Biologic Drugs to Treat Asthma and Chronic Spontaneous Urticaria: Update

Systematic Review

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Executive Summary

Background

Asthma is a heterogenous chronic airway disease defined by a history of respiratory symptoms including wheeze, shortness of breath, chest tightness, and cough.[1] Goals of asthma treatment are to control symptoms and minimize risk of mortality, exacerbations, persistent airflow limitations, and treatment-related side effects.[1,2]

Chronic spontaneous urticaria (CSU) is the appearance of urticaria (hives), angioedema, or both, for more than 6 weeks because of unknown causes.[3] Treatment can involve the identification of underlying causes, avoidance of aggravating factors, tolerance induction, or use of pharmacological treatment, including use of omalizumab in patients unresponsive to high doses of H_1-antihistamines.[3]

This report systematically reviews the evidence for 5 biologic drugs for the treatment of asthma or CSU. Dupilumab (DUPIXENT) is a homologous antibody against interleukin-4 (IL-4) or its receptor, and is approved as an add-on maintenance treatment for moderate to severe asthma in patients with eosinophilic phenotype or with oral corticosteroid-dependent asthma.[1] Benralizumab (FASENRA), mepolizumab (NUCALA), and reslizumab (CINQAIR) are monoclonal antibodies against interleukin-5 (IL-5) or its receptor, and are approved to treat severe asthma in patients with an eosinophilic phenotype.[1] Omalizumab (XOLAIR) is an anti-immunoglobin E monoclonal antibody approved to treat uncontrolled allergic asthma and CSU resistant to antihistamines.[3]

PICOS and Key Questions

This report focuses on adults and children with asthma or CSU. We identified randomized controlled trials (RCTs) that evaluated the effectiveness and safety of the following US Food and Drug Administration (FDA)-approved biologic agents for asthma (Key Questions 1 and 2): benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab; and the following FDA-approved agent for CSU (Key Questions 3 and 4): omalizumab. Eligible comparators included active treatment with another FDA-approved biologic, placebo, or usual care. Eligible outcomes for asthma included measures of symptom control, quality of life, oral steroid use, severe exacerbations requiring emergency department (ED) or hospital admission, all-cause ED or hospital admission, and mortality. Eligible outcomes for CSU included symptom control and response, quality of life, and use of antiurticaria medications.

Methods

We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE, the Cochrane Library, ClinicalTrials.gov, and the International Standard Randomised Controlled Trials Number registry, from August 1, 2017 through July 7, 2020. We conducted active surveillance of the literature until December 31, 2020. We selected studies for inclusion based on the PICOS criteria described in the previous section. We rated the risk of bias of eligible studies using standard instruments adapted from national and international quality standards.[4,5] When not reported by the authors, we used Stata (version 16.1) to calculate incident rate ratios (IRR), risk ratios (RR), and associated 95% confidence intervals (CI) based on data provided in the study. We conducted pooled analyses using a random effects model when at least 2 similar studies for an

outcome were available. We rated the quality of the body of evidence for each drug comparison and indication (asthma or CSU) for up to 6 selected outcomes (i.e., symptom control, exacerbations [asthma only], steroid use [asthma only], antiurticarial medication use [CSU only], quality of life, overall adverse events [AEs], and serious adverse events [SAEs]) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[6,7]

The previous Drug Effectiveness Review Project (DERP) systematic review on biologics for asthma and CSU included existing systematic reviews and only included primary studies if they were not covered within an existing systematic review.[8] For this update, we relied entirely on primary RCTs and only used the previous DERP review to identify potentially eligible studies conducted before our update search. We re-evaluated all previously included studies against the study selection criteria for this update, conducted new data abstraction from primary studies that had been included in the prior report or that had only been covered by an existing systematic review in the prior report, and conducted new risk-of-bias ratings for previously included studies for consistency of methods and reporting with newly included studies.

Key Findings

Asthma: Benralizumab, Dupilumab, Mepolizumab, Omalizumab, and Reslizumab

- We identified 44 RCTs in 52 publications reporting on the use of biologics for asthma.[9-60] All but 3 RCTs used placebo controls. Two RCTS[11,26] used a "best standard of care" control, and 1 RCT used a no-treatment control group.[57]
- We rated 8 studies as high risk for bias for various methodological issues[10,11,19,34,38,47,57]; the rest were rated as moderate risk of bias, typically for extensive manufacturer involvement in study design, execution, and reporting.
- Most trials evaluated the add-on efficacy of the biologic drug compared to placebo or control while maintaining standard background asthma controller and rescue therapy in both groups (i.e., add-on efficacy trials). A fewer number of studies evaluated the add-on efficacy of the biologic drug compared to placebo while tapering inhaled or oral maintenance steroids (or other controller treatment) in both groups (i.e., steroid-sparing trials).
- In the included studies, outcomes were reported between 12 and 52 weeks of duration. For brevity, in some places we do not list the specific follow-up periods, but those can be identified in the full evidence tables in Appendix B.

Benralizumab Compared to Placebo

- Symptom control
  - 6 add-on efficacy RCTs[9,39,45,46,50,60] (N = 2,749), 1 steroid-sparing RCT[48] (N = 220); benralizumab was found to be more effective as measured by the difference in mean change from baseline on the Asthma Control Questionnaire (ACQ; range of individual study and pooled estimates: -0.1 to -0.55 points at 12 to 56 weeks); moderate quality of evidence (QoE)
  - 3 add-on efficacy RCTs[9,50,60] (N = 1,100); benralizumab was more effective as measured by the proportion achieving a minimally important difference (MID; 0.5 points) at 12 to 24 weeks on the ACQ (pooled RR, 1.17; 95% CI, 1.06 to 1.28); high QoE

- Quality of life
  - 4 add-on efficacy RCTs[39,45,46,50] (N = 1,860), 1 steroid-sparing RCT[48] (N = 220); benralizumab was more effective as measured by the difference in mean change from baseline on the Asthma Quality of Life Questionnaire (AQLQ; range of estimates from 0.18 to 0.45 points at 12 to 56 weeks); low QoE
  - 1 add-on efficacy RCT[50] (N = 211); benralizumab was more effective as measured by the proportion achieving an MID (0.5 points) on the AQLQ (RR, 1.34; 95% CI, 0.94 to 1.90); low QoE
- Exacerbations
  - 4 add-on efficacy RCTs[39,45,46,60] (N = 2,233), 1 steroid-sparing RCT (N = 220); benralizumab was more effective as measured by annualized rate of exacerbations (pooled IRR, 0.59; 95% CI, 0.47 to 0.79 for every 4 week dose; IRR, 0.55; 95% CI, 0.43 to 0.67 for every 8 week dose); moderate QoE
  - 2 add-on efficacy RCTs[45,50] (N = 1,537); benralizumab was more effective as measured by annualized rate of exacerbations requiring ED or hospital visits (pooled IRR, 0.67; 95% CI, 0.38 to 0.96 for every 4-week dose; pooled IRR, 0.70; 95% CI, -0.12 to 1.52 for every 8-week dose); low QoE
  - 3 add-on efficacy RCTs[45,50,60] (N = 1,595); benralizumab was more effective as measured by incidence of exacerbations (pooled RR, 0.75 [95% CI, 0.65 to 0.89]); moderate QoE
- Steroid use
  - 1 steroid-sparing RCT[48] (N = 220); benralizumab was more effective as measured by the proportion of participants reducing oral maintenance oral steroid dose by 50% or more (RR, 1.79; 95% CI, 1.28 to 2.50 for every 4 week dose; RR, 1.76; 95% CI, 1.26 to 2.47 for every 8 week dose); moderate QoE
- Overall AEs
  - 7 RCTs[9,39,45,46,48,50,60] (N = 2,897); fewer events occurred among participants allocated to benralizumab (pooled RR, 0.94; 95% CI, 0.90 to 0.98); high QoE
- SAEs
  - 7 RCTs[9,39,45,46,48,50,60] (N = 2,897); fewer events occurred among participants allocated to benralizumab (pooled RR, 0.76; 95% CI, 0.61 to 0.96); moderate QoE

Dupilumab Compared to Placebo

- Symptom control
  - 2 add-on efficacy RCTs[44,51] (N = 2,367), 2 steroid-sparing RCTs[37,53] (N = 314); dupilumab was more effective as measured by difference in mean change from baseline on the ACQ (pooled estimate, -0.28; 95% CI, -0.37 to -0.19 for add-on efficacy trials at 24 weeks, pooled estimate, -0.55; 95% CI, -0.79 to -0.31 for steroid-sparing RCTs at 12 to 24 weeks); moderate QoE
  - 1 add-on efficacy RCT[44] (N = 465); dupilumab was more effective as measured by the proportion of participants achieving an MID (0.5 points) on the ACQ (RR, 1.22; 95% CI, 1.06 to 1.40); moderate QoE
- Quality of life
  - 2 add-on efficacy RCTs[44,51] (N = 2,367); dupilumab was more effective as measured by difference in mean change from baseline on the AQLQ (pooled estimate, 0.23; 95% CI, 0.08 to 0.38 at 24 weeks); moderate QoE

    - 1 add-on efficacy RCT[44] (N = 465); dupilumab was more effective as measured by proportion of participants achieving an MID (0.5 points) on the AQLQ (RR, 1.81; 95% CI, 1.28 to 2.57 for 200-mg dose; RR, 1.27; 95% CI, 1.05 to 1.53 for 300-mg dose); moderate QoE
- Exacerbations
    - 2 add-on efficacy RCTs[44,51] (N = 2,367), 1 steroid-sparing RCT[53] (N = 210); dupilumab was more effective as measured by annualized rate of severe exacerbations (IRR, 0.30; 95% CI, not reported [NR]), moderate QoE
    - 1 add-on efficacy RCT[51] (N = 1,902); dupilumab more effective as measured by rate of exacerbations requiring ED visit or hospitalization (IRR, 0.53; 95% CI, 0.25 to 0.82); low QoE
- Steroid use
    - 2 steroid-sparing RCTs[37,53] (N = 314); dupilumab was more effective at reducing the use of maintenance steroids as measured by various steroid outcomes, moderate QoE
- Overall AEs
    - 4 RCTs[37,44,51,53] (N = 2,367); no significant difference between dupilumab and placebo (pooled RR, 0.99; 95% CI, 0.95 to 1.03); high QoE
- SAEs
    - 4 RCTs[37,44,51,53] (N = 2,367); no significant difference between dupilumab and placebo (pooled RR, 1.05; 95% CI, 0.80 to 1.38); moderate QoE

Mepolizumab Compared to Placebo

- Symptom control
    - 2 add-on efficacy RCTs[42,49] (N = 941), 1 steroid-sparing RCT[41] (N = 135); mepolizumab was more effective as measured by difference in mean change from baseline on ACQ (range of estimates, -0.43 to -0.52); moderate QoE
- Exacerbations
    - 2 add-on efficacy RCTs[42,49] (N = 941), 1 steroid-sparing RCT[41] (N = 135); mepolizumab was more effective as measured by annualized rate of exacerbations (IRR range, 0.42 to 0.68); moderate QoE
    - 2 add-on efficacy RCTs[42,49] (N = 941); mepolizumab was more effective as measured by the annualized rate of exacerbations requiring ED or hospitalization (IRR range, 0.31 to 0.32); low QoE
- Steroid use
    - 1 steroid-sparing RCT[41] (N = 135); mepolizumab was more effective as measured by the proportion of participants able to reduce oral steroid doses by 50% or more (RR, 1.61; 95% CI, 1.07 to 2.41); low QoE
- Overall AEs
    - 3 RCTs[41,42,49] (N = 556); fewer events occurred among participants allocated to mepolizumab versus placebo (pooled RR, 0.93; 95% CI, 0.88 to 0.99); high QoE
- SAEs
    - 3 RCTs[41,42,49] (N = 556); fewer events occurred among participants allocated to mepolizumab versus placebo (pooled RR, 0.63; 95% CI, 0.41 to 0.97); moderate QoE

Omalizumab compared to placebo or control

- Symptom control
  - 3 add-on efficacy RCTs[28,30,31] (N = 721); omalizumab was more effective as measured by difference in mean change in days with asthma symptoms (pooled estimate, -0.48; 95% CI, -0.74 to -0.23); high QoE
  - 2 add-on efficacy RCTs[26,32] (N = 449); omalizumab was more effective as measured by the difference in mean change from baseline on the ACQ; findings were mixed regarding achieving an MID (0.5 points; range of estimates, 0 to -0.87); very low QoE
  - 2 add on efficacy RCTs[28,30] (N = 691); omalizumab was more effective as measured by the difference in mean change from baseline on the Asthma Control Test (ACT; pooled estimate, 0.52; 95% CI, 0.14 to 0.91); low QoE
  - 5 add-on efficacy RCTs[19,26,28,31,58] (N = 1,489), 3 steroid-sparing RCTs[13,21,23] (N = 1,486); omalizumab was more effective as measured by the proportion of participants with a patient or physician global evaluation rating of effectiveness of good or excellent (range of pooled RRs, 1.11 to 1.60); moderate QoE
- Quality of life
  - 5 add-on efficacy RCTs[19,29,38,57,58] (N = 1,791), 1 steroid-sparing RCT[13] (N = 525); omalizumab was more effective as measured by difference in mean change from baseline on the AQLQ (range, 0.29 to 1.19 in 4 studies); moderate QoE
  - 3 add-on efficacy RCTs[19,29,58] (N = 1,662), 1 steroid-sparing RCT[13] (N = 525); omalizumab was more effective as measured by the proportion of respondents achieving an MID (0.5 points) on the AQLQ (individual study and pooled RRs range, 1.14 to 1.24); high QoE
  - 1 steroid-sparing RCT[23] (N = 627); no difference between omalizumab versus placebo as measured by difference in mean change from baseline on the Pediatric AQLQ (0.04; 95% CI, NR); low QoE
  - 1 steroid-sparing RCT[21] (N = 334); no difference in proportion of participants achieving a large MID (1.5 points) on the Pediatric Asthma Quality of Life (PAQLQ; RRs, 1.45 to 1.67 across trial phases but did not exclude a null effect); low QoE
- Exacerbations
  - 12 add-on efficacy RCTs[10,11,16,19,25,26,29-32,47,58] (N = 3,646), 4 steroid-sparing RCTs[13,21,47,54] (N = 2,032); omalizumab was more effective as measured by the incidence of exacerbations (pooled RR, 0.71; 95% CI, 0.61 to 0.82 for add-on efficacy trials; range of pooled RRs, 0.55 to 0.67 across trial phases in steroid-sparing RCTs); high QoE
  - 3 add-on efficacy RCTs[19,26,30] (N = 1,309); omalizumab was more effective as measured by the incidence or rate of exacerbations requiring ED or hospital visits (RRs and IRRs range from 0.23 to 0.66 across studies); moderate QoE
- Steroid use
  - 3 steroid-sparing RCTs[13,18,54] (N = 1,317); omalizumab was more effective as measured by the proportion of participants who reduced their maintenance inhaled steroid dose by 50% or more (pooled RRs range, 1.39 to 1.40 across trial phases); high QoE
- Overall AEs
  - 17 RCTs[11,13,16,18,19,21,23,25,26,28-32,54,58,59] (N = 23,751); no difference in events between omalizumab versus placebo (pooled RR, 1.00; 95% CI, 0.97 to 1.03); high QoE

- SAEs
  - 16 RCTs[11,13,16,18,19,23,25,26,28-32,54,58,59] (N = 23,561); fewer events occurred among participants allocated to omalizumab versus placebo (pooled RR, 0.77; 95% CI, 0.59 to 0.99); moderate QoE

Reslizumab Compared to Placebo

- Symptom control
  - 6 add-on efficacy RCTs[17,35,36,40,52] (N = 2,234), 1 steroid-sparing RCT[52] (N = 177); reslizumab was more effective as measured by difference in mean change from baseline in ACQ (pooled estimate, -0.25; 95% CI, -0.33 to -0.17 from 5 add-on efficacy trials at 15 to 16 weeks); moderate QoE
  - 5 add-on efficacy RCTs[17,35,36,40] (N = 1,766); reslizumab was more effective than placebo as measured by the proportion of participants achieving an MID (0.5 points) on the ACQ (range of pooled RRs, 1.24 to 1.28 from 4 add-on efficacy trials at 15 to 52 weeks); high QoE
- Quality of life
  - 4 add-on efficacy RCTs[35,36,52] (N = 1,632), 1 steroid-sparing RCT[52] (N = 177); reslizumab was more effective as measured by difference in mean change from baseline on the AQLQ (range of pooled estimates, 0.24 to 0.21 at 15 to 52 weeks); moderate QoE
  - 3 add-on efficacy RCTs[35,36] (N = 1,164); reslizumab was more effective as measured by the proportion of participants achieving an MID (0.5 points) on the AQLQ (range of pooled RRs, 1.14 to 1.35 at 16 to 52 weeks); high QoE
- Exacerbations
  - 3 add-on efficacy RCTs[36,52] (N = 1,421), 1 steroid-sparing RCT[52] (N = 177); reslizumab was more effective as measured by annualized rate of exacerbations (pooled IRR, 0.53; 95% CI, 0.36 to 0.71 in add-on efficacy trials at 52 weeks); high QoE
  - 3 add-on efficacy RCTs[36,52] (N = 1,421); no difference between reslizumab versus placebo as measured by annualized rate of exacerbations requiring ED or hospital visit (pooled IRR, 0.73; 95% CI, 0.36 to 1.09); low QoE
- Steroid use
  - 1 steroid-sparing RCT[52] (N = 177); no difference between reslizumab versus placebo as measured by percentage change in oral maintenance steroid dose (difference in mean percentage dose change, -17.8; 95% CI, -39.0 to 3.5); low QoE
- Overall AEs
  - 7 RCTs[17,35,36,40,52] (N = 2,411); no difference between reslizumab versus placebo (pooled RR, 0.92; 95% CI, 0.84 to 1.00); high QoE
- SAEs
  - 7 RCTs[17,35,36,40,52] (N = 2,411); no difference between reslizumab versus placebo (pooled RR, 0.94; 95% CI, 0.68 to 1.31); moderate QoE

Chronic Spontaneous Urticaria: Omalizumab

- We identified 10 RCTs in 13 publications evaluating 1 or more dosing regimens of omalizumab compared to placebo.[61-73]
- We rated 2 studies as high risk of bias for various methodological issues[70-73]; 8 were rated as moderate risk of bias.[61-69]

- Symptom control
  - 8 RCTs[61-69] (N = 1,252); omalizumab was more effective than placebo as measured by the difference in mean change in urticaria activity score over 7 days (UAS7; pooled estimate, -8.85; 95% CI, -10.61 to -7.08 at 12 weeks in 5 RCTs; pooled estimate -7.79; 95% CI, -10.60 to -4.97 at 24 to 28 weeks in 3 RCTs); moderate QoE
  - 5 RCTs[64-67,70] (N = 1,066); omalizumab was more effective than placebo as measured by proportion achieving remission defined as UAS7 ≤ 6 (pooled RR at 12 weeks, 3.09; 95% CI, 2.31 to 4.13 in 4 RCTs; pooled RR at 20 to 24 weeks, 1.98; 95% CI, 1.34 to 2.92 in 2 RCTs); high QoE
  - 5 RCTs[61,62,64,66,67,70] (N = 916); omalizumab was more effective than placebo as measured by proportion achieving complete response defined as UAS7 = 0 (pooled RR, 6.82; 95% CI, 3.72 to 12.51 at 12 weeks in 4 RCTs; pooled RR, 3.16; 95% CI, 1.94 to 5.17 at 20 to 28 weeks in 3 RCTs); high QoE
- Quality of life
  - 7 RCTs[61,62,64-69] (1,206); omalizumab was more effective than placebo as measured by difference in mean change from baseline on the Dermatology Life Quality Index (pooled estimate, -3.55; 95% CI, -4.77 to -2.33 at 12 weeks in 5 RCTs); high QoE
- Antiurticarial medication use
  - 6 RCTs[65-70] (N = 927); omalizumab more effective than placebo as measured by various outcomes related to antihistamine or related medication use; very low QoE
- Overall AEs
  - 8 RCTs[61-69] (N = 1,252); no difference between omalizumab and placebo (pooled RR, 1.07; 95% CI, 0.66 to 2.10); high QoE
- SAEs
  - 7 RCTs[61-67,69] (N = 1,222); no difference between omalizumab and placebo (pooled RR, 1.17; 95% CI, 0.66 to 2.10); moderate QoE

Ongoing Studies

- 13 RCTs of biologics for asthma are ongoing, including 1 head-to-head study comparing omalizumab to mepolizumab.
- 2 RCTs comparing dupilumab to placebo for CSU are ongoing.

Conclusions

The evidence suggested that for people with asthma, between 12 and 52 weeks follow-up, the biologics evaluated in this review (i.e., benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab) were more effective than placebo for controlling symptoms, improving quality of life, and reducing exacerbations, though the QoE varied from *very low* to *high* depending on the specific outcome and biologic agent. Four of the 5 agents also reduced steroid use (low to high QoE); no difference in steroid use was observed for reslizumab (low QoE). Among people with CSU, between 12 to 60 weeks follow-up, the evidence suggests that omalizumab (the only intervention in this report that is FDA-approved to treat CSU) was more effective than placebo for controlling symptoms (moderate to high QoE), improving quality of life (high QoE), and reducing the use of antiurticarial medications (very low QoE). The evidence for asthma and CSU suggested either fewer AEs (including SAEs) with biologics, or no difference in events, compared to placebo (moderate to high QoE, depending on drug and outcome). For asthma, the evidence

suggests these agents are more effective than placebo among children, adolescents, and adults. For CSU, the evidence suggests these agents are more effective than placebo among adolescents and adults; no CSU trials included participants younger than 12 years.

Although the identified evidence demonstrated that the evaluated biologic drugs treating asthma and CSU performed better than placebos, we identified no head-to-head studies, which might limit evidence-based decision-making for this drug class. However, we identified 1 head-to-head RCT and 14 additional placebo-controlled studies that are ongoing. Head-to-head studies will be needed to evaluate the effectiveness of a biologic drug versus another and against other asthma treatment options. Given the small number of registered head-to-head studies and the dearth of published evidence, a network meta-analysis (NMA) might be beneficial for future consideration. We identified 2 NMAs with evidence on indirect comparisons. We did not assess the NMAs for risk of bias; however, both found that biologic drugs to treat asthma were superior to a placebo and not significantly different from one another.

List of Brand Names and Generics

Table 1 describes current biologics approved by US Food and Drug Administration (FDA) for asthma or chronic spontaneous urticaria (CSU).

Table 1. Included Biologic Drugs for the Treatment of Asthma or CSU

Generic Name	Brand Name	Manufacturer	Approved Indication	Dosage(s), Form	Date of FDA Approval
Dupilumab	**DUPIXENT**	**Sanofi and Regeneron**	**Asthma**	**400-mg or 600-mg initial dose, then 200 or 300 mg every 2 weeks,[a] SC**	**October 2018**
Benralizumab	FASENRA	AstraZeneca	Asthma	30 mg every 4 weeks for the initial 3 doses, then every 8 weeks, SC	November 2017
Reslizumab	CINQAIR	Teva Pharmaceuticals	Asthma	3 mg/kg every 4 weeks, IV	March 2016
Mepolizumab	NUCALA	GlaxoSmithKline	Asthma	100 mg (age 12 and over) or 40 mg (age 6 to 11) every 4 weeks, SC	November 2015
Omalizumab	XOLAIR	Genentech and Novartis	Asthma, CSU	Asthma: 75 to 375 mg every 2 to 4 weeks based on weight and serum IgE levels, SC CSU: 150 or 300 mg every 4 weeks, SC	June 2003

Notes. [a] Higher dose and more frequent interval recommended for persons on oral steroids. ***Bold*** *indicates drugs newly approved since the last DERP report.*
Abbreviations. CSU: chronic spontaneous urticaria; FDA: US Food and Drug Administration; IgE: immunoglobin E; IV: intravenous infusion; SC: subcutaneous injection.

Background

This report is an updated systematic review of biologic drugs to treat asthma and chronic spontaneous urticaria (CSU).

Asthma

Asthma is a heterogenous chronic airway disease defined by a history of respiratory symptoms including wheeze, shortness of breath, chest tightness, and cough.[1] Goals of asthma treatment are to control symptoms and minimize risk of mortality, exacerbations, persistent airflow limitations, and treatment-related side effects.[1] More recently, individual treatment has been geared toward treating the specific asthma phenotype, which includes allergic, nonallergic, aspirin-sensitive, severe, exercise-induced, neutrophilic, fixed-obstruction, and occupational.[74] Allergic asthma is the most common phenotype, describing between 40% and 50% of cases, and can be identified through allergy testing for environmental allergens, eosinophilia, blood immunoglobin E (IgE) levels, and exhaled nitric oxide testing.

Clinical practice guidelines call for a stepwise approach with therapy determined by the frequency and severity of symptoms, and response to previous therapies. The 2020 Global Initiative for Asthma guidelines recommend low-dose inhaled corticosteroids (ICS) in combination with long-acting beta-agonists (LABAs) as needed for Step 1 treatment, which would typically be used for intermittent, mild symptoms.[1] The preferred Step 2 treatment includes daily low-dose ICS with as-needed short-acting beta agonists (SABAs) in children or in fixed-dose combination with LABAs for adults and adolescents. Daily leukotriene receptor antagonists (LTRAs) are alternative options for Step 2 for those who are unable or unwilling to use ICS. Preferred Step 3 controller options for adults and adolescents include low- or medium-dose ICS-LABA with or without as-needed SABAs or the addition of LTRA or allergen immunotherapy (for persons with dust mite allergy). The preferred Step 3 controller options for children include a medium-dose ICS or low-dose ICS-LABAs combination. The preferred Step 4 treatment varies depending on what has been tried for Step 3, but often includes low- or medium-dose ICS-LABAs with additional controllers, including LTRAs or tiotropium, with SABAs as needed. Patients with poor symptom control despite Step 4 treatment are candidates for specialty asthma care, including phenotypic assessment, and add-on controller regimens, including high-dose ICS-LABAs, low-dose oral steroids, bronchial thermoplasty, azithromycin, or biologics (e.g., anti-IgE, anti-interleukins).[1] In December 2020, the National Asthma Education and Prevention Program Expert Panel published selected topic updates; asthma biologic therapy was not selected as one of the topics for updating as it was considered an emerging therapeutic option at the time of topic prioritization.[2]

Chronic Spontaneous Urticaria

CSU, also called chronic idiopathic urticaria (CIU), is the appearance of urticaria (hives), angioedema, or both for more than 6 weeks because of unknown causes.[3] CSU affects more than 500,000 people in the US and is most common among women over the age of 40.[75] External factors can aggravate the symptoms of CSU, though most patients have no known allergic cause.[3] The treatment goal for CSU is to treat the disease until it is gone. Treatment can involve the identification of underlying causes, avoidance of aggravating factors, tolerance

induction, or use of pharmacological treatment, including use of omalizumab in patients unresponsive to high doses of H_1-antihistamines.[3]

For this report, we analyzed 5 biologic drugs for the treatment of asthma or CSU (Table 1). Dupilumab is a homologous antibody against interleukin-4 (IL-4) or its receptor and is approved as an add-on maintenance treatment for moderate to severe asthma in patients with eosinophilic phenotype or with oral corticosteroid-dependent asthma.[1] Benralizumab, mepolizumab, and reslizumab are monoclonal antibodies against interleukin-5 (IL-5) or its receptor and are approved to treat severe asthma in patients with an eosinophilic phenotype.[1] Omalizumab is an anti-IgE monoclonal antibody approved to treat uncontrolled allergic asthma and CSU resistant to antihistamines.[3] Dupilumab, mepolizumab, and benralizumab are available in prefilled syringes or in autoinjectors that can be self-administered by the patient or a caregiver at home. Omalizumab is only approved for administration in a health care setting; however, the US Food and Drug Administration (FDA) accepted an application for a prefilled omalizumab syringe for self-administration in August 2020 with a decision expected in early 2021.[76] Reslizumab is only available by intravenous infusion.

The previous Drug Effectiveness Review Project (DERP) systematic review was completed in 2018.[8] DERP participants commissioned an update of that review to evaluate newly published studies and a new agent to the drug class (i.e., dupilumab).

PICOS

Population

- Adults or children with persistent or chronic asthma
- Adults or children with CSU

Interventions

- Benralizumab (asthma)
- Dupilumab (asthma)
- Mepolizumab (asthma)
- Omalizumab (asthma and CSU)
- Reslizumab (asthma)

Comparators

- Anti-IL-4 or anti-IL-5 antibodies vs. each other
- Placebo-controlled or usual-care-controlled

Outcomes

Asthma

- Severe exacerbations requiring emergency department (ED) or hospital admission
- Symptom control
- Oral steroid use
- Quality of life assessed using validated scales
- All-cause ED or hospital admissions
- Mortality

- Adverse events (AEs)
- Serious adverse events (SAEs)

CSU

- Response (e.g., Urticaria Activity Score [UAS7] ≤ 6 or complete response [UAS7 = 0])
- Symptoms (e.g., itching)
- Quality of life assessed using validated scales
- Use of other antiurticaria medications
- AEs
- SAEs

Study Designs

- Randomized controlled trials (RCTs)

Key Questions

1. What is the effectiveness of biologic medications to treat asthma?
2. What are the harms of biologic medications to treat asthma?
3. What is the effectiveness of biologic medications to treat CSU?
4. What are the harms of biologic medications to treat CSU?
5. What are the characteristics of ongoing studies of biologic medications to treat asthma or CSU?

Methods

We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE, the Cochrane Library, ClinicalTrials.gov, and the International Standard Randomised Controlled Trials Number (ISRCTN) registry from August 1, 2017, through July 7, 2020. We also searched several websites to identify eligible published studies potentially missed by our electronic search. We conducted active surveillance of the literature through December 31, 2020. We selected studies for inclusion based on the PICOS criteria described above. We rated the risk of bias of eligible studies using standard instruments adapted from national and international quality standards.[4,5] We used Stata (version 16.1) to calculate incident rate ratios (IRRs), risk ratios (RRs), and associated 95% confidence intervals (CIs) based on data provided in the study when not reported by authors. We synthesized the evidence separately for each drug; for the studies focused on asthma, we also synthesized the evidence by trial design based on whether the trial evaluated the efficacy of add-on therapy alone vs. efficacy of add-on therapy during a steroid (or other treatment) reduction cointervention.

For continuous outcomes, we reported effect sizes as absolute or standardized mean differences. For rates we reported effect sizes as IRRs and for categorical outcomes we reported effect sizes as RRs. We conducted meta-analyses to generate pooled estimates using random effects models when at least 2 similar studies for an outcome were available without substantial heterogeneity in the pooled estimate. For studies evaluating effectiveness outcomes for more than 1 dosage or dosing interval, we combined groups for use in the pooled analysis by summing the count of events (for categorical outcomes) or by combining the summary statistics (for

continuous outcomes)[77] across the dosage groups. For pooled analyses of safety outcomes, we combined dosage arms if studies evaluated more than 1 active treatment dosage for use in the pooled analyses.

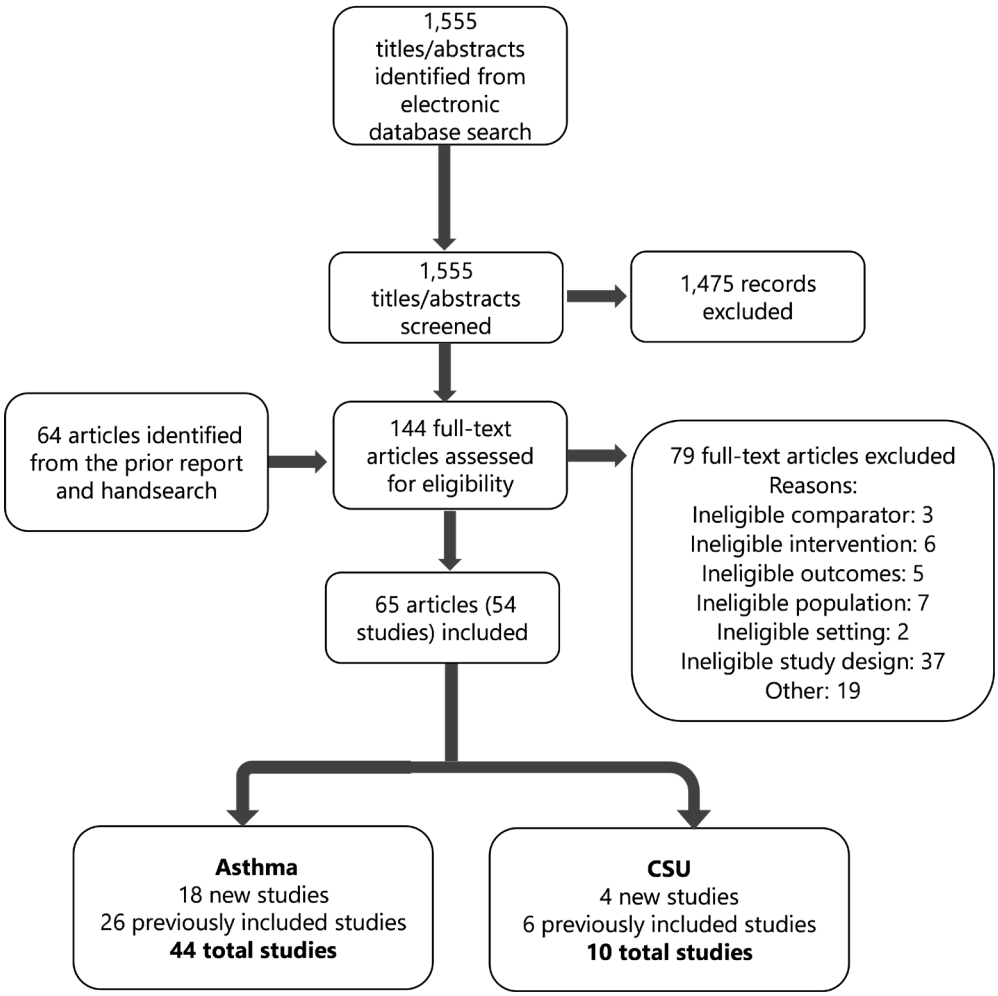
We rated the quality of the body of evidence for each drug comparison and indication (asthma or CSU) for up to 6 selected outcomes (i.e., symptom control, exacerbations [asthma only], steroid use [asthma only], antiurticarial medication use [CSU only], quality of life, overall AEs, and SAEs) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[6,7]

The previous DERP systematic review on biologics for asthma and CSU included existing systematic reviews and only included primary studies if they were not covered within an existing systematic review.[8] For this update, we relied entirely on primary RCTs and only used the previous DERP review to identify potentially eligible studies conducted before our update search. We re-evaluated all previously included studies against the study selection criteria for this update, conducted new data abstraction from primary studies that had been included in the prior report or that had only been covered by an existing systematic review in the prior report, and conducted new risk-of-bias ratings for previously included studies for consistency of methods and reporting with newly included studies. A list of excluded studies and the rationale for exclusion can be found in a supplementary document, Appendix E.

Findings

We identified 44 RCTs (18 new studies for this update) reporting on the use of biologics for asthma[9-60] and 10 RCTs (4 new studies for this update) reporting on use of biologics for CSU,[61-73] for a total of 54 RCTs in 65 publications for this update (Figure 1 and Appendix C). No studies evaluating head-to-head comparisons were identified. All but 1 RCT[59] reported effectiveness outcomes (Key Question 1 or 3), and all but 3 RCTs[47,57,70] reported safety outcomes (Key Question 2 or 4).

Figure 1. Literature Flow Diagram



Abbreviations. CSU: chronic spontaneous urticaria.

Overview of Effectiveness Outcome Measures Reported

Table 2 summarizes the most common outcomes used to report symptom control and quality of life among studies evaluating the efficacy of biologics for asthma and CSU. In addition to standard measures of symptom control and quality of life, studies evaluating asthma commonly reported on the impact of treatment on asthma exacerbations. Studies used varying definitions of exacerbations, and the specific definition used by each study is reported in the detailed evidence tables (Appendix B, Tables B1-B18). A common component of all study definitions of exacerbation is worsening symptoms that required systemic (oral or intravenous) steroids, or required doubling of existing oral or inhaled steroid dose for at least 2 or 3 consecutive days. Other components of the definition used by some studies included unscheduled physician visits, ED visits, hospital admissions, decline in lung function (forced expiratory volume in 1 second [FEV_1] < 60% of predicted or peak expiratory flow [PEF] > 30% decrease from baseline), and missed work or school. We report data for exacerbations as defined by the study and for exacerbations requiring an ED or hospital visit when specifically reported as such. We also noted that some studies captured asthma exacerbations as AEs or SAEs. In studies reporting

exacerbations as AEs and that itemized AEs, we captured these data as part of our reporting under the key question related to effectiveness (KQ 1).

Table 2. Summary of Outcome Measures for Asthma and Chronic Spontaneous Urticaria

Measure	Full Name	Description	Minimally Important Difference
AAS[78]	Angioedema Activity Score	**Items**: 5 self-administered items in a daily diary **Scale**: 0 (worst) to 15 (best) for daily score; 0 (worst) to 105 (best) for weekly score **Scoring**: Each item is scored on a 3-point Likert scale; the daily score is the sum of item scores each day; daily AAS scores are then summed to a 7-day weekly score, and each weekly score can be summed to a 28-day score	4.5 to 8
ACQ[79-82]	Asthma Control Questionnaire	**Items:** 7 items, consisting of 5 self-administered items with 1-week recall of symptoms, 1 item about bronchodilator use, and 1 item of % FEV_1 measured in a clinic. ACQ-5 is the self-administered items, ACQ-6 includes bronchodilator items, and ACQ-7 is the full item set **Scale:** 0 (totally controlled) to 6 (severely uncontrolled) **Scoring:** Each item is measured on 7-point Likert scale or 7 categories for % FEV_1; overall score is calculated from the mean across items	0.5
ACT[83,84]	Asthma Control Test	**Items:** 5 self-reported items related to symptoms and daily functioning over past 4 weeks; assesses shortness of breath and general asthma symptoms, use of rescue medications, effect of asthma on daily functioning, and overall self-assessment of asthma control; for ages 12 and up **Scale:** 5 (poor control) to 25 (complete control) with scores > 19 indicating well-controlled asthma **Scoring:** Each item is scored on 5-point Likert scale, sum of scores across all items yield the total score	3
AQLQ[85-87]	Asthma Quality of Life Questionnaire	**Items:** 32 items assessing disease-specific health-related quality-of-life that include domains of activity limitations, symptoms, emotional function, and environmental stimuli with 2-week recall **Scale:** 1 (severely impaired) to 7 (not impaired at all) **Scoring:** Each item is scored on 7-point Likert scale; total and domain scores are calculated by taking the mean of all questions overall or for each domain	0.5
ASUI[88,89]	Asthma Symptom Utility Index	**Items:** 11 items; interviewer-administered questionnaire with 2-week recall; assesses 4 symptoms (cough, wheeze, shortness of breath, awakening at night), medication side effects on 2 dimensions (frequency and severity) **Scale:** 0 (worst possible symptoms) to 1 (no symptoms) **Scoring:** Each item is assessed on 4-point scale for frequency (not at all, 1 to 3 days, 4 to 7 days, 8 to 14 days), and severity (not applicable, mild, moderate, severe); scores are then converted to a 0 to 1 scale	0.09

Measure	Full Name	Description	Minimally Important Difference
C-ACT[89]	Childhood Asthma Control Test	**Items:** 4 items completed by child (perception of asthma control, activity limitation, coughing, awakenings) and 3 items completed by parent (daytime complaints, daytime wheezing, awakenings); for ages 4 to 11 years **Scale:** 0 (poor control) to 27 (complete control); scores > 19 indicate well-controlled asthma **Scoring:** Each item is scored on 4-point (or 6-point for parent items) Likert scale, sum of scores across all items yield the total score	2
CU-Q2oL[90]	Chronic Urticaria Quality of Life Questionnaire	**Items:** 23-item disease-specific self-administered questionnaire that includes 6 dimensions: pruritus, swelling, impact on life activities, sleep problems, limits, and looks **Scale:** 0 (no impairment) to 100 (greatest impairment) **Scoring:** Each item is scored on a 5-point Likert scale. The individual items are summed to generate the overall score, which is then converted to a 0 to 100 scale	3 small 8 moderate 19 large
DLQI[78,91]	Dermatology Life Quality Index	**Items:** 10 self-administered items concerning impact of skin disease on different aspects of health-related quality of life with 1-week recall **Scale:** 0 (no impairment) to 30 (highest impairment) **Scoring:** Each item is scored on a 4-point Likert scale	2.2 to 3.2
ISS7[92]	Itch Severity Score over 7 days	**Items:** 1 item assessing itch severity evaluated in the morning and in the evening **Scale:** 0 (not severe at all) to 21 (most severe) **Scoring:** The daily score is the average of the morning and evening scores on a 4-point Likert scale of 0 (none) to 3 (severe). The weekly Itch Severity Score is the sum of the daily Itch Severity Scores over 7 days	5
PAQLQ[93-95]	Pediatric Asthma Quality of Life Questionnaire	**Items:** 23 items in 3 domains covering symptoms, activity limitations, and emotional functioning; for children aged 7 to 17 years **Scale:** 1 (severely impaired) to 7 (not impaired at all) **Scoring:** Each item is scored on 7-point Likert scale; total and domain scores are calculated by taking the mean of all questions overall or for each domain	0.5
SGRQ[96-98]	St. George's Respiratory Questionnaire	**Items:** 50 or 76 items (depending on version) that includes 2 domains: frequency and severity of symptoms and impact on activities, can be used with a 1-month, 3-month, or 12-month recall **Scale:** 0 (no symptoms/limitations) to 100 (severe symptoms/ limitations) **Scoring:** Varies by item and item scores are converted into a domain score and an overall score, both reported on the same scale	4

Measure	Full Name	Description	Minimally Important Difference
UAS7[78,92,99,100]	Urticaria Activity Score over 7 days	**Items:** Diary-based patient-reported measure that assesses the key sign (hives) and symptom (itch) of CSU each day **Scale:** 0 (none) to 6 (intense) daily score; 0 (none) to 42 (intense) weekly score. A weekly score of 0 is considered full treatment response; a weekly score of 1 to 6 indicates well-controlled urticaria and a good response to treatment **Scoring:** Number of hives and intensity of itching are reported each day on a 4-point Likert scale; daily score is sum of the hives and itching score; weekly score is the sum of each daily score	9.5 to 11

Abbreviations. CSU: chronic spontaneous urticaria; FEV_1: forced expiratory volume in 1 second.

Summary of Findings from RCTs for Asthma

We identified 44 RCTs in 52 publications (1 publication reported on 2 RCTs) reporting on the use of biologics for asthma.[9-60] Seven RCTs evaluated benralizumab,[9,39,45,46,48,50,60] 4 RCTs evaluated dupilumab,[37,44,51,53] 3 RCTs evaluated mepolizumab,[41,42,49] 23 RCTs evaluated omalizumab,[10-16,18-34,38,47,54-59] and 7 RCTs evaluated reslizumab.[17,35,36,40,52] All but 3 RCTs used placebo controls; 2 RCTs[11,26] used a "best standard of care" control, and 1 RCT used a no-treatment control group.[57]

Benralizumab

Seven studies evaluated 1 or more dosing regimens of benralizumab compared to placebo.[9,39,45,46,48,50,60] The GRADE summary of findings is presented in Table 3.

Table 3. Summary of Findings (GRADE) Benralizumab for Asthma

No. Studies (No. Participants)	Outcome	Quality of the Evidence	Relationship	Rationale
6 add-on efficacy RCTs (N = 2,749)[9,39,45,46,50,60] 1 steroid-sparing RCT (N = 220)[48]	ACQ (MCB)	●●●○ (moderate)	Favors benralizumab	Downgraded 1 level for serious indirectness
3 add-on efficacy RCTs (N = 1,100)[9,50,60]	ACQ (MID response)	●●●● (high)	Favors benralizumab	Not downgraded
3 add-on efficacy trials (N = 1,809)[39,45,46,50] 1 steroid-sparing RCT (N = 220)[48]	AQLQ (MCB)	●●○○ (low)	Favors benralizumab	Downgraded 1 level for serious inconsistency and 1 level for serious indirectness
1 add-on efficacy RCT (N = 211)[50]	AQLQ (MID response)	●●○○ (low)	Favors benralizumab	Downgraded 2 levels for very serious imprecision

No. Studies (No. Participants)	Outcome	Quality of the Evidence	Relationship	Rationale
4 add-on efficacy RCTs (N = 2,233)[39,45,46,60] 1 steroid-sparing RCT (N = 220)[48]	Annualized rate of exacerbations	●●●○ (moderate)	Favors benralizumab	Downgraded 1 level for serious indirectness
3 add-on efficacy RCTs (N = 1,595)[45,50,60]	Incidence of exacerbation	●●●○ (moderate)	Favors benralizumab	Downgraded 1 level for serious imprecision
2 add-on efficacy RCTs (N = 1,537)[45,46]	Annualized rate of exacerbations requiring ED or hospital visit	●●○○ (low)	Favors benralizumab	Downgraded 1 level for serious inconsistency and 1 level for serious imprecision
1 steroid-sparing RCT (N = 220)[48]	Proportion of participants reducing oral steroid dose by 50% or more	●●●○ (moderate)	Favors benralizumab	Downgraded 1 level for serious imprecision
7 RCTs (N = 2,897)[9,39,45,46,48,50]	Overall AEs	●●●● (high)	Favors benralizumab	Not downgraded
7 RCTs (N = 2,897)[9,39,45,46,48,50]	SAEs	●●●○ (moderate)	Favors benralizumab	Downgraded 1 level for serious imprecision

Note. For methods and interpretation of GRADE ratings, see Appendix A.
Abbreviations. ACQ: Asthma Control Questionnaire; AE: adverse event; AQLQ: Asthma Quality of Life Questionnaire; ED: emergency department; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; MCB: mean change from baseline; MID: minimally important difference; RCT: randomized controlled trial; SAE: serious adverse event.

Study Characteristics

Seven industry-sponsored RCTs conducted over the years 2011 to 2020 evaluated benralizumab compared to placebo (CALIMA,[45] SIROCCO,[46] BISE,[50] Park et al.,[39] SOLANA,[9] ZONDA,[48] and ANDHI[60]). A summary of these trials is in Table 4 with additional details in Appendix B, Table B1. We rated the risk of bias for these studies as moderate because of extensive manufacturer involvement in study design, execution, and reporting. All were multicenter studies conducted in more than 1 country; 6 studies were phase 3 RCTs,[9,45,46,48,50,60] whereas Park et al. was a phase 2a trial. ANDHI,[60] BISE,[50] Park et al.,[39] SOLANA,[9] and ZONDA[48] enrolled adults, while CALIMA[45] and SIROCCO[46] enrolled participants aged 12 and older.

BISE[50] enrolled persons taking low- to moderate-dose ICS, whereas the other 6 studies required participants to be taking moderate- to high-dose ICS. ANDHI,[60] SOLANA,[9] ZONDA[48], and Park et al[39] enrolled only participants with eosinophilic (i.e., allergic) asthma while SIROCCO[46] did not limit enrollment to persons with allergic asthma but reported all results by subgroup based on baseline eosinophil level (< 300/µL [33% of those enrolled] vs. ≥ 300/µL (67% of those enrolled). CALIMA also did not limit enrollment to persons with allergic asthma, but reported only findings among the 56% of enrolled persons with eosinophils ≥ 300/µL, which they reported was the primary group of interest.[45] The BISE trial enrolled persons with (30%) and without (70%) allergic

asthma but did not report findings separately.[50] The ZONDA trial, which was designed to evaluate benralizumab as add-on therapy during a steroid-tapering cointervention, required all participants to have been using oral steroids for at least 6 months before entering the study.[48]

Five trials (all phase 3) evaluated a dose of 30 mg by subcutaneous (SC) injection given every 4 weeks[9,45,46,48,50]; 3 of these trials also evaluated a dose of 30 mg SC given every 8 weeks.[45,46,48] Another phase 3 trial evaluated a dose of 30 mg SC given every 4 weeks for the first 3 doses and then every 8 weeks.[60] The dosage used in the phase 2a trial was 20 mg SC every 4 weeks for the first 3 doses and then every 8 weeks.[39] All studies allowed SABAs for rescue medication during the trial and continued participants on their existing dosages of ICS, and most also continued existing dosages of other controller medications (e.g., LABAs). In BISE,[50] all existing ICS treatment was converted to standardized dosages during the run-in period, and existing LABAs were withdrawn. In ZONDA,[48] participants taking oral steroids other than prednisone or prednisolone were converted to equivalent dosages, and all participants had their oral steroid dosages optimized during the run-in period to the lowest possible dosage required to maintain asthma control. During the active-treatment phase of the trial, the oral steroid dose was continued during weeks 0 to 4, then tapered by 2.5 mg to 5.0 mg every 4 weeks through week 24, then maintained at the lower dose through week 28. For methodological reasons, we considered this study separately in our synthesis of effectiveness outcomes.

Table 4. Evidence Table (Brief Version) RCTs of Benralizumab for Asthma

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Bleecker et al., 2016[46] SIROCCO NCT01928771 Phase 3 RCT of add-on therapy Moderate	Aged 12 to 75, treatment with medium- to high-dose ICS and LABA, at least 2 exacerbations requiring systemic steroids in prior year, ACQ score ≥ 1.5; allergic asthma (67%) and non-allergic asthma (33%) enrolled	Benralizumab 30 mg SC every 4 wks (n = 399) Benralizumab 30 mg SC every 8 wks (n = 398) Placebo (n = 407) Continued stable doses of other asthma controllers, SABA rescue for symptoms	At 48 wks • Symptom control • QoL • Adverse events • Mortality (Annualized exacerbation rate)
Ferguson et al., 2017[50] BISE NCT02322775 Phase 3 RCT of add-on therapy Moderate	Aged 18 to 75, low- to medium-dose ICS with or without other controller medications, evidence of uncontrolled symptoms; allergic (30%) and non-allergic asthma (70%) enrolled	Benralizumab 30 mg SC every 4 wks (n = 106) Placebo (n = 105) Controller ICS converted to standardized doses, LABAs withdrawn at enrollment, SABA rescue for symptoms	At 12 wks • Symptom control • QoL • Exacerbations • Adverse events • Mortality (FEV_1 change)
FitzGerald et al., 2016[45] CALIMA NCT01914757	Aged 12 to 75, treatment with medium- to high-dose ICS and LABA, at least 2 exacerbations requiring	Benralizumab 30 mg SC every 4 wks (n = 425) Benralizumab 30 mg SC every 8 wks (n = 441)	At 56 wks • Symptom control • QoL • Exacerbations

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Phase 3 RCT of add-on therapy Moderate	systemic steroids in prior year, ACQ score ≥ 1.5; allergic (56%) and non-allergic asthma (44%) enrolled	Placebo (n =440) Continued stable doses of other asthma controllers, SABA rescue for symptoms	• Adverse events • Mortality (Annualized exacerbation rate in subgroup with eosinophils > 300/μL)
Harrison et al., 2020[60] ANDHI NCT03170271 Phase 3 RCT of add-on therapy Moderate	Aged 18 to 75; treatment with high-dose ICS plus another asthma controller; blood eosinophil count at least 150/μL; ≥ 2 exacerbations in prior year; ACQ score ≥ 1.5	Benralizumab 30 mg SC every 4 wks first 3 doses, then every 8 wks (n = 427) Placebo (n = 229) Continued stable doses of other asthma controllers	At 24 wks • Symptom control • Exacerbations • Adverse events • Mortality (Annualized exacerbation rate)
Nair et al., 2017[48] ZONDA NCT02075255 Phase 3 RCT of add-on therapy with steroid tapering Moderate	Aged 18 to 75, blood eosinophil count at least 150/μL, medium- to high-dose ICS and LABA, oral steroids for control for at least 6 months	Benralizumab 30 mg SC every 4 wks (n = 72) Benralizumab 30 mg SC every 8 wks (n = 73) Placebo (n = 75) Oral steroids adjusted to lowest possible dose to control symptoms before randomization, oral steroid dose reduced by standard amount at regular intervals, continued stable doses of other controllers, SABA rescue for symptoms	At 28 wks • Symptom control • QoL • Exacerbations • Steroid use • Adverse events • Mortality (Percentage reduction in steroid dose with asthma control maintained)
Panettieri et al., 2020[9] **SOLANA** **NCT02869438** Phase 3 RCT of add-on therapy Moderate	Aged 18 to 75; eosinophilic severe asthma requiring ICS/OCS and LABA; ≥ 2 exacerbations requiring OCS in prior year; ACQ score ≥ 1.5	Benralizumab 30 mg SC every 4 wks (n = 118) Placebo (n = 115) Cointerventions NR	At 8 to 12 wks • Symptom control • Adverse events (Change in pre-BD FEV_1)
Park et al., 2016[39] NCT01412736 Phase 2a RCT of add-on therapy Moderate	Aged 20 to 75, eosinophilic asthma, medium- to high-dose ICS and LABA, 2 to 6 exacerbations requiring systemic steroids in past year, ACQ score ≥ 1.5	Benralizumab 20 mg SC every 4 wks first 3 doses, then every 8 wks (n = 25) Placebo (n = 26) Continued stable doses ICS and LABA	At 52 wk • Symptom control • Exacerbations • Adverse events • Mortality (Annualized exacerbation rate)

Abbreviations. ACQ: Asthma Control Questionnaire; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonists; OCS: oral corticosteroids; QoL: quality of life; pre-BD: pre-bronchodilator; NCT: US National Clinical Trial; NR: not reported; RCT: randomized controlled trial; SABA: short-acting beta-2 agonists; SC: subcutaneous; wk: week.

Detailed individual study results are provided in Appendix B, Table B2 (effectiveness) and Table B3 (safety).

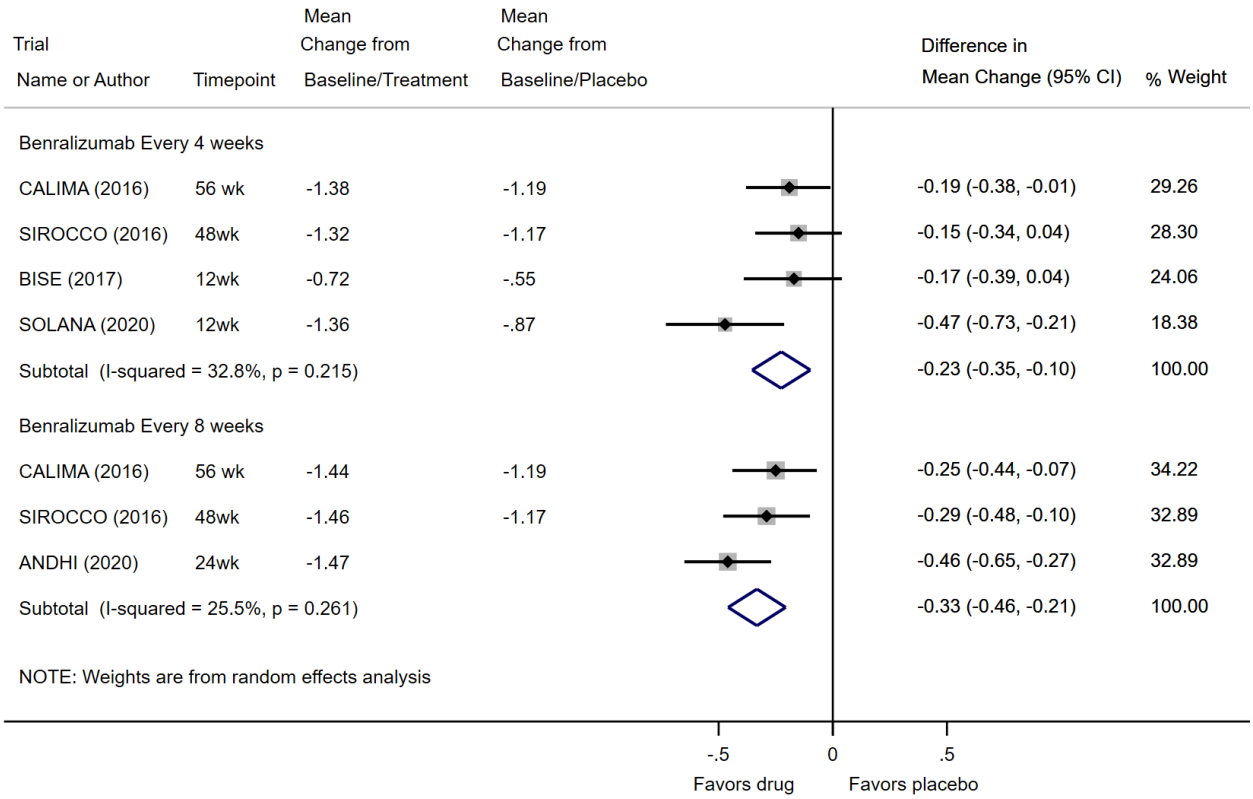
KQ 1: Symptom Control

Across both the add-on efficacy trials and the trial that included steroid-tapering, benralizumab was more effective than placebo for improving symptom control as measured by the Asthma Control Questionnaire (ACQ; moderate quality of evidence [QoE]).

Add-on Efficacy Trials

CALIMA, SIROCCO, BISE, SOLANA, ANDHI, and Park et al. evaluated benralizumab as add-on therapy; larger improvements in the ACQ score were observed compared to placebo for both 4-week ($P = .001$) and 8-week ($P < .001$) dosing intervals (Figure 2).[39,45,46,50] Park et al. could not be included in the quantitative synthesis but reported a larger improvement (calculated difference in mean change from baseline, -0.1; *P* value not reported [NR] and not calculable).[39] CALIMA, SIROCCO, and Park et al. reported findings among the subgroup of participants with baseline eosinophil counts greater than 300 per µL.[39,45,46] Only SIROCCO also reported findings among the subgroup of participants with baseline eosinophil counts less than 300 per µL; however, findings suggested no statistically significant difference between benralizumab and placebo in this subgroup (Appendix B, Table B2).[46]

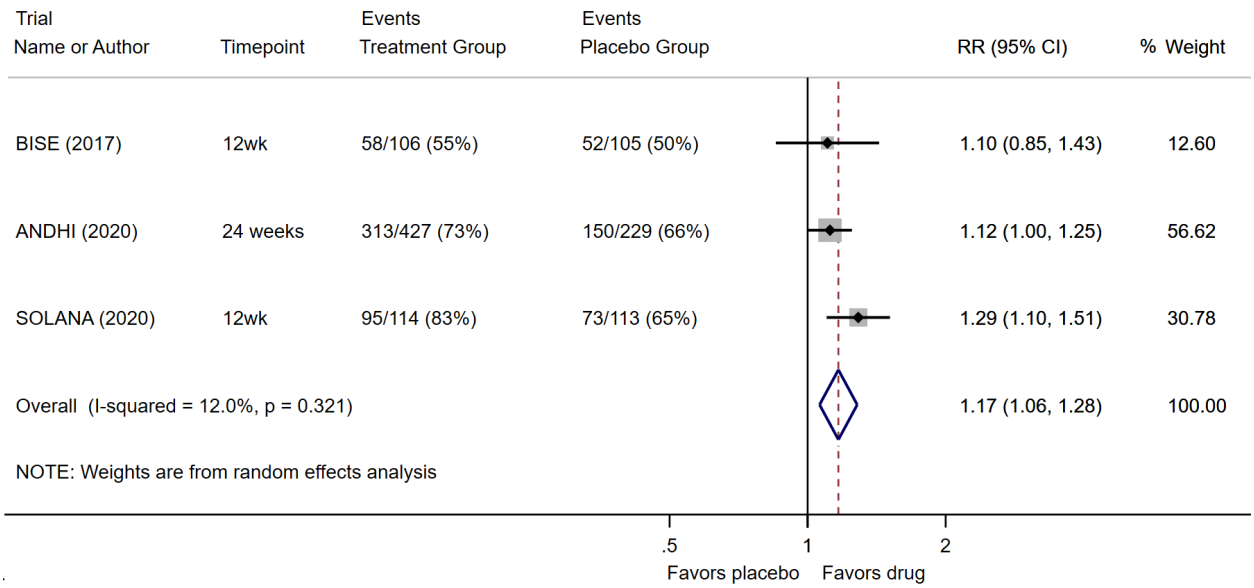
Figure 2. Benralizumab vs. Placebo, Asthma Control Questionnaire



Abbreviations. CI: confidence interval; wk: week.

Pooled estimates of 3 RCTs demonstrated a significantly higher proportion of participants achieving a minimally important change in ACQ score (0.5 points) among participants allocated to benralizumab compared to those allocated to placebo (*P* = .001; Figure 3). However, the difference in mean change from baseline (Figure 2), did not achieve the minimally important difference (MID).

Figure 3. Benralizumab vs. Placebo, ACQ MID Response



Abbreviations. CI: confidence interval; MID: minimally important difference; wk: week.

The SOLANA trial also reported statistically significant improvements on symptom control as measured by the St. George's Respiratory Questionnaire (SGRQ) at 8 and 12 weeks follow-up (Appendix B, Table B2).[9]

Add-on Efficacy With Steroid-Tapering Trial

In ZONDA, the authors reported significantly larger improvements in the ACQ score for the 8-week dosing interval (difference in mean change from baseline, -0.55; 95% CI, -0.86 to -0.23) but not for the 4-week dosing interval (-0.24; 95% CI, -0.55 to 0.08).[48]

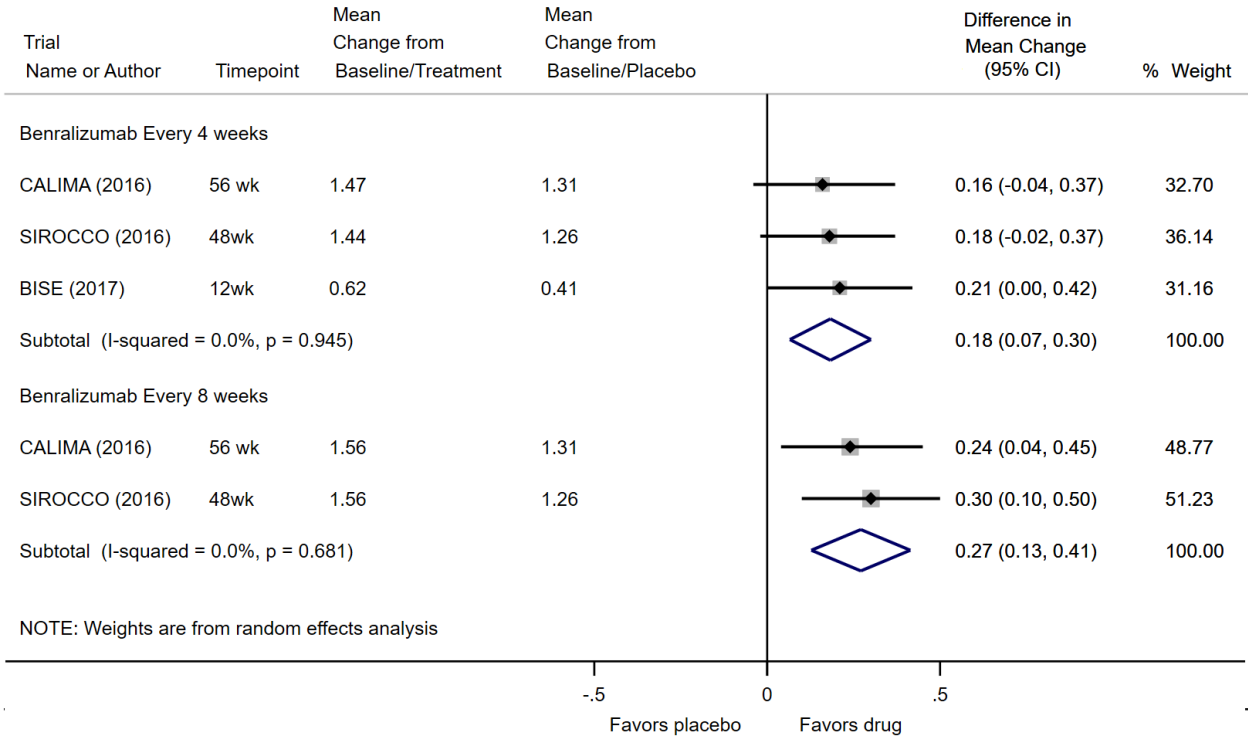
KQ 1: Quality of Life

Across both the add-on efficacy trials and the trial that included steroid-tapering, benralizumab was more effective than placebo for improving quality of life as measured by the Asthma Quality of Life Questionnaire (AQLQ; low QoE).

Add-on Efficacy Trials

CALIMA, SIROCCO, and BISE evaluated benralizumab as add-on therapy; larger improvements in the AQLQ score were observed compared to placebo for both the 4-week (P = .002) and 8-week (P < .001) dosing intervals (Figure 4).[45,46,50] However, the difference in mean change from baseline (Figure 2) did not achieve the MID for this measure (0.5 points). CALIMA and SIROCCO only reported these findings among the subgroup of participants with baseline eosinophil counts greater than 300 per µL.[45,46] SIROCCO also reported findings among the subgroup of participants with baseline eosinophil counts less than 300 per µL; findings suggested no statistically significant difference between benralizumab and placebo in this subgroup (Appendix B, Table B2).[46] The BISE trial also reported the proportion of participants achieving a minimally important change in AQLQ score (43% in the benralizumab every 4 weeks group vs. 32% in the placebo group; calculated RR, 1.34; 95% CI, 0.94 to 1.90).[50]

Figure 4. Benralizumab vs. Placebo, Asthma Quality of Life Questionnaire



Abbreviations. CI: confidence interval; wk: week.

Add-on Efficacy With Steroid-Tapering Trial

In ZONDA, significantly larger improvements were observed for the 8-week dosing interval (difference in mean change from baseline, 0.45; 95% CI, 0.14 to 0.74), but not for the 4-week dosing interval (0.23; 95% CI, -0.08 to 0.53).[48]

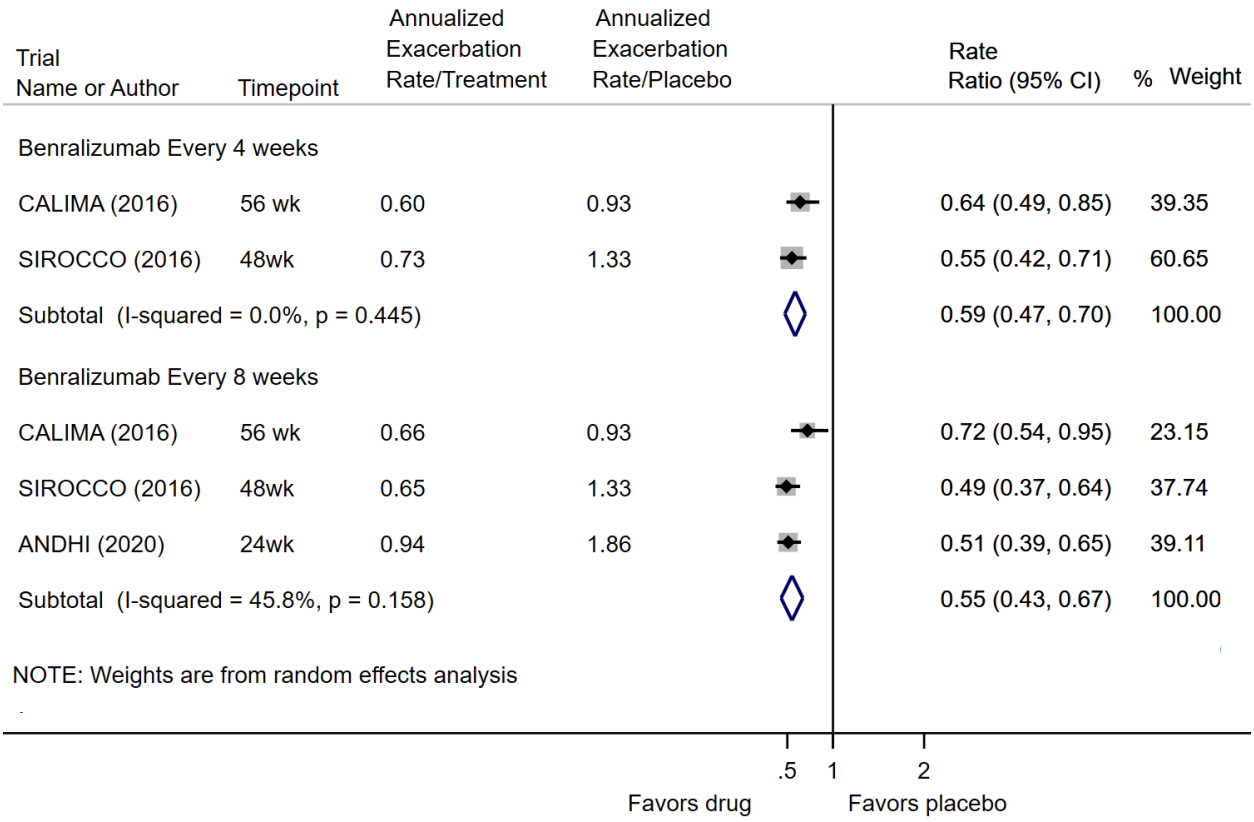
KQ 1: Exacerbations

Across both the add-on efficacy trials and the trial that also included steroid-tapering, benralizumab was more effective than placebo for reducing the rate of exacerbations (moderate QoE). Across the add-on efficacy trials, benralizumab was also more effective than placebo for reducing the incidence of exacerbations (moderate QoE) and for reducing the rate of exacerbations requiring ED or hospital visits (low QoE).

Add-on Efficacy Trials

CALIMA, SIROCCO, ANDHI, and Park et al. evaluated benralizumab as add-on therapy and observed a lower annualized rate of exacerbations ($P < .001$ for both 4-week and 8-week dosing, Figure 5).[39,45,46] These findings were all reported among participants with baseline eosinophil counts greater than 300 per µL. Park et al. could not be included in the quantitative synthesis, but the mean annualized exacerbation rate was 1.9 in the benralizumab group compared to 3.5 in the placebo group (IRR, 5%; *P* value NR and not calculable).[39] The SIROCCO trial also reported findings among the subgroup of participants with baseline eosinophils less than 300 per µL: a lower rate of exacerbations was observed for the 4-week dosing interval (IRR, 0.70; 95% CI, 0.50 to 1.00; $P = .04$), but not for the 8-week dosing interval (IRR, 0.83; 95% CI, 0.59 to 1.16).[46]

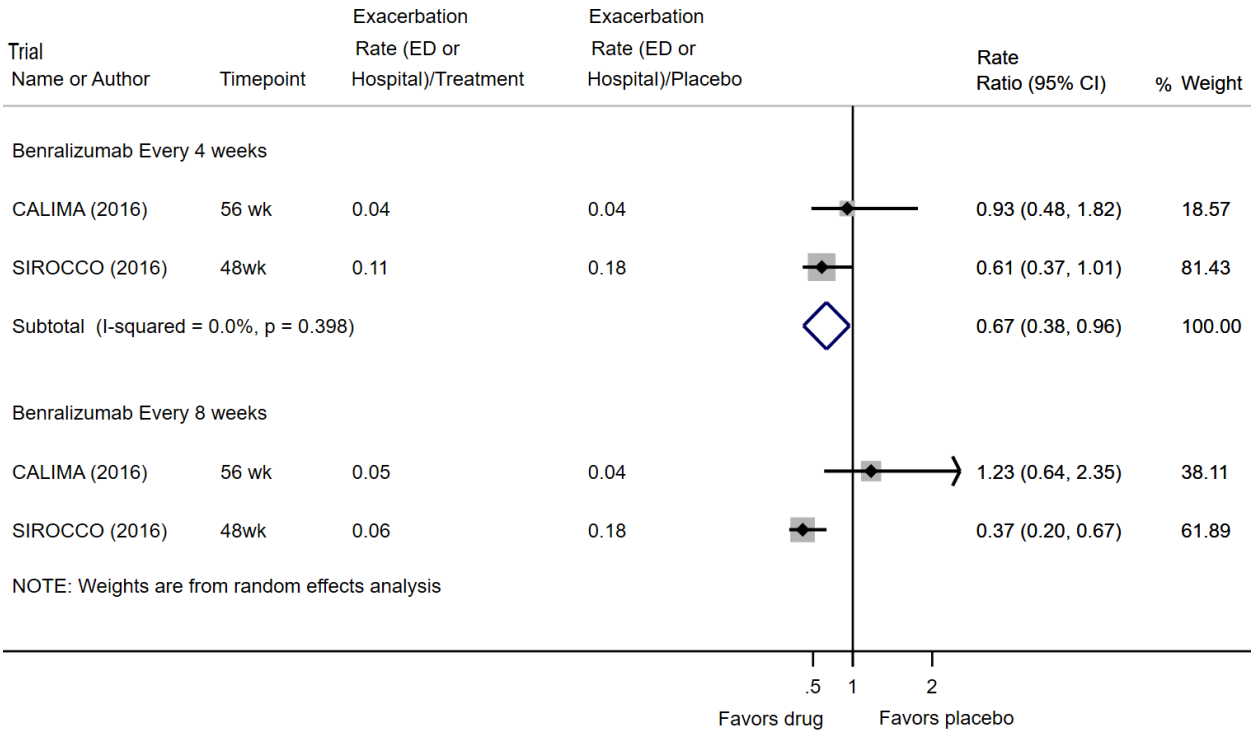
Figure 5. Benralizumab vs. Placebo, Annualized Rate of Exacerbations



Abbreviations. CI: confidence interval; wk: week.

In a pooled estimate using data from CALIMA and SIROCCO, a lower annualized rate of exacerbations requiring ED or hospital visit among the subgroup of participants with baseline eosinophil counts greater than 300 per µL was observed for the 4 week dosing interval ($P < .001$), but findings for the for 8-week dosing were too heterogenous to pool with only 2 studies (Figure 6).[45,46]

Figure 6. Benralizumab vs. Placebo, Annualized Rate of Exacerbations Requiring ED or Hospital Visits



Abbreviations. CI: confidence interval; ED: emergency department; wk: week.

Three studies reported the number of participants with exacerbations over follow-up. The pooled RR over 12 to 56 weeks of followup was 0.75 (95% CI, 0.65 to 0.86; Appendix D, Figure D1)..[45,50,60] BISE and CALIMA also evaluated the number of participants with exacerbations requiring an ED or hospital visit; the BISE study reported no such exacerbations in either treatment or placebo group,[50] while the CALIMA study reported no significant difference of treatment with either 4-week dosing intervals (RR, 0.82; 95% CI, 0.44 to 1.55) or 8-week dosing intervals (RR, 1.04; 95% CI, 0.57 to 1.88).[45] We note that the CALIMA analyses were limited to the subgroup of participants with baseline eosinophils greater than 300 per μL.

Add-on Efficacy With Steroid-Tapering Trial

In ZONDA, the annualized rate of exacerbations was lower among participants on both the 4-week dosing interval (IRR, 0.45; 95% CI, 0.27 to 0.76) and the 8-week dosing interval (0.30; 95% CI, 0.17 to 0.53).[48] The annualized rate of exacerbations requiring ED or hospital visits was also lower for the 8-week dosing interval (IRR, 0.07; 95% CI, 0.01 to 0.63), but not for the 4-week dosing interval (IRR, 0.44; 95% CI, 0.13 to 1.49).[48] The number of participants experiencing an exacerbation was lower for both the 4-week and 8-week dosing intervals compared to placebo (8-week calculated RR, 0.45; 95% CI, 0.27 to 0.76; 4-week calculated RR, 0.51; 95% CI, 0.33 to 0.79).[48]

KQ 1: Steroid Use

In 1 trial of add-on efficacy with steroid-tapering, benralizumab was more effective than placebo for reducing proportion of participants able to reduce their steroid dose by 50% or more (moderate QoE).

Add-on Efficacy Trials

No studies reported steroid use outcomes.

