bias (CH EC score)	Transferability score	Source of funding
Oba 2014	Cost-effectiveness trial based study, US	1-year omalizumab in addition to RM vs. placebo in addition to RM	1-year RM	1-year, health system	Not clearly reported	Not clearly reported	AQLO 378 \$ / 0.5-point increase Controlled day 523 \$ / day	11.5/18	13/16	Not reported
Suzuki 2017	Cost-utility Markov model, Brazil	Lifetime omalizumab in addition to ST	Lifetime ST	Lifetime, health system	280,400 R\$ (2015 Brazilian Real)	5.20 QALY	53,890 R\$ / QALY	13/20	13/16	Novartis
Van Nooten 2012	Cost-utility Markov model, The Netherlands	5-year omalizumab in addition to ST followed by ST	Lifetime ST	Lifetime, societal	55,865 € (2010 Euro)	1.46 QALY	38,371 € / QALY	14.5/20	13/16	Novartis
Vennema 2016	Cost-effectiveness pre-post study, Spain	1-year omalizumab in addition to ST	1-year ST	1-year, societal	8,731 € (2016 Euro)	6.35 (mean) increase in ACT score; 7.72 avoided exacerbations	4,124 € / 3 points increase in ACT score; 1,131 € / avoided exacerbation	10/18	13/16	Novartis
Wu 2007	Cost-utility Markov model, US	10-year omalizumab in addition to ST	10-year ST	10-year, societal	131,000 \$ (2005 US Dollar)	Not clearly defined QALY	821,000 \$ / QALY	14.5/20	12/16	National Heart, Lung, and Blood Institute
Zafari 2016	Cost-utility Markov model, US	5-year omalizumab in addition to ST	5-year ST	5-year (lifetime in SA), health system	101,600 \$ (2013 US Dollar)	0.18 QALY	552,000 \$ / QALY (Lifetime SA 529,000 \$ /	14/20	13/16	Canadian Resp Dis Network

Author, year	Design, Country	Intervention	Control	Time horizon, perspective	Difference in cost (year value)	Difference in outcome	ICER	Risk of bias (CH EC score)	Transferability score	Source of funding
							QALY)			
Zafari 2018	Cost-utility Markov model, US	10-year omalizumab in addition to ST	10-year ST	10-year, health system	179,415 \$ (2013 US Dollar)	0.38 QALY	463,605 \$ / QALY	14.5/20	12.5/16	Canadian Resp Dis Network
Zhou 2018	Cost-utility Markov model, China	5-year omalizumab in addition to ST	5-year ST	5-year, health system	49,047 \$ (2012-2014 US Dollar)	0.233 QALY	211,217 \$ / QALY	16/20	13/16	Shanghai Municipal Health Commission

Table S5: Studies excluded from the health economic evaluation

No.	Author	Reason for exclusion
1	Basu 2017	Did not report health consequences of each alternative. Reported direct costs associated with an asthma related exacerbation
2	Bermejo 2017	No economic evaluation
3	Cooper 2018	No economic evaluation
4	Han 2019	Did not evaluate allergic patients
5	Kolbin, A, Frolov, M 2016	Conference abstract
6	Kolbin, A, Namazova-Baranova, L 2016	Conference abstract
7	Lam2018	Did not evaluate allergic patients
8	Likhar 2016	Conference abstract
9	Martínez-Moragón 2019	Not published in English. Available full text only in Spanish.
10	McQueen 2018	Systematic review used as source of primary studies
11	Rodríguez-Martínez 2018	Systematic review used as source of primary studies
12	Tadrous 2017	Only reported costs. Did not report health consequences of each alternative. Mentioned that there were not significant differences in clinically relevant outcomes
13	Yoshikawa 2016	Did not report health consequences of each alternative. Reported the cost saving due to hospital-free days

14	Whittington 2016	Did not evaluate allergic patients
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Table S6: Direct unitary cost per each type of biologic treatment

	Unitary cost
Benralizumab	
Benralizumab 30 mg by subcutaneous injection once every 4 weeks for 3 doses; then every 8 weeks	4,728.23 ^e
Dupilumab	
Dupilumab 200 mg or 300 mg by subcutaneous injection once every 2 weeks	2,774.65 ^e
Omalizumab	
Omalizumab 150 mg, 1 vial	315.12 € ^a 394.34 € ^b
Administration and monitoring costs of omalizumab (first year)	260 £ ^c children 268 £ ^c
Administration costs of omalizumab (second and thereafter)	146 £ ^c children 151 £ ^c
Hospitalization due to asthma	3,910 € ^d
Emergency unit accesses	154 € ^d
General physician visit	70 € ^d
Clinically significant non-severe exacerbation	1,308 € ^d
Clinically significant severe exacerbation	1,316 € ^d
Non-severe exacerbation	64.70 € ^b
Severe exacerbation	359.59 € ^b
Productivity loss per hour	30.55 € ^d

- a) Reported in 2011 Euros by Dal Negro et al [DalNegro2012].
- b) Reported in 2001-2006 Euros by Dewilde et al [Dewilde2006].
- c) Reported in 2010 Pounds sterling by Faria et al [Faria2014].
- d) Reported in 2010 Euros by van Nooten et al [vanNooten2013].
- e) Reported in 2018 US Dollars by ICER [ICER2018].

Table S7: Evidence profiles of the economic evidence

Comparison 1: Benralizumab in addition to standard therapy vs. standard therapy

Quality assessment							Summary of resources and costs			Quality
N°. of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Incremental cost per patient*	Incremental effect per patient*	ICER	
ICER per QALY (high quality study - not funded by Industry)										
1 ^a	Cost-utility, Markov model	Not serious ¹	Not serious	Serious ²	Serious ³	Not serious	581,000 \$ (lifetime horizon)	1.41 QALYs (lifetime horizon)	412,000 \$ / QALY	⊕⊕⊕○ MODERATE
ICER per QALY (high quality study - funded by Industry)										
1 ^b	Cost-utility, Markov model	Not serious ⁴	Not serious	Serious ⁵	Serious ⁶	Not serious	NR £ (lifetime horizon)	NR QALYs (lifetime horizon)	39,135 £ / QALY	⊕⊕○○ LOW

*Incremental cost and effect due to the addition of Benralizumab.

ICER: Incremental cost-effectiveness ratio. QALY: Quality adjusted life years. \$: US Dollar. £: British pounds. NR: Not reported.

1. Markov model study with low risk of bias (CHEC score 13 or higher).
2. One single study performed in the USA. The results may not be applicable to other countries.
3. The deterministic sensitivity analysis showed large variations in the ICER value from 250,000 \$ to 950,000 \$ (0.85 to 0.81 utilities gained, respectively). Furthermore, at a threshold of 50,000, the probability for benralizumab to be cost-effective was 0%.
4. One single study performed in the UK. The results may not be applicable to other countries.
5. The ICER varied from 34,270 £ reported by AstraZeneca to 73,560 £ found by the University of Exeter in the deterministic sensitivity analysis (zero asthma related mortality).
6. AstraZeneca financed the original model critiqued by the University of Exeter. The University explored ICER sensitivity through changes in the age-stratified probabilities for hospitalised patients, oral corticosteroids use at baseline (42%), administration cost of benralizumab, and treatment discontinuation rate (0.0041/cycle).

Comparison 2: Dupilumab in addition to standard therapy vs. standard therapy

Quality assessment							Summary of resources and costs			Quality
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N°. of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Incremental cost per patient*	Incremental effect per patient*	ICER	
ICER per QALY (high quality study - not funded by Industry)										
1 ^a	Cost-utility, Markov model	Not serious ¹	Not serious	Serious ²	Serious ³	Not serious	704,000 \$ (lifetime horizon)	1.51 QALYs (lifetime horizon)	464,000 \$ / QALY	⊕⊕⊕○ MODERATE

*Incremental cost and effect due to the addition of Dupilumab.

ICER: Incremental cost-effectiveness ratio. QALY: Quality adjusted life years. \$: US Dollar.

1. Markov model study with low risk of bias (CHEC score 13 or higher).
2. One single study performed in the USA. The results may not be applicable to other countries.
3. The deterministic sensitivity analysis showed large variations in the ICER value from 300,000 \$ to 1,000,000 \$ (0.85 to 0.81 utilities gained, respectively). Furthermore, at a threshold of 50,000, the probability for Dupilumab to be cost-effective was 0%.

Comparison 3: Omalizumab in addition to standard therapy vs. standard therapy

Quality assessment							Summary of resources and costs			Quality
Nº. of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Ppublication bias	Incremental cost per patient (range)*	Incremental effect per patient (range)*	ICER (range)	
ICER per QALY (high quality studies - not funded by Industry)										
7 ^{a-g}	Cost-utility, Markov model	Not serious ¹	Not serious ²	Not serious ³	Serious ⁴	Not serious	39,720 £ to 179,415 \$ (5year to lifetime horizon)	0.18 to 0.67 QALYs (5year to lifetime horizon)	53,348 £ to 821,000 \$ / QALY	⊕⊕⊕○ MODERATE
ICER per QALY (high quality studies - funded by Industry)										
5 ^{h-l}	Cost-utility, Markov model	Not serious ¹	Not serious ²	Not serious ⁵	Serious ⁶	Serious ⁷	33,854 € to 91,100 \$ (5year to lifetime horizon)	0.32 to 1.46 QALYs (5year to lifetime horizon)	31,209 € to 287,200 \$ / QALY	⊕⊕○○ LOW
ICER per QALY (low quality studies)										
3 ^{m-o}	Cost-utility, pre-post study	Very serious ⁸	Not serious ⁹	Not serious ¹⁰	Not serious ¹¹	Serious ¹²	3,581 € to 5,169 € (10 months to 1 year horizon)	0.13 to 0.22 QALYs (10 months to 1 year horizon)	23,880 € to 26,865 € / QALY	⊕○○○ VERY LOW
ICER per avoid exacerbation (low quality studies)										
4 ^{p-s}	Cost-effectiveness, pre-post study	Very serious ⁸	Not serious ⁹	Not serious ¹³	Not serious ¹¹	Serious ¹⁴	8,731 € to NR (1 year horizon)	NR to 7.72 avoided exacerbations (1 year horizon)	1,131 € to 17,721 € / avoided exacerbation	⊕○○○ VERY LOW
ICER per increase in ACT (Asthma Control Test) score										
2 ^{p,s}	Cost-effectiveness, pre-post study	Very serious ⁸	Not serious ⁹	Not serious ¹³	Not serious ¹¹	Serious ¹⁵	8,731 € to 9,979 € (1 year horizon)	6.35 to 8.4 mean increase in ACT score (1 year horizon)	3,555 € to 4,124 € / 3 points increase in ACT score	⊕○○○ VERY LOW
ICER per increase in AQLQ (Juniper Asthma-Related Quality of Life Questionnaire) score										

Quality assessment							Summary of resources and costs			Quality
Nº. of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Incremental cost per patient (range)*	Incremental effect per patient (range)*	ICER (range)	
1 ^t	Cost-effectiveness, trial based study	Very serious ⁸	Not serious	Not serious	Not serious	Serious ¹⁶	NR	NR	378 \$ / 0.5-point increase in AQLQ score	⊕○○○ VERY LOW
ICER per controlled day										
1 ^t	Cost-effectiveness, trial based study	Very serious ⁸	Not serious	Not serious	Not serious	Serious ¹⁶	NR	NR	523 \$ / day	⊕○○○ VERY LOW

*Incremental cost and effect due to the addition of omalizumab. Range (minor and maximum value) as reported by the studies.

ICER: Incremental cost-effectiveness ratio. QALY: Quality adjusted life years. ACT: Asthma Control Test. €: Euro. \$: US Dollar. NR: Not clearly reported in the study. AQLQ: Juniper Asthma-Related Quality of Life Questionnaire.

7. Markov model studies with low risk of bias (CHEC score 13 or higher).
8. All studies reported an ICER higher than 30,000 €, which is the willingness to pay threshold in most European countries.
9. Six studies were performed in high-income countries (two in the UK^{a,c}, three in the USA^{d,e,f}, one in Japan^b), and one in China^g. Three studies^{a,c,g} included children, whereas the rest only adults.
10. Reported ICERs varied from 53,348 £ to 821,000 \$ per QALY.
11. Four studies were performed in high-income countries (two in Europe^{h,i}, two in North America^{j,l}), one in Brazil. All included adults.
12. Reported ICERs varied from 31,209 € to 287,200 \$ per QALY.
13. All studies financed by Novartis (manufacturer of omalizumab) reported lower ICERs compared to those not financed by Industry.
14. CHEC score lower than 13 (see limitations and transferability assessment section). Cost-utility analysis based on a pre-post study has several limitations. The most important is the bias of not including all clinical health states and the potential exclusion of severe patients. Mortality was impossible to be measured (all included patients were alive). Utilities in post-omalizumab are conditioned by pre-omalizumab results.
15. All studies reported an ICER lower than 30,000 €, which is the willingness to pay threshold in most European countries.
16. All studies conducted in European countries (2 in Italy, 1 in Spain).
17. Reported ICERs showed scarce variation.
18. Two studies financed by Novartis, one by a research centre.
19. All studies conducted in European countries.
20. Three studies with ICER lower or equal than 2,273 € / avoided exacerbation were financed by Novartis. The higher ICER (17,721 €) was reported by a study non-Industry funded.
21. Novartis financed the studies.
22. Source of funding not reported.

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Tables S8: Benralizumab efficacy and safety compared to standard of care for allergic asthma

a. Exacerbation

Annual asthma exacerbation rates

Chipps 2018 reported the annual asthma exacerbation rate. Estimates were calculated using a negative binomial model, with adjustment for study code, treatment, region, oral corticosteroid use at time of randomization, and prior exacerbations. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred.

Annual Exacerbation rates - All patients (met atopy and IgE criteria)

Measure	Benralizumab QW8 (n=297)	Placebo (n= 271)
Exacerbation rate (95% CI)	0.80 (0.67 to 0.96)	1.27 (1.08 to 1.49)
Rate ratio vs placebo (95% CI)	0.63 (0.50 to 0.81)	-
Absolute difference vs placebo	- 0.47 (-0.72 to -0.21)	-

b. Asthma control

Asthma Control Questionnaire-6

Chipps 2018 reported on ACQ-6 change is from baseline (ie, last value before randomization) to EOT (SIROCCO: week 48; CALIMA: week 56) in all patients that met atopy and IgE criteria, but did not report by baseline serum IgE concentrations or atopy status. Estimates were calculated using a mixed effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit per treatment.