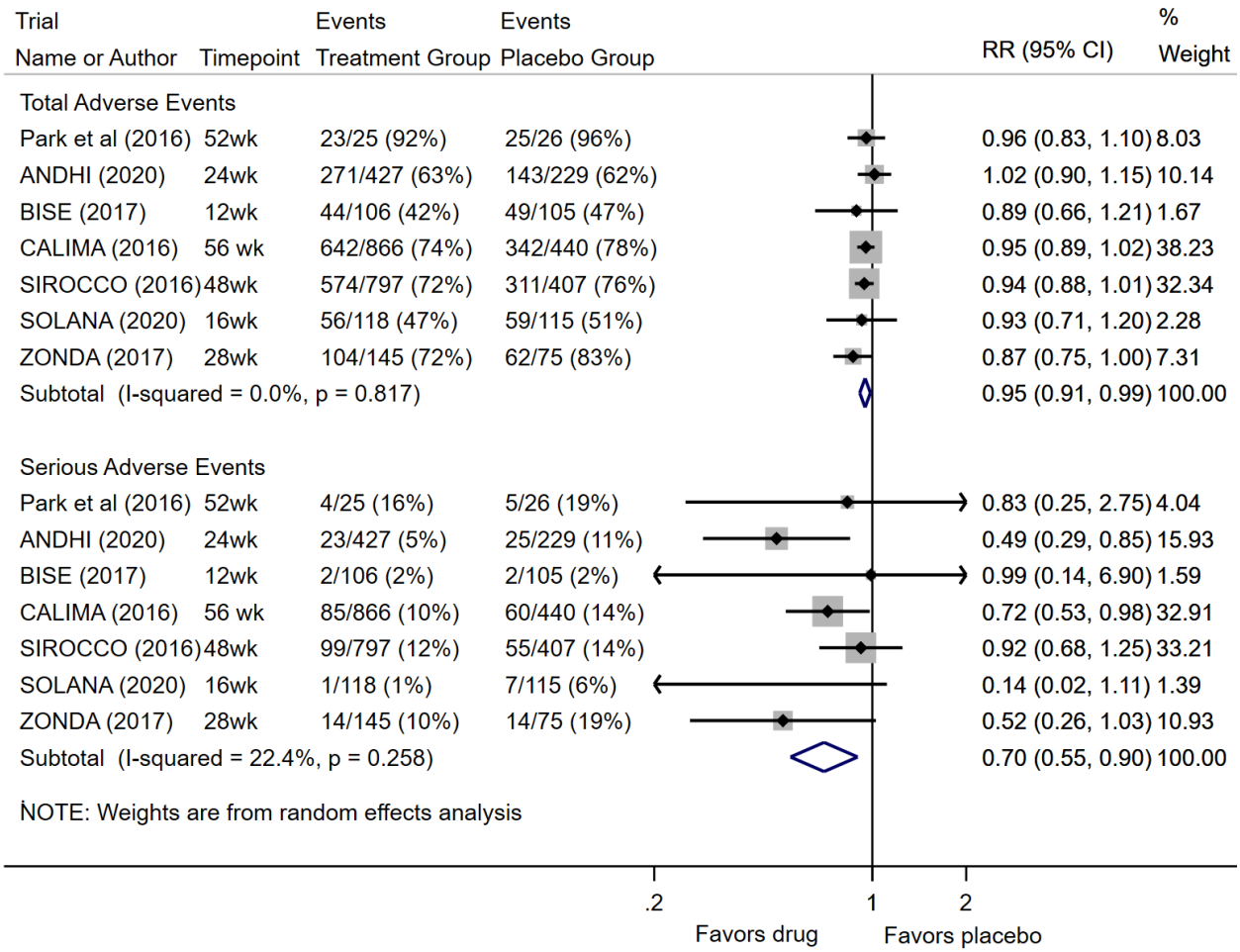
Add-on Efficacy With Steroid-Tapering Trial

In ZONDA, a higher proportion of participants in both the 4-week dosing interval (calculated RR, 1.79; 95% CI, 1.28 to 2.50) and 8-week dosing interval (calculated RR, 1.76; 95% CI, 1.26 to 2.47) were able to reduce their maintenance dose of oral steroids by 50% or more at 28 weeks follow-up.[48] Similarly, a higher proportion of participants in both dosing groups no longer required oral steroids at the end of follow-up (4-week calculated RR, 3.0; 95% CI, 1.50 to 5.87; 8-week calculated RR, 2.75; 95% CI, 1.39 to 5.47).[48] Additional steroid outcomes were also reported (Appendix B, Table B2).

KQ 2: AEs

The same 7 trials that contributed to effectiveness outcomes also reported AEs outcomes.[9,39,45,46,48,50,60] Pooled analyses indicated that fewer total AEs occurred in the benralizumab group compared to placebo (high QoE; Figure 7 upper panel). Further, fewer SAEs also occurred, but we downgraded this outcome 1 level because of imprecision due to the rarity of observed events (moderate QoE; Figure 7 lower panel). No differences between groups in discontinuations because of AEs were observed in 5 of the 7 studies reporting this outcome, but these events were rare and estimates were imprecise (Appendix B, Table B3).[9,45,46,48,50,60]

Figure 7. Benralizumab vs. Placebo, Adverse Events



Abbreviations. CI: confidence interval; wk: week.

KQ 2: Mortality

Six of the 7 studies also reported mortality; however, events were rare (12 deaths of 2,008 total participants across studies [0.60%]); thus, estimates of treatment effect were imprecise (Appendix B, Table B3).[39,45,46,48,50,60]

Dupilumab

Four RCTs evaluated 1 or more dosing regimens of dupilumab compared to placebo. The GRADE summary of findings is provided in Table 5.

Table 5. Summary of Findings (GRADE) Dupilumab for Asthma

No. Studies (No. Participants)	Outcome	Quality of the Evidence	Relationship	Rationale
2 add-on efficacy RCTs (N = 2,367)[44,51] 2 steroid-sparing RCTs (N = 314)[37,53]	ACQ (MCB)	●●●○ (moderate)	Favors dupilumab	Downgraded 1 level for serious indirectness
1 add-on efficacy RCT (N = 465)[44]	ACQ (MID response)	●●●○ (moderate)	Favors dupilumab	Downgraded 1 level for serious imprecision
2 add-on efficacy RCTs (N = 2,367)[44,51]	AQLQ (mean change from baseline)	●●●○ (moderate)	Favors dupilumab	Downgraded 1 level for serious indirectness
1 add-on efficacy RCT (N = 465)[44]	AQLQ (MID response)	●●●○ (moderate)	Favors dupilumab	Downgraded 1 level for serious imprecision
2 add-on efficacy RCTs (N = 2,367)[44,51] 1 steroid-sparing RCT (N = 210)[53]	Annualized rate of severe exacerbations	●●●○ (moderate)	Favors dupilumab	Downgraded 1 level for serious imprecision
1 add-on efficacy RCT (N = 1,902)[51]	Rate of exacerbations requiring ED or hospitalizations	●●○○ (low)	Favors dupilumab	Downgraded 2 levels for very serious imprecision
1 add-on efficacy RCT (N = 465)[44]	Incidence of severe exacerbations	●●●○ (moderate)	Favors dupilumab	Downgraded 1 level for serious imprecision
1 steroid-sparing RCT (N = 104)[37]	Incidence of exacerbations (none required hospitalization)	●●○○ (low)	Favors dupilumab	Downgraded 2 levels for very serious imprecision
2 steroid-sparing RCTs (N = 314)[37,53]	Steroid use (reduction)	●●●○ (moderate)	Favors dupilumab	Downgraded 1 level for serious imprecision
4 RCTs (N = 2,681)[37,44,51,53]	Overall AEs	●●●● (high)	No difference	Not downgraded
4 RCTs (N = 2,681)[37,44,51,53]	SAEs	●●●○ (moderate)	No difference	Downgraded 1 level for serious imprecision

Note. For methods and interpretation of GRADE ratings, see Appendix A.
Abbreviations. ACQ: Asthma Control Questionnaire; AE: adverse event; AQLQ: Asthma Quality of Life Questionnaire; ED: emergency department; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; MCB: mean change from baseline; MID: minimally important difference; RCT: randomized controlled trial; SAE: serious adverse event.

Study Characteristics

Four industry-sponsored RCTs reported in 5 publications conducted over the years 2013 to 2019 evaluated dupilumab compared to placebo.[37,43,44,51,53] A summary of these trials is in Table 6 with additional details in Appendix B, Table B4. We rated the risk of bias of these trials as moderate for extensive manufacturer involvement in study design, execution, and reporting. All were multicenter studies. Two RCTs were conducted in multiple countries among children and adults aged 12 years and older,[51] 1 RCT was conducted in multiple countries among adults aged 18 years and older,[44] and 1 RCT was conducted in the US among adults aged 18 years and older.[37] Wenzel et al. 2013[37] was a phase 2a trial, Wenzel et al. 2016[44] was a phase 2b trial, and LIBERTY ASTHMA VENTURE[53] and LIBERTY ASTHMA QUEST[51] were phase 3 trials.

Study inclusion and exclusion criteria were reasonably similar across the 4 included RCTs. All were conducted among participants who had asthma for at least 12 months that was not well controlled with ICS, or LABAs, or both, and excluded participants with chronic obstructive pulmonary disease or other lung diseases, and current smokers. Wenzel et al. 2013 enrolled only participants with baseline eosinophils greater than 300 per μL.[37] LIBERTY ASTHMA VENTURE and LIBERTY ASTHMA QUEST enrolled participants without respect to baseline level of eosinophils, but reported findings overall and for the subgroups of participants with baseline eosinophils less than 150 per μL, 150 to 300 per μL, and greater than 300 per μL.[51,53] Wenzel et al. 2016 enrolled participants without regard to baseline eosinophils but defined the primary endpoint for the subgroup with baseline eosinophils greater than 300 per μL.[44]

LIBERTY ASTHMA QUEST[51] and Wenzel et al. 2016[44] were RCTs of the effectiveness of dupilumab as an add-on therapy. The dosages evaluated in LIBERTY ASTHMA QUEST[51] were a 200-mg dose every 2 weeks for 52 weeks with a loading dose of 400 mg and a 300-mg dose every 2 weeks for 52 weeks with a loading dose of 600 mg. Wenzel et al. 2016[44] evaluated the same doses over a period of 24 weeks. Both studies allowed continued use of combinations of high-dose ICS and LABA, with SABA as necessary for symptom relief.[44,51] LIBERTY ASTHMA VENTURE[53] and Wenzel et al. 2013[37] evaluated dupilumab as an add-on therapy during a steroid-tapering cointervention. LIBERTY ASTHMA VENTURE evaluated a dose of 300 mg every 2 weeks for 24 weeks with a loading dose of 600 mg.[53] In this study, glucocorticoid dose was reduced every 4 weeks during weeks 4 to 20, while background asthma controllers were kept at stable doses with SABA as necessary for symptom relief.[53] Wenzel et al. 2013 evaluated a dose of 300 mg every week for 52 weeks.[37] Combination therapy with ICS and LABAs at stable doses was allowed for 4 weeks, followed by LABA discontinuation at week 4 and tapering of ICS during weeks 6 through 9.[37]

Table 6. Evidence Table (Brief Version) RCTs of Dupilumab for Asthma

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Castro et al., 2018[51] LIBERTY ASTHMA QUEST NCT02414854 Phase 3 RCT of effectiveness of add-on therapy Moderate	Aged 12 and older, treatment with medium- to high-dose ICS plus up to 2 additional controllers, worsening asthma in prior year that led to hospitalization, emergency medical care, or treatment with systemic steroids for ≥3 days, ACQ score ≥ 1.5; no minimum requirement for eosinophils but 82% had atopic medical history	Dupilumab 200 mg SC every 2 wks, loading dose 400 mg (n = 631) Dupilumab 300 mg SC every 2 wks, loading dose 600 mg (n = 633) Placebo (n = 638) High-dose ICS; continued stable dose asthma-controller medicines; LABA, long-acting muscarinic antagonists, LTRAs, and methylxanthines; SABA as necessary for symptom relief	At 52 wks • Symptom control • QoL • Exacerbations • Adverse events • Mortality (Annualized rate of severe asthma exacerbations)
Rabe et al., 2018[53] LIBERTY ASTHMA VENTURE NCT02528214 Phase 3 RCT of add-on therapy with steroid tapering Moderate	Aged 12 and older, treatment with systemic glucocorticoids in prior 6 months, high-dose inhaled glucocorticoid, up to 2 controllers in prior 3 months; no minimum requirement for eosinophils but 80% had atopic medical history	Dupilumab 300 mg SC every 2 wks, loading dose 600 mg (n = 103) Placebo (n = 107) Glucocorticoid dose (prednisone or prednisolone) with dose reduced every 4 wks during weeks 4 to 20, background asthma controllers at stable dose, SABA as needed	At 24 wks • Symptom control • Steroid use • Adverse events • Mortality (Percentage reduction in oral glucocorticoid dose while asthma control was maintained)
Wenzel et al., 2016[44] Corren et al., 2019[43] None NCT01854047 Phase 2b trial of effectiveness of add-on therapy Moderate	Aged 18 and older, treatment with medium- to high-dose ICS and LABA with a stable dose for 1 month or longer; ACQ-5 total score 1.5 or higher; 1 or more systemic corticosteroid burst therapy, hospital admission, or an emergency or urgent medical care visit that required treatment with systemic steroids for worsening asthma in prior year, no minimum requirement for eosinophils but primary endpoint defined based on subgroup with ≥ 300/µL	Dupilumab 200 mg SC every 2 or 4 wks, 400-mg loading dose (n = 150) Dupilumab 300 mg SC every 2 or 4 wks, 600-mg loading dose (n = 157) Placebo (n = 158) High-dose ICS and LABA use in 1 of 3 approved combinations	At 24 wks • Symptom control • QoL • Exacerbations • Adverse events • Mortality (Change from baseline in FEV_1 at week 12 in subpopulation of patients with baseline eosinophil count of ≥ 300/µL)

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Wenzel et al., 2013[37] None NCT 01312961 Phase 2a trial of add-on therapy with LABA discontinuation and steroid tapering Moderate	Aged 18 to 65 years, asthma not well controlled with medium-dose to high-dose inhaled glucocorticoids plus LABAs; ACQ-5 ≥ 1.5 and ≤ 3.0, eosinophils ≥ 300/μL, at least 1 asthma exacerbation within prior 2 years resulting in treatment with 1 or more systemic steroid or hospitalization or an emergency care visit	Dupilumab 300 mg SC every 1 wk (n = 52) Placebo (n = 52) Combination therapy with ICS and LABAs, ICS dose based on pretrial doses for 4 wks Discontinuation of LABA at week 4 and tapering of ICS during weeks 6 through 9	At 12 wks • Symptom control • Exacerbations • Adverse events • Mortality (Occurrence of asthma exacerbation)

Abbreviations. ACQ: Asthma Control Questionnaire; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LTRA: leukotriene receptor antagonist; NCT: US National Clinical Trial; QoL: quality of life; RCT: randomized controlled trial; SABA: short-acting beta-2 agonist; SC: subcutaneous; wk: week.

Detailed individual study results are provided in Appendix B, Table B5 (effectiveness) and Table B6 (safety).

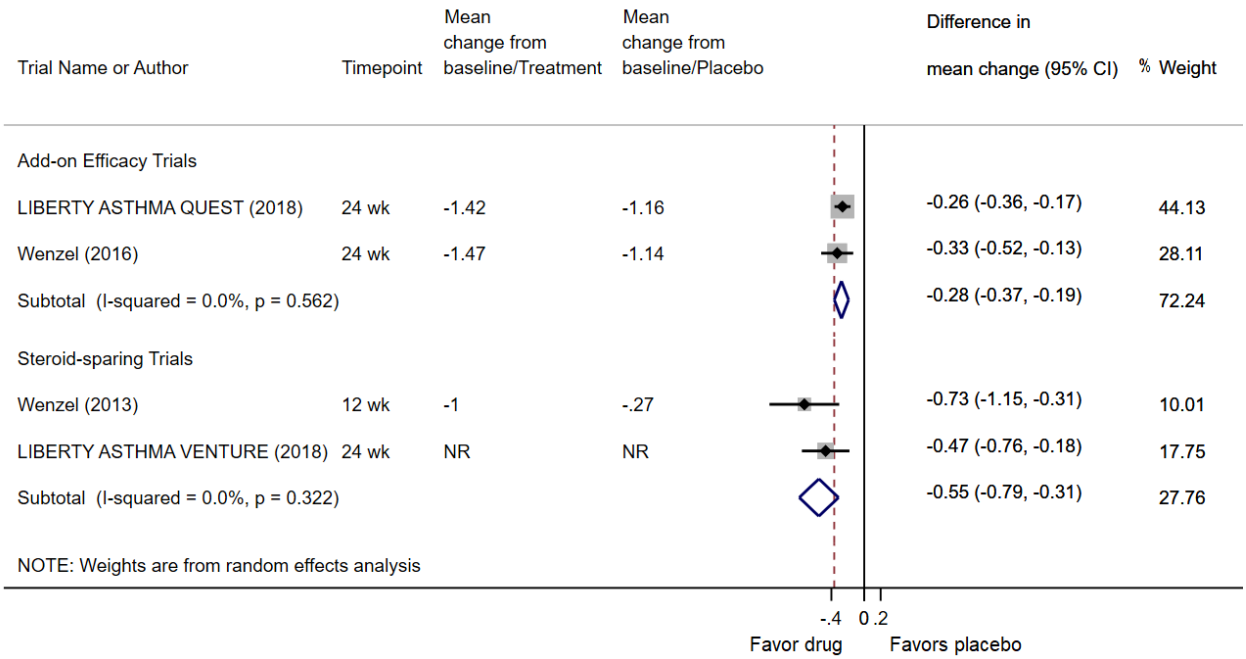
KQ 1: Symptom Control

Across both add-on efficacy trials and steroid tapering trials, dupilumab was more effective than placebo for improving symptom control as measured by the ACQ (moderate QoE).

Add-on Efficacy Trials

Wenzel et al. 2016[44] and LIBERTY ASTHMA QUEST[51] evaluated dupilumab as add-on therapy; larger improvements from baseline in ACQ score were observed compared to placebo for dupilumab (200-mg and 300-mg dosages combined; $P < .001$; Figure 8 upper panel) at 24 weeks.[44,51] However, the mean difference was less than the MID associated with this measure (0.5 points). Findings were also reported at 1 year in LIBERTY ASTHMA QUEST[51] (difference in mean change from baseline 200-mg dose, -0.39; 95% CI, -0.53 to -0.25; 300-mg dose, -0.22; 95% CI, -0.36 to -0.08). Wenzel et al. 2016 reported that a significantly higher proportion of participants achieved an MID in ACQ score for participants allocated to dupilumab compared to placebo (combined dose groups calculated RR, 1.22; 95% CI, 1.06 to 1.40).[44] Wenzel et al. 2016 also reported findings among participants based on baseline eosinophil levels (Appendix B, Table B5).[44]

Figure 8. Dupilumab vs. Placebo, Asthma Control Questionnaire



Abbreviations. CI: confidence interval; wk: week.

Add-on Efficacy with Steroid-Tapering Trials

Wenzel et al. 2013[37] and LIBERTY ASTHMA VENTURE[53] evaluated a 300-mg dosage of dupilumab as add-on therapy with a steroid-tapering cointervention[53] or LABA discontinuation with a steroid-tapering cointervention.[37] Significantly larger improvements in ACQ score were observed for dupilumab compared to placebo in pooled estimates ($P < .001$; Figure 8, lower panel). This finding did achieve a reduction considered to be a MID.

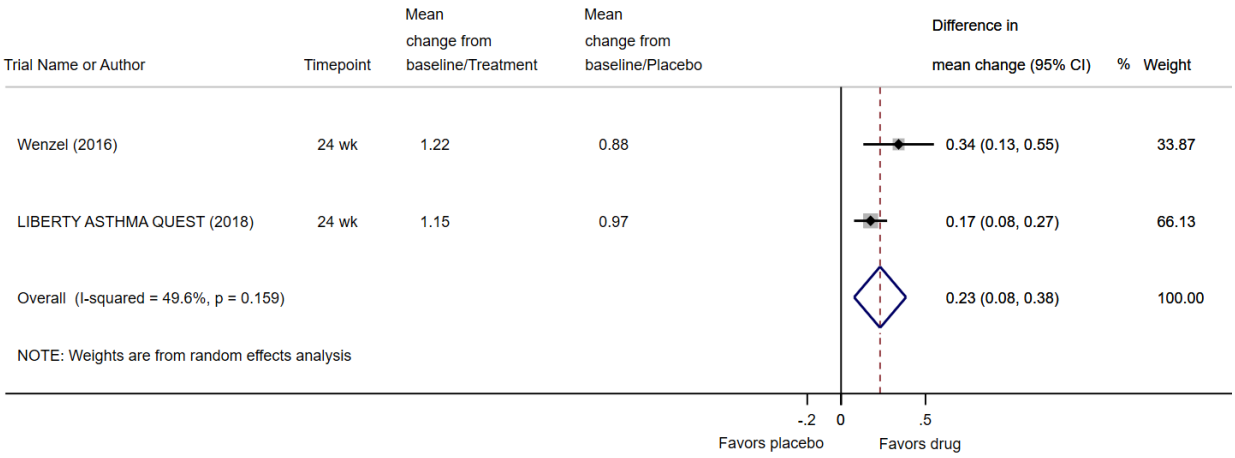
KQ 1: Quality of Life

Across the add-on efficacy trials, dupilumab was more effective than placebo for improving quality of life as measured by the AQLQ (moderate QoE).

Add-on Efficacy Trials

Wenzel et al. 2016[44] and LIBERTY ASTHMA QUEST[51] evaluated dupilumab as add-on therapy; larger improvements were observed in AQLQ score in the 200-mg and 300-mg dosage groups compared to placebo at 12 weeks,[44] at 24 weeks[44,51] (pooled estimates, Figure 9; $P = .007$), and at 1 year.[44] In addition, a significantly larger proportion of participants allocated to dupilumab achieved an MID response compared to placebo (200-mg dosage calculated RR, 1.25; 95% CI, 1.03 to 1.52; 300-mg dose calculated RR, 1.27; 95% CI, 1.05 to 1.53).[44] However, our pooled analysis at 24 weeks did not render a mean reduction that achieved a MID. Wenzel et al. also reported findings for subgroups based on baseline eosinophils (Appendix B, Table B5).[44] In LIBERTY ASTHMA VENTURE,[53] larger improvements were observed at 1 year in the 200-mg dosage group (difference in mean change, 0.29; 95% CI, 0.15 to 0.44) and in the 300-mg dosage group (difference in mean change, 0.26; 95% CI, 0.12 to 0.40).

Figure 9. Dupilumab vs. Placebo, Asthma Quality of Life Questionnaire



Abbreviations. CI: confidence interval; wk: week.

Add-on Efficacy With Steroid-Tapering Trial

Wenzel et al. 2013[37] and LIBERTY ASTHMA VENTURE[53] did not report any quality-of-life measures.

KQ 1: Exacerbations

Across both add-on efficacy trials and 1 steroid-tapering trial, dupilumab was more effective than placebo for reducing the annualized rate of severe exacerbations (moderate QoE). In 1 add-on efficacy trial, dupilumab was more effective than placebo for reducing the rate of exacerbations requiring ED or hospital admissions (low QoE). In the other add-on efficacy trial, dupilumab was more effective than placebo for reducing the incidence of severe exacerbations, (moderate QoE). In 1 steroid-sparing trial, dupilumab was more effective than placebo for reducing the incidence of exacerbations, none of which required hospitalization (low QoE).

Add-on Efficacy Trials

In Wenzel et al. 2016,[44] the adjusted annualized rate of severe exacerbations favored dupilumab compared to placebo at 24 weeks in the 200-mg dosage group (relative risk reduction vs. placebo, 70%; 95% CI, 43.5% to 84.1%, equivalent to an IRR of about 0.30; P = .0002,) and the 300-mg dosage group (relative risk reduction vs. placebo, 70.5%; 95% CI, 45.4% to 84.1%, equivalent to an IRR of about 0.29; P = .0001). In prespecified subgroup analyses, significant reductions in these rates were observed for participants with baseline eosinophil levels greater than or equal to 300 per µL and less than 300 per µL. This RCT also reported a significantly lower proportion of participants with a severe exacerbation among those allocated to dupilumab compared to placebo at 24 weeks (combined dose groups calculated RR, 0.38; 95% CI, 0.25 to 0.58).[44]

In LIBERTY ASTHMA QUEST,[51] the adjusted annualized rate of severe asthma exacerbations was lower for dupilumab at 1 year compared to placebo in the 200-mg dosage group (IRR, 0.52; 95% CI, 0.41 to 0.66) and 300-mg dosage group (IRR, 0.54; 95% CI, 0.43 to 0.68). The rate of

exacerbations requiring ED visits or hospitalizations was also significantly lower among participants allocated to dupilumab (combined dose groups IRR, 0.53; 95% CI, 0.25 to 0.82).[51]

In prespecified subgroup analyses in LIBERTY ASTHMA QUEST, the rates of severe asthma excerabations among participants with baseline eosinophils between 150 and 300 per µL and greater than 300 per µL were significantly lower among participants allocated to either dose of duplimumab compared to placebo; however, among participants with baseline levels less than 150 per µL, no significant difference in the exacerbation rate was observed.[51] In Wenzel et al. 2016, the rate of severe exacerbations was significantly reduced compared to placebo, regardless of baseline eosinophil level.[44]

Add-on Efficacy With Steroid-Tapering Trials

In Wenzel et al. 2013,[37] dupilumab significantly reduced the incidence of exacerbation at 12 weeks (calculated RR, 0.13; 95% CI, 0.04 to 0.41). There were no exacerbations requiring hospitalizations in either the dupilumab or placebo arm.[37] In LIBERTY ASTHMA VENTURE, participants allocated to dupilumab had a significantly lower rate of severe exacerbations compared to participants allocated to placebo (IRR, 0.41; 95% CI, 0.26 to 0.63).[53] This finding was observed in subgroup analyses among persons with baseline eosinophils greater than or equal to 300 per µL and less than 300 per µL.[53]

KQ 1: Steroid Use

Across both steroid-sparing trials, dupilumab was more effective than placebo at reducing steroid use (moderate QoE).

Add-on Efficacy Trials

Wenzel et al. 2016[44] and LIBERTY ASTHMA QUEST[51] did not report steroid use outcomes.

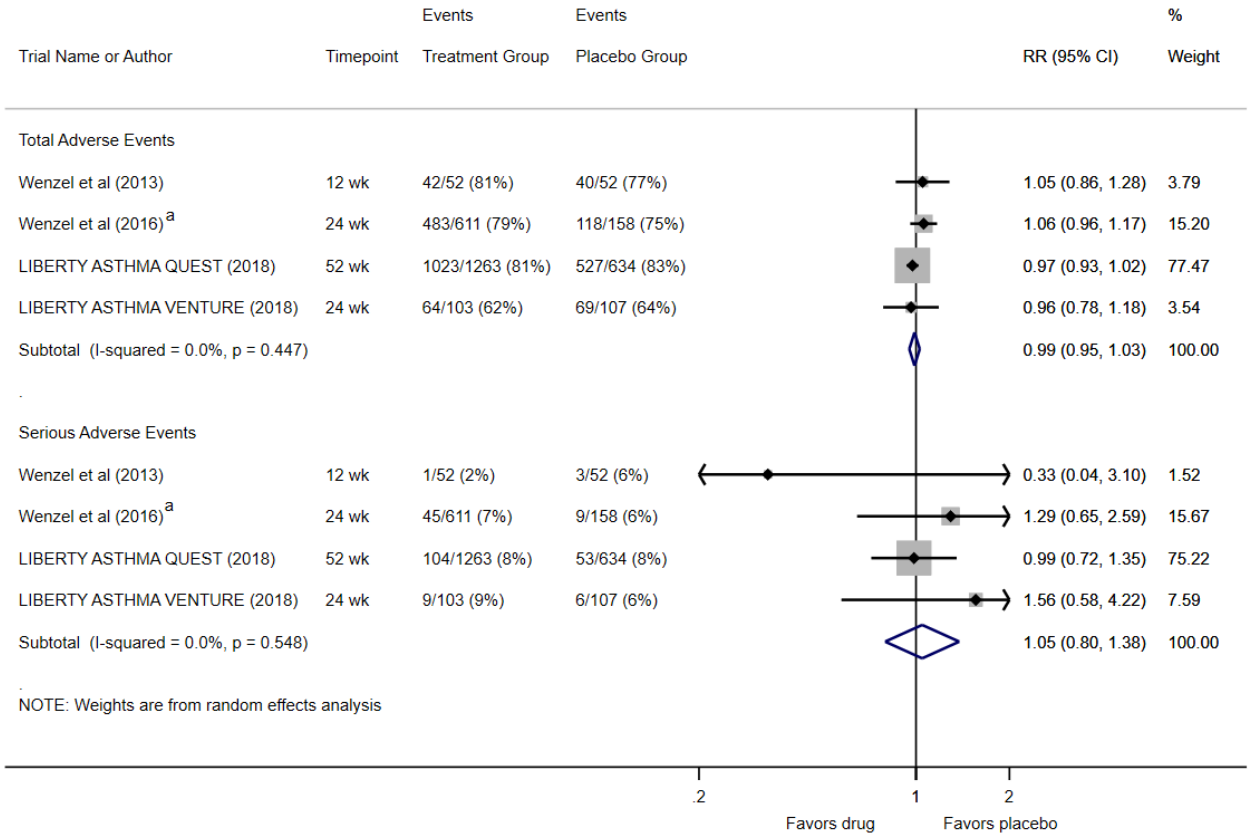
Add-on Efficacy With Steroid-Tapering Trials

Wenzel et al. 2013[37] and LIBERTY ASTHMA VENTURE[53] evaluated 300 mg of dupilumab as add-on therapy with a steroid-tapering or LABA-discontinuation and steroid-tapering cointervention, and used different measures of steroid use. Wenzel et al. 2013[37] found that fewer participants in the dupilumab group required systemic glucocorticoid treatment by 12 weeks compared to placebo (2% vs. 10%), but this result was imprecise and was not statistically significant (calculated RR, 0.20; 95% CI, 0.02 to 1.65). LIBERTY ASTHMA VENTURE[53] assessed 4 measures of steroid use at 24 weeks; 8% of those in the dupilumab group had a 50% or greater reduction in oral steroid use at 24 weeks compared to 53% in the placebo group (calculated RR, 1.49; 95% CI, 1.22 to 1.83). More than half (52%) of the dupilumab group no longer required oral glucocorticoid at 24 weeks compared to 29% in the placebo group (calculated RR, 1.81; 95% CI, 1.28 to 2.57).[53] Additional steroid use outcomes for this study are reported in Appendix B, Table B5.

KQ 2: AEs

The same 4 trials that contributed to effectiveness outcomes also reported AE outcomes.[37,44,51,53] Pooled analyses indicated that there was no significant difference in the number of participants with AEs (high QoE, $P = .58$) or SAEs (moderate QoE, $P = .74$) in dupilumab groups compared to placebo (Figure 10). SAEs were rare, and estimates were imprecise (Appendix B, Table B6).

Figure 10. Dupilumab vs. Placebo, Adverse Events



Note. [a] *Represents adverse events across all dupilumab dose groups evaluated in the study, including 2 doses outside of the FDA-approved dosing range.*
Abbreviations. CI: confidence interval; FDA: US Food and Drug Administration; wk: week.

KQ 2: Mortality

Only 1 study reported mortality; no deaths were reported in either the dupilumab or placebo group.[37]

Mepolizumab

Three studies evaluated mepolizumab compared to placebo. The GRADE summary of findings is summarized in Table 7.

Table 7. Summary of Findings (GRADE) Mepolizumab for Asthma

No. Studies (No. Participants)	Outcome	Quality of the Evidence	Relationship	Rationale
2 add-on efficacy RCTs (N = 941)[42,49] 1 steroid-sparing RCT (N = 135)[41]	ACQ (MCB)	●●●○ (moderate)	Favors mepolizumab	Downgraded 1 level for serious indirectness
2 add-on efficacy RCTs (N = 941)[42,49] 1 steroid-sparing RCT (N = 135)[41]	Annualized rate of exacerbations	●●●○ (moderate)	Favors mepolizumab	Downgraded 1 level for serious imprecision
2 add-on efficacy RCTs (N = 941)[42,49]	Annualized rate of exacerbations requiring ED or hospitalization,	●●○○ (low)	Favors mepolizumab	Downgraded 2 levels for very serious imprecision
1 steroid-sparing RCT (N = 135)[41]	Incidence of exacerbations requiring hospitalization	●●○○ (low)	Favors mepolizumab	Downgraded 2 levels for very serious imprecision
1 steroid-sparing RCT (N = 135)[41]	Proportion of participants reducing oral steroid dose by 50%	●●○○ (low)	Favors mepolizumab	Downgraded 2 levels for very serious imprecision
1 steroid-sparing RCT (N = 135)[41]	Proportion of participants reducing oral steroid dose by 100%	●●○○ (low)	Favors mepolizumab	Downgraded 2 levels for very serious imprecision
3 RCTs (N = 1,071)[41,42,49]	AEs	●●●● (high)	Favors mepolizumab	Not downgraded
3 RCTs (N = 1,071)[41,42,49]	SAEs	●●●○ (moderate)	Favors mepolizumab	Downgraded 1 level for serious imprecision

Note. For methods and interpretation of GRADE ratings, see Appendix A.
Abbreviations. ACQ: Asthma Control Questionnaire; AE: adverse event; ED: emergency department; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; MCB: mean change from baseline; RCT: randomized controlled trial; SAE: serious adverse event.

Study Characteristics

Three phase 3 industry-sponsored RCTs (SIRIUS,[41] MENSA,[42] and MUSCA[49]) evaluated mepolizumab compared to placebo. A summary of these trials is in Table 8 with additional details in Appendix B, Table B7. We rated the risk of bias of these trials as moderate for extensive manufacturer involvement in study design, execution, and reporting. All were multicenter studies conducted in more than 1 country between the years 2012 and 2016. MENSA and MUSCA enrolled with participants aged 12 to 75 with eosinophilic asthma on high-dose ICS with at least 2 exacerbations requiring systemic steroids in the prior year.[42,49] SIRIUS enrolled participants

aged 18 to 82 and required participants to have a 6-month history of maintenance systemic steroids in addition to treatment with high-dose ICS and another controller medication.[41]

MENSA and MUSCA were designed to assess the efficacy of a 100-mg dosage of mepolizumab as add-on therapy compared to placebo.[42,49] SIRIUS was designed to assess the efficacy of add-on mepolizumab (100 mg) compared to placebo during a steroid-tapering cointervention in both study groups.[41] SIRIUS used a 3- to 8-week optimization phase during a run-in period to establish the lowest dose of maintenance oral steroids associated with acceptable asthma control, which was continued into the double-blind treatment phase.[41] Starting at week 4 of the double-blind treatment phase, oral steroid doses were reduced according to a prespecified schedule of 1.25- to 10-mg per day every 4 weeks through week 20, until the oral dose was eliminated or loss of asthma control occurred.[41] The steroid dose achieved by week 20 was maintained in the final 4 weeks of the double-blind phase.[41] A final follow-up visit to assess safety outcomes occurred at 32 weeks.[41] All participants in SIRIUS continued treatment with high-dose ICS and an additional controller medication (LABA, LTRA, or theophylline) throughout the study.[41]

Table 8. Evidence Table (Brief Version) RCTs of Mepolizumab for Asthma

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Bel et al., 2014[41] SIRIUS NCT01691508 Phase 3 RCT of add-on therapy with steroid tapering Moderate	Aged 12 to 75, eosinophilic asthma, maintenance systemic steroids, high-dose ICS and controller medication (LABA, LTRA, or theophylline)	Mepolizumab 100 mg SC every 4 wks (n = 69) Placebo (n = 66) Oral steroids adjusted to lowest possible dose to control symptoms before randomization; oral steroid dose reduced by standard amount at regular intervals, continued stable doses of other controllers, SABA rescue for symptoms	At 24 wks • Symptom control • QoL • Exacerbations • Steroid use At 32 wk • Adverse events • Mortality (Percentage reduction in steroid dose with asthma control maintained)
Chupp et al., 2017[49] MUSCA NCT02281318 Phase 3 RCT of add-on therapy Moderate	Aged 12 to 75, eosinophilic asthma, high-dose ICS and controller medication, at least 2 exacerbations requiring systemic steroids in prior year	Mepolizumab 100 mg SC every 4 wks (n = 276) Placebo (n = 280) Continued stable doses of other asthma controllers, SABA rescue for symptoms	At 24 wks • Symptom control • QoL • Exacerbations • Adverse events • Mortality (HRQOL mean change)
Ortega et al., 2014[42] MENSA NCT01691521	Aged 18 to 82, eosinophilic asthma, high-dose ICS and controller medication, at least 2 exacerbations	Mepolizumab 100 mg SC every 4 wks (n = 194) Placebo (n = 191)	At 32 wks • Symptom control • QoL • Exacerbations At 40 wk

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Phase 3 RCT of add-on therapy Moderate	requiring systemic steroids in prior year	Continued stable doses of other asthma controllers, SABA rescue for symptoms	• Adverse events • Mortality (Annualized exacerbation rate)

Abbreviations. HRQOL: health-related quality of life; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonists; LTRA: leukotriene receptor antagonists; NCT: US National Clinical Trial; QoL: quality of life; RCT: randomized controlled trial; SABA: short-acting beta-2 agonists; SC: subcutaneous; wk: week.

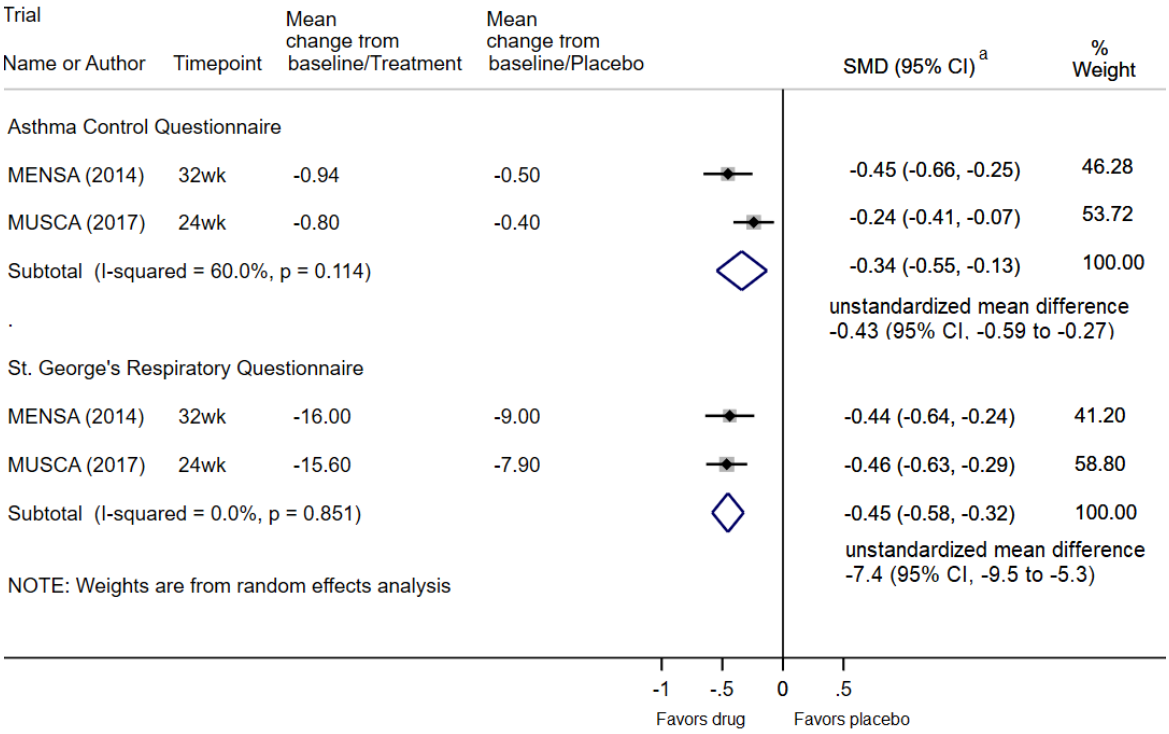
Detailed individual study results are provided in Appendix B, Table B8 (effectiveness) and Table B9 (safety).

KQ 1: Symptom Control

Add-on Efficacy Trials

MUSCA[49] and MENSA,[42] which evaluated mepolizumab as add-on therapy, both reported a mean change from baseline in the ACQ-5 and SGRQ, both measures of symptom control. Pooled analyses suggested mepolizumab is significantly more effective at improving symptoms compared to placebo at 24 to 32 weeks follow-up ($P = .001$ for ACQ; $P < .001$ for SGRQ; Figure 11). MUSCA also reported a significantly higher proportion of participants achieving a minimally important difference in ACQ at 24 weeks (59% for mepolizumab vs. 42% for placebo; calculated RR, 1.4; 95% CI, 1.18 to 1.66).[49]

Figure 11. Mepolizumab vs. Placebo, Symptom Control



Note. [a] *An SMD of 0.2 is considered a small effect, an SMD of 0.5 is considered a medium effect and an SMD of 0.8 is considered a large effect.*[101]
Abbreviations. CI: confidence interval; SMD: standardized mean difference; wk: week.

Add-on Efficacy With Steroid-Tapering Trial

SIRIUS, which was a trial of add-on therapy with a steroid-tapering intervention, also reported measures of symptom control.[41] The mean change from baseline in the ACQ and SGRQ was significantly larger for mepolizumab compared to placebo (ACQ, -0.52; 95% CI, -0.87 to -0.17; SGRQ, -5.8; 95% CI, -10.6 to -1.0), and these average effects exceeded the threshold for MID on both measures.[41]

KQ 1: Quality of Life

No studies reported measures of quality of life.

KQ 1: Exacerbations

Add-on Efficacy Trials

MUSCA and MENSA both reported exacerbation outcomes at 32 and 24 weeks, respectively, but MENSA did not provide enough information to conduct a pooled analysis. In MUSCA, participants allocated to mepolizumab had a significantly lower annualized exacerbation rate (IRR, 0.42; 95% CI, 0.31 to 0.56) and a lower rate of exacerbations requiring an ED visit or hospitalization (IRR, 0.32; 95% CI, 0.12 to 0.90) compared to placebo.[49] MENSA also reported a lower annualized exacerbation rate among persons allocated to mepolizumab compared to placebo (0.83 vs. 1.74; calculated IRR, 0.48) and a lower annualized rate of exacerbations requiring an ED visit or hospitalization (0.03 vs. 0.10, 69% decrease; 95% CI, 9% to 89% decrease).[42]

Add-on Efficacy With Steroid-Tapering Trial

SIRIUS, the trial of add-on therapy with steroid tapering, reported exacerbation outcomes at 24 weeks.[41] The annualized exacerbation rate was lower among participants allocated to mepolizumab compared to placebo (IRR, 0.68; 95% CI, 0.47 to 0.99), and the number of participants experiencing an exacerbation requiring hospitalization was 11% in the placebo group and 0% in the treatment group (calculated RR, 0.07; 95% CI, 0.004 to 1.17).[41]

KQ 1: Steroid Use

Add-on Efficacy Trials

No studies reported steroid use outcomes.

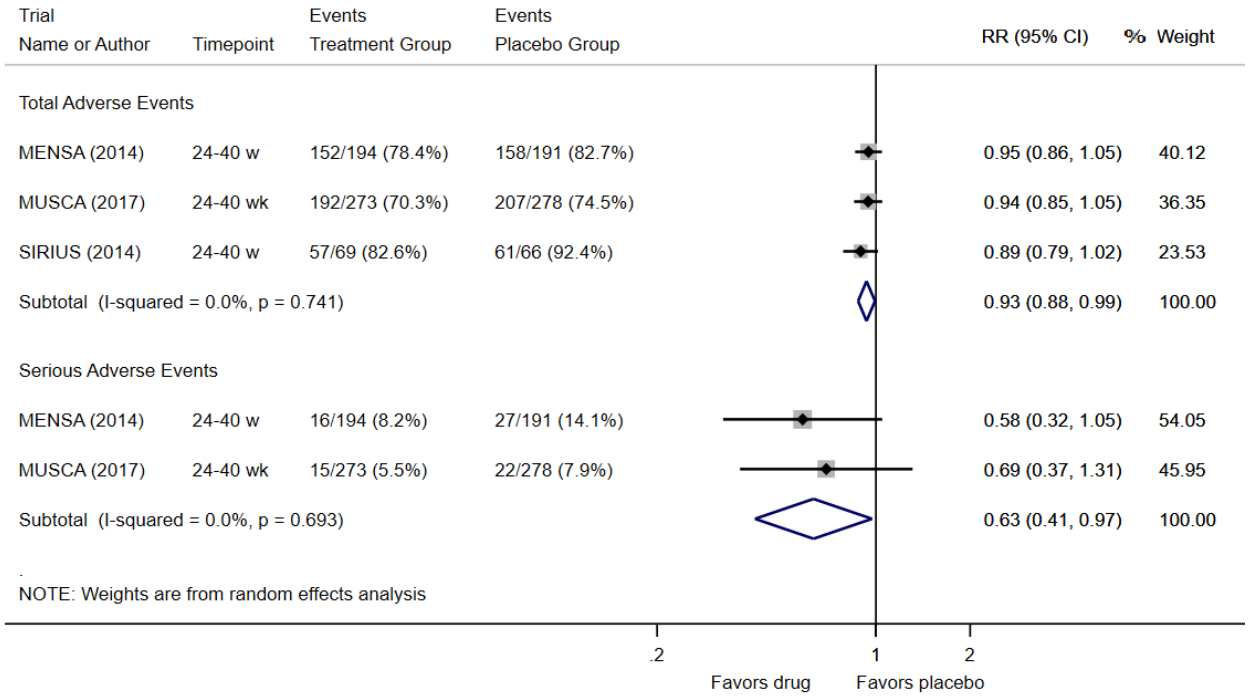
Add-on Efficacy With Steroid-Tapering Trial

In SIRIUS,[41] the median percentage reduction in oral steroid use at 24 weeks (the end of the study after the steroid-tapering phase) was 50% in the mepolizumab group compared to 0% in the placebo group (P = .007).[41] The proportion of participants with a 50% or more reduction in oral steroid dose was 54% in the treatment group compared to 33% in the placebo group (calculated RR, 1.61; 95% CI, 1.07 to 2.41). However, no significant difference in the proportion of participants no longer requiring oral steroids was observed (14% vs. 8%; calculated RR, 1.91; 95% CI, 0.69 to 5.3).

KQ 2: AEs

The same 3 trials that contributed to effectiveness outcomes also reported AE outcomes.[41,42,49] Pooled analyses indicated that fewer AEs occurred in the mepolizumab group compared to placebo (Figure 12). Pooled analyses of the MENSA and MUSCA trials also observed fewer SAEs in the mepolizumab group compared to placebo (Figure 12). We did not include SIRIUS[41] in this pooled analysis because the findings introduced substantial heterogeneity for reasons that we cannot explain based on study or population characteristics. In SIRIUS, 1 of 69 (1.4%) people experienced SAEs in the mepolizumab group compared to 12 of 66 (18.2%) in the placebo group (calculated RR, 0.07; 95% CI, 0.01 to 0.60).

Figure 12. Mepolizumab vs. Placebo, Adverse Events



Abbreviations. CI: confidence interval; RR: risk ratio; wk: week.

KQ 2: Mortality

Of the 3 studies evaluating mepolizumab, only MUSCA reported mortality. No deaths were reported in either the treatment or placebo group.[49]

Omalizumab

Twenty-three RCTs evaluated 1 or more dosing regimens of omalizumab.[10-16,18-34,38,47,54-59] One RCT used a no-treatment control group,[57] and 2 RCTs[11,26] used a control group characterized as optimized asthma therapy and best standard-of-care treatment. The rest of the RCTs used placebo comparators. The GRADE summary of findings is summarized in Table 9. There was strong variation in QoE ratings for outcomes related to omalizumab, ranging from very low to high.

Table 9. Summary of Findings (GRADE) Omalizumab for Asthma

No. Studies (No. Participants)	Outcome	Quality of the Evidence	Relationship	Rationale
3 add-on efficacy RCTs (N = 721)[28,30,31]	Number of days with asthma symptoms (mean change from baseline)	●●●● (high)	Favors omalizumab	Not downgraded
2 add-on efficacy RCTs (N = 449)[26,32]	ACQ (mean change from baseline)	●○○○ (very low)	Favors omalizumab	Downgraded 1 level for serious risk of bias, 1 level for serious inconsistency, and 1 level for serious imprecision
2 add on efficacy RCTs (N = 691)[28,30]	ACT or C-ACT (mean change from baseline or mean change in score at follow-up)	●●○○ (low)	Favors omalizumab	Downgraded 1 level for serious indirectness and 1 level for serious imprecision
5 add-on efficacy RCTs (N = 1,489)[19,26,28,31,58] 3 steroid-sparing RCTs (N = 1,486)[13,21,23]	Global evaluation of treatment effectiveness (patient or physician reported as excellent or good)	●●●○ (moderate)	Favors omalizumab	Downgraded 1 level for serious inconsistency
5 add-on efficacy RCTs (N = 1,791)[19,29,38,57,58] 1 steroid-sparing RCT (N = 525)[13]	QoL (AQLQ mean change from baseline)	●●●○ (moderate)	Favors omalizumab	Downgraded 1 level for serious indirectness
3 add-on efficacy RCTs (N = 1,662)[19,29,58] 1 steroid-sparing RCT (N = 525)[13]	QoL (AQLQ MID response)	●●●● (high)	Favors omalizumab	Not downgraded
1 steroid-sparing RCTs (N = 627)[23]	QoL (PAQLQ mean change from baseline)	●●○○ (low)	No difference	Downgraded 1 level for serious indirectness and 1 level for serious imprecision

No. Studies (No. Participants)	Outcome	Quality of the Evidence	Relationship	Rationale
1 steroid-sparing RCT (N = 334)[21]	QoL (PAQLQ large MID)	●●○○ (low)	No difference	Downgraded 2 levels for very serious imprecision
12 add-on efficacy RCTs (N = 3,646)[10,11,16,19,25,26,29-32,47,58] 4 Steroid-sparing RCTs (N = 2,032)[13,21,47,54]	Incidence of exacerbations	●●●● (high)	Favors omalizumab	Not downgraded
4 add-on efficacy RCTs (N = 1,632)[16,26,29,32] 4 steroid-sparing RCTs (N = 2,032)[13,21,23,54]	Rate of exacerbations	●●●● (high)	Favors omalizumab	Not downgraded
3 add-on efficacy RCTs (N = 1,199)[11,19,58] 1 steroid-sparing RCT (N = 246)[18]	Annualized rate of exacerbations	●●●● (high)	Favors omalizumab	Not downgraded
3 add-on efficacy RCTs (N = 1,309)[19,26,30]	Incidence or rate of exacerbations requiring ED visit or Hospitalization	●●●○ (moderate)	Favors omalizumab	Downgraded 1 level for serious imprecision
3 steroid-sparing RCTs (N = 1,405)[13,21,54]	Incidence of exacerbations requiring hospitalization	●●●○ (moderate)	Favors omalizumab	Downgraded 1 level for serious imprecision
1 add-on efficacy RCT (N = 312)[11]	Steroid use (requirement for use of oral steroids)	●●○○ (low)	Favors omalizumab	Downgraded 1 level for serious risk of bias and 1 level for serious imprecision
3 steroid-sparing RCTs (N = 1,317)[13,18,54]	Steroid use (50% or more reduction in ICS dose)	●●●● (high)	Favors omalizumab	Not downgraded
4 steroid-sparing RCTs (N = 1,651)[13,18,23,54]	Steroid use (proportion no longer requiring ICS)	●●●● (high)	Favors omalizumab	Not downgraded
17 RCTs (N = 23,751)[11,13,16,18,19,21,23,25,26,28-32,54,58,59]	Overall AEs	●●●● (high)	No difference	Not downgraded
16 RCTs (N = 23,561)[11,13,16,18,19,23,25,26,28-32,54,58,59]	SAEs	●●●○ (moderate)	Favors omalizumab	Downgraded 1 level for serious imprecision

Abbreviations. ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; C-ACT: Childhood Asthma Control Test; ED: emergency department; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; ICS: inhaled corticosteroid; MID: minimally important difference; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; QoL: quality of life; RCT: randomized controlled trial; SAE: serious adverse event.

Study Characteristics

A summary of these trials is in Table 10 with additional details in Appendix B, Table B10. These trials were published over the years 2001 to 2019, and we rated 8 studies as high risk for bias for various methodological issues, including lack of intervention masking,[11,26,57] no description of randomization and allocation concealment or baseline differences among groups,[10,11,47,57] selective outcome reporting,[10,11,19] selection bias related to recruitment[34] or unexplained post-randomization exclusions,[19,47] deviation from intervention protocol,[47] and high attrition.[38] We rated the rest of the RCTs as moderate risk of bias primarily because of extensive manufacturer involvement in study design, execution, and reporting.

Of the 23 included studies, 15 were entirely sponsored by the manufacturer,[13,16,19,21,23,25,26,28,29,31,32,34,54,58,59] 6 had partial funding from the manufacturer,[11,18,30,33,38,47] 1 reported no sponsor information,[57] and 1 was funded by a government agency.[10] All but 1 study[57] were multicenter trials. Six studies were phase 4 postmarketing RCTs,[16,26,28,30,31,34] 4 studies were phase 3 RCTs,[10,13,23,29] 1 study was a phase 2 RCT,[38] and trial phase was not reported in the remaining 12 studies. Six studies were conducted in the US,[10,25,33,47,54,58,59] and the rest were conducted in other countries or globally in multiple countries.

Eight studies were conducted among adults,[25,31-33,38,47,57,59] 4 were conducted among participants under age 18 years,[10,21,23,30] and the rest were conducted among participants aged 12 and older. Study entry criteria were reasonably similar across studies. In addition to requiring moderate to severe asthma, most required participants to have allergic asthma, including evidence of a positive skin prick or radioallergosorbent test (RAST) for 1 or more environmental allergens. Two studies specifically focused on participants with nonallergic asthma,[32,33] and 1 study[38] included persons with asthma and nasal polyps who had either positive or negative skin prick tests.

All studies used weight and serum IgE-based dosages at a frequency of either 2 or 4 weeks, depending on the dose, which is consistent with FDA labeling for this drug. Most studies were designed to evaluate the efficacy of omalizumab as add-on therapy to existing asthma controller medications and rescue medications as needed. However, 6 RCTs were designed to evaluate the efficacy of omalizumab as add-on therapy during a steroid-tapering cointervention.[13,18,21,23,47,54] In 5 of these studies, doses of ICS were standardized and optimized during a run-in period to maintain control.[13,18,21,23,47,54] Following the run-in, the stable dose of ICS was continued during the initial phase of the trial, followed by a steroid reduction phase where the dose of ICS was reduced by a prespecified amount at regular intervals until the dose was eliminated or asthma control worsened.[13,18,21,23,47,54] In the sixth study, it does not appear that steroid doses were standardized or optimized during a run-in period, and doses of both ICS and oral steroids were tapered during the steroid reduction phase.[47] All but 2 trials evaluating add-on efficacy used a placebo control; study authors described the control groups in the 2 non-placebo-controlled trials as "best standard of care"[11] and "optimized asthma therapy."[26,27]

In addition to the standard add-on efficacy trials and the trials designed with a steroid-tapering cointervention, we identified 1 study that was designed to evaluate the efficacy of omalizumab during a more generalized treatment reduction cointervention that involved substituting a standardized dose of ICS and discontinuation of all other asthma controller medications.[33] We

also identified 1 RCT that enrolled participants already taking stable doses of omalizumab and then randomized them to continue treatment or switch to a placebo.[34] For methodological reasons, we considered these 2 studies separately from the add-on efficacy trials and the steroid-sparing trials in our synthesis of effectiveness outcomes.

Table 10. Evidence Table (Brief Version) RCTs of Omalizumab for Asthma

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Ayres et al., 2004[11] Effectiveness of add-on therapy RCT High	Aged 12 to 75, poorly controlled, persistent moderate-to-severe asthma, positive skin prick tests to at least 2 allergens	Omalizumab (weight and IgE-based dose) SC every 4 wks (n = 206) Best standard of care (n = 106) Continued stable doses of other asthma controllers including ICS or oral steroids	At 1 year • Symptom control • Exacerbations • Steroid use • Adverse events • Mortality (Annualized exacerbation rate)
Bardelas et al., 2012[28] NCT00267202 Phase 4 effectiveness of add-on therapy RCT Moderate	Aged 12 and older, poorly controlled allergic asthma, ACT score ≤ 19, positive skin prick test to at least 1 allergen	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 136) Placebo (n = 135) Continued doses of asthma controllers including ICS, LABA, theophylline, zileuton, LTRAs	At 8, 16, and 24 wks • Symptom control • Adverse events • Mortality (Change in ACT score)
Bousquet et al., 2011;[26] Siergiejko et al., 2011[27] NCT00264849 Phase 4 effectiveness of add-on therapy RCT High	Aged 12 to 75, severe persistent allergic asthma with ≥ 1 severe exacerbations requiring systemic steroids in past year, positive skin prick test to at least 1 allergen	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 275) Optimized asthma therapy (n = 133) Continued stable doses of asthma controllers including ICS, LABAs, oral steroids, theophylline, cromones, LTRAs, asthma therapy optimized during first 4 wks of 8-wk run-in	At 16 and 32 wks • Symptom control • Exacerbations • Adverse events • Mortality (Persistency of GETE response)
Busse et al., 2001;[13] Lanier et al., 2013;[14] Finn et al., 2002[15] Phase 3 steroid-sparing RCT Moderate	Aged 12 to 17, symptomatic despite treatment with ICS, positive skin prick test to at least 1 allergen	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 268) Placebo (n = 257) Continued stable doses of immunotherapy and nonasthma medications, ICS switched to standardized doses of BPD at trial entry and adjusted up or down during	At 16, 28, and 52 wks • Symptom control • Exacerbations • QoL • Steroid use • Adverse events • Mortality (Number of exacerbations during

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
		run-in to maintain control, ICS dose maintained during weeks 1 to 16, then reduced by 25% every 2 wks for 8 wks	steroid stable phase and steroid reduction phase)
Busse et al., 2011[30] ICATA NCT00377572 Phase 4 effectiveness of add-on therapy RCT Moderate	Aged 6 to 20, residing in inner city, persistent uncontrolled asthma, positive skin prick test to at least 1 allergen	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 208) Placebo (n = 211) Asthma regimen adjusted per NAEP guidelines to achieve control with treatment adjustments based on symptoms every 3 months; education and environmental remediation (bedding covers, pest traps, vacuum cleaner)	At 16, 28, and 52 wks • Symptom control • Exacerbations • Adverse events (Number of days with symptoms)
Busse et al., 2013[16] Phase 4 effectiveness of add-on therapy RCT Moderate	Aged 12 to 75, atopic asthma and inadequate symptom control with or without controller medications despite normal lung function (FEV_1 > 80%)	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 159) Placebo (n = 174) Continued stable doses of ICS, LABA, or other controllers	At 16, 28, and 52 wks • Symptom control • Exacerbations • Adverse events (Exacerbation rate)
Chanez et al., 2010[31] NCT00454051 Phase 4 effectiveness of add-on therapy RCT Moderate	Aged 18 and older, severe persistent allergic asthma with severe exacerbation requiring systemic steroids or hospitalization/ED visit in past year, high-dose ICS, perennial allergy	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 20) Placebo (n = 11) Continued asthma controllers, including high dose ICS and LABA, and oral steroids in some participants	At 16 wks • Symptom control • Exacerbations • Adverse events (Fce3RI expression on blood basophils and pDC2)
Garcia et al., 2013[32] NCT01007149 Effectiveness of add-on therapy RCT Moderate	Aged 18 to 70, uncontrolled severe, persistent nonatopic asthma, high-dose ICS plus LABA, at least 2 exacerbations requiring systemic steroids, at least 1 hospitalization/ED visit in past year, negative allergen tests	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 20) Placebo (n = 21) Continued asthma controllers including ICS, LABA, and oral steroids in some participants	At 16 wks • Symptom control • Exacerbations • Adverse events (Fce3RI expression on blood basophils and pDC2)

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Gevaert et al., 2013[38] NCT01393340 Phase 2 effectiveness of add-on therapy RCT High	Aged 18 and older, comorbid asthma and nasal polyps	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 16) Placebo (n = 8) Standardized asthma maintenance managed by respiratory physician; systemic steroids, ICS doses (BPD) ≥ 1,000 µg/day, antibiotics, LTRAs and nasal decongestants not permitted	At 16 wks • QoL • Adverse events (Nasal endoscopic polyp score)
Hanania et al., 2011[29] EXTRA NCT00314574 Phase 3 effectiveness of add-on therapy RCT Moderate	Aged 12 to 75, severe allergic asthma, poorly controlled with high-dose ICS and LABA, at least 1 exacerbation requiring systemic steroids during past year, objective evidence of perennial allergy	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 427) Placebo (n = 423) Continued asthma controllers including ICS, LABA, and oral steroids and no dosage modifications allowed	At 48 wks • Symptom control • Exacerbations • QoL • Adverse events • Mortality (Exacerbation rate)
Holgate et al., 2004[18] Steroid-sparing RCT Moderate	Aged 12 to 75, severe asthma requiring high-dose ICS, positive skin test for allergens	Omalizumab (weight/IgE-based dose) SC every 2 or 4 wks (n = 126) Placebo (n = 120) Continued use of LABAs, ICS dose optimized during run-in; continued ICS dose during first 16 wks, then ICS dose reduced every 2 wks by 250 µg/day for next 12 wks until appearance of symptoms or zero dose; maintained lowest ICS dose achieved in the final 4 wks of trial	At 16 and 32 wks • Exacerbations • QoL • Steroid use • Adverse events (Percentage reduction in ICS dose)
Hoshino et al., 2012[57] UMIN000002765 Effectiveness of add-on therapy RCT High	Aged 20 to 75, severe allergic asthma despite high-dose ICS and LABA, positive skin prick test to at least 1 allergen	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 14) No treatment (n = 16) Continued asthma controllers including ICS, LABA, and others, if applicable	At 16 wks • QoL (Airway wall thickness)

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Humbert et al., 2005[19,20] INNOVATE Effectiveness of add-on therapy RCT High	Aged 12 to 75, severe persistent asthma requiring high-dose ICS and LABA, at least 2 exacerbations requiring systemic steroids or 1 requiring ED or hospital visit, positive skin prick test to at least 1 allergen	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 245) Placebo (n = 237) Continued asthma controller medications, including ICS, theophylline, LTRAs, oral beta-agonists, and oral steroids (if used as maintenance therapy and at least 1 exacerbation occurred while using	At 28 wks • Symptom control • Exacerbations • QoL • Adverse events (Exacerbation rate)
Lanier et al., 2009;[23] Kulus et al., 2010[24] NCT00079937 Phase 3 steroid-sparing RCT Moderate	Aged 6 to 11, moderate to severe allergic asthma not controlled by medium- to high-dose ICS with or without other controllers, history of exacerbations, positive skin prick test or RAST for at least 1 allergen	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 421) Placebo (n = 206) ICS and other controllers optimized during run-in, symptomatic patients at end of run-in randomized, stable doses of all meds for first 2 wks, then ICS adjusted down by 25% to 50% every 8 wks based on symptom control; SABA allowed for rescue	At 24 and 52 wks • Symptom control • Exacerbations • QoL • Steroid use • Adverse events • Mortality (Exacerbation rate)
Ledford et al., 2017[34] XPORT NCT01125748 Discontinuation RCT High	Aged 17 to 70, moderate to severe persistent asthma receiving long-term omalizumab treatment on stable doses of other controllers for at least 2 months	Continuation of omalizumab every 2 to 4 wks based on body weight and IgE levels (n = 88) Placebo substituted for discontinued omalizumab (n = 88) Continued ICS, LABAs. LTRAs, 5-lipoxygenase inhibitors, anticholinergics, mast cell stabilizers, theophylline, oral steroids, allergen immunotherapy	At 52 wks • Symptom control • Exacerbations • Adverse events • Mortality (Proportion with severe asthma exacerbations)
Milgrom et al., 2001;[21] Lemanske et al., 2002[22] Steroid-sparing RCT Moderate	Aged 6 to 12, allergic asthma, positive skin prick test to at least 1 allergen	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 225) Placebo (n = 109) ICS doses converted to dose equivalence of BPD and adjusted to maintain previous	At 16 and 28 wks • Symptom control • Exacerbations • QoL • Steroid use • Adverse events (NR)

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
		level of asthma control, ICS dose maintained for first 16 wks, then tapered by 25% every 2 wks for 8 wks until elimination or worsening, minimum effective dose maintained for last 4 wks	
Mukherjee et al., 2019[47] NCT02049294 Steroid-sparing RCT High	Aged 18 to 75 with symptomatic asthma and positive skin prick test to allergens, treatment with high-dose ICS with or without oral steroids	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 5) Placebo (n = 6) Stable steroid dose through week 16, then standard reduction in steroid dose through week 32	At 32 wks • Symptom control • Exacerbations (Reduction in sputum eosinophilia)
Ohta et al., 2009[25] NCT00232050 Effectiveness of add-on therapy RCT Moderate	Aged 20 to 75, moderate to severe asthma, ICS and 1 or more controller medication, positive skin prick or RAST to allergen	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 158) Placebo (n = 169) Continued ICS dose and doses of other controller medications, rescue medications as needed	At 16 wks • Exacerbations • Adverse events (Change in morning peak expiratory flow)
PIllai et al., 2016[33] NCT01113437 Treatment-reduction RCT Moderate	Aged 18 to 60, moderate to severe, uncontrolled nonatopic asthma, negative skin prick or RAST test to 12 common allergens	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 9) Placebo (n = 9) Usual asthma regimen for first 12 to 14 wks, then discontinuation of inhaled and oral LTRA, theophylline and substitution with ICS/LABA combination, attempt to decrease oral steroids based on predetermined regimen and dosage at entry	At 14 and 20 wks • Symptom control • QoL • Adverse events (Change in median FEV_1)
Sly et al., 2017[10] RELAX ACTRN12611001106921 Phase 3 effectiveness of add-on therapy RCT High	Aged 6 to 15, history of ED visit for severe exacerbation in the previous winter, positive skin prick test to allergens	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks timed over winter season (n = 14) Placebo (n = 13) Continued standard asthma treatment including ICS	At 26 and 72 wks • Symptom control • QoL • Adverse events (Proportion with asthma exacerbations)

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Soler et al., 2001;[54] Buhl et al., 2002[55,56] Steroid-sparing RCT Moderate	Aged 12 to 75, stable asthma with daily symptom score ≥ 3, positive skin prick test to at least 1 allergen, treatment with ICS	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 274) Placebo (n = 272) Participants switched to BPD ICS and dose adjusted to establish lowest dose for asthma control during run-in, ICS dose maintained during first 16 wks, then dose tapered by 25% every 2 wks over the next 12 wks until elimination or loss of control, lowest dose maintained for final 4 wks	At 16, 28, and 52 wks • Symptom control • Exacerbations • QoL • Steroid use • Adverse events • Mortality (Number of exacerbations during steroid-stable and steroid-reduction phases)
Vignola et al., 2004[58] SOLAR Effectiveness of add-on therapy RCT Moderate	Aged 12 to 75, allergic asthma, positive skin prick test to at least 1 allergen, moderate to severe perennial allergic rhinitis symptoms, high score on asthma and rhinitis quality-of-life measures	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks (n = 209) Placebo (n = 196) ICS dose standardized during run-in, during trial ICS doses adjusted up or down to achieve lowest dose to control symptoms, other controllers and nasal steroids continued at stable doses	At 28 wks • Symptom control • Exacerbations • QoL • Adverse events • Mortality (Proportion with exacerbations, improvement in both asthma and rhinitis)
Zielen et al., 2013[59] Effectiveness of add-on therapy RCT Moderate	Aged 18 to 65, asthma, positive skin prick test to at least 1 allergen	Omalizumab (weight and IgE-based dose) SC every 2 or 4 wks, low IgE subgroup (n = 18) Omalizumab (weight/IgE-based dose) SC every 2 or 4 wks, high IgE subgroup (n = 16) Placebo (n = 16) Continued SABAs, LTRAs, low-dose ICS at stable doses; high-dose ICS, LABA, and oral steroids, theophylline not permitted	At 16 wks • Adverse events • Mortality (Maximum percentage drop in FEV_1 during first 30 minutes of allergen bronchoprovocation)

Abbreviations. ACT: asthma control test; BPD: budesonide dipropionate; ED: emergency department; Fce3RI: high affinity IgE receptor; FEV_1: forced expiratory volume in 1 second; GETE: global evaluation of treatment effectiveness; ICS: inhaled corticosteroids; IgE: immunoglobin E; LABA: long-acting beta agonists; LTRA: leukotriene receptor antagonists; NAEP: National Asthma Education Program; NCT: US National Clinical Trial; pDC2: plasmacytoid dendritic cells; QoL: quality of life; RAST: radioallergosorbent test; RCT: randomized controlled trial; SABA: short-acting beta agonists; SC: subcutaneous; wk: week.

Detailed individual study results are provided in Appendix B, Table B11 (effectiveness) and Table B12 (safety).

KQ 1: Symptom Control

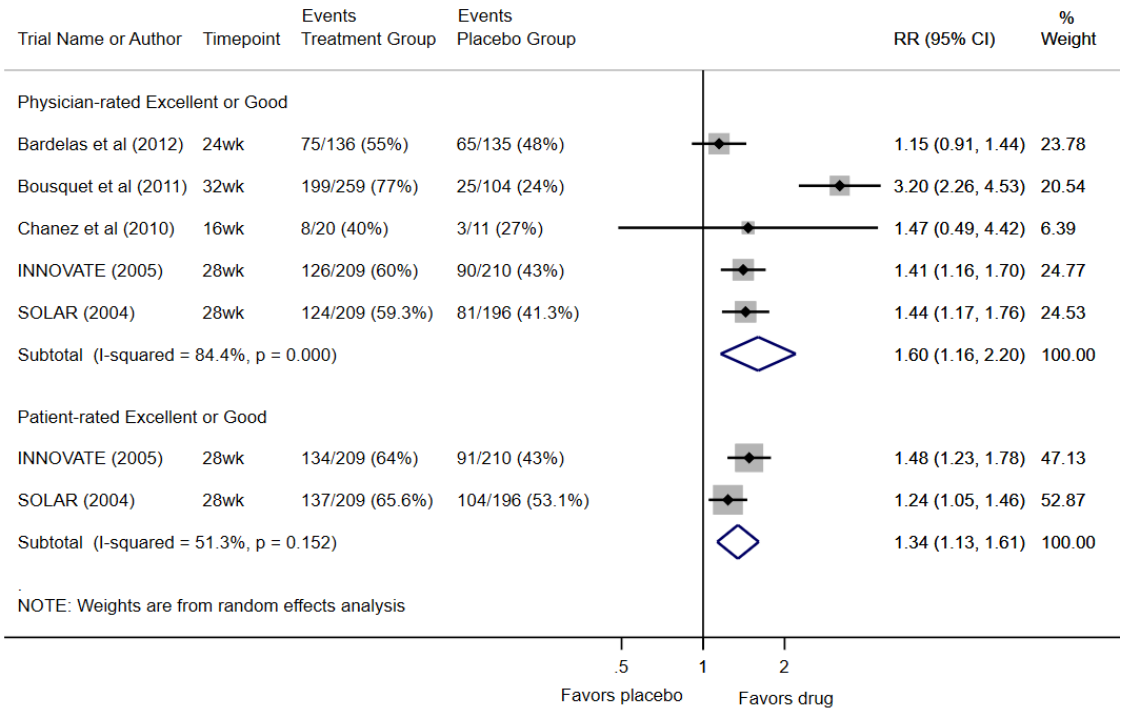
Across the add-on efficacy trials, omalizumab was more effective than placebo for improving symptom control, but QoE varied by measure: number of days with asthma symptoms (high QoE); ACQ mean change from baseline (very low QoE); and ACT/C-ACT (low QoE). Across add-on efficacy trials and the trials that included steroid-tapering, omalizumab was more effective than placebo on patient- or physician-rated measure of global treatment effectiveness (moderate QoE).

Add-on Efficacy Trials

Ten studies reported various measures of asthma symptom control.[11,16,19,26,28-32,58] However, studies did not report data usable in quantitative synthesis for many outcomes; study-specific results are reported in Appendix B, Table B11.

Five studies reported using the global evaluation of treatment effectiveness (GETE) rating by either the physician or the patient, or both.[19,26,28,31,58] Pooled estimates (Figure 13) suggested that a significantly higher proportion of physicians and patients rated the effectiveness of treatment as excellent or good among participants allocated to omalizumab compared to those allocated to placebo or control (P = .004 for physician-rated effectiveness; P = .001 for patient-rated effectiveness), though moderate to substantial heterogeneity was observed. The magnitude of effect in the Bousquet et al.[26] study was substantially larger compared to the other studies; this RCT was an open-label trial (high risk of bias) that used a control group of optimized asthma therapy (no placebo). Sensitivity analyses excluding the Bousquet et al.[26] study demonstrated no heterogeneity and a smaller but still statistically significant pooled estimate for physician rating of treatment effectiveness as excellent or good (RR, 1.34; 95% CI, 1.19 to 1.51; 4 RCTs, I^2=0%; P < .001).

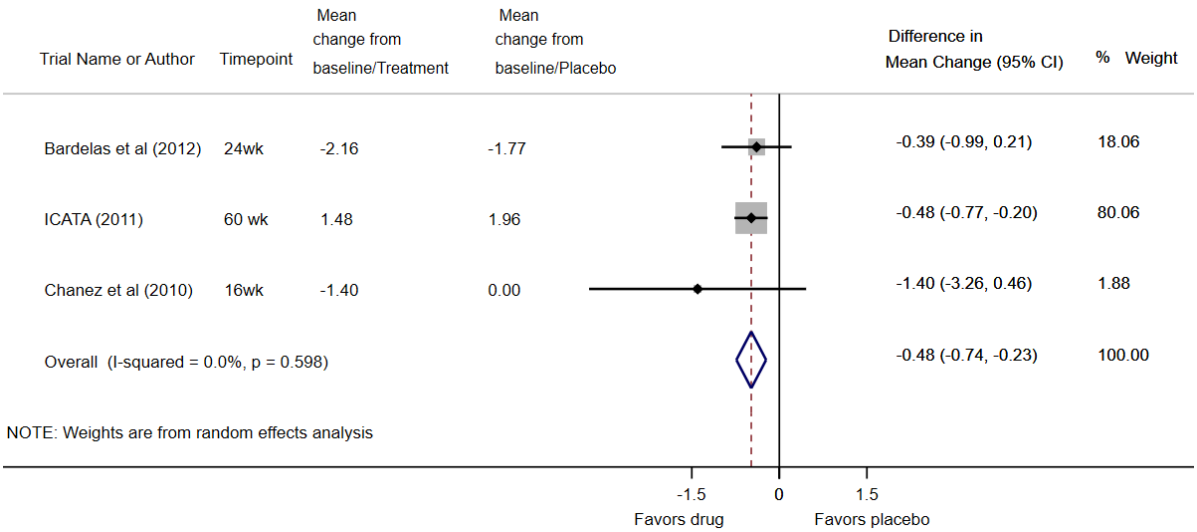
Figure 13. Omalizumab vs. Placebo, Global Evaluation of Treatment Effectiveness, Add-on Efficacy RCTs



Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; wk: week.

Three RCTs reported changes in the number of days with asthma symptoms over the past 1 to 2 weeks.[28,30,31] The pooled estimate suggests significantly fewer days with asthma symptoms for participants allocated to omalizumab compared to placebo ($P < .001$; Figure 14).

Figure 14. Omalizumab vs. Placebo, Change in Days with Asthma Symptoms, Add-on Efficacy RCTs

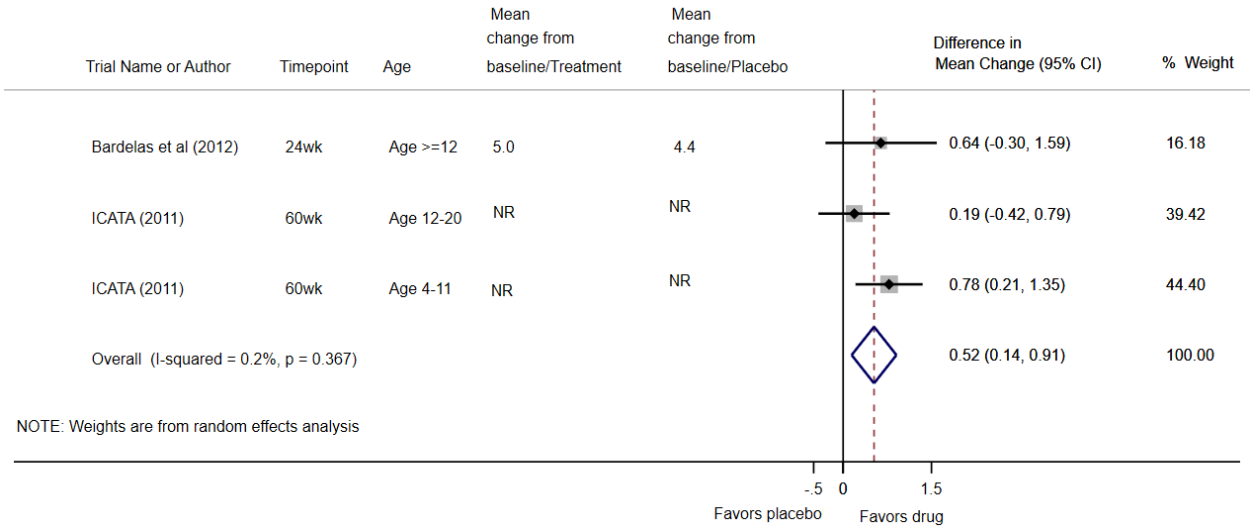


Abbreviations. CI: confidence interval; RCT: randomized controlled trial; wk: week.

Two RCTs reported a change from baseline in the ACQ.[26,32] In Garcia et al., which enrolled participants with nonallergic asthma, the difference in the change in ACQ score from baseline between participants allocated to omalizumab compared to placebo was 0 (calculated 95% CI, -0.78 to 0.78) at 16 weeks.[32] In Bousquet et al., a high risk-of-bias trial (open label), the difference in the mean change from baseline was -0.67 (95% CI, -0.88 to -0.46) at 16 weeks and -0.87 (95% CI, -1.09 to -0.65) at 32 weeks compared to a control group receiving optimized asthma therapy.[26]

Two studies reported symptom control with the Asthma Control Test (ACT) or C-ACT (ACT for children).[28,30] Pooled estimates at 24 to 60 weeks (Figure 15) suggest a significantly larger improvement for participants allocated to omalizumab compared to participants allocated to placebo (*P* = .007), though the average magnitude of improvement is lower than the MID for this outcome (3 points).

Figure 15. Omalizumab vs. Placebo, Asthma Control Test, Add-on Efficacy Trials



Abbreviations. CI: confidence interval; NR: not reported; wk: week.

Two studies reported changes in asthma symptom scores.[16,29] In Busse et al. 2013, improvements in daytime or nighttime asthma symptom scores were not different between participants allocated to omalizumab versus placebo (difference in mean change in daytime scores, -0.05; 95% CI, -0.19 to 0.09; difference in mean change in nighttime scores, 0.01; 95% CI, -0.12 to 0.14).[16] In EXTRA, the authors reported a significantly larger improvement in change in daily asthma symptom score from baseline among participants allocated to omalizumab compared to placebo (difference in mean change, -0.26; 95% CI, -0.42 to -0.1).[29]

Two RCTs[11,58] reported symptom control using the Wasserfallen asthma symptom score; pooled estimates suggested a larger improvement in symptoms among those allocated to omalizumab compared to placebo or control, but this estimate was not statistically significant (pooled mean difference, -3.36; 95% CI, -6.95 to 0.22; Appendix D, Figure D2).

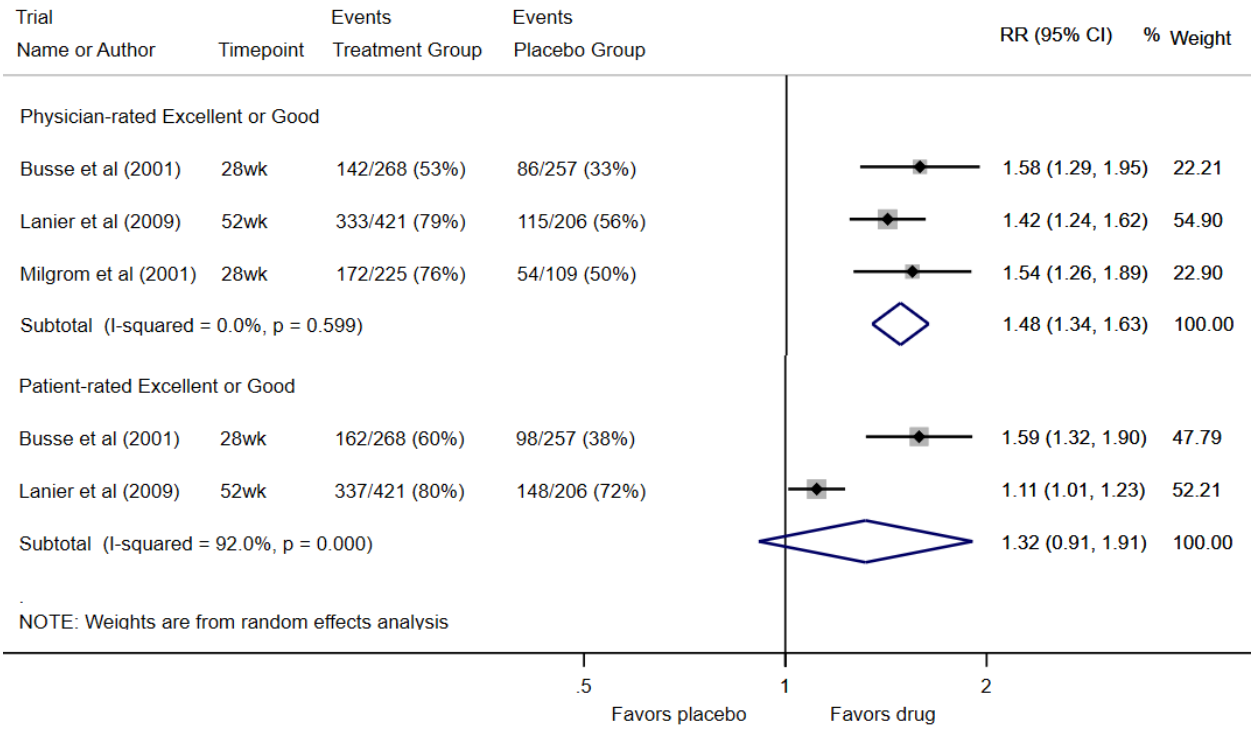
Additional outcomes related to nocturnal awakenings and number of nights with asthma symptoms are reported in Appendix B, Table B11.

Add-on Efficacy With Steroid-Tapering Trials

Four studies reported various measures of asthma symptom control.[13,21,23,47] However, studies did not report data usable in quantitative synthesis for most outcomes; study-specific results are reported in Appendix B, Table B11.

Three studies reported using the GETE rating by the physician, the patient, or both, at 28 to 52 weeks (at the end of the steroid-reduction phases; Figure 16).[13,21,23] Pooled estimates of physician ratings suggested a significantly higher proportion rated the effectiveness of treatment as excellent or good among participants allocated to omalizumab compared to those allocated to placebo ($P < .001$). We did not pool the patient ratings from 2 RCTs reporting these outcomes because of substantial heterogeneity in the estimates.[13,23]

Figure 16. Omalizumab vs. Placebo, Global Evaluation of Treatment Effectiveness, Steroid-Sparing Trials



Abbreviations. CI: confidence interval; RR: risk ratio; wk: week.

Busse et al., 2001, reported a change in daily asthma symptoms at the end of the 16-week stable-steroid phase.[13] Significantly larger improvements were observed among participants allocated to omalizumab compared to placebo (actual values only reported on a figure; $P = .001$).[13] Lanier et al. reported on changes in the nocturnal asthma symptom score at the end of the 24-week steroid-stable phase.[23] No significant differences were observed ($P = .11$; calculated difference, -0.13).[23]

Other Trials

In a trial evaluating the continuation of omalizumab compared to a switch from omalizumab to a placebo, Ledford et al. reported significantly larger improvement from baseline for both the ACQ

(*P* = .004, calculated difference from placebo -0.41) and ACT (*P* = .019, calculated difference from placebo 1.72) among the group continuing omalizumab.[34] In a trial comparing omalizumab to placebo with a non-ICS treatment reduction cointervention among participants with nonatopic asthma, Pillai et al. reported no significant differences in the median change from baseline in ACQ scores after both the treatment-stable phase and the treatment-reduction phase.[33]

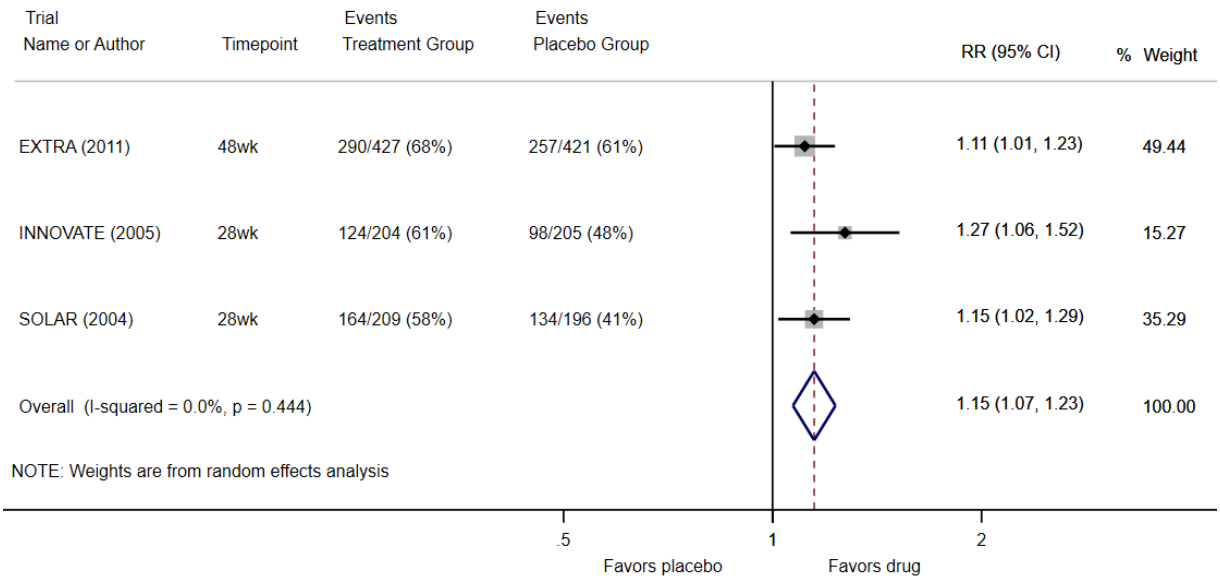
KQ 1: Quality of Life

Across the add-on efficacy trials and the trials that included steroid-tapering, omalizumab was more effective than placebo for improving quality of life as measured by the AQLQ mean change from baseline (moderate QoE), and MID response on the AQLQ (high QoE). However, in 2 trials of add-on efficacy with steroid-tapering in children ages 6 to 11, there was no difference in change in quality of life as measured by the Pediatric AQLQ (PAQLQ) mean change from baseline in 1 trial[23] (low QoE) and no difference as measured by a large MID response in the PAQLQ in another trial[21] (low QoE).

Add-on Efficacy Trials

Five RCTs[19,29,38,57,58] reported quality-of-life outcomes, all with the AQLQ, but data suitable for pooling were not available. Across the 5 RCTs, the mean improvement from baseline in the AQLQ score was larger for participants allocated to omalizumab compared to placebo or control (range 0.29 to 1.19 in 4 studies, and NR in 1 study[58]). The difference in the mean change from baseline between treatment and placebo groups was statistically significant in 4 studies (*P* value NR and not calculable in the fifth study[38]). Three RCTs reported the proportion of participants achieving an MID in this measure (0.5 points).[19,29,58] In pooled estimates, participants allocated to omalizumab were significantly more likely to achieve an MID response compared to participants allocated to placebo (*P* < .001; Figure 17).

Figure 17. Omalizumab vs. Placebo, AQLQ Minimally Important Difference, Add-on Efficacy RCTs



Abbreviations. CI: confidence interval; RR: risk ratio: wk: week.

Add-on Efficacy With Steroid-Tapering Trials

Four of the 5 RCTs designed with steroid reduction cointerventions reported quality-of-life outcomes.[13,18,21,23]

Two studies reported quality of life using the AQLQ. Busse et al. reported a significantly larger improvement in the mean change from baseline in the AQLQ in the steroid-stable, steroid-reduction, and double-blind extension phase (actual difference vs. placebo, NR; $P < .01$ for comparison in each trial phase).[13] In this RCT, the proportion of participants achieving an MID improvement was also significantly higher among participants allocated to omalizumab (range of calculated RRs,1.14 to 1.24 across trial phases).[13] Holgate et al. reported the proportion of participants achieving an MID improvement at the end of the steroid-reduction phase; a significantly higher proportion achieved an MID response among participants allocated to omalizumab compared to placebo (calculated RR, 1.48; 95% CI, 1.13 to 1.93).[18]

Two studies reported using the PAQLQ because these were trials conducted exclusively in children.[21,23] Lanier et al. reported no significant difference in the mean change from baseline in PAQLQ scores between participants allocated to omalizumab and those allocated to placebo (mean difference, 0.04; $P = .676$).[23] Milgrom et al. reported the proportion of participants who achieved a large improvement on the PAQLQ (defined as 1.5 points or more).[21] No significant difference in the proportion achieving a large improvement was observed during the steroid-stable phase (calculated RR, 1.45; 95% CI, 0.64 to 3.32) or the steroid-reduction phase (calculated RR, 1.67; 95% CI, 0.82 to 3.38), though results were very imprecise.[21] We note that the established MID for this measure is 0.5 points.

Other Trials

Pillai et al., which compared omalizumab to placebo with a non-ICS treatment-reduction cointervention among participants with nonatopic asthma, reported quality-of-life outcomes with the mini-AQLQ.[33] No significant difference in the median change from baseline was observed between groups at the end of the treatment-stable phase or at the end of the treatment-reduction phase (Appendix B, Table B11).[33]

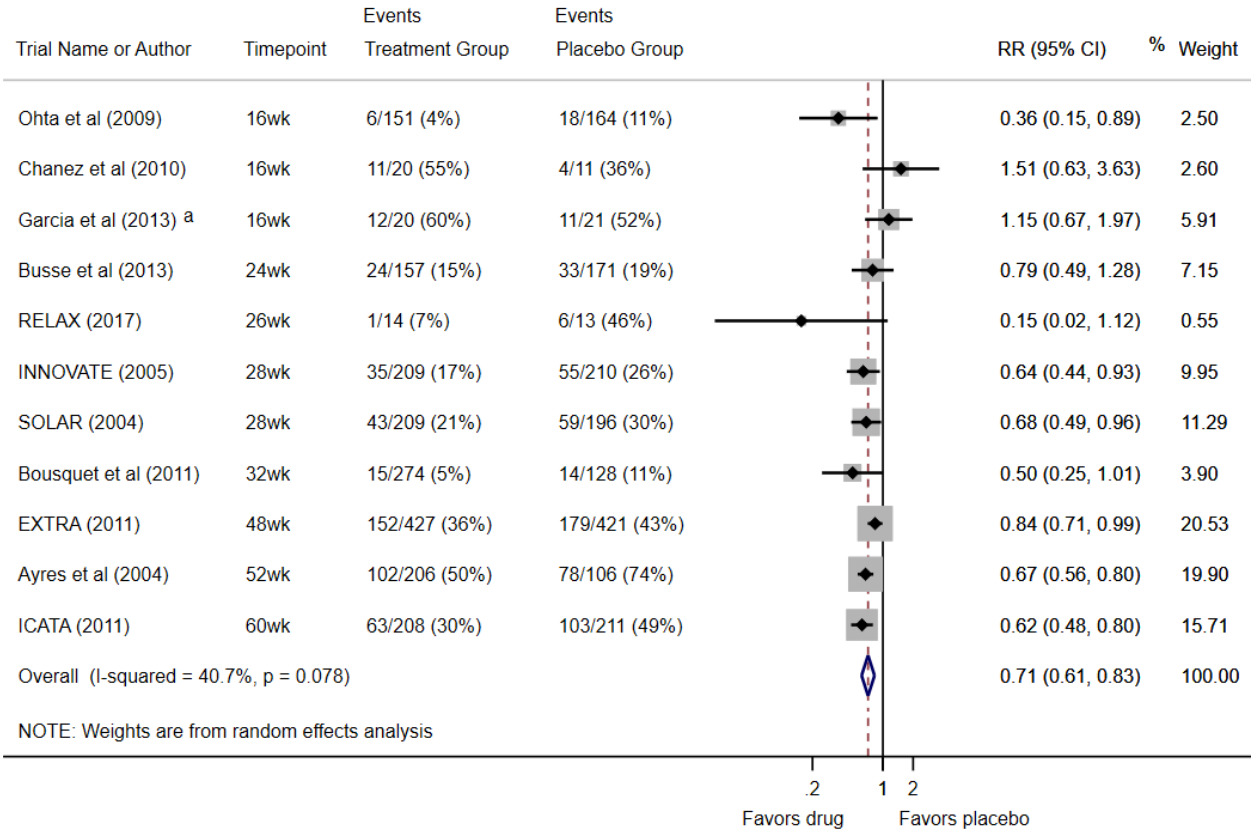
KQ 1: Exacerbations

Across add-on efficacy trials and trials that included steroid-tapering, omalizumab was more effective than placebo for reducing the incidence and rate of exacerbations (high QoE), and for reducing the incidence and rate of exacerbations requiring ED visits or hospitalizations (moderate QoE).

Add-on Efficacy Trials

Twelve RCTs reported on the incidence of asthma exacerbations during study follow-up.[10,11,16,19,25,26,29-32,47,58] Pooled estimates suggested a significantly lower incidence of exacerbation in participants allocated to omalizumab compared to placebo or control ($P < .001$; Figure 18).

Figure 18. Omalizumab vs. Placebo, Incidence of Exacerbation, Add-on Efficacy RCTs



Notes. [a] *Enrolled participants with nonatopic asthma. Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; wk: week.*

Three RCTs reported adjusted annualized rates of asthma exacerbations[11,19,58]; however, only data from 2 of these could be synthesized quantitatively.[11,58] The pooled IRR for the annualized asthma exacerbation rate was 0.72 (95% CI, 0.54 to 0.90; $P < .001$; 2 RCTs; $I^2 = 2.2\%$; Appendix D, Figure D3). The calculated IRR in the study that could not be pooled was 0.50 (95% CI, incalculable).[11]

Four RCTs reported on rates of asthma exacerbation over various durations of study follow-up ranging from 16 to 48 weeks.[16,26,29,32] The pooled estimate for the IRR suggests a significantly lower rate of exacerbation with omalizumab compared to placebo (pooled IRR, 0.68; 95% CI, 0.58 to 0.79; $P < .001$; 4 RCTs; $I^2 = 0\%$; Appendix D, Figure D4).

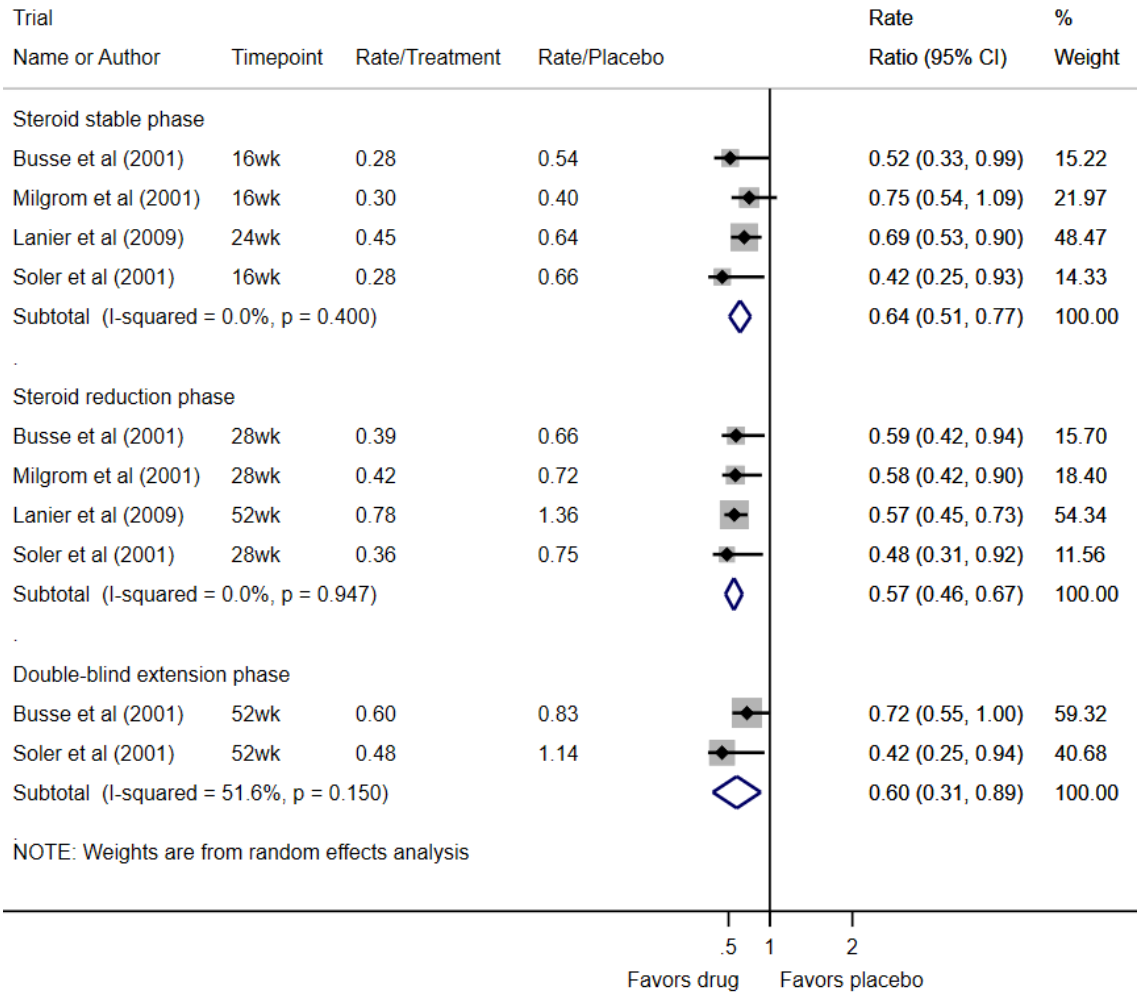
Several studies also reported outcomes related to serious exacerbations or exacerbations requiring ED visits or hospitalizations, but could not be pooled. In INNOVATE, the adjusted annualized rate of severe exacerbations, defined as PEF or FEV_1 less than 60% of personal best or exacerbations requiring treatment with systemic steroids, was significantly lower with omalizumab compared to placebo (calculated IRR, 0.50; reported $P = .002$).[20] Further, the incidence of exacerbations requiring hospitalization was also significantly less frequent (calculated RR, 0.52; 95% CI, 0.27 to 0.99).[20] However, the rate and incidence of exacerbations requiring an ED visit were not statistically different between groups (Appendix B, Table B11).[19]

In Bousquet et al., severe exacerbations, defined as requiring treatment with systemic steroids and hospital admission or intubation, ED visit, breathlessness at rest, PEF or FEV_1 less than 60% of predicted or more than 30% fall from personal best on 2 successive days, occurred significantly less frequently with omalizumab compared to a control group receiving optimized asthma therapy (IRR, 0.56; 95% CI, 0.34 to 0.92).[26] In ICATA, significantly fewer exacerbations requiring an ED visit or hospitalization occurred among participants allocated to omalizumab compared to placebo (calculated RR, 0.23; 95% CI, 0.07 to 0.81).[30]

Add-on Efficacy With Steroid-Tapering Trials

Five studies reported exacerbation-related outcomes.[13,18,21,23,54] Four of the 5 trials reported asthma exacerbation rates.[13,21,23,54] In these trials, exacerbation rates were reported for each of the separate trial phases: steroid-stable phase (usually the first 16 to 24 weeks), steroid-reduction phase (next 12 to 28 weeks), and double-blind extension phase (continuation of allocated treatment with the lowest effective dose of ICS). Pooled estimates of the rate of exacerbation suggested a significantly lower rate with omalizumab compared to placebo across all trial phases ($P < .001$ for all phases; Figure 19).

Figure 19. Omalizumab vs. Placebo, Exacerbation Rate, Steroid-Sparing RCTs



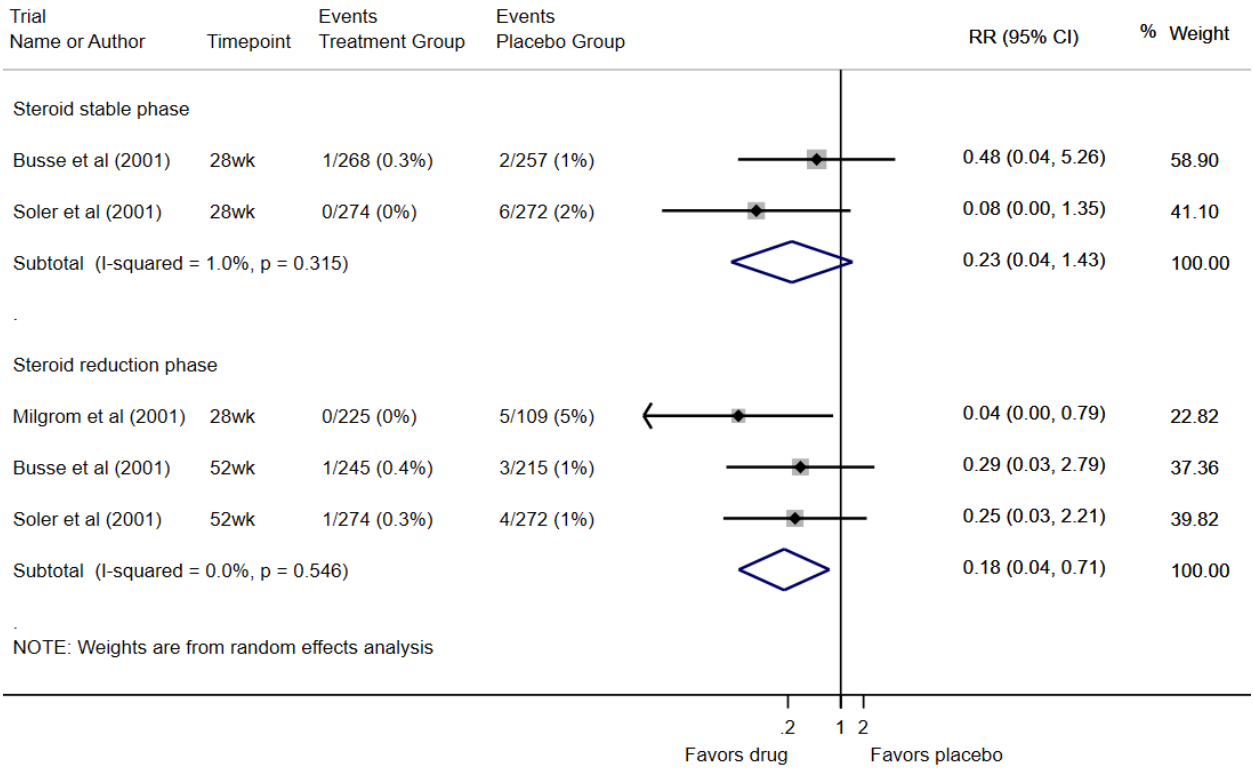
Abbreviations. CI: confidence interval; RCT: randomized controlled trial.

The fifth study to report exacerbation rates (Holgate et al.[18]) reported an IRR for an annualized rate of asthma exacerbation of 0.65 during the steroid-stable phase and 0.56 during the steroid-reduction phase, but data to calculate CIs around these estimates were not provided.[18]

Four studies also reported the incidence of exacerbations, and pooled estimates also demonstrated a reduced incidence of exacerbations among participants allocated to omalizumab compared to placebo across all trial phases (Appendix D, Figure D5).[13,21,47,54]

Three studies reported the incidence of exacerbations requiring hospitalizations.[13,21,54] Pooled estimates suggested a significantly lower incidence of these exacerbations for participants allocated to omalizumab compared to placebo during the steroid reduction phase (*P* = .01); however, events were not common, so estimates were imprecise and could not exclude a null-effect during the steroid-stable trial phases (*P* = 0.11; Figure 20).

Figure 20. Omalizumab vs. Placebo, Incidence of Exacerbation Requiring Hospitalization, Steroid-Sparing RCTs



Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; wk: week.

Lanier et al. reported on the rate of severe exacerbations, defined as requiring treatment with systemic corticosteroids and peak FEV_1 less than 60% of personal best.[23] In this trial, omalizumab resulted in a significantly lower rate of severe exacerbations across both the steroid-stable phase (IRR, 0.55; 95% CI, 0.32 to 0.95) and the steroid-reduction phase (IRR, 0.49; 95% CI, 0.30 to 0.80).[23]

Other Trials

Ledford et al., which randomized participants to continue existing long-term treatment with omalizumab or to switch to a placebo, reported fewer exacerbations among persons allocated to

continued omalizumab (calculated RR, 0.63; 95% CI, 0.44 to 0.90).[34] Exacerbations were defined as clinically significant worsening of asthma requiring systemic steroids, 3 or more days of increased doses of ICS, hospitalization, or an ED visit.[34] The time to first exacerbation was also longer among participants allocated to continue on omalizumab (hazard ratio [HR], 0.49; 95% CI, 0.28 to 0.86).[34]

KQ 1: Steroid Use

Among add-on efficacy trials that included a steroid-tapering, omalizumab was more effective than placebo at increasing the proportion of participants who were able to reduce their ICS dose by 50% or more (high QoE), and in increasing the proportion of participants who no longer required ICS (high QoE).

Add-on Efficacy Trials

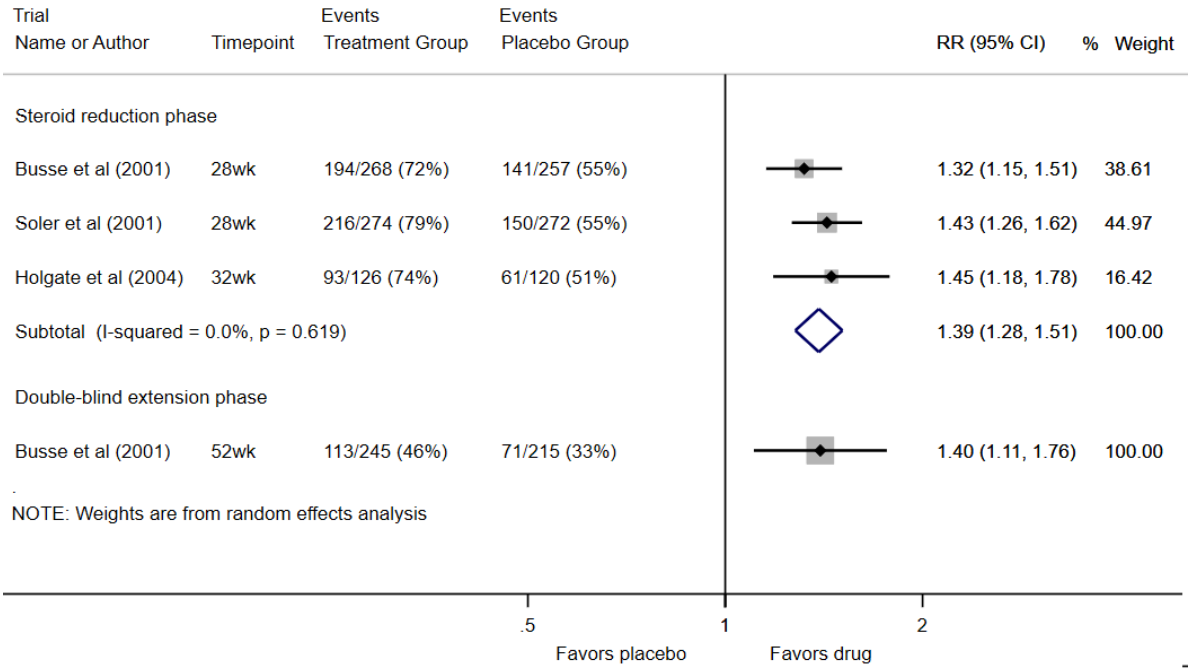
Ayres et al. was the only add-on efficacy trial reporting steroid use outcomes.[11] Significantly fewer participants allocated to omalizumab required treatment with oral steroids compared to a control group that received the best standard of care (52% vs. 65%; calculated RR, 0.80; 95% CI, 0.65 to 0.98).[11]

Add-on Efficacy With Steroid-Tapering Trials

Three RCTs with a steroid-reduction cointervention reported the proportion of participants who were able to reduce the dose of ICS by 50% or more.[13,18,54] Pooled estimates suggest that significantly more participants were able to reduce the ICS dose by 50% or more among participants allocated to omalizumab compared to placebo at the end of the steroid-reduction phase ($P < .001$; Figure 21).

Lanier et al.,[23] which did not report usable data for the pooled analysis, reported the percentage reduction in ICS dose at the end of the steroid-reduction phase. In this study, participants allocated to the omalizumab group reduced their ICS dose by 4%, whereas the dose increased by 2% among participants allocated to placebo ($P = .053$). Holgate et al.,[18] which was included in the pooled analysis, reported several additional steroid use outcomes consistent with findings from the pooled analysis (Appendix B, Table B11).

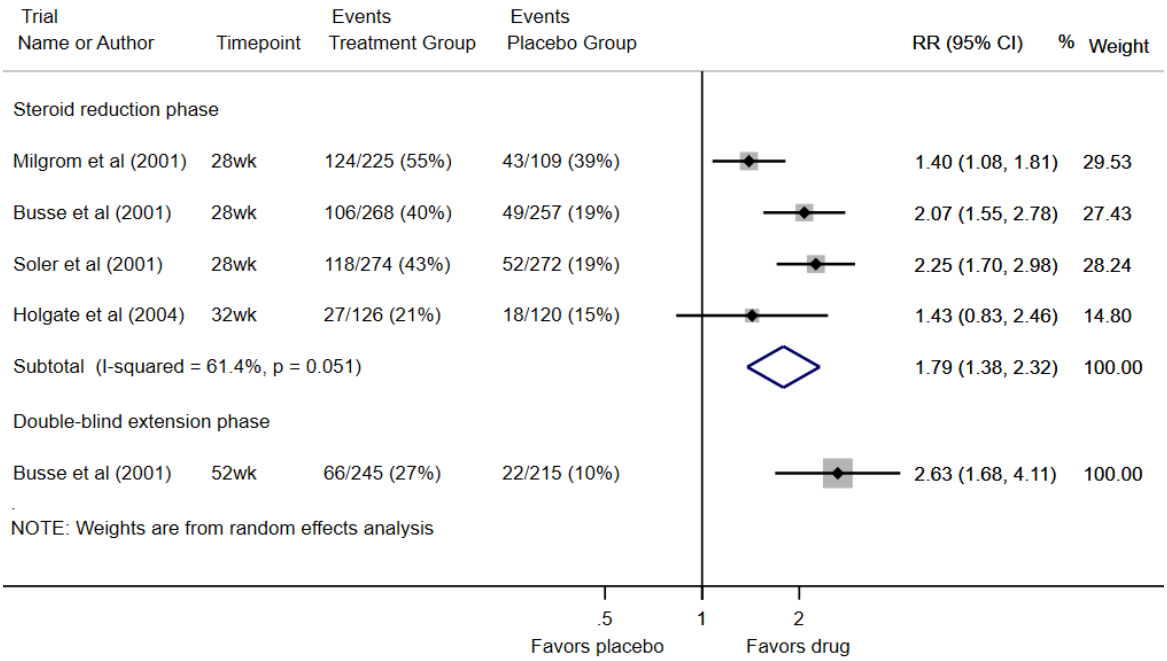
Figure 21. Omalizumab vs. Placebo, Proportion Reducing ICS Dose by 50% or More, Steroid-Sparing RCTs



Abbreviations. CI: confidence interval; ICS: inhaled corticosteroid; RR: risk ratio; wk: week.

Four studies reported the proportion of participants who no longer required ICS by the end of the steroid-reduction phase.[13,18,21,54] In pooled estimates (Figure 22), participants allocated to omalizumab were significantly more likely to have completely reduced their ICS dose compared to participants allocated to placebo ($P < .001$).

Figure 22. Omalizumab vs. Placebo, Proportion With Complete ICS Reduction, Steroid-Sparing RCTs



Abbreviations. CI: confidence interval; ICS: inhaled corticosteroid; RCT: randomized controlled trial; RR: risk ratio; wk: week.

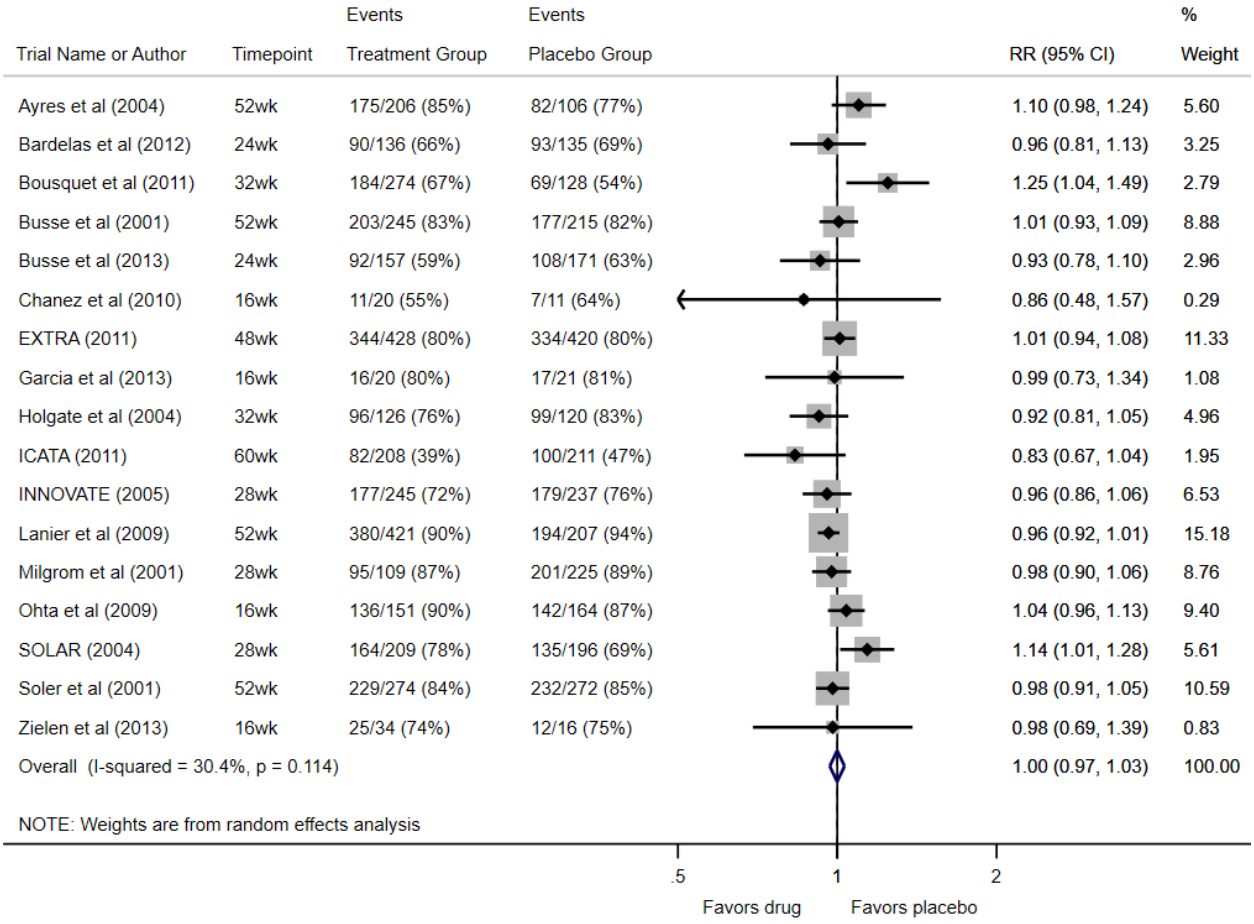
Other Trials

In a trial evaluating omalizumab compared to placebo with a treatment-reduction intervention among participants with nonatopic asthma, Pillai et al. reported the median ICS dose of budesonide dipropionate (BPD) at the end of the treatment-stable phase to be 1,800 µg per day (range: 500 to 2,000) among participants allocated to the placebo group and 2,000 µg per day (range: 800 to 4,000) among participants allocated to omalizumab.[33] At the end of the treatment-reduction phase, the ICS dosage was reduced to a median of 200 µg per day in both treatment arms.[33]

KQ 2: AEs

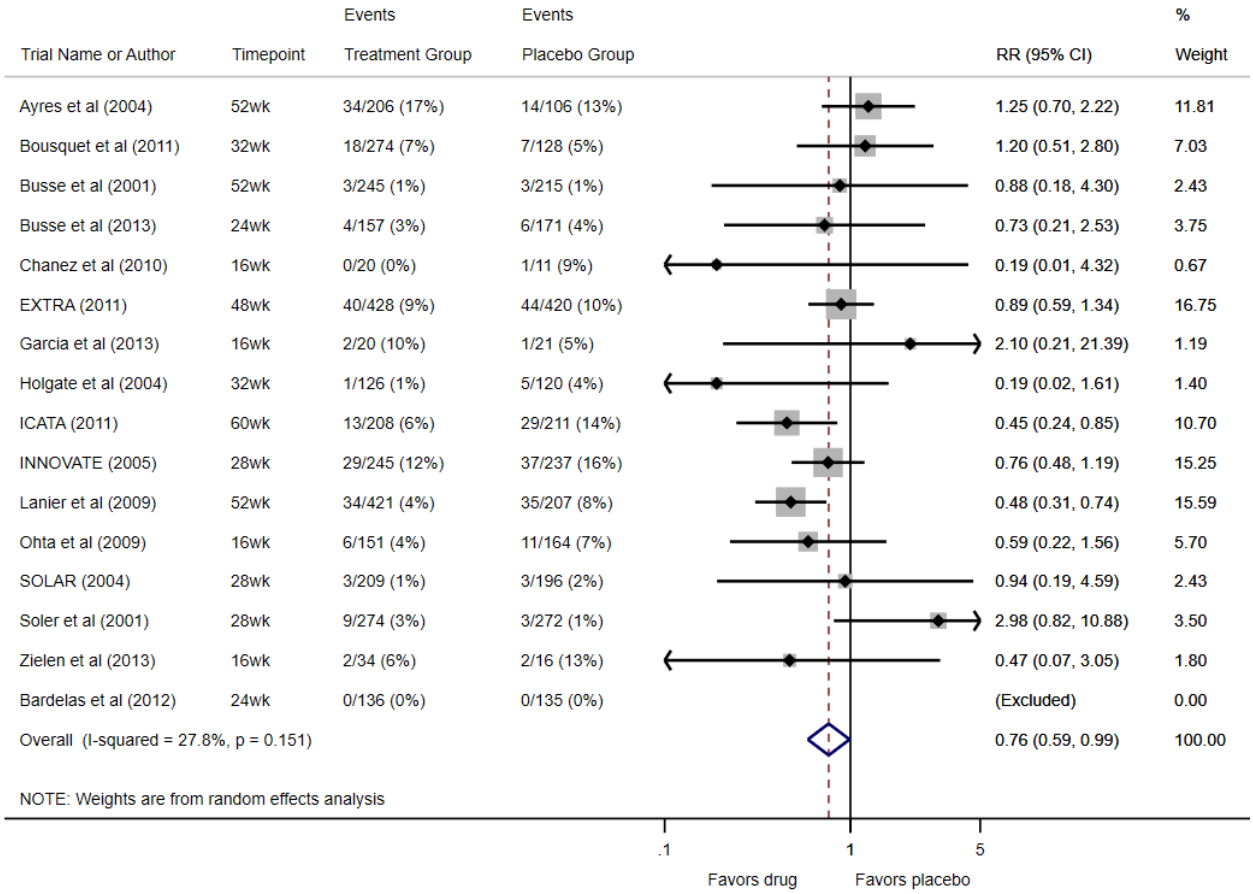
Seventeen studies reported overall AEs at 16 to 60 weeks of follow-up.[11,13,16,18,19,21,23,25,26,28-32,54,58,59] Pooled analyses indicated no difference (P = .97) in overall AEs between active treatment and placebo (high QoE; Figure 23). All but 1 RCT[21] also reported SAEs. In pooled estimates, these events occurred at a significantly lower incidence in persons allocated to omalizumab as compared to placebo (P = .04), but these events were rare and we downgraded for imprecision (moderate QoE; Figure 24). Fifteen studies[10,11,13,16,18,19,21,23,25,29,32-34,38,54,58] reported discontinuations because of AEs, and no significant differences between active treatment and placebo were observed; however, these events were also rare, so estimates were imprecise (pooled RR, 1.21; 95% CI, 0.68 to 2.17; P = .52; I^2 = 20.4%; Appendix D, Figure D6).

Figure 23. Omalizumab vs. Placebo, Adverse Events



Abbreviations. CI: confidence interval; RR: risk ratio; wk: week.

Figure 24. Omalizumab vs. Placebo, Serious Adverse Events



Abbreviations. CI: confidence interval; RR: risk ratio; wk: week.

KQ 2: Mortality

Nine studies reported mortality outcomes.[11,13,23,26,28,29,34,54,58,59] In 5 studies[23,28,54,58,59] no deaths occurred in either study group, and in the remaining 4 studies, deaths were very rare (6 deaths out of 1,738 participants; Appendix B, Table B12).

Reslizumab

Seven studies (published in 5 articles) evaluated reslizumab compared to placebo.[17,35,36,40,52] The GRADE summary of findings is presented in Table 11.

Table 11. Summary of Findings (GRADE) Reslizumab for Asthma

No. Studies (No. Participants)	Outcome	Quality of the Evidence	Relationship	Rationale
6 add-on efficacy RCTs (N = 2,234)[17,35,36,40,52] 1 steroid-sparing RCT (N = 177)[52]	ACQ (MCB)	●●●○ (moderate)	Favors reslizumab	Downgraded 1 level for serious indirectness
5 add-on efficacy RCTs (N = 1,766)[17,35,36,40]	ACQ (MID response)	●●●● (high)	Favors reslizumab	Not downgraded
3 add-on efficacy RCTs (N = 1,164)[35,36]	Asthma Symptom Utility Index	●●●○ (moderate)	Favors reslizumab	Downgraded 1 level for serious indirectness
4 add-on efficacy RCTs (N = 1,632)[35,36,52] 1 steroid-sparing RCT (N = 177)[52]	AQLQ (MCB)	●●●○ (moderate)	Favors reslizumab	Downgraded 1 level for serious indirectness
3 add-on efficacy RCTs (N = 1,164)[35,36]	AQLQ (MID response)	●●●● (high)	Favors reslizumab	Not downgraded
3 add-on efficacy RCTs (N = 1,421)[36,52] 1 steroid-sparing RCT (N = 177)[52]	Annualized rate of exacerbations	●●●● (high)	Favors reslizumab	Not downgraded
3 add-on efficacy RCTs (N = 1,421)[36,52]	Annualized rate of exacerbations requiring ED or hospital visit	●●○○ (low)	Favors reslizumab	Downgraded 2 levels for very serious imprecision
3 add-on efficacy RCTs (N = 1,059)[17,36]	Incidence of exacerbations	●●●● (high)	Favors reslizumab	Not downgraded
1 steroid-sparing RCT (N = 177)[52]	Percentage change in oral steroid dose	●●○○ (low)	No difference	Downgraded 2 levels for very serious imprecision
7 RCTs (N = 2,411)[17,35,36,40,52]	Total adverse events	●●●● (high)	No difference	Not downgraded
7 RCTs (N = 2,411)[17,35,36,40,52]	SAEs	●●●○ (moderate)	No difference	Downgraded 1 level for serious imprecision

Abbreviations. ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; ED: emergency department; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; MCB: mean change from baseline; MID: minimally important difference; RCT: randomized controlled trials; SAE: serious adverse event.

Study Characteristics

Seven industry-sponsored RCTs (reported in 5 publications), conducted over the years 2008 to 2018, evaluated reslizumab compared to placebo.[17,35,36,40,52] A summary of these trials is in Table 12 with additional details in Appendix B, Table B13; all were multicenter studies. Six studies were phase 3 RCTs,[35,36,40,52] and the phase was not reported for the Castro et al. trial.[17] Corren et al. was conducted in the US among adults aged 18 to 65,[40] and Castro et al. was conducted in the US and Canada among adults aged 18 to 75.[17] The remaining 5 RCTs were conducted at multiple sites in multiple countries among participants aged 12 to 75[35,36] or participants aged 12 and older.[52] We rated the risk of bias as moderate for all studies because of extensive manufacturer involvement in study design, execution, and reporting.

Study inclusion and exclusion criteria were similar; all studies were conducted with participants who had asthma that was poorly controlled by at least a medium-dose ICS[35,36,40,52] or a high-dose of ICS.[17,52] Six of the studies enrolled participants based on higher baseline blood eosinophils (e.g., more than 300 or 400 per µL).[17,35,36,52] Corren et al did not enroll participants based on baseline blood eosinophils, and 80% of those enrolled had levels less than 400 per µL.[40] Six of the studies were add-on therapy efficacy trials[17,35,36,40,52] that assessed 110 mg SC[52] or 3.0 mg per kg IV (intravenous)[17,35,36,40] of reslizumab every 4 weeks compared to placebo. The FDA-approved dose of reslizumab is 3 mg per kg IV, and a 110-mg SC dose approximates a dose of 1 mg per kg IV for a 70-kg person.[52] One of the studies reported in Bernstein et al.[52] assessed 110 mg SC of reslizumab every 4 weeks as add on-therapy during a steroid-tapering cointervention. This study included participants with oral corticosteroid-dependent severe asthma who required an average daily maintenance dose of oral corticosteroids (5 to 40 mg of prednisone or equivalent) during the 3 months before study entry; participants had their oral steroid doses optimized during the run-in period to the lowest possible dosage to maintain asthma control.[52] During the active-treatment phase of the trial, the minimally effective oral steroid dose was continued during the first 4 weeks of the treatment period, reduced from week 5 through week 20, and maintained at the lower dose for the final 4 weeks of active treatment.[52]

Table 12. Evidence Table (Brief Version) RCTs of Reslizumab for Asthma

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Bernstein et al., 2020 (study 1)[52] NCT02452190 Phase 3 RCT of add-on therapy Moderate	Aged 12 and older with uncontrolled severe asthma, eosinophils ≥ 300/µL, at least a medium dose of ICS with 1 or more additional asthma controllers, ACQ score ≥ 1.5	Reslizumab 110 mg SC[a] every 4 wks (n = 236) Placebo (n = 232) Continued inhaled asthma controller regimen; oral corticosteroids as needed	At 32 or 52 wks • Symptom control • QoL • Exacerbations • Adverse events • Mortality (Frequency of exacerbations)
Bernstein et al., 2020 (study 2)[52] NCT02501629	Aged 12 and older with severe asthma, eosinophils ≥ 300/µL, daily maintenance	Reslizumab 110 mg SC[a] every 4 wks (n = 88) Placebo (n = 89)	At 24 wks • Symptom control • QoL • Steroid use

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Phase 3 RCT of add-on therapy with steroid tapering Moderate	oral corticosteroid, and high-dose ICS plus another controller	Continued ICS use; minimal effective oral corticosteroid dose optimized during run-in and continued for first 4 weeks of double-blind treatment, then reduced from weeks 5 to 20, maintained at lowest dose for last 4 weeks	• Exacerbations • Adverse events • Mortality (Percentage reduction in daily oral steroid dose)
Castro et al., 2011[17] Phase 2 RCT of add-on therapy Moderate	Aged 18 to 75 with poorly controlled asthma using high-dose ICS with at least 1 other agent, ACQ score ≥ 1.5, induced sputum eosinophils ≥ 3%	Reslizumab 3.0 mg/kg IV every 4 wks (n = 53) Placebo (n = 53) Continued ICS use	At 15 wks • Symptom control • Exacerbations • Adverse events (Change in ACQ score)
Bjermer et al., 2016[35] BREATH-3 NCT01270464 Phase 3 RCT of add-on therapy Moderate	Aged 12 to 75 with inadequately controlled asthma receiving treatment with at least a medium-dose ICS, ACQ score ≥ 1.5, eosinophils ≥ 400/µL	Reslizumab 3.0 mg/kg IV every 4 wks (n = 106) Placebo (n = 105) Continued long-acting bronchodilators, LTRA, or cromolyn	At 16 wks • Symptom control • QoL • Adverse events • Mortality (FEV_1 change)
Castro et al., 2015[36] BREATH-2 NCT01285323 Phase 3 RCT of add-on therapy Moderate	Aged 12 to 75 with inadequately controlled asthma receiving treatment with at least a medium-dose ICS with or without another controller drug, ACQ score ≥ 1.5, eosinophils ≥ 400/µL	Reslizumab 3.0 mg/kg IV every 4 wk (n = 232) Placebo (n = 232) Continued usual asthma treatment, including LABAs, ICS, oral corticosteroids LTRAs, and cromolyn	At 16 or 52 wk • Symptom control • QoL • Exacerbations • Adverse events • Mortality (Incidence and rate exacerbations)
Castro et al., 2015[36] BREATH-1 NCT01287039 Phase 3 RCT of add-on therapy Moderate	Aged 12 to 75 with inadequately controlled asthma receiving treatment with at least a medium-dose ICS with or without another controller, ACQ score ≥ 1.5, eosinophils ≥ 400/µL	Reslizumab 3.0 mg/kg IV every 4 wk (n = 245) Placebo (n = 244) Continued usual asthma treatment, including LABAs, ICS, oral corticosteroids, LTRAs, and cromolyn	At 16 or 52 wk • Symptom control • QoL • Exacerbations • Adverse events • Mortality (Incidence and rate of exacerbations)
Corren et al., 2016[40] NCT01508936 Phase 3 RCT of add-on therapy Moderate	Aged 18 to 65 with inadequately controlled asthma on at least a medium-dose ICS, ACQ score ≥ 1.5, allergic asthma (20%)	Reslizumab 3.0 mg/kg IV every 4 wk (n = 398) Placebo (n = 98) Continued LABAs, LTRAs, 5-lipoxengase inhibitors, or cromolyn; rescue medications as needed	At 16 wk • Symptom control • Adverse events • Mortality (FEV_1 change)

Note. [a] *The FDA-approved dose is 3 mg/kg IV; the dose of 110 mg SC approximates a 1 mg/kg dose IV for a 70-kg person.*
Abbreviations. ACQ: Asthma Control Questionnaire; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; IV: intravenous; LABA: long-active beta agonists; LTRA: leukotriene receptor antagonists; NCT: US National Clinical Trial; QoL: quality of life; RCT: randomized controlled trial; SC: subcutaneous; wk: week.

Detailed individual study results are provided in Appendix B, Table B14 (effectiveness) and Table B15 (safety).

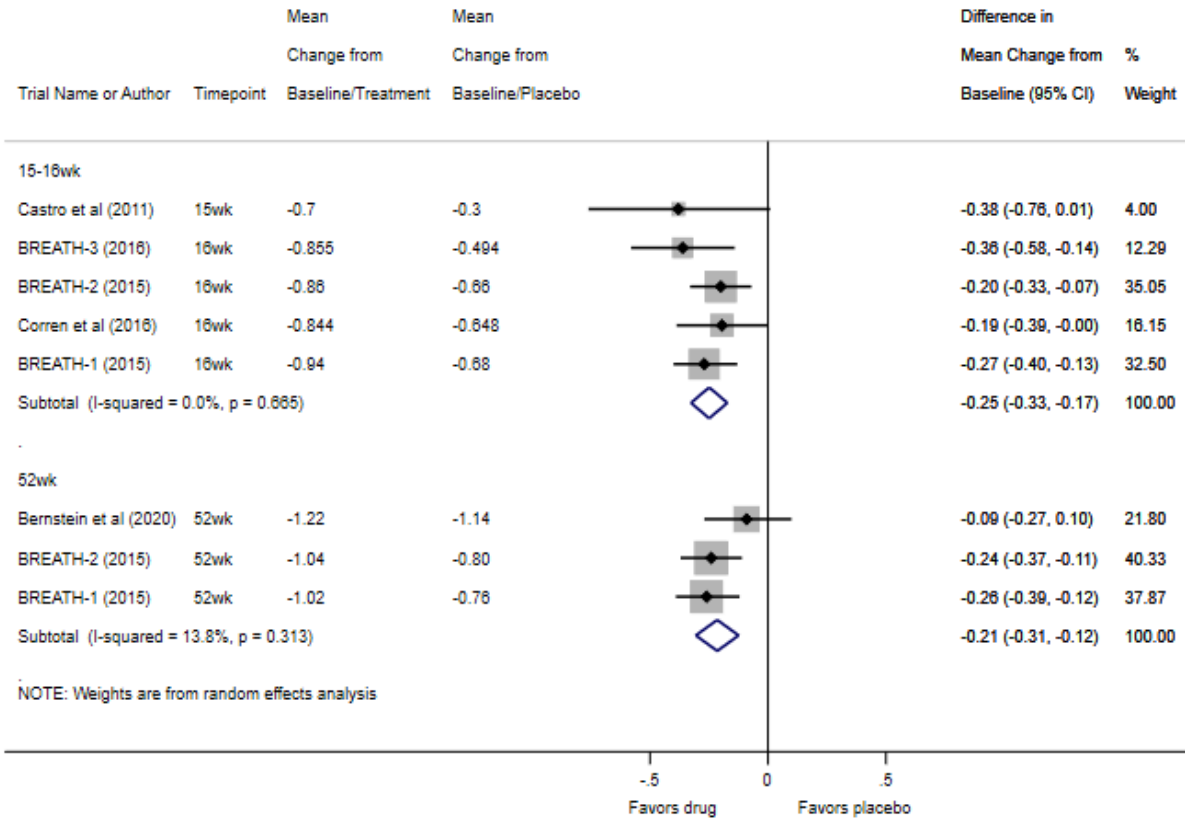
KQ 1: Symptom Control

Across both the add-on efficacy trials and the steroid-tapering trial, reslizumab was more effective than placebo for improving symptom control as measured by the ACQ (moderate QoE for mean change from baseline; high QoE for MID response). Across the add-on efficacy trials, reslizumab was also more effective than placebo for improving symptom control as measured by the Asthma Symptom Utility Index (moderate QoE).

Add-on Efficacy Trials

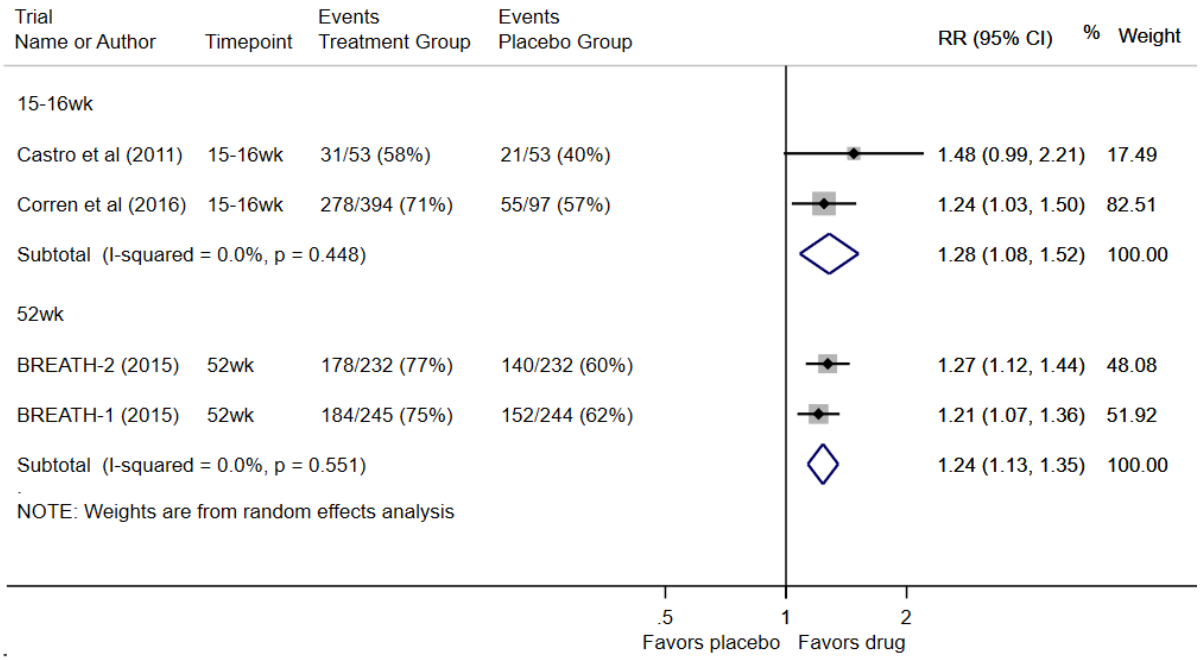
Six studies (in 5 publications) evaluated reslizumab as add-on therapy and reported symptom control measures.[17,35,36,40,52] In pooled estimates (Figure 25), significantly larger improvements from baseline were observed for the ACQ score among participants allocated to reslizumab compared to participants allocated to the placebo for both the 15- to 16-week ($P < .001$; 5 RCTs reporting[17,35,36,40]) and 52-week time points ($P < .001$; 3 RCTs reporting[36,52]). However, these differences in mean changes from baseline did not achieve the MID for ACQ scores. Nevertheless, five studies also reported the proportion of participants achieving an MID in the change from baseline in the ACQ score (0.5 points or more).[17,35,36,40] In pooled analyses (Figure 26), a significantly higher proportion of participants achieved an MID response in the reslizumab groups at a 15- to 16-week time point ($P = .004$; 2 RCTs reporting[17,40]) and at a 52-week time point ($P < .001$; 2 RCTs reporting[36]). The BREATH-3 trial reported no significant difference in the proportion of participants achieving a minimally important different between reslizumab and placebo, but actual values were not reported, and this study could not be included in pooled analyses.[35]

Figure 25. Reslizumab vs. Placebo, Asthma Control Questionnaire, Add-on Efficacy Trials



Abbreviation. CI: confidence interval; wk: week.

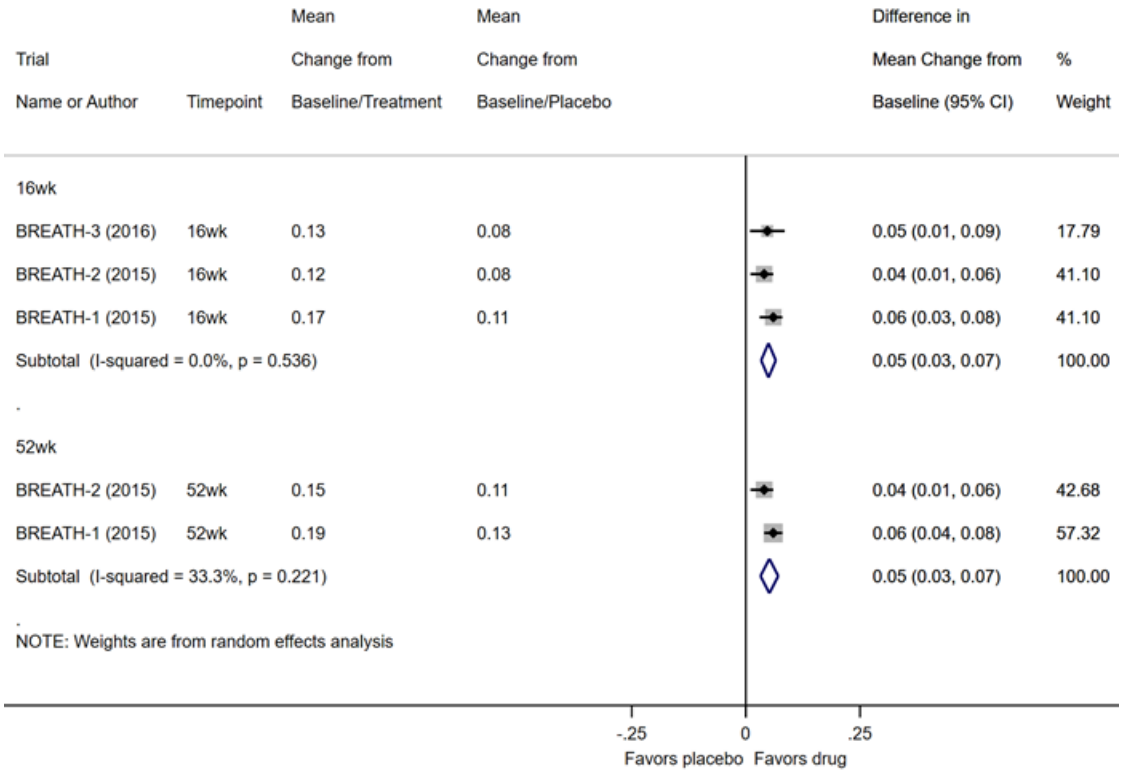
Figure 26. Reslizumab vs. Placebo, Asthma Control Questionnaire MID Response, Add-on Efficacy Trials



Abbreviations. CI: confidence interval; MID: minimally important difference; RR: risk ratio; wk: week.

The BREATH-1, BREATH-2, and BREATH-3 trials also reported symptom control using the Asthma Symptom Utility Index (ASUI).[35,36] Pooled estimates at 16 weeks (3 RCTs reporting[35,36]) and 52 weeks (2 studies reporting[36]) demonstrated a significantly larger mean change from baseline for participants allocated to reslizumab compared to placebo ($P < .001$ for both 16 weeks and 52 weeks; Figure 27). The average difference in change of 0.05 at both timepoints, although statistically significant, did not reach an MID of 0.09 or greater.

Figure 27. Reslizumab vs. Placebo, Asthma Symptom Utility Index, Add-on Efficacy Trials



Abbreviations. CI: confidence interval; wk: week.

Bernstein et al. also reported the change from baseline in the daily asthma symptom score.[52] Scores in both placebo and reslizumab groups decreased at 52 weeks, but there was not a statistically significant difference (difference in mean change, -0.10; 95% CI, -0.35 to 0.15).[52] This study also reported the change from baseline in SGRQ score[52]; a statistically significant improvement in the reslizumab group compared to placebo at 32 weeks was observed (difference in mean change, -3.3; 95% CI, -6.02 to -0.66).[52] Although this finding was statistically significant, on average, it did not achieve an MID (change of ≥ 4). However, this study used a lower dose than the current FDA-approved dosage regimen.

Add-on Efficacy With Steroid-Tapering Trial

The Bernstein et al. trial of add-on therapy with a steroid-tapering cointervention reported a decrease in ACQ score at week 24 for both the reslizumab and placebo groups, but no statistically significant difference (mean difference, -0.17; 95% CI, -0.46 to 0.11).[52] However, again, this trial used a lower dose than the current FDA-approved dosing regimen.

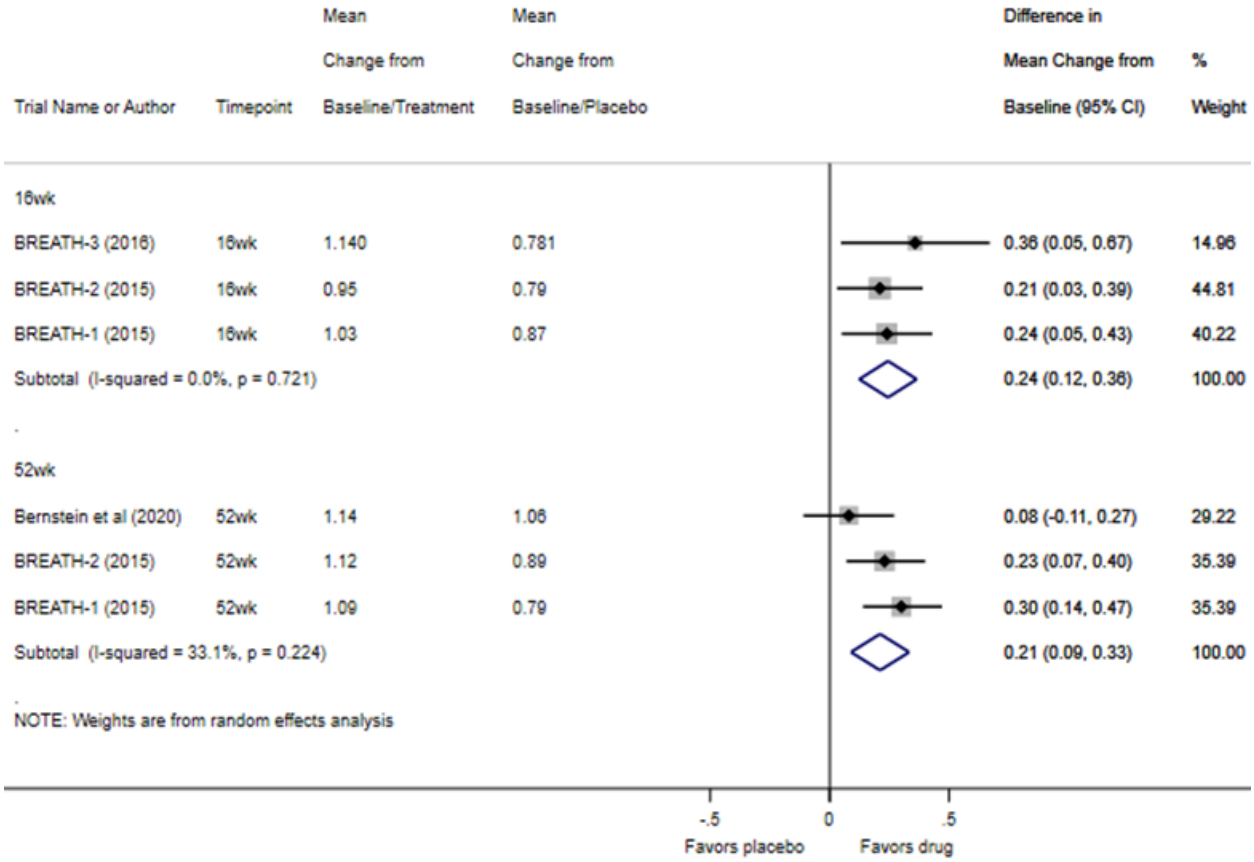
KQ 1: Quality of Life

Across both the add-on efficacy trials and the trial that included steroid-tapering, reslizumab was more effective than placebo for improving quality of life as measured by the AQLQ (moderate QoE for mean change from baseline, high QoE for MID response).

Add-on Efficacy Trials

Four RCTs evaluating the add-on efficacy of reslizumab reported quality-of-life outcomes.[35,36,52] In pooled analysis (Figure 28), a significantly larger improvement in the mean change from baseline in AQLQ score in the reslizumab group was observed compared to placebo at both the 16-week ($P < .001$; 3 RCTs reporting[35,36]) and 52-week time points ($P = .001$; 3 RCTs reporting[36,52]). Although this finding was statistically significant, on average, it did not achieve an MID.

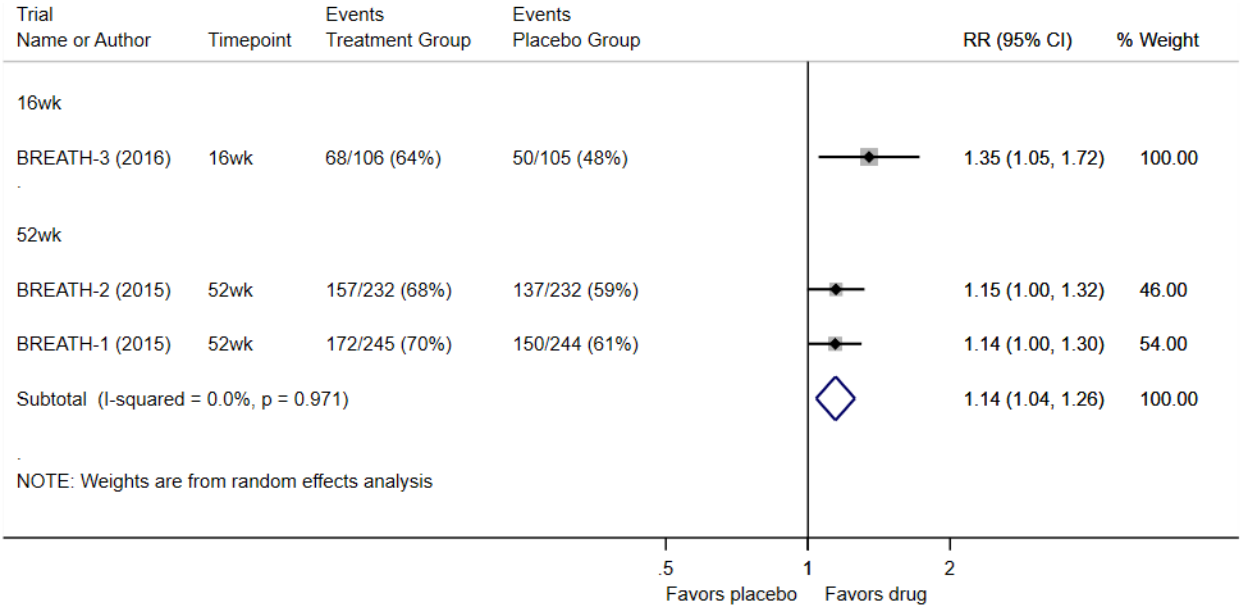
Figure 28. Reslizumab vs. Placebo, Asthma Quality of Life Questionnaire, Add-on Efficacy Trials



Abbreviations. CI: confidence interval; wk: week.

The BREATH-1, BREATH-2, and BREATH-3 trials also reported the proportion of participants achieving an MID in AQLQ score (0.5 points or more).[35,36] A significantly greater proportion of participants allocated to reslizumab achieved a minimally important difference compared to placebo at 16 weeks in BREATH-3 and at 52 weeks in pooled analysis of the BREATH-1 and BREATH-2 trials ($P = .005$; Figure 29).

Figure 29. Reslizumab vs. Placebo, Asthma Quality of Life Questionnaire MID Response, Add-on Efficacy Trials



Abbreviations. CI: confidence interval; MID: minimally important difference; RR: risk ratio; wk: week.

Add-on Efficacy With Steroid-Tapering Trial

The Bernstein et al. trial of add-on therapy with a steroid-tapering cointervention observed no statistically significant difference between the reslizumab and placebo groups at 24 weeks follow-up (difference in mean change from baseline, 0.25; 95% CI, -0.06 to 0.55).[52]

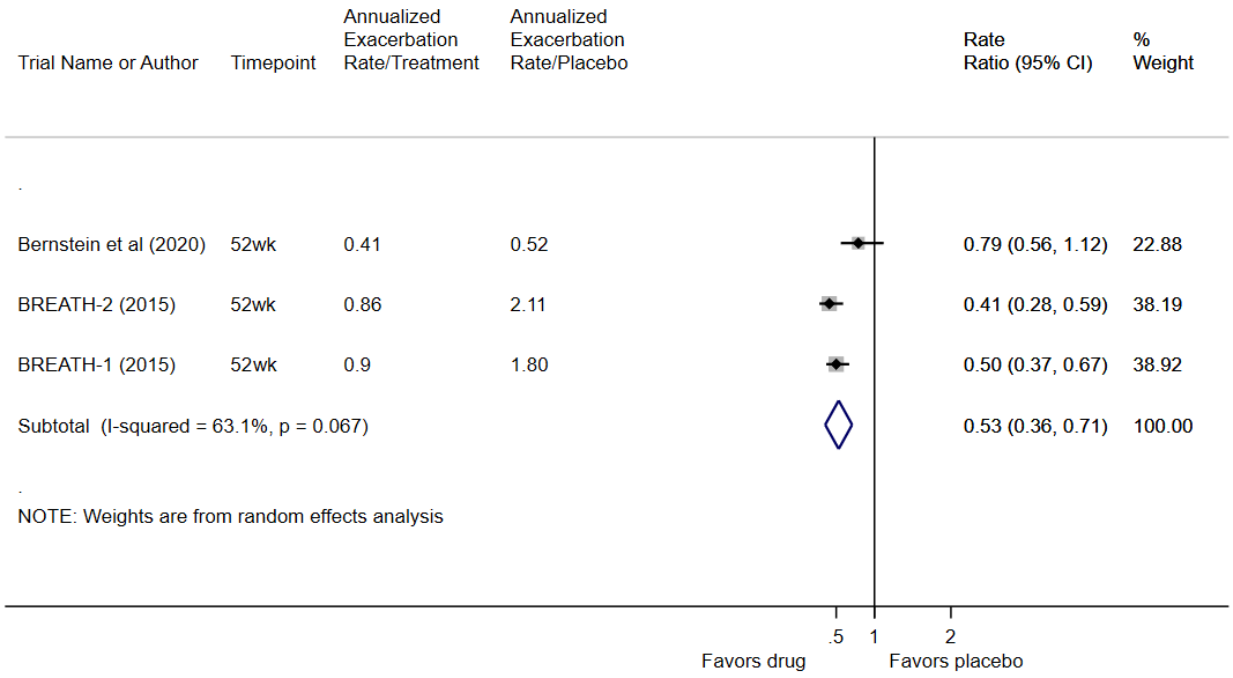
KQ 1: Exacerbations

Across both the add-on efficacy trials and the steroid-tapering trial, reslizumab was more effective than placebo for reducing the rate of exacerbations (high QoE). Across the add-on efficacy trials, there was no difference between reslizumab and placebo for reducing the annualized rate of exacerbations requiring ED or hospital visits (low QoE); reslizumab was more effective than placebo for reducing the incidence of exacerbations (high QoE).