ACQ-6 change is from baseline - All patients (met atopy and IgE criteria)

Measure	Benralizumab QW8 (n=217)	Placebo (n= 197)
LS mean change	-1.21	-1.04
LS mean difference vs placebo (95% CI)	-0.17 (-0.34 to 0.00)	-

* Low numbers represent better symptom control.

c. Lung function

Pre-bronchodilator Forced Expiratory Volume in 1 Second (Litres) Change (Baseline–EOT)

Chipps 2018 reported on pre-bronchodilator forced expiratory volume in 1 second change from baseline (ie, last value before randomization) to end of treatment [EOT] (SIROCCO: week 48; CALIMA: week 56). Estimates were calculated by using a mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, oral corticosteroid use at time of randomization, and visit.

Pre-bronchodilator FEV1 change is from baseline - All patients (met atopy and IgE criteria)

Measure	Benralizumab QW8 (n=257)	Placebo (n= 233)
LS mean change	0.277	0.222
LS mean difference vs placebo (95% CI)	0.055 (-0.025 to 0.136)	-

QW8=every 8 weeks (first 3 doses every 4 weeks); LS= least squares

d. Quality of life

Chipps 2018 reported on QoL changes from baseline to end of treatment (EOT) measured with the (AQLQ(S)+12), in all patients that met atopy and IgE criteria, but did not report it by baseline serum IgE concentrations or atopy status.

AQLQ(S)+12

(AQLQ(S)+12* Change from baseline to EOT - All patients (met atopy and IgE criteria)

Measure	Benralizumab QW8 (n=209)	Placebo (n= 195)
LS mean change	1.24	1.14
LS mean difference vs placebo (95% CI)	0.1 (-0.08 to 0.28)	-

QW8=every 8 weeks (first 3 doses every 4 weeks); LS= least squares

* High numbers suggest better quality of life

e. Safety

Chipps 2018 did not report on any serious adverse events or any drug-related adverse event in the subgroup of population (from SIROCCO and CALIMA studies) that met atopy or IgE criteria. However, the studies of Nair 2017 and Fitzgerald 2016 reported on these outcomes on patients with severe asthma regardless the atopy status.

Any serious adverse event unrelated to asthma exacerbation (Nair 2017)

Measure	Benralizumab QW8 (n=73)	Placebo (n= 75)
Number of events (SAE)	6	11
Risk ratio vs placebo (95% CI)	0.56 (0.22 to 1.44)	-

Any drug-related adverse events (Fitzgerald 2016)

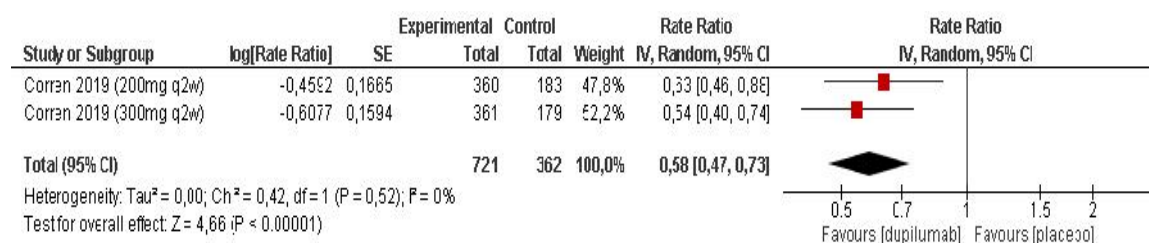
Measure	Benralizumab QW8 (n=230)	Placebo (n= 248)
Number of events (AE)*	34	26
Risk ratio vs placebo (95% CI)	1.41 (0.07 to 2.27)	-

* Urgent care visit or admission to hospital for patients with blood eosinophil counts ≥ 300 cells/u L and high-dose ICS plus LABA

Figures S1: Forest Plots for efficacy and safety of dupilumab compared to standard of care for allergic asthma

a. Exacerbation

Exacerbation rate ratio (by allergic asthma)* †

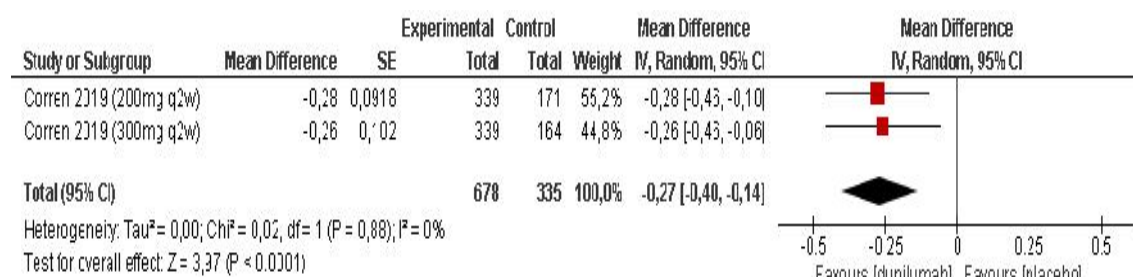


*Corren 2019 reported a post-hoc analysis from the pooled intention to treat population of the LIBERTY ASTHMA QUEST, in patients with evidence of allergic asthma. Allergic asthma ($n=1083$) was defined as total serum IgE ≥ 30 IU/mL and ≥ 1 positive pre-natal aeroallergen-specific IgE ≥ 0.35 kU/L at baseline.

†Annualized rate of severe exacerbation (number of exacerbations per person year) was defined as a deterioration of asthma requiring: i) the use of systemic corticosteroids for ≥ 3 days or ii) hospitalization/emergency room visit because of asthma, requiring systemic corticosteroids. Outcome assessment was performed on week 52 (Corren 2019).

b. Asthma control

Asthma Control Questionnaire-5 (by allergic asthma)* †

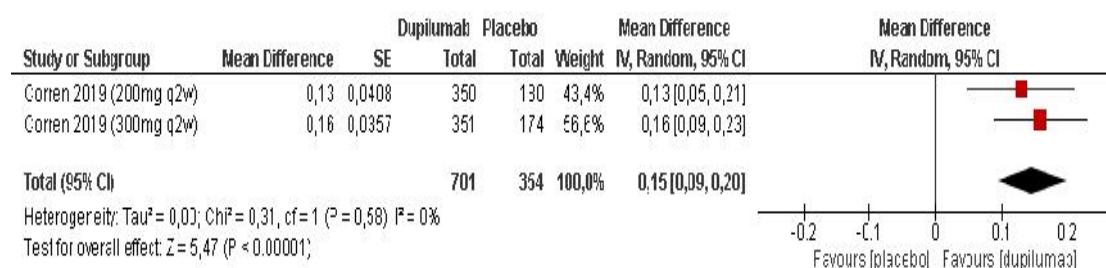


*ACQ-5 mean difference between groups assessed at week 24.