Add-on Efficacy Trials

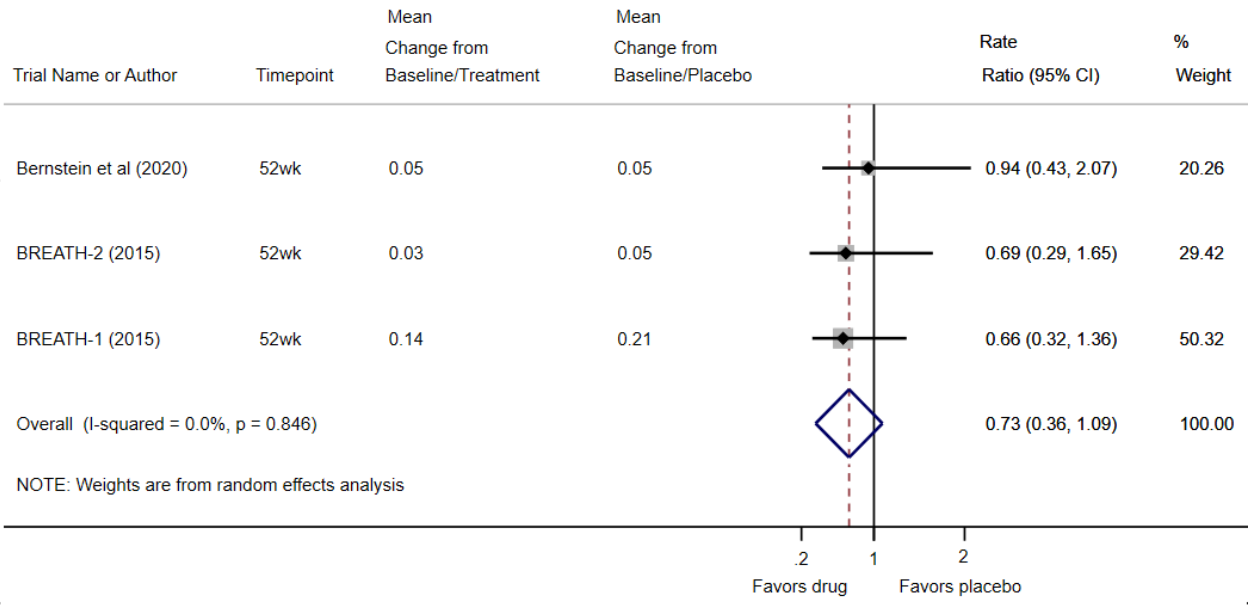
Three studies that evaluated the efficacy of reslizumab as add-on therapy reported exacerbation outcomes.[17,36,52] In pooled analysis, the adjusted annualized rate of exacerbations was lower among participants allocated to reslizumab compared to placebo ($P < .001$; Figure 30). However, this pooled estimate, which included the Bernstein et al. trial that used a lower dose of reslizumab,[52] demonstrated moderate heterogeneity. The Bernstein et al. trial found in a subgroup analysis of age groups (participants aged 12 to 17, 18 to 64, and 65 or over) that adults aged 65 years or older had a slightly greater reduction in the frequency of exacerbations with reslizumab compared to placebo, as compared to the other age groups.[52] These same 3 RCTs also reported annualized rated of exacerbations requiring ED or hospital visits, but there was no significant difference for the pooled estimate between the reslizumab and placebo groups ($P < .001$; Figure 31).[17,36,52]

Figure 30. Reslizumab vs. Placebo, Annualized Rate of Exacerbations, Add-on Efficacy Trials



Abbreviations. CI: confidence interval; wk: week.

Figure 31. Reslizumab vs. Placebo, Annualized Rate of Exacerbations Requiring ED or Hospital Visit, Add-on Efficacy Trials



Abbreviations. CI: confidence interval; ED: emergency department; wk: week.

Three RCTs reported the number of participants experiencing at least 1 exacerbation.[17,36] In pooled analysis, participants allocated to reslizumab were significantly less likely to experience

an exacerbation as compared to participants allocated to placebo (pooled RR, 0.63; 95% CI, 0.53 to 0.76; 3 RCTs; I^2 = 14.3%; Appendix D, Figure D7).

BREATH-1[36] and BREATH-2[36] also reported time to first exacerbation, which was increased with reslizumab compared to placebo (BREATH-2: HR, 0.49; 95% CI, 0.35 to 0.67; BREATH-2: HR 0.58; 95% CI, 0.44 to 0.75).[36]

Add-on Efficacy With Steroid-Tapering Trial

The Bernstein et al. trial evaluating add-on efficacy of reslizumab with a steroid-tapering cointervention reported no significant difference in the annualized rate of exacerbations between the reslizumab and placebo groups (IRR, 0.82; 95% CI, 0.50 to 1.32).[52] The time to exacerbation between groups was also not significantly different (HR, 0.80; 95% CI, 0.52 to 1.25).[52]

KQ 1: Steroid Use

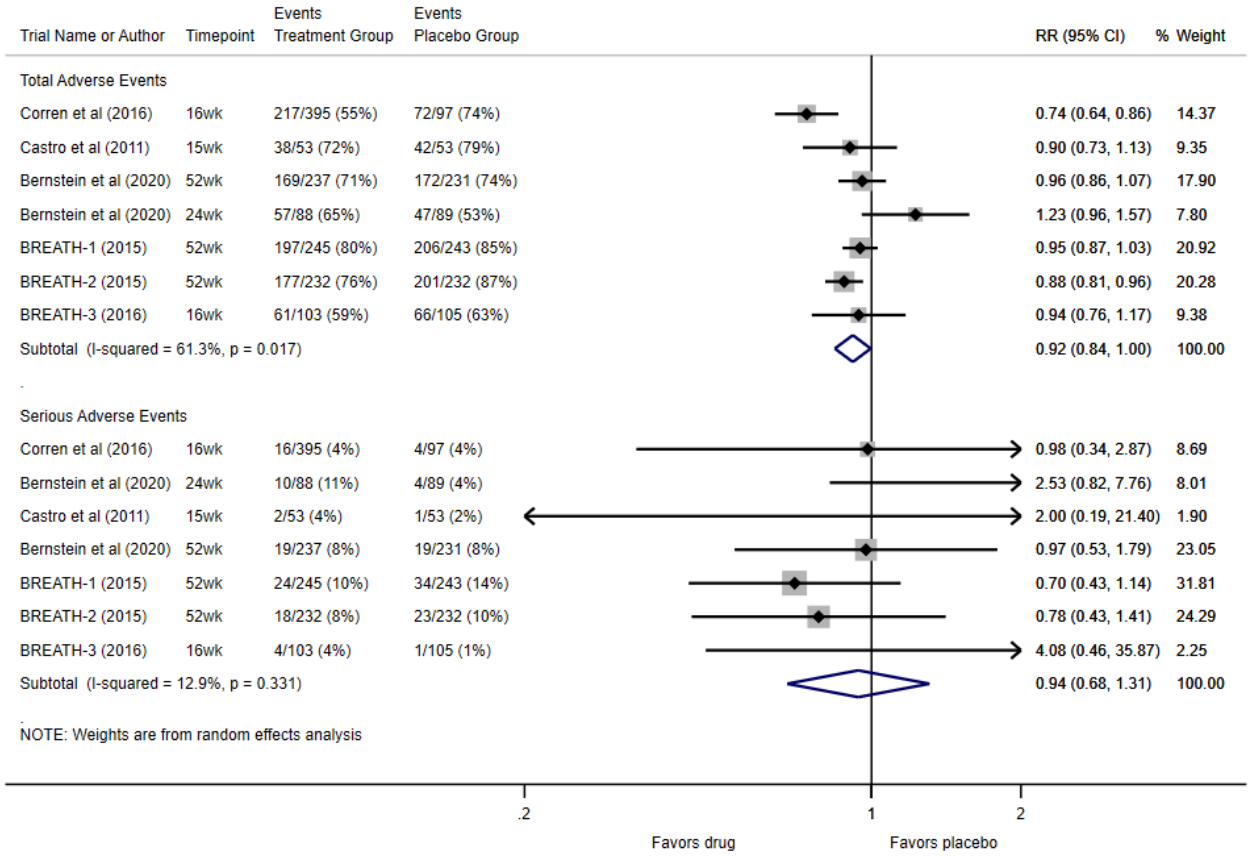
In the trial of add-on efficacy with steroid-tapering, there was no difference between reslizumab and placebo in the percentage change in oral steroid dose (low QoE).

The Bernstein et al. add-on efficacy trial with a steroid-tapering cointervention reported no significant difference in the percentage change in oral steroid dose between the reslizumab and placebo groups at weeks 20 to 24 (difference in mean percentage change, -17.8; 95% CI, -39.0 to 3.5) or in the percentage reduction from baseline in oral corticosteroid by various categories of reduction (odds ratio [OR], 1.23; 95% CI, 0.70 to 2.16; Appendix B, Table B14).[52]

KQ 2: AEs

The same 7 studies (published in 5 articles) that contributed to the key question on effectiveness also reported AE outcomes.[17,35,36,40,52] Pooled analyses indicated no significant difference in overall AEs among participants allocated to reslizumab compared to placebo (*P* = .04; high QoE; Figure 32, upper panel). However, the pooled estimate was moderately heterogenous likely due to the inclusion of the Bernstein et al. add-on efficacy trial with a steroid-tapering cointervention. In sensitivity analysis, excluding this RCT resulted in a significant pooled estimate of 0.90 and with reduced statistical heterogeneity (95% CI, 0.83 to 0.96; I^2 = 49.8%). The pooled estimate for SAEs also indicated no statistically significant difference between groups (Figure 32, lower panel; *P* = .72; moderate QoE); we downgraded the QoE for this outcome for imprecision. All studies also reported AEs leading to trial discontinuation; these events were rare, and there were no statistically significant differences between the reslizumab and placebo groups.

Figure 32. Reslizumab vs. Placebo, Adverse Events



Notes. [a] *Refers to the add-on efficacy with steroid tapering cointervention trial.* [b] *Refers to the add-on efficacy Bernstein trial. Abbreviations. CI: confidence interval; RR: risk ratio; wk: week.*

KQ 2: Mortality

Six of the 7 studies reported mortality.[35,36,40,52] Events were rare (2 deaths out of 2,300 total participants across studies), so estimates of treatment effect were imprecise (Appendix B, Table B15).

Summary of Findings From RCTs for Chronic Spontaneous Urticaria

Ten studies in 13 publications evaluated 1 or more dosing regimens of omalizumab compared to placebo for CSU.[61-73] The GRADE summary of findings is provided in Table 13.

Table 13. Summary of Findings (GRADE) Biologic Drugs for Chronic Spontaneous Urticaria

No. Studies (No. Participants)	Outcome	Quality of the Evidence	Relationship	Rationale
8 RCTs (N = 1,252)[61-69]	Urticaria activity score over 7 days (MCB)	●●●○ (moderate)	Favors omalizumab	Downgraded 1 level for serious indirectness
5 RCTs (N = 1,066)[64-67,70]	Urticaria activity score over 7 days remission (score ≤ 6)	●●●● (high)	Favors omalizumab	Not downgraded
5 RCTs (N = 916)[61,62,64,66,67,70]	Urticaria activity score over 7 days complete response (score = 0)	●●●● (high)	Favors omalizumab	Not downgraded
7 RCTs (N = 1,206)[61,62,64-69]	Dermatology Life Quality Index (MCB)	●●●● (high)	Favors omalizumab	Not downgraded
6 RCTs (N = 927)[65-70]	Antiurticarial medication use (various measures used)	●○○○ (very low)	Favors omalizumab	Downgraded 1 level for serious imprecision, 1 level for serious inconsistency, and 1 level for serious indirectness
8 RCTs (N = 1,252)[61-69]	Overall AEs	●●●● (high)	No difference	Not downgraded
7 RCTs (N = 1,222)[61-67,69]	SAEs	●●●○ (moderate)	No difference	Downgraded 1 level for serious imprecision

Note. For methods and interpretation of GRADE ratings, see Appendix A.
Abbreviations. AE: adverse event; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; MCB: mean change from baseline; RCT: randomized controlled trial; SAE: serious adverse event.

Study Characteristics

We identified 10 industry-sponsored RCTs evaluating omalizumab, reported in 13 publications[61-73] published between 2004 and 2016 and conducted among 1,416 participants. A summary of these trials is in Table 14 with additional details in Appendix B, Table B16. We rated 2 studies as high risk of bias for lack of intention-to-treat analysis, differential attrition, lack of information about randomization and allocation concealment coupled with baseline imbalances[70]; and selection bias related to open-label phase followed by randomization of only responders to double-blind treatment and extensive crossovers.[71-73] We rated the rest of the RCTs as moderate risk of bias for extensive manufacturer involvement in study design, execution, and reporting.

All but 1 RCT[70] were multicenter. One RCT was phase 4 (XTEND-CIU[71-73]), 5 RCTs were phase 3 (X-ACT,[61,62] POLARIS,[64] ASTERIA II,[65] ASTERIA I,[66] GLACIAL[67]), and 3 RCTs were phase 2 (MYSTIQUE,[63] Metz et al.,[68] Jorg et al.[70]). One study did not report any trial phase (Maurer et al.[69]).

Three studies were conducted in Germany,[61,62,68,69] 1 in Switzerland,[70] 1 in the US,[71-73] and the remaining were conducted in multiple countries. Four studies were conducted among adults,[61,62,68-70] 1 enrolled adults in Germany and participants aged 12 and older in other countries,[67] and the rest were conducted among participants aged 12 and older.[63-66,71-73] Study inclusion and exclusion criteria were largely similar across studies. All were conducted among participants who had CSU or CIU for at least 3 months with itching and hives present before enrollment, and excluded participants who had an underlying cause for chronic urticaria other than CSU. Of note was that the inclusion criteria for the X-ACT[61,62] and GLACIAL[67] trials specified that participants were allowed to be on more than the approved dose of H_1-antihistamines (2 to 4 times for X-ACT and up to 4 times for GLACIAL), while some other studies specified that patients were on approved doses of H_1-antihistamines.[64,66,68]

All RCTs but 1 (XTEND-CIU)[71-73] were designed as efficacy trials that assessed omalizumab as add-on therapy to existing medications. The MYSTIQUE[63] phase 2 trial assessed a single dose of 300 mg, and Maurer et al.[69] assessed the same weight- and serum IgE-based dosing regimen used for the asthma indication. The rest of the add-on efficacy studies evaluated either 300 mg every 4 weeks or both 150 mg and 300 mg every 4 weeks, consistent with FDA labeling for this product. XTEND-CIU[71-73] was a phase 4 post-marketing trial that consisted of an open-label phase during which all participants (N = 205) received 300 mg of omalizumab every 4 weeks for 24 weeks; participants with adequate control in the final 2 weeks of the open-label phase as defined by a Urticaria Activity Score over 7 days (UAS7) of 6 or less (N = 134) were then randomized to either continue treatment or switched to a placebo through week 48. Participants with clinical worsening for 2 consecutive weeks during the double-blind phase could be transitioned back to open-label treatment. We rated this study as high risk of bias because of this study design, which limited the double-blind period to responders from an earlier trial and that included significant cross-overs in the placebo group.

Table 14. Evidence Table (Brief Version) RCTs of Omalizumab for CSU

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Hide et al., 2017[64] POLARIS NCT02329223 Phase 3 RCT of add-on therapy Moderate	Aged 12 to 75, CSU diagnosis for 6 months, refractory to conventional H_1AH; itch and hives for 8 consecutive wk at any time before enrollment; UAS7 ≥ 16; itch component of UAS7 ≥ 8 during 7 days before randomization; UAS ≥ 4; current use of approved dose of an H_1AH for 3 consecutive days	Omalizumab 300 mg SC every 4 wks (n = 73) Omalizumab 150 mg SC every 4 wks (n = 71) Placebo (n = 74) Continued stable doses of H_1AH medications, diphenhydramine rescue for symptoms	At 12 and 24 wks • Symptom control • QoL • Adverse events • Mortality (Change from baseline to week 12 in ISS7 score)

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Jorg et al., 2017[70] NCT01803763 Phase 2 RCT of add-on therapy High	Aged 18 to 70, CSU and symptoms ≥ 6 wks, refractory to conventional H_1AH, hives present ≥ 2x weekly	Omalizumab 300 mg SC every 4 wks (n = 20) Placebo (n = 10) Continued stable doses of medications (H_1AH up to 4x single dose, H_2AH, montelukast, short-term prednisolone for exacerbations)	At 12 and 20 wks • Symptom control • Antiurticarial medication use (FceRI receptor density change on basophils at week 12 and 2 months after treatment)
Kaplan et al., 2013[67] GLACIAL NCT01264939 Phase 3 RCT of add-on therapy Moderate	Aged 12 to 75 (18 to 75 in Germany), CIU/CSU ≥ 6 months; itch and hives ≥ 6 consecutive wks before enrollment with H_1AH plus H_2AH, LTRAs, or both; UAS7 ≥ 16; ISS7 ≥ 8 during 7 days before randomization; UAS ≥ 4; treatment with H_1AH (up to 4 times the approved dosage) plus H_2AH, LTRAs, or both H_2AH and LTRAs for ≥ 3 consecutive days	Omalizumab 300 mg SC every 4 wks (n = 252) Placebo (n = 84) Continued stable doses of H_1AH plus H_2AH, LTRAs, or both; diphenhydramine rescue for symptoms	At 12, 24, and 40 wks • Symptom control • QoL • Antiurticarial medication use • Adverse events • Mortality (Change from baseline to week 12 in ISS7 score)
Maurer et al., 2018;[71] Casale et al., 2018;[73] Casale et al., 2019[72] XTEND-CIU NCT02392624 Phase 4/ postmarketing discontinuation RCT High	Aged 12 to 75, CIU/CSU refractory to conventional H_1AH; UAS7 ≥ 16 in previous 7 days	Omalizumab 300 mg SC every 4 wks (n = 81) Placebo (n = 53) 24-wk open-label phase followed by randomization of persons with adequate control (UAS7 ≤ 6) to either discontinuation or continuation through week 48	At 48 and 60 wks • Symptom control • QoL • Adverse events • Mortality (Percentage of patients with CIU/CSU clinical worsening [UAS7 ≥ 12 for ≥ 2 consecutive weeks between weeks 24 and 48])
Maurer et al., 2013[65] ASTERIA II NCT01292473 Phase 3 RCT of add-on therapy Moderate	Aged 12 to 75, CIU ≥ 6 months, itch and hives ≥ 8 wks with H_1AH, UAS7 ≥ 16, ISS7 ≥ 8, UAS ≥ 4, receipt of second-generation H_1AH for ≥ 3 consecutive days before randomization, no missing e-diary entries in 7 days before randomization	Omalizumab 150 mg SC every 4 wks (n = 83) Omalizumab 300 mg SC every 4 wks (n = 79) Placebo (n = 79) Continued stable doses of H_1AH, 1 additional H_1AH allowed during follow-up; diphenhydramine rescue	At 12 and 28 wks • Symptom control • QoL • Antiurticarial medication use • Adverse events • Mortality (Change from baseline to week 12 in ISS7 score)

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Maurer et al., 2011[69] RCT of add-on therapy Moderate	Aged 18 to 70, moderate to severe CU, body weight 20 to 150 kg, total serum IgE: 30 to 700 IU/mL, serum IgE–anti-TPO antibody ≥ 5.0 IU/mL within last 3 months, UAS7 ≥ 10	Omalizumab (weight/IgE-based dose) SC every 2 or 4 wks (n = 27) Placebo (n = 22) H_1AH rescue, no other medications permitted	At 24 wks • Symptom control • QoL • Antiurticarial medication use • Adverse events • Mortality (Change from baseline to week 24 in UAS7 score)
Metz et al., 2017[68] NCT01599637 Phase 2 RCT of add-on therapy Moderate	Aged 18 to 75, CSU ≥ 6 months, refractory to conventional H_1AH, itch and hives ≥ 6 wk before baseline, UAS7 ≥ 16, itch component of UAS7 ≥ 8 during the 14 days before randomization, current use of approved dose of an H_1AH	Omalizumab 300 mg SC every 4 wks (n = 20) Placebo (n = 10) Continued stable doses of H_1AH, loratadine rescue for angioedema or other reasons	At 12 wks • Symptom control • QoL • Antiurticarial medication use • Adverse events (Change from baseline to week 12 in the FceRI + or IgE + skin cells)
Saini et al., 2011[63] MYSTIQUE NCT00130234 Phase 2 RCT of add-on therapy Moderate	Aged 12 to 75, CIU > 3 months, moderate to severe CIU despite antihistamine, UAS ≥ 4, UAS7 ≥ 12 despite stable doses of H_1AH	Omalizumab 300 mg SC single dose (n = 25) Placebo (n = 21) Continued stable doses of H_1AH, diphenhydramine rescue	At 4 and 16 wks • Symptom control • Adverse events (Change from baseline to week 4 in UAS7 score)
Saini et al., 2015[66] ASTERIA I NCT01287117 Phase 3 RCT of add-on therapy Moderate	Aged 12 to 75, CIU/CSU ≥ 6 months, itch and hives ≥ 8 consecutive wk despite H_1AH, current use of approved dose of H_1AH for ≥ 3 consecutive days; UAS ≥ 4; UAS7 ≥ 16, itch component of UAS7 ≥ 8 during 7 days before randomization; willing/able to complete a symptom diary with an electronic handheld device 2x daily during study; no missing e-diary entries in 7 days before randomization	Omalizumab 150 mg SC every 4 wks (n = 80) Omalizumab 300 mg SC every 4 wks (n = 81) Placebo (n = 80) Continued stable doses of H_1AH for first 12 weeks, 1 additional H_1AH allowed during weeks 13-24, diphenhydramine rescue for itch relief	At 12, 24, and 40 wks • Symptom control • QoL • Antiurticarial medication use • Adverse events • Mortality (Change from baseline to week 12 in ISS7 score)

Citation Trial Name Trial Number Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Staubach et al., 2016;[61] Staubach et al., 2018[62] X-ACT NCT01723072 Phase 3 RCT of add-on therapy Moderate	Aged 18 to 75, wheals and ≥ 4 occurrence of angioedema in last 6 months who remained symptomatic despite H_1AH at 2 to 4x the approved dose, UAS7≥14, CU-Q2oL ≥ 30	Omalizumab 300 mg SC every 4 wk (n = 44) Placebo (n = 47) Daily H_1AH, clemastine and betamethasone rescue	At 4, 12, 28, and 36 wks • Symptom control • QoL • Adverse events (Change from baseline to week 28 in CU-Q2oL score)

Abbreviations. CIU: chronic idiopathic urticaria; CSU: chronic spontaneous urticaria; CU: chronic urticaria; CU-Q2oL: Chronic Urticaria Quality-of-Life Questionnaire; FceRI: high-affinity IgE receptor; H_1AH: H_1-antihistamines; H_2AH: H_2-antihistamines; IgE: immunoglobin E; ISS7: Itch Severity Score over 7 days; LTRA: leukotriene receptor antagonist; NCT: US National Clinical Trial; QoL: quality of life; RCT: randomized controlled trial; SC: subcutaneous; TPO: thyroid peroxidase; UAS: Urticaria Activity Score; UAS7: Urticaria Activity Score over 7 days; wk: week; x: times.

Detailed individual study results are provided in Appendix B, Table B17 (effectiveness) and Table B18 (safety).

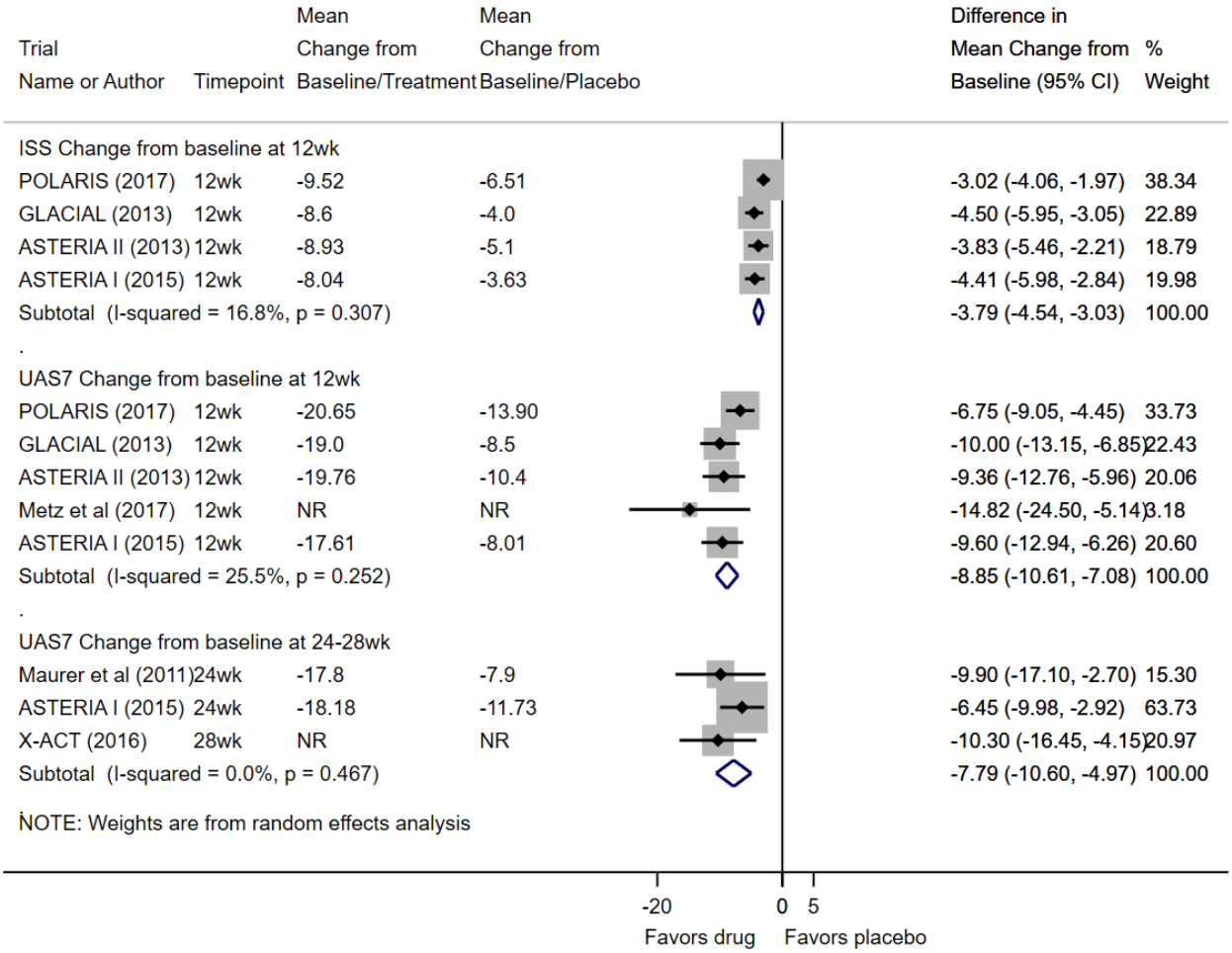
KQ 1: Symptom Control

Across the add-on efficacy trials, omalizumab was more effective than placebo for improving symptom control as measured by the UAS7 mean change from baseline (moderate QoE). Omalizumab was also more effective than placebo at having participants achieve complete UAS7 response (high QoE) and UAS7 remission (high QoE).

Add-on Efficacy Trials

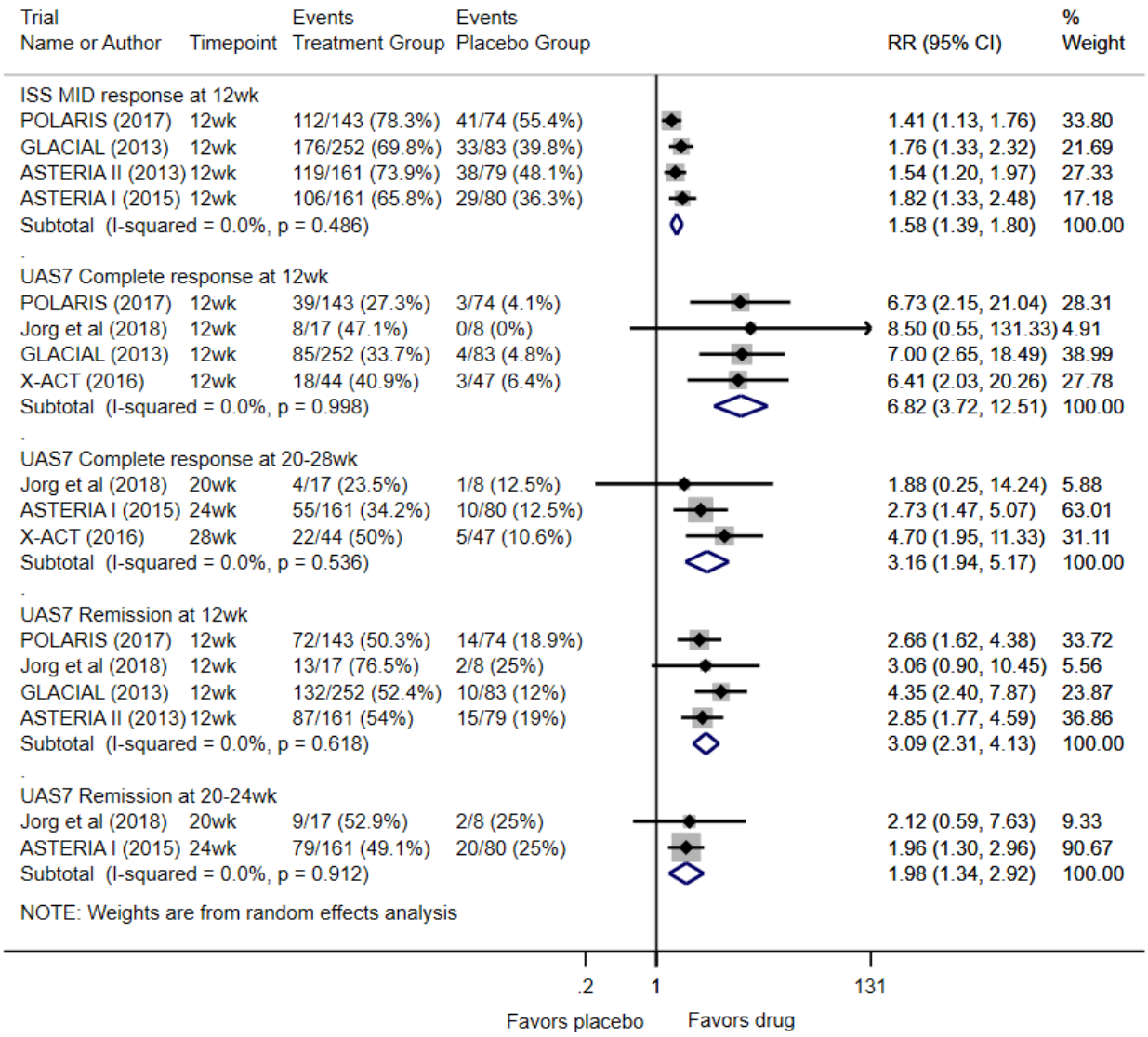
All 9 RCTs reported symptom control measures.[61-70] Pooled analyses reporting data suitable for use in quantitative analyses indicated that, compared to placebo, participants in the omalizumab groups had significantly lower Itch Severity Score over 7 days (ISS7) and UAS7 at 12 weeks, and lower UAS7 scores at 24 weeks ($P < .001$ for all 3 pooled estimates; Figure 33). However, the pooled difference in mean change from baseline (Figure 33) did not achieve the MID for either ISS7 (≥ 5 points) or UAS7 (≥ 9.5 points). Pooled analyses also indicated that a significantly greater number of omalizumab participants achieved an MID in ISS7 at 12 weeks ($P < .001$), a complete response (UAS7 score of 0) at 12 weeks ($P < .001$) and at 20 to 28 weeks ($P < .001$), and remission (UAS7 score ≤ 6) at 12 weeks ($P < .001$) and at 20 to 24 weeks ($P = .001$) compared to placebo (Figure 34).

Figure 33. Omalizumab vs. Placebo, Symptom Control, Add-on Efficacy Trials



Abbreviations. CI: confidence interval; ISS: Itch Severity Score; UAS7: Urticaria Activity Score over 7 days; wk: week.

Figure 34. Omalizumab vs. Placebo, Response and Remission, Add-on Efficacy Trials



Abbreviations. CI: confidence interval; MID: minimally important difference; RR: risk ratio; ISS: weekly Itch Severity Score; UAS7: Urticaria Activity Score over 7 days; wk: week.

We observed similar findings for UAS7 and ISS7 measures among the studies or time points that could not be included in the quantitative synthesis. Jorg et al., a high risk-of-bias phase 2 RCT, reported no statistically significant difference between omalizumab and placebo in the proportion of participants achieving a complete response at 12 weeks and at 20 weeks based on ISS7 scores, but these results were very imprecise (Appendix B, Table B17).[70] GLACIAL reported a significantly larger improvement in ISS7 among omalizumab patients at 24 weeks (difference from placebo, -4.5; 95% CI, -6.1 to -3.0).[67] ASTERIA I reported a significantly larger improvement in ISS among omalizumab patients who received a 300-mg dose at 24 weeks compared to placebo (difference from placebo, NR; $P < .0001$) but no statistically significant difference in ISS score for patients who received a 150-mg dose.[66] MYSTIQUE, a phase 2 RCT, could not be included in the quantitative synthesis because symptom-control outcomes were only reported at 4 weeks after a single dose.[63] The authors reported a significantly larger improvement in UAS7

(difference from placebo in mean change from baseline, -13.0; *P* <.001), a greater proportion of omalizumab patients had more than 50% score improvement in UAS7 (calculated RR, 3.4; 95% CI, 1.5 to 7.4), and no difference between groups in the proportion of patients with 100% score improvement in UAS7 (calculated RR, 16.1; 95% CI, 0.99 to 260.9).[63] Additional measures of urticaria symptom control were reported by 2 studies including patient and physician global assessment scores and Skindex scores (Appendix B, Table B17); the authors reported larger improvements on these outcomes for participants allocated to omalizumab compared to placebo.[68,69]

The X-ACT trial,[61,62] the GLACIAL trial,[67] and the ASTERIA-II trial[65] also reported measures specific to control of angioedema. In X-ACT, the difference in mean change from baseline in the Angioedema Activity Score (AAS) between participants allocated to omalizumab compared to participants allocated to placebo was -14.1 at 12 weeks follow-up (*P* = .002) and -9.8 at 28 weeks follow-up (*P* = .036).[61] The study also reported fewer days with angioedema among participants allocated to omalizumab (14.6 vs. 49.5; *P* value NR).[61,62] In the GLACIAL trial, the proportion of angioedema-free days between weeks 4 and 12 were 88.1% compared to 91.0% (*P* < .001).[67] In ASTERIA-II, a significant difference in the mean number of angioedema-free days was observed for the 300-mg dosage (95.5) compared to placebo (89.2; *P* < .001), but not for the 150-mg dosage (91.6; *P* not significant [NS]).[65]

Other Trials

XTEND-CIU, the high risk-of-bias phase 4 discontinuation RCT, reported that a smaller proportion of patients experienced clinical worsening (UAS7 ≥ 12 for ≥ 2 weeks) at 48 weeks in the group that continued omalizumab treatment compared to the group that was randomized to switch to a placebo after the open-label phase (calculated RR, 0.35; 95% CI, 0.22 to 0.56).[71-73]

KQ 1: Quality of Life

Across the add-on efficacy trials, omalizumab was more effective than placebo for improving quality of life as measured by the Dermatology Life Quality Index (DLQI; high QoE).

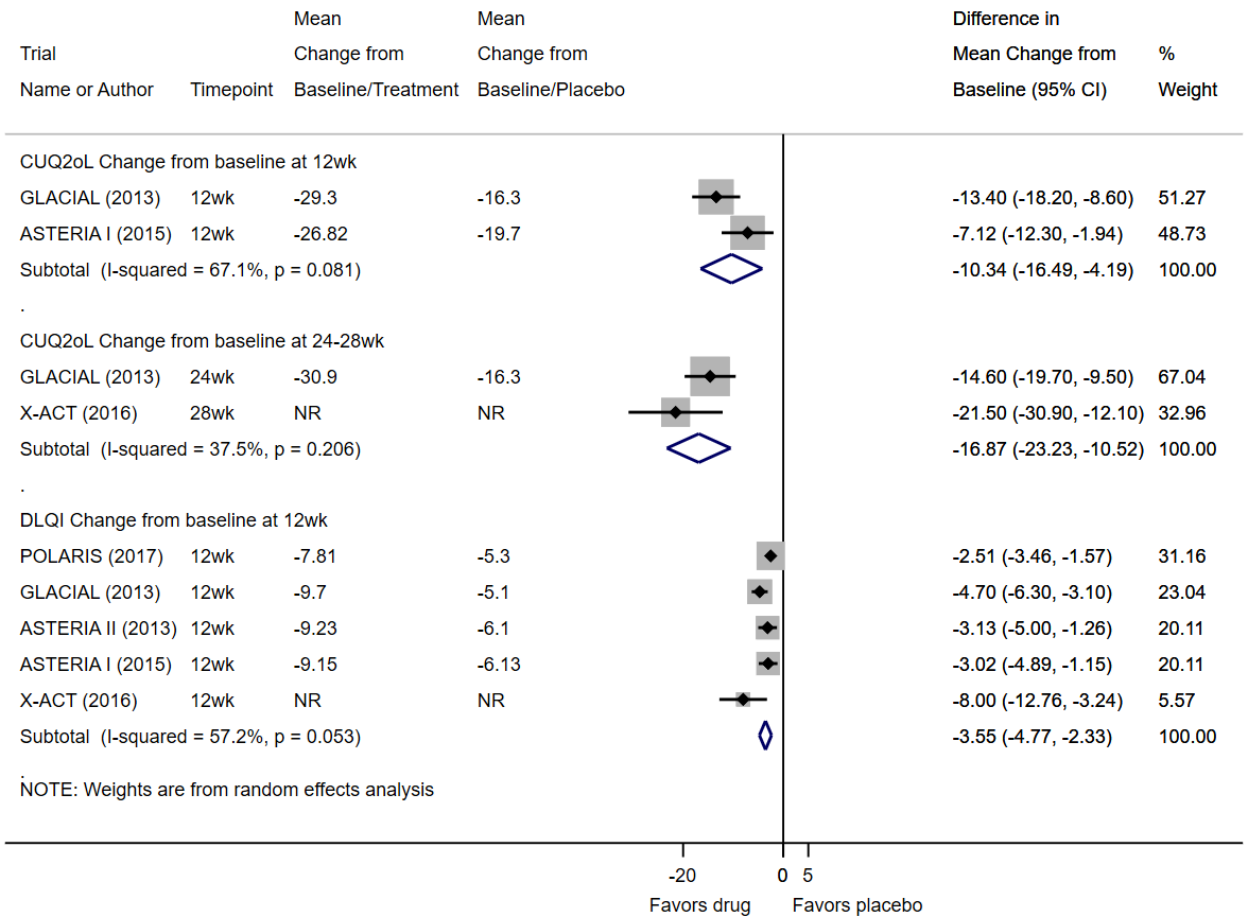
Add-on Efficacy Trials

Seven of the RCTs evaluating the add-on efficacy of omalizumab reported quality-of-life outcomes.[61,62,64-69] Pooled analyses indicated that compared to placebo, participants in the omalizumab groups had significantly greater improvements in Chronic Urticaria Quality of Life Questionnaire (Cu-Q2oL) scores at 12 weeks (*P* = .001) and at 24 to 28 weeks (*P* < .001), and significantly greater improvements in DLQI scores at 12 weeks (*P* < .001; Figure 35). However, these estimates demonstrated moderate to substantial heterogeneity.

Several other studies also reported quality-of-life outcomes but could not be included in the quantitative synthesis. Metz et al. reported significantly smaller mean scores at 12 weeks follow-up for the CU-Q2oL (*P* = .001) and the DLQI (*P* = .006), indicating less impairment on QoL for participants allocated to omalizumab compared to placebo.[68] Maurer et al. reported significantly larger percentage improvements in the CU-Q2oL and DLQI score at 24 weeks follow-up (both *P* < .01) for participants allocated to omalizumab compared to participants allocated to placebo.[69] X-ACT found significant improvements in CU-Q2oL at 4 weeks follow-up and DLQI at 4 weeks and 28 weeks follow-up (*P* < .001 for all three) and in several other QoL outcomes for

participants allocated to omalizumab compared to participants allocated to placebo including the angioedema quality-of-life measure and the World Health Organization-5 health-related quality-of-life measure (Appendix B, Table B17).[61,62]

Figure 35. Omalizumab vs. Placebo, Quality of Life



Abbreviations. CI: confidence interval; CU-Q2oL: Chronic Urticaria Quality-of-Life Questionnaire; DLQI: Dermatological Life Quality Index; NR: not reported; wk: week.

Other Trials

XTEND-CIU reported a lower proportion of omalizumab patients experiencing DLQI worsening (change of 3 points or more) for the group that continued treatment compared to the group that was randomized to switch to a placebo after the open-label phase (calculated RR, 0.30; 95% CI, 0.19 to 0.48, Appendix B, Table B17).[71-73]

KQ 1: Antiurticarial Medication Use

Across the add-on efficacy trials, omalizumab was more effective than placebo for reducing antiurticarial medication use (very low QoE).

Six RCTs reported antiurticarial medication use.[65-70] Quantitative synthesis of this outcome was not conducted because of the differences in how antiurticarial medication use was measured. The trials varied in the units used to report antiurticarial medication use (e.g., number of tablets per day, mean days of use per week) and whether antiurticarial medications were aggregated

(e.g., sum of all antiurticarial medications used, use of specific antiurticarial medication); detailed results are in Appendix B, Table B17. ASTERIA I, ASTERIA II, and Metz et al. reported statistically significant reductions in antiurticarial medication use among participants allocated to omalizumab patients compared to participants allocated to placebo.[65,66,68] Specifically, ASTERIA I reported that participants who received 150 mg of omalizumab and participants who received 300 mg both experienced a significantly greater reduction in antihistamine tablet use per week (difference from placebo NR; $P < .03$ for both treatment groups).[66] ASTERIA II similarly reported that participants who received 300 mg experienced a significantly greater reduction in antihistamine tablet use per week (difference from placebo, NR; $P = .01$), but no difference in use was reported between participants who received 150 mg of omalizumab compared to participants who received the placebo.[65] Metz et al. reported a significantly greater reduction in the mean days per week of loratadine use among participants allocated to omalizumab compared to participants allocated to placebo (difference from placebo, NR; $P = .0143$).[68]

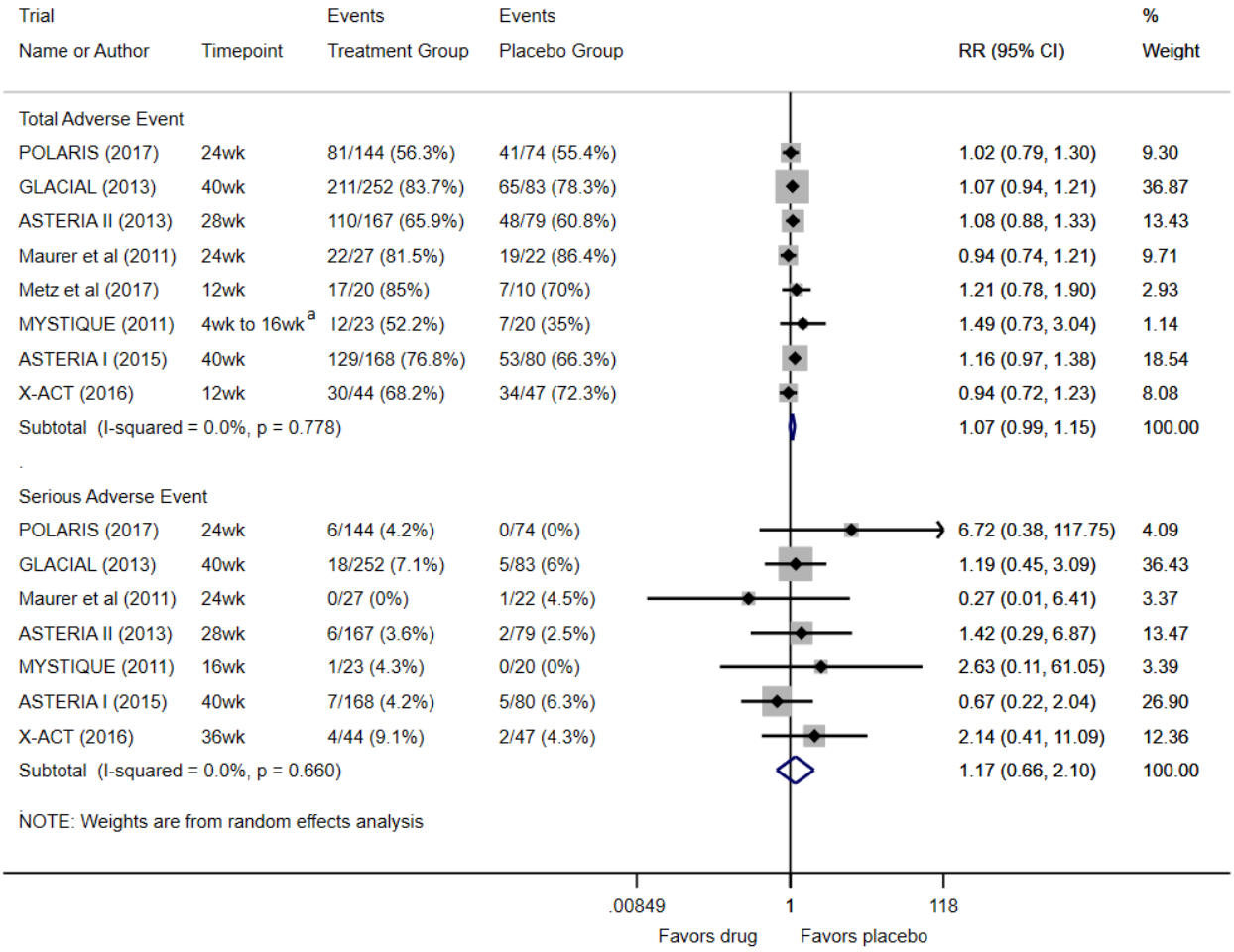
GLACIAL[67] and Jorg et al.[70] reported no difference in antiurticarial medication use between participants allocated to omalizumab and participants allocated to placebo. Specifically, GLACIAL reported no difference in antiurticarial tablet use over 24 hours between participants allocated to omalizumab and participants allocated to placebo (difference, -1.20 tablets; 95% CI, -2.70 to 0.40).[67] Jorg et al.[70] reported no differences between participants in the frequency of use of an H_1-antihistamine per day (2.5 vs. 2.8 in placebo) and frequency of use of montelukast per day (1.0 vs. 1.0 in placebo; calculated $P > .05$ for both). Findings were more challenging to interpret for Maurer et al.[69]; this study reported the mean change from baseline in tablet use in the past 7 days (calculated difference between groups, -3.0; *P* value NR and incalculable).

KQ 2: AEs

Nine of the CSU trials reported AEs.[61-69,71-73] Pooled analyses indicated no differences between active treatment and placebo groups in overall AEs (8 RCTs; $P = .10$; high QoE) or SAEs (7 RCTs; $P = .59$; moderate QoE), though estimates for SAEs were rare and we downgraded for imprecision (Figure 36). No differences between active treatment and placebo groups in discontinuations because of AEs were observed by the 7 studies reporting this outcome, but these events were not common, and estimates were imprecise (Appendix B, Table F3).[63-69]

The XTEND-CIU trial only reported treatment-related AEs; 6% occurred among participants allocated to continue omalizumab compared to 2% among participants allocated to switch from omalizumab to placebo (calculated RR, 3.27; 95% CI, 0.39 to 27.23).[71-73]

Figure 36. Omalizumab vs. Placebo, Adverse Events



Notes. [a] *The MYSTIQUE trial reported total adverse events from 0 to 4 weeks and from 4 to 16 weeks. The pooled relative risk for total adverse events using the number of total adverse events from 0 to 4 weeks is 1.06 (95% CI, 0.98 to 1.15; P = .13).*
Abbreviations. CI: confidence interval; RR: relative risk; wk: week.

KQ 2: Mortality

Six of the CSU trials reported mortality;[64-67,69,71-73] no deaths were reported across any studies (Appendix B, Table B18).

Ongoing Studies

We identified 14 ongoing RCTs of biologic drugs to treat asthma or CSU.{, #2400;, #2662;, #2399;, #2460;, #2386;, #2408;, #2404;, #2347;, #2663;, #2332;, #2499;, #2403;, #2311;, #2315} Twelve were for asthma, including 1 head-to-head study of omalizumab compared to mepolizumab.[111] The rest were placebo-controlled studies, including 6 studies on dupilumab,[102,105,107-109,114] 1 study on benralizumab,{, #2449} 2 studies on mepolizumab,[104,110] 1 study on omalizumab,[112] and 1 study on reslizumab.[106] Two studies were on CSU, both comparing dupilumab to placebo.[115,116] Table 15 summarizes the ongoing studies by indication. One study was scheduled to complete in summer 2020{, #2400}; the rest are scheduled to complete in 2021,[104-106,115,116] 2022,[107-111,114] or 2023.[112-114] The head-to-head study is expected to be completed in late 2022.[111,118]

Table 15. Ongoing Studies of Biologic Drugs for Asthma or Chronic Spontaneous Urticaria

NCT Number Trial Name	Drug Comparator	Phase	Estimated Sample Size Duration	Primary Study Outcome	Expected Study Completion Date
Asthma					
NCT02948959[102] VOYAGE	Dupilumab Placebo	3	N = 407 (actual) 52 weeks	Annualized rate of severe exacerbation events	August 2020 (actual)
NCT03292588[104] MUPPITS-2	Mepolizumab Placebo	2	N = 320 56 weeks	Number of asthma exacerbations	March 2021
NCT03884842[105]	Dupilumab Placebo	3	N = 32 16 weeks	Proportion of patients that achieve at least 1 doubling dose improvement in PC20 methacholine or a 50% reduction in FEV_1 reversibility after bronchodilator	June 2021
NTR7496[106] RESSAPEA	Reslizumab Placebo	4	N = 33 12 weeks	Change from baseline in regional image-based hyperinflation	July 2021
NCT04203797[107]	Dupilumab Placebo	4	N = 140 12 weeks	Change in constant work rate exercise endurance time	April 2022
NCT04400318[108] VESTIGE	Dupilumab Placebo	4	N = 153 36 weeks	Change in pre-bronchodilator FEV_1	June 2022
NCT03782532[109]	Dupilumab Placebo	3	N = 486 36 weeks	Change in pre-bronchodilator FEV_1	September 2022
NCT03562195[110]	Mepolizumab Placebo	3	N = 300 52 weeks	Number of clinically significant exacerbations of asthma	November 2022

NCT Number Trial Name	Drug Comparator	Phase	Estimated Sample Size Duration	Primary Study Outcome	Expected Study Completion Date
NCT03476109[111] PREDICTUMAB	Omalizumab Mepolizumab	4	N = 100 22 months	Efficacy on asthma symptoms, lung function, severe exacerbation	December 2022
NCT04195958[112] EDURO	Omalizumab Placebo	4	N = 150 28 weeks	Change in endurance time (minutes) during cardiopulmonary exercise testing at a constant work rate	January 2023
NCT03953300[117] CHINOOK	Benralizumab Placebo	4	N = 81 52 weeks	Change in eosinophil numbers expressed as number/mm^2 in submucosa as measured by major basic protein staining in endobronchial biopsies	September 2023
NCT03694158[114] I-DAG	Dupilumab Placebo	4	N = 126 48 weeks	Rate of asthma exacerbation	October 2023
CSU					
NCT03749135[115] DUPICSU	Dupilumab Placebo	2	N = 72 16 weeks	UAS7	May 2021
NCT04180488[116] CUPID	Dupilumab Placebo	3	N = 184 24 weeks	Change from baseline in ISS7	November 2021

Abbreviations. CSU: chronic spontaneous urticaria; FEV_1: forced expiratory volume in 1 second; IgE: immunoglobin E; ISS7: Itch Severity Score over 7 days; NCT: US National Clinical Trial; PC20: provocative concentration of methacholine resulting in 20% drop in FEV_1; UAS7: Urticaria Activity Score over 7 days.

Discussion

Overall, this update includes 43 RCTs focused on biologic drugs to treat asthma and 10 RCTs of omalizumab to treat CSU; no RCTs evaluated head-to-head comparisons of the included drugs. A high-level summary of findings is provided in Table 16. We rated 44 RCTs as having moderate risk of bias because of extensive manufacturer involvement in study design, execution, or reporting; the other 9 RCTs were rated as high risk of bias for various methodological issues. All studies evaluated biologics as add-on therapy. For asthma, this included evaluation as add-on therapy to existing standard asthma management, which depending on severity of the enrolled population could have included ICS, LABA, LTRAs, other asthma controllers, and SABA for rescue therapy. In addition, some studies evaluated biologics as add-on therapy for asthma during steroid-tapering cointerventions, typically occurring after 4 to 12 weeks of a stable steroid (ICS or oral) dose. For CSU, biologics were evaluated as add-on therapy to existing CSU management, which depending on severity of the enrolled population could have included H_1- or H_2-antihistamines, LTRAs, and H_1-antihistamines for rescue therapy.

Table 16. Summary of Biologics as Add-on Therapy for Asthma and CSU Compared to Placebo

Drug Indication	Improved Symptom Control (QoE)	Improved Quality of Life (QoE)	Reduced exacerbations Definition (QoE)	Reduced Use of Steroid (asthma) or Antiurticarial Medication (CSU) (QoE)	Overall AEs and SAEs (QoE)
Benralizumab Asthma	*Favors drug* (moderate to high)	*Favors drug* (low)	*Favors drug* Study defined (moderate) Requiring ED or hospital visit (low)	*Favors drug* (moderate)	*Favors drug* AE (high) SAE (moderate)
Dupilumab Asthma	*Favors drug* (moderate)	*Favors drug* (moderate)	*Favors drug* Study defined *or* requiring ED or hospital visit (low to moderate[a])	*Favors drug* (moderate)	*No difference* AE (high) SAE (moderate)
Mepolizumab Asthma	*Favors drug* (moderate)	NR	*Favors drug* Study defined (moderate)	*Favors drug* (low to moderate[a])	*Favors drug* AE (high) SAE (moderate)
Omalizumab Asthma	*Favors drug* (very low to high[a])	*Favors drug*[b] (low to high[a])	*Favors drug* Study defined (high) Requiring hospitalization (moderate)	*Favors drug* (high[c])	*No difference* AE (high) *Favors drug* SAE(moderate)
Omalizumab CSU	*Favors drug* (moderate to high [a])	*Favors drug* (high)	*NA*	*Favors drug* (very low QoE)	*No difference* AE (high) SAE (moderate)

Drug Indication	Improved Symptom Control (QoE)	Improved Quality of Life (QoE)	Reduced exacerbations Definition (QoE)	Reduced Use of Steroid (asthma) or Antiurticarial Medication (CSU) (QoE)	Overall AEs and SAEs (QoE)
Reslizumab Asthma	*Favors drug* (moderate to high [a])	*Favors drug* (moderate to high[a])	*Favors drug* Study-defined (high) Requiring ED or hospital visit (low)	*No difference* (low QoE)	*No difference* AE (high) SAE (moderate)

Notes. [a] Varies by outcome. [b] One exception. [c] For steroid sparing trials, low for add-on efficacy trials. See GRADE summary tables in each drug section for details.
Abbreviations. AE: adverse event; CSU: chronic spontaneous urticaria; ED: emergency department; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; NR: not reported; QoE: GRADE quality of evidence; SAE: serious adverse event.

We did not conduct formal subgroup analyses, but noted the following patterns related to effectiveness. Across the 3 asthma trials (all evaluating omalizumab) that enrolled persons with nonallergic asthma phenotypes, no difference in effectiveness across a variety of outcomes was observed.[32,33,38] For asthma, the evidence suggests these agents are more effective than placebo among children, adolescents, and adults. For CSU, the evidence suggests these agents are more effective than placebo among adolescents and adults; no CSU trials included participants younger than 12 years.

The evidence we included in this review has several limitations. We did not identify any head-to-head trials. Nearly all studies were industry-sponsored and involved extensive manufacturer involvement in study design, execution, and reporting. Although the extent to which manufacturer involvement influenced study execution or reporting is not definitively known for this body of evidence, findings from a Cochrane systematic review suggested that industry sponsorship is associated with more favorable results than sponsorship by other sources.[119] RCT data on effectiveness and safety beyond 1 year is not available. Most of the RCTs evaluating the effectiveness of add-on therapy generally enrolled or primarily reported outcomes for the participants with the allergic asthma phenotype; thus, the applicability of findings to other asthma phenotypes is not certain. Further, although many statistically significant differences across studies and outcomes were observed, the average magnitude of some differences may not be so clinically relevant. Determining characteristics of persons most likely to receive a meaningful clinical benefit is an area for future research. Finally, most studies included a run-in phase over which baseline asthma or CSU symptoms were recorded. In several studies, this run-in phase was used to optimize standard management with existing controller medications. In other studies, no dose optimization during the run-in phase occurred. Thus, treatment effects may have differed across studies because of differences in whether background therapy was optimized before active study treatment.

This review has several limitations. We included only studies published in English for currently FDA-approved biologics. We did not include data presented in press releases or conference abstracts; thus, this report might not reflect all known data on the efficacy or safety of biologics

for these conditions. We stratified our synthesis of effectiveness outcomes by trial design, specifically distinguishing between trials evaluating the add-on efficacy of biologics and trials evaluating the add-on efficacy during other controller medication-tapering cointerventions, ICS, or oral steroid tapering in most cases. Studies with such cointerventions typically involved longer run-in phases and optimization of standard controller regimens during the run-in, which could lead to heterogeneity of treatment effect. Though we presented findings from these 2 trial types separately, we conclude that the magnitude and direction of effect on most outcomes appear similar between the 2 types of trials.

We highlight 2 recent network meta-analyses (NMAs). We did not undertake a formal quality assessment of the NMAs but simply report the key results as additional contextual information. NMAs have some limitations, including that only comparisons available within the network can be evaluated; assumptions about the studies have to be met for findings to be valid, including similarity of study, population; and intervention characteristics among included studies. Ramonell et al. published an NMA in 2020 that compared the efficacy of benralizumab, dupilumab, mepolizumab, and reslizumab for prevention of acute asthma exacerbations among patients with severe eosinophilic asthma (defined as eosinophil count ≥ 250 per μL).[120] This NMA included a search through July 2019 that identified 9 placebo-controlled RCTs (2 on benralizumab, 4 on dupilumab, 2 on mepolizumab, and 1 on reslizumab). The analysis reported that all drugs were more effective than placebo at preventing asthma exacerbations and identified no statistically significant differences among these drugs in indirect head-to-head comparisons.[120] Edris et al. published an NMA in 2019 that also compared the efficacy of benralizumab, dupilumab, mepolizumab, and reslizumab, in addition to several other biologics that were not included in our review because they are not FDA-approved, for exacerbation rates among persons with eosinophilic asthma. This NMA included a search through 2018, identified 30 placebo-controlled RCTs, and reported similar findings of superiority of all drugs compared to placebo and no differences among drugs in indirect comparisons.[121]

When reviewing this update report, state Medicaid administrators might consider using the findings and conclusions as a tool in their evidence-based decision-making process, such as clarifying place-in-therapy for biologic agents, criteria related to phenotyping before use, and in-office vs. home self-administration. Currently, the body of direct evidence is limited to placebo-controlled trials, and the indirect evidence is inconclusive with respect to comparative effectiveness and safety, which could hinder determining program placement.

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Appendix A. Clinical Evidence Methods

Search Strategy

We searched Drug Effectiveness Review Project (DERP) clinical evidence sources to identify randomized controlled trials (RCTs), systematic reviews (with and without meta-analyses), and technology assessments using the terms *omalizumab*, *mepolizumab*, *reslizumab*, *benralizumab*, *dupilumab*, *asthma*, *urticaria*, and terms for drug trade names. Systematic reviews and technology assessments were used for reference list searching and not as evidence sources. We limited searches of evidence sources to citations published after August 1, 2017 (the search date in the previous report).

We searched the following DERP evidence sources and grey literature:

- Cochrane Library (Wiley Interscience)
- Ovid MEDLINE
- Google
- Google Scholar
- Agency for Healthcare Research and Quality EPC Reports and Effective Healthcare Program
- Canadian Agency for Drugs and Technologies in Health
- Institute for Clinical and Economic Review
- National Institute for Health and Care Excellence

Ovid MEDLINE Search Strategy

1	(Dupilumab* or Dupixent or REGN668 or SAR231893 or REGN-668 or SAR-231893).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2	(Benralizumab* or Fasenra or BIW8405 or MEDI563 or BIW-8405 or MEDI-563).mp.
3	(Reslizumab* or Cinqair or CEP38072 or CEP-38072 or DCP835 or DCP-835 or SCH-55700 or SCH55700).mp.
4	(Mepolizumab* or Nucala or SB240563 or SB-240563).mp.
5	Omalizumab/ or (Omalizumab* or Xolair).mp.
6	2 or 3 or 4 or 5
7	limit 6 to yr="2018 -Current"
8	1 or 7
9	exp Asthma/
10	exp Urticaria/
11	asthma*.ti,ab,kf.
12	urticaria*.ti,ab,kf.

13 or/9-12

14 8 and 13

15 limit 14 to "humans only (removes records about animals)"

16 english.lg.

17 15 and 16

Cochrane Library Search Strategy

#1 (Dupilumab* or Dupixent or REGN668 or SAR231893 or REGN-668 or SAR-231893):ti,ab,kw

#2 (Benralizumab* or Fasenra or BIW8405 or MEDI563 or BIW-8405 or MEDI-563):ti,ab,kw

#3 (Reslizumab* or Cinqair or CEP38072 or CEP-38072 or DCP835 or DCP-835 or SCH-55700 or SCH55700):ti,ab,kw

#4 (Mepolizumab* or Nucala or SB240563 or SB-240563):ti,ab,kw

#5 [mh "Omalizumab"] or (Omalizumab* or Xolair):ti,ab,kw

#6 6-#5

#7 #6 with Publication Year from 2017 to 2020, in Trials

#8 #6 with Cochrane Library publication date Between Jan 2017 and Jul 2020, in Cochrane Reviews, Cochrane Protocols

#9 #1 or #7 or #8

#10 [mh "Asthma"]

#11 [mh "Urticaria"]

#12 asthma*:ti,ab,kw

#13 urticaria*:ti,ab,kw

#14 122-#13

#15 #9 and #14

#16 conference abstract:pt or abstract:so

#17 #15 not #16

Ongoing Studies

We searched the following DERP sources for ongoing studies using the search terms *omalizumab*, *mepolizumab*, *reslizumab*, *benralizumab*, *dupilumab*, *asthma*, *urticaria*:

- ClinicalTrials.gov
- ISRCTN Registry

Inclusion Criteria

Population

- Adult or children with persistent or chronic asthma
- Adults or children with CSU

Interventions

- Dupilumab
- Benralizumab
- Reslizumab
- Mepolizumab
- Omalizumab

Comparators

- Anti-IL-4 or anti-IL-5 antibodies versus each other
- Placebo-controlled or usual care-controlled

Outcomes

Asthma

- Severe exacerbations requiring emergency department or hospital admission
- Symptom control
- Oral steroid use
- Quality of life assessed using validated scales
- All-cause emergency department or hospital admissions
- Mortality
- Adverse events (AE)
- Serious adverse events (SAE)

CSU

- Response (e.g., Urticaria Activity Score [UAS7] ≤ 6 or complete response [UAS7 = 0])
- Symptoms (e.g., itching)
- Quality of life assessed using validated scales
- Use of other antiurticaria medications
- AE
- SAE

Study Designs

- RCTs

Exclusion Criteria

We excluded studies if they were not published in English, not conducted in humans, not conducted in a country designated as *very high* using the United National Human Development Index, and conference abstracts.

Screening

Two experienced researchers independently screened all titles and abstracts of identified documents. In cases in which there was disagreement about eligibility, a third experienced researcher resolved the disagreement. This method was repeated for full-text review of documents that could not be excluded by title and abstract screening.

Data Abstraction

One experienced researcher abstracted and entered data from eligible studies in a standardized way using DistillerSR. A second experienced researcher reviewed all the data entered. We attempted to resolve discrepancies through discussion. When discussion did not resolve the issue, a third experienced researcher settled disagreements.

Participant Characteristics and Association with Outcomes

When discussing risk and protective factors or variables in statistical models in DERP research products, in almost all cases, we are referring to associations of participant characteristics with outcomes, and not causation of outcomes. This is important because participant characteristics, such as race and ethnicity, serve as proxy or surrogate measures for underlying etiological factors not measured or evaluated in analyses. Etiological factors that might cause differences in outcomes for subgroups of participants could include systemic racism or other forms of systemic discrimination, stress, poverty, housing instability, or epigenetics. For example, by describing any differences in outcomes by race and ethnic groups, we are noting observed associations; these associations are not caused by biological determinants of being Black, White, or Hispanic.

Risk of Bias Assessment

Risk of Bias of Included Studies

We assessed the risk of bias of the included RCTs using standard instruments developed and adapted by DERP that are modifications of instruments used by national and international standards for quality.[4,5] One experienced researcher independently rated the risk of bias of included studies. A second experienced researcher reviewed each assessment. Disagreement was managed by discussion.

Randomized Controlled Trials

Low-risk-of-bias randomized controlled trials include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Low-risk-of-bias randomized controlled trials also have low potential for bias from conflicts of interest and funding source(s). Moderate-risk-of-bias randomized controlled trials have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. High-risk-of-bias randomized controlled trials have clear flaws that could introduce significant bias.

Quality of Evidence Assessment

Overall Quality of Evidence

We assigned each outcome a summary judgment for the overall quality of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[6,7] Two independent experienced researchers assigned ratings, with disagreements resolved by a third rater. The GRADE system defines the overall quality of a body of evidence for an outcome in the following manner:

- **High:** Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are randomized controlled trials with few or no limitations, and the estimate of effect is likely stable.
- **Moderate:** Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are randomized controlled trials with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low:** Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are randomized controlled trials with serious limitations or nonrandomized studies without special strengths.
- **Very low:** Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable:** Researchers did not identify any eligible articles.

Appendix B. Full Evidence Tables

Benralizumab Asthma Studies

Table B1. Benralizumab Asthma Study Characteristics

Bleecker et al., 2016[46]; SIROCCO; NCT01928771				
Study Characteristics	Phase 3 RCT (effectiveness of add-on therapy vs. placebo; 374 clinical research centers in 17 countries: Australia, Brazil, Bulgaria, Czech Republic, France, Italy, Mexico, Peru, Poland, Russia, South Africa, South Korea, Spain, Turkey, the United Kingdom, the US, and Vietnam *Years conducted:* 2013-2015 *Sponsor(s):* AstraZeneca, Kyowa Hakko Kirin *Risk of bias:* Moderate			
Interventions (N randomized)	Benralizumab 30 mg SC every 8 wk for 48 wk (n = 398)	Benralizumab 30 mg SC every 4 wk for 48 wk (n = 399)	Placebo (n = 407)	
	Cointervention(s): Patients continued receiving their background asthma controller treatments at stable dosage during the study; SABAs were allowed as rescue drugs.			
Population	*Inclusion Criteria:* Aged 12 to 75; weight ≥ 40 kg; asthma needing treatment with medium dosage (only for aged 12 to 17) or high-dosage ICS plus LABA for at least 1 yr before enrollment; 2 or more documented asthma exacerbations needing systemic corticosteroids or temporary increase in usual maintenance dosage of oral corticosteroids within 1 yr before enrollment; documented treatment with ICS plus LABA with or without oral corticosteroids and additional asthma controllers for at least 3 months before enrollment; prebronchodilator FEV_1 of less than 80% predicted (< 90% for aged 12 to 17; documented post-bronchodilator reversibility of at least 12% and at least 200 mL in FEV_1 within 12 months before enrollment; ACQ-6 at least 1.5. *Exclusion Criteria:* History of anaphylaxis with any biologic drug; clinically important pulmonary disease other than asthma; helminthic parasitic infection within 24 weeks before enrollment that was not treated or did not respond to standard-of-care treatment			
	Mean age (SD) Placebo: 49 (15) Benralizumab q4w: 50 (13) Benralizumab q8w: 48 (15) N (%) female 796 (66)	*Race/ethnicity* 874 (72) white 46 (4) black or African American 154 (13) Asian 130 (11) other 230 (19) Hispanic or Latino 974 (81) not Hispanic or Latino	*Asthma duration/severity* Median (range) Placebo: 14 (1 to 72) Benralizumab q4w: 15 (1 to 70) Benralizumab q8w: 14 (1 to 67) Mean (SD) ACQ-6 Placebo: 2.87 (0.94) Benralizumab q4w: 2.77 (0.96) Benralizumab q8w: 2.80 (0.88)	*Comorbidities* Allergic rhinitis: 646 (54) Nasal polyposis: 237 (20) Eosinophilic asthma: 809 (67)

			Mean (SD) number of of exacerbations in past 12 months Placebo: 3.0 (1.8) Benralizumab q4w: 2.9 (1.8) Benralizumab q8w: 2.8 (1.5)	
Ferguson et al., 2017[50]; BISE; NCT02322775				
Study Characteristics	Phase 3 RCT (effectiveness of add-on therapy vs. placebo); 52 clinical research centers in 6 countries (Canada, Germany, Hungary, Poland, Slovakia, US) *Years conducted:* 2015 *Sponsor(s):* AstraZeneca *Risk of bias:* Moderate			
Interventions (N randomized)	Benralizumab 30 mg SC every 4 weeks for 12 weeks (n = 106)		Placebo (n = 105)	
	Cointervention(s): All existing ICS treatment was converted to either 180-µg or 200-µg budesonide DPI twice daily on enrollment on the basis of the approved dosage in the country of investigation; LABAs were withdrawn upon enrollment; rescue use of SABA; asthma exacerbations were treated with oral or other systemic corticosteroids according to standard practice.			
Population	*Inclusion Criteria:* Aged 18 to 75; weight ≥ 40 kg; evidence of asthma on the basis of a PBD reversibility FEV_1 of at least 12%; receiving low- to medium-dosage ICS (ie, 100–500 µg fluticasone dry powder formulation or equivalent total daily dosage) or low-dosage ICS plus LABA fixed-combination therapy, with or without controller medication; morning PBD FEV_1 50% to 90%; 1 or more symptoms within 7 days before randomization: daytime or nighttime asthma symptom score of 1 or more for 2 or more days, rescue short-acting β2 agonist use for 2 or more days, or 1 or more nighttime awakenings due to asthma *Exclusion Criteria:* Clinically important pulmonary disease other than asthma; history of anaphylaxis with any biological agent; helminth infection diagnosed within 24 weeks before			
	Mean age (SD) Placebo: 51 (13) Benralizumab: 48 (14) N (%) female 129 (61)	*Race/ethnicity* White: 197 (93) Black or African American: 11 (5) Asian: 1 (1) Other: 2 (1) Hispanic or Latino: 9 (4) Not Hispanic or Latino: 202 (96)	*Asthma duration/severity* Median (range) years Placebo: 13.0 (0 to 69) Benralizumab: 15 (0 to 66) Mean (SD) ACQ-6 score Placebo: 2.09 (0.90) Benralizumab: 2.12 (0.84)	*Comorbidities* N (%) allergic rhinitis: 135 (64) N (%) baseline blood eosinophil count ≥300 cells per µL: 61 (29)
FitzGerald et al., 2016[45]; CALIMA; NCT01914757				
Study Characteristics	Phase 3 RCT (effectiveness of add-on therapy vs. placebo); 303 clinical research centers in 11 countries: US, Canada, Germany, Sweden, Poland, Romania, Ukraine, Argentina, Chile, Japan, Philippines			

	Years conducted: 2013-2015 *Sponsor(s):* AstraZeneca, Kyowa Hakko Kirin *Risk of bias:* Moderate			
Interventions (N randomized)	Benralizumab 30 mg SC every 4 weeks for 52 weeks (n = 425)	Benralizumab 30 mg SC every 8 weeks for 48 weeks (n = 441)	Placebo (n = 440)	
	Cointervention(s): background asthma controller medications at stable dosage; short-acting beta agonists as rescue medication			
Population	*Inclusion Criteria:* Aged 12 to 75; ≥ 40 kg; history of physician-diagnosed asthma requiring treatment with medium- to high-dosage ICS (> 250 µg [medium] or ≥ 500 µg [high] fluticasone dry powder formulation or equivalent total daily dosage) plus LABA, for ≥ 12 months before enrollment; ≥ 2 asthma exacerbations in 12 months before enrollment requiring use of a systemic corticosteroid or temporary increase in patient's usual maintenance dosage of oral corticosteroids; treatment with inhaled corticosteroids (≥ 500 µg/day fluticasone propionate dry powder formulation or equivalent total daily dosage) plus LABA for ≥ 3 months before enrollment, with or without oral corticosteroids and additional asthma controllers; pre-bronchodilator FEV_1 ≤ 80% predicted (< 90% predicted for patients aged 12 to 17) at screening; ACQ-6 score ≥ 1.5 at enrollment; post-bronchodilator reversibility in FEV_1 of ≥ 12% and ≥ 200 mL in FEV_1 within 12 months before enrollment *Exclusion Criteria:* Clinically important pulmonary disease other than asthma or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil; any disorder or major physical impairment that is not stable; acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days; any clinically significant abnormal findings during screening/run-in period			
	Mean age (SD) Placebo: 49 (15) Benralizumab q4w: 50 (14) Benralizumab q8w: 49 (14) N (%) female 807 (62)	*Race/ethnicity* White: 1,101 (84) Black or African American: 39 (3) Asian: 163 (12) Other: 3 (1) Hispanic or Latino: 300 (23) Not Hispanic or Latino: 1,006 (77)	*Asthma duration/severity* Time (range) since asthma diagnosis, years Placebo: 16 (1 to 70) Benralizumab q4w: 16 (1 to 69) Benralizumab q8w: 17 (1 to 65) Mean (SD) ACQ-6 score Placebo: 2.69 (0.92) Benralizumab q4w: 2.69 (0.91) Benralizumab q8w: 2.75 (0.93)	*Comorbidities* N (%) with allergic rhinitis: 717 (55) N (%) with nasal polyps: 197 (15) N (%) with allergic asthma: 798 (56%)
Harrison et al., 2020[60]; ANDHI; NCT03170271				
Study Characteristics	Phase 3 RCT (effectiveness of add-on therapy vs. placebo); 321 clinical sites in 14 countries: Belgium, Canada, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, UK, USA *Years conducted:* 2017-2020 *Sponsor(s):* AstraZeneca *Risk of bias:* Moderate			

Interventions (N randomized)	Benralizumab 30 mg SC every 4 weeks for first 3 doses then every 8 weeks for 52 weeks (n = 25)		Placebo (n = 26)	
	Cointervention(s): Patients continued receiving their background asthma controller treatments at stable dosage during the study			
Population	*Inclusion Criteria:* Age 18 to 75; weight ≥40 kg; history of physician-diagnosed asthma; ≥2 exacerbations in 12 months before study; treatment with high-dose ICS plus another asthma controller for 3 months before enrollment; prebronchodilator FEV1 <80% predicted; eosinophils ≥300 cells/µL (or ≥150 with one of the following: maintenance oral corticosteroid use at study entry, history of nasal polyposis, ≥3 exacerbations in past year; FVC <65% predicted, ≥18 years at asthma diagnosis); ACQ-6 of ≥1.5 at screening and randomization; postbronchodilator FEV1 ≥12% or PEF variability of ≥10%. *Exclusion Criteria:* Clinically important pulmonary disease; acute respiratory infection within 30 days; helminth parasitic infection within 24 weeks; history of alcohol or drug abuse in past 12 months; immunodeficiency disorder; current or former smokers with history of ≥10 pack years; previous benralizumab treatment; treatment with other investigational medication within 5 half-lives; receipt of immunoglobin or blood products within 30 days; receipt of live attenuated vaccine within 30 days; enrollment in another interventional study.			
	Mean age (SD) Placebo: 53.3 (12.5) Benralizumab: 52.5 (12.7) N (%) Female 399 (61)	*Race/ethnicity* N (%) White: 482 (86) N (%) Black: 53 (8) N (%) Asian: 18 (3) N (%) Native Hawaiian or other Pacific Islander: 1 (<1) N (%) Hispanic or Latino: 74 (11) N (%) Other: 7 (1) N (%) Missing: 95 (14)	*Asthma duration/severity* Duration: NR Mean (SD) ACQ-6 at baseline Placebo: 3.07 (0.97) Benralizumab: 3.04 (0.87) Rate of exacerbations in past 12 months: Placebo: 3.1 Benralizumab: 3.2	*Comorbidities* Nasal polyposis: 228 (35) Eosinophilic asthma: 656 (100)
Nair et al., 2017[48]; ZONDA; NCT02075255				
Study Characteristics	Phase 3 steroid-sparing RCT; 89 centers globally; Argentina, Bulgaria, Canada, Chile, France, Germany, South Korea, Poland, Spain, Turkey, Ukraine, US *Years conducted:* 2014-2016 *Sponsor(s):* AstraZeneca *Risk of bias:* Moderate			
Interventions (N randomized)	Benralizumab 30 mg SC q4w until week 28 (n = 72)	Benralizumab 30 mg SC q4w for first 3 doses and then q8w until week 28 (n = 73)	Placebo (n = 75)	
	Cointervention(s): All the patients had been treated continuously with oral glucocorticoids for 6 months or more before enrollment and were receiving oral prednisone or prednisolone at trial entry. Patients who were receiving any other oral glucocorticoid at enrollment were switched to an equivalent dose of oral prednisone or prednisolone. During the run-in phase, the oral glucocorticoid dose was adjusted to the minimum dose that could be received without loss of asthma control.			

	No additional asthma-controller medication was initiated unless it was used for the treatment of exacerbations (medication was provided by the trial investigators).			
Population	*Inclusion Criteria:* Aged 18 to 75 years with a blood eosinophil count of 150 cells or more per cubic millimeter and had asthma that had been treated with medium-dose to high-dose ICS and LABA therapy for at least 12 months before enrollment and treated with high-dose ICS and LABA therapy for at least 6 months before enrollment. Patients had been receiving oral glucocorticoid therapy for at least 6 continuous months directly before enrollment. *Exclusion Criteria:* Clinically important pulmonary disease other than asthma or had ever been diagnosed with pulmonary or systemic disease (other than asthma) that was associated with elevated peripheral eosinophil counts; any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that was not stable in the opinion of the investigator; known history of allergy or reaction to the study drugs; history of anaphylaxis to any biologic therapy			
	Mean age (SD) Placebo: 49.9 (11.7) Benralizumab q4w: 50.2 (12.0) Benralizumab q8w: 52.9 (10.1) N (%) female Placebo: 48 (64) Benralizumab q4w: 40 (56) Benralizumab q8w: 47 (64)	*Race/ethnicity* N (%) white Placebo: 70 (93) Benralizumab q4w: 69 (96) Benralizumab q8w: 66 (90) N (%) black or African American Placebo: 1 (1) Benralizumab q4w: 0 (0) Benralizumab q8w: 1 (1) N (%) Asian Placebo: 4 (5) Benralizumab q4w: 3 (4) Benralizumab q8w: 5 (7) N (%) other Placebo: 0 (0) Benralizumab q4w: 0 (0) Benralizumab q8w: 1 (1)	*Asthma duration/severity* Median time (range) since asthma diagnosis, years Placebo: 10.5 (1.1 to 54.5) Benralizumab q4w: 13.3 (1.2 to 52.3) Benralizumab q8w: 16.3 (1.3 to 53.0) Mean (SD) ACQ-6 score Placebo: 2.7 (1.0) Benralizumab q4w: 2.6 (1.1) Benralizumab q8w: 2.4 (1.2) Mean (SD) number of exacerbations in previous year Placebo: 2.5 (1.8) Benralizumab q4w: 2.8 (2.0) Benralizumab q8w: 3.1 (2.8)	*Comorbidities* N (%) with allergic rhinitis Placebo: 30 (40) Benralizumab q4w: 42 (58) Benralizumab q8w: 40 (55) N (%) with atopy Placebo: 37 (49) Benralizumab q4w: 29 (40) Benralizumab q8w: 29 (40) N (%) with nasal polyps Placebo: 28 (37) Benralizumab q4w: 22 (31) Benralizumab q8w: 20 (27)
Panettieri et al., 2020[9]; SOLANA; NCT02869438				
Study Characteristics	Phase 3 RCT (effectiveness of add-on therapy vs. placebo; 49 centers in 6 countries (Chile, Germany, Philippines, South Korea, US) *Years conducted:* 2016-2018 *Sponsor(s):* AstraZeneca *Risk of bias:* Moderate			

Interventions (N randomized)	Benralizumab 30 mg SC every 4 weeks for 12 weeks (n = 118)			Placebo (n = 115)
	Cointervention(s): NR			
Population	*Inclusion Criteria:* Aged 18 to 75, weight ≥ 40 kg; physician-diagnosed severe asthma requiring treatment with inhaled corticosteroids/long-acting beta 2 agonists for ≥ 30 days before enrollment; peripheral blood eosinophil counts ≥300 cells/µl; at least 2 documented asthma exacerbations requiring systemic corticosteroid therapy or a temporary increase in maintenance oral corticosteroid dosage within 12 months; preBD FEV_1 < 80%; postBD FEV_1 reversibility ≥ 12% and ≥ 200 mL; ACQ-6 score ≥ 1.5 *Exclusion Criteria:* Clinically important pulmonary disease other than asthma; life-threatening asthma (within 12 months) upper or lower respiratory tract infections requiring antibiotics or antiviral meds within 30 days; ≥20% change in mean PBD FEV_1 at randomization from the mean of PBD FEV_1 values recorded at screening.			
	Mean age (SD) 51.4 (NR) N (%) female 157 (67%)	*Race/ethnicity* 136 (58%) white 7 (3%) black 79 (34%) Asian 11 (5%) other 62 (27%) Hispanic or Latino 171 (73%) not Hispanic or Latino	*Asthma duration/severity* Duration: NR Mean (SD) ACQ-6 score Placebo: 2.61 (0.89) Benralizumab: 2.65 (0.88) Mean (SD) number of exacerbations in the last 12 months: Placebo: 2.4 (0.83) Benralizumab: 2.5 (1.27) Mean (SD) number of exacerbations requiring hospitalization in past 12 months Placebo: 0.1 (0.37) Benralizumab: 0.1 (3.5)	*Comorbidities* Eosinophilic asthma: 233 (100%)
Park et al., 2016[39]; NCT01412736				
Study Characteristics	Phase 2a RCT (effectiveness of add-on therapy vs. placebo); 32 sites in South Korea and Japan *Years conducted:* 2011-2013 *Sponsor(s):* Kyowa Hakko Kirin Co. Ltd. *Risk of bias:* Moderate			
Interventions (N randomized)	Benralizumab 20 mg SC every 4 weeks for first 3 doses then every 8 weeks for 52 weeks (n = 25)			Placebo (n = 26)
	Cointervention(s): Subjects maintained the same dose of ICS/LABA from the start of the screening period until week 52			

Population	*Inclusion Criteria:* Eosinophilic asthma defined as ELEN index positivity with ≥ 2% sputum eosinophils or FeNO ≥ 50 ppb; aged 20 to 75 years with asthma treated with medium- to high-dose ICS/LABA combination therapy for at least 1 year; documented history of 2 to 6 exacerbations requiring treatment with systemic corticosteroids (additional treatment with > 15 mg/day prednisone, or other medications at a similar dose, for at least 3 consecutive days) in the past year; had a morning prebronchodilator FEV_1 ≥ 40% but < 90% predicted, and ACQ-6 score ≥ 1.5 on at least 2 occasions during screening; demonstrate postbronchodilator FEV_1 reversibility ≥ 12% and ≥ 200 mL, or a positive response to methacholine challenge (PC 20 ≤ 8 mg/mL) *Exclusion Criteria:* Current smoker or a history of smoking			
	Mean age (SD) Placebo: 50.8 (11.8) Benralizumab 20 mg: 55.6 (8.9) N (%) female Placebo: 17 (65.4) Benralizumab 20 mg: 19 (76.0)	*Race/ethnicity* Placebo N (%) Japan: 11 (42.3) N (%) South Korea: 15 (57.7) Benralizumab 20 mg N (%) Japan: 11 (44.0) N (%) South Korea: 14 (56.0)	*Asthma duration/severity* Placebo Asthma onset, N (%) Childhood: 7 (26.9) Asthma onset, N (%) Later: 19 (73.1) Benralizumab 20 mg Asthma onset, N (%) Childhood: 1 (4.0) Asthma onset, N (%) Later: 24 (96.0) Placebo Mean (SD) ACQ-6 score Placebo: 1.6 (0.6) Benralizumab: 1.9 (0.7) Mean (SD) number of asthma exacerbations in past year Placebo: 2.6 (1.0) Benralizumab: 2.6 (1.1)	*Comorbidities* NR

Abbreviations. ACQ-6: Asthma Control Questionnaire; DPI: dry-powder inhaler; ELEN: composite index that combines eosinophil/lymphocyte ratio and eosinophil/neutrophil ratio; FeNo: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; LABA: long-acting beta-agonist; NCT: US National Clinical Trial; NR: not reported; PBD: pre-bronchodilator; post-BD: post-bronchodilator; ppb: parts per billion; q4w: every 4 weeks; q8w: every 8 weeks; RCT: randomized controlled trial; SABA: short-acting beta-agonists; SC: subcutaneous; SD: standard deviation; wk: week; yr: year.

Table B2. Effectiveness Outcomes From RCTs of Benralizumab for Asthma

Outcome	Group (n)	Result
Bleecker et al., 2016[46]; SIROCCO; NCT01928771		
Annualized rate of exacerbations (48 wk)	Placebo (n = 267) (subgroup with ≥ 300 eosinophils/µL)	Mean (95% CI) rate: 1.33 (1.12 to 1.58)
	Placebo (n = 140) (subgroup with < 300 eosinophils/µL)	Mean (95% CI) rate: 1.21 (0.96 to 1.52)
	Benralizumab every 8 wk (n = 267) (subgroup with ≥ 300 eosinophils/µL)	Mean (95% CI) rate: 0.65 (0.53 to 0.80) IRR (95% CI): 0.49 (0.37 to 0.64); *P* < .0001
	Benralizumab every 8 wk (n = 131) (subgroup with < 300 eosinophils/µL)	Mean (95% CI) rate: 1.00 (0.78 to 1.28) IRR (95% CI): 0.83 (0.59 to 1.16); *P* = .27
	Benralizumab every 4 wk (n = 275) (subgroup with ≥ 300 eosinophils/µL)	Mean (95% CI) rate: 0.73 (0.60 to 0.89) IRR (95% CI): 0.55 (0.42 to 0.71); *P* < .0001
	Benralizumab every 4 wk (n = 124) (subgroup with < 300 eosinophils/µL)	Mean (95% CI) rate: 0.85 (0.65 to 1.11) IRR (95% CI): 0.70 (0.5 to 1.0); *P* = .047
Time to first asthma exacerbation	Placebo (n = 407) Benralizumab every 8 weeks (n = 398) Benralizumab every 4 weeks (n = 399)	Time to first asthma exacerbation (95% CI) Benralizaumab q8w: HR 0.60 (95% CI, 0.46 to 0.78); *P* = .0002 compared to placebo Benralizaumab q4w: HR 0.63 (95% CI, 0.49 to 0.82); *P* = .0005 compared to placebo
Exacerbations requrining ED or hospital (48 wk)	Placebo (n = 267) (subgroup with ≥ 300 eosinophils/µL)	Events of total N (%): 37 of 267 (14%)
	Benralizumab every 8 wk (n = 267) (subgroup with ≥ 300 eosinophils/µL)	Events of total N (%): 18 of 267 (7%) Calculated RR (95% CI): 0.49 (0.28 to 0.83)
	Benralizumab every 4 wk (n = 275) (subgroup with ≥ 300 eosinophils/µL)	Events of total N (%): 28 of 275 (10%) Calculated RR (95% CI): 0.73 (0.46 to 1.17)
Rate of exacerbations requiring ED Visits or hospitalization (48 wk)	Placebo (n = 267) (subgroup with ≥ 300 eosinophils/µL)	Mean (95% CI) rate: 0.18 (0.13 to 0.25)
	Benralizumab every 8 wk (n = 275) (subgroup with ≥ 300 eosinophils/µL)	Mean (95% CI) rate: 0.06 (0.04 to 0.11) IRR (95% CI): 0.37 (0.20 to 0.67); *P* = .001
	Benralizumab every 4 wk (n = 267) (subgroup with ≥ 300 eosinophils/µL)	Mean (95% CI) rate: 0.11 (0.07 to 0.16) IRR (95% CI): 0.61 (0.37 to 1.01); *P* = .053
ACQ mean change from baseline (48 wk)	Placebo (n = 267) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: -1.17 (NR)
	Placebo (n = 140) (subgroup with < 300 eosinophils/µL)	Mean (SD) change from baseline: -0.89 (NR)
	Benralizumab every 8 wk (n = 267) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: -1.46 (NR) Difference from placebo (95% CI): -0.29 (-0.48 to -0.10); *P* = .003
	Benralizumab every 8 wk (n = 131) (subgroup with < 300 eosinophils/ µL)	Mean (SD) change from baseline: -1.11 (NR) Difference from placebo (95% CI): -0.22 (-0.48 to 0.05); *P* = .11
	Benralizumab every 4 wk (n = 275) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: -1.32 (NR) Difference from placebo (95% CI): -0.15 (-0.34 to 0.04); *P* = .11

Outcome	Group (n)	Result
	Benralizumab every 4 wk (n = 124) (subgroup with < 300 eosinophils/ µL)	Mean (SD) change from baseline: -0.89 (NR) Difference from placebo (95% CI): 0 (-0.27 to 0.27); *P* = .99
Daily asthma symptom score mean change from baseline (48 wk)	Placebo (n = 267) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: -1.04 (NR)
	Placebo (n = 140) (subgroup with < 300 eosinophils/ µL)	Mean (SD) change from baseline: -0.77 (NR)
	Benralizumab every 8 wk (n = 267) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: -1.3 (NR) Difference from placebo (95% CI): -0.25 (-0.45 to -0.05); *P* = .01
	Benralizumab every 8 wk (n = 131) (subgroup with < 300 eosinophils/ µL)	Mean (SD) change from baseline: -1.06 (NR) Difference from placebo (95% CI): -0.29 (-0.57 to -0.01); *P* = .04
	Benralizumab every 4 wk (n = 275) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: -1.12 (NR) Difference from placebo (95% CI): -.08 (-0.27 to 0.12); *P* = .44
	Benralizumab every 4 wk (n = 124) (subgroup with < 300 eosinophils/ µL)	Mean (SD) change from baseline: -0.97 (NR) Difference from placebo (95% CI): -0.20 (-0.48 to 0.08); *P* = .17
AQLQ mean change from baseline (48 wk)	Placebo (n = 267) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: 1.26 (NR)
	Benralizumab every 8 wk (n = 267) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: 1.56 (NR) Difference from placebo (95% CI): 0.30 (0.10 to 0.50); *P* = .004
	Benralizumab every 4 wk (n = 275) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: 1.44 (NR) Difference from placebo (95% CI): 0.18 (-0.02 to 0.37); *P* = .08
Ferguson et al., 2017[50]; BISE; NCT02322775		
Exacerbations (12 wk)	Placebo (n = 105)	Events of total N (%): 2 of 105 (2%)
	Benralizumab every 4 wk (n = 106)	Events of total N (%): 1 of 106 (1%) Calculated RR (95% CI): 0.50 (0.05 to 5.38)
Exacerbations requiring ED or hospital (12 wk)	Placebo (n = 105)	Events of total N (%): 0 of 105 (0%)
	Benralizumab every 4 wk (n = 106)	Events of total N (%): 0 of 106 (0%)
ACQ mean change from baseline (12 wk)	Placebo (n = 105)	Mean (SD) change from baseline: -0.55 (NR)
	Benralizumab every 4 wk (n = 106)	Mean (SD) change from baseline: -0.72 (NR) Difference from placebo (95% CI): -0.17 (-0.39 to 0.04); *P* = .11
ACQ MID response (12 wk)	Placebo (n = 105)	Events of total N (%): 52 of 105 (50%)
	Benralizumab every 4 wk (n = 106)	Events of total N (%): 58 of 106 (55%) Reported OR (95% CI): 1.25 (0.72 to 2.19) Calculated RR (95% CI): 1.10 (0.85 to 1.43)

Outcome	Group (n)	Result
Daily asthma symptom score mean change from baseline (12 wk)	Placebo (n = 105)	Mean (SD) change from baseline: -0.45 (NR)
	Benralizumab every 4 wk (n = 106)	Mean (SD) change from baseline: -0.57 (NR) Difference from placebo (95% CI): -0.13 (-0.35 to 0.10); *P* = .27
AQLQ mean change from baseline (12 wk)	Placebo (n = 105)	Mean (SD) change from baseline: 0.41 (NR)
	Benralizumab every 4 wk (n = 106)	Mean (SD) change from baseline: 0.62 (NR) Difference from placebo (95% CI): 0.21 (0 to 0.42); *P* = .06
AQLQ MID response (12 wk)	Placebo (n = 105)	Events of total N (%): 34 of 105 (32%)
	Benralizumab every 4 wk (n = 106)	Events of total N (%): 46 of 106 (43%) Reported OR (95% CI): 1.65 (0.92 to 2.96) Calculated RR (95% CI): 1.34 (0.94 to 1.91)
FitzGerald et al., 2016[45]; CALIMA; NCT01914757		
Annualized rate of exacerbations (56 wk)	Placebo (n = 248) (subgroup with ≥ 300 eosinophils/µL)	Mean rate: 0.93
	Benralizumab every 8 wk (n = 239) (subgroup with ≥ 300 eosinophils/µL)	Mean rate: 0.66 IRR (95% CI): 0.72 (0.54 to 0.95); *P* = .02
	Benralizumab every 4 wk (n = 241) (subgroup with ≥ 300 eosinophils/µL)	Mean rate: 0.60 IRR (95% CI): 0.64 (0.49 to 0.85); *P* = .02
Exacerbations (56 wk)	Placebo (n = 248) (subgroup with ≥ 300 eosinophils/µL)	Events of total N (%): 126 of 248 (51%)
	Benralizumab every 8 wk (n = 239) (subgroup with ≥ 300 eosinophils/µL)	Events of total N (%): 95 of 239 (40%) Calculated RR (95% CI): 0.79 (0.64 to 0.95)
	Benralizumab every 4 wk (n = 241) (subgroup with ≥ 300 eosinophils/µL)	Events of total N (%): 84 of 241 (35%) Calculated RR (95% CI): 0.69 (0.55 to 0.85)
Time to first asthma exacerbation	Placebo (n = 248) Benralizumab every 8 wk (n = 239) Benralizumab every 4 wk (n = 241)	Benralizumab every 8 weeks vs. placebo: HR 0.73 (95% CI, 0.55 to 0.95); *P* = .02 Benralizumab every 4 weeks vs. placebo: HR 0.61 (95% CI, 0.46 to 0.80); *P* = .0004
Exacerbations requring ED or hospital (56 wk)	Placebo (n = 248) (subgroup with ≥ 300 eosinophils/µL)	Events of total N (%): 20 of 248 (8%)
	Benralizumab every 8 wk (n = 239) (subgroup with ≥ 300 eosinophils/µL)	Events of total N (%): 20 of 239 (8%) Calculated RR: 1.04 (95% CI, 0.57 to 1.88)
	Benralizumab every 4 wk (n = 241) (subgroup with ≥ 300 eosinophils/µL)	Events of total N (%): 16 of 241 (7%) Calculated RR (95% CI): 0.82 (0.44 to 1.55)
Rate of exacerbations requiring ED visits or hospitalization (56 wk)	Placebo (n = 248) (subgroup with ≥ 300 eosinophils/µL)	Mean (95% CI) rate: 0.04 (0.02 to 0.07)
	Benralizumab every 8 wk (n = 239) (subgroup with ≥ 300 eosinophils/µL)	Mean (95% CI) rate: 0.05 (0.03 to 0.08) IRR (95% CI): 1.23 (0.64 to 2.35); *P* = .54
	Benralizumab every 4 wk (n = 241) (subgroup with ≥ 300 eosinophils/µL)	Mean (95% CI) rate: 0.04 (0.02 to 0.06) IRR (95% CI): 0.93 (0.48 to 1.82); *P* = .84
ACQ mean change from baseline (56 wk)	Placebo (n = 248) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: -1.19 (NR)
	Benralizumab every 8 wk (n = 239) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: -1.44 (NR) Difference from placebo (95% CI): -0.25 (-0.44 to -0.07); *P* = .008

Outcome	Group (n)	Result
	Benralizumab every 4 wk (n = 241) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: -1.38 (NR) Difference from placebo (95% CI): -0.19 (-0.38 to -0.01); *P* = .04
Daily asthma symptom score mean change from baseline (56 wk)	Placebo (n = 248) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: -1.16 (NR)
	Benralizumab every 8 wk (n = 239) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: -1.4 (NR) Difference from placebo (95% CI): -0.23 (-0.43 to -0.04); *P* = .02
	Benralizumab every 4 wk (n = 241) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: -1.28 (NR) Difference from placebo (95% CI): -0.12 (-0.32 to 0.07); *P* = .22
AQLQ mean change from baseline (56 wk)	Placebo (n = 248) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: 1.31 (NR)
	Benralizumab every 8 wk (n = 239) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: 1.56 (NR) Difference from placebo (95% CI): 0.24 (0.04 to 0.45); *P* = .02
	Benralizumab every 4 wk (n = 241) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: 1.47 (NR) Difference from placebo (95% CI): 0.16 (-0.04 to 0.37); *P* = .12
Harrison et al., 2020[60]; ANDHI; NCT03170271		
Adjusted annualized rate of exacerbations-(24wk)	Placebo (229)	Mean (SD) change from baseline or rate: 1.86
	Benralizumab every 8 wk (427)	Mean (SD) rate: 0.94 Difference from placebo (95% CI): -0.92; *P* < .0001 IRR 0.51 (95% CI 0.39 to 0.65)
Exacerbations (24wk)	Placebo (229)	Events/Total N (%): 107/229 (47%);
	Benralizumab every 8 wk (427)	Events/Total N (%): 123/427 (29%) Calculated RR (95% CI): 0.62 (0.50 to 0.76)
Time to first exacerbation	Benralizumab every 8 wk (427) Placebo (229)	HR 0.52 (95% CI, 0.40 to 0.67), favoring benralizumab
ACQ MID Response (24wk)	Placebo (229)	Events/Total N (%): 150/229 (66%);
	Benralizumab every 8 wk (427)	Events/Total N (%): 313/427 (73%) Reported OR (95% CI): 1.53 (1.07 to 2.20) Calculated RR (95% CI): 1.12 (1.002 to 1.25)
ACQ mean change from baseline (24wk)	Placebo (229)	Mean (SD) change from baseline or rate: -1.01
	Benralizumab every 8 wk (427)	Mean (SD) change from baseline: -1.47 (0.06) Difference from placebo (95% CI): -0.46 (-0.65 to -0.27); *P* > .0001
SGRQ MID response (24wk)	Placebo (212)	Events/Total N (%): 144/212 (68%)
	Benralizumab every 8 wk (392)	Events/Total N (%): 314/392 (80%) Reported OR (95% CI): 1.91 (1.30 to 2.81) Calculated RR (95% CI):1.179 (1.06 to 1.31)

Outcome	Group (n)	Result
SGRQ mean change from baseline (24wk)	Placebo (229)	Mean (SD) change from baseline: -14.94 (1.34)
	Benralizumab every 8 wk (427)	Mean (SD) change from baseline: -23.06 (1.00) Difference from placebo (95% CI): -8.11 (-11.41 to -4.82); *P* < .0001
Nair et al., 2017[48]; ZONDA; NCT02075255		
Annualized rate of exacerbations (28 wk)	Placebo (n = 75)	Mean rate: 1.83
	Benralizumab every 8 wk (n = 73)	Mean rate: 0.54 IRR (95% CI): 0.30 (0.17 to 0.53); *P* < .001
	Benralizumab every 4 wk (n = 72)	Mean rate: 0.83 IRR (95% CI): 0.45 (0.27 to 0.76); *P* = .003
Exacerbations (28 wk)	Placebo (n = 75)	Events of total N (%): 39 of 75 (52%)
	Benralizumab every 8 wk (n = 73)	Events of total N (%): 17 of 73 (23%) Reported OR (95% CI): 0.28 (0.14 to 0.56) Calculated RR (95% CI): 0.45 (0.28 to 0.72)
	Benralizumab every 4 wk (n = 72)	Events of total N (%): 19 of 72 (26%) Reported OR (95% CI): 0.32 (0.16 to 0.65) Calculated RR (95% CI): 0.51 (0.33 to 0.79)
Time to first asthma exacerbation	Placebo (n = 75) Benralizumab every 8 wk (n = 73) Benralizumab every 4 wk (n = 72)	Benralizumab q4w vs. placebo: HR 0.39 (95% CI, 0.22 to 0.66); *P* < .001 Benralizumab q8w vs. placebo: HR 0.32 (95% CI, 0.17 to 0.57); *P* < .001
Rate of exacerbations requiring ED visits or hospitalization (28 wk)	Placebo (n = 75)	Mean rate: 0.32
	Benralizumab every 8 wk (n = 73)	Mean rate: 0.02 IRR (95% CI): 0.07 (0.01 to 0.63); *P* = .02
	Benralizumab every 4 wk (n = 72)	Mean rate: 0.14 IRR (95% CI): 0.44 (0.13 to 1.49); *P* = .19

Outcome	Group (n)	Result
Percentage reduction from baseline in OCS by category		Percentage reduction from baseline in OCS by category N (%) with ≥ 90% reduction from baseline Placebo: 9 (12) Benralizumab q4w: 24 (33) Benralizumab q8w: 27 (37) N (%) ≥ 75% reduction from baseline Placebo: 15 (20) Benralizumab q4w: 38 (53) Benralizumab q8w: 37 (51) N (%) ≥ 50% reduction from baseline Placebo: 28 (37) Benralizumab q4w: 48 (67); OR 3.59 (95% CI, 1.79 to 7.22); *P* < .001 Benralizumab q8w: 48 (66); OR 3.03 (95% CI, 1.57 to 5.86); *P* < .001 N (%) ≥ 0% reduction from baseline Placebo: 40 (53) Benralizumab q4w: 55 (76) Benralizumab q8w: 58 (79) N (%) with any increase or no change Placebo: 35 (47) Benralizumab q4w: 17 (24) Benralizumab q8w: 15 (21) OR (95% CI) across all groups. Benralizumab q4w vs. placebo: 4.09 (2.22 to 7.57); *P* < .001 Benralizumab q8w vs. placebo: 4.12 (2.22 to 7.63); *P* < .001
50% or more reduction in oral steroid use (28 wk)	Placebo (n = 75)	Events of total N (%): 28 of 75 (37%)
	Benralizumab every 8 wk (n = 73)	Events of total N (%): 48 of 73 (66%) Reported OR (95% CI): 3.03 (1.57 to 5.86) Calculated RR: 1.76 (95% CI, 1.26 to 2.47)
	Benralizumab every 4 wk (n = 72)	Events of total N (%): 48 of 72 (67%) Reported OR (95% CI): 3.59 (1.79 to 7.22) Calculated RR (95% CI): 1.79 (1.28 to 2.50)
Median reduction in steroid dosage (28 wk)	Placebo (n = 75)	Median: 25.0
	Benralizumab every 8 wk (n = 73)	Median: 75.0
	Benralizumab every 4 wk (n = 72)	Median: 75.0
Proportion no longer requiring oral glucocorticoid (28 wk)	Placebo (n = 42)	Events of total N (%): 8 of 42 (19%)
	Benralizumab every 8 wk (n = 42)	Events of total N (%): 22 of 42 (52%) Reported OR (95% CI): 4.19 (1.58 to 11.12) Calculated RR (95% CI): 2.75 (1.39 to 5.47)
	Benralizumab every 4 wk (n = 39)	Events of total N (%): 22 of 39 (56%) Reported OR (95% CI): 5.23 (1.92 to 14.21) Calculated RR (95% CI):3.0 (1.50 to 5.87)
Steroid dosage less than 5 mg/day (28 wk)	Placebo (n = 75)	Events of total N (%): 25 of 75 (33%)
	Benralizumab every 8 wk (n = 73)	Events of total N (%): 48 of 73 (66%) Calculated RR: 1.97 (1.38 to 2.83)
	Benralizumab every 4 wk (n = 72)	Events of total N (%): 48 of 72 (67%)

Outcome	Group (n)	Result
		Calculated RR (95% CI): 2.0 (1.40 to 2.87)
ACQ mean change from baseline (28 wk)	Placebo (n = 75)	Mean (SD) change from baseline: -0.57 (NR)
	Benralizumab every 8 wk (n = 73)	Mean (SD) change from baseline: -1.12 (NR) Difference from placebo (95% CI): -0.55 (-0.86 to -0.23); *P* = .001
	Benralizumab every 4 wk (n = 72)	Mean (SD) change from baseline: -0.81 (NR) Difference from placebo (95% CI): -0.24 (-0.55 to 0.08); *P* = .14
AQLQ mean change from baseline (28 wk)	Placebo (n = 75)	Mean (SD) change from baseline: 0.63 (NR)
	Benralizumab every 8 wk (n = 73)	Mean (SD) change from baseline: 1.08 (NR) Difference from placebo (95% CI): 0.45 (0.14 to 0.76); *P* = .004
	Benralizumab every 4 wk (n = 72)	Mean (SD) change from baseline: 0.85 (NR) Difference from placebo (95% CI): 0.23 (-0.08 to 0.53); *P* = .15
Panettieri et al., 2020[9]; SOLANA; NCT02869438		
ACQ MID response (12 wk)	Benralizumab (n = 114)	Events of total N (%): 95 of 114 (83%) Reported OR (95% CI): 2.54 (1.35 to 4.76) Calculated RR (95% CI): 1.29 (1.10 to 1.51)
	Placebo (n = 113)	Events of total N (%): 73 of 113 (65%)
ACQ well or partially controlled (score < 1.5) (12 wk)	Benralizumab (n = 118)	Events of total N (%): 71 of 118 (60%) Reported OR (95% CI): 2.21 (95% CI, 1.24 to 3.94) Calculated RR (95% CI): 1.38 (1.07 to 1.79)
	Placebo (n = 115)	Events of total N (%): 50 of 115 (43%)
ACQ well or partially controlled (score < 1.5) (8 wk)	Benralizumab (n = 118)	Events of total N (%): 64 of 118 (54%) Reported OR (95% CI): 1.98 (1.12 to 3.50) Calculated RR (95% CI): 1.36 (1.03 to 1.80)
	Placebo (n = 115)	Events of total N (%): 46 of 115 (40%)
ACQ mean change from baseline (12 wk)	Benralizumab (n = 114)	Mean (SD) change from baseline: -1.36 (1.15) Difference from placebo (95% CI): -0.47 (-0.73 to -0.21); *P* =.0004
	Placebo (n = 113)	Mean (SD) change from baseline: -0.87 (1.11)
ACQ mean change from baseline (8 wk)	Benralizumab (n = 115)	Mean (SD) change from baseline: -1.16 (1.13) Difference from placebo (95% CI): -0.31 (-0.55 to -0.07); *P* = .01
	Placebo (n = 115)	Mean (SD) change from baseline: -0.83 (1.02)
ACQ mean change from	Benralizumab (n = 114) Placebo (n = 113)	Mean (SD) change from baseline: NR

Outcome	Group (n)	Result
baseline (4 to 12 wk)		Difference from placebo (95% CI): -0.40 (-0.60 to -0.19); *P* = .0002
SGRQ mean change from baseline (12 wk)	Benralizumab (n = 114)	Mean (SD) change from baseline: -23.34 (22.30) Difference from placebo (95% CI): -8.60 (-13.3 to -3.90); *P* = .0004
	Placebo (n = 113)	Mean (SD) change from baseline: -14.39 (18.84)
SGRQ mean change from baseline (8 wk)	Benralizumab (n = 115)	Mean (SD) change from baseline: -19.9 (21.53) Difference from placebo (95% CI): -5.94 (-10.50 to -1.35); *P* = .01
	Placebo (n = 113)	Mean (SD) change from baseline: -13.80 (16.71)
SGRQ mean change from baseline (4 to 12 wk)	Benralizumab (n = 114) Placebo (n = 113)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -7.26 (-11.13 to -3.38); *P* = .0003
Park et al., 2016[39]; NCT01412736		
Annualized rate of exacerbations (52 wk)	Placebo (n = 21) (subgroup with ≥ 300 eosinophils/µL)	Mean rate: 3.5
	Benralizumab every 4 wk (n = 19) (subgroup with ≥ 300 eosinophils/µL)	Mean (SD) change from baseline: 1.9 (NR) Rate reduction 45%
Median time to first asthma	Placebo (n = 26) Benralizumab every 4 wk (19)	Median time (days) to first asthma exacerbation (95% CI) Placebo: 152 (34 to not applicable) Benralizumab: 281 (103 to not applicable) *P* value NR
ACQ mean change from baseline (52 wk)	Placebo (n = 21) (subgroup with ≥ 300 eosinophils/µL)	Mean change from baseline: -0.8 (NR)
	Benralizumab every 4 wk (n = 19) (subgroup with ≥ 300 eosinophils/µL)	Mean change from baseline: -0.9 (NR)

Abbreviations. ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; CI: confidence interval; ED: emergency department; HR: hazard ratio; IRR: incident rate ratio; MID: minimally important difference; NCT: US National Clinical Trial; NR: not reported; OCS: oral corticosteroids; OR: odds ratio; q4w: every 4 weeks; q8w: every 8 weeks; RCT: randomized controlled trial; RR: risk ratio; SD: standard deviation; SGRQ: St. George's Respiratory Questionnaire; wk: week.

Table B3. Safety Outcomes From RCTs of Benralizumab for Asthma

Safety Outcomes (time point)	Intervention Group 1 Number Events of Total Number (%) Calcualted RR (95% CI)	Intervention Group 2 Number Events of Total Number (%) Calculated RR (95% CI)	Comparator Group Number Events of Total Number (%)
Bleecker et al., (2016)[46]; SIROCCO			
	Benralizumab 30 mg SC every 4 weeks	Benralizumab 30 mg SC every 8 weeks	Placebo
Total adverse events (48 wk)	293 of 403 (73%) 0.95 (0.88 to 1.03)	281 of 394 (71%) 0.93 (0.86 to 1.0)	311 of 407 (76%)
SAEs (48 wk)	47 of 403 (12%) 0.86 (0.60 to 1.24)	52 of 394 (13%) 0.98 (0.69 to 1.4)	55 of 407 (14%)
Adverse events leading to discontinuation (48 wk)	9 of 403 (2%) 3.0 (0.83 to 11.1)	8 of 394 (2%) 2.8 (0.74 to 10.3)	3 of 407 (1%)
Mortality (48 wk)	2 of 403 (0%) 1.00 (0.14 to 7.13)	1 of 394 (0%) 0.52 (0.05 to 5. 7)	2 of 407 (0%)
Ferguson et al., 2017[50]; BISE			
	Benralizumab 30 mg SC every 4 weeks	NA	Placebo
Total adverse events (12 wk)	44 of 106 (42%) 0.89 (0.66 to 1.21)	NA	49 of 105 (47%)
SAEs (12 wk)	2 of 106 (2%) 0.99 (0.14 to 6.9)	NA	2 of 105 (2%)
Adverse events leading to discontinuation (12 wk)	1 of 106 (1%) 0.5 (0.05 to 5.4)	NA	2 of 105 (2%)
Mortality (12 wk)	1 of 106 (1%) 3.0 (0.12 to 72.1)	NA	0 of 105 (0%)
Treatment-related adverse events (12 wk)	4 of 106 (1%) 0.99 (0.25 to 3. 9)	NA	4 of 105 (4%)
FitzGerald et al., 2016[45]; CALIMA			
	Benralizumab 30 mg SC every 4 weeks	Benralizumab 30 mg SC every 8 weeks	Placebo
Total adverse events (56 wk)	322 of 438 (74%) 0.95 (0.88 to 1.02)	320 of 428 (75%) 0.96 (0.89 to 1.04)	342 of 440 (78%)
SAEs (56 wk)	45 of 438 (10%) 0.75 (0.52 to 1.08)	40 of 428 (9%) 0.69 (0.46 to 1)	60 of 440 (14%)
Adverse events leading to discontinuation (56 wk)	8 of 438 (2%) 2.0 (0.61 to 6.6)	10 of 428 (2%) 2. 6 (0.81 to 8.2)	4 of 440 (1%)
Mortality (56 wk)	2 of 438 (0%) 5.0 (0.24 to 104.3)	2 of 428 (0%) 5.2 (0.25 to 106.8)	0 of 440 (0%)
Treatment-related adverse events (56 wk)	51 of 438 (12%) 1.4 (0.95 to 2.1)	54 of 428 (13%) 1.5 (1.0 to 23)	36 of 440 (8%)
Harrison et al., 2020[60]; ANDHI; NCT03170271			
	Benralizumab 30 mg SC every 4 weeks for first 3 doses and then every 8 weeks	NA	Placebo
Total Adverse Events (24 wk)	271 of 427 (63%) 1.02 (0.90 to 1.15)	NA	143 of 229 (62%)

Safety Outcomes (time point)	Intervention Group 1 Number Events of Total Number (%) Calcualted RR (95% CI)	Intervention Group 2 Number Events of Total Number (%) Calculated RR (95% CI)	Comparator Group Number Events of Total Number (%)
Serious Adverse Events (24 wk)	23 of 427 (5%) 0.49 (0.29 to 0.85)	NA	25 of 229 (11%)
Adverse Events Leading to Discontinuation (24 wk)	6 of 427 (1%) 1.61 (0.33 to 7.91)	NA	2 of 229 (1%)
Mortality (24 wk)	0 of 427 (0%)	NA	0 of 229 (0%)
Nair et al., 2017[48]; ZONDA			
	Benralizumab 30 mg SC every 4 weeks	Benralizumab 30 mg SC every 4 weeks for first 3 doses and then every 8 weeks	Placebo
Total adverse events (28 wk)	49 of 72 (68%) 0.82 (0.68 to 0.99)	55 of 73 (75%) 0.91 (0.77 to 1.1)	62 of 75 (83%)
SAEs (28 wk)	7 of 72 (10%) 0.52 (0.22 to 1.2)	7 of 73 (10%) 0.51 (0.22 to 1.2)	14 of 75 (19%)
Adverse events leading to discontinuation (28 wk)	0 of 72 (0%) 0.21 (0.01 to 4.3)	3 of 73 (4%) 1.5 (0.27 to 9.0)	2 of 75 (3%)
Mortality (28 wk)	0 of 72 (0%)	2 of 73 (3%) 5.2 (0.25 to 105.1)	0 of 75 (0%)
Panettieri et al., 2020[9]; SOLANA			
	Benralizumab 30 mg SC every 4 weeks	Placebo	
Total adverse events (16 wk)	56 of 118 (47%) 0.93 (0.71 to 1.20)	59 of 115 (51%)	
SAEs (16 wk)	1 of 118 (1%) 0.14 (0.02 to 1.11)	7 of 115 (6%)	
Adverse events leading to discontinuation (16 wk)	2 of 118 (2%) 4.87 (0.24 to 100.4)	0 of 115 (0%)	
Mortality (16 wk)	NR	NR	
Park et al., 2016[39]			
	Benralizumab 20 mg SC every 4 weeks	NA	Placebo
Total adverse events (52 wk)	23 of 25 (92%) 0.96 (0.83 to 1.1)	NA	25 of 26 (96%)
SAEs (52 wk)	4 of 25 (16%) 0.83 (0.25 to 2.8)	NA	5 of 26 (19%)
Adverse events leading to discontinuation (52 wk)	NR	NA	NR
Mortality (52 wk)	0 of 25 (0%)	NA	0 of 26 (0%)

Abbreviations. CI: confidence interval; NA: not available; NR: not reported: RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; SC: subcutaneous; wk: week.

Dupilumab Asthma Studies

Table B4. Study Characteristics From RCTs of Dupilumab for Asthma

Characteristic	Details			
Castro et al., 2018[51]; LIBERTY ASTHMA QUEST; NCT02414854				
Study Characteristics	Phase 3 RCT (effectiveness of add-on therapy vs. placebo); 389 study sites; Argentina, Australia, Brazil, Canada, Chile, Colombia, France, Germany, Hungary, Italy, Japan, Rep. of Korea, Mexico, Poland, Russian Fed, South Africa, Spain, Taiwan, Turkey, Ukraine, United Kingdom, US *Years conducted:* 2015-2017 *Sponsor(s):* Sanofi and Regeneron Pharmaceuticals *Risk of bias:* Moderate			
Interventions (N randomized)	Dupilumab 200 mg SC every 2 weeks, loading dose 400 mg (n = 631)	Dupilumab 300 mg SC every 2 weeks, loading dose 600 mg (n = 633)	Combined placebo (n = 638)	
	Cointervention(s): High-dose inhaled glucocorticoid; background asthma-controller medicines were continued at a stable dose throughout the trial; use of LABA, long-acting muscarinic antagonists, antileukotriene agents, and methylxanthines was permitted; patients were permitted to use a SABA as necessary for symptom relief.			
Population	*Inclusion Criteria:* Aged ≥ 12 yrs with physician-diagnosed persistent asthma for ≥ 12 months according to guidelines; treatment with medium- to high-dose ICS (fluticasone propionate at total daily dose of ≥ 500 µg or equivalent) plus up to 2 additional controllers (e.g., a LABA or LTRA); PBD FEV_1 ≤ 80% predicted or ≤ 90% predicted in aged 12 to 17); FEV_1 reversibility of at least 12% and 200 mL; ACQ-5 score 1.5 or higher; worsening of asthma in the previous year that led to hospitalization, emergency medical care, or treatment with systemic steroids for ≥ 3 days; patients were recruited irrespective of a minimum baseline blood eosinophil count or biomarkers of inflammation. *Exclusion Criteria:* Weight < 30 kg; COPD or other lung diseases that impair lung function; severe asthma exacerbation within 1 month before enrollment; current smoker or cessation of smoking within 6 months before visit 1; previous smoker with smoking history > 10 pack-years.			
	Mean age (SD) 47.9 (15.3) N (%) female 1,197 (62.9)	*Race/ethnicity* NR	*Asthma duration/severity* Mean (SD) ACQ-5 score : 2.76 (0.77) Mean (SD) number of exacerbations in past year: 2.09 (2.15) N (%) with use of high-dose ICS: 979 (51.5)	*Comorbidities* N (%) with ongoing atopic or allergic condition: 1,565 (82.3) N (%) with nasal polyposis or chronic rhinosinusitis: 439 (23.1)

Characteristic	Details			
Rabe et al., 2018[53]; LIBERTY ASTHMA VENTURE; NCT02528214				
Study Characteristics	Phase 3, steroid-sparing RCT; sites (details not specified) in 15 different countries; Argentina, Brazil, Canada, Chile, Hungary, Israel, Italy, Mexico, Netherlands, Poland, Romania, Russia, Spain, Ukraine, US *Years conducted:* 2015-2017 *Sponsor(s):* Sanofi and Regeneron Pharmaceuticals *Risk of bias:* Moderate			
Interventions (N randomized)	Dupilumab 300 mg SC every 2 weeks, loading dose 600 mg (n = 103)	Placebo (n = 107)		
	Cointervention(s): Glucocorticoid dose (prednisone or prednisolone) with dose reduced every 4 weeks during weeks 4 to 20, background asthma controllers at stable dose, short-acting β2-agonist as needed			
Population	*Inclusion Criteria:* Patients aged 12 years and older with physician-diagnosed asthma for at least 1 year; receiving regular systemic glucocorticoids in the previous 6 months (5 to 35 mg per day of prednisone or prednisolone or equivalent), a high-dose inhaled glucocorticoid in the previous 4 weeks (fluticasone propionate at a total daily dose of > 500 µg or equipotent equivalent), and up to 2 controllers in the previous 3 months (i.e., a long-acting β2-agonist or leukotriene-receptor antagonist); FEV_1 before bronchodilator use of 80% or less of the predicted normal value; FEV_1 reversibility of at least 12% and 200 mL, or airway hyperresponsiveness documented in the previous 12 months *Exclusion Criteria:* Patients with COPD or other chronic lung disease, hospitalized or emergency treatment for asthma in previous 4 weeks, using 12 or more puffs of rescue medication in previous week, respiratory tract infection in previous 4 weeks, current smokers, former smokers with cessation in the past 6 months or >10 pack-years, comorbid disease that might interfere with treatment			
	Mean age (SD) 51.3 (12.6) N (%) female 127 (60)	*Race/ethnicity* NR	*Asthma duration/severity* NR Mean (SD) number of severe exacerbations in the previous year: 2.09 (2.16) Mean (SD) ACQ-5 score: 2.50 (1.16) Mean (SD) adjusted oral steroid dose: 11.26 (6.12) Adjusted dose defined as the lowest dose that a patient could receive without having an increase of 0.5 in the ACQ-5, a severe exacerbation, or any clinical significant event leading to an upward adjustment in dose.	*Comorbidities* N (%) with allergic rhinitis: 119 (56.7) N (%) with nasal polyposis: 71 (33.8)

Characteristic	Details			
Wenzel et al., 2016[44,123]; NCT01854047				
Study Characteristics	Phase 2b RCT (effectiveness of add-on therapy vs. placebo); 174 sites in 16 countries; Country: Argentina, Australia, Chile, France, Italy, Japan, the Republic of Korea, Mexico, New Zealand, Poland, Russia, South Africa, Spain, Turkey, Ukraine, US *Years conducted:* 2013-2015 *Sponsor(s):* Sanofi and Regeneron Pharmaceuticals, Inc. *Risk of bias:* Moderate			
Interventions (N randomized)	Dupilumab 200 mg SC every 2 weeks for 24 weeks, loading dose 400 mg (n = 150)	Dupilumab 300 mg SC every 2 weeks for 24 weeks, loading dose 600 mg (n = 157)	Placebo (n = 158)	
	Cointervention(s): High-dose ICS and LABA use in 1 of 3 approved combinations, SABA as necessary for sympom relief			
Population	*Inclusion Criteria:* Age ≥ 18 years, asthma diagnosis for 12 months or longer, treatment with medium- to high-dose ICS + LABA with a stable dose for 1 month or longer; PBD FEV_1 40% to 80% of predicted, with reversibility of at least 12% and at least 200 mL in FEV_1 after 200 to 400 mg salbutamol; ACQ-5 total score 1.5 or higher; 1 or more systemic corticosteroid burst therapy, hospital admission, or an emergency or urgent medical care visit that required treatment with systemic steroids for worsening asthma within 1 year before screening *Exclusion Criteria:* COPD or other lung disease impairing pulmonary function; beta-adrenergic-receptor blocker use, use of systemic corticosteroids within 28 days of or during the screening period; current smoker, more than 10 pack-years smoking history, or cessation of smoking within 6 months of screening			
	Mean age (SD) 48.6 (13.0) N (%) female 490 (63)	*Race/ethnicity* N (%) white: 607 (78) N (%) black or African American: 42 (5) N (%) Asian: 115 (15) N (%) American Indian or Alaska Native: 1 (< 1) N (%) Native Hawaiian or Pacific Islander: 1 (< 1) N (%) other: 10 (1)	*Asthma duration/severity* Mean (SD) duration of asthma, years 22.0 (15.4) Mean (SD) ACQ-5 score: 2.7 (0.81) Mean (SD) number exacerbations in past year: 2.2 (2.1)	*Comorbidities* N (%) with allergic rhinitis: 494 (65) N (%) with nasal polyposis: 125 (16)

Characteristic	Details			
Wenzel et al., 2013[37]; NCT 01312961				
Study Characteristics	Phase 2a, steroid-sparing RCT; 28 sites in the US *Years conducted:* 2011-2012 *Sponsor(s):* Sanofi and Regeneron Pharmaceuticals *Risk of bias:* Moderate			
Interventions (N randomized)	Dupilumab 300 mg SC (n = 52) every week for 12 weeks	Placebo (n = 52)		
	Cointervention(s): Combination therapy with inhaled glucocorticoids and LABAs dose based on pretrial doses for 4 weeks. Discontinuation of LABAs at week 4, and tapering and discontinuation of inhaled steroids during weeks 6 through 9.			
Population	*Inclusion Criteria:* Adults aged 18 to 65 yrs with persistent, moderate to severe asthma for at least 12 months, an elevated blood eosinophil count (≥ 300 cells per µL) or an elevated sputum eosinophil level (≥ 3%) at screening, and symptoms that were not well controlled with medium-dose to high-dose inhaled glucocorticoids plus LABAs (fluticasone [≥ 250 µg] and salmeterol [50 µg] twice daily or the equivalent; ACQ-5) score ≥ 1.5 and ≤ 3.0 and FEV_1 ≥ 50% predicted with evidence of reversibility or positive methaholine challenge; at least 1 asthma exacerbation within 2 years defined a treatment with 1 or more systemic steroid or hospitalization or an emergency care visit. *Exclusion Criteria:* Clinically relevant abnormal lab. values suggesting an unknown disease requiring further evaluation; COPD or other lung diseases; beta-adrenergic receptor blockers; smoker or cessation within past 6 months; previous smoking (> 10 cigarette pack-years); In-patient hospitalization or emergency care visit due to asthma exacerbation in the 2 months prior; plan to begin allergen immunotherapy within the study period; recent exposure to another investigative antibody, alcohol or drug abuse; reversal of sleep pattern (e.g., night shift workers); treatment with drugs known to prolong QTc interval; concomitant severe diseases or diseases for which the use of ICS or LABA are contraindicated; use of injectable glucocorticosteroids or oral systemic glucocorticosteroids within 2 months or more than 3 courses within the 6 months prior, pregnancy or intention to become pregnant during the course of the study, breast feeding, or unwillingness to use a highly effective method of contraception in women of child-bearing potential, recent parasitic infection or travel to a parasitic endemic area			
	Mean age (SD) Placebo: 41.6 (13.1) Dupilumab: 37.8 (13.2) N (%) female Placebo: 26 (50) Dupilumab: 26 (50)	*Race/ethnicity* White: Placebo: 38 (73) Dupilumab: 45 (87) Black: Placebo: 9 (17) Dupilumab: 5 (10) Asian: Placebo: 3 (6) Dupilumab: 1 (2)	*Asthma duration/severity* Mean (SD) duration of asthma: Placebo: 26.9 (14.8) Dupilumab: 24.2 (12.6) Mean (SD) ACQ-5 score Placebo: 2.1 (0.5) Dupilumab: 2.1 (0.5) Mean (SD) number of asthma exacerbations in previous 2 yr Placebo: 1.4 (1.3)	*Comorbidities* NR

Characteristic	Details			
		Other: Placebo: 2 (4) Dupilumab: 1 (2)	Dupilumab: 1.4 (1.0)	

Abbreviations. µg: microgram; µL: microliter; ACQ-5: Asthma Control Questionnaire; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LTRA: leukotriene receptor antagonist; NCT: US National Clinical Trial; NR: not reported; PBD: pre-bronchodilator; QTc: corrected Q to T interval on electrocardiogram; RCT: randomized controlled trial; SABA: short-acting beta-agonists; SC: subcutaneous; SD: standard deviation; yrs: years.

Table B5. Effectiveness Outcomes From RCTs of Dupilumab for Asthma

Outcome	Group (n)	Result
Castro et al., 2018[51]; LIBERTY ASTHMA QUEST; NCT02414854		
Adjusted annualized rate of severe asthma exacerbations (1 yr)	Dupilumab 200 mg (n = 631)	Mean (95% CI) rate: 0.46 (0.39 to 0.53) IRR vs. placebo: 0.523 (95% CI, 0.413 to 0.662) Defined as a deterioration of asthma leading to treatment for 3 days or more with systemic glucocorticoids or hospitalization or an ED visit leading to treatment with systemic glucocorticoids
	Dupilumab 300 mg (n = 633)	Mean (95% CI) rate: 0.52 (0.45 to 0.61); IRR vs. placebo: 0.540 (95% CI, 0.430 to 0.680)
	Placebo (200 mg) (n = 317)	Mean (95% CI) rate: 0.87 (0.72 to 1.05)
	Placebo (300 mg) (n = 321)	Mean (95% CI) rate: 0.97 (0.81 to 1.16)
	Subgroup findings: Exacerbations rates were significantly lower among subgroups of patients with ≥ 300 eosinophils/µL and among participants with between 150 and 300 eosinophils/µL but rates among participants with eosinophils < 150 per µL were not significantly different.	
Rate of exacerbations requiring ED visits or hospitalization (1 yr)	Combined dupilumab groups (n = 1,263)	Mean (95% CI) rate: 0.035 (0.025 to 0.048) IRR vs. placebo: 0.532 (95% CI, 0.247 to 0.816)
	Combined placebo groups (n = 638)	Mean (95% CI) rate: 0.065 (95% CI, 0.047 to 0.090)
AQLQ mean change from baseline (24 wk)	Dupilumab 200 mg (n = 631)	Mean (SE) change from baseline: 1.14 (0.04) Difference from placebo (95% CI): 0.20 (0.06 to 0.34)
	Dupilumab 300 mg (n = 633)	Mean (SE) change from baseline: 1.15 (0.04) Difference from placebo (95% CI): 0.15 (0.01 to 0.28)
	Placebo (200 mg) (n = 317)	Mean (SE) change from baseline: 0.94 (0.06)
	Placebo (300 mg) (n = 321)	Mean (SE) change from baseline: 1.00 (0.06)
AQLQ mean change from baseline (1 yr)	Dupilumab 200 mg (n = 631)	Mean (SE) change from baseline 1.28 (0.04) Difference from placebo (95% CI): 0.29 (0.15 to 0.44)
	Dupilumab 300 mg (n = 633)	Mean (SE) change from baseline: 1.29 (0.04) Difference from placebo (95% CI): 0.26 (0.12 to 0.40)
	Placebo (200 mg) (n = 317)	Mean (SE) change from baseline 0.99 (0.06)
	Placebo (300 mg) (n = 321)	Mean (SE) change from baseline: 1.03 (0.06)
ACQ mean change from baseline (24 wk)	Dupilumab 200 mg (n = 631)	Mean (SE) change from baseline: -1.44 (0.04) Difference from placebo (95% CI): -0.35 (-0.48 to -0.21)
	Dupilumab 300 mg (n = 633)	Mean (SE) change from baseline: -1.40 (0.04) Difference from placebo (95% CI): -0.19 (-0.32 to -0.05)
	Placebo (200 mg) (n = 317)	Mean (SE) change from baseline: -1.10 (0.06)
	Placebo (300 mg) (n = 321)	Mean (SE) change from baseline: -1.21 (0.06)
ACQ mean change from baseline (1 yr)	Dupilumab 200 mg (n = 631)	Mean SE) change from baseline: -1.54 (0.04)

Outcome	Group (n)	Result
		Difference from placebo (95% CI): -0.39 (-0.53 to -0.25)
	Dupilumab 300 mg (n = 633)	Mean (SE) change from baseline: -1.52 (0.04) Difference from placebo (95% CI): -0.22 (-0.36 to -0.08)
	Placebo (200 mg) (n = 317)	Mean (SE) change from baseline: -1.15 (0.06)
	Placebo (300 mg) (n = 321)	Mean (SE) change from baseline: -1.30 (0.06)
Rabe et al., 2018[53]; LIBERTY ASTHMA VENTURE; NCT02528214		
Annualized rate of severe exacerbations (24 wk)	Placebo (n = 107)	Mean (95% CI): 1.60 (1.25 to 2.04)
	Dupilumab (n = 103)	Mean (95% CI): 0.65 (0.44 to 0.96) IRR (95% CI): 0.41 (0.26 to 0.63)
	Subgroup findings: The rate of severe exacerbations was significantly lower for dupilumab compared to placebo among persons with baseline eosinophils ≥ 300 per µL and among persons with baseline eosinophils < 300 per µL.	
50% or more reduction in oral steroid use (24 wk)	Placebo (n = 107)	Events of total N (%): 57 of 107 (53%)
	Dupilumab 300 mg (n = 103)	Events of total N (%): 82 of 103 (80%) Reported OR (95% CI): 3.98 (2.06 to 7.67); *P* < .001 Calculated RR (95% CI): 1.49 (1.22 to 1.83) *Subgroup findings:* significantly higher incidence of achieving outcome compared to placebo among subgroup of persons with baseline eosinophils ≥ 300 per µL and among persons with baseline eosinophils < 300 per µL.
100% reduction in oral steroid use (24 wk)	Placebo (n = 107)	Events of total N (%): 31 of 107 (29%)
	Dupilumab 300 mg (n = 103)	Events of total N (%): 54 of 103 (52%) Reported OR (95% CI): 2.74 (1.47 to 5.10); *P* = .002 Calculated RR (95% CI): 1.81 (1.28 to 2.57) *Subgroup findings:* significantly higher incidence of achieving outcome compared to placebo among subgroup of persons with baseline eosinophils ≥ 300 per µL but no signficant different among persons with baseline eosinophils < 300 per µL.
Mean dose reduction in oral steroid (mg/day) (24 wk)	Dupilumab 300 mg (n = 103)	Difference from placebo (95% CI): -2.8 (-4.3 to -1.3)
Percentage change in oral glucocorticoid dose with asthma control maintained (24 wk)	Dupilumab 300 mg (n = 103)	Difference from placebo (95% CI): -28.2 (-40.7 to -15.8); *P* < .001 *Subgroup findings:* significant reductions compared to placebo among subgroup of persons with baseline eosinophils ≥ 300 per µL and among persons with baseline eosinophils < 300 per µL.
ACQ mean change from baseline (24 wk)	Dupilumab 300 mg (n = 103)	Difference from placebo (95% CI): -0.47 (-0.76 to -0.18)
Wenzel et al., 2016[44]; Corren et al., 2019;[43] NCT01854047		
Adjusted annualized rate of severe exacerbations (24 wk)	**Placebo (n = 158)**	**Mean (95% CI) rate: 0.897 (0.1.30 to 0.619)**
	Dupilumab 200 mg (n = 150)	Mean (95% CI) rate: 0.269 (CI, 0.157 to 0.461) Risk reduction vs. placebo: 70.0%; *P* = .0002

Outcome	Group (n)	Result
		Defined as deterioration of asthma that required use of systemic corticosteroids for at least 3 days, or hospital admission or ED visit because of asthma treated with systemic corticosteroids
	Dupilumab 300 mg (n = 157)	Mean (95% CI) rate: 0.265 (95% CI, 0.157 to 0.445) Risk reduction vs. placebo 70.5%; *P* = .0001
	Subgroup findings: Exacerbations rates were significantly lower for persons allocated to both dupilumab dose groups compared to placebo among both the subgroup of patients with ≥300 eosinophils/μL at baseline and among participants with < 300 eosinophils per μL at baseline.	
Severe exacerbations (24 wk)	**Placebo (n = 158)**	Events of total N (%): 41 of 158 (26%)
	Dupilumab 200 mg (n = 150)	Events of total N (%): 13 of 148 (9%) Calculated RR (95% CI): 0.34 (0.19 to 0.61) Defined as deterioration of asthma that required use of systemic corticosteroids for at least 3 days, or hospital admission or ED visit because of asthma treated with systemic corticosteroids
	Dupilumab 300 mg (n = 157)	Events of total N (%): 17 of 156 (11%) Calculated RR (95% CI): 0.42 (0.25 to 0.71)
AQLQ MID response (24 wk)	Placebo (n = 158)	Events of total N (%): 81 of 158 (51%)
	Dupilumab 200 mg (n = 150)	Events of total N (%): 96 of 150 (64%); *P* < .01 vs. placebo Calculated RR (95% CI): 1.81 (1.28 to 2.57)
	Dupilumab 300 mg (n = 157)	Events of total N (%): 102 of 157 (65%); *P* < .01 vs. placebo Calculated RR (95% CI): 1.27 (1.05 to 1.53)
AQLQ mean change from baseline (12 wk)	Placebo (n = 158)	Mean (SE) change from baseline: 0.85 (0.08)
	Dupilumab 200 mg (n = 150)	Mean (SE) change from baseline: 1.14 (0.08) Difference from placebo (95% CI): 0.30 (0.07 to 0.52); *P* = .009
	Dupilumab 300 mg (n = 157)	Mean (SE) change from baseline: 1.15 (0.08) Difference from placebo (95% CI): 0.30 (0.08 to 0.52); *P* = .008
AQLQ mean change from baseline (24 wk)	Placebo (n = 158)	Mean (SE) change from baseline: 0.88 (0.09)
	Dupilumab 200 mg (n = 150)	Mean (SE) change from baseline: 1.20 (0.09) Difference from placebo (95% CI): 0.31 (0.08 to 0.55); *P* = .009
	Dupilumab 300 mg (n = 157)	Mean (SE) change from baseline: 1.24 (0.08) Difference from placebo (95% CI): 0.36 (0.12 to 0.59); *P* = .003
	Subgroup findings: among persons with baseline eosinophils less than 300 per μL, no significant difference in mean change from baseline between either dose of dupilumab and placebo.	
ACQ MID response (24 wk)	Placebo (n = 158)	Events of total N (%): 97 of 158 (61%)
	Dupilumab 200 mg (n = 150)	Events of total N (%): 115 of 150 (77%); *P* < .01 vs. placebo Calculated RR (95% CI): 1.25 (1.07 to 1.45)
	Dupilumab 300 mg (n = 157)	Events of total N (%): 114 of 157 (73%); *P* < .05 vs. placebo Calculated RR (95% CI): 1.18 (1.01 to 1.38)

Outcome	Group (n)	Result
ACQ mean change from baseline (12 wk)	Placebo (n = 158)	Mean (SE) change from baseline: -1.13 (0.08)
	Dupilumab 200 mg (n = 150)	Mean (SE) change from baseline: -1.35 (0.08) Difference from placebo (95% CI): -0.22 (-0.44 to -0.01); *P* = .004
	Dupilumab 300 mg (n = 157)	Mean (SE) change from baseline: -1.32 (0.08) Difference from placebo (95% CI): -0.20 (-0.41 to 0.01); *P* = .07
	Subgroup findings: Significantly larger improvements for persons allocated to dupilumab 200-mg dose for persons with baseline eosinophils less than and greater than 300 per µL. For 300-mg dose, signifcantly larger improvements among persons with baseline eosinophils greater than 300 per µL but no significant difference among persons with baseline eosinophils less than 300 per µL.	
ACQ mean change from baseline (24 wk)	Placebo (n = 158)	Mean (SE) change from baseline: -1.14 (0.08)
	Dupilumab 200 mg (n = 150)	Mean (SE) change from baseline: -1.49 (0.08) Difference from placebo (95% CI): -0.35 (-0.57 to -0.14); *P* = .002
	Dupilumab 300 mg (n = 157)	Mean (SE) change from baseline: -1.45 (0.08) Difference from placebo (95% CI): -0.31 (-0.52 to -0.09); *P* = .005
Wenzel et al., 2013[37]; NCT 01312961		
Exacerbations (12 wk)	Dupilumab 300 mg (n = 52)	Events of total N (%): 3 of 52 (6%) Reported OR (95% CI): 0.08 (0.02 to 0.28) Calculated RR (95% CI): 0.13 (0.04 to 0.41) Defined as occurrence of reduction of 30% or more in morning PEF from baseline on 2 consecutive days, at least 6 additional reliever inhalations of SABAs in 24-hour period relative to baseline on 2 consecutive days, or requirement for systemic steroids of increase of ICS of at least 4 times the most recent dose, or hospitalization for asthma
	Placebo (n = 52)	Events of total N (%): 23 of 52 (44%)
Exacerbations requiring hospitalizations (12 wk)	Dupilumab 300 mg (n = 52)	Events of total N (%): 0 of 52 (0%) RR cannot be calculated
	Placebo (n = 52)	Events of total N (%): 0 of 52 (0%)
Probability of exacerbation (12 wk)	Dupilumab (n = 52)	Dupilumab: 0.06 (95% CI, 0.00 to 0.12) Difference vs. placebo: 0.10 (95% CI, 0.03 to 0.34); *P* < .001
	Placebo (n = 52)	Placebo: 0.46 (95% CI 0.32 to 0.60)
Required systemic glucocorticoid treatment (12 wk)	Dupilumab 300 mg (n = 52)	Events of total N (%): 1 of 52 (2%) Calculated RR (95% CI): 0.20 (0.02 to 1.65)
	Placebo (n = 52)	Events of total N (%): 5 of 52 (10%)
ACQ mean change from baseline (12 wk)	Dupilumab 300 mg (n = 52)	Mean (SD) change from baseline: -1.00 (0.16) Difference from placebo (95% CI): -0.73 (-1.15 to -0.30); *P* = .001
	Placebo (n = 52)	Mean (SD) change from baseline: -0.27 (0.16)
Proportion no longer requiring oral glucocorticoid (24 wk)	Placebo (n = 107)	Events of total N (%): 31 of 107 (29%)
	Dupilumab 300 mg (n = 103)	Events of total N (%): 5 4 of 103 (52%) Reported OR (95% CI): 2.74 (1.47 to 5.10); *P* = .002 Calculated RR (95% CI): 1.81 (1.28 to 2.57)

Outcome	Group (n)	Result
ACQ mean change from baseline (24 wk)	Dupilumab 300 mg (n = 103)	Difference from placebo (95% CI): -0.47 (-0.76 to -0.18)

Abbreviations. µL: microliter; ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; CI: confidence interval; ED: emergency department; ICS: inhaled corticosteroids; IRR: incident rate ratio; MID: minimally important difference; NCT: US National Clinical Trial; OR: odds ratio; PEF: peak expiratory flow; RCT: randomized controlled trial; RR: risk ratio; SABA: short-acting beta-agonists; SD: standard deviation; SE: standard error; wk: week; yr: year.

Table B6. Safety Outcomes From RCTs of Dupilumab for Asthma

Safety Outcomes (time point)	Intervention Group 1 Number Events of total Number (%) RR (95% CI)		Comparator Group Number Events of total Number (%)
Rabe et al., 2018[53]; LIBERTY ASTHMA VENTURE			
	Dupliumab 300 mg SC every 2 weeks, loading dose 600 mg		Placebo
Total adverse events (24 wk)	64 of 103 (62%) 0.9 (0.78 to 1.2)		69 of 107 (64%)
SAEs (24 wk)	9 of 103 (9%) 1.56 (0.58 to 4.2)		6 of 107 (6%)
Adverse events leading to discontinuation (24 wk)	1 of 103 (1%) 0.26 (0.03 to 2.3)		4 of 107 (4%)
Mortality (24 wk)	NR		NR
Adverse events leading to death (24 wk)	0 of 103 (0%)		0 of 107 (0%)
Castro et al., 2018[51]; LIBERTY ASTHMA QUEST			
	Dupilumab 200 mg SC, loading dose 400 mg	Dupilumab 300 mg SC, loading dose 600 mg	Placebo
Total adverse events (52 wk)	508 of 631 (81%) 0.97 (0.92 to 1.02)	515 of 632 (82%) 0.98 (0.93 to 1.03)	527 of 634 (83%)
SAEs (52 wk)	49 of 631 (8%) 0.93 (0.64 to 1.35)	55 of 632 (9%) 1.04 (0.73 to 1.49)	53 of 634 (8%)
Adverse events leading to discontinuation (52 wk)	19 of 631 (3%) 0.66 (0.37 to 1.16)	44 of 632 (7%) 1.52 (0.97 to 2.40)	29 of 634 (5%)
Mortality (52 wk)	NR	NR	NR
Adverse events leading to death (52 wk)	1 of 631 (0.2%) 0.34 (0.03 to 3.21)	4 of 632 (0.6%) 1.34 (0.30 to 5.95)	3 of 634 (0%)
Wenzel et al., 2016[44]; Corren et al., 2019[43]			
	Dupilumab 200 mg SC every 2 weeks	Dupilumab 300 mg SC every 2 weeks	Placebo
Total adverse events (24 wk)	119 of 148 (80%) 1.08 (0.95 to 1.22)	121 of 156 (78%) 1.04 (0.92 to 1.18)	118 of 158 (75%)
SAEs (24 wk)	10 of 148 (7%) 1.19 (0.50 to 2.84)	13 of 156 (8%) 1.46 (0.64 to 3.32)	9 of 158 (6%)
Adverse events leading to discontinuation (24 wk)	6 of 148 (4%) 1.28 (0.40 to 4.11)	4 of 156 (3%) 0.81 (0.22 to 2.96)	5 of 158 (3%)
Mortality (24 wk)	NR	NR	NR
Adverse events leading to death (24 wk)	0 (0%)	0 (0%)	0 (0%)

Wenzel et al., 2013[37]		
	Dupilumab 300 mg SC weekly	Placebo
Total adverse events (12 wk)	42 of 52 (81%) 1.05 (0.86 to 1.28)	40 of 52 (77%)
SAEs (12 wk)	1 of 52 (2%) 0.33 (0.04 to 3.1)	3 of 52 (6%)
Adverse events leading to discontinuation (12 wk)	3 of 52 (6%) 1.0 (0.21 to 4.7)	3 of 52 (6%)
Mortality (12 wk)	0 of 52 (0%)	0 of 52 (0%)

Abbreviations. CI: confidence interval; NR: not reported; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; SC: subcutaneous; wk: week.

Mepolizumab Asthma Studies

Table B7. Study Characteristics From RCTs of Mepolizumab for Asthma

Characteristic	Details			
Bel et al., 2014[41]; SIRIUS; NCT01691508				
Study Characteristics	Phase 3 steroid-sparing RCT; 38 centers in 10 countries; Germany, France, Czech Republic, US, United Kingdom, Australia, Canada, Netherlands, Poland, and Mexico *Years conducted:* 2012-2013 *Sponsor(s):* GlaxoSmithKline *Risk of bias*: Moderate			
Interventions (N randomized)	Mepolizumab 100 mg SC once every 4 weeks until week 20 (n = 69)	Placebo (n = 66)		
	Cointervention(s): All patients underwent a 3- to 8-week optimization phase to establish the lowest dose of maintenance oral steroids associated with acceptable asthma control (reduction until exacerbation or increase of at least 0.5 points on ACQ-r. After optimization, participants were randomized to drug or placebo and were maintained on their optimized steroid dose (weeks 0 to 4) and then entered reduction phase (weeks 4 to 20) where oral steroid doses were reduced according to a prespecified schedule of 1.25 to 10 mg per day every 4 weeks. No additional reductions were made during the last phase (maintenance) between weeks 20 and 24. All participants were treated with high-dose ICS and an additional controller (LABA, LTRA, or theophylline).			
Population	*Inclusion Criteria:* Aged 12 and older; eligible patients had at least a 6-month history of maintenance treatment with systemic glucocorticoids (5 to 35 mg per day of prednisone or its equivalent). The presence of eosinophilic inflammation was determined by a blood eosinophil level of either 300 cells or more per µL during the 12-month period before screening or 150 cells or more per µL during the optimization phase. *Exclusion Criteria:* Smoking history, concurrent respiratory disease, current or previous history of cancer in remission for less than 12 months prior screening, liver disease, cardiovascular disease, other conditions that could lead to elevated eosinophils, immunodeficiency, received omalizumab within 130 days of visit 1, pregnancy, alcohol/substance abuse			
Chupp et al., 2017[49]; MUSCA; NCT02281318				
	Mean age (range) Placebo: 50 (28 to 70) Mepolizumab: 50 (16 to 74) N (%) female Placebo: 30 (45) Mepolizumab: 44 (64)	*Race/ethnicity* N (%) white Placebo: 61 (92) Mepolizumab: 67 (97) N (%) Asian Placebo: 2 (3) Mepolizumab: 1 (1) N (%) other Placebo: 3 (5)	*Asthma duration/severity* Mean (SD) duration of asthma Placebo: 20.1 (14.4) Mepolizumab: 17.4 (11.8) Mean (SD) ACQ-5 score Placebo: 2.0 (1.2) Mepolizumab: 2.2 (1.3)	*Comorbidities* N (%) allergic rhinitis Placebo: 34 (52) Mepolizumab: 28 (41) N (%) sinusitis Placebo: 19 (29) Mepolizumab: 16 (23) N (%) nasal polyps Placebo: 17 (26)

Characteristic	Details			
		Mepolizumab: 1 (1) N (%) Hispanic Placebo: 3 (5) Mepolizumab: 2 (3)	Mean (SD) number severe exacerbations in previous year Placebo: 2.9 (2.8) Mepolizumab: 3.3 (3.4)	Mepolizumab: 16 (23)
Study Characteristics	Phase 3 traditional RCT (effectiveness of add-on therapy vs. placebo); 146 hospitals or research centers in 19 countries; Argentina, Belgium, Bulgaria, Canada, Czech Republic, Estonia, France, Germany, Greece, Italy, Netherlands, Norway, Peru, Russia, Slovakia, Spain, Ukraine, United Kingdom, and US *Years conducted:* 2014-2016 *Sponsor(s):* GlaxoSmithKline *Risk of bias*: Moderate			
Interventions (N randomized)	Mepolizumab 100 mg SC every 4 weeks (n = 276)		Placebo (n = 280)	
	Cointervention(s): Other standard care asthma control medications were continued, including at least 1 additional medication other than ICS.			
Population	*Inclusion Criteria:* Aged 12 years and older with severe eosinophilic asthma who had at least 2 exacerbations requiring treatment with systemic corticosteroids in the past year, despite treatment with regular high-dose inhaled corticosteroids, additional controller medication(s) for at least 3 months, and FEV_1 < 80% predicted in those aged ≥18 years, or < 90% predicted in those aged 12 to 17 years *Exclusion Criteria:* Current or former smokers with a smoking history of ≥ 10 pack-years, concurrent respiratory disease, received omalizumab within 130 days, severe or clinically significant cardiovascular disease, or other eosinophilic diseases			
	Mean age (SD) Placebo: 52 (13) Mepolizumab: 50 (14) N (%) female Placebo: 176 (64) Mepolizumab: 149 (54)	*Race/ethnicity* NR	*Asthma duration/severity* Mean (SD) duration of asthma, years Placebo: 19.6 (15.0) Mepolizumab: 19.5 (14.7) Mean (SD) ACQ-5 score Placebo: 2.2 (1.2) Mepolizumab: 2.2 (1.1) Mean (SD) SGRQ score Placebo: 46.3 (18.9) Mepolizumab: 47.4 (18.1)	*Comorbidities* N (%) with nasal polyps Placebo: 47 (17) Mepolizumab: 58 (21) N (%) with positive atopic status Placebo: 124 (45) Mepolizumab: 127 (46)
Ortega et al., 2014[42]; MENSA; NCT01691521				
Study Characteristics	Phase 3 traditional RCT (effectiveness of add-on therapy vs. placebo); 135 clinical sites in 16 countries: Argentina, Australia, Belgium, Canada, Chile, France, Germany, Italy, Japan, Korea, Mexico, Russia, Spain, Ukraine, United Kingdom, US *Years conducted:* 2012-2014			

Characteristic	Details			
	Sponsor(s): GlaxoSmithKline *Risk of bias*: Moderate			
Interventions (N randomized)	Mepolizumab 100 mg SC every 4 weeks for 32 weeks (n = 194)		Placebo (n = 191)	
	Cointervention(s): Continued current asthma maintenance therapy			
Population	*Inclusion Criteria:* Aged 12 years and older with a clinical asthma diagnosis, FEV_1 < 80% predicted value for adults or < 90% for children, at least 2 asthma exacerbations in the previous year treated with systemic glucocorticoids and fluticasone propionate or an equivalent medication, an eosinophil count of at least 150 cells per µL at screening or at least 300 cells per µL in the previous year, and at least 1 of the following: FEV_1 reversibility of more than 12%, positive methacholine or mannitol challenge results, or FEV_1 variability (≥20%) between 2 visits in the past year. *Exclusion Criteria:* Current smokers or former smokers with ≥ 10 pack-years, concurrent respiratory disease, malignancy, liver disease, severe or clinically significant cardiovascular disease, other conditions that could lead to elevated eosinophils, alcohol or substance abuse, immunodeficiency, omalizumab use in the past 130 days, use of any monoclonal antibody, use of other investigational medications, hypersensitivity to monoclonal antibody or biologics, and subjects who were pregnant or breast feeding.			
	Mean age (range) Placebo: 49 (12 to 76) Mepolizumab SC: 51 (12 to 81) N (%) female Placebo: 107 (56) Mepolizumab SC: 116 (60)	*Race/ethnicity* NR	*Asthma duration/severity* Mean (SD) duration of asthma, years Placebo: 19.5 (14.6) Mepolizumab SC: 20.5 (12.9) Mean (SD) ACQ score Placebo: 2.28 (1.19) Mepolizumab SC: 2.26 (1.27)	*Comorbidities* N (%) allergic rhinitis Placebo: 95 (50) Mepolizumab IV: 91 (48) Mepolizumab SC: 95 (49)

Abbreviations. ACQ: Asthma Control Questionnaire; FEV_1: forced expiratory volume in 1 second; IV: intravenous; ICS: inhaled corticosteroids; LABA: long-acting beta-agonists; LTRA: leukotriene receptor antagonists; NCT: US National Clinical Trial; NR: not reported; RCT: randomized controlled trial; SC: subcutaneous; SD: standard deviation; SGRQ: St. George's Respiratory Questionnaire.