†Higher ACQ-5 scores indicate poorer control (scale from 0 [no impairment] to 6 [maximum impairment]). Minimal important difference: 0.5 points.

c. Lung function

Pre-bronchodilator Forced Expiratory Volume in 1 Second (Litres) Change (Baseline-12W) (by allergic asthma)* †



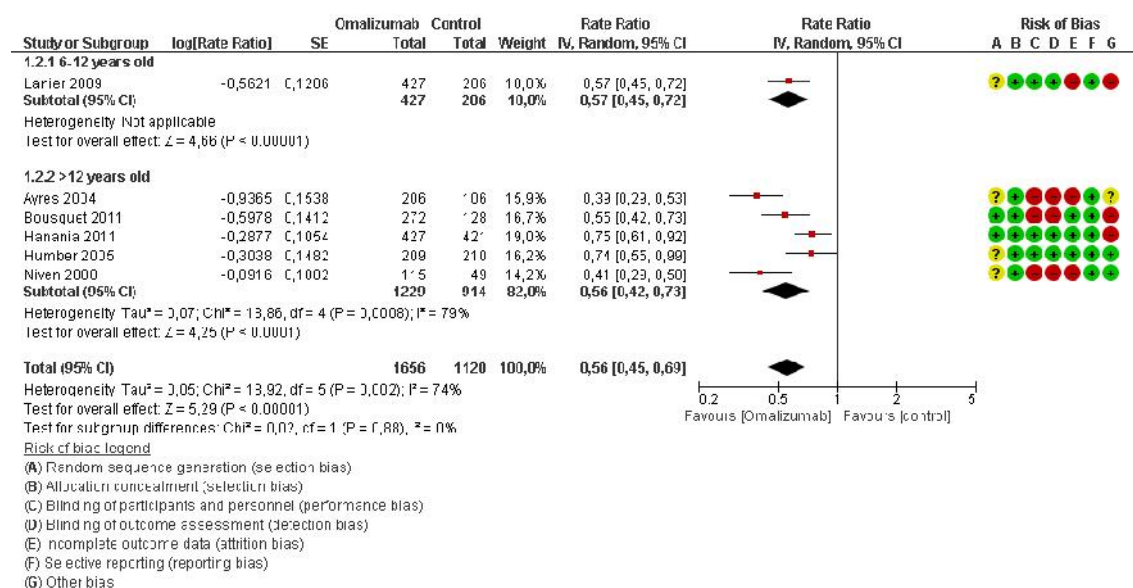
*Change from baseline reported at week 12 (Corren 2019)

†Minimal important difference: 0.20L (Guidelines development group consensus)

Figures S2: Forest Plots for omalizumab efficacy and safety compare to standard of care for allergic asthma

a. Exacerbation

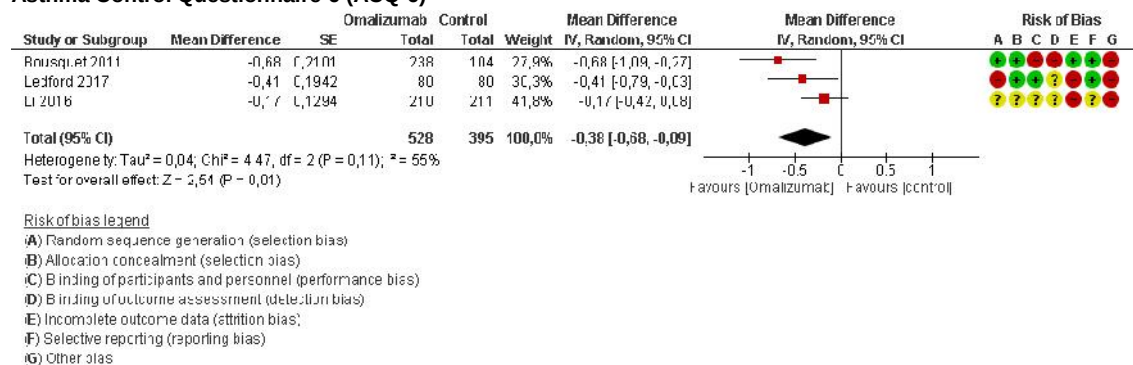
Clinically significant asthma exacerbations rate (By age)*



*Annualized rate of clinical significant asthma exacerbation were defined as episodes of asthma worsening requiring treatment with systemic corticosteroids. Outcome assessment range from weeks 24-28 (Bousquet2011, Humber2005) to weeks 48-52 (Ayres2004, Hanania2011, Lanier2009, Niven2008).

b. Asthma control

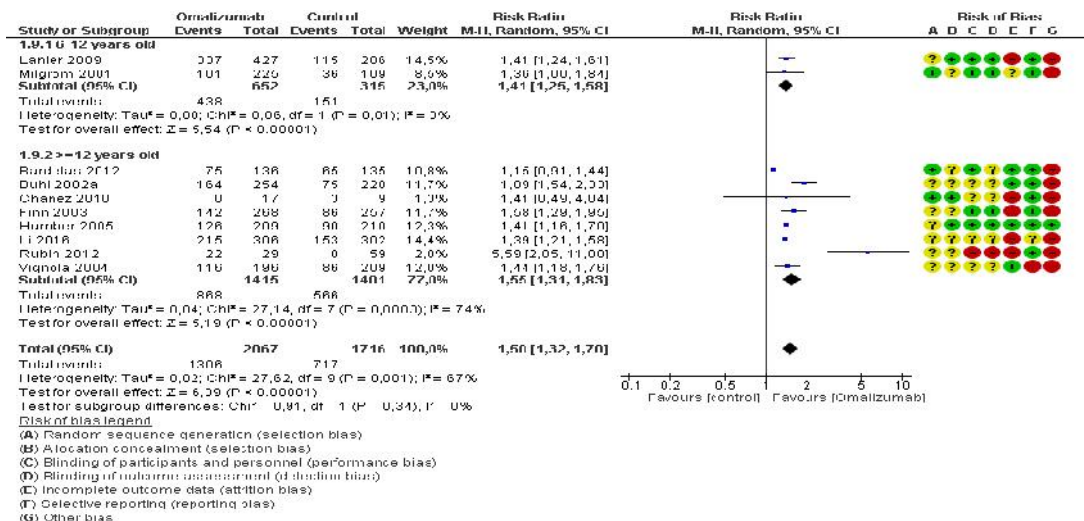
Asthma Control Questionnaire-6 (ACQ-6)*



*Bousquet2011, Li2016 assessed ACQ-6 at 24-32 weeks and Ledford2017 at 52 weeks. All studies include 12-75 years old patients.

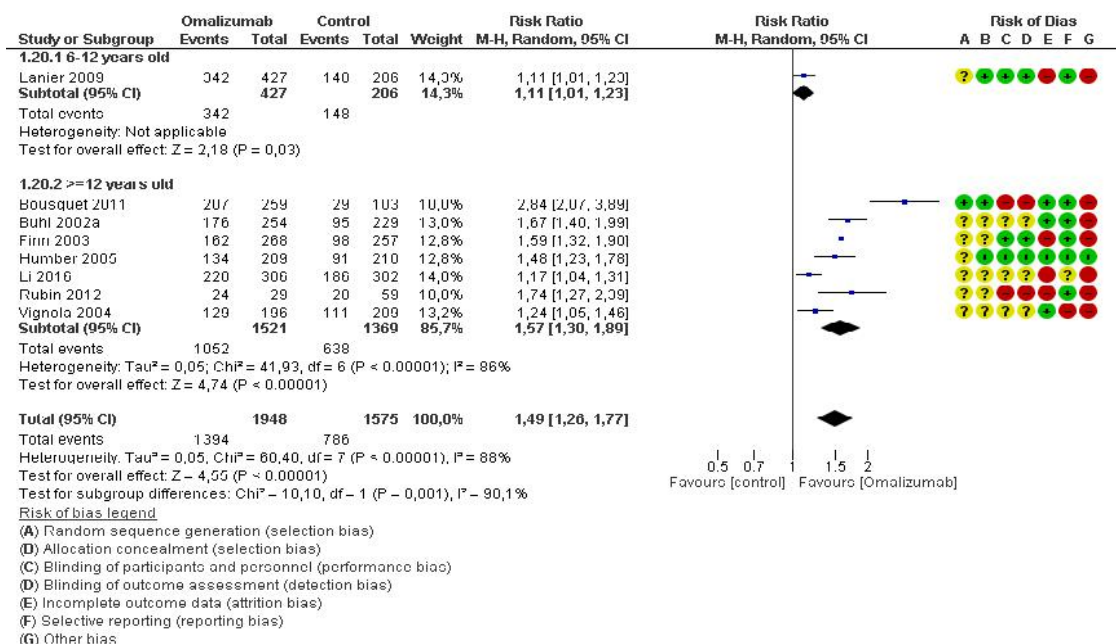
c. Global evaluation of treatment effectiveness (GETE) (By age)

Assessed by physicians/investigators*



***Lanier2009** assessed GETE (physicians) in children of 6 to <12 years old and follow them for 52 weeks. All but two studies assessed GETE at 24-28 weeks, and the remaining two studies, **Chanez2010** and **Rubin2012** at 16-20 weeks.

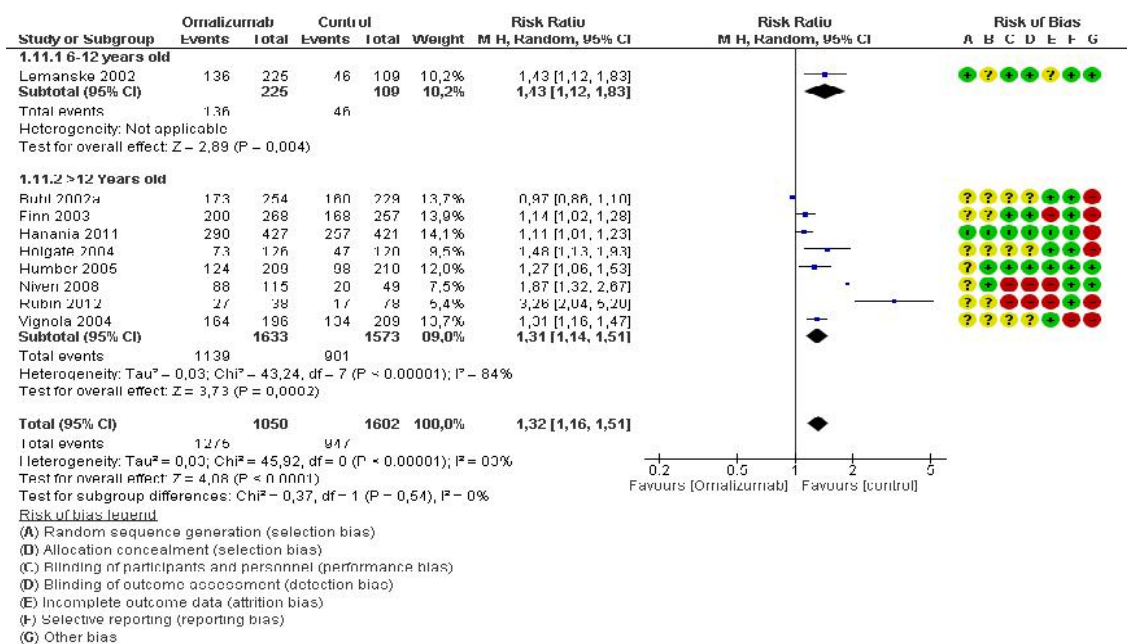
Assessed by Patients*



* Two studies assessed GETE (patients) at 24-32 week and the other two studies at 20 weeks (**Rubin2012**) and 52 weeks (**Lanier2009**).

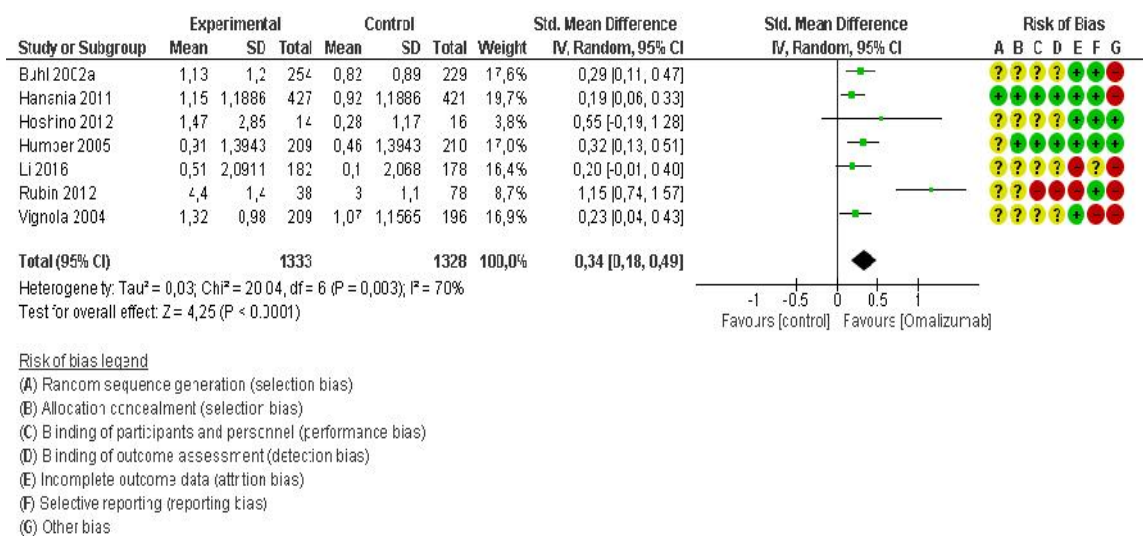
d. Quality of life

Clinically improvement of Asthma Quality of Life Questionnaire (S) (≥ 0.5)*



*Two studies assessed clinically improvement AQOLQ at 20-32 weeks and the other two studies Finn2003 and Buhl2002a at 48-52 weeks.

The mean change of Asthma Quality of Life Questionnaire (AQLQ)*



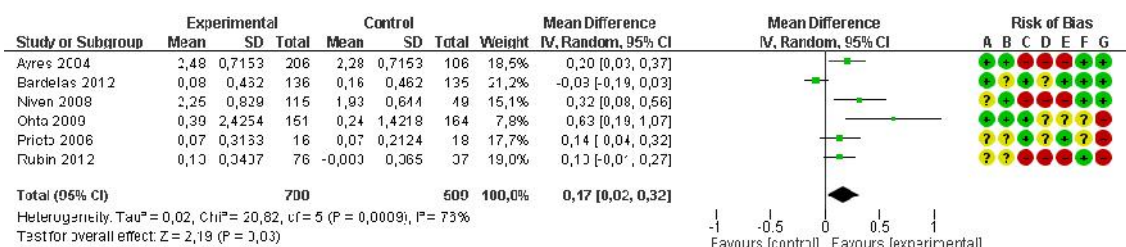
*Hishino2012 included allergic asthma patients aged 20–75 years and assessed AQOLQ at 12-16 weeks. Also Li2016, Rubin2012, and Vignola2004 assessed QOLQ at 20-28 weeks.