Table B8. Effectiveness Outcomes From RCTs of Mepolizumab for Asthma

Outcome	Group (n)	Result
Bel et al., 2014[41]; SIRIUS; NCT01691508		
Adjusted annualized rate of exacerbations at 24 wk	Placebo (n = 66)	Mean (SD): 2.12 (NR)
	Mepolizumab (n = 69)	Mean (SD): 1.44 (NR) IRR (95% CI): 0.68 (0.47 to 0.99); *P* = .04 Defined as worsening of asthma leading to the doubling (or more) of the existing maintenance dose of oral glucocorticoids for ≥ 3 days or ED visit or hospitalization
Number of participants with exacerbations requiring hospitalization at 24 wk	Placebo (n = 66)	Events of total N (%): 7 of 66 (11)
	Mepolizumab (n = 69)	Events of total N (%): 0 of 69 (0) Calculated RR (95% CI): 0.07 (0.004 to 1.17)
50% or more reduction in oral steroid at 24 wk	Placebo (n = 66)	Events of total N (%): 22 of 66 (33)
	Mepolizumab (n = 69)	Events of total N (%): 37 of 69 (54) OR (95% CI) vs. placebo: 2.26 (1.10 to 4.65); *P* = .03 Calculated RR (95% CI): 1.61 (1.07 to 2.41); *P* = .02
Median percentage reduction in oral steroid use at 24 wk	Placebo (n = 66)	Median (95% CI) percentage reduction: 0.00 (-20.0 to 33.3)
	Mepolizumab (n = 69)	Median (95% CI) percentage reduction: 50.0 (20.0 to 75.0) Difference from placebo (95% CI): NR; *P* = .007
Proportion no longer requiring oral glucocorticoid at 24 wk	Placebo (n = 66)	Events of total N (%): 5 of 66 (8)
	Mepolizumab (n = 69)	Events of total N (%): 10 of 69 (14.0) OR (95% CI): 1.67(0.49 to 5.75); *P* = .41 Calculated RR (95% CI): 1.91 (0.69 to 5.3); *P* = .22
Categories of reduction in oral steroid use at 24 wk	Placebo (n = 66) Mepolizumab (n = 69)	OR 2.39; 95% CI, 1.25 to 4.56; *P* = .008 for mepolizumab vs. placebo N (%) with category of reduction 90% to 100% Placebo: 7 (110 Mepolizumab: 12 (17) 75% to <90%: Placebo: 5 (8) Mepolizumab: 12 (17) 50 to <75% Placebo: 10 (15) Mepolizumab: 9 (13) >0% to <50%: Placebo: 7 (11) Mepolizumab: 7 (10) No decrease, lack of asthma control, or withdrawal from treatment Placebo: 37 (56) Mepolizumab: 25 (36)
ACQ mean change from baseline at 24 wk	Placebo (n = 66) Mepolizumab (n = 69)	Difference from placebo (95% CI): -0.52 (-0.87 to -0.17); *P* = .004
SGRQ mean change from baseline at 24 wk	Placebo (n = 66) Mepolizumab (n = 69)	Difference from placebo (95% CI): -5.8 (-10.6 to -1.0); *P* = .02

Outcome	Group (n)	Result
Chupp et al., 2017[49]; MUSCA; NCT02281318		
Annualized rate of exacerbations at 24 wk	Placebo (n = 277)	Mean (SD) rate: 1.21 (NR)
	Mepolizumab (n = 274)	Mean (SD) rate: 0.51 (NR) IRR (95% CI): 0.42 (0.31 to 0.56); *P* < .0001 Defined as worsening of asthma requiring systemic corticosteroids administered intravenously or orally for ≥3 days or as a single intramuscular dose, or ED visit, or hospitalization
Rate of exacerbations requiring ED visits or hospitalization at 24 wk	Placebo (n = 277)	Mean (SD) rate: 0.10 (NR)
	Mepolizumab (n = 274)	Mean (SD) rate: 0.03 (NR) IRR (95% CI): 0.32 (0.12 to 0.90); *P* = .031
Rate of exacerbations requiring hospitalizations at 24 wk	Placebo (n = 277)	Mean (SD) rate: 0.07 (NR)
	Mepolizumab (n = 274)	Mean (SD) rate: 0.02 (NR) IRR: 0.31 (0.08 to 1.24); *P* = .098
ACQ MID response at 24 wk	Placebo (n = 277)	Events of total N (%): 116 of 276 (42)
	Mepolizumab (n = 274)	Events of total N (%): 161 of 274 (59) OR (95% CI): 2.0 (1.4 to 2.8); *P* = .0014 Calculated RR (95% CI): 1.40 (1.18 to 1.66); *P* < .0001
ACQ change from baseline at 24 wk	Placebo (n = 277)	Mean (SD) change from baseline: -0.4 (0.1)
	Mepolizumab (n = 274)	Mean (SD) change from baseline: -0.8 (0.1) Difference from placebo (95% CI): -0.4 (-0.6 to -0.2); *P* < .0001
Asthma symptom score change from baseline at 24 wk	Placebo (n = 277)	Mean (SD) change from baseline: -0.5 (1.0)
	Mepolizumab (n = 274)	Mean (SD) change from baseline: -0.7 (1.0)
SGRQ MID response at 24 wk	Placebo (n = 277)	Events of total N (%): 151 of 275 (55.0)
	Mepolizumab (n = 274)	Events of total N (%): 198 of 273 (73) OR (95% CI): 2.2(1.6 to 3.2); *P* < .0001
SGRQ change from baseline at 24 wk	Placebo (n = 277)	Mean (SD) change from baseline: -7.9 (1.0)
	Mepolizumab (n = 274)	Mean (SD) change from baseline: -15.6 (1.0) Difference from placebo (95% CI): -7.7 (-10.5 to -4.9); *P* < .0001
Ortega et al., 2014[42]; MENSA; NCT01691521		
Annualized rate of exacerbations at 32 wk	Placebo (n = 191)	Mean (SD) rate: 1.74 (NR)
	Mepolizumab (n = 194)	Mean (SD) rate: 0.83 (NR) Defined as worsening of asthma requiring systemic steroids for ≥3 days or ED visit or hospitalization
Annualized rate of exacerbations requiring hospitalization at 32 wk	Placebo (n = 191)	Mean (SD) rate: 0.10 (NR)
	Mepolizumab (n = 194)	Mean (SD) rate: 0.03 (NR) Difference from placebo (95% CI): NR; *P* = .03 % decrease compared to placebo 69 (95% CI, 9 to 89)
Annualized rate of exacerbations requiring ED visits or hospitalization at 32 wk	Placebo (n = 191)	Mean (SD) rate: 0.20 (NR)
	Mepolizumab (n = 194)	Mean (SD) rate: 0.08 (NR) Difference from placebo (95% CI): NR; *P* = .02 Percentage reduction compared to placebo 61 (95% CI, 17 to 82)
Number of participants with exacerbations	Placebo (n = 191)	Events of total N (%): 25 of 191 (13)
	Mepolizumab (n = 194)	Events of total N (%): 12 of 194 (6) Relative reduction 61%, *P* = .02

Outcome	Group (n)	Result
requiring ED visits or hospitalization at 32 wk		
ACQ mean change from baseline at 32 wk	Placebo (n = 191)	Mean (SD) change from baseline: -0.50 (0.07)
	Mepolizumab (n = 194)	Mean (SD) change from baseline: -0.94 (0.07) Difference from placebo (95% CI): -0.44(-0.63 to -0.25); *P* < .001
SGRQ mean change from baseline at 32 wk	Placebo (n = 191)	Mean (SD) change from baseline: -9.0 (1.2)
	Mepolizumab (n = 194)	Mean (SD) change from baseline: -16.0 (1.1) Difference from placebo (95% CI): -7.0 (-10.2 to -3.8); *P* < .001

Abbreviations. ACQ: Asthma Control Questionnaire; CI: confidence interval; ED: emergency department; IRR: incident rate ratio; MID: minimally important difference; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; RR: risk ratio; SD: standard deviation; SGRQ: St. George's Respiratory Questionnaire; wk: week.

Table B9. Safety Outcomes From RCTs of Mepolizumab for Asthma

Safety Outcomes (time point)	Intervention Groups Number events of total number (%); calculated RR (95% CI)	
Bel et al., 2014[41]; SIRIUS; NCT01691508		
	Mepolizumab 100 mg SC every 4 weeks	Placebo
Total adverse events (32 wk)	57 of 69 (82.6%) 0.89 (0.79 to 1.02)	61 of 66 (92.4%)
SAEs (32 wk)	1 of 69 (1.4%) 0.07 (0.01 to 0.60)	12 of 66 (18.2%)
Adverse events leading to discontinuation (32 wk)	3 of 69 (4.3%)	3 of 66 (4.5%)
Mortality (32 wk)	NR	NR
Chupp et al., 2017;[49] MUSCA; NCT02281318		
	Mepolizumab 100 mg SC every 4 weeks	Placebo
Total adverse events (24 wk)	192 of 273 (70.3%) 0.94 (0.85 to 1.05)	207 of 278 (74.5%)
SAEs (24 wk)	15 of 273 (5.5%) 0.69 (0.37 to 1.31)	22 of 278 (7.9%)
Adverse events leading to discontinuation (24 wk)	2 of 273 (0.7%)	3 of 278 (1.1%)
Mortality (24 wk)	0 of 273 (0%)	0 of 278 (0%)
Ortega et al., 2014;[42] MENSA; NCT01691521		
	Mepolizumab 100 mg SC every 4 weeks	Placebo
Total adverse events (40 wk)	152 of 194 (78.4%) 0.95 (0.86 to 1.05)	158 of 191 (82.7%)
SAEs (4 0 wk)	16 of 194 (8.2%) 0.58 (0.32 to 1.05)	27 of 191 (14.1%)
Adverse events leading to discontinuation (40 wk)	1 of 194 (0.5%)	4 of 191 (2.1%)
Mortality (40 wk)	NR	NR

Abbreviations. CI: confidence interval; mg: milligram; NR: not reported; RCT: randomized controlled trial; RR: risk ratio; SC: subcutaneous; SAE: serious adverse event; wk: week.

Omalizumab Asthma Studies

Table B10. Study Characteristics for RCTs of Omalizumab for Asthma

Characteristic	Details			
Ayres et al., 2004[11]				
Study Characteristics	Phase NR, RCT (efficacy of add-on therapy vs. placebo); 49 centers in 5 European countries; France, Germany, Spain, Switzerland, United Kingdom *Years conducted:* NR *Sponsor(s):* NR; some authors are Novartis employees *Risk of bias:* High			
Interventions (N randomized)	Omalizumab SC dose based on weight and serum IgE levels every 2 or 4 weeks (n = 206)	Best Standard Care (BSC) (n = 106)		
	Cointervention(s): Step 3 or 4 treatment according to NHLBI guidelines; including daily treatment with moderate-to-high doses of inhaled corticosteroids with or without a long-acting bronchodilator; Step 4 patients received daily systemic steroids.			
Population	*Inclusion Criteria:* Aged 12 to 75; persistent (> 2 years) moderate to severe allergic asthma, poorly controlled according to guidelines; FEV_1 reversibility of ≥ 12% within 30 min of inhaled salbutamol; receiving ≥ 400 µg /day (< 18) or ≥ 800 µg/day (adult) inhaled BDP (or equivalent); positive skin prick test to 2 or more clinically relevant antigens; serum total IgE level of 30 to 700 IU/mL; body weight suitable for optimum dosing of omalizumab *Exclusion Criteria:* Pregnancy; lactation; female patients not using adequate contraception; smoking history of ≥ 10 pack-years; active lung disease other than allergic asthma; other significant systemic disease; immunocompromised; elevated serum IgE levels for reasons other than atopy; receiving desensitization immunotherapy			
	Mean age (SD) Median, years (range) BSC: 39 (12 to 71) Omalizumab: 38 (12 to 73) N (%) female 220 (71)	*Race/ethnicity* NR	*Asthma duration/severity* Duration: NR Mean (SD) Wasserfallen asthma symptom score BSC: 17.0 (10.2) Omalizumab: 17.4 (10.6) N (%) using systemic steroids BSC: 19 (18) Omalizumab: 47 (23)	*Comorbidities* Rhinitis: 205 (65.7%)
Bardelas et al., 2012[28]; NCT00267202				
Study Characteristics	Phase 4/postmarketing RCT (efficacy of add-on therapy vs. placebo); multiple site in the US, but sites not otherwise described *Years conducted:* 2005-2008 *Sponsor(s):* Novartis and Genentech *Risk of bias:* Moderate			

Characteristic	Details			
Interventions (N randomized)	150 or 300 mg omalizumab every 4 weeks or 225, 300, or 375 mg every 2 weeks based on weight and serum IgE levels (n = 136)			Placebo (n = 135)
	Cointervention(s): Participants remained on current asthma maintenance therapies with no changes. Maintenance therapies included inhaled corticosteroid alone or in combination with long-acting beta-agonist or LTRA, theophylline, or zileuton. Oral or IV steroids allowed for exacerbations.			
Population	*Inclusion Criteria:* Aged 12 and older with inadequately controlled allergic asthma defined as ACT total score of ≤ 19 and at least 1 of the following: symptoms > 2 days a week, nighttime awakenings ≥ 1 time a week, short-acting bronchodilator use >2 days/week, or FEV_1 <80% expected volume who were treated with medium-dose inhaled corticosteroid plus a long-acting bronchodilator or a LTRA, theophylline, or zileuton. Positive skin prick test or radioallergosorbent test to 1 or more perennial aeroallergens within the prior 12 months, physician diagnosis of asthma or symptoms consistent with asthma for at least 12 months, body weight ≤ 150 kg, and nonsmoking history of ≥ 1 year and ≤ 10 pack-years for former smokers *Exclusion Criteria:* History of intubation for asthma or anaphylaxis; systemic steroid use within 4 weeks of screening; <3 months stable oral corticosteroid use; active lung disease; current or anticipated use of beta-blockers or use of methotrexate, gold salts, cyclosporin, or troleandomycin; elevated serum IgE levels for reasons other than atopy			
	Mean age (SD) Placebo: 40.7 (14.6) Omalizumab: 41.9 (14.9) N (%) female Placebo: 87 (64) Omalizumab: 93 (68)	*Race/ethnicity* N(%) black Placebo: 25 (19) Omalizumab: 30 (22) N(%) white Placebo: 102 (76) Omalizumab: 102 (75) N(%) Asian Placebo: 3 (2) Omalizumab: 0 (0) N (%) other Placebo: 5 (4) Omalizumab: 4 (3)	*Asthma duration/severity* Duration: NR Mean (SD) ACT score Placebo: 13.7 (3.5) Trmnt1: 13.9 (3.3)	*Comorbidities*
Bousquet et al., 2011[26]; Siergiejko et al., 2011[27]; NCT00264849				
Study Characteristics	Phase 4/postmarketing RCT (efficacy of add-on therapy vs. placebo); 106 centers in 14 countries; Belgium, Canada, Denmark, Germany, Hungary, Israel, Italy, Norway, Poland, Spain, Sweden, Switzerland, Turkey, United Kingdom *Years conducted:* 2005-2008 *Sponsor(s):* Novartis Pharma *Risk of bias:* High			
Interventions (N randomized)	Omalizumab 75 to 300 mg every 4 weeks or 225 to 375 mg every 2 weeks for 32 weeks (n = 275)		Optimized asthma therapy (n = 133)	

Characteristic	Details			
	Cointervention(s): Additional asthma medications (e.g., OCS, theophyllines, cromones, LTRAs) were allowed if established >4 weeks before randomization. Short-acting b2-agonists were permitted as rescue medication. During first 4 weeks of 8 week run-in, asthma therapy was optimized according to GINA 2004 guidelines. No further adjustments were permitted during second 4 weeks of run-in. Participants need to continue to demonstrate inadequate asthma control despite treatment with high-dose ICS (> 1,000 µg BPD or equivalent) and a LABA in order to be randomized.			
Population	*Inclusion Criteria:* Aged 12 to 75 years with severe persistent allergic (IgE-mediated) asthma with ≥ 2 severe asthma exacerbations (requiring treatment with systemic corticosteroids) while receiving ≥ 800 µg BDP or equivalent plus a LABA during the 3 years before screening, with ≥ 1 severe exacerbation within the previous year; body weight of 20 to 150 kg and baseline serum total IgE level of 30 to 700 IU/mL; positive skin prick or RAST to at least 1 perennial allergen; ≥ 12% reversibility in FEV_1 within 30 min of taking 2 to 4 doses of 100 µg salbutamol; FEV_1 between 40% and 80% of predicted. *Exclusion Criteria:* Pregnancy, nursing, or potential pregnancy; systemic corticosteroids (for reasons other than asthma); b-adrenergic antagonists; immunosuppressants, anticholinergics, or desensitization therapy with < 3 months of stable maintenance doses before the first visit; history of food or drug-related anaphylaxis or allergy to antibiotics; aspirin or nonsteroidal anti-inflammatory drug-related asthma; smoking history > 10 pack-years, active lung disease other than allergic asthma, elevated serum IgE levels for reasons other than allergy, significant underlying medical conditions, or abnormal ECG or laboratory test values; previous treatment with omalizumab			
	Mean age (SD) 45.7 (12.87) N (%) female 259 (64.8)	*Race/ethnicity* NR	*Asthma duration/severity* Duration: NR Mean (SD) number of clinically significant exacerbations in prior year: 2.1 (1.26) % with 1 or more hospitalizations due to asthma: 22.4% Mean FEV_1 (% of predicted), Mean (SD): 259 (64.8)	*Comorbidities* NR
Busse et al., 2001[13]; Lanier et al., 2013[14]; Finn et al., 2002[15]				
Study Characteristics	Phase 3 steroid-sparing RCT; multicenter study at US sites that were not otherwise described *Years conducted:* NR *Sponsor(s):* Novartis *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab 150 mg or 300 mg SC every 4 weeks or 225 mg, 300 mg, or 375 mg every 2 weeks based on body weight and serum IgE levels (n = 268)		Placebo (n = 257)	
	Cointervention(s): Rescue albuterol, stable doses of immunotherapy or other nonasthma medication continued; no other asthma medications permitted, except those used to treat exacerbations. Participants were switched from their prescribed ICS doses to an equivalent dose of BPD at trial entry, at the end of the second week of the 4- to 6-week run-in, the dose of BDP was			

Characteristic	Details			
	adjusted up or down to maintain previous asthma control. A stable BPD does was maintined 4 weeks before randomization. The dose of steroid was maintained during weeks 1-16 after randomization, and then reduced by 25% of baseline dose every 2 weeks for 8 weeks during weeks 16-28. If worsening occurred, BDP was increased by ≥25% and patient was reevaluated for tapering after 1 week of improvement.			
Population	*Inclusion Criteria:* Aged 12 to 17 years who were symptomatic despite ICS treatment, had asthma for at least 1 year, serum IgE levels of 30 to 700 IU/mL, FEV_1 reversibility of ≥ 12% within 30 minutes after albuterol, baseline FEV_1 ≥ 40% and ≤ 80% of predicted value, treatment with 420 to 840 µg/day of BDP or its equivalent ICS for ≥ 3 months, and a positive skin prick test for at least 1 common allergen *Exclusion Criteria:* Prior exposure or sensitivity to omalizumab; acute upper respiratory tract infection within 1 month; < 3 months of stable immunotherapy; elevated IgE levels for reasons other than atopy; regular treatment with β-adrenergic antagonists; and requirement of omalizumab doses of >750 mg per 4 weeks on the basis of serum IgE and body weight			
	Mean age (SD) Placebo: 39.0 (NR) Omalizumab: 39.3 (NR) N (%) female Placebo: 146 (56.8) Omalizumab: 164 (61.2)	*Race/ethnicity* N(%) black Placebo: 16 (6.2) Omalizumab: 21 (7.8) N(%) white Placebo: 229 (89.1) Omalizumab: 238 (88.8) N(%) other Placebo: 12 (4.7) Omalizumab: 9 (3.4)	*Asthma duration/severity* Mean duration of asthma (range), years Placebo: 22.7 (2 to 60) Omalizumab: 20.6 (1 to 61) Mean (SD) asthma symptom score during run-in Placebo: 4.24 (1.17) Omalizumab: 4.31 (1.17)	*Comorbidities* NR
Busse et al., 2011[30]; ICATA; NCT00377572				
Study Characteristics	Phase 4/postmarketing RCT (efficacy of add-on therapy vs. placebo); 8 clinical sites in the US *Years conducted:* 2006-2009 *Sponsor(s):* National Institute of Allergy and Infectious Diseases, Novartis (unrestricted grant), Dey Pharma (Epipens) *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab SC (75 to 375 mg based on weight and IgE level) every 2 or 4 wk for 60 wk (n = 208)		Placebo (n = 211)	
	Cointervention(s): Based on treatment algorithm, participants were placed on appropriate asthma regimen based on NAEP guideline on the basis of symptoms and FEV_1 with goal to achieve control; asthma medications covered by participant's insurance, except for study drug and oral prednisone. Education about environmental allergen remediation provided, bedding covers, pest traps, and vacuum cleaner was also provided to participants. Except for study drug, treatment adjustments were made on the basis of symptoms every 3 months.			
Population	*Inclusion Criteria:* Inner city children (6 to 20 yrs) with persistent allergic asthma (physician's diagnosis or documentation of symptoms of asthma for more than 1 year before study entry); symptoms of persistent asthma or evidence of uncontrolled			

Characteristic	Details			
	disease as indicated by hospitalization or unscheduled urgent care in the 6 to 12 months preceding study entry; at least 1 positive skin prick test for a perennial allergen; weight between 20 and 150 kg; total serum levels of IgE: 30 to 1,300 IU/mL *Exclusion Criteria:* Significant medical illness, hypersensitivity to omalizumab or related drug, history of severe anaphylactoid or anaphylactic reaction, cancer or being investigated for cancer			
	Mean age (SD) Placebo: 10.8 (3.4) Omalizumab: 10.9 (3.6) N (%) female Placebo: 91 (43) Omalizumab: 86 (41)	*Race/ethnicity* N (%) black Placebo: 121 (57) Omalizumab: 131 (63) N (%) Hispanic Placebo: 84 (40) Omalizumab: 71 (34) N (%) other or mixed Placebo: 6 (3) Omalizumab: 6 (3)	*Asthma duration/severity* Mean (SD) duration of asthma, years Placebo: 7.0 (3.8) Omalizumab: 7.5 (4.0) Mean (SD) C-ACT score (for aged 4 to 11) Placebo: 20.7 (3.9) Omalizumab: 20.5 (3.8) Mean (SD) ACT score (for aged 12 and up) Placebo: 20.3 (3.1) Omalizumab: 20.3 (3.8) N (%) with ≥ 1 hospitalization in prior year Placebo: 52 (25) Omalizumab: 52 (25)	*Comorbidities* NR
Busse et al., 2013[16]				
Study Characteristics	Phase 4/postmarketing RCT (efficacy of add-on therapy vs. placebo); 81 centers in the US *Years conducted:* NR *Sponsor(s):* Genentech *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab SC every 2 or 4 weeks based on IgE levels and bodyweight (n = 159)		Placebo (n = 174)	
	Cointervention(s): Stable doses of ICS, LABA, or other doses of asthma medications were allowed but no modifications after the run-in period were allowed.			
Population	*Inclusion Criteria:* Aged 12 to 75 years with atopic asthma (elevated serum total IgE levels ≥ 30 to ≤ 1,300 IU/mL) and inadequate symptom control despite ICS with or without other controller medications despite having normal lung function (baseline predicted value FEV_1 > 80%) *Exclusion Criteria:* Chronic systemic corticosteroids within 3 months, received a burst of oral corticosteroids within 2 weeks, received omalizumab therapy at any time within 12 months, had significant medical illness, active lung disease other than			

Characteristic	Details			
	asthma, were pregnant/lactating, or had taken immunosuppressants or other investigational drugs within the 30 days before screening			
	Mean age (SD) Placebo: 38.1 (15.1) Omalizumab: 36.0 (14.7) N (%) female Placebo: 116 (68) Omalizumab: 110 (70)	*Race/ethnicity* N (%) black or African American Placebo: 42 (25) Omalizumab: 37 (24) N (%) white Placebo: 118 (69) Omalizumab: 113 (72) N (%) Asian Placebo: 4 (2.3) Omalizumab: 5 (3.2) N (%) American Indian/Alaska Native Placebo: 3 (1.8) Omalizumab: 1 (0.6) N (%) other Placebo: 4 (2.3) Omalizumab: 1 (0.6)	*Asthma duration/severity* Duration: NR Nocturnal asthma symptom score Placebo: 1.0 (0.8) Omalizumab: 1.1 (0.9) Daytime asthma symptom score Placebo: 1.5 (0.7) Omalizumab: 1.5 (0.7)	*Comorbidities* NR
Chanez et al., 2010[31]; NCT00454051				
Study Characteristics	Phase 4/postmarketing RCT (efficacy of add-on therapy vs. placebo); 6 centers in France *Years conducted:* 2006-2008 *Sponsor(s):* Novartis Pharma SAS *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab SC dose based on total IgE and body weight every 2 or 4 weeks (n = 20)		Placebo (n = 11)	
	Cointervention(s): All concomitant treatments were allowed; maintenance asthma treatment was to remain unchanged throughout the study period. All patients were treated with high dose ICS in combination with a LABA; 22.6% (n=7) were also receiving oral corticosteroids.			
Population	*Inclusion Criteria:* Aged 18 years and older with severe persistent allergic asthma and FEV_1 < 80% of predicted, frequent daily symptoms (≥ 4 days/week average) or nocturnal awakening (≥ 1/week average), multiple severe asthma exacerbations (≥2), severe asthma exacerbations requiring an unscheduled medical intervention with systemic corticosteroid in the past year, or hospitalization/ED for an asthma exacerbation in the past year, high dose ICS > 1,000 µg BPD or equivalent and an inhaled long-acting b2-agonist, allergy to a perennial allergen, total serum IgE level ≥ 30 to ≥ 700 IU/mL and suitable serum total IgE level and weight according to omalizumab dosing tables			

Characteristic	Details			
	Exclusion Criteria: Smoking history >20 pack-years, asthma exacerbation within 4 weeks before randomization, history of food or drug-related severe anaphylactoid/anaphylactic reaction, elevated serum IgE levels for reasons other than allergy, previous use of omalizumab, uncontrolled chronic diseases including cancer			
	Mean age (SD) 47.4 (14.4) N (%) female 19 (61.3)	*Race/ethnicity* NR	*Asthma duration/severity* Mean (SD) asthma duration, years: 31.4 (18.6) Mean (SD) asthma exacerbations requiring systemic corticosteroids in previous year: 4.4 (3.2)	*Comorbidities* NR
Garcia et al., 2013[32]; NCT01007149				
Study Characteristics	Phase NR, RCT (efficacy of add-on therapy vs. placebo); 10 centers in France *Years conducted:* 2009-2011 *Sponsor(s):* Novartis Pharma SAS *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab dose based on weight and IgE level every 2 or 4 weeks (n = 20)			Placebo (n = 21)
	Cointervention(s): All patients were treated with high-dose inhaled corticosteroids in association with long-acting beta-agonists and 37% (n=15) were taking oral corticosteroids. Maintenance asthma treatment was unchanged throughout the study period.			
Population	*Inclusion Criteria:* Aged 18 to 70 with uncontrolled, severe, persistent, nonatopic asthma on daily high-dose ICS (> 1,000 µg BPD or equivalent) plus LABA and experiencing 2 exacerbations requiring systemic corticosteroids and/or at least 1 hospitalization or ED visit in the past year, negative findings on blood multiallergic testing (skin prick and RAST), total serum IgE 30 to 700 IU/mL *Exclusion Criteria:* Current or former smokers with a more than 10 pack-years or who quit within the past 3 years, treatment of an asthma exacerbation in the past 4 weeks, previous use of omalizumab, pregnancy, breastfeeding, or uncontrolled other chronic diseases			
	Mean age (SD) Placebo: 54.6 (13) Omalizumab: 55.0 (10) N (%) female Placebo: 13 (61) Omalizumab: 13 (65)	*Race/ethnicity* NR	*Asthma duration/severity* Duration: NR Mean (SD) ACQ score Placebo: 2.2 (1.2) Omalizumab: 2.2 (0.98) Mean (SD) number of asthma exacerbations requiring systemic corticosteroids in the past year Placebo: 5.48 (4.60) Omalizumab: 5.05 (3.10)	*Comorbidities* N (%) with aspirin- or other NSAID-related asthma Placebo: 5 (23.8) Omalizumab: 4 (20.0)

Characteristic	Details			
Gevaert et al., 2013[38]; NCT01393340				
Study Characteristics	Phase 2 RCT (efficacy of add-on therapy vs. placebo); 2 university-based ENT departments in Belgium *Years conducted:* 2007-2008 *Sponsor(s):* Ghent University; Flemish Scientific Research Board; Belgian Research Fund; Interuniversity Attraction Poles Program; Global Allergy and Asthma European Network; Novartis *Risk of bias:* High			
Interventions (N randomized)	Omalizumab SC every 2 weeks based on weight and IgE levels every 2 or 4 weeks for 16 weeks (n = 16)			Placebo (n = 8)
	Cointervention(s): Maintenance treatment for asthma was standardized and controlled by a respiratory physician. Systemic steroids, ICS BPD dose ≥ 1,000 µg/day, antibiotics, LTRA, or nasal decongestants were not permitted.			
Population	*Inclusion Criteria:* Aged 18 years and older with chronic rhinosinusitis with nasal polyposis and comorbid asthma for more than 2 years; participants with both positive and negative skin prick tests were included; total IgE levels between 30 and 700 IU/mL *Exclusion Criteria:* NR			
	Median age (IQR), years Placebo: 45 (42 to 54) Omalizumab: 50 (44 to 56) N (%) female Placebo: 4 (50) Omalizumab: 3 (20)	*Race/ethnicity* NR	*Asthma duration/severity* NR, but all were required to have asthma for at least 2 years Median (IQR) AQLQ score Placebo: 4.73 (4.92 to 6.28) Omalizumab: 5.75 (5.41 to 6.38)	*Comorbidities* N (%) with allergy Placebo: 6 (75) Omalizumab: 7 (47) N (%) with aspirin hypersensitivity Placebo: 4 (50) Omalizumab: 8 (53)
Hanania et al., 2011[29]; EXTRA; NCT00314574				
Study Characteristics	Phase 3 RCT (efficacy of add-on therapy vs. placebo); 193 sites in the US and 4 sites in Canada *Years conducted:* 2005-2009 *Sponsor(s):* Genentech, Novartis Pharmaceuticals *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab SC min dose 0.008 mg/kg of body weight per IgE (IU/mL) every 2 wk or 0.016 mg/kg per IgE (IU/mL) every 4 wk for 48 wk (n = 427)			Placebo (n = 423)
	Cointervention(s): No dosage modifications of omalizumab, high-dose ICS, LABAs, or oral steroids or other controller medications allowed during study.			
Population	*Inclusion Criteria:* Aged 12 to 75 years, severe allergic asthma for at least 1 year, inadequate control despite treatment with high-dose ICS plus LABAs, with or without other controller medications; at least 1 asthma exacerbation during past 12 months requiring systemic steroids; objective evidence of allergy to perennial aeroallergen, baseline PBD FEV_1 40% to 80% of predicted, serum IgE 30 to 700 IU/mL, body weight 30 to 150 kg			

Characteristic	Details			
	Exclusion Criteria: Asthma exacerbation requiring intubation in the prior 12 months, exacerbation requiring treatment with systemic corticosteroids (or an increase in the baseline dose of OCS) in the past 30 days; active lung disease other than asthma; treatment with omalizumab in the prior 12 months, elevated serum IgE levels for reasons other than allergy; smoking history of 10 or more pack-years			
	Mean age (SD) Placebo: 45.3 (13.9) Omalizumab: 43.7 (14.3) N (%) female Placebo: 295 (70.1) Omalizumab: 262 (61.4)	*Race/ethnicity* White: Placebo: 318 (75.5) Omalizumab: 313 (73.3) Black: Placebo: 86 (20.4) Omalizumab: 90 (21.1) Asian or Pacific Islander: Placebo: 11 (2.6) Omalizumab: 12 (2.8) American Indian or Alaska Native: Placebo: 1 (0.2) Omalizumab: 3 (0.7) Other: Placebo: 5 (1.2) Omalizumab: 9 (2.1)	*Asthma duration/severity* Mean (SD) duration in years Placebo: 24.7 (15.8) Omalizumab: 22.8 (15.4) Mean (SD) AQLQ: Placebo: 3.9 (1.1) Omalizumab: 4.0 (1.1) Mean no. of asthma exacerbations requiring systemic corticosteroid treatment in the past year Placebo: 1.9 (1.5) Omalizumab: 2.0 (2.2) Mean total asthma symptom severity score Placebo: 3.9 (1.8	*Comorbidities* NR
Holgate et al., 2004[18]				
Study Characteristics	Phase NR steroid-sparing RCT; multicenter study globally; Argentina, Brazil, Canada, Czech Republic, France, Germany, Italy, Mexico, Netherlands, New Zealand, Poland, Russia, South Africa, Sweden, United Kingdom *Years conducted:* NR *Sponsor(s):* Novartis Pharma AG, Genentech *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab SC 150 or 300 mg every 4 weeks, or 225, 300, or 375 mg every 2 weeks (n = 126)		Placebo (n = 120)	
	Cointervention(s): SABAs were allowed as needed, along with continued use of LABAs; ICS were optimized during run-in phase, first 16 weeks of 32 weeks continued the optimized ICS dose; the ICS dose was then reduced every 2 weeks by 250 µg/day for the next 12 weeks until complete withdrawal or appearance of symptoms; the final 4 weeks continued the stable reduced dose reached at the end of the 12-week reduction phase.			
Population	*Inclusion Criteria:* Aged 12 to 75 years with severe asthma; all patients required ≥ 1,000 µg/day fluticasone for symptom control, demonstrated positive skin prick tests to aeroallergens and had serum total IgE 30 to 700 IU/mL			

Characteristic	Details			
	Exclusion Criteria: Theophylline or LTRAs, or with a history of anaphylaxis, recent near-fatal asthma, respiratory infection within 4 weeks of the study, parasitic infection or an elevated serum total IgE for reasons other than atopy were excluded. Patients taking oral steroids at baseline were included in a separate analysis, not reported in this manuscript.			
	Mean (range) Placebo: 40.5 (12 to 71 Omalizumab: 41.1 (12 to 75) N (%) female Placebo: 69 (57.5) Omalizumab: 81 (64.3)	*Race/ethnicity* NR	*Asthma duration/severity* Mean (SD) duration of disease, years Placebo: 22.3 (14.9) Omalizumab: 22.6 (15.7) Patients with history of emergency asthma treatment in previous year, N (%) Placebo: 30 (25.0) Omalizumab: 45 (35.7)	*Comorbidities* NR
Hoshino et al., 2012[57]; UMIN000002765				
Study Characteristics	Phase NR, RCT (efficacy of add-on therapy vs. placebo); site(s) not specified in Japan *Years conducted:* NR *Sponsor(s):* NR *Risk of bias:* High			
Interventions (N randomized)	Omalizumab SC 150 to 300 mg every 4 weeks or 225 to 375 mg every 2 weeks for 16 weeks (n = 14)		Control (no treatment) (n = 16)	
	Cointervention(s): All groups received conventional therapy as recommended by GINA; doses of ICS, LABA, and other concomitant asthma medications were kept constant in the last 4 weeks of the run-in period before randomization and were maintained during the treatment period.			
Population	*Inclusion Criteria:* Nonsmokers aged 20 to75 years, with severe allergic asthma, who were symptomatic despite treatment with a high-dose ICS plus LABA, with positive immediate responses on skin prick test to at least 1 common perennial allergen; total serum IgE ≥ 30 to ≤ 700 IU/mL; FEV_1 reversibility of ≥ 12% after inhalation of 200 µg salbutamol; methacholine provocation concentration causing 20% fall in FEV_1 < 8 mg/mL; treatment with ≥ 400 µg fluticasone propionate or its equivalent ICS and LABA for 8 weeks; other asthma medications, including theophylline and LTRAs taken regularly from > 8 weeks before randomization, were permitted; maintenance oral corticosteroids (maximum prednisolone 20 mg/day) were permitted if at least 1 exacerbation occurred in previous year *Exclusion Criteria:* Prior omalizumab treatment; requirement of omalizumab doses of > 750 mg per 4 weeks on the basis of serum IgE and body weight; treatment for an exacerbation within 4 weeks of randomization			
	Mean age (SD) Control: 51.2 (18.7) Omalizumab: 59.2 (11.4)	*Race/ethnicity* NR	*Asthma duration/severity* Mean (SD) duration of asthma, years	*Comorbidities* NR

Characteristic	Details			
	N (%) female Control: 12 (75) Omalizumab: 11 (78.6)		Control: 10.9 (7.2) Omalizumab: 16.3 (11.5) Mean (SD) FEV_1 % of predicted Control: 68.4 (12.2) Omalizumab: 65.3 (13.9)	
Humbert et al., 2005[19,20]; INNOVATE				
Study Characteristics	Phase NR, RCT (efficacy of add-on therapy vs. placebo); 108 centers in 14 countries; Australia, Belgium, Canada, France, Germany, Hungary, Israel, Italy, Mexico, Netherlands, South Africa, Spain, United Kingdom, US *Years conducted:* NR *Sponsor(s):* Novartis *Risk of bias:* High			
Interventions (N randomized)	Omalizumab SC dose based on weight and IgE level every 2 or 4 weeks (n = 245)		Placebo (n = 237)	
	Cointervention(s): Additional asthma medications, taken regularly from >4 weeks before randomization were permitted, including theophyllines, oral b2-agonists, and LTRAs; maintenance oral corticosteroids (maximum 20 mg/day) were permitted providing at least 1 of the exacerbations in the previous 12 months had occurred while on this therapy,			
Population	*Inclusion Criteria:* Aged 12 to 75; positive skin prick test to ≥ 1 perennial aeroallergen; total serum IgE level of ≥ 30 to ≤ 700 IU/mL; severe persistent asthma requiring regular treatment with > 1,000 µg/day BDP or equivalent and LABA; FEV_1 ≥ 40 to < 80% of predicted normal value and continuing asthma symptoms; FEV_1 reversibility ≥ 12% from baseline within 30 min of inhaled (up to 400 µg) or nebulized (up to 5 mg) salbutamol; ≥ 2 asthma exacerbations requiring systemic corticosteroids, or 1 severe exacerbation [PEF/FEV_1 < 60% of personal best, requiring systemic corticosteroids] resulting in hospitalization or ED treatment, in the past 12 months *Exclusion Criteria:* Smokers or smoking history of ≥ 10 pack-years; treatment for an exacerbation within 4 weeks of randomization (the run-in could be extended if necessary); use of methotrexate, gold salts, troleandomycin or cyclosporine within 3 months of the first visit; prior omalizumab treatment			
	Mean age (SD) Placebo: 43 (13) Omalizumab: 43 (13) N (%) female 279 (67%)	*Race/ethnicity* Caucasian: 327 (78) Black: 28 (7) Oriental: 5 (1) Other: 59 (14)	*Asthma duration/severity* Placebo: 22.7 (14.72) Omalizumab: 23.3 (15.23) Mean (SD) asthma daily symptom score Placebo: 3.3 (2.0) Omalizumab: 3.2 (2.1) Mean (SD) duration of asthma, years Placebo: 22.7 (14.7) Omalizumab: 22.3 (15.2)	*Comorbidities* NR

Characteristic	Details			
			Mean (SD) number of exacerbations in prior year Placebo: 2.41 (1.1) Omalizumab: 2.64 (1.6)	
Lanier et al., 2009[23]; Kulus et al., 2010[24]; NCT00079937				
Study Characteristics	Phase 3 steroid-sparing RCT; 90 centers in 7 countries: Argentina, Brazil, Canada, Colombia, Poland, South Africa, US *Years conducted:* 2004-2008 *Sponsor(s):* Novartis *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab 75 to 375 mg SC once or twice a month based on IgE and body weight (n = 421)		Placebo (n = 206)	
	Cointervention(s): ICS and other asthma control medications optimized during first 4 weeks for run-in, stable dose required for last 4 weeks of run-in for randomization, patients who remained symptomatic at end of run-in were randomized; steroid stable phase for first 24 weeks, then 28-week phase where ICS adjusted downward by 25% to 50% no more frequently than every 8 weeks based on criteria (FEV_1 equal or higher than baseline, ≤ 1 nighttime awakening requiring rescue medication in prior 7 days, use of rescue medication ≤ 3 times/day on 2 or fewer days within prior 7 days, mean daytime symptom score < 1.5 and daytime symptom score < 2 on any individual day in prior 7 days, no clinically significant exacerbations within the prior 4 weeks. Inhaled and nebulized b2-agonists allowed throughout the study.			
Population	*Inclusion Criteria:* Aged 6 to 11 years with moderate to severe allergic asthma inadequately controlled with medium- to high-dose ICS (> 200 µg/d fluticasone via DPI or equivalent) with or without other asthma control medications and a history of exacerbations (≥ 2 within 1 year, ≥ 3 within 2 years, or ≥ 1 severe exacerbation requiring hospitalization within 1 year), positive skin prick test or positive RAST for at least 1 common allergen, and increase ≥ 12% in FEV_1 after a maximum of 5 mg of nebulized albuterol, total serum IgE 30 to 1,300 IU/mL *Exclusion Criteria:* Use of systemic corticosteroids for reasons other than asthma, ß-adrenergic antagonists, anticholinergics, or immunosuppressants (not indicated for asthma); < 3 months of stable maintenance doses of desensitization therapy; history of food-related or drug related severe anaphylaxis or allergy to mAbs; asthma associated with aspirin or other nonsteroidal anti-inflammatory drugs; active lung disease; elevated IgE levels for reasons other than allergic asthma; cancer; abnormal electrocardiogram results in the previous month; or clinically significant laboratory abnormalities at the first visit			
	Mean age (SD) 8.6 (1.7) N (%) female 203 (32.3)	*Race/ethnicity* N (%) black: 99 (15.8) N (%) white : 377 (60.0) N (%) Asian: 2 (0.3) N (%) other: 150 (23.9)	*Asthma duration/severity* Duration: NR Asthma severity, N (%) Severe persistent: 402 (64) Moderate persistent: 219 (35) Mild persistent: 6 (1) Intermittent: 1 (0.2)	*Comorbidities* NR

Characteristic	Details			
Ledford et al., 2017[34]; XPORT; NCT01125748				
Study Characteristics	Phase 4/postmarketing RCT (discontinuation of long-term therapy vs. continuation); Multiple sites in the US *Years conducted:* 2010-2013 *Sponsor(s):* Novartis and Genentech *Risk of bias:* High			
Interventions (N randomized)	Continued omalizumab every 2 to 4 weeks based on body weight and IgE levels (n = 88)			Placebo (omalizumab discontinuation) (n = 88)
	Cointervention(s): Permitted ICSs, LABAs, LTRAs, 5-lipoxygenase inhibitors, anticholinergics (oral, inhaled, and/or nasal), mast cell stabilizers, theophylline, and/or chronic oral corticosteroids (prednisone equivalent, 2 to 40 mg/d or 5 to 80 mg every other day for at least 4 weeks before screening), allergen immunotherapy			
Population	*Inclusion Criteria:* Aged 17 to 70 years with moderate to severe persistent allergic asthma receiving long-term omalizumab and on stable doses of other asthma treatments for 2 or more months *Exclusion Criteria:* Current participation in another clinical study; acute asthma exacerbation that required initiation of systemic corticosteroids in past 2 months, increase in systemic corticosteroid dose, doubling of ICS dose, or ED visit or hospitalization in past 2 months; significant or unstable systemic disease; active lung disease other than asthma; 10 pack-year or longer smoking history; use of an experimental drug within 30 days before study screening; pregnancy, lactation, or any planned pregnancy during the study year; or increased serum IgE levels for reasons other than allergy			
	Mean age (SD) 51.5 (13) N (%) female 123 (70)	*Race/ethnicity* N (%) black: 21 (12) N (%) white: 148 (84.1)	*Asthma duration/severity* Mean (SD) duration of asthma , years 27.5 (17) Mean (SD) ACT score 21.3 (3.7) Mean (SD) ACQ score 1.0 (0.8)	*Comorbidities* NR
Milgrom et al., 2001[21]; Lemanske et al., 2002[22]				
Study Characteristics	Phase NR steroid-sparing RCT; multiple clinical sites in the US *Years conducted:* NR *Sponsor(s):* Genentech and Novartis *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab SC based on body weight and IgE levels every 2 or 4 weeks (n = 225)			Placebo (n = 109)
	Cointervention(s): During run-in, all patients were switched to BDP 42 µg/puff in doses equivalent to participant's previous maintenance dose; then dose was adjusted to maintain the previous level of asthma control. Participants who met criteria at the end of the run-in period were randomized. Participants were maintained on baseline dose of BPD for first 16 weeks (stable-			

Characteristic	Details			
	steroid phase), then dose was tapered gradually by 25% every 2 weeks for 8 weeks until total elimination or worsening of asthma. The minimum effective dose was maintained during the last 4 weeks of the study. Albuterol as rescue medication was permitted, prohibited all other asthma medications (except for treatment of exacerbations).			
Population	*Inclusion Criteria:* Aged 6 to 12 years with allergic asthma for at least 1 year, positive skin prick test for at least 1 common allergen, total serum IgE level between 30 and 1,300 IU/mL, body weight < 90 kg, FEV_1 ≥ 60% of predicted normal volume, at least 12% increase in FEV_1 over baseline within 30 minutes of taking 1 or 2 puffs of albuterol (90 mg/puff), and no significant change in the regular asthma medication and no acute asthma exacerbation requiring corticosteroid rescue for at least 4 weeks before enrollment *Exclusion Criteria:* Previous treatment with omalizumab, known hypersensitivity to any study drug, history of active lung disease other than asthma in past month, other significant systemic disease in past 3 months, elevated IgE levels for reasons other than asthma, children requiring doses > 750 mg per 4 weeks			
	Mean age (range) Placebo: 9.5 (6 to 12) Omalizumab: 9.4 (5 to 12) N (%) female Placebo: 67 (30) Omalizumab: 36 (33)	*Race/ethnicity* N (%) black Placebo: 14 (12.8) Omalizumab: 38 (16.9) N (%) white Placebo: 86 (78.9) Omalizumab: 168 (74.7) N (%) other Placebo: 9 (8.3) Omalizumab: 19 (8.4)	*Asthma duration/severity* Mean duration in years (range) Placebo: 6.1 (1 to 12) Omalizumab: 6.1 (1 to 12) Mean daytime asthma symptom score (median) Placebo: 0.57 (0.38) Omalizumab: 0.52 (0.31) Mean number of ED visits in past year Placebo: 0.6 Omalizumab: 0.6	*Comorbidities* NR
Mukherjee et al., 2019[47]; NCT02049294				
Study Characteristics	Phase NR, steroid-sparing RCT; 6 academic medical centers in Canada *Years conducted:* 2014-2017 *Sponsor(s):* Novartis and AllerGen NCE (Canadian Severe Asthma Clinical Trials Consortium) *Risk of bias:* High			
Interventions (N randomized)	Omalizumaub dose dependent on body weight and IgE level (n = 5)		Placebo (n = 6)	
	Cointervention(s): At 16 weeks into double-blind treatment, standardized steroid reduction every 4 weeks until week 32			
Population	*Inclusion Criteria:* Adults aged 18 to 75 with confirmed asthma (12% bronchodilator reversibility or PC20 methacholine less than 8 mg/mL), atopy (skin prick test positive to common aeroallergens and elevated serum IgE levels), symptomatic (ACQ-5 ≥ 1.5) with evidence of sputum eosinophils (> 3%) despite high-dose maintenance corticosteroid therapy (≥ 1,500 µg fluticasone propionate or equivalent with or without additional prednisone)			

Characteristic	Details			
	Exclusion Criteria: Current smokers, former smokers with >20 pack-years, comorbid disease, current or previous omalizumab use, current use of other biologic medications, post bronchodilator FEV_1 < 50%, pregnant or lactating women			
	Mean age (SD) Placebo: 58.8 (9.5) Omalizumab: 54.5 (17.3) N (%) female Placebo: 1 (20) Omalizumab: 1 (25)	*Race/ethnicity* NR	*Asthma duration/severity* Duration: NR ACQ-5 Placebo: 2.2 (0.67) Omalizumab: 1.79 (0.5) Median (min, max) inhaled corticosteroid use Placebo: 1,500 (1,250, 2,400) Omalizumab: 1,450 (800, 2,000)	*Comorbidities* NR
Ohta et al., 2009[25]; NCT00232050				
Study Characteristics	Phase NR, RCT (efficacy of add-on therapy vs. placebo); 73 centers in Japan *Years conducted:* 2002-2005 *Sponsor(s):* Novartis Pharma K.K. *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab SC every 2 or 4 weeks at a dose based on weight and baseline IgE levels (n = 158)		Placebo (n = 169)	
	Cointervention(s): Doses of inhaled steroids and other concomitant asthma medications were kept stable during treatment; patients were permitted to use rescue medication as needed.			
Population	*Inclusion Criteria:* Aged 20 to 75; moderate to severe asthma; treatment with BDI inhaler at ≥800 mg/day (or equivalent) and 1 or more additional controller meds (LABA, sustained-release theophylline, LTRA, oral corticosteroid); positive skin test or in vitro reactivity to perennial aeroallergen; serum total IgE of 30 to 700 IU/mL; insufficient asthma control meeting 1 of 5 criteria: asthma symptoms interfere with night sleep ≥ 1 day/wk, asthma symptoms restrict daily activities, rescue meds needed ≥ 1 day/wk, PEF diurnal variation ≥ 1 day/wk, FEV or mean PEF value in range of 40-80% of predicted normal value *Exclusion Criteria:* Complicated pulmonary disease considered to interfere with evaluation; chronic use of oral corticosteroid; use of immunosuppressant drug within 3 months of first visit; positive skin reaction to study drug; history of anaphylaxis			
	Mean age (SD) Placebo: 49 (14) Omalizumab: 49 (15) N (%) female 171 (54)	*Race/ethnicity* 315 (100) Asian	*Asthma duration/severity* Mean (SD) in years Placebo: 18 (13) Omalizumab: 20 (15) N (%) GINA 2002 Classification Moderate persistent: 14 (4) Severe persistent: 301 (96)	*Comorbidities* NR

Characteristic	Details			
			Hospitalization due to asthma in previous year: 32 (10) ER visits due to asthma in previous year: 62 (20)	
PIllai et al., 2016[33]; NCT01113437				
Study Characteristics	Phase NR, treatment-reduction RCT; 3 hospital-based clinics in the United Kingdom *Years conducted:* 2010-2012 *Sponsor(s):* Guy's and St. Thomas' Charity (NIHR); Novartis United Kingdom *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab SC every 2 or 4 weeks, dosed based on body weight and IgE levels (n = 9)		Placebo (n = 9)	
	Cointervention(s): Patients were asked to comply with their usual medications during the first treatment phase. At 12 to 14 weeks, treatment reduction phase occurred. Patients were instructed to discontinue all inhaled and oral LTRA and theophylline and substitute with budesonide/formoterol combination therapy (Symbicort 100/6 Turbohaler 2 puffs twice daily for 4 weeks and reduced to 1 puff twice daily unti lthe end of the study) with terbutaline turbhaler for rescue medication as needed. For patients taking regular oral steroids, an attempt was also made to reduce the dosage according to a predetermined regimen depending on dosage at entry.			
Population	*Inclusion Criteria:* Aged 18 to 60; moderate or severe nonatopic asthma treated with ICS for at least 6 months; day and night symptoms 3 or more days/week in the 3 months before screening visit despite taking ICS with or without b2-agonists or LTRA; PBD FEV1 40 to 80% of predicted, reversibility ≥ 12% in response to inhaled b2-agonists in past 2 years; negative skin prick and/or in vitro IgE tests to a range of 12 common aeroallergens *Exclusion Criteria:* Smoking in past year or total smoking history > 0.5 pack-years; pregnant or lactating females or those at risk of pregnancy; treatment with > 2,000 µg/day beclometasone, 1,600 µg/day budesonide or 1,000 µg/day fluticasone by inhalation or regular systemic steroids; hospitalization for asthma or exacerbation requiring systemic corticosteroid therapy within 3 months; history of life-threatening asthma, defined as an asthma episode that required intubations and/or was associated with hypercapnia, respiratory arrest and/or hypoxic seizure; pre-bronchodilator FEV_1 < 40% predicted; autoimmune disease, renal or hepatic impairment, hyperimmunoglobulin E syndrome, allergic bronchopulmonary aspergillosis, or diabetes mellitus			
	Median (range) in years Placebo: 54 (25 to 59) Omalizumab: 47 (22 to 66) N (%) female 8 (50)	*Race/ethnicity* NR	*Asthma duration/severity* Duration: NR Median (range) ACQ score Placebo: 2.42 (0.71 to 3.28) Omalizumab: 2.28 (1.43 to 3.43)	*Comorbidities* Comorbidities: NR
Sly et al., 2017[10]; RELAX; ACTRN12611001106921				
Study Characteristics	Phase 3 RCT (efficacy of add-on therapy vs. placebo specifically during winter); 3 children's hospitals in Australia *Years conducted:* 2012-2014			

Characteristic	Details			
	Sponsor(s): National Health and Medical Research Council *Risk of bias:* High			
Interventions (N randomized)	Omalizumab every 2 or 4 weeks based on weight and IgE level timed over the winter season (n = 14)			Placebo (n = 13)
	Cointervention(s): Standard asthma treatment as prescribed by their treating physician including inhaled corticosteroids			
Population	*Inclusion Criteria:* Aged 6 to 15 years with an ED visit for severe acute asthma exacerbation in the previous winter, positive skin prick test responses to aeroallergens, atopic family history *Exclusion Criteria:* Hypersensitivity to omalizumab, treatment with omalizumab in the past 30 days, prolonged high dose of oral steroids, participation in another RCT in the past 3 months, significant medical condition other than asthma that was likely to interfere with study			
	Mean age (SD) 11 (3) N (%) female 13 (48)	*Race/ethnicity* NR	*Asthma duration/severity* Mean (SD) in years: 7.7 (4.5) Mean (SD) ACT score Placebo: 17 (4.2) Omalizumab: 16 (5.8) Median (IQR) no. of exacerbations in prior 12 months Placebo: 2.0 (1.5, 3.0) Omalizumab: 2.7 (1.8, 3.0)	*Comorbidities* NR
Soler et al., 2001[54]; Buhl et al., 2002[55,56]				
Study Characteristics	Phase NR, steroid-sparing RCT; multicenter globally, number of sites not specified in Europe, South Africa, Australia, and US *Years conducted:* NR *Sponsor(s):* Novartis Pharma AG and Genentech Inc. *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab SC 150 to 300 mg every 4 weeks or 450 to 750 mg every 2 weeks for 28 weeks based on body weight and IgE levels (n = 274)			Placebo (n = 272)
	Cointervention(s): After screening, patients entered a run-in period of 4 to 6 weeks, during which time all patients were switched to inhaled BDP and the dose was adjusted to establish the lowest dose required for control of asthma symptoms. Patients were maintained on this dose of BDP for the final 4 weeks of run-in. The baseline dose of concomitant BDP was maintained during the first 16 weeks of the study (steroid-stable phase). In the following 12 weeks (steroid-reduction phase), the BDP dose was reduced by 25% every 2 weeks over the first 8 weeks until total elimination, or until there was a decrease in FEV_1 of ≤ 20% compared to the last measurement of the previous phase or the development of an event defining asthma worsening. Once the lowest effective dose of BDP for asthma control was established, patients were maintained on this dose for the remaining 4 weeks of the core study. The use of rescue inhaled salbutamol was permitted throughout the core study. The core study was			

Characteristic	Details			
	followed by a 24-week double-blind extension during which patients continued on randomized treatment and the lowest effective dose of BDP (which could be adjusted accordingly). During the extension phase, the use of concomitant asthma medication was liberalized, and investigators were allowed to administer additional asthma medication and/or switch patients to other asthma medications if deemed necessary.			
Population	*Inclusion Criteria:* Aged 12 to 75 yrs with a diagnosis of asthma of at ≥ 1 yr duration who met the standard criteria of the American Thoracic Society and a positive skin-prick test to at least 1 of the allergens *Dermatophagoides farinae*, *D. pteronyssinus*, dog or cat; serum total IgE level ≥ 30 and ≤ 700 IU/mL and body weight ≤ 50 kg; baseline FEV_1 off bronchodilators ≥ 40% and ≤80% of predicted increasing by ≥ 12% within 30 min of taking inhaled salbutamol; a mean total daily symptom score of ≥ 3.0 (maximum 9) during the 14 days before randomization; treatment with inhaled corticosteroids in doses equivalent to 500 to 1,200 mg of BDP per day for ≥ 3 months before randomization and use of $ß_2$-adrenoceptor agonists on an as-needed or regular basis. Asthma had to be stable, with no significant change in regular medication and no acute exacerbation requiring additional corticosteroid treatment for ≥ 1 month before the screening visit. *Exclusion Criteria:* Patients regularly taking oral corticosteroids were not included.			
	Mean (range) Placebo: 39.0 (12 to 72) Omalizumab: 40.0 (12 to 76) N (%) female Placebo: 145 (53) Omalizumab: 133 (49)	*Race/ethnicity* N (%) Caucasian Placebo: 242 (89) Omalizumab: 265 (93) N (%) other Placebo: 30 (11) Omalizumab: 18 (7)	*Asthma duration/severity* Mean (range) duration of asthma, years Placebo: 19.1 (1 to 63) Omalizumab: 20.3 (2 to 68) N (%) with moderate asthma severity Placebo: 213 (78.3) Omalizumab: 214 (78.1) N (%) with severe asthma severity (baseline FEV_1 ≤65% predicted and a mean total symptom score of >4 for the last 14 days of the run-in period Placebo: 59 (21.7) Omalizumab:	*Comorbidities* N (%) with a history of atopic dermatitis: Placebo: 28 (10.3) Omalizumab: 24 (8.8) N (%) with a history of seasonal allergic rhinitis: Placebo: 177 (65.1) Omalizumab: 183 (66.8) N (%) with a history of perennial allergic rhinitis: Placebo: 209 (76.8
Vignola et al., 2004[58]; SOLAR				
Study Characteristics	Phase NR, RCT (efficacy of add-on therapy vs. placebo); study sites in 11 countries; Argentina, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Norway, Sweden, United Kingdom *Years conducted:* NR *Sponsor(s):* Novartis, Genentech *Risk of bias:* Moderate			

Characteristic	Details			
Interventions (N randomized)	Omalizumab SC dose dependent on body weight and IgE every 2 or 4 weeks (n = 209)			Placebo (n = 196)
	Cointervention(s): ICS doses standardized during run-in period, during trial investigators were allowed to adjust ICS dose up or down to achieve optimal lowest dose; other asthma therapy and nasal steroids were used if dose stable during run-in phase.			
Population	*Inclusion Criteria:* Aged 12 to 75 years; history of allergic asthma for at least 1 year with ≥ 12% increase in FEV_1 after 400 µg salbutamol; IgE level ≥ 30 to ≤ 1,300 IU/mL; positive skin-prick test to 1 or more indoor allergen to which the patient would be exposed on a daily basis for the duration of the study, thus helping ensure that it was clinically relevant to the patient's disease; history of moderate to severe perennial allergic rhinitis symptoms for ≥ 2 years; receiving ≥ 400 µg/day ICS; history of ≥ 2 unscheduled medical visits for asthma during past year or ≥3 in past 2 years; total score of >64/192 (32 items, amended to use a 0 to 6 scale) in AQLQ; > 56/168 (28 items, 0–6 scale) in Rhinitis Quality of Life Questionnaire *Exclusion Criteria:* Treatment with systemic corticosteroids, long-acting antihistamines, cromolyn sodium, nedocromil sodium, oral b2-adrenoreceptor agonists, theophylline, LTRAs, inhaled anticholinergics, methotrexate, gold salts, cyclosporin, allergen-specific immunotherapy; active (in season) seasonal allergic rhinitis; acute sinusitis; chest infection; persistent nonallergic rhinitis; pregnancy; platelet count of ≤ 130			
	Mean age (SD) Placebo: 39 (15) Omalizumab: 38 (15) N (%) female 223 (55)	*Race/ethnicity* NR	*Asthma duration/severity* Mean (SD) duration of asthma, years Placebo: 20.4 (13.2) Omalizumab: 19.2 (13.3) Mean (SD) number of exacerbations requiring oral steroids in past year Placebo: 2.1 (1.4) Omalizumab: 2.1 (1.3)	*Comorbidities* Allergic rhinitis: 405 (100)
Zielen et al., 2013[59]				
Study Characteristics	Phase NR, RCT (efficacy of add-on therapy vs. placebo); multicenter, sites in Germany *Years conducted:* NR *Sponsor(s):* Novartis *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab SC based on body weight and IgE level (low IgE group) (n = 18)	Omalizumab SC based on body weight and IgE level (high IgE group) (n = 16)		Placebo (n = 16)
	Cointervention(s): Concomitant medication including short-acting beta-agonists, LTRAs, low-dose ICS were permitted provided they remained stable through the study. High-dose ICS, long-acting beta-agonists, oral steroids (within first 4 weeks) and antihistamines (within 24 h of bronchoprovocation and skin prick tests) and theophylline were not permitted.			
Population	*Inclusion Criteria:* Aged 18 to 65; weight 40 to 150 kg; asthma with PBD FEV_1 ≥ 65% predicted; no asthma exacerbation for ≥4 weeks; well-characterized skin reactivity to a specific allergen within 2 years; 20% fall in FEV_1 in response to methacholine at a			

Characteristic	Details			
	provocative concentration ≤16 mg/mL and 20% fall in FEV_1 in response to an allergen at a cumulative provocative dose in a bronchoprovocation test *Exclusion Criteria:* History of asthma attack requiring ED visit in previous 6 weeks; history of an asthma attack requiring intubation and mechanical ventilation in prior 12 months; asthma exacerbation requiring oral or intravenous corticosteroids in previous 3 months; history of intolerance to methacholine or allergen bronchoprovocation; current smokers with smoking history of ≥5 pack-years; elevated IgE due to suspected parasitosis			
	Mean age (SD) Placebo: 34 (10) Omalizumab low IgE: 36 (12) Omalizumab high IgE: 29 (11) N (%) female 22 (44)	*Race/ethnicity* Caucasian: 49 (98) Black: 1 (2)	*Asthma duration/severity* Duration: NR Severity: NR	*Comorbidities* NR

Abbreviations. µg: microgram; ACQ: Asthma Control Questionnaire; ACT: asthma control test; AQLQ: Asthma Quality of Life Questionnaire; BDI: beclomethasone dipropionate inhaler; BDP: beclomethasone dipropionate; BPD: budesonide dipropionate; BSC: best standard care; C-ACT: Childhood Asthma Control Test; ECG: electrocardiogram; ED: emergency department; ENT: ear, nose, throat; FEV_1: forced expiratory volume in 1 second; GINA: Global Initiative for Asthma; h: hour; ICS: inhaled corticosteroids; IgE; immunoglobin E; IQR; interquartile ratio; IU: international unit; IV: intravenous; LABA: long-acting beta-agonists; LTRA: leukotriene receptor antagonist; mAbs: monoclonal antibodies; NAEP: National Asthma Education Program; NHLBI: National Heart, Lung, and Blood Institute; NR: not reported; NSAID: nonsteroidal anti-inflammatory drug; OCS: oral corticosteroids; PBD: pre-bronchodilator; PC20: provocative concentration of methacholine resulting in 20% drop in FEV_1; PEF: peak expiratory flow; RAST: radioallergosorbent test; RCT: randomized controlled trial; SABA: short-acting beta-agonists; SC: subcutaneous; SD: standard deviation; wk: week.

Table B11. Effectiveness Outcomes for RCT of Omalizumab for Asthma

Outcome	Group (n)	Result
Ayres et al., 2004[11]		
Adjusted annualized rate of exacerbations (1 yr)	Best standard care (n = 89)	Mean (SD) rate: 2.86 (NR) Exacerbation defined as use of systemic steroids
	Best standard care (n = 89)	Mean (SD) rate: 9.76 (NR) Exacerbation defined as ≥ 1 course of systemic steroids or antibiotics for ≥ 2 days, ≥ 2 missed school/work days (or significantly reduced performance for nonworking adult patients as judged by patient), unscheduled physician visit, hospitalization or ED visit.
	Omalizumab (n = 191)	Mean (SD) rate: 1.12 (NR) IRR: NR 60.8% reduction (95% CI, 46.9% to 71.0%) Exacerbation defined as use of systemic steroids
	Omalizumab (n = 191)	Mean (SD) rate: 4.92 (NR) Calculated IRR (95% CI): 0.50 (unable to calculate) 49.6% reduction (95% CI, 27.8% to 64.8%) Exacerbation defined as ≥ 1 course of systemic steroids or antibiotics for ≥ 2 days, ≥ 2 missed school/work days (or significantly reduced performance for nonworking adult patients as judged by patient), unscheduled physician visit, hospitalization or ED visit.
Median time to first asthma exacerbation	Best standard care (n = 89) Omalizumab (n = 191)	BSC: 75 days Omalizumab: 126 days Kaplan-Meier survival analysis *P* = .03 Median time to first clinically significant asthma excerbation BSC: 266 days Omalizumab: could not be estimated because fewer than 50% experienced this event Kaplain-Meier survival analysis *P* = .001
Exacerbations (1 yr)	Best standard care (n = 106)	Events of total N (%): 78 of 106 (74%) Exacerbations defined as ≥ 1 of the following events because of asthma: course of systemic corticosteroids or antibiotics for ≥ 2 days, ≥ 2 missed school/work days (or significantly reduced performance for nonworking adult patients, as judged by the patient), unscheduled physician visit, or hospitalization/ED visit.
	Omalizumab (n = 206)	Events of total N (%): 102 of 206 (50%) Calculated RR (95% CI): 0.67 (0.56 to 0.80) Exacerbations defined as ≥ 1 of the following events because of asthma: course of systemic corticosteroids or antibiotics for ≥ 2 days, ≥ 2 missed school/work days (or significantly reduced performance for nonworking adult patients, as judged by the patient), unscheduled physician visit, or hospitalization/ED visit.
Required systemic steroids (1 yr)	Best standard care (n = 89)	Events of total N (%): 58 of 89 (65%)
	Omalizumab (n = 191)	Events of total N (%): 99 of 191 (52%) Calculated RR (95% CI): 0.80 (0.65 to 0.98)
Number with all-cause ED visit (1 yr)	Best standard care (n = 89)	Events of total N (%): 17 of 89 (19%)
	Omalizumab (n = 191)	Events of total N (%): 24 of 191 (13%) Calculated RR (95% CI): 0.66 (0.37 to 1.16)

Outcome	Group (n)	Result
Number with all-cause hospitalization (1 yr)	Best standard care (n = 89)	Events of total N (%): 8 of 89 (9%)
	Omalizumab (n = 191)	Events of total N (%): 16 of 191 (8%) Calculated RR (95% CI): 0.93 (0.41 to 2.09)
Wasserfallen asthma symptom score mean change from baseline (1 yr)	Best standard care (n = 89)	Mean (SD) change from baseline: 0.7
	Omalizumab (n = 191)	Mean (SD) change from baseline: 6.2 Difference from placebo (95% CI): NR; *P* < .001
Bardelas et al., 2012[28]; NCT00267202		
ACT mean change from baseline (8 wk)	Omalizumab (n = 136)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): 0.35 (NR); *P* = .432
ACT mean change from baseline (16 wk)	Omalizumab (n = 136)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): 0.58 (NR); *P*= .230
ACT mean change from baseline (24 wk)	Omalizumab (n = 136)	Mean (SD) change from baseline: 5.01 Difference from placebo (95% CI): 0.64 (-0.3 to 1.59); *P* = .178
Number of days per week with asthma symptoms mean change from baseline (24 wk)	Omalizumab (n = 136)	Mean (SD) change from baseline: -2.16 (NR) Difference from placebo (95% CI): NR (-0.99 to 0.21); *P* = .202
	Placebo (n = 135)	Mean (SD) change from baseline: -1.77 (NR)
Nocturnal awakenings per week mean change from baseline (24 wk)	Omalizumab (n = 136)	Mean (SD) change from baseline: -1.45 (NR) Difference from placebo (95% CI): NR (-0.71 to -0.07); *P* = .019
	Placebo (n = 135)	Mean (SD) change from baseline: -1.06 (NR)
Physician-rated global evaluation of treatment effectiveness, score of excellent or good (24 wk)	Omalizumab (n = 136)	Events of total N (%): 75 of 136 (55%) Reported RR (95% CI): NR; *P* = .118 Calculated RR (95% CI): 1.15 (0.91 to 1.44)
	Placebo (n = 135)	Events of total N (%): 65 of 135 (48%)
Bousquet et al., 2011[26]; Siergiejko et al., 2011[27]; NCT00264849		
Rate of exacerbations (32 wk)	Best standard care (n = 128)	Mean (SD) rate: 0.98
	Omalizumab (n = 272)	Mean (SD) rate: 0.55 IRR (95% CI): 0.57 (0.42 to 0.78); *P* < .001 Defined as requiring treatment with systemic steroids
	Best standard care (n = 128)	Mean (SD) rate: 0.42

Outcome	Group (n)	Result
Rate of severe exacerbations (32 wk)	Omalizumab (n = 272)	Mean (SD) rate: 0.24 IRR (95% CI): 0.56 (0.34 to 0.92); *P* = .0023 Defined as requiring treatment with systemic steroids *and* hospital admission or intubation, ED visit, breathlessness at rest, PEF or FEV_1 < 60% of predicted/personal best, >30% fall from personal best PEF on 2 successive days
Persistency of response (32 wk)	Best standard care (n = 128) Omalizumab (n = 274)	Persistency of response BSC: 18 of 29 (63.3%; 95% CI, 46.5 to 82.0) Omalizumab: 171 of 190 (91.4%; 95% CI, 87.4 to 95.5) Persistency of nonresponse BSC: 57 of 63 (90.5%; 95% CI, 83.2 to 97.7) Omalizumab: 44 of 71 (62.0%; 95% CI, 50.7 to 73.3) OCS reduction among subgroup of 82 participants (59 omalizumab, 23 OAT) that were receiving OCS at baseline Mean (SD) % change in dose from baseline: OAT: 18.3% (85.13) Omalizumab: -45% (50.22) *P* = .002
Rate of exacerbations requiring hospitalization (32 wk)	Best standard care (n = 128)	Mean (SD) rate: 0.14
	Omalizumab (n = 272)	Mean (SD) rate: 0.05 IRR (95% CI): 0.33 (0.12 to 0.94); *P* = .037
Rate of exacerbations requiring ED visit (32 wk)	Best standard care (n = 128)	Mean (SD) rate: 0.83
	Omalizumab (n = 272)	Mean (SD) rate: 0.35 IRR (95% CI): 0.40 (0.24 to 0.65); *P* < .001
ACQ mean change from baseline (16 wk)	Best standard care (n = 128)	Mean (SE) change from baseline: -0.11 (0.10)
	Omalizumab (n = 272)	Mean (SE) change from baseline: -0.78 (0.07) Difference from placebo (95% CI): -0.67 (-0.88 to -0.46); *P* < .001
ACQ mean change from baseline (32 wk)	Best standard care (n = 128)	Mean (SE) change from baseline: -0.04 (0.11)
	Omalizumab (n = 272)	Mean (SE) change from baseline: -0.91 (0.08) Difference from placebo (95% CI): -0.87 (-1.09 to -0.65); *P* < .001
Physician-rated global evaluation of treatment effectiveness, score of excellent or good (16 wk)	Best standard care (n = 93)	Events of total N (%): 29 of 93 (31%)
	Omalizumab (n = 261)	Events of total N (%): 190 of 261 (73%) Calculated RR (95% CI): 2.33 (1.71 to 3.19)
Physician-rated global evaluation of treatment effectiveness, score of	Best standard care (n = 104)	Events of total N (%): 25 of 104 (24%)
	Omalizumab (n = 259)	Events of total N (%): 199 of 259 (77%) Calculated RR (95% CI): 3.20 (2.26 to 4.53)

Outcome	Group (n)	Result
excellent or good (32 wk)		
Busse et al., 2001[13]; Lanier et al., 2013[14]; Finn et al., 2002[15]		
Rate of exacerbations (16 wk) Steroid-stable phase	Omalizumab (n = 268)	Mean (SD) rate: 0.28 (NR) Reported IRR: NR; *P* = .006 Calculated IRR (95% CI): 0.52 (0.33 to 0.99)
	Placebo (n = 257)	Mean (SD) rate: 0.54 (NR)
Rate of exacerbations (28 wk) Steroid-reduction phase	Omalizumab (n = 268)	Mean (SD) rate: 0.39 (NR) Reported IRR: NR; *P* = .003 Calculated IRR (95% CI): 0.59 (0.42 to 0.94)
	Placebo (n = 257)	Mean (SD) rate: 0.66 (NR)
Rate of exacerbations (1 yr) 24-wk extension phase	Omalizumab (n = 268)	Mean (SD) rate: 0.60 (NR) Reported IRR: NR; *P* = .023 Calculated IRR (95% CI): 0.72 (0.55 to 1.00)
	Placebo (n = 257)	Mean (SD) rate: 0.83 (NR)
Exacerbations (16 wk) Steroid-stable phase	Omalizumab (n = 268)	Events of total N (%): 39 of 268 (15%) Calculated RR (95% CI): 0.62 (0.43 to 0.90) Defined as worsening requiring systemic steroids or doubling of the baseline inhaled ICS dose
	Placebo (n = 257)	Events of total N (%): 60 of 257 (23%) Defined as worsening requiring systemic steroids or doubling of the baseline inhaled ICS dose
Exacerbations (28 wk) Steroid-reduction phase	Omalizumab (n = 268)	Events of total N (%): 57 of 268 (21%) Calculated RR (95% CI): 0.66 (0.49 to 0.88) Defined as worsening requiring systemic steroids or doubling of the baseline inhaled ICS dose
	Placebo (n = 257)	Events of total N (%): 83 of 257 (32%) Defined as worsening requiring systemic steroids or doubling of the baseline inhaled ICS dose
Exacerbations (1 yr) 24-wk extension phase	Omalizumab (n = 245)	Events of total N (%): 78 of 245 (32%) Calculated RR (95% CI): 0.74 (0.59 to 0.95) Defined as worsening requiring systemic steroids or doubling of the baseline inhaled ICS dose
	Placebo (n = 215)	Events of total N (%): 92 of 215 (43%) Defined as worsening requiring systemic steroids or doubling of the baseline inhaled ICS dose
Excacerbations requiring hospital (28 wk)	Omalizumab (n = 268)	Events of total N (%): 1 of 268 (0.3%) Calculated RR (95% CI): 0.48 (0.04 to 5.26)
	Placebo (n = 257)	Events of total N (%): 2 of 257 (1%)
Excacerbations requiring hospital (1 yr)	Omalizumab (n = 245)	Events of total N (%): 1 of 245 (0.4%) Calculated RR (95% CI): 0.29 (0.03 to 2.79)
	Placebo (n = 215)	Events of total N (%): 3 of 215 (1%)
Median reduction in ICS dose (28 wk)	Omalizumab (n = 268) Placebo (n = 257)	Placebo: 50% Omalizumab: 75% *P* < .001

Outcome	Group (n)	Result
50% or more reduction in inhaled steroid use (28 wk) Steroid-reduction phase	Omalizumab (n = 268)	Events of total N (%): 194 of 268 (72%) Calculated RR (95% CI): 1.32 (1.15 to 1.51)
	Placebo (n = 257)	Events of total N (%): 141 of 257 (55%)
50% or more reduction in inhaled steroid use (1 yr) 24-wk extension phase	Omalizumab (n = 245)	Events of total N (%): 113 of 245 (46%) Calculated RR (95% CI): 1.40 (1.11 to 1.76)
	Placebo (n = 215)	Events of total N (%): 71 of 215 (33%)
Proportion no longer requiring ICS (28 wk) Steroid-reduction phase	Omalizumab (n = 268)	Events of total N (%): 106 of 268 (40%) Calculated RR (95% CI): 2.07 (1.55 to 2.78)
	Placebo (n = 257)	Events of total N (%): 49 of 257 (19%)
Proportion no longer requiring ICS (1 yr) 24-wk extension phase	Omalizumab (n = 245)	Events of total N (%): 66 of 245 (27%) Calculated RR (95% CI): 2.63 (1.68 to 4.11)
	Placebo (n = 215)	Events of total N (%): 22 of 215 (10%)
Daily asthma symptom score mean change from baseline (16 wk) Steroid-stable phase	Omalizumab (n = 268)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): NR; *P* = .001 Data only reported in figure
Patient-rated global evaluation of treatment effectiveness, score of excellent or good (28 wk) Steroid-reduction phase	Omalizumab (n = 268)	Events of total N (%): 162 of 268 (60%) Calculated RR (95% CI): 1.59 (1.32 to 1.90)
	Placebo (n = 257)	Events of total N (%): 98 of 257 (38%)
Physician-rated global evaluation of treatment effectiveness, score of excellent or good (28 wk)	Omalizumab (n = 268)	Events of total N (%): 142 of 268 (53%) Calculated RR (95% CI): 1.59 (1.29 to 1.95)
	Placebo (n = 257)	Events of total N (%): 86 of 257 (33%)