DESCRIPTIVE RESULTS

An additional study, Finn 2003, reported the least-square mean change from baseline of omalizumab vs. placebo: 0.93 vs. 0.66 at 16 weeks, 0.97 vs. 0.7 at 28 weeks, and 1.19 vs. 0.91 at 52 weeks.

e. Lung function

Pre-bronchodilator Forced Expiratory Volume in 1 second (FEV1). Absolute FEV1 (L)*



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

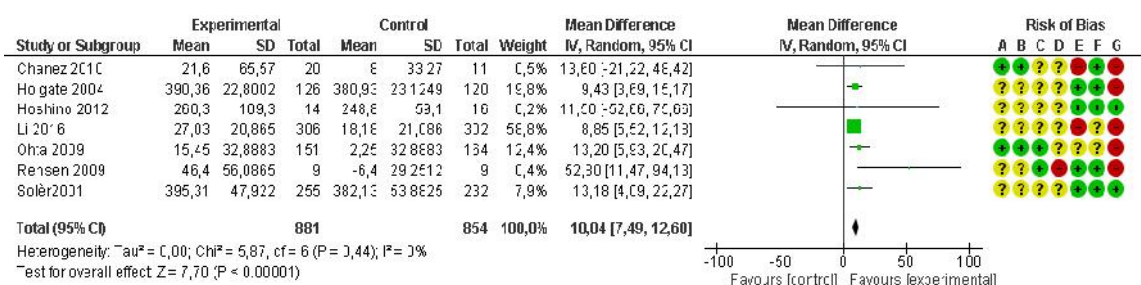
*Ayres2004, reported absolute FEV1 (L) without standard deviations (SD), which were imputed for the experimental and control groups. All studies reported data in a population >12 years old.

DESCRIPTIVE RESULTS

Lanier2003 reported between group differences in FEV1 at week 48 and 52 in 0.040 L (p=0.28) and 0.052 L (p=0.16), respectively.

Milgrom2001 reported FEV1 in children (6-12 years old) for 28 weeks follow up. Mean FEV-1 was 1,7971 L in the omalizumab group and 1,8552 L in the placebo group at week 0; it was 1,8910 L (change from baseline 0.0939 L) versus 1,8835 L (change from baseline 0.0283 L) at week 28.

Morning peak expiratory flow rate (PEF)



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

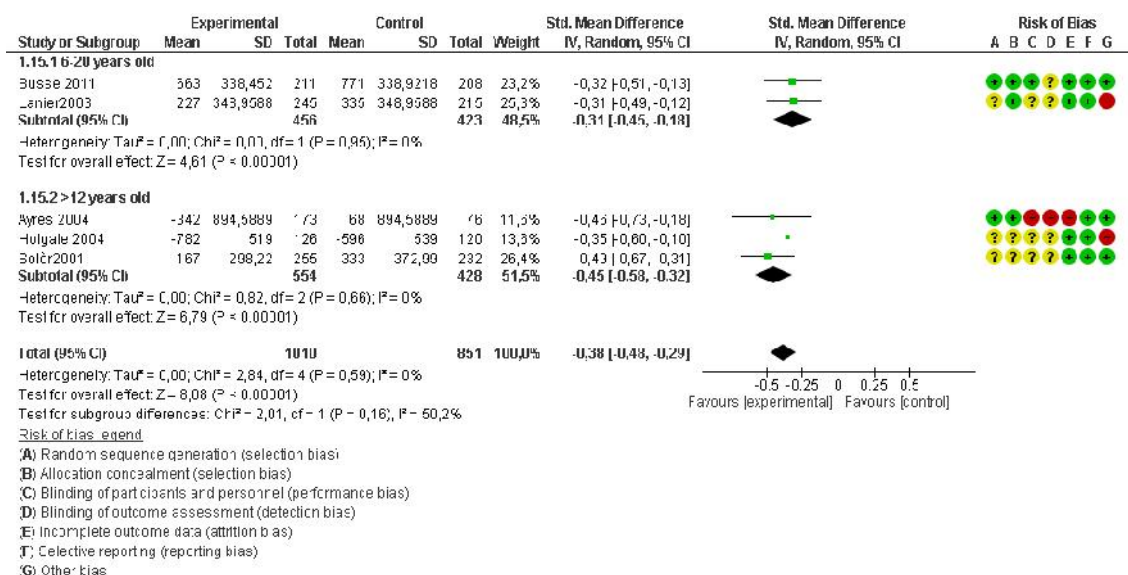
*One study included ≥ 12 years old patients, only Rensen2009 included adults from 18-29 years old. Soler2001 and Holgate2004 reported morning PEF in a graph. We extracted data using the plot digitizer [Jelicic 2016] and SD was imputed for the experimental and control groups.

DESCRIPTIVE RESULTS

Milgrom2001 reported PEF in children (6-12 years old) for 28 weeks follow up. Mean morning PEF was 261.3 L/min in the omalizumab group and 264.0 L/min in the placebo group at week 0; it was 269.8 L/min (change from baseline 8.5 L/min) vs 265.0 L/min (change from baseline 1 L/min) at the end of the study (week 28).

f. Use of inhaled corticosteroid (ICS)

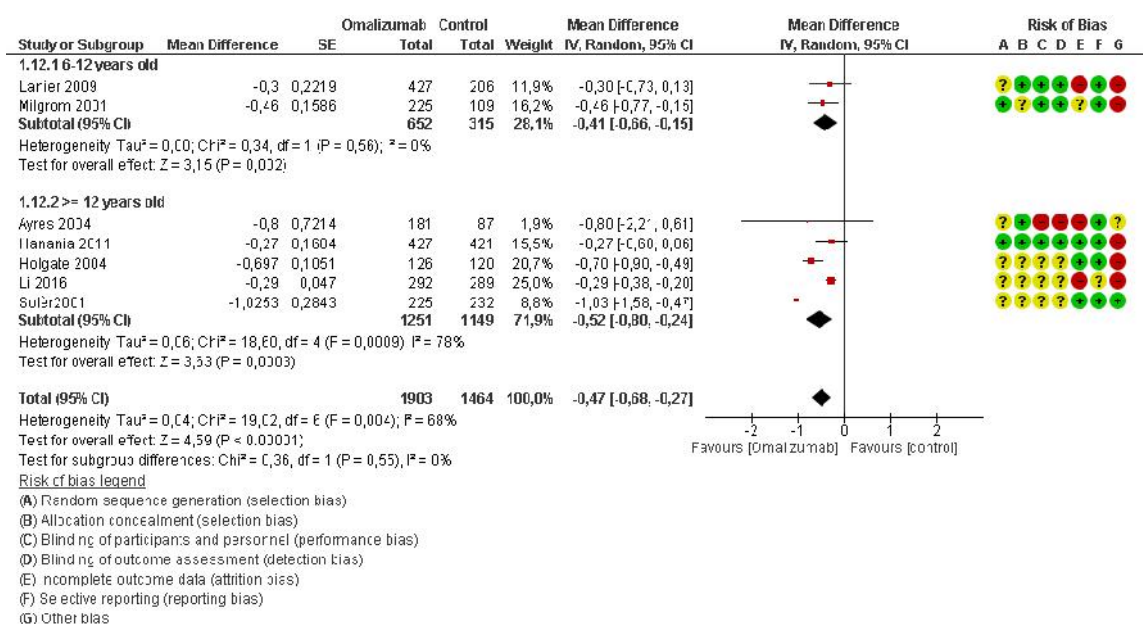
Decrease in inhaled corticosteroid (ICS) dose (by age)



Ayres2004 and Lanier2003 reported data without SD, therefore standard deviations were imputed for the experimental and control groups. Soler2001 reported median and interquartile range, therefore mean and SD were imputed. Reported data express mean in reduction (from baseline) of ICS dose or mean of ICS prescribed.

g. Rescue Medication Use

The change from baseline of rescue medication use (puffs/day)



* The effect of Ayres2004, Soler2001, Chanez2010 were imputed from median (range); Three studies assessed rescue medication use at 26-32 weeks and the other three studies, Ayres2004, Lanier2009, and Hanania 2011 at 48-52 weeks.

DESCRIPTIVE RESULTS

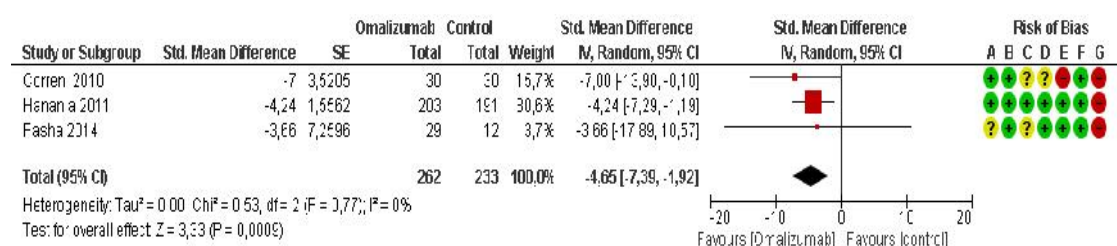
Bardelas2012 reported Oral corticosteroid bursts rate of 0.157 in omalizumab group and a rate of 0.254 in the placebo group, the rate ratio was 0.63(0.26-1.53).

Humber2005 reported a reduction of 0.5puffs/day in the omalizumab group versus placebo group.

Chanez2010 reported the median (range) of the number of rescue SABA puffs per week change from baseline of 1.0(-45-17) in the Omalizumab group and of 0.0(-22-4) in the placebo group.

h. FeNO

FeNO level change from baseline *



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

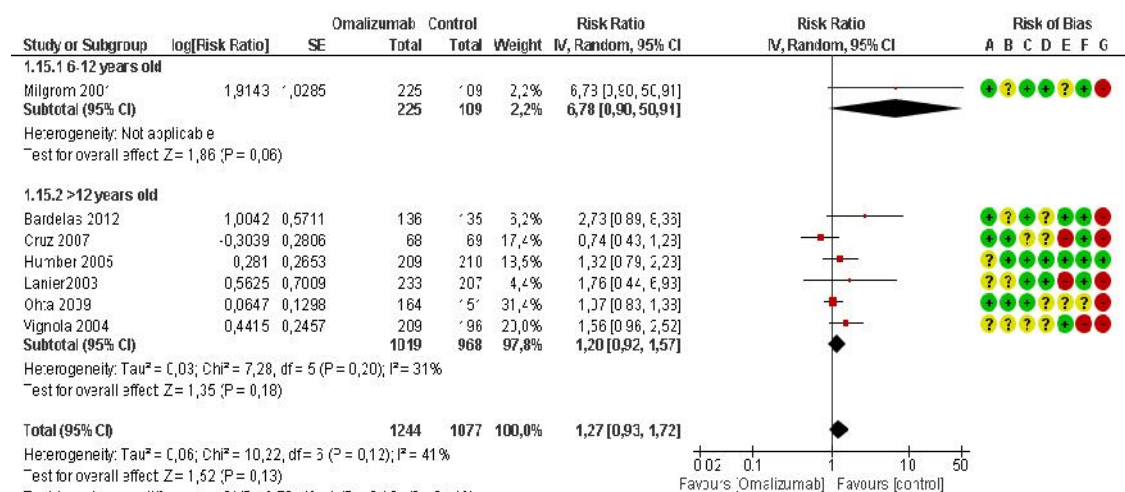
*Corren2010 reported FeNO level change at 16 weeks after 24h of the cat allergen room challenge. Pasha2014 reported FeNO in a graph by median and interquartile range (IQR), therefore we extracted data using plot digitizer [Jelicic 2016] and mean and SD was imputed for the experimental and control groups.

DESCRIPTIVE RESULTS

Zielen2013 reported FeNO change according to IgE level. The median percentage change was -7.2 (for IgE 30-300 IU/ml) and -16 (for IgE 700–2,000 IU/ml) in the Omalizumab group and 64 in the placebo group.

i. Safety

Any drug-related Adverse Events (AE) (By age)*

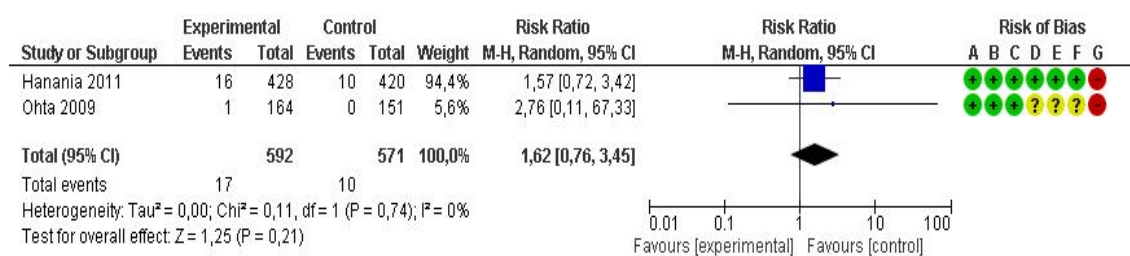


Risk of bias legend

- (A) Random sequence generation (selection bias)
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- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

* Three studies assessed AE at 26–28 weeks and the other three are Ohta2009 at 16 weeks and Lanier2003 and Cruz2007 at 52 weeks.

Any drug-related Serious Adverse Events (SAE)*



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

*Ohta 2009 evaluate SAE at 16 weeks and Hanania 2011 at 48 weeks.