Outcome	Group (n)	Result
Steroid-reduction phase		
AQLQ MID response (16 wk) Steroid-stable phase	Omalizumab (n = 268)	Events of total N (%): 172 of 268 (64%) Calculated RR (95% CI): 1.24 (1.07 to 1.49)
	Placebo (n = 257)	Events of total N (%): 133 of 257 (52%)
AQLQ MID response (28 wk) Steroid-reduction phase	Omalizumab (n = 268)	Events of total N (%): 178 of 268 (66%) Calculated RR (95% CI): 1.21 (1.05 to 1.39)
	Placebo (n = 257)	Events of total N (%): 141 of 257 (55%)
AQLQ MID response (1 yr) 24-wk extension phase	Omalizumab (n = 245)	Events of total N (%): 183 of 245 (75%) Calculated RR (95% CI): 1.14 (1.01 to 1.29)
	Placebo (n = 215)	Events of total N (%): 141 of 215 (66%)
AQLQ mean change from baseline (16 wk) Steroid-stable phase	Omalizumab (n = 268)	Mean (SD) change from baseline: 0.93 (NR) Difference from placebo (95% CI): NR; *P* < .01
	Placebo (n = 257)	Mean (SD) change from baseline: 0.66 (NR)
AQLQ mean change from baseline (28 wk) Steroid-reduction phase	Omalizumab (n = 268)	Mean (SD) change from baseline: 0.97 (NR) Difference from placebo (95% CI): NR; *P* < .01
	Placebo (n = 257)	Mean (SD) change from baseline: 0.7 (NR)
AQLQ mean change from baseline (1 yr) 24-wk extension phase	Omalizumab (n = 268)	Mean (SD) change from baseline: 1.19 (NR) Difference from placebo (95% CI): NR; *P* < .01
	Placebo (n = 257)	Mean (SD) change from baseline: 0.91
Busse et al., 2011[30]; ICATA; NCT00377572		
Exacerbations (60 wk)	Omalizumab (n = 208)	Events of total N (%): 63 of 208 (30%) Calculated RR (95% CI): 0.62 (0.48 to 0.80)
	Placebo (n = 211)	Events of total N (%): 103 of 211 (49%)
ACT mean score at follow-up (60 wk)	Omalizumab (n = 195)	Mean (SE) change from baseline: 22.5 (0.22) Difference from placebo (95% CI): 0.19 (-0.42 to 0.79); *P* = .54
	Placebo (n = 191)	Mean (SE) change from baseline: 22.3 (0.22)
C-ACT mean score at follow-up (60 wk)	Omalizumab (n = 195)	Mean (SE) change from baseline: 23.0 (0.21) Difference from placebo (95% CI): 0.78 (0.21 to 1.35); *P* = .007
	Placebo (n = 191)	Mean (SE) change from baseline: 22.2 (0.21)
Number of days with	Omalizumab (n = 195)	Mean (SD) change from baseline: 1.48 (NR) Difference from placebo (95% CI): -0.48 (-0.77 to -0.2); *P* < .001

Outcome	Group (n)	Result
asthma symptoms in prior 2 weeks mean change from baseline (60 wk)	Placebo (n = 191)	Mean (SD) change from baseline: 1.96 (NR)
Busse et al., 2013[16]		
Rate of exacerbations (24 wk)	Omalizumab (n = 157)	Mean (SD) rate: 0.21 (NR) IRR (95% CI): 0.73 (0.44 to 1.24); *P* = .25 Defined as worsening of asthma requiring treatment with oral or IV steroids or doubling of baseline ICS dose for 3 or more days
	Placebo (n = 171)	Mean (SD) rate: 0.26 Defined as worsening of asthma requiring treatment with oral or IV steroids or doubling of baseline ICS dose for 3 or more days
Exacerbations (24 wk) 2607	Omalizumab (n = 157)	Events of total N (%): 24 of 157 (15%) Calculated RR (95% CI): 0.79 (0.49 to 1.28) IRR in preplanned subgroups defined by high (≥300/µl) and low (< 300/µl) eosinophil counts. High: IRR 0.41 (95% CI, 0.20 to 0.82) Low: IRR 1.07 (95% CI, 0.45 to 2.53)
	Placebo (n = 171)	Events of total N (%): 33 of 171 (19%)
Daytime asthma symptom score mean change from baseline (24 wk)	Omalizumab (n = 157)	Mean (SD) change from baseline: -0.73 (0.72) Difference from placebo (95% CI): -0.05 (-0.19 to 0.09); NS
	Placebo (n = 171)	Mean (SD) change from baseline: -0.67 (0.72)
Nocturnal asthma symptom score mean change from baseline (24 wk)	Omalizumab (n = 157)	Mean (SD) change from baseline: -0.48 (0.77) Difference from placebo (95% CI): 0.01 (-0.12 to 0.14)
	Placebo (n = 171)	Mean (SD) change from baseline: -0.49 (0.67)
Chanez et al., 2010[31]; NCT00454051		
Exacerbations (16 wk)	Omalizumab (n = 20)	Events of total N (%): 11 of 20 (55%) Calculated RR (95% CI): 1.51 (0.63 to 3.64) Exacerbation not defined
	Placebo (n = 11)	Events of total N (%): 4 of 11 (36%) Exacerbation not defined
Number of days with asthma symptoms in past week median change from baseline (16 wk)	Omalizumab (n = 20)	Median change from baseline: -1.4 Difference from placebo (95% CI): NR; *P* = .140
	Placebo (n = 11)	Median change from baseline: 0.0
Nights with nocturnal awakenings in past week	Omalizumab (n = 20)	Median change from baseline: -0.6 Difference from placebo (95% CI): NR; *P* = .405
	Placebo (n = 11)	Median change from baseline: -0.3

Outcome	Group (n)	Result
median change from baseline (16 wk)		
Physician-rated global evaluation of treatment effectiveness, score of excellent or good (16 wk)	Omalizumab (n = 20)	Events of total N (%): 8 of 20 (40%) Calculated RR (95% CI): 1.47 (0.49 to 4.43)
	Placebo (n = 11)	Events of total N (%): 3 of 11 (27%)
Garcia et al., 2013[32]; NCT01007149		
Rate of exacerbations (16 wk)	Omalizumab (n = 20)	Mean (SD) rate: 0.80 (1.47) Reported IRR: NR; *P* = .278 Calculated IRR: 0.76 Exacerbation not defined
	Placebo (n = 21)	Mean (SD) rate: 1.43 (1.94)
Exacerbations (16 wk)	Omalizumab (n = 20)	Events of total N (%): 12 of 20 (60%) Calculated RR (95% CI): 1.15 (0.67 to 1.97) Exacerbation not defined
	Placebo (n = 21)	Events of total N (%): 11 of 21 (52%)
ACQ mean change from baseline (16 wk)	Omalizumab (n = 20)	Mean (SD) change from baseline: -0.5 (1.43) Difference from placebo (95% CI): 0 (calculated -0.78 to 0.78); *P* = .744
	Placebo (n = 21)	Mean (SD) change from baseline: -0.5 (0.98)
Gevaert et al., 2013[38]; NCT01393340		
AQLQ mean change from baseline (16 wk)	Omalizumab (n = 15)	Mean (SD) change from baseline: 0.81 (NR) Difference from placebo (95% CI): NR Only within group *P* values reported
	Placebo (n = 8)	Mean (SD) change from baseline: 0.27 (NR)
Hanania et al., 2011[29]; EXTRA; NCT00314574		
Exacerbations (48 wk)	Omalizumab (n = 427)	Events of total N (%): 152 of 427 (36%) Calculated RR (95% CI): 0.84 (0.71 to 0.99) Defined as worsening asthma symptoms requiring treatment with systemic corticosteroids for 3 or more days; for patients receiving long-term OCS, an exacerbation was a 20-mg or more increase in the average daily dose of oral prednisone (or a comparable dose of another systemic corticosteroid)
	Placebo (n = 421)	Events of total N (%): 179 of 421 (43%)
Rate of asthma exacerbation (48 wk)	Omalizumab (n = 427) Placebo (n = 421)	Placebo: 0.66 Omalizumab: 0.88 *P* = .006 IRR (95% CI): 0.75 (0.61 to 0.92)
Time to first asthma exacerbation (48 wk)	Omalizumab (n = 427) Placebo (n = 421)	Time to first asthma exacerbation HR 0.74 (95% CI, 0.60 to 0.93); *P* = .008
Daily asthma symptom score	Omalizumab (n = 427)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -0.26 (-0.42 to -0.1)

Outcome	Group (n)	Result
mean change from baseline (48 wk)		
AQLQ MID response (48 wk)	Omalizumab (n = 427)	Events of total N (%): 290 of 427 (68%) Calculated RR (95% CI): 1.11 (1.01 to 1.23)
	Placebo (n = 421)	Events of total N (%): 257 of 421 (61%)
AQLQ mean change from baseline (48 wk)	Omalizumab (n = 427)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): 0.29 (0.15 to 0.43)
Holgate et al., 2004[18]		
Adjusted annualized rate of exacerbations (16 wk) Steroid-stable phase	Omalizumab (n = 126)	Mean (SD) rate: 0.15 (NR) Calculated IRR: 0.65
	Placebo (n = 120)	Mean (SD) rate: 0.23 (NR)
Adjusted annualized rate of exacerbations (32 wk) Steroid-reduction phase	Omalizumab (n = 126)	Mean (SD) rate: 0.19 (NR) Calculated IRR: 0.56 (95% CI not calculable)
	Placebo (n = 120)	Mean (SD) rate: 0.34 (NR)
50% or more reduction in inhaled steroid use (32 wk) Steroid-reduction phase	Omalizumab (n = 126)	Events of total N (%): 93 of 126 (74%) Calculated RR (95% CI): 1.45 (1.18 to 1.78)
	Placebo (n = 120)	Events of total N (%): 61 of 120 (51%)
Proportion no longer requiring ICS (32 wk) Steroid-reduction phase	Omalizumab (n = 126)	Events of total N (%): 27 of 126 (21%) Calculated RR (95% CI): 1.43 (0.83 to 2.46)
	Placebo (n = 120)	Events of total N (%): 18 of 120 (15%)
Mean dose reduction in ICS µg of day (32 wk) Steroid-reduction phase	Omalizumab (n = 126)	Mean (SD): 782 (NR) Difference from placebo (95% CI): NR; *P* = .003
	Placebo (n = 120)	Mean (SD): 596 (NR)
Percentage reduction in ICS (32 wk)	Omalizumab (n = 126)	Mean (SD): 57.2 (NR) Difference from placebo (95% CI): NR; *P* = .003
	Placebo (n = 120)	Mean (SD): 43.3 (NR)

Outcome	Group (n)	Result
Steroid-reduction phase		
AQLQ MID response (32 wk) Steroid-reduction phase	Omalizumab (n = 126)	Events of total N (%): 73 of 126 (58%) Reported RR: NR; *P* < .01 Calculated RR (95% CI): 1.48 (1.13 to 1.93)
	Placebo (n = 120)	Events of total N (%): 47 of 120 (39%)
Hoshino et al., 2012[57]; UMIN000002765		
AQLQ mean change from baseline (16 wk)	No treatment (n = 16)	Mean (SD) change from baseline: 0.28 (NR)
	Omalizumab (n = 14)	Mean (SD) change from baseline: 1.47 (NR) Difference from placebo (95% CI): NR
Humbert et al., 2005[19,20]; INNOVATE		
Adjusted annualized rate of exacerbations (28 wk)	Omalizumab (n = 209)	Mean (95% CI) rate: 0.68 (0.53 to 0.87) IRR (95% CI): 0.806 (calculated 0.60 to 1.08); *P* =.153 Post hoc adjustment for baseline differences: 0.738 (95% CI, 0.552 to 0.998); *P* = .042 Defined as worsening asthma symptoms requiring treatment with systemic steroids
	Placebo (n = 210)	Mean (95% CI) rate: 0.91 (0.73 to 1.14)
Adjusted annualized rate of severe exacerbations (28 wk)	Omalizumab (n = 209)	Mean (95% CI) rate: 0.24 (0.17 to 0.35) Calculated IRR: 0.50; *P* = .002 Defined as exacerbations with PEF or FEV_1 < 60% of personal best, requiring treatment with systemic steroids
	Placebo (n = 210)	Mean (95% CI) rate: 0.48 (0.36 to 0.64)
Exacerbations (28 wk)	Omalizumab (n = 209)	Events of total N (%): 35 of 209 (17%) Calculated RR (95% CI): 0.64 (0.44 to 0.93)
	Placebo (n = 210)	Events of total N (%): 55 of 210 (26%)
Exacerbations requiring ED visit (28 wk)	Omalizumab (n = 209)	Events of total N (%): 9 of 209 (24%) Calculated RR (95% CI): 0.65 (0.29 to 1.46)
	Placebo (n = 210)	Events of total N (%): 14 of 210 (44%)
Exacerbations requiring hospitalization (28 wk)	Omalizumab (n = 209)	Events of total N (%): 13 of 209 (6%) Calculated RR (95% CI): 0.52 (0.27 to 0.99)
	Placebo (n = 210)	Events of total N (%): 25 of 210 (12%)
Rate of exacerbations requiring ED visit (28 wk)	Omalizumab (n = 209)	Mean (SD) rate: 0.04 (NR) IRR (95% CI): 0.66 (0.21 to 2.1); *P* = .48
	Placebo (n = 210)	Mean (SD) rate: 0.06 (NR)
Rate of exacerbations requiring hospitalization (28 wk)	Omalizumab (n = 209)	Mean (SD) rate: 0.06 (NR) IRR (95% CI): 0.54 (0.25 to 1.17); *P* = .117
	Placebo (n = 210)	Mean (SD) rate: 0.12 (NR)
Patient-rated global evaluation of treatment	Omalizumab (n = 209)	Events of total N (%): 134 of 209 (64%) Calculated RR (95% CI): 1.48 (1.23 to 1.78)
	Placebo (n = 210)	Events of total N (%): 91 of 210 (43%)

Outcome	Group (n)	Result
effectiveness, score of excellent or good (28 wk)		
Physician-rated global evaluation of treatment effectiveness, score of excellent or good (28 wk)	Omalizumab (n = 209)	Events of total N (%): 126 of 209 (60%) Calculated RR (95% CI): 1.41 (1.16 to 1.70)
	Placebo (n = 210)	Events of total N (%): 90 of 210 (43%)
Asthma symptom score, mean change from baseline	Omalizumab (n = 209) Placebo (n = 210)	Mean change from baseline was significantly greater with omalizumab compared with placebo during the overall treatment period (*P* = .039)
AQLQ MID response (28 wk)	Omalizumab (n = 204)	Events of total N (%): 124 of 204 (61%) Calculated RR (95% CI): 1.27 (1.06 to 1.52)
	Placebo (n = 205)	Events of total N (%): 98 of 205 (48%)
AQLQ mean change from baseline (28 wk)	Omalizumab (n = 209)	Mean (SD) rate: 0.91 (NR) Difference from placebo (95% CI): 0.45 (NR); *P* < .001
	Placebo (n = 210)	Mean (SD) rate: 0.46 (NR)
Lanier et al., 2009[23]; Kulus et al., 2010[24]; NCT00079937		
Rate of exacerbations (24 wk) Steroid-stable phase	Omalizumab (n = 421)	Mean (SD) rate: 0.45 (NR) IRR (95% CI): 0.69 (0.53 to 0.9); *P* = .007 Defined as requiring a doubling of baseline ICS dose and/or treatment with systemic steroids for 3 or more days
	Placebo (n = 206)	Mean (SD) rate: 0.64
Rate of exacerbations (1 yr) Steroid-reduction phase	Omalizumab (n = 421)	Mean (SD) rate: 0.78 (NR) IRR (95% CI): 0.57 (0.45 to 0.73); *P* < .001 Defined as requiring a doubling of baseline ICS dose or treatment with systemic steroids for 3 or more days
	Placebo (n = 206)	Mean (SD) rate: 1.36 (NR)
Rate of severe exacerbations (24 wk) Stable steroid phase	Omalizumab (n = 421)	Mean (SD) rate: 0.10 (NR) IRR (95% CI): 0.55 (0.32 to 0.95); *P* = .031 Defined as requiring treatment with systemic corticosteroids and peak FEV_1 < 60% of personal best
	Placebo (n = 206)	Mean (SD) rate: 0.18 (NR)
Rate of severe exacerbations (1 yr) Steroid-reduction phase	Omalizumab (n = 421)	Mean (SD) rate: 0.12 (NR) IRR (95% CI): 0.49 (0.3 to 0.8); *P* = .004 Defined as requiring treatment with systemic corticosteroids and peak FEV_1 < 60% of personal best
	Placebo (n = 206)	Mean (SD) rate: 0.24 (NR)
Percentage change in ICS (1 yr)	Omalizumab (n = 421)	Mean (SD): -4.0 (NR) Difference from placebo (95% CI): NR; *P* = .053
	Placebo (n = 206)	Mean (SD): 2.0 (NR)

Outcome	Group (n)	Result
Nocturnal asthma symptom score mean change from baseline (24 wk)	Omalizumab (n = 421)	Mean (SD) change from baseline: -0.63 (0.72) Difference from placebo (95% CI): NR; *P* = .114
	Placebo (n = 206)	Mean (SD) change from baseline: -0.50 (0.71)
Patient-rated global evaluation of treatment effectiveness, score of excellent or good (1 yr)	Omalizumab (n = 421)	Events of total N (%): 337 of 421 (80%) Calculated RR (95% CI): 1.11 (1.01 to 1.23)
	Placebo (n = 206)	Events of total N (%): 148 of 206 (72%)
Physician-rated global evaluation of treatment effectiveness, score of excellent or good (1 yr)	Omalizumab (n = 421)	Events of total N (%): 333 of 421 (79%) Calculated RR (95% CI): 1.42 (1.24 to 1.62)
	Placebo (n = 206)	Events of total N (%): 115 of 206 (56%)
PAQLQ mean change from baseline (24 wk)	Omalizumab (n = 421)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): 0.04 (NR); *P* = .676
Ledford et al., 2017[34]; XPORT; NCT01125748		
Exacerbations (1 yr)	Omalizumab (n = 88)	Events of total N (%): 29 of 88 (33%) Calculated RR (95% CI): 0.63 (0.44 to 0.90) Reported unadjusted OR (95% CI): 0.45 (0.24 to 0.83) Reported adjusted OR (95% CI): 0.44 (0.23 to 0.82) adjusted for age, sex, ICS use, prior trial participation, number of severe exacerbations in year before study, % predicted FEV_1 Defined as clinically significant worsening of asthma requiring systemic steroids, 3 or more days of increased ICS use, or hospitalizations/ED visit
	Placebo (n = 88)	Events of total N (%): 46 of 88 (52%)
Time to exacerbations (1 yr)	Omalizumab (n = 88) Placebo (n = 88)	HR (95% CI): 0.49 (0.28 to 0.86)
ACQ mean change from baseline (1 yr)	Omalizumab (n = 88)	Mean (SD) change from baseline: 0.22 (NR) Difference from placebo (95% CI): -0.41; *P* = .0039
	Placebo (n = 88)	Mean (SD) change from baseline: 0.63 (NR)
ACT mean change from baseline (1 yr)	Omalizumab (n = 88)	Mean (SD) change from baseline: -1.16 (NR) Difference from placebo (95% CI): 1.72; *P* = .0188
	Placebo (n = 88)	Mean (SD) change from baseline: -2.88 (NR)
Milgrom et al., 2001[21]; Lemanske et al., 2002[22]		
Rate of exacerbations (0 to 16 wk)	Omalizumab (n = 225)	Mean (SD) rate: 0.3 (NR) IRR (95% CI): NR; *P* = .093 Calculated IRR (95% CI): 0.75 (0.54 to 1.09)

Outcome	Group (n)	Result
Steroid-stable phase		Defined as doubling of ICS dose or need for systemic steroids
	Placebo (n = 109)	Mean (SD) rate: 0.4 (NR)
Rate of exacerbations (17 to 28 wk) Steroid-reduction phase	Omalizumab (n = 225)	Mean (SD) rate: 0.42 (NR) IRR (95% CI): NR; *P* < .001 Calculated IRR (95% CI): 0.58 (0.42 to 0.90) Defined as doubling of ICS dose or need for systemic steroids
	Placebo (n = 109)	Mean (SD) rate: 0.72 (NR)
Exacerbations (0 to 16 wk) Steroid-stable phase	Omalizumab (n = 225)	Events of total N (%): 35 of 225 (16%) Calculated RR (95% CI): 0.68 (0.43 to 1.07) Defined as requiring treatment with doubling of BDP dose or systemic corticosteroid
	Placebo (n = 109)	Events of total N (%): 25 of 109 (23%)
Exacerbations (17 to 28 wk) Steroid-reduction phase	Omalizumab (n = 225)	Events of total N (%): 41 of 225 (18%) Calculated RR (95% CI): 0.47 (0.33 to 0.68) Defined as requiring treatment with doubling of BDP dose or systemic corticosteroid
	Placebo (n = 109)	Events of total N (%): 42 of 109 (39%)
Excacerbations requiring ED or hospital (0 to 28 wk)	Omalizumab (n = 225)	Events of total N (%): 0 of 225 (0%) Calculated RR (95% CI): 0.04 (0.02 to 0.79) Defined as exacerbations requiring hospitalization
	Placebo (n = 109)	Events of total N (%): 5 of 109 (5%)
Percentage reduction in ICS dose from baseline	Omalizumab (n = 225) Placebo (n = 109)	Median % reduction in ICS dose from baseline (*P* = .001) Placebo: 66.7 Omalizumab: 100 % category of ICS dose reduction (*P* = .002) 75% to 100% Placebo: 49.5 Omalizumab: 65.3 50% to 75% Placebo: 17.4 Omalizumab: 15.1 25% to 50% Placebo: 13.8 Omalizumab: 6.7 0% to 25% Placebo: 18.3 Omalizumab: 12.4 <0% Placebo: 0.9 Omalizumab: 0.4
Proportion no longer requiring ICS (28 wk)	Omalizumab (n = 225)	Events of total N (%): 124 of 225 (55%) Calculated RR (95% CI): 1.40 (1.07 to 1.81)
	Placebo (n = 109)	Events of total N (%): 43 of 109 (39%)
Nocturnal asthma symptom scores (28 wk)	Omalizumab (n = 225) Placebo (n = 109)	Mean scores lower in the omalizumab group than placebo at all evaluations (point estimates and significance NR)
Physician-rated global	Omalizumab (n = 225)	Events of total N (%): 172 of 225 (76%) Calculated RR (95% CI): 1.54 (1.26 to 1.89)

Outcome	Group (n)	Result
evaluation of treatment effectiveness, score of excellent or good (28 wk)		Reported RR: NR: *P* < .001 Patient-rated global evaluation was reported as "nearly identical" to physician ratings
	Placebo (n = 109)	Events of total N (%): 54 of 109 (50%)
PAQLQ large MID response large (0 to 16 wk) Steroid-stable phase	Omalizumab (n = 225)	Events of total N (%): 21 of 225 (9%) Calculated RR (95% CI): 1.45 (0.64 to 3.32) Defined as improvement greater than 1.5 points
	Placebo (n = 109)	Events of total N (%): 7 of 109 (6%)
PAQLQ large MID large (17 to 28 wk) Steroid-reduction phase	Omalizumab (n = 225)	Events of total N (%): 31 of 225 (14%) Reported RR: NR; *P* = .2258 Calculated RR (95% CI): 1.67 (0.82 to 3.38) Defined as greater than 1.5 points
	Placebo (n = 109)	Events of total N (%): 9 of 109 (8%)
PAQLQ (0 to 28 wk)	Omalizumab (n = 225) Placebo (n = 109)	No significant difference at 16 weeks. At 28 weeks there was favorable difference for omalizumab over placebo (*P* < .05, data not reported). Unclear whether study was reporting scores at these time points, or mean change from baseline.
Mukherjee et al., 2019[47]; NCT02049294		
Exacerbations (32 wk)	Omalizumab (n = 4)	Events of total N (%): 1 of 4 (25%) Calculated RR (95% CI): 0.31 (0.05 to 1.80) Exacerbation occurred during second phase of study (weeks 17-32) which included the steroid taper. Exacerbations not defined
	Placebo (n = 5)	Events of total N (%): 4 of 5 (80%) Exacerbations occurred during second phase of study (weeks 17-32) which included the steroid taper.
ACQ mean change from baseline (32 wk)	Omalizumab (n = 4)	Mean (SD) change from baseline: -0.33 (NR) Difference from placebo (95% CI): -0.24; *P* > .05
	Placebo (n = 5)	Mean (SD) change from baseline: -0.57 (NR)
Ohta et al., 2009[25]; NCT00232050		
Exacerbations requiring steroids (16 wk)	Omalizumab (n = 151)	Events of total N (%): 6 of 151 (4%) Calculated RR (95% CI): 0.36 (0.15 to 0.89)
	Placebo (n = 164)	Events of total N (%): 18 of 164 (11%)
Other outcomes		Changes from baseline in asthma symptom score, daily activity score, sleep score (all ascertained via daily diary cards and scores calculated via the rating standard of the Japanese Society of Allergology) are only depicted on figures. Authors report that for each outcome, there was improvement in favor of the omalizumab group, but differences between groups for changes from baseline were not statistically significant.
PIllai et al., 2016[33]; NCT01113437		
ICS dose	Omalizumab (n = 8) Placebo (n = 8)	Medan (range) ICS equivalent µg per day at baseline and 12 to 14 weeks Placebo: 1,800 (500 to 2,000)

Outcome	Group (n)	Result
		Omalizumab: 2,000 (800 to 4,000) At 20 weeks Placebo: reduced to 200 µg Omalizumab: reduced to 200 µg
ACQ median change from baseline (12-14 wk)	Omalizumab (n = 8)	Median change (range): -0.50 (-1.85 to 0.72) Difference from placebo (95% CI): NR; *P* = NS
	Placebo (n = 8)	Median change (range): -0.35 (-1.00 to 0.57)
ACQ median change from baseline (20 wk)	Omalizumab (n = 8)	Median change (range): -0.71 (-1.14 to 0.14) Reported difference from placebo: NR; *P* = NS Calculated difference from placebo: -0.4
	Placebo (n = 8)	Median change (range): -0.28 (-1.71 to 1.14)
Mini-AQLQ median change from baseline (12-14 wk)	Omalizumab (n = 8)	Median change (range): 0.18 (-1.00 to 2.26); NS Reported difference from placebo: NR; *P* = NS Calculated difference from placebo: -0.43
	Placebo (n = 8)	Median change (range): 0.37 (-1.34 to 1.87)
Mini-AQLQ median change from baseline (20 wk)	Omalizumab (n = 8)	Median change (range): 0.46 (-0.40 to 2.06) Reported difference from placebo: NR: *P* = NS Calculated difference from placebo: -0.20
	Placebo (n = 8)	Median change (range): 0.67 (-1.60 to 2.30)
Sly et al., 2017[10]; RELAX; ACTRN12611001106921		
Exacerbations (26 wk)	Omalizumab (n = 14)	Severe events of total N (%): 1 of 14 (7%) Calculated RR (95% CI): 0.15 (0.02 to 1.19) Reported RR: NR (reported as 10.8 times greater in placebo group); *P* = .024 Moderate events: IRR 1.24; *P* = .58 Exacerbations as defined by ATS/ ESR criteria
	Placebo (n = 13)	Events of total N (%): 6 of 13 (46%)
Exacerbations (72 wk) Follow-up period after double-blind treatment period	Omalizumab (n = 14) Placebo (n = 13)	Severe exacerbations (after treatment completed); IRR 0.45; *P* = .45
Time to first exacerbation		Mean (SD) days to severe exacerbations Placebo: 107.0 (115.9) Omalizumab: 240.5 (87.9) *P* = .08 Mean (SD) days to first moderate exacerbation Placebo: 87.3 (89.6) Omalizumab: 177.3 (140.6) *P* = .91
Soler et al., 2001[54]; Buhl et al., 2002[55,56]		
Rate of exacerbations (0 to 16 wk) Steroid-stable phase	Omalizumab (n = 274)	Mean (95% CI) rate: 0.28 (0.15 to 0.41) IRR (95% CI): NR; *P* < .001 Calcualted IRR (95% CI): 0.42 (0.25 to 0.93) Exacerbations defined as doubling of ICS dose or requirement for systemic steroids

Outcome	Group (n)	Result
	Placebo (n = 272)	Mean (95% CI) rate: 0.66 (0.49 to 0.83)
Rate of exacerbations (17 to 28 wk) Steroid-reduction phase	Omalizumab (n = 274)	Mean (95% CI) rate: 0.36 (0.24 to 0.48) IRR (95% CI): NR; *P* < .001 Calculated IRR (95% CI): 0.48 (0.31 to 0.92) Defined as doubling of ICS dose or requirement for systemic steroids
	Placebo (n = 272)	Mean (95% CI) rate: 0.75 (0.58 to 0.92) Defined as doubling of ICS dose or requirement for systemic steroids
Rate of exacerbations (29 to 52 wk) Double-blind extension phase	Omalizumab (n = 274)	Mean (95% CI) rate: 0.48 (0.30 to 0.66) IRR (95% CI): NR; *P* < .001 Calculated IRR (95% CI): 0.42 (0.25 to 0.94) Defined as doubling of ICS dose or requirement for systemic steroids
	Placebo (n = 272)	Mean (95% CI) rate: 1.14 (0.81 to 1.46)
Exacerbations (0 to 16 wk) Steroid-stable phase	Omalizumab (n = 274)	Events of total N (%): 35 of 274 (13%) Calculated RR (95% CI): 0.42 (0.29 to 0.60) Defined as doubling of ICS dose or requirement for systemic steroids
	Placebo (n = 272)	Events of total N (%): 83 of 272 (31%)
Exacerbations (17 to 28 wk) Steroid-reduction phase	Omalizumab (n = 274)	Events of total N (%): 43 of 274 (16%) Calculated RR (95% CI): 0.53 (0.38 to 0.73) Defined as doubling of ICS dose or requirement for systemic steroids
	Placebo (n = 272)	Events of total N (%): 81 of 272 (30%)
Exacerbations (29 to 52 wk) Double-blind extension phase	Omalizumab (n = 254)	Events of total N (%): 61 of 254 (24%) Calculated RR (95% CI): 0.59 (0.45 to 0.77) Defined as doubling of ICS dose or requirement for systemic steroids
	Placebo (n = 229)	Events of total N (%): 93 of 229 (41%) Defined as doubling of ICS dose or requirement for systemic steroids
Exacerbations requiring hospitalization (28 wk) Steroid-reduction phase	Omalizumab (n = 274)	Events of total N (%): 0 of 274 (0%) Calculated RR (95% CI): 0.08 (0.004 to 1.35)
	Placebo (n = 272)	Events of total N (%): 6 of 272 (2%)
Exacerbations requiring hospitalization (29 to 52 wk)	Omalizumab (n = 274)	Events of total N (%): 1 of 274 (0.3%) Calculated RR (95% CI): 0.25 (0.03 to 2.21)
	Placebo (n = 272)	Events of total N (%): 4 of 272 (1%)
Percentage reduction in ICS dose and median dose (28 wk)	Omalizumab (n = 254) Placebo (n = 229)	Significantly greater percentage reduction in ICS dose for omalizumab vs. placebo but data only portrayed on a figure, actual values NR Median dose of ICS Placebo: 300 µg (IQR 100 to 600) Omalizumab: 100 µg (IQR 0 to 400) *P* < .001

Outcome	Group (n)	Result
50% or more reduction in inhaled steroid use (28 wk)	Omalizumab (n = 274)	Events of total N (%): 216 of 274 (79%) Calculated RR (95% CI): 1.43 (1.26 to 1.62)
	Placebo (n = 272)	Events of total N (%): 150 of 272 (55%)
Proportion no longer requiring ICS (28 wk)	Omalizumab (n = 274)	Events of total N (%): 118 of 274 (43%) Calculated RR (95% CI): 2.25 (1.70 to 3.00)
	Placebo (n = 272)	Events of total N (%): 52 of 272 (19%)
Median asthma symptom scores (28 wk)	Omalizumab (n = 274) Placebo (n = 272)	Median asthma symptom scores only presented on a figure, actual values NR. Scores reported to be significantly more improved for omalizumab compared to placebo; significant imporvements for both daytime and night symptoms (*P* values from < .05 to < .01 depending on week).
AQLQ (16 wk, 28 wk)	Omalizumab (n = 274) Placebo (n = 272)	Omalizumab was significantly more effective than placebo at the end of the steroid stable phase, steroid reduction phase, and the double blind extension period (actual values NR, *P* < .001 for comparison at each phase). Omalizumab was significantly more effective than placebo at the end of the steroid stable phase (*P* < .05), steroid reduction phase (*P* < .01), and the double-blind extension phase (*P* < .05) for proportion of participants achieving an MID response; actual values NR.
Vignola et al., 2004[58]; SOLAR		
Adjusted annualized rate of exacerbations (28 wk)	Omalizumab (n = 209)	Mean (SD) rate: 0.25 (NR) Reported IRR: NR; *P* =.02 Calculated IRR (95% CI): 0.63 (0.42 to 0.93)
	Placebo (n = 196)	Mean (SD) rate: 0.40 (NR) Defined as worsening of asthma requiring treatment with systemic steroids or doubling of the baseline ICS dose
Exacerbations (28 wk)	Omalizumab (n = 209)	Events of total N (%): 43 of 209 (21%) Calculated RR (95% CI): 0.68 (0.49 to 0.96) Defined as worsening of asthma requiring treatment with systemic steroids or doubling of the baseline ICS dose
	Placebo (n = 196)	Events of total N (%): 59 of 196 (30%)
Physician-rated global evaluation of treatment effectiveness, score of excellent or good (28 wk)	Omalizumab (n = 209)	Events of total N (%): 124 of 209 (59.3%) Reported RR: NR: *P* < .001 Calculated RR (95% CI): 1.44 (1.17 to 1.76)
	Placebo (n = 196)	Events of total N (%): 81 of 196 (41.3%)
Patient-rated global evaluation of treatment effectiveness, score of excellent or good (28 wk)	Omalizumab (n = 209)	Events of total N (%): 137 of 209 (65.6%) Reported RR: NR: *P* = .009 Calculated RR (95% CI): 1.24 (1.05 to 1.46)
	Placebo (n = 196)	Events of total N (%): 104 of 196 (53.1%)
Wasserfallen Asthma	Omalizumab (n = 209)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -1.8 (NR); *P* = .023

Outcome	Group (n)	Result
Symptom Score mean change from baseline (28 wk)		
AQLQ MID response (28 wk)	Omalizumab (n = 209)	Events of total N (%): 164 of 209 (58%) Calculated RR (95% CI): 1.15 (1.02 to 1.30)
	Placebo (n = 196)	Events of total N (%): 134 of 196 (41%)
AQLQ mean change from baseline (28 wk)	Omalizumab (n = 209)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): NR; < 0.05 Data presented in figure, no specific values reported

Abbreviations. µL: microliter; ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; ATS/ESR: American Thoracic Society/European Society of Respiratory Medicine; BDP: beclomethasone dipropionate; BSC: best standard care; C-ACT: Child version of Asthma Control Test; CI: confidence interval; ED: emergency department; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; IRR: incidence rate ratio; IQR: interquartile ratio; MID: minimally important difference; NR: not reported; OAT: optimized asthma therapy; OCS: oral corticosteroids; OR: odds ratio; PAQLQ: pediatric Asthma Quality of Life Questionnaire; PEF: peak expiratory flow; RCT: randomized controlled trial; RR: risk ratio; SD: standard deviation; SE: standard error; wk: week; yr: year.

Table B12. Safety Outcomes in RCTs of Omalizumab for Asthma

Safety Outcomes (time point)	Intervention Group Number Events of Total Number (%) RR (95% CI)	Comparator Group Number Events of Total Number (%)
Ayres et al., 2004[11]		
	Omalizumab (weight/IgE dosing[a])	Best Standard Asthma Care
Total adverse events (52 wk)	175 of 206 (85%) 1.10 (0.98 to 1.24)	82 of 106 (77%)
SAEs (52 wk)	34 of 206 (17%) 1.25 (0.70 to 2.2)	14 of 106 (13%)
Adverse events leading to discontinuation (52 wk)	15 of 206 (7%) 16.0 (0.97 to 265.2)	0 of 106 (0%)
Mortality (52 wk)	1 of 206 (0%) 1.54 (0.06 to 37.7)	0 of 106 (0%)
Bardelas et al., 2012[28]; NCT00267202		
	Omalizumab (weight/IgE dosing[a])	Placebo
Total adverse events (24 wk)	90 of 136 (66%) 0.96 (0.81 to 1.13)	93 of 135 (69%)
SAEs (24 wk)	0 of 136 (0%) Cannot determine	0 of 135 (0%) Cannot determine
Adverse events leading to discontinuation (24 wk)	NR	NR
Mortality (24 wk)	0 of 136 (0%) Cannot determine	0 of 135 (0%) Cannot determine
Bousquet et al., 2011[26]; Siergiejko et al., 2011[26]; NCT00264849		
	Omalizumab (weight/IgE dosing[a])	Optimized Asthma Therapy
Total adverse events (32 wk)	184 of 274 (67%) 1.25 (1.04 to 1.49)	69 of 128 (54%)
SAEs (32 wk)	18 of 274 (7%) 1.20 (0.51 to 2.80)	7 of 128 (5%)
Adverse events leading to discontinuation (32 wk)	NR	4 of 128 (3%)
Mortality (32 wk)	0 of 274 (0%) 0.16 (0.01 to 3.81)	1 of 128 (1%)
Busse et al., 2001[13]; Lanier, 2013[14]; Finn, 2002[15]		
	Omalizumab (weight/IgE dosing[a])	Placebo
Total adverse events (28 wk)	239 of 268 (89%) 1.0 (0.94 to 1.06)	229 of 257 (89%)
Total adverse events (52 wk)	203 of 245 (83%) 1.01 (0.93 to 1.09)	177 of 215 (82%)
SAEs (28 wk)	7 of 268 (3%) 1.12 (0.38 to 3.28)	6 of 257 (2%)
SAEs (52 wk)	3 of 245 (1%) 0.88 (0.18 to 4.30)	3 of 215 (1%)
Adverse events leading to discontinuation (28 wk)	2 of 268 (1%) 4.8 (0.23 to 99.4)	0 of 257 (0%)
Adverse events leading to discontinuation (52 wk)	0 of 245 (0%) Cannot be determined	0 of 215 (0%)

Safety Outcomes (time point)	Intervention Group Number Events of Total Number (%) RR (95% CI)	Comparator Group Number Events of Total Number (%)
Mortality (28 wk)	0 of 268 (0%) 0.32 (0.01 to 7.8)	1 of 257 (0%)
Mortality (52 wk)	NR	NR
Treatment-related adverse events (52 wk)	6 of 245 (2%) 1.76 (0.44 to 6.9)	3 of 215 (1%)
Busse et al., 2011[30]; ICATA; NCT00377572		
	Omalizumab (weight/IgE dosing[a])	**Placebo**
Total adverse events (60 wk)	82 of 208 (39%) 0.83 (0.67 to 1.03)	100 of 211 (47%)
SAEs (60 wk)	13 of 208 (6%) 0.45 (0.24 to 0.85)	29 of 211 (14%)
Adverse events leading to discontinuation (60 wk)	NR	NR
Mortality (60 wk)	NR	NR
Busse et al., 2013[16]		
	Omalizumab (weight/IgE dosing[a])	**Placebo**
Total adverse events (24 wk)	92 of 157 (59%) 0.93 (0.78 to 1.10)	108 of 171 (63%)
SAEs (24 wk)	4 of 157 (3%) 0.73 (0.21 to 2.53)	6 of 171 (4%)
Adverse events leading to discontinuation (24 wk)	3 of 157 (2%) 3.27 (0.34 to 31.09)	1 of 171 (1%)
Mortality (24 wk)	NR	NR
Chanez et al., 2010[31]; NCT00454051		
	Omalizumab (weight/IgE dosing[a])	**Placebo**
Total adverse events (16 wk)	11 of 20 (55%) 0.86 (0.48 to 1.57)	7 of 11 (64%)
SAEs (16 wk)	0 of 20 (0%) 0.19 (0.01 to 4.32)	1 of 11 (9%)
Adverse events leading to discontinuation (16 wk)	NR	NR
Mortality (16 wk)	NR	NR
Garcia et al., 2013[32]; NCT01007149		
	Omalizumab (weight/IgE dosing[a])	**Placebo**
Total adverse events (16 wk)	16 of 20 (80%) 0.99 (0.73 to 1.34)	17 of 21 (81%)
SAEs (16 wk)	2 of 20 (10%) 2.10 (0.21 to 21.4)	1 of 21 (5%)
Adverse events leading to discontinuation (16 wk)	0 of 20 (0%) Cannot be determined	0 of 21 (0%)
Mortality (16 wk)	NR	NR
Gevaert et al., 2013[38]; NCT01393340		
	Omalizumab (weight/IgE dosing[a])	**Placebo**
Total adverse events (16 wk)	NR	NR

Safety Outcomes (time point)	Intervention Group Number Events of Total Number (%) RR (95% CI)	Comparator Group Number Events of Total Number (%)
SAEs (16 wk)	NR	NR
Adverse events leading to discontinuation (16 wk)	0 of 15 (0%) 0.19 (0.01 to 4.14)	1 of 8 (13%)
Mortality (16 wk)	NR	NR
Hanania et al., 2011[29]; EXTRA; NCT00314574		
	Omalizumab (weight/IgE dosing[a])	Placebo
Total adverse events (48 wk)	344 of 428 (80%) 1.01 (0.94 to 1.08)	334 of 420 (80%)
SAEs (48 wk)	40 of 428 (9%) 0.89 (0.60 to 1.34)	44 of 420 (10%)
Adverse events leading to discontinuation (48 wk)	16 of 428 (4%) 1.57 (0.72 to 3.42)	10 of 420 (2%)
Mortality (48 wk)	0 of 428 (0%) 0.14 (0.01 to 2.71)	3 of 420 (1%)
Holgate et al., 2004[18]		
	Omalizumab (weight/IgE dosing[a])	Placebo
Total adverse events (32 wk)	96 of 126 (76%) 0.92 (0.81 to 1.05)	99 of 120 (83%)
SAEs (32 wk)	1 of 126 (1%) 0.19 (0.02 to 1.61)	5 of 120 (4%)
Adverse events leading to discontinuation (32 wk)	0 of 126 (0%) 0.19 (0.01 to 3.93)	2 of 120 (2%)
Mortality (32 wk)	NR	NR
Humbert et al., 2005[19]; INNOVATE		
	Omalizumab (weight/IgE dosing[a])	Placebo
Total adverse events (28 wk)	177 of 245 (72%) 0.96 (0.86 to 1.06)	179 of 237 (76%)
SAEs (28 wk)	29 of 245 (12%) 0.76 (0.48 to 1.12)	37 of 237 (16%)
Adverse events leading to discontinuation (28 wk)	11 of 245 (4%) 2.66 (0.86 to 8.24)	4 of 237 (2%)
Mortality (28 wk)	NR	NR
Treatment-related adverse events (28 wk)	29 of 245 (12%) 1.28 (0.75 to 2.15)	22 of 237 (9%)
Lanier et al., 2009[23]; Kulus et al., 2010[24]; NCT00079937		
	Omalizumab (weight/IgE dosing[a])	Placebo
Total adverse events (52 wk)	380 of 421 (90%) 0.96 (0.92 to 1.01)	194 of 207 (94%)
SAEs (52 wk)	34 of 421 (4%) 0.48 (0.31 to 0.74)	35 of 207 (8%)
Adverse events leading to discontinuation (52 wk)	3 of 421 (1%) 0.74 (0.12 to 4.38)	2 of 207 (1%)
Mortality (52 wk)	0 of 421 (0%) Cannot be determined	0 of 207 (0%)

Safety Outcomes (time point)	Intervention Group Number Events of Total Number (%) RR (95% CI)	Comparator Group Number Events of Total Number (%)
Ledford et al., 2017[34]; XPORT; NCT01125748		
	Omalizumab (weight/IgE dosing[a])	Placebo
Total adverse events (52 wk)	NR	NR
SAEs (52 wk)	NR	NR
Adverse events leading to discontinuation (52 wk)	0 of 88 (2%) 0.20 (0.01 to 4.11)	2 of 88 (2%)
Mortality (52 wk)	0 of 88 (0%) 0.33 (0.01 to 8.07)	1 of 88 (1%)
Milgrom et al., 2001[21]; Lemanske et al., 2002[22]		
	Omalizumab (weight/IgE dosing[a])	Placebo
Total adverse events (28 wk)	95 of 109 (87%) 0.98 (0.90 to 1.06)	201 of 225 (89%)
SAEs (28 wk)	NR	NR
Adverse events leading to discontinuation (28 wk)	1 of 225 (0%) 0.48 (0.03 to 7.67)	1 of 109 (1%)
Mortality (28 wk)	NR	NR
Treatment-related adverse events (28 wk)	14 of 225 (6%) 6.78 (0.90 to 50.91)	1 of 109 (1%)
Ohta et al., 2009[25]; NCT00232050		
	Omalizumab (weight/IgE dosing[a])	Placebo
Total adverse events (16 wk)	136 of 151 (90%) 1.04 (0.96 to 1.13)	142 of 164 (87%)
SAEs (16 wk)	6 of 151 (4%) 0.59 (0.22 to 1.56)	11 of 164 (7%)
Adverse events leading to discontinuation (16 wk)	6 of 151 (4%) 0.93 (0.32 to 2.71)	7 of 164 (4%)
Mortality (16 wk)	NR	NR
PIllai et al., 2016[33]; NCT01113437		
	Omalizumab (weight/IgE dosing[a])	Placebo
Total adverse events (20 wk)	NR	NR
SAEs (20 wk)	NR	NR
Adverse events leading to discontinuation (20 wk)	1 of 9 (11%) 3.0 (0.14 to 65.2)	0 of 9 (0%)
Mortality (20 wk)	NR	NR
Sly et al., 2017[10]; RELAX; ACTRN12611001106921		
	Omalizumab (weight/IgE dosing[a])	Placebo
Total adverse events (72 wk)	NR	NR
SAEs (72 wk)	NR	NR
Adverse events leading to discontinuation (72 wk)	1 of 14 (7%) 2.80 (0.12 to 63.2)	0 of 13 (0%)
Mortality (72 wk)	NR	NR

Safety Outcomes (time point)	Intervention Group Number Events of Total Number (%) RR (95% CI)	Comparator Group Number Events of Total Number (%)
Soler et al., 2001[54]; Buhl et al., 2002[55,56]		
	Omalizumab (weight/IgE dosing[a])	**Placebo**
Total adverse events (28 wk)	NR	NR
Total adverse events (52 wk)	229 of 274 (84%) 0.98 (0.91 to 1.05)	232 of 272 (85%)
SAEs (28 wk)	9 of 274 (3%) 2.98 (0.82 to 10.88)	3 of 272 (1%)
SAEs (52 wk)	NR	NR
Adverse events leading to discontinuation (28 wk)	0 of 274 (0%) 0.09 (0.01 to 1.62)	5 of 272 (2%)
Adverse events leading to discontinuation (52 wk)	NR	NR
Mortality (28 wk)	0 of 274 (0%) Cannot be determined	0 of 272 (0%)
Mortality (52 wk)	NR	NR
Vignola et al., 2004[58]; SOLAR		
	Omalizumab (weight/IgE dosing[a])	**Placebo**
Total adverse events (28 wk)	164 of 209 (78%) 1.14 (1.01 to 1.28)	135 of 196 (69%)
SAEs (28 wk)	3 of 209 (1%) 0.9 (0.19 to 4.60)	3 of 196 (2%)
Adverse events leading to discontinuation (28 wk)	0 of 209 (0%) Cannot be determined	0 of 196 (0%)
Mortality (28 wk)	0 of 209 (0%) Cannot be determined	0 of 196 (0%)
Treatment-related adverse events (28 wk)	35 of 209 (17%) 1.37 (0.84 to 2.21)	24 of 196 (12%)
Zielen et al., 2013[59]		
	Omalizumab (weight/IgE dosing[a]); low IgE subgroup	**Omalizumab (weight/IgE dosing[a]); high IgE subgroup**	**Placebo**
Total adverse events (16 wk)	9 of 18 (50%) 0.67 (0.39 to 1.15)	16 of 16 (100%) 1.32 (0.98 to 1.78)	12 of 16 (75%)
SAEs (16 wk)	1 of 18 (6%) 0.44 (0.04 to 4.45)	1 of 16 (6%) 0.50 (0.05 to 4.98)	2 of 16 (13%)
Adverse events leading to discontinuation (16 wk)	NR	NR	NR
Mortality (16 wk)	0 of 18 (0%) Cannot be determined	0 of 16 (0%) Cannot be determined	0 of 16 (0%)
Treatment-related adverse events (16 wk)	1 of 18 (6%) 0.22 (0.03 to 1.79)	2 of 16 (13%) 0.50 (0.11 to 2.35)	4 of 16 (25%)

Notes. [a] The current FDA label specifies dosage and frequency based on the pretreatment serum total immunoglobulin (IgE) level (IU/mL) and body weight. Abbreviations. CI: confidence interval; FDA: US Food and Drug Administration; IgE: immunoglobin E; NR: not reported; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; wk: week.

Reslizumab Asthma Studies

Table B13. Study Characteristics From RCTs of Reslizumab for Asthma

Characteristic	Details			
Bernstein et al., 2020[52]; NCT02452190				
Study Characteristics	Phase 3 traditional RCT (effectiveness of add-on therapy vs. placebo); 155 study sites in 20 countries; Ukraine, Hungary, Germany, Argentina, Russia, Israel, Poland, Romania, South Africa, Japan, Mexico, Belgium, Czech Republic, Turkey, Canada, Spain, New Zealand, France, and Australia *Years conducted:* 2015-2018 *Sponsor(s):* Teva Branded Pharmaceutical Products R&D *Risk of bias:* Moderate			
Interventions (N randomized)	Reslizumab 110 mg SC every 4 weeks for 48 weeks (n = 236)		Placebo (n = 232)	
	Cointervention(s): Patients maintained their inhaled asthma controlled regimen without change throughout the study; oral corticosteroid use (prednisone 10 mg or less daily, or equivalent) was allowed.			
Population	*Inclusion Criteria:* Aged 12 years and older with a diagnosis of asthma, ACQ-6 score of at least 1.5, 2 or more asthma exacerbations requiring the use of systemic corticosteroids in the past year, a blood eosinophil count of 300 cells per µL or more, and an FEV_1 reversibility of 12% or more to inhaled short-acting ß-agonist within 12 months; at least a medium dose (> 250 µg/day fluticasone or equivalent) of ICS for at least 3 months with at least 1 additional asthma controller for at least 3 months. For patients using ICS and LABA combinations, the mid-strength approved maintenance dose in the local country met this inhaled corticosteroid criterion. *Exclusion Criteria:* Clinically significant, uncontrolled medical condition that would have interfered with the study; another underlying lung disorder; known hypereosinophilic syndrome; diagnosis of malignancy within 5 years except for nonmelanoma skin cancers; pregnant or lactating woman; required treatment for an asthma exacerbation within 4 weeks or during the screening/run-in period; current smoker or had a smoking history ≥ 10 pack-years; currently using any systemic immunosuppressive or immunomodulatory biologic or nonbiologic, except maintenance OCS for the treatment of asthma; previously exposed to benralizumab or reslizumab			
	Mean age (SD) Placebo: 44.8 (17.7) Reslizumab: 46.9 (17.6) N (%) female Placebo: 128 (56) Reslizumab: 144 (62)	*Race/ethnicity* Race/ethnicity: NR	*Asthma duration/severity* Mean (SD) time since diagnosis, years Placebo: 17.5 (13.5) Reslizumab: 18.0 (14.0) Mean (SD) ACQ-6 score Placebo: 2.6 (0.8) Reslizumab: 2.6 (0.8)	*Comorbidities* N (%) with aspirin sensitivity Placebo: 23 (10) Reslizumab: 26 (11) N (%) with chronic rhinosinusitis with nasal polyps Placebo: 38 (17)

Characteristic	Details			
			Mean (SD) number of asthma exacerbations requiring systemic corticosteroids in the past 12 months Placebo: 2.3 (0.8) Reslizumab: 2.4 (1.0)	Reslizumab: 37 (16)
Castro et al., 2011[17]				
Study Characteristics	Not reported traditional RCT (effectiveness of add-on therapy vs. placebo); 25 sites in 2 countries; US, Canada *Years conducted:* 2008-2010 *Sponsor(s):* Ception Therapeutics, Inc. (acquired by Cephalon, Inc.) *Risk of bias:* Moderate			
Interventions (N randomized)	Reslizumab 3.0 mg/kg IV every 4 weeks for 12 weeks (n = 53)		Placebo (n = 53)	
	Cointervention(s): Patients continued doses of ICS that they were on at the time of enrollment.			
Population	*Inclusion Criteria:* Aged 18 to 75 years with asthma (1) confirmed by airway hyperreactivity (20% reduction in FEV_1 after administration of methacholine up to 16 mg/mL) or by airway reversibility (> 12% improvement in FEV_1 after administration of a beta-agonist), (2) treated with high-dose ICS (> 440 mg of fluticasone twice per day) in combination with at least 1 other agent (including short or long-acting beta -agonists, LTRA, and cromolyn sodium), (3) that was poorly controlled as indicated by an ACQ-5 score of 1.5 or more, and (4) associated with induced sputum eosinophils of 3% or more *Exclusion Criteria:* Using systemic corticosteroids (including oral corticosteroids), had a clinically significant comorbidity, or had hypereosinophilic syndrome			
	Mean age (SD) Placebo: 45.8 (11.7) Reslizumab: 44.9 (13.9) N (%) female Placebo: 29 (55) Reslizumab: 34 (64)	*Race/ethnicity* Race/ethnicity: NR	*Asthma duration/severity* Mean (SD) time ince asthma diagnosis, years Placebo: 26.1 (16.1) Reslizumab: 23.3 (11.4) Mean (SD) ACQ score Placebo: 2.5 (0.73) Reslizumab: 2.8 (0.79)	*Comorbidities* N (%) with aspirin sensitivity Placebo: 5 (9) Reslizumab: 3 (6) N (%) with nasal polyps Placebo: 16 (30) Reslizumab: 22 (42) N (%) with allergic rhinitis Placebo: 44 (83) Reslizumab: 41 (77)
Bjermer et al., 2016[35]; BREATH-3; NCT01270464				
Study Characteristics	Phase 3 traditional RCT (effectiveness of add-on therapy vs. placebo); 68 locations globally; Argentina, Belgium, Brazil, Canada, Colombia, Hungary, Israel, Mexico, Poland, Sweden, Netherlands, US *Years conducted:* 2011-2013			

Characteristic	Details			
	Sponsor(s): Teva Branded Pharmaceutical Products R&D Inc. *Risk of bias:* Moderate			
Interventions (N randomized)	Reslizumab 3.0 mg/kg IV every 4 weeks for 16 weeks (n = 106)		Placebo (n = 105)	
	Cointervention(s): Patients receiving treatment with at least a medium-dose ICS (fluticasone propionate ≥ 440 µg/d or equivalent). Could also be taking long-acting bronchodilators, LTRA, or cromolyn.			
Population	*Inclusion Criteria:* Aged 12 to 75 years with inadequately controlled asthma (ACQ-7≥1.5), airway reversibility (≥12% to SABA), receiving treatment with at least a medium-dose ICS, had at least 1 blood eosinophil count ≥400 cells/µl, could be on long-acting bronchodilators, LTRA, or cromolyn *Exclusion Criteria:* Other confounding lung disorders or pulmonary conditions; other clinically relevant comorbidities with potential to interfere with the study schedule, procedures or safety; hypereosinophilic syndrome; use of systemic corticosteroids 30 days prior; current smoker; use of systemic immunosuppressive or immunomodulating agents ≤6 months prior			
	Mean age (SD) Placebo: 44.2 (NR) Reslizumab : 43.0 (NR) N (%) female Placebo: 62 (59) Reslizumab: 61 (58)	*Race/ethnicity* N (%) white Placebo: 85 (81) Reslizumab: 90 (85) N (%) black Placebo: 7 (7) Reslizumab: 5 (5) N (%) Asian Placebo: 0 (0) Reslizumab: 2 (2) N (%) other Placebo: 13 (12) Reslizumab: 9 (8)	*Asthma duration/severity* Mean (SD) time since diagnosis, years Placebo: 20.7 (NR) Reslizumab: 20.4 (NR) Mean (SD) ACQ score Placebo: 2.47 (NR) Reslizumab: 2.59 (NR) % with exacerbation within past year Placebo: 54 Reslizumab 3.0 mg/kg: 57	*Comorbidities* NR
Castro et al., 2015[36]; BREATH-2; NCT01285323				
Study Characteristics	Phase 3 traditional RCT (effectiveness of add-on therapy vs. placebo); 104 clinical research centers; US, Argentina, Brazil, Canada, France, Germany, Greece, Korea, Mexico, Peru, Romania, Russia, Slovakia, Taiwan, Ukraine *Years conducted:* 2011-2014 *Sponsor(s):* Teva Branded Pharmaceutical Products R&D *Risk of bias:* Moderate			
Interventions (N randomized)	Reslizumab 3 mg/kg IV every 4 weeks for 52 weeks (n = 232)		Placebo (n = 232)	

Characteristic	Details			
	Cointervention(s): Patients continued their usual asthma treatment, including but not limited to LABAs, inhaled corticosteroids, oral corticosteroids (≤ 10 mg per day of prednisone or equivalent), LTRAs, and cromolyn sodium, at constant doses.			
Population	*Inclusion Criteria:* Aged 12 to 75 years with at least 1 blood eosinophil count of 400 cells per µL or higher during a 2-4 week screening period and inadequately controlled ACQ-7 score ≥ 1.5 who were receiving at least a medium dose of inhaled corticosteroids with or without another controller drug (including oral corticosteroids). Had at least 1 asthma exacerbation that needed a systemic corticosteroid within the past 12 months and a FEV_1 reversibility of 12% or more with albuterol. *Exclusion Criteria:* Any clinically meaningful comorbidity that could interfere with the study; known hypereosinophilic syndrome; another confounding underlying lung disorder; current smoker; current use of systemic immunosuppressive, immunomodulating, or other biologic agents within 6 months before screening; prior use of an antihuman interleukin-5 monoclonal antibody (e.g., reslizumab, mepolizumab, or benralizumab); inadequately controlled, aggravating medical factors; pregnant or nursing; history of concurrent immunodeficiency; current suspected drug and alcohol abuse; requirement for treatment for an asthma exacerbation within 4 weeks of screening or during the screening period			
	Median age (IQR) Placebo: 48 (39.5 to 57) Reslizumab: 48 (37 to 56.5) N (%) female Placebo: 150 (65) Reslizumab: 144 (62)	*Race/ethnicity* N (%) white: Placebo: 169 (73) Reslizumab: 168 (72) N (%) black: Placebo: 4 (2) Reslizumab: 6 (3) N (%) Asian: Placebo: 21 (9) Reslizumab: 16 (7) N (%) other: Placebo: 38 (16) Reslizumab: 42 (18)	*Asthma duration/severity* Mean (SD) time since diagnosis, years Placebo: 18.7 (13.3) Reslizumab: 18.2 (14.4) Mean (SD) ACQ-7 score Placebo: 2.61 (0.79) Reslizumab: 2.57 (0.89) Mean (SD) number of asthma exacerbations in past 12 months Placebo: 2.0 (1.8) Reslizumab: 1.9 (1.6)	*Comorbidities* NR
Corren et al., 2016[40]; NCT01508936				
Study Characteristics	Phase 3 traditional RCT (effectiveness of add-on therapy vs. placebo); 66 study locations across the US *Years conducted:* 2012-2013 *Sponsor(s):* Teva Branded Pharmaceutical Products R&D, Inc. *Risk of bias:* Moderate			
Interventions (N randomized)	Reslizumab 3.0 mg/kg IV every 4 weeks for 16 weeks (n = 398)		Placebo (n = 98)	

Characteristic	Details			
	Cointervention(s): Patients were asked to refrain from SABAs and LABAs for 6 hours and 12 hours, respectively, before study visits; participants could be taking LABAs, LTRAs, 5-lipoxengase inhibitors, or cromolyn, if regimen was stable for 30 days before screening.			
Population	*Inclusion Criteria:* Aged 18 to 65 years with asthma (ACQ-7 score≥1.5) inadequately controlled by at least a medium-dose ICS at screening (fluticasone propionate ≥ 440 µg/day or equivalent). Patients could be taking LABAs, LTRAs, 5-lipoxengase inhibitors, or cromolyn, if regimen was stable for 30 days before screening and not expected to change throughout the study. Patients had to demonstrate airway reversibility (≥ 12% to SABA) at screening. No limit on FEV_1 for entry into study. *Exclusion Criteria:* Underlying lung disorders or pulmonary conditions with symptoms of asthma and blood eosinophilia; other clinically relevant comorbidities with potential to interfere with the study schedule, procedures, or the safety of the patient; known hyper-eosinophilic syndrome; current smoker; history of use of systemic immunosuppressive or immunomodulating therapy including anti-immunoglobulin E or anti-tumor necrosis factor monoclonal antibodies or interferon-α ≤6 months before study entry; use of systemic corticosteroids within 30 days before screening			
	Mean age (SD) Placebo: 45.1 (NR) Reslizumab: 44.9 (NR) N (%) female Placebo: 54 (55) Reslizumab: 261 (66)	*Race/ethnicity* N (%) white Placebo: 73 (74) Reslizumab: 260 (65) N (%) black Placebo: 21 (21) Reslizumab: 113 (28) N (%) Asian Placebo: 2 (2) Reslizumab: 10 (3)	*Asthma duration/severity* Mean (SD) duration since diagnosis, years Placebo: 25.8 (NR) Reslizumab: 26.2 (NR) N (%) exacerbations within previous 12 months Placebo: 37 (38) Reslizumab: 166 (42) Mean (SD) ACQ score Placebo: 2.6 Reslizumab: 2.6	*Comorbidities* NR
Bernstein et al., 2020[52]; NCT02501629				
Study Characteristics	Phase 3 steroid-sparing RCT; 78 study sites in 17 countries; Ukraine, US, Germany, Poland, Argentina, Russia, Mexico, Israel, Spain, Australia, South Korea, France, the Netherlands, Belgium, Hungary, Czech Republic, and Italy *Years conducted:* 2015-2017 *Sponsor(s):* Teva Branded Pharmaceutical Products R&D *Risk of bias:* Moderate			
Interventions (N randomized)	Reslizumab 110 mg SC every 4 weeks for 24 weeks (n = 88)		Placebo (n = 89)	
	Cointervention(s): To achieve the patient's minimal effective oral corticosteroid requirement, the oral corticosteroid dose was reduced at weekly intervals for up to 10 weeks or until asthma signs and symptoms worsened (minimum 1 day in optimization). Oral corticosteroid optimization was considered finished when patients had worsening of asthma signs and			

Characteristic	Details			
	symptoms, or if patients optimized to an oral corticosteroid dose of less than 5 mg of prednisone without worsening of asthma signs and symptoms. Patients whose minimal effective oral corticosteroid dose remained in the range of 5 to 40 mg prednisone daily at the end of optimization could advance in the study.			
Population	*Inclusion Criteria:* Aged 12 years and older with asthma, FEV_1 reversibility of 12% or more after inhaled reliever medication, or a historical FEV_1 reversibility or a positive methacholine challenge within 24 months, a blood eosinophil count of 300 cells per µL or more within the past 12 months while on at least a medium total daily dose of ICS; average daily maintenance dose of OCS for asthma during the 3 months of 5 to 40 mg; required high-dose ICS (≥880 µg of inhaled fluticasone propionate, or equivalent) plus another controller for at least 6 months; doses and regimens needed to have been stable for at least 30 days *Exclusion Criteria:* Clinically significant, uncontrolled medical condition that would have interfered with the study; another underlying lung disorder; known hypereosinophilic syndrome; history of malignancy within 5 years of the screening visit, except for non-melanoma skin cancers; pregnant or lactating woman; asthma exacerbation within 4 weeks; current smoker or had a smoking history ≥ 10 pack-years; currently using any systemic immunosuppressive or immunomodulatory biologic or nonbiologic, except maintenance OCS for the treatment of asthma; previously exposed to benralizumab or reslizumab			
	Mean age (SD) Placebo: 53.1 (12.0) Reslizumab: 55.5 (12.7) N (%) female Placebo: 57 (64) Reslizumab: 60 (68)	*Race/ethnicity* Race/ethnicity: NR	*Asthma duration/severity* Mean (SD) time since diagnosis, years Placebo: 20.1 (14.2) Reslizumab: 22.3 (16.0) Mean (SD) ACQ-6 score Placebo: 2.4 (1.2) Reslizumab: 2.3 (1.1) Mean (SD) number of asthma exacerbations requiring systemic corticosteroids in the past 12 months Placebo: 1.85 (1.2) Reslizumab: 2.1 (1.6)	*Comorbidities* N (%) with aspirin sensitivity Placebo: 7 (8) Reslizumab: 5 (6) N (%) with chronic rhinosinusitis with nasal polyps Placebo: 13 (15) Reslizumab: 10 (11)
Castro et al., 2015[36]; BREATH-1; NCT01287039				
Study Characteristics	Phase 3 traditional RCT (effectiveness of add-on therapy vs. placebo); 128 clinical research centers; US, Australia, Belgium, Chile, Colombia, Czech Republic, Denmark, Hungary, Israel, Malaysia, New Zealand, Philippines, Poland, Russia, South Africa, Sweden, Thailand *Years conducted:* 2011-2014 *Sponsor(s):* Teva Branded Pharmaceutical Products R&D *Risk of bias:* Moderate			

Characteristic	Details			
Interventions (N randomized)	Reslizumab 3.0 mg/kg IV every 4 weeks for 52 weeks (n = 245)		Placebo (n = 244)	
	Cointervention(s): Patients continued their usual asthma treatment, including but not limited to LABAs, inhaled corticosteroids, oral corticosteroids (≤10 mg per day of prednisone or equivalent), LTRAs, and cromolyn sodium, at constant doses.			
Population	*Inclusion Criteria:* Aged 12 to 75 years with at least 1 blood eosinophil count of 400 cells per µL or higher during a 2–4 week screening period and inadequately controlled ACQ-7 score ≥ 1.5 who were receiving at least a medium dose of inhaled corticosteroids with or without another controller drug (including oral corticosteroids). Had at least 1 asthma exacerbation that needed a systemic corticosteroid within the past 12 months and a FEV_1 reversibility of 12% or more with albuterol *Exclusion Criteria:* Any clinically meaningful comorbidity that could interfere with the study; known hypereosinophilic syndrome; another confounding underlying lung disorder; current smoker; current use of systemic immunosuppressive, immunomodulating, or other biologic agents within 6 months before screening; prior use of an antihuman interleukin-5 monoclonal antibody (e.g., reslizumab, mepolizumab, or benralizumab); inadequately controlled, aggravating medical factors; pregnant or nursing; history of concurrent immunodeficiency; current suspected drug and alcohol abuse; requirement for treatment for an asthma exacerbation within 4 weeks of screening or during the screening period			
	Median age (IQR) Placebo: 49 (38 to 57) Reslizumab: 48 (38 to 57) N (%) female Placebo: 161 (66) Reslizumab: 142 (58)	*Race/ethnicity* N (%) white: Placebo: 182 (75) Reslizumab: 173 (71) N (%) black: Placebo: 20 (8) Reslizumab: 14 (6) N (%) Asian: Placebo: 33 (14) Reslizumab: 50 (20) N (%) other: Placebo: 9 (4) Reslizumab: 8 (3)	*Asthma duration/severity* Mean (SD) time since diagnosis (years) Placebo: 18.8 (14.2) Reslizumab: 19.7 (15.2) Mean (SD) ACQ-7 score Placebo: 2.76 (0.88) Reslizumab: 2.66 (0.85) Mean (SD) number of asthma exacerbations in past 12 months Placebo: 2.1 (2.3) Reslizumab: 1.9 (1.6)	*Comorbidities* NR

Abbreviations. ACQ: Asthma Control Questionnaire; d: day; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; IQR: interquartile ratio; IV: intravenous; LABA: long-acting beta-agonist; LTRA: leukotriene receptor antagonists; NCT: US National Clinical Trial; NR: not reported; OCS: oral corticosteroids; RCT: randomized controlled trial; SABA: short-acting beta-agonists; SC: subcutaneous; SD: standard deviation.

Table B14. Effectiveness Outcomes From RCTs of Reslizumab for Asthma

Outcome	Group	Result
Bernstein et al., 2020[52] (study 1)		
Exacerbations requiring ED visits or hospitalization (52 wk)	Placebo (n = 230)	Mean (SD) rate: 0.05 (NR)
	Reslizumab (n = 234)	Mean (SD) rate: 0.05 (NR) IRR (95% CI): 0.94 (0.43 to 2.07) Exacerbation defined as 1) use of systemic steroids at least doubling from stable maintenance oral dose for 3 days or more, 2) asthma-specific hospital admission or ED visit.
Adjusted annualized rate of exacerbations (52 wk)	Placebo (n = 230)	Mean (SD) rate: 0.52 (NR)
	Reslizumab (n = 234)	Mean (SD) rate: 0.41 (NR) IRR (95% CI): 0.79 (0.56 to 1.12); *P* = .19
Probability of not experiencing an exacerbation (52 wk)	Placebo (n = 230)	Kaplan-Meier estimate of the probability of not experiencing an exacerbation: 0.66 (95% CI, 0.59 to 0.72)
	Reslizumab (n = 234)	Kaplan-Meier estimate of the probability of not experiencing an exacerbation: 0.66 95% CI, 0.59 to 0.71) HR 0.97 (95% CI, 0.71 to 1.34)
ACQ mean change from baseline (52 wk)	Placebo (n = 230)	Mean (SE) change from baseline: -1.14 (0.080)
	Reslizumab (n = 234)	Mean (SE) change from baseline: -1.22 (0.078) Difference from placebo (95% CI): -0.09 (-0.27 to 0.10)
Asthma symptom score mean change from baseline (52 wk)	Placebo (n = 230)	Mean (SE) change from baseline: -1.4 (0.12)
	Reslizumab (n = 234)	Mean (SE) change from baseline: -1.5 (0.12) Difference from placebo (95% CI): -0.10 (-0.35 to 0.15)
St. George's Respiratory Questionnaire mean change from baseline (32 wk)	Placebo (n = 230)	Mean (SE) change from baseline: -13.1 (1.38)
	Reslizumab (n = 234)	Mean (SE) change from baseline: -16.4 (1.32) Difference from placebo (95% CI): -3.30 (-6.02 to -0.66)
AQLQ mean change from baseline (52 wk)	Placebo (n = 230)	Mean (SE) change from baseline: 1.06 (0.089)
	Reslizumab (n = 234)	Mean (SE) change from baseline: 1.14 (0.087) Difference from placebo (95% CI): 0.08 (-0.11 to 0.27)
Bernstein et al., 2020[52] (study 2)		
Adjusted annualized rate of exacerbations (24 wk)	Placebo (n = 89)	Mean (95% CI) rate: 1.86 (1.28 to 2.68)
	Reslizumab (n = 88)	Mean (95% CI) rate: 1.51 (1.05 to 2.18) IRR (95% CI): 0.82 (0.50 to 1.32)
Probability of not experiencing an exacerbation by 24 wk	Placebo (n = 89)	Kaplan-Meier estimate of not having an exacerbation by week 24: 0.52 (95% CI, 0.41 to 0.62)
	Reslizumab (n = 88)	Kaplan-Meier estimate of not having an exacerbation by week 24: 0.57 (95% CI, 0.46 to 0.67) HR 0.80 (95% CI, 0.52 to 1.25)
	Placebo (n = 89)	Percentage change from baseline: -40.34

Outcome	Group	Result
Percentage change in OCS dose (20-24 wk)	Reslizumab (n = 88)	Percentage change from baseline: -58.08 Difference from placebo (95% CI): -17.75 (-38.99 to 3.49)
Percentage reduction from baseline in OCS by category (20-24 wk)		Percentage reduction from baseline in OCS by category N (%) with 90% to 100% reduction from baseline Placebo: 20 (22) Reslizumab: 18 (20) N (%) with 75% to <90% reduction from baseline Placebo: 4(4) Reslizumab: 8 (9) N (%) with 50% to <75% reduction from baseline Placebo: 8 (9) Reslizumab: 13 (15) N (%) with >0% to <50% reduction from baseline Placebo: 9 (10) Reslizumab: 7 (8) N (%) with no decrease from baseline Placebo: 48 (54) Reslizumab: 42 (48) OR (95% CI): 1.23 (0.70 to 2.16); *P* = .47
ACQ mean change from baseline (24 wk)	Placebo (n = 89)	Mean (SE) change from baseline: -0.45 (0.389)
	Reslizumab (n = 88)	Mean (SE) change from baseline: -0.62 (0.397) Difference from placebo (95% CI): -0.17 (-0.46 to 0.11)
AQLQ mean change from baseline (24 wk)	Placebo (n = 89)	Mean (SE) change from baseline: 0.67 (0.396)
	Reslizumab (n = 88)	Mean (SE) change from baseline: 0.92 (0.407) Difference from placebo (95% CI): 0.25 (-0.06 to 0.55)
Castro et al., 2011[17]		
Number of patients with > 1 exacerbation (15 wk)	Placebo (n = 53)	Events of total N (%): 10 of 53 (19%)
	Reslizumab (n = 53)	Events of total N (%): 4 of 53 (8%) Reported OR (95% CI): 0.33 (0.10 to 1.15) Calculated RR (95% CI): 0.40 (0.13 to 1.20) Exacerbations included 20% decrease from baseline in FEV_1, emergency treatment for asthma, admittance to the hospital for asthma, oral corticosteroid treatment for asthma worsening.
ACQ mean change from baseline (15 wk)	Placebo (n = 53)	Mean (SD) change from baseline: -0.3 (1.01)
	Reslizumab (n = 53)	Mean (SD) change from baseline: -0.7 (1.02) Difference from placebo (95% CI): -0.38 (-0.76 to 0.01); *P* = .0541
ACQ minimally important difference (15 wk)	Placebo (n = 53)	Events of total N (%): 21 of 53 (40%)
	Reslizumab (n = 53)	Events of total N (%): 31 of 53 (58%) Reported OR (95% CI): 2.06 (0.88 to 4.86) Calculated RR (95% CI):1.48 (0.99 to 2.21)
Bjermer et al., 2016[35]; BREATH-3		
ACQ mean change from baseline (ACQ-7; 16 wk)	Placebo (n = 103)	Mean (SE) change from baseline: -0.494 (0.1235)
	Reslizumab (n = 101)	Mean (SE) change from baseline: -0.855 (0.1237) Difference from placebo (95% CI): -0.36 (-0.58 to -0.14); *P* = .0013

Outcome	Group	Result
AQLQ minimally important difference (16 wk)	Placebo (n = 105)	Events of total N (%): 50 of 105 (48%)
	Reslizumab (n = 106)	Events of total N (%): 68 of 106 (64%) Calculated RR (95% CI): 1.35 (1.05 to 1.72)
ASUI mean change from baseline (16 wk)	Placebo (n = 105)	Mean (SE) change from baseline: 0.082 (0.0218)
	Reslizumab (n = 106)	Mean (SE) change from baseline: 0.129 (0.0218) Difference from placebo (95% CI): 0.05 (0.01 to 0.09); *P* = .016
AQLQ mean change from baseline (16 wk)	Placebo (n = 101)	Mean (SE) change from baseline: 0.781(0.182)
	Reslizumab (n = 99)	Mean (SE) change from baseline: 1.14 (0.183) Difference from placebo (95% CI): 0.36 (0.05 to 0.67); *P* = .0241
Castro et al., 2015[36]; BREATH-2		
Rate of exacerbations requiring ED visits or hospitalization (52 wk)	Placebo (n = 232)	Mean (SD) rate: 0.05 (NR)
	Reslizumab (n = 232)	Mean (SD) rate: 0.03 (NR) IRR (95% CI): 0.69 (0.29 to 1.65); *P* = .402 Exacerbations defined as worsening of asthma that resulted in use of systemic steroids in those not already receiving them or doubling of ICS or systemic dose for 3 or more days, or ED visit or hospital admission or unscheduled physician visit, and associated with decrease of FEV_1 of 20% or more, reduction in PEF of 30% or more on 2 consecutive days, or a worsening of signs and symptoms
Number of patients with ≥ 1 exacerbation (52 wk)	Placebo (n = 232)	Events of total N (%): 105 of 232 (45%)
	Reslizumab (n = 232)	Events of total N (%): 59 of 232 (25%) Calculated RR (95% CI): 0.56 (0.43 to 0.73)
Adjusted annualized rate of exacerbations (52 wk)	Placebo (n = 232)	Mean (SD) rate: 2.11 (NR)
	Reslizumab (n = 232)	Mean (SD) rate: 0.86 (NR) IRR (95% CI): 0.41 (0.28 to 0.59); *P* < .0001
Time to first exacerbation		Time to first exacerbation, reslizumab vs. placebo HR (95% CI): 0.486 (0.353 to 0.670)
ACQ mean change from baseline (16 wk)	Placebo (n = 232)	Mean (SD) change from baseline: -0.66 (NR)
	Reslizumab (n = 232)	Mean (SD) change from baseline: -0.86 (NR) IRR (95% CI): -0.20 (-0.33 to -0.07); *P* = .0032
ACQ mean change from baseline (52 wk)	Placebo (n = 232)	Mean (SD) change from baseline: -0.80 (NR)
	Reslizumab (n = 232)	Mean (SD) change from baseline: -1.04 (NR) IRR (95% CI): -0.24 (-0.37 to -0.11); *P* = .0003
ACQ minimally important difference (52 wk)	Placebo (n = 232)	Events of total N (%): 140 of 232 (60%)
	Reslizumab (n = 232)	Events of total N (%): 178 of 232 (77%) *P* = .0002 Calculated RR (95% CI): 1.27 (1.12 to 1.44)
ASUI mean change from baseline (16 wk)	Placebo (n = 232)	Mean change from baseline: 0.08
	Reslizumab (n = 232)	Mean change from baseline: 0.12 IRR (95% CI): 0.04 (0.01 to 0.06); *P* = .0037

Outcome	Group	Result
ASUI mean change from baseline (52 wk)	Placebo (n = 232)	Mean change from baseline: 0.11
	Reslizumab (n = 232)	Mean change from baseline: 0.15 IRR (95% CI): 0.04 (0.01 to 0.06); *P* = .0011
AQLQ mean change from baseline (52 wk)	Placebo (n = 232)	Mean change from baseline: 0.89
	Reslizumab (n = 232)	Mean change from baseline: 1.12 IRR (95% CI): 0.23 (0.07 to 0.40); *P* = .0052
AQLQ mean change from baseline (16 wk)	Placebo (n = 232)	Mean change from baseline: 0.79
	Reslizumab (n = 232)	Mean change from baseline: 0.95 IRR (95% CI): 0.21 (0.03 to 0.39); *P* = .0259
AQLQ minimally important difference (52 wk)	Placebo (n = 232)	Events of total N (%): 137 of 232 (59%) [reported as 62% in article]
	Reslizumab (n = 232)	Events of total N (%): 157 of 232 (68%) [reported as 73% in article] *P* = .02 Calculated RR (95% CI): 1.15 (1.00 to 1.32)
Castro et al., 2015[36]; BREATH-1		
Adjusted annualized rate of asthma exacerbations (52 wk)	Placebo (n = 244)	Mean (SD) rate: 1.80 (NR)
	Reslizumab (n = 245)	Mean (SD) rate: 0.9 (NR) IRR (95% CI): 0.50 (0.37 to 0.67); *P* < .0001 Exacerbations defined as worsening asthma resulting in use of systemic steroids in patients not already receiving them or doubling of dose of either ICS or systemic steroid for 3 or more days, or the need for ED visit, hospital admission, or unscheduled physician visit, and associated with decrease in FEV_1 of 20% or more, reduction in PEF of 30% or more on 2 consecutive days, or a worsening of signs or symptoms as identified by physician assessment
Rate of exacerbations requiring ED visits or hospitalization (52 wk)	Placebo (n = 244)	Mean (SD) rate: 0.21 (NR)
	Reslizumab (n = 245)	Mean (SD) rate: 0.14 (NR) IRR (95% CI): 0.66 (0.32 to 1.36); *P* = .257
Number of patients with ≥1 exacerbation (52 wk)	Placebo (n = 244)	Events of total N (%): 132 of 244 (54%)
	Reslizumab (n = 245)	Events of total N (%): 92 of 245 (38%) Calculated RR (95% CI): 0.69 (0.57 to 0.85)
Time to first exacerbation		Time to exacerbation, reslizumab vs. placebo HR 0.58 (95% CI, 0.44 to 0.75); *P* < .0001
ACQ mean change from baseline (16 wk)	Placebo (n = 244)	Mean (SD) change from baseline: -0.68 (NR)
	Reslizumab (n = 245)	Mean (SD) change from baseline: -0.94 (NR) IRR (95% CI): -0.27 (-0.40 to -0.13); *P* = .0001
ACQ mean change from baseline (52 wk)	Placebo (n = 244)	Mean (SD) change from baseline: -0.76 (NR)
	Reslizumab (n = 245)	Mean (SD) change from baseline: -1.02 (NR) IRR (95% CI): -0.26 (-0.39 to -0.12); *P* = .0002
ACQ minimally important	Placebo (n = 244)	Events of total N (%): 152 of 244 (62%)

Outcome	Group	Result
difference (52 wk)	Reslizumab (n = 245)	Events of total N (%): 184 of 245 (75%) *P* = .0002 Calculated RR (95% CI): 1.21 (1.07 to 1.36)
ASUI mean change from baseline (52 wk)	Placebo (n = 244)	Mean (SD) change from baseline: 0.13 (NR)
	Reslizumab (n = 245)	Mean (SD) change from baseline: 0.19 (NR) IRR (95% CI): 0.06 (0.04 to 0.08); *P* < .0001
ASUI mean change from baseline (16 wk)	Placebo (n = 244)	Mean (SD) change from baseline: 0.11 (NR)
	Reslizumab (n = 245)	Mean (SD) change from baseline: 0.17 (NR) IRR (95% CI): 0.06 (0.03 to 0.08); *P* < .0001
AQLQ mean change from baseline (52 wk)	Placebo (n = 244)	Mean (SD) change from baseline: 0.79 (NR)
	Reslizumab (n = 245)	Mean (SD) change from baseline: 1.09 (NR) IRR (95% CI): 0.30 (0.14 to 0.47); *P* = .0004
AQLQ mean change from baseline (16 wk)	Placebo (n = 244)	Mean (SD) change from baseline: 0.87 (NR)
	Reslizumab (n = 245)	Mean (SD) change from baseline: 1.03 (NR) Difference from placebo (95% CI): 0.24 (0.05 to 0.43); *P* = .0143
AQLQ minimally important difference (52 wk)	Placebo (n = 244)	Events of total N (%): 150 of 244 (61%) [reported as 65% in article]
	Reslizumab (n = 245)	Events of total N (%): 172 of 245 (70%) [reported as 74% in article] *P* = .03 Calculated RR (95% CI): 1.14 (1.00 to 1.30)
Corren et al., 2016[40]		
ACQ mean change from baseline (16 wk)	Placebo (n = 97)	Mean (SE) change from baseline: -0.648 (0.0878)
	Reslizumab (n = 395)	Mean (SE) change from baseline: -0.844 (0.0453) Difference from placebo (95% CI): -0.195 (-0.387 to -0.004); *P* = .0457
ACQ minimally important difference (16 wk)	Placebo (n = 97)	Events of total N (%): 55 of 97 (57%)
	Reslizumab (n = 394)	Events of total N (%): 278 of 394 (71%) *P* = .01 Calculated RR (95% CI): 1.24 (1.03 to 1.50)

Abbreviations. ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; ASUI: Asthma Symptoms Utility Index; CI: confidence interval; ED: emergency department; FEV_1: : forced expiratory volume in 1 second; HR: hazard ratio; NR: not reported; OCS: oral corticosteroids; OR: odds ratio; PEF: peak expiratory flow ; RCT: randomized controlled trial; RR: risk ratio; SD: standard deviation; SE: standard error; wk: week.