Supplementary file 2: Search Strategies

Search strategy for evidence of effects

MEDLINE PubMed 30/01/2019	<table><tr><td>#12</td><td>Add</td><td>Search #5 OR #8 OR #11</td><td>770</td><td>07:35:20</td></tr><tr><td>#11</td><td>Add</td><td>Search #9 AND #10</td><td>13</td><td>07:34:32</td></tr><tr><td>#10</td><td>Add</td><td>Search "Vaccines"[Mesh] OR vaccin*[ti]</td><td>248570</td><td>07:34:22</td></tr><tr><td>#9</td><td>Add</td><td>Search #6 NOT #8</td><td>2676</td><td>07:34:07</td></tr><tr><td>#8</td><td>Add</td><td>Search #6 AND #7</td><td>680</td><td>07:33:51</td></tr><tr><td>#7</td><td>Add</td><td>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])</td><td>1107735</td><td>07:33:45</td></tr><tr><td>#6</td><td>Add</td><td>Search #3 NOT #5</td><td>3356</td><td>07:33:37</td></tr><tr><td>#5</td><td>Add</td><td>Search #3 AND #4</td><td>77</td><td>07:33:22</td></tr><tr><td>#4</td><td>Add</td><td>Search systematic[sb]</td><td>126175</td><td>07:33:11</td></tr><tr><td>#3</td><td>Add</td><td>Search #1 AND #2</td><td>3433</td><td>07:32:42</td></tr><tr><td>#2</td><td>Add</td><td>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]</td><td>47689</td><td>07:32:25</td></tr><tr><td>#1</td><td>Add</td><td>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]</td><td>447588</td><td>07:32:11</td></tr></table>	#12	Add	Search #5 OR #8 OR #11	770	07:35:20	#11	Add	Search #9 AND #10	13	07:34:32	#10	Add	Search "Vaccines"[Mesh] OR vaccin*[ti]	248570	07:34:22	#9	Add	Search #6 NOT #8	2676	07:34:07	#8	Add	Search #6 AND #7	680	07:33:51	#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])	1107735	07:33:45	#6	Add	Search #3 NOT #5	3356	07:33:37	#5	Add	Search #3 AND #4	77	07:33:22	#4	Add	Search systematic[sb]	126175	07:33:11	#3	Add	Search #1 AND #2	3433	07:32:42	#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]	47689	07:32:25	#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]	447588	07:32:11																																																																																																																								
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	36	limit 35 to "systematic review" (175)	
	37	35 not 36 (5190)	
	38	limit 37 to "therapy (best balance of sensitivity and specificity)" (1491)	
The Cochrane Library 30/01/2019 Cochrane Central Register of Controlled Trials Issue 1 of 12, January 2019 [1180 hits]	#1	MeSH descriptor: [Asthma] explode all trees	10851
	#2	MeSH descriptor: [Rhinitis, Allergic] explode all trees	2786
	#3	MeSH descriptor: [Rhinitis] explode all trees	3553
	#4	MeSH descriptor: [Sinusitis] explode all trees	888
	#5	MeSH descriptor: [Nasal Polyps] explode all trees	319
	#6	MeSH descriptor: [Dermatitis, Atopic] explode all trees	1518
	#7	MeSH descriptor: [Dermatitis] explode all trees	3660
	#8	MeSH descriptor: [Urticaria] explode all trees	674
	#9	MeSH descriptor: [Eosinophilic Esophagitis] explode all trees	57
	#10	MeSH descriptor: [Food Hypersensitivity] explode all trees	825
	#11	allerg*:ti,ab	17766
	#12	asthma*:ti,ab	26324
	#13	(atopic NEXT dermatitis):ti,ab	2555
	#14	dermatitis:ti,ab	4394
	#15	urticaria:ti,ab	1357
	#16	erythema:ti,ab	4071
	#17	rhinosinusitis:ti,ab	950
	#18	(allergic NEXT rhinitis):ti,ab	5127
	#19	(food NEAR5 react*):ti,ab	80023
	#20	(eosinophilic NEXT esophagitis):ti,ab	152
	#21	esophagitis:ti	997
	#22	eosinophil*:ti	1029
	#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	124342
	#24	mepolizumab:ti,ab	172
	#25	reslizumab:ti,ab	70
	#26	benralizumab:ti,ab	94
	#27	dupilumab:ti,ab	141
	#28	omalizumab:ti,ab	637
	#29	lebrikizumab:ti,ab	49
	#30	tralokinumab:ti,ab	41
	#31	tezepelumab:ti,ab	8
	#32	brodalumab:ti,ab	70
	#33	ligelizumab:ti,ab	14
	#34	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33	1466
	#35	#23 AND #34	1180

Search strategy for economic evidence

MEDLINE PubMed 27/08/2019	#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] 457361 12:53:56 #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]) 51477 12:57:47 #3 Add Search #1 AND #2 3851 12:59:59 #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])) 850194 13:03:29 #5 Add Search #3 AND #4 270 13:06:48
EMBASE Ovid Embase <1974 to 2019 January 29> 30/01/2018	Ovid Embase 1 exp asthma/ (237991) 2 exp allergic rhinitis/ (36816) 3 *rhinitis/ (5649) 4 exp sinusitis/ (39314) 5 *nose polyp/ (5041) 6 exp atopic dermatitis/ (38417) 7 *dermatitis/ (9465) 8 exp urticaria/ (40115) 9 exp eosinophilic esophagitis/ (5319) 10 exp food allergy/ (31742) 11 allergy.ti.ab. (92943) 12 allergic.ti.ab. (146253) 13 asthma*.ti.ab. (206208) 14 atopic dermatitis.ti.ab. (28752) 15 dermatitis.ti. (36058) 16 urticaria.ti. (8720)

	17	erythema.ti. (7091)
	18	rhinosinusitis.ti. (5540)
	19	allergic rhinitis.ti,ab. (24674)
	20	(food adj5 (allerg* or react*)).ti,ab. (23811)
	21	eosinophilic esophagitis.ti,ab. (4268)
	22	esophagitis.ti. (7426)
	23	eosinophil*.ti. (30459)
	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 (548337)
	25	mepolizumab.ti,ab. (677)
	26	reslizumab.ti,ab. (226)
	27	benralizumab.ti,ab. (194)
	28	dupilumab.ti,ab. (396)
	29	omalizumab.ti,ab. (3891)
	30	lebrikizumab.ti,ab. (103)
	31	tralokinumab.ti,ab. (69)
	32	tezepelumab.ti,ab. (12)
	33	brodalumab.ti,ab. (275)
	34	ligelizumab.ti,ab. (13)
	35	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (5365)
	36	limit 35 to "systematic review" (175)
	37	35 not 36 (5190)
	38	limit 37 to "therapy (best balance of sensitivity and specificity)" (1491)
The Cochrane Library 27/08/2019 Cochrane Central Register of Controlled Trials Issue 8 of 12, August 2019	#1	MeSH descriptor: [Asthma] explode all trees 10992
	#2	MeSH descriptor: [Rhinitis, Allergic] explode all trees 2837
	#3	MeSH descriptor: [Rhinitis] explode all trees 3627
	#4	MeSH descriptor: [Sinusitis] explode all trees 925
	#5	MeSH descriptor: [Nasal Polyps] explode all trees 335
	#6	MeSH descriptor: [Dermatitis, Atopic] explode all trees 1613
	#7	MeSH descriptor: [Dermatitis] explode all trees 3808
	#8	MeSH descriptor: [Urticaria] explode all trees 698
	#9	MeSH descriptor: [Eosinophilic Esophagitis] explode all trees 62
	#10	MeSH descriptor: [Food Hypersensitivity] explode all trees 869

#11	allerg*:ti,ab	23024	
#12	asthma*:ti,ab	30618	
#13	(atopic NEXT dermatitis):ti,ab	3409	
#14	dermatitis:ti,ab	5674	
#15	urticaria:ti,ab	1624	
#16	erythema:ti,ab	5107	
#17	rhinosinusitis:ti,ab	1155	
#18	(allergic NEXT rhinitis):ti,ab	5852	
#19	(food NEAR5 react*):ti,ab	99337	
#20	(eosinophilic NEXT esophagitis):ti,ab	199	
#21	esophagitis:ti	1138	
#22	eosinophil*:ti	1199	
#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		152516
#24	MeSH descriptor: [Antibodies, Monoclonal, Humanized] explode all trees	6142	
#25	mepolizumab:ti,ab	230	
#26	reslizumab:ti,ab	96	
#27	benralizumab:ti,ab	131	
#28	dupilumab:ti,ab	221	
#29	omalizumab:ti,ab	792	
#30	lebrikizumab:ti,ab	67	
#31	tralokinumab:ti,ab	64	
#32	tezepelumab:ti,ab	18	
#33	brodalumab:ti,ab	97	
#34	ligelizumab:ti,ab	21	
#35	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	7538	
#36	#23 AND #35	1986	
#37	MeSH descriptor: [Costs and Cost Analysis] explode all trees	9937	
#38	MeSH descriptor: [Health Care Costs] explode all trees	3299	
#39	economic*:ti,ab	16322	
#40	cost*:ti	12210	
#41	cost:ti,ab	45833	
#42	costs:ti,ab	25393	

	#43	cost effect*:ti,ab	41337	
	#44	cost utility:ti,ab	2787	
	#45	#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44	70316	
	#46	#36 AND #45	69	