Table B15. Safety Outcomes From RCTs of Reslizumab for Asthma

Safety Outcomes (time point)	Intervention Group Number Events of Total Number (%) RR (95% CI)	Comparator Group Number Events of Total number (%)
Bernstein et al., 2020[52]		
	Reslizumab 110 mg SC every 4 weeks	Placebo
Total adverse events (52 wk)	169 of 237 (71%) 0.96 (0.86 to 1.07)	172 of 231 (74%)
SAEs (52 wk)	19 of 237 (8%) 0.97 (0.53 to 1.79)	19 of 231 (8%)
Adverse events leading to discontinuation (52 wk)	5 of 237 (2%) 4.87 (0.57 to 41.40)	1 of 231 (0%)
Mortality (52 wk)	0 of 237 (0%)	0 of 231 (0%)
Bernstein et al., 2020[52]		
	Reslizumab 110 mg SC every 4 weeks	Placebo
Total adverse events (24 wk)	57 of 88 (65%) 1.23 (0.96 to 1.57)	47 of 89 (53%)
SAEs (24 wk)	10 of 88 (11%) 2.53 (0.82 to 7.76)	4 of 89 (4%)
Adverse events leading to discontinuation (24 wk)	0 of 88 (0%) 0.34 (0.01 to 8.16)	1 of 89 (1%)
Mortality (24 wk)	1 of 88 (1%) 3.03 (0.13 to 73.48)	0 of 89 (0%)
Castro et al., 2011[17]		
	Reslizumab 3.0 mg/kg IV every 4 weeks	Placebo
Total adverse events (15 wk)	38 of 53 (72%) 0.90 (0.73 to 1.13)	42 of 53 (79%)
SAEs (15 wk)	2 of 53 (4%) 2.00 (0.19 to 21.40)	1 of 53 (2%)
Adverse events leading to discontinuation (15 wk)	1 of 53 (2%) 1.00 (0.06 to 15.57)	1 of 53 (2%)
Bjermer et al., 2016[35]; BREATH-3		
	Reslizumab 3.0 mg/kg IV every 4 weeks	Placebo
Total adverse events (16 wk)	61 of 103 (59%) 0.94 (0.76 to 1.17)	66 of 105 (63%)
SAEs (16 wk)	4 of 103 (4%) 4.08 (0.46 to 35.87)	1 of 105 (1%)
Adverse events leading to discontinuation (16 wk)	6 of 103 (6%) 0.61 (0.23 to 1.62)	10 of 105 (10%)
Mortality (16 wk)	0 of 106 (0%)	0 of 105 (0%)
Treatment-related adverse events (16 wk)	12 of 103 (12%) 1.53 (0.65 to 3.59)	8 of 105 (8%)
Castro et al., 2015[36]; BREATH-2		
	Reslizumab 3.0 mg/kg IV every 4 weeks	Placebo
Total adverse events (52 wk)	177 of 232 (76%) 0.88 (0.81 to 0.96)	201 of 232 (87%)
SAEs (52 wk)	18 of 232 (8%) 0.78 (0.43 to 1.41)	23 of 232 (10%)

Safety Outcomes (time point)	Intervention Group Number Events of Total Number (%) RR (95% CI)	Comparator Group Number Events of Total number (%)
Adverse events leading to discontinuation (52 wk)	8 of 232 (3%) 0.89 (0.35 to 2.26)	9 of 232 (4%)
Mortality (52 wk)	0 of 232 (0%)	0 of 232 (0%)
Castro et al., 2015[36]; BREATH-1		
	Reslizumab 3.0 mg/kg IV every 4 weeks	**Placebo**
Total adverse events (52 wk)	197 of 245 (80%) 0.95 (0.87 to 1.03)	206 of 243 (85%)
SAEs (52 wk)	24 of 245 (10%) 0.70 (0.43 to 1.14)	34 of 243 (14%)
Adverse events leading to discontinuation (52 wk)	4 of 245 (2%) 0.50 (0.15 to 1.63)	8 of 243 (3%)
Mortality (52 wk)	0 of 245 (0%) 0.33 (0.01 to 8.08)	1 of 243 (0%)
Corren et al., 2016[40]		
	Reslizumab 3.0 mg/kg IV every 4 weeks	**Placebo**
Total adverse events (16 wk)	217 of 395 (55%) 0.74 (0.64 to 0.86)	72 of 97 (74%)
SAEs (16 wk)	16 of 395 (4%) 0.98 (0.34 to 2.87)	4 of 97 (4%)
Adverse events leading to discontinuation (16 wk)	32 of 395 (8%) 0.65 (0.35 to 1.22)	12 of 97 (12%)
Mortality (16 wk)	0 of 395 (0%)	0 of 97 (0%)
Treatment-related adverse events (16 wk)	28 of 395 (7%) 0.43 (0.24 to 0.76)	16 of 97 (16%)

Abbreviations. CI: confidence interval; IV: intravenous; kg: kilogram; mg: milligram; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; SC: subcutaneous; wk: week.

Omalizumab Chronic Spontaneous Urticaria Studies

Table B16. Study Characteristics From RCTs of Omalizumab for Chronic Spontaneous Urticaria

Hide et al., 2017[64]; POLARIS; NCT02329223				
Study Characteristics	Phase 3 RCT; 41 sites across Japan and Korea *Years conducted:* 2014-2015 *Sponsor(s):* Novartis *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab 300 mg SC every 4 weeks for 12 weeks (n = 73)	Omalizumab 150 mg SC every 4 weeks for 12 weeks (n = 71)	Placebo (n = 74)	
	Cointervention(s): All patients required to take stable doses of their prescreening H_1-antihistamines medications for study duration and were provided diphenhydramine 10-mg or 25-mg tablets for additional itch relief on an as-needed basis (up to a maximum of 75 mg/day with 25-mg tablets in Korea or 80 mg/day with 10-mg tablets in Japan)			
Population	*Inclusion Criteria:* Aged 12 to 75 years old with CSU diagnosis for 6 months that was refractory to conventional H_1-antihistamines at time of randomization; itch and hives for 8 consecutive weeks at any time before enrollment; UAS7 ≥16; itch component of UAS7 ≥ 8 during 7 days before randomization; in-clinic UAS ≥ 4 on at least 1 screening visit day; on approved dose of an H_1-antihistamine for CSU for 3 consecutive days immediately before day 14 screening visit and documented current use *Exclusion Criteria:* Weight < 20 kg, clearly defined underlying etiology for chronic urticaria other than CSU and any skin diseases other than CSU with chronic itching			
	Mean age (SD) Placebo: 42.5 (14.3) Omalizumab 300 mg: 44.6 (14.9) Omalizumab 150 mg: 43.6 (12.2) N (%) female Placebo: 48 (64.9) Omalizumab 300 mg: 40 (54.8) Omalizumab 150 mg: 43 (60.6)	*Race/ethnicity* N (%) Japanese Placebo: 36 (48.6) Omalizumab 300 mg: 35 (47.9) Omalizumab 150 mg: 34 (47.9) N (%) Korean Placebo: 38 (51.4) Omalizumab 300 mg: 38 (52.1) Omalizumab 150 mg: 37 (52.1)	*CSU duration/severity* Mean duration in years (SD) Placebo: 4.7 (6.2) Omalizumab 300 mg: 3.6 (4.0) Omalizumab 150 mg: 5.1 (6.2) UAS7 mean (SD) Placebo: 30.1 (6.5) Omalizumab 300 mg: 31.8 (7.1) Omalizumab 150 mg: 29.6 (7.4) ISS7 mean (SD) Placebo: 13.7 (3.3) Omalizumab 300 mg: 14.6 (3.7) Omalizumab 150 mg: 13.2 (4.0)	*Comorbidities* Angioedema: N (%) Placebo: 15 (20.3) Omalizumab 300 mg: 12 (16.4) Omalizumab 150 mg: 12 (16.9)

Jorg et al., 2018;[70] NCT01803763				
Study Characteristics	Phase 2 RCT; Switzerland *Years conducted:* 2012-2014 *Sponsor(s):* Novartis *Risk of bias:* High			
Interventions (N randomized)	Omalizumab 300 mg SC every 4 weeks for 16 weeks (n = 20)	Placebo (n = 10)		
	Cointervention(s): Patients allowed to take usual medications (H_1-antihistamines up to a fourfold single dose, H2- antihistamines, montelukast, short-term prednisolone for CSU exacerbations)			
Population	*Inclusion Criteria:* Patients aged 18 to 70 with CSU and symptoms for at least 6 weeks, with hives present at least twice weekly, and symptoms refractory to standard doses of H_1-antihistamines at the time of randomization *Exclusion Criteria:* Inducible urticaria, allergic urticaria, treatment with omalizumab in last year, hypersensitivity to omalizumab, history of cancer in previous 5 years, parasitic infections, active tuberculosis or ongoing recent antituberculous therapy, prior treatment with systemic immunosuppressive agents (short-term prednisolone for CSU exacerbations was allowed), pregnant or nursing			
	Mean age (SD) Placebo: 42.4 (13.3) Omalizumab: 41.8 (15.2) N (%) female Placebo: 8 (80) Omalizumab: 8 (40)	*Race/ethnicity* NR	*CSU duration/severity* Median months (IQR) Placebo: 27.0 (19.8, 64.8) Omalizumab: 19.5 (12.0, 33.8) Median (IQR) UAS7 Placebo: 18.5 (11.3, 23.5) Omalizumab: 11.0 (2.5, 21.5)	*Comorbidities* Angioedema, N (%) Placebo: 7 (70) Omalizumab: 9 (45)
Kaplan et al., 2013;[67] GLACIAL; NCT01264939				
Study Characteristics	Phase 3 RCT; 65 centers globally; Australia, Germany, New Zealand, Poland, Singapore, United Kingdom, US *Years conducted:* 2011-2012 *Sponsor(s):* Genentech, Inc. and Novartis Pharma AG *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab 300 mg SC every 4 weeks for 24 weeks (n = 252)	Placebo (n = 84)		
	Cointervention(s): Participants were required to maintain stable doses of their prerandomization combination therapy with H_1-antihistamine treatment plus H_2-antihistamines, LTRAs, or both. For the duration of the study, patients were provided with 25 mg of diphenhydramine as rescue medication for symptom relief.			
Population	*Inclusion Criteria:* Aged 12 to 75 years (18 to 75 in Germany); CIU/CSU for 6 months or longer; itch and hives for more than 6 consecutive weeks before enrollment despite therapy with H_1-antihistamines plus H_2-antihistamines, LTRAs, or both; UAS7 of 16 or greater; weekly ISS of 8 or greater during 7 days before randomization; an in-clinic physician-assessed UAS of 4 or greater			

	on 1 of the screening visit days; treatment with a regimen that included an H_1-antihistamine (up to 4 times the approved dosage) plus H_2-antihistamines, LTRAs, or both H_2-antihistamines and LTRAs for CIU/CSU for 3 or more consecutive days *Exclusion Criteria:* Clearly defined underlying cause for chronic urticaria; systemic or topical doses of steroids administered daily or every other day for 5 or more consecutive days, hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, or intravenous immunoglobulin within 30 days; history of malignancy; hypersensitivity to omalizumab; treatment with omalizumab within previous year; evidence of parasitic infection; history of anaphylactic shock; women who are pregnant, breast-feeding, or of childbearing potential and not using acceptable contraception.			
	Mean age (SD) 43.1 (14.1) N (%) female 241 (71.9)	*Race/ethnicity* N (%) white: 298 (89.0)	*CSU duration/severity* Time since diagnosis, mean (SD): 7.4 (9.5) UAS7: 30.9 (6.6) Weekly ISS: 14.0 (3.6)	*Comorbidities* N(%) with angioedema: 178 (53.1)
Maurer et al., 2013;[65] ASTERIA II; NCT01292473				
Study Characteristics	Phase 3 RCT; 61 clinical sites in 8 countries; Denmark, France, Germany, Italy, Poland, Spain, Turkey, and the US *Years conducted:* 2011-2012 *Sponsor(s):* Genentech and Novartis Pharma *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab 150 mg SC every 4 weeks for 12 weeks (n = 83)	Omalizumab 300 mg SC every 4 weeks for 12 weeks (n = 79)	Placebo (n = 79)	
	Cointervention(s): Participants continued to receive stable doses of their baseline H_1-antihistamines throughout the study; during follow-up participants were also allowed use of 1 additional H_1-antihistamine; rescue medication (up to 3 doses of 25 mg of diphenhydramine in 24 hours) was also provided.			
Population	*Inclusion Criteria:* Aged 12 to 75 years with chronic idiopathic urticaria for at least 6 months, hives associated with itching for past 8 weeks despite use of H_1-antihistamines, UAS7 score ≥ 16, weekly itch-severity score ≥ 8, clinician assessed UAS score ≥ 4, receipt of second-generation H_1-antihistamine for at least 3 consecutive days immediately before randomization, and no missing electronic-diary entries for the 7 days before randomization *Exclusion Criteria:* Underlying cause for chronic urticaria (e.g., physical urticaria), routine use of systemic glucocorticoids, hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, or intravenous immune globulin within the previous 30 days, use of any H_2-antihistamine or LTRA within 7 days, the use of H_1- antihistamines at greater-than-licensed doses within 3 days, history of cancer, weight of < 20 kg, known hypersensitivity to omalizumab, treatment with omalizumab within the previous year, or pregnancy			
	Mean age (SD) Placebo: 43.1 (12.5) Omalizumab 150 mg: 43.0 (13.2)	*Race/ethnicity* N (%) nonwhite Placebo: 6 (8) Omalizumab 150 mg: 6 (7)	*CSU duration/severity* Mean (SD) time since diagnosis, years Placebo: 7.2 (10.7) Omalizumab 150 mg: 7.2 (8.9) Omalizumab 300 mg: 6.1 (7.3)	*Comorbidities* N (%) with angioedema Placebo: 30 (38)

	Omalizumab 300 mg: 44.3 (13.7) N (%) female Placebo: 55 (70) Omalizumab 150 mg: 65 (79) Omalizumab 300 mg: 63 (80)	Omalizumab 300 mg: 9 (11) N (%) white Placebo: 70 (89) Omalizumab 150 mg: 70 (85) Omalizumab 300 mg: 68 (86) N (%) not avilable Placebo: 3 (4) Omalizumab 150 mg: 6 (7) Omalizumab 300 mg: 2 (3)	Mean (SD) UAS7 Placebo: 31.0 (6.6) Omalizumab 150 mg: 31.4 (7.0) Omalizumab 300 mg: 29.5 (6.9) Weekly Itch Severity Score, mean (SD) Placebo: 14.0 (3.4) Omalizumab 150 mg: 14.2 (4.1) Omalizumab 300 mg: 13.7 (3.5)	Omalizumab 150 mg: 38 (46) Omalizumab 300 mg: 32 (41)
Maurer et al., 2011[69]				
Study Characteristics	RCT, phase NR; 16 centers in Germany *Years conducted:* 2007-2009 *Sponsor(s):* Novartis *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab (weight/IgE based dose) SC every 2 or 4 weeks for 24 weeks (n = 27)			Placebo (n = 22)
	Cointervention(s): H_1-blocking antihistamines on demand for rescue medication; no other medications permitted			
Population	*Inclusion Criteria:* Aged 18 to 70 years with moderate to severe CU based on existing guidelines, body weight between 20 to 150 kg, total serum IgE level between 30 IU/mL and 700 IU/mL, serum IgE–anti-TPO antibody level of 5.0 IU/mL or greater within last 3 months, and weekly UAS score of 10 or greater *Exclusion Criteria:* Acute urticaria, chronic diarrhea, severe renal dysfunction, or increased serum IgE levels for reasons other than allergy or urticaria. Epilepsy, allergy to antibiotics, malignancy within the past 5 years, or cerebrovascular attacks or ischemia or who had taken oral or parenteral corticosteroids, methotrexate, cyclosporine, or other immunosuppressant medications during 4 weeks before screening.			
	Mean age (SD) Placebo: 42.3 (15.0) Omalizumab: 39.1 (9.0) N (%) female Placebo: 19 (86.4) Omalizumab: 19 (70.4)	*Race/ethnicity* N (%) white Placebo: 22 (100) Omalizumab: 27 (100)	*CSU duration/severity* Duration: NR Mean (SD) UAS7 score Placebo: 21.3 (7.6) Omalizumab: 24.6 (7.4)	*Comorbidities* NR
Maurer et al., 2018;[71] Casale et al., 2019;[72] Casale et al., 2018;[73] XTEND-CIU; NCT02392624				
Study Characteristics	Phase 4/postmarketing discontinuation RCT; NR; US *Years conducted:* 2015-2016			

	Sponsor(s): Genentech, Novartis *Risk of bias:* High			
Interventions (N randomized)	Omalizumab 300 mg SC every 4 weeks (n = 81)			Placebo (n = 53)
	Cointervention(s): 24 wk open-label phase followed by randomization of persons with adequate control (UAS7 ≤ 6) to either discontinuation or continuation through week 48. Participants with clinical worsening (UAS7 ≥ 12 for ≥ 2 consecutive weeks) were eligibile to be transitioned back to open-label omalizumab.			
Population	*Inclusion Criteria:* Aged 12 to 75; antihistamine-resistant CIU/CSU; UAS7 score 16 or more during previous 7 days *Exclusion Criteria:* NR			
	Mean age (SD) Placebo: 49 (13) Omalizumab: 43 (15) N (%) female 100 (75)	*Race/ethnicity* N (%) white: 110 (82)) N (%) black: 13 (10) N (%) Asian: 5 (4) N (%) American Indian or Alaska Native: 2 (1) N (%) other: 4 (3)	*CSU duration/severity* Mean (SD) duration, months Placebo: 76.6 (67.3) Omalizumab: 77.0 (118.8) Mean (SD) UAS7 score Placebo: 32.9 (7.0) Omalizumab: 32.4 (7.2) Mean no. of days with angioedema in the previous week Placebo: 2.8 (3.0) Omalizumab: 1.8 (2.6)	*Comorbidities* NR
Metz et al., 2017;[68] NCT01599637				
Study Characteristics	Phase 2 RCT; 4 centers in Germany *Years conducted:* 2012-2013 *Sponsor(s):* Novartis Pharmaceuticals *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab 300 mg SC every 4 weeks for 12 weeks (n = 20)			Placebo (n = 10)
	Cointervention(s): Continued stable doses of H_1-antihistamines; Loratadine was allowed to be used as a rescue medication on an as needed basis up to 4 times the recommended dose of 10 mg, for angioedema or other reasons specified by the patient.			
Population	*Inclusion Criteria:* Aged 18 to 75 years, diagnosed with CSU who remained symptomatic despite H_1-antihistamine treatment at approved doses, defined as presence of itch and hives for over 6 weeks before baseline, with UAS7 score of at least 16 and itch component of UAS7 of at least 8 during the 14 days before randomization. Patients had to have had a CSU diagnosis for at least 6 months and be on an approved dose of an H_1-antihistamine for CSU before entering the study. *Exclusion Criteria:* Weight > 130 kg or < 40 kg; heavy smoking; chronic urticaria other than CSU; diseases with symptoms of urticaria or angioedema; history or presence of atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus or			

	other skin disease associated with itch; evidence of parasitic infection; any clinically relevant major systemic disease that could potentially complicate interpretation of study results; asthma and atopic dermatitis; history of clinically significant hypersensitivity to omalizumab or similar drugs, or to local anesthetics, and history of anaphylactic shock			
	Mean age (SD) Placebo: 41.1 (8.0) Omalizumab: 37.5 (11.0) N (%) female Placebo: 8 (80) Omalizumab: 18 (90)	*Race/ethnicity* N (%) Caucasian Placebo: 10 (100) Omalizumab: 20 (100)	*CSU duration/severity* Duration: NR Mean (SD) UAS7 Placebo: 31.6 (7.7) Omalizumab: 32.2 (8.0)	*Comorbidities* NR
Saini et al., 2011;[63] MYSTIQUE; NCT00130234				
Study Characteristics	Phase 2 RCT; 26 study centers in the US and Germany *Years conducted:* 2004-2007 *Sponsor(s):* Genentech, Novartis *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab 300 mg SC single dose (n = 25)			Placebo (n = 21)
	Cointervention(s): stable dose of H_1-antihistamines; 25-mg diphenhydramine to use as a rescue medication on an as-needed basis. Maximum allowable daily dose was 75 mg in the US and 50 mg in Germany.			
Population	*Inclusion Criteria:* Aged 12 to 75; history of CIU (> 3 mo) with no clearly defined cause; moderate to severe CIU despite antihistamine; daily UAS of 4+ and UAS7 of 12+ despite stable doses of H_1-antihistamine *Exclusion Criteria:* Weight < 40 kg; pregnancy/lactation; other skin disease associated with pruritus; prior treatment with omalizumab in prior 12 months; contraindication to diphenhydramine; treatment with any investigational agent within 30 days; clinically relevant major systemic disease that could complicate interpretation of study results			
	Mean age (SD) 41 (15) N (%) female 61 (68)	*Race/ethnicity* American Indian or Alaska Native: 2 (2) Asian: 5 (6) Black or African American: 8 (9) White: 75 (83)	*CSU duration/severity* Duration: NR Mean (SD) UAS7: 28 (8)	*Comorbidities* NR
Saini et al., 2015;[66] ASTERIA I; NCT01287117				
Study Characteristics	Phase 3 RCT; 53 centers across study countries; Denmark, France, Germany, Italy, Poland, Spain, Turkey, US *Years conducted:* 2011-2012 *Sponsor(s):* Genentech, Novartis *Risk of bias:* Moderate			

Interventions (N randomized)	Omalizumab 150 mg SC every 4 weeks for 24 weeks (n = 80)	Omalizumab 300 mg SC every 4 weeks for 24 weeks (n = 81)	Placebo (n = 80)	
	Cointervention(s): For the first 12 weeks of the treatment period, participants were required to maintain stable doses of their prerandomization H_1-antihistamine treatment. During weeks 13 to 24 of the treatment period, patients were allowed to add 1 additional H_1-antihistamine. Diphenhydramine 25 mg as needed for itch relief (up to a maximum of 3 doses per 24 hours, or less if required by local regulations) throughout the entire study period.			
Population	*Inclusion Criteria:* Aged 12 to 75 years with a diagnosis of CIU/CSU for ≥ 6 months and hives and itching for ≥ 8 consecutive weeks at any time before enrollment despite H1 antihistamine treatment. Additional criteria: use of approved dosage of an H_1 antihistamine for ≥ 3 consecutive days immediately before day 14 with documented use on day of initial screening visit; in-clinic physician-assessed UAS ≥ 4; UAS7 ≥ 16 and itch component of UAS7 ≥ 8 during 7 days before randomization; willing/able to complete a symptom diary with an electronic hand-held device 2x daily during study; no missing eDiary entries during 7 days before randomization *Exclusion Criteria:* Clearly defined underlying etiology for chronic urticaria; presence of a disease with symptoms of urticaria or angioedema (e.g., hereditary or acquired angioedema); routine doses of systemic steroids, hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, or intravenous immunoglobulin; use of H_2-antihistamines or LTRAs; use of H_1-antihistamines at greater than approved doses; history of malignancy; weight < 20 kg; hypersensitivity to omalizumab; previous treatment with omalizumab within previous year			
	Mean age (SD) Placebo: 40.4 (15.6) Omalizumab 150 mg: 41.1 (14.0) Omalizumab 300 mg: 42.4 (13.2) N (%) female Placebo: 52 (65.0) Omalizumab 150 mg: 64 (80.0) Omalizumab 300 mg: 60 (74.1)	*Race/ethnicity* N (%) white Placebo: 64 (80.0) Omalizumab 150 mg: 63 (78.8) Omalizumab 300 mg: 74 (91.4) N (%) black Placebo: 10 (12.5) Omalizumab 150 mg: 9 (11.3) Omalizumab 300 mg: 5 (6.2) N (%) other Placebo: 6 (7.5) Omalizumab 150 mg: 8 (10.0) Omalizumab 300 mg: 2 (2.5)	*CSU duration/severity* Time since diagnosis (years), mean (SD) Placebo: 7.0 (9.7) Omalizumab 150 mg: 7.6 (9.2) Omalizumab 300 mg: 6.2 (8.0 UAS7, mean (SD) Placebo: 31.1 (6.7) Omalizumab 150 mg: 30.3 (7.3) Omalizumab 300 mg: 31.3 (5.8) Weekly ISS, mean (SD) Placebo: 14.4 (3.5) Omalizumab 150 mg: 14.1 (3.8) Omalizumab 300 mg: 14.2 (3.3)	*Comorbidities* N (%) angioedema Placebo: 44 (55.0) Omalizumab 150 mg: 38 (47.5) Omalizumab 300 mg: 34 (42.0)

Staubach et al., 2016;[61] Staubach et al., 2018;[62] X-ACT; NCT01723072				
Study Characteristics	Phase 3 RCT; 24 centers in Germany *Years conducted:* 2013-2014 *Sponsor(s):* Novartis Pharma GmbH *Risk of bias:* Moderate			
Interventions (N randomized)	Omalizumab 300 mg SC every 4 weeks for 24 weeks (n = 44)			Placebo (n = 47)
	Cointervention(s): Daily H_1-antihistamines, clemastine and betamethasone for rescue medication			
Population	*Inclusion Criteria:* Adults aged 18 to 75 years with wheals and at least 4 occurrences of angioedema in the last 6 months who remained symptomatic despite H_1-anthistamine at 2 to 4 times the approved dose and had UAS7 scores of ≥ 14 and CU-Q2oL score of ≥ 30 *Exclusion Criteria:* Non-urticaria-associated angioedema, angioedema associated with C1-inhibitor deficiency, receiving H_1-anthestimane at greater than 4 times the approved dose, history of sensitivity to omalizumab or omalizumab treatment in the past 6 months or systemic corticosteroids, hydroxychloroquine, methotrexate, cyclophosphamide or intravenous immunoglobulin in past 30 days, use of H_2-antihistamines or leukotriene antagonists (montelukast or zafirlukast) in past 7 days; serious psychological, metabolic, or pathologic conditions, pregnancy and breastfeeding			
	Mean age (range) Placebo: 41.1 (20 to 61) Omalizumab: 44.9 (20 to 73) N (%) female Placebo: 33 (70) Omalizumab: 30 (68)	*Race/ethnicity* N (%) nonwhite Placebo: 1 (2) Omalizumab: 2 (5)	*CSU duration/severity* Duration of disease,years Mean (SD) Placebo: 7.4 (8.8) Omalizumab: 8.4 (9.3) Mean (SD) UAS7 Placebo: 27.9 (8.7) Omalizumab: 26.5 (8.2) Mean (SD) AAS Placebp: 28.1 (24.1) Omalizumab: 22.5 (20.6) Frequency daily angioedema episodes N (%) Placebo: 6 (12.8) Omalizumab: 3 (6.8)	*Comorbidities* NR

Abbreviations. AAS: Angioedema Activity Score; CIU: chronic idiopathic urticaria; CSU: chronic spontaneous urticaria; CU: chronic urticaria; CU-Q2oL; Chronic Urticaria Quality-of-Life Questionnaire; IgE: immunoglobin-E; ISS; Itch Severity Score; IU: international unit; LTRA: leukotriene receptor antagonist; NR: not reported; RCT: randomized controlled trial; SC: subcutaneous; SD: standard deviation; TPO: thyroid peroxidase; UAS: Urticaria Activity Score; wk: week.

Table B17. Effectiveness Outcomes From RCTs of Omalizumab for Chronic Spontaneous Urticaria

Outcome	Group	Result
Hide et al., 2017[64]; POLARIS; NCT02329223		
UAS7 mean change from baseline (12 wk)	Omalizumab 300 mg (n = 73)	Mean (SE) change from baseline: -22.4 (1.24) Difference from placebo (95% CI): -8.56 (-12.1 to -5.0); *P* < .001
UAS7 mean change from baseline (12 wk)	Omalizumab 150 mg (n = 70)	Mean (SE) change from baseline: -18.8 (1.29) Difference from placebo (95% CI): -4.9 (-8.4 to -1.3; *P* = .007
UAS7 mean change from baseline (12 wk)	Placebo (n = 74)	Mean (SE) change from baseline: -13.9 (1.27)
UAS7 score of 0, complete response (12 wk)	Omalizumab 300 mg (n = 73)	Events of total N (%): 26 of 73 (36%) Reported OR (95% CI): 15.30 (4.27 to 54.90); *P* < .001 Calculated RR (95% CI): 8.8 (2.8 to 27. 8)
UAS7 score of 0, complete response (12 wk)	Omalizumab 150 mg (n = 70)	Events of total N (%): 13 of 70 (19%) Reported OR (95% CI): 5.36 (1.43 to 20.08); *P* = .013 Calculated RR (95% CI): 4.58 (1.37 to 15.4)
UAS7 score of 0, complete response (12 wk)	Placebo (n = 74)	Events of total N (%): 3 of 74 (4%)
UAS7 score ≤ 6, remission (12 wk)	Omalizumab 300 mg (n = 73)	Events of total N (%): 42 of 73 (58%) Reported OR (95% CI): 7.56 (3.40 to 16.78); *P* < .001 Calculated RR (95% CI): 3.0 (1.8 to 5.1)
UAS7 score ≤ 6, remission (12 wk)	Omalizumab 150 mg (n = 70)	Events of total N (%): 30 of 70 (43%) Reported OR (95% CI): 3.41 (1.56 to 7.45); *P* = .002 Calculated RR (95% CI): 2.3 (1.3 to 3.9)
UAS7 score ≤ 6, remission (12 wk)	Placebo (n = 74)	Events of total N (%): 14 of 74 (19%)
ISS mean change from baseline (12 wk)	Omalizumab 300 mg (n = 73)	Mean (SE) change from baseline: -10.22 (0.57) Difference from placebo (95% CI): -3.7 (-5.3 to -2.1); *P* < .001
ISS mean change from baseline (12 wk)	Omalizumab 150 mg (n = 70)	Mean (SE) change from baseline: -8.80 (0.59) Difference from placebo (95% CI): -2.29 (-3.92 to -0.65); *P* = .006
ISS mean change from baseline (12 wk)	Placebo (n = 74)	Mean (SE) change from baseline: -6.51 (0.58)
ISS MID response (12 wk)	Omalizumab 300 mg (n = 73)	Events of total N (%): 64 of 73 (88%) Reported OR (95% CI): 5.51 (2.36 to 12.86); *P* < .001 Calculated RR (95% CI): 1.6 (1.3 to 2.0)
ISS MID response (12 wk)	Omalizumab 150 mg (n = 70)	Events of total N (%): 48 of 70 (69%) Reported OR (95% CI): 1.84 (0.92 to 3.69); *P* = .086 Calculated RR (95% CI): 1.2 (0.96 to 1.60)
ISS MID response (12 wk)	Placebo (n = 74)	Events of total N (%): 41 of 74 (55%)
DLQI mean change from baseline (12 wk)	Omalizumab 300 mg (n = 73)	Mean (SD) change from baseline: -8.4 (0.52) Difference from placebo (95% CI): -3.1 (-4.6 to -1.7); *P* < .001

Outcome	Group	Result
DLQI mean change from baseline (12 wk)	Omalizumab 150 mg (n = 70)	Mean (SD) change from baseline: -7.2 (0.53) Difference from placebo (95% CI): -1. 9 (-3.4 to -0.44); *P* = .011
DLQI mean change from baseline (12 wk)	Placebo (n = 74)	Mean (SD) change from baseline: -5.3 (0.52)
Jorg et al., 2018[70]; NCT01803763		
UAS7 score of 0, complete response (12 wk)	Placebo (n = 8)	Events of total N (%): 0 of 8 (0%)
UAS7 score of 0, complete response (12 wk)	Omalizumab 300 mg (n = 17)	Events of total N (%): 8 of 17 (47%) Reported OR (95% CI): 15.21 (0.76 to 305.06) Calculated RR (95% CI): 8.5 (0.6 to 131.3)
UAS7 score of 0, complete response (20 wk)	Placebo (n = 8)	Events of total N (%): 1 of 8 (13%)
UAS7 score of 0, complete response (20 wk)	Omalizumab 300 mg (n = 17)	Events of total N (%): 4 of 17(24%) Reported OR (95% CI): 1.67 (0.21 to 12.97) Calculated RR (95% CI): 1.9 (0.25 to 14.2)
UAS7 score ≤ 6, remission (12 wk)	Placebo (n = 8)	Events of total N (%): 2 of 8 (25%)
UAS7 score ≤ 6, remission (12 wk)	Omalizumab 300 mg (n = 17)	Events of total N (%): 13 of 17 (76%) Reported OR (95% CI): 7.80 (1.28 to 47.53) Calculated RR (95% CI): 3.1 (0.90 to 10.5)
UAS7 score ≤ 6, remission (20 wk)	Placebo (n = 8)	Events of total N (%): 2 of 8 (25%)
UAS7 score ≤ 6, remission (20 wk)	Omalizumab 300 mg (n = 17)	Events of total N (%): 9 of 17 (53%) Reported OR (95% CI): 2.91 (0.52 to 16.35) Calculated RR (95% CI): 2.12 (0.59 to 7.62)
ISS score of 0, complete response (12 wk)	Placebo (n = 8)	Events of total N (%): 0 of 8 (0%)
ISS score of 0, complete response (12 wk)	Omalizumab 300 mg (n = 17)	Events of total N (%): 8 of 17 (47%) Reported OR (95% CI): 15.21 (0.76 to 305.06) Calculated RR (95% CI): 8.5 (0.55 to 131.3)
ISS score of 0, complete response (20 wk)	Placebo (n = 8)	Events of total N (%): 1 of 8 (13%)
ISS score of 0, complete response (20 wk)	Omalizumab 300 mg (n = 17)	Events of total N (%): 4 of 17 (24%) Reported OR (95% CI): 1.67 (0.21 to 12.97) Calculated RR (95% CI): 1.88 (0.25 to 14.24)
Antiurticarial medication use	Omalizumab 300 mg (n = 17) Placebo (n = 8)	Cumulative frequency per day (95% CI) of rescue H_1-antihistamine use during trial Placebo: 2.8 (2.1 to 3.5) Omalizumab: 2.5 (1.8 to 3.3) Calculated difference in mean frequency *P* = .7074 Cumulative frequency per day (95% CI) of Montelukast use during trial Placebo: 1.0 (1.0 to 1.0) Omalizumab: 1.0 (0.9 to 1.0) Calculated difference in mean frequency *P* > .05

Outcome	Group	Result
Kaplan et al., 2013;[67] GLACIAL; NCT01264939		
UAS7 mean change from baseline (12 wk)	Placebo (n = 83)	Mean (SD) change from baseline: -8.5 (NR)
UAS7 mean change from baseline (12 wk)	Omalizumab 300 mg (n = 252)	Mean (SD) change from baseline: -19.0 (NR) Difference from placebo (95% CI): -10 (-13.2 to -6.9); *P* < .001
UAS7 score of 0, complete response (12 wk)	Placebo (n = 83)	Events of total N (%): 4 of 83 (5%);
UAS7 score of 0, complete response (12 wk)	Omalizumab 300 mg (n = 252)	Events of total N (%): 85 of 252 (34%) Reported RR (95% CI): NR; *P* < .001 Calculated RR (95% CI): 7.0 (2.6 to 18.5)
UAS7 score ≤ 6, remission (12 wk)	Placebo (n = 83)	Events of total N (%): 10 of 83 (12%);
UAS7 score ≤ 6, remission (12 wk)	Omalizumab 300 mg (n = 252)	Events of total N (%): 132 of 252 (52%) Reported RR (95% CI): NR; *P* < .001 Calculated RR (95% CI): 4.4 (, 2.4 to 7.9)
ISS mean change from baseline (12 wk)	Placebo (n = 83)	Mean (SD) change from baseline: -4.0 (NR)
ISS mean change from baseline (12 wk)	Omalizumab 300 mg (n = 252)	Mean (SD) change from baseline: -8.6 (NR) Difference from placebo (95% CI): -4.5 (-6 to -3.1); *P* < .001
ISS mean change from baseline (24 wk)	Placebo (n = 83)	Mean (SD) change from baseline: -4.0 (NR)
ISS mean change from baseline (24 wk)	Omalizumab 300 mg (n = 252)	Mean (SD) change from baseline: -8.6 (NR) Difference from placebo (95% CI): -4.5 (-6.1 to -3.0); *P* < .001
ISS MID response (12 wk)	Placebo (n = 83)	Events of total N (%): 33 of 83 (40%)
ISS MID response (12 wk)	Omalizumab 300 mg (n = 252)	Events of total N (%): 176 of 252 (70%) Reported RR (95% CI): NR; *P* < .001 Calculated RR (95% CI): 1.8 (1.3 to 2.3)
Time to achieve ISS MID response	Placebo (n = 83) Omalizumab 300 mg (n = 252)	Time to achieve MID response in weekly ISS, median (wk) Placebo: 5.0 Omalizumab: 2.0; *P* < .001
Angioedema-free days	Placebo (n = 83) Omalizumab 300 mg (n = 252)	Proportion of angioedema-free days from wks 4 to 12, % (95% CI) Placebo: 88.1 (83.6 to 92.7) Omalizumab: 91.0 (88.2 to 93.8); *P* < .001
CU-Q2oL mean change from baseline (12 wk)	Placebo (n = 83)	Mean (SD) change from baseline: -16.3 (NR)
CU-Q2oL mean change from baseline (12 wk)	Omalizumab 300 mg (n = 252)	Mean (SD) change from baseline: -29.3 (NR) Difference from placebo (95% CI): -13.4 (-18.2 to -8.6); *P* < .001

Outcome	Group	Result
CU-Q2oL mean change from baseline (24 wk)	Placebo (n = 83)	Mean (SD) change from baseline: -16.3 (NR)
CU-Q2oL mean change from baseline (24 wk)	Omalizumab 300 mg (n = 252)	Mean (SD) change from baseline: -30.9 (NR) Difference from placebo (95% CI): -14.6 (-19.7 to -9.5); *P* < .001
DLQI mean change from baseline (12 wk)	Placebo (n = 83)	Mean (SD) change from baseline: -5.1 (NR)
DLQI mean change from baseline (12 wk)	Omalizumab 300 mg (n = 252)	Mean (SD) change from baseline: -9.7 (NR) Difference from placebo (95% CI): -4.7 (-6.3 to -3.1); *P* < .001
Antihistamine tablet use change from baseline (12 wk)	Placebo (n = 83)	Mean (SD) change from baseline: -2.7 (NR) (number of tablets of 25 mg of diphenhydramine over 24 hours)
Antihistamine tablet use change from baseline (12 wk)	Omalizumab 300 mg (n = 252)	Mean (SD) change from baseline: -3.9 (NR) Difference from placebo (95% CI): -1.2 (-2.7 to 0.40); *P* = .15 (number of tablets of 25 mg of diphenhydramine over 24 hours)
Maurer et al., 2018[71]; Casale et al., 2019[72]; Casale et al., 2018[73]; XTEND-CIU; NCT02392624		
UAS7 clinical worsening (24 wk after switch; 48 wk after open label)	Placebo (n = 53)	Events of total N (%): 32 of 53 (60%) (UAS7 ≥12 for ≥2 consecutive wks during the double blind treatment period [wk 24 and 48])
UAS7 clinical worsening (24 wk after switch; 48 wk after open label)	Omalizumab 300 mg (n = 81)	Events of total N (%): 17 of 81 (21%) Reported RR (95% CI): NR; *P* < .0001 Calculated RR (95% CI): 0.35 (0.22 to 0.56) (UAS7 ≥12 for ≥2 consecutive wks during the double blind treatment period [wks 24 and 48])
Time to CSU worsening	Placebo (n = 53) Omalizumab 300 mg (n = 81)	HR NR, but *P* < .0001 favoring omalizumab
DLQI at least 3 points worsening (24 wk after switch; 48 wk after open label)	Placebo (n = 53)	Events of total N (%): 35 of 53 (66%)
DLQI at least 3 points worsening (24 wk after switch; 48 wk after open label)	Omalizumab 300 mg (n = 81)	Events of total N (%): 16 of 81 (20%) Reported RR (95% CI): NR; *P* < .0001 Calculated RR (95% CI): 0.30 (0.19 to 0.48)
Maurer et al., 2013[65]; ASTERIA II; NCT01292473		
UAS7 mean change from baseline (12 wk)	Omalizumab 150 mg (n = 82)	Mean (SD) change from baseline: -17.9 (13.2) Difference from placebo (95% CI): -7.7 (-11.5 to -3. 9); *P* < .05
UAS7 mean change from baseline (12 wk)	Omalizumab 300 mg (n = 79)	Mean (SD) change from baseline: -21.7 (12.8) Difference from placebo (95% CI): -12.4 (-16.1 to -8.7); *P* < .05
UAS7 mean change from baseline (12 wk)	Placebo (n = 79)	Mean (SD) change from baseline: -10.4 (11.6)

Outcome	Group	Result
UAS7 score ≤ 6, remission (12 wk)	Omalizumab 300 mg (n = 79)	Events of total N (%): 52 of 79 (66%) Reported RR (95% CI): NR; *P* < .001 Calculated RR (95% CI): 3.5 (2.1 to 5.6)
UAS7 score ≤ 6, remission (12 wk)	Omalizumab 150 mg (n = 82)	Events of total N (%): 35 of 82 (43%) Reported RR (95% CI): NR; *P* < .01 Calculated RR (95% CI): 2.2 (1.3 to 3.8)
UAS7 score ≤ 6, remission (12 wk)	Placebo (n = 79)	Events of total N (%): 15 of 79 (19%)
ISS mean change from baseline (12 wk)	Omalizumab 300 mg (n = 79)	Mean (SD) change from baseline: -9.8 (6.0) Difference from placebo (95% CI): -4.8 (-6.5 to -3.1); *P* < .001
ISS mean change from baseline (12 wk)	Omalizumab 150 mg (n = 82)	Mean (SD) change from baseline: -8.1 (6.4) Difference from placebo (95% CI): -3.0 (-4.9 to -1.2); *P* < .01
ISS mean change from baseline (12 wk)	Placebo (n = 79)	Mean (SD) change from baseline: -5.1 (5.6)
ISS MID response (12 wk)	Omalizumab 300 mg (n = 79)	Events of total N (%): 62 of 79 (78%) Reported RR (95% CI): NR; *P* < .001 Calculated RR (95% CI): 1.6 (1.3 to 2.1)
ISS MID response (12 wk)	Omalizumab 150 mg (n = 82)	Events of total N (%): 57 of 82 (70%) Reported RR (95% CI): NR: *P* < .01 Calculated RR (95% CI): 1.5 (1.1 to 1.9)
ISS MID response (12 wk)	Placebo (n = 79)	Events of total N (%): 38 of 79 (48%)
Time to ISS MID	Omalizumab 300 mg (n = 79) Omalizumab 150 mg (n = 82) Placebo (n = 79)	Omalizaumab 150 mg vs. placebo: HR 1.6 (95% CI, 1.1 to 2.3) Omalizumab 300 mg vs. placebo: HR 2.1 (95% CI, 1.5 to 3.0)
Angioedema-free days	Omalizumab 300 mg (n = 79) Omalizumab 150 mg (n = 82) Placebo (n = 79)	Mean (SD) number of angioedema free days during week 4 through week 12 Placebo: 89.2 (19.0) Omalizumab 150 mg: 91.6 (17.4), *P* NS Omalizumab 300 mg: 95.5 (14.5), *P* < .001
CU-Q2oL mean change from baseline (12 wk)	Omalizumab 300 mg (n = 79)	Mean (SD) change from baseline: -31.4 (NR) Difference from placebo (95% CI): *P* NR, exploratory analysis
CU-Q2oL mean change from baseline (12 wk)	Omalizumab 150 mg (n = 82)	Mean (SD) change from baseline: -27.0 (NR) Difference from placebo (95% CI): *P* NR, exploratory analysis
CU-Q2oL mean change from baseline (12 wk)	Placebo (n = 79)	Mean (SD) change from baseline: -17.7 (NR)
DLQI mean change from baseline (12 wk)	Omalizumab 300 mg (n = 79)	Mean (SD) change from baseline: -10.2 (6.8) Difference from placebo (95% CI): -3.8 (-5.9 to -1.7); *P* < .001
DLQI mean change from baseline (12 wk)	Omalizumab 150 mg (n = 82)	Mean (SD) change from baseline: -8.3 (6.3) Difference from placebo (95% CI): -2.5 (-4.6 to -0.4); *P* = .02

Outcome	Group	Result
DLQI mean change from baseline (12 wk)	Placebo (n = 79)	Mean (SD) change from baseline: -6.1 (7.5)
Antihistamine tablet use change from baseline (12 wk)	Omalizumab 300 mg (n = 79)	Mean (SD) change from baseline in number of tablets of diphenhydramine used per week: -4.1 (5.4) Difference from placebo (95% CI): NR; *P* = .01
Antihistamine tablet use change from baseline (12 wk)	Omalizumab 150 mg (n = 82)	Mean (SD) change from baseline in number of tablets of diphenhydramine used per week: -3.7 (6.0) Difference from placebo (95% CI): NR; *P* = .07
Antihistamine tablet use change from baseline (12 wk)	Placebo (n = 79)	Mean (SD) change from baseline in number of tablets of diphenhydramine used per week: -2.2 (5.0)
Maurer et al., 2011[69]		
Physician Global Assessment Score of 0 (24 wk)	Placebo (n = 22)	Events of total N (%): 1 of 22 (5%);
Physician Global Assessment Score of 0 (24 wk)	Omalizumab (weight-based dose) (n = 27)	Events of total N (%): 18 of 27 (67%) Reported RR (95% CI): NR Calculated RR (95% CI): 14.7 (2.2 to 101.4)
Patient Global Assessment Score of 0 (24 wk)	Placebo (n = 22)	Events of total N (%): 3 of 22 (14%)
Patient Global Assessment Score of 0 (24 wk)	Omalizumab (weight-based dose) (n = 27)	Events of total N (%): 16 of 27 (59%) Reported RR (95% CI): NR Calculated RR (95% CI): 4.4 (1.5 to 13.9)
UAS7 mean change from baseline (24 wk)	Omalizumab (weight-based dose) (n = 27)	Mean (SD) change from baseline: -17.8 (NR) Difference from placebo (95% CI): -9.9 (-17.1 to -2.7); *P* = .0089
UAS7 mean change from baseline (24 wk)	Placebo (n = 22)	Mean (SD) change from baseline: -7.9 (NR)
Skindex percentage improvement (24 wk)	Omalizumab (weight-based dose) (n = 27)	Mean (SD): 50 (NR) Difference from placebo (95% CI): NR; *P* < .01
Skindex percentage improvement (24 wk)	Placebo (n = 22)	Mean (SD): 6.3 (NR)
CU-Q2oL percentage improvement (24 wk)	Omalizumab (weight-based dose) (n = 27)	Mean (SD): 53.2 (NR) Difference from placebo (95% CI): NR; *P* < .01
CU-Q2oL percentage improvement (24 wk)	Placebo (n = 22)	Mean (SD): 5.9 (NR)
DLQI percentage improvement (24 wk)	Omalizumab (weight-based dose) (n = 27)	Mean (SD): 62.4 (NR) Difference from placebo (95% CI): NR; *P* < .01
DLQI percentage improvement (24 wk)	Placebo (n = 22)	Mean (SD): 15.3 (NR)

Outcome	Group	Result
Loratidine and clemastine tablet use in past 7 days (24 wk)	Omalizumab (weight-based dose) (n = 27)	Mean (SD) change from baseline: -7.9 (NR) Difference from placebo (95% CI): NR
Loratidine and clemastine tablet use in past 7 days (24 wk)	Placebo (n = 22)	Mean (SD) change from baseline: -4.9 (NR)
Metz et al., 2017[68]; NCT01599637		
UAS7 mean change from baseline (12 wk)	Omalizumab 300 mg (n = 20)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -14.82; *P* = .0027
UAS7 response (12 wk)	Omalizumab 300 mg (n = 20) Placebo (n = 10)	Defined as >90% reduction from baseline score Placebo: <15% (figure only, actual value NR) Omalizumab: >50% (figure only, actual value NR)
Patient Global Assessment Mean Score at follow-up (12 wk)	Omalizumab 300 mg (n = 20)	Mean (SD): 0.9 (1.5) Difference from placebo (95% CI): NR; *P* = .0336
Patient Global Assessment Mean Score at follow-up (12 wk)	Placebo (n = 10)	Mean (SD): 1.9 (0.99)
Physician Global Assessment Mean Score at follow-up (12 wk)	Omalizumab 300 mg (n = 20)	Mean (SD): 0.8 (1.01) Difference from placebo (95% CI): NR: *P* = .0191
Physician Global Assessment Mean Score at follow-up (12 wk)	Placebo (n = 10)	Mean (SD): 2.0 (1.31)
Skindex mean score at follow-up (12 wk)	Omalizumab 300 mg (n = 20)	Mean (SD): 6.17 (7.12) Difference from placebo (95% CI): NR; *P* = .0001
Skindex mean score at follow-up (12 wk)	Placebo (n = 10)	Mean (SD): 22.63 (10.28)
CU-Q2oL mean score at follow-up (12 wk)	Omalizumab 300 mg (n = 20)	Mean (SD): 14.51 (22.32) Difference from placebo (95% CI): NR; *P* = .0013
CU-Q2oL mean score at follow-up (12 wk)	Placebo (n = 10)	Mean (SD): 53.53 (29.82)
DLQI mean score at follow-up (12 wk)	Omalizumab 300 mg (n = 20)	Mean (SD): 3.8 (6.59) Difference from placebo (95% CI): NR; *P* = .0058
DLQI mean score at follow-up (12 wk)	Placebo (n = 10)	Mean (SD): 14.6 (10.77)
Mean days per week loratidine use (12 wk)	Omalizumab 300 mg (n = 20)	Mean (SD): -1.5 (1.91) Difference from placebo (95% CI): NR; *P* = .0143
Mean days per week loratidine use (12 wk)	Placebo (n = 10)	Mean (SD) change from baseline: 1.3 (3.41)

Outcome	Group	Result
Saini et al., 2011[63]; MYSTIQUE; NCT00130234		
UAS7 mean change from baseline (4 wk)	Omalizumab 300 mg (n = 25)	Mean (SD) change from baseline: -19.9 (12.38) Difference from placebo (95% CI): -13.0 (NR); *P* < .001
UAS7 mean change from baseline (4 wk)	Placebo (n = 21)	Mean (SD) change from baseline: -6.9 (9.84)
UAS7 100% score improvement (4 wk)	Omalizumab 300 mg (n = 25)	Events of total N (%): 9 of 25 (36%) Reported RR (95% CI): NR Calculated RR (95% CI): 16.1 (0.99 to 260.9)
UAS7 100% score improvement (4 wk)	Placebo (n = 21)	Events of total N (%): 0 of 21 (0%)
UAS7 ≥ 50% score improvement (4 wk)	Omalizumab 300 mg (n = 25)	Events of total N (%): 20 of 25 (80%) Reported RR (95% CI): NR Calculated RR (95% CI): 3.4 (1.5 to 7.4)
UAS7 ≥ 50% score improvement (4 wk)	Placebo (n = 21)	Events of total N (%): 5 of 21 (24%)
Saini et al., 2015[66]; ASTERIA I; NCT01287117		
UAS7 mean change from baseline (12 wk)	Omalizumab 300 mg (n = 81)	Mean (SD) change from baseline: -20.75 (12.17) Difference from placebo (95% CI): -12.8 (-16.4 to -9.16); *P* < .0001
UAS7 mean change from baseline (12 wk)	Omalizumab 150 mg (n = 80)	Mean (SD) change from baseline: -14.44 (12.95) Difference from placebo (95% CI): -6.54 (-10.33 to -2.75); *P* = .0008
UAS7 mean change from baseline (12 wk)	Placebo (n = 80)	Mean (SD) change from baseline: -8.01 (11.47)
UAS7 mean change from baseline (24 wk)	Omalizumab 300 mg (n = 81)	Mean (SD) change from baseline: -22.11 (12.46) Difference from placebo (95% CI): NR; *P* < .0001
UAS7 mean change from baseline (24 wk)	Omalizumab 150 mg (n = 80)	Mean (SD) change from baseline: -14.21 (13.33) Difference from placebo (95% CI): *P* > .05
UAS7 mean change from baseline (24 wk)	Placebo (n = 80)	Mean (SD) change from baseline: -11.73 (12.53)
UAS7 score of 0, complete response (24 wk)	Omalizumab 300 mg (n = 81)	Events of total N (%): 39 of 81 (48%) Reported RR (95% CI): NR; *P* < .0001 Calculated RR (95% CI): 3.9 (2.1 to 7.2)
UAS7 score of 0, complete response (24 wk)	Omalizumab 150 mg (n = 80)	Events of total N (%): 16 of 80 (20%); Reported RR (95% CI): NR; *P* NS Calculated RR (95% CI): 1.6 (0.77 to 3.3)
UAS7 score of 0, complete response (24 wk)	Placebo (n = 80)	Events of total N (%): 10 of 80 (13%)
UAS7 score of 0, complete response (40 wk)	Omalizumab 300 mg (n = 81)	Events of total N (%): 8 of 81 (10%) Reported RR (95% CI): NR Calculated RR (95% CI): 0.72 (0.30 to 1.69)
UAS7 score of 0, complete response (40 wk)	Omalizumab 150 mg (n = 80)	Events of total N (%): 9 of 80 (11%) Reported RR (95% CI): NR Calculated RR (95% CI): 0.82 (0.36 to 1.87)

Outcome	Group	Result
UAS7 score of 0, complete response (40 wk)	Placebo (n = 80)	Events of total N (%): 11 of 80 (14%)
UAS7 score ≤ 6, remission (24 wk)	Omalizumab 300 mg (n = 81)	Events of total N (%): 50 of 81 (62%) Reported RR (95% CI): NR; *P* < .0001 Calculated RR (95% CI): 2.47 (1.6 to 3.7)
UAS7 score ≤ 6, remission (24 wk)	Omalizumab 150 mg (n = 80)	Events of total N (%): 29 of 80 (36%) Reported RR (95% CI): NR; *P* NS Calculated RR (95% CI): 1.5 (0.90 to 2.3)
UAS7 score ≤ 6, remission (24 wk)	Placebo (n = 80)	Events of total N (%): 20 of 80 (25%)
UAS7 score ≤ 6, remission (40 wk)	Omalizumab 300 mg (n = 81)	Events of total N (%): 13 of 81 (16%) Reported RR (95% CI): NR Calculated RR (95% CI): 0.71 (0.37 to 1.36)
UAS7 score ≤ 6, remission (40 wk)	Omalizumab 150 mg (n = 80)	Events of total N (%): 15 of 80 (19%) Reported RR (95% CI): NR Calculated RR (95% CI): 0.83 (0.45 to 1.53)
UAS7 score ≤ 6, remission (40 wk)	Placebo (n = 80)	Events of total N (%): 18 of 80 (23%);
ISS mean change from baseline (12 wk)	Omalizumab 300 mg (n = 81)	Mean (SD) change from baseline: -9.40 (5.73) Difference from placebo (95% CI): -5. 8 (-7.5 to -4.1); *P* < .0001
ISS mean change from baseline (12 wk)	Omalizumab 150 mg (n = 80)	Mean (SD) change from baseline: -6.66 (6.28) Difference from placebo (95% CI): -3.0 (-4.7 to -1.2); *P* = .0012
ISS mean change from baseline (12 wk)	Placebo (n = 80)	Mean (SD) change from baseline: -3.63 (5.22)
ISS mean change from baseline (24 wk)	Omalizumab 300 mg (n = 81)	Mean (SD) change from baseline: -9.84 (5.95) Difference from placebo (95% CI): NR; *P* < .0001
ISS mean change from baseline (24 wk)	Omalizumab 150 mg (n = 80)	Mean (SD) change from baseline: -6.47 (6.50) Difference from placebo (95% CI): NR; *P* > .05
ISS mean change from baseline (24 wk)	Placebo (n = 80)	Mean (SD) change from baseline: -5.41 (5.76)
ISS MID response (12 wk)	Omalizumab 300 mg (n = 81)	Events of total N (%): 61 of 81 (75%) Reported RR (95% CI): NR; *P* < .0001 Calculated RR (95% CI): 2.1 (1.5 to 2.9)
ISS MID response (12 wk)	Omalizumab 150 mg (n = 80)	Events of total N (%): 45 of 80 (56%) Reported RR (95% CI): NR; *P* = .0226 Calculated RR (95% CI): 1.6 (1.1 to 2.2)
ISS MID response (12 wk)	Placebo (n = 80)	Events of total N (%): 29 of 80 (36%)
Time to ISS MID	Omalizumab 150 mg (n = 80) Placebo (80)	Time to MID in weekly ISS (weeks), median (95% CI) Hazard ratio vs. placebo (95% CI); *P*-value vs. placebo Placebo: 4.0 (2.0 to 6.0) Omalizumab 150 mg: 2.0 (2.0 to 3.0); 1.49 (1.04 to 2.14); *P* = .0301

Outcome	Group	Result
		Omalizumab 300 mg: 1.0 (1.0 to 2.0); 2.34 (1.63 to 3.36); *P* < .0001
CU-Q2oL mean change from baseline (12 wk)	Omalizumab 300 mg (n = 81)	Mean (SD) change from baseline: -30.5 (19.1) Difference from placebo (95% CI): NR; *P* < .05
CU-Q2oL mean change from baseline (12 wk)	Omalizumab 150 mg (n = 80)	Mean (SD) change from baseline: -23.1 (18.6) Difference from placebo (95% CI): NR; *P* > .05
CU-Q2oL mean change from baseline (12 wk)	Placebo (n = 80)	Mean (SD) change from baseline: -19.7 (19.7)
DLQI mean change from baseline (12 wk)	Omalizumab 300 mg (n = 81)	Mean (SD) change from baseline: -10.29 (7.23) Difference from placebo (95% CI): -4.1 (-6.0 to -2.2); *P* < .0001
DLQI mean change from baseline (12 wk)	Omalizumab 150 mg (n = 80)	Mean (SD) change from baseline: -8.00 (7.24) Difference from placebo (95% CI): -1.3 (-3.5 to 0.84); *P* = .2286
DLQI mean change from baseline (12 wk)	Placebo (n = 80)	Mean (SD) change from baseline: -6.13 (6.25)
Antihistamine tablets per week (12 wk)	Omalizumab 300 mg (n = 81)	Mean (SD) change from baseline: -4.2 (6.4) Difference from placebo (95% CI): NR; *P* < .03
Antihistamine tablets per week (12 wk)	Omalizumab 150 mg (n = 80)	Mean (SD) change from baseline: -2.9 (7.1) Difference from placebo (95% CI): NR; *P* < .03
Antihistamine tablets per week (12 wk)	Placebo (n = 80)	Mean (SD) change from baseline: -1.0 (5.2)
Staubach et al., 2016[61]; Staubach et al., 2018[62]; X-ACT; NCT01723072		
UAS7 mean change from baseline (28 wk)	Omalizumab 300 mg (n = 44)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -10.3 (-16.2 to -3.9); *P* = .002
UAS7 score of 0, complete response (12 wk)	Omalizumab 300 mg (n = 44)	Events of total N (%): 18 of 44 (41%) Reported RR (95% CI): NR Calculated RR (95% CI): 6.4 (2.0 to 20.3)
UAS7 score of 0, complete response (12 wk)	Placebo (n = 47)	Events of total N (%): 3 of 47 (6%)
UAS7 score of 0, complete response (28 wk)	Omalizumab 300 mg (n = 44)	Events of total N (%): 22 of 44 (50%) Reported RR (95% CI): NR Calculated RR (95% CI): 4.7 (2.0 to 11.3)
UAS7 score of 0, complete response (28 wk)	Placebo (n = 47)	Events of total N (%): 5 of 47 (11%)
AAS mean change from baseline (4 wk)	Omalizumab 300 mg (n = 44)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -15.6; *P* < .001
AAS mean change from baseline (12 wk)	Omalizumab 300 mg (n = 44)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -14.1; *P* = .002

Outcome	Group	Result
AAS mean change from baseline (28 wk)	Omalizumab 300 mg (n = 44)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -9.8; *P* = .036
Mean days with angioedema (28 wk)	Omalizumab 300 mg (n = 44)	Mean (SD): 14.6 (19.5) Difference from placebo (95% CI): NR
Mean days with angioedema (28 wk)	Placebo (n = 47)	Mean (SD): 49.5 (50.8)
CU-Q2oL mean change from baseline (4 wk)	Omalizumab 300 mg (n = 44)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -20.7 (-29.0 to -12.5); *P* < .001
CU-Q2oL mean change from baseline (28 wk)	Omalizumab 300 mg (n = 44)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -21.5 (-30. 9 to -12.1); *P* < .001
DLQI mean change from baseline (4 wk)	Omalizumab 300 mg (n = 44)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -7.2; *P* < .001
DLQI mean change from baseline (12 wk)	Omalizumab 300 mg (n = 44)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -8; *P* < .001
DLQI mean change from baseline (28 wk)	Omalizumab 300 mg (n = 44)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -6.1; *P* < .001
WHO-5 mean change from baseline (28 wk)	Omalizumab 300 mg (n = 44)	Mean (SD) change from baseline: 8.6 (NR) Difference from placebo (95% CI): 4.8; *P* < .001
WHO-5 mean change from baseline (28 wk)	Placebo (n = 47)	Mean (SD) change from baseline: 3.8 (NR)
AE-QoL mean change from baseline (12 wk)	Omalizumab 300 mg (n = 44)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -26; *P* < .001
AE-QoL mean change from baseline (28 wk)	Omalizumab 300 mg (n = 44)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -22.7; *P* < .001
AE-QoL mean change from baseline (4 wk)	Omalizumab 300 mg (n = 44)	Mean (SD) change from baseline: NR Difference from placebo (95% CI): -17.6; *P* < .001

Abbreviations. AAS: Angioedema Activity Score; AE-QoL: Angioedema Quality of Life measure; CI: confidence interval; CSU: chronic spontaneous urticaria; CU-Q2oL: Chronic Urticaria Quality of Life Questionnaire DLQI: Dermatology Life Quality Index; ISS: Itch Severity Score; mg: milligram; MID: minimally important difference; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; RR: risk ratio; SD: standard deviation; SE: standard error; UAS7: weekly Urticaria Activity Score; WHO-5: world health organization quality of life measure; wk: week.

Table B18. Safety Outcomes From RCTs of Omalizumab for Chronic Spontaneous Urticaria

Safety Outcomes (time point)	Intervention Group 1 Number Events of Total Number (%) Calculated RR (95% CI)	Intervention Group 2 Number Events of Total Number (%) Calculated RR (95% CI)	Comparator Group Number Events of Total Number (%)
Hide et al., 2017[64]; POLARIS; NCT02329223			
	Omalizumab 300 mg	Omalizumab 150 mg	Placebo
Total adverse events (24 wk)	40 of 73 (55%) 0.99 (0.74 to 1.32)	41 of 71 (58%) 1.04 (0.78 to 1.39)	41 of 74 (55%)
SAEs (24 wk)	3 of 73 (4%) 7.09 (0.37 to 135.0)	3 of 71 (4%) 7.29 (0.38 to 138.7)	0 of 74 (0%)
Adverse events leading to discontinuation (24 wk)	0 of 73 (0%) Cannot be determined	1 of 71 (1%) 3.13 (0.13 to 75.5)	0 of 74 (0%)
Mortality (24 wk)	0 of 73 (0%) Cannot be determined	0 of 71 (0%) Cannot be determined	0 of 74 (0%)
Treatment-related adverse events (24 wk)	7 of 73 (10%) 0.79 (0.31 to 2.0)	6 of 71 (8%) 0.69 (0.26 to 1.85)	9 of 74 (12%)
Kaplan et al., 2013[67]; GLACIAL; NCT01264939			
	Omalizumab 300 mg	NA	Placebo
Total adverse events (24 wk)	164 of 252 (65%) 1.03 (0.86 to 1.24)	NA	53 of 84 (63%)
Total adverse events (40 wk)	211 of 252 (84%) 1.07 (0.94 to 1.21)	NA	65 of 83 (78%)
SAEs (24 wk)	7 of 252 (3%) 0.77 (0.20 to 2.90)	NA	3 of 83 (4%)
SAEs (40 wk)	18 of 252 (7%) 1.19 (0.45 to 3.09)	NA	5 of 83 (6%)
Adverse events leading to discontinuation (40 wk)	3 of 252 (1%) 0.99 (0.10 to 9.37)	NA	1 of 83 (1%)
Adverse events leading to discontinuation (24 wk)	NR	NA	NR
Mortality (24 wk)	NR	NA	NR
Mortality (40 wk)	0 of 252 (0%)	NA	0 of 83 (0%)
Treatment-related adverse events (40 wk)	28 of 252 (11%) 0.84 (0.44 to 1.61)	NA	11 of 83 (13%)
Maurer et al., 2013[65]; ASTERIA II; NCT01292473			
	Omalizumab 150 mg	Omalizumab 300 mg	Placebo
Total adverse events (28 wk)	59 of 88 (67%) 1.10 (0.88 to 1.39)	51 of 79 (65%) 1.06 (0.83 to 1.35)	48 of 79 (61%)
SAEs (28 wk)	1 of 88 (1%) 0.45 (0.04 to 4.86)	5 of 79 (6%) 2.5 (0.5 to 12.5)	2 of 79 (3%)

Safety Outcomes (time point)	Intervention Group 1 Number Events of Total Number (%) Calculated RR (95% CI)	Intervention Group 2 Number Events of Total Number (%) Calculated RR (95% CI)	Comparator Group Number Events of Total Number (%)
Adverse events leading to discontinuation (28 wk)	2 of 88 (2%) 4.49 (0.22 to 92.2)	0 of 79 (0%) Cannot be determined	0 of 79 (0%)
Mortality (28 wk)	0 of 88 (0%) Cannot be determined	0 of 79 (0%) Cannot be determined	0 of 79 (0%)
Treatment-related adverse events (28 wk)	8 of 88 (9%) 2.39(0.66 to 8.71)	7 of 79 (9%) 2.33 (0.63 to 8.70)	3 of 79 (4%)
Maurer et al., 2011[69]			
	Omalizumab 75 to 375 mg (weight based)	NA	Placebo
Total adverse events (24 wk)	22 of 27 (81%) 0.94 (0.74 to 1.21)	NA	19 of 22 (86%)
SAEs (24 wk)	0 of 27 (0%) 0.27 (0.01 to 6.41)	NA	1 of 22 (5%)
Adverse events leading to discontinuation (24 wk)	0 of 27 (0%) 0.27 (0.01 to 6.41)	NA	1 of 22 (5%)
Mortality (24 wk)	0 of 27 (0%) Cannot be determined	NA	0 of 22 (0%)
Treatment-related adverse events (24 wk)	6 of 27 (22%) 0.98 (0.34 to 2.78)	NA	5 of 22 (23%)
Maurer et al., 2018[71]; Casale et al., 2019[72]; Casale et al., 2018[73]; XTEND-CIU; NCT02392624			
	Omalizumab 300 mg	NA	Placebo
Total adverse events (60 wk)	NR	NA	NR
SAEs (60 wk)	NR	NA	NR
Adverse events leading to discontinuation (60 wk)	NR	NA	NR
Mortality (60 wk)	0 of 81 (0%) Cannot be determined	NA	0 of 53 (0%)
Treatment-related adverse events (60 wk)	5 of 81 (6%) 3.27 (0.39 to 27.23)	NA	1 of 53 (2%)
Metz et al., 2017[68]; NCT01599637			
	Omalizumab 300 mg	NA	Placebo
Total adverse events (12 wk)	17 of 20 (85%) 1.21 (0.78 to 1.90)	NA	7 of 10 (70%)
SAEs (12 wk)	NR	NA	NR

Safety Outcomes (time point)	Intervention Group 1 Number Events of Total Number (%) Calculated RR (95% CI)	Intervention Group 2 Number Events of Total Number (%) Calculated RR (95% CI)	Comparator Group Number Events of Total Number (%)
Adverse events leading to discontinuation (12 wk)	1 of 20 (5%) 1.57 (0.07 to 35.46)	NA	0 of 10 (0%)
Mortality (12 wk)	NR	NA	NR
Saini et al., 2011[63]; MYSTIQUE; NCT00130234			
	Omalizumab 300 mg	NA	Placebo
Total adverse events (1wk to 4 wk)	12 of 25 (48%) 1.01 (0.55 to 1.85)	NA	10 of 21 (48%)
Total adverse events (4 wk to 16 wk)	12 of 23 (52%) 1.49 (0.73 to 3.04)	NA	7 of 20 (35%)
SAEs (16 wk)	1 of 23 (4%) 2.63 (0.11 to 61.05)	NA	0 of 20 (0%)
Adverse events leading to discontinuation (16 wk)	0 of 23 (0%) Cannot be determined	NA	0 of 20 (0%)
Mortality (16 wk)	NR	NA	NR
Saini et al., 2015[66]; ASTERIA I			
	Omalizumab 150 mg	Omalizumab 300 mg	Placebo
Total adverse events (24 wk)	60 of 87[a] (69%) 1.35 (1.04 to 1.74)	46 of 81 (57%) 1.11 (0.83 to 1.47)	41 of 80 (51%)
Total adverse events (40 wk)	72 of 87[a] (52%) 1.25 (1.04 to 1.5)	57 of 81 (47%) 1.06 (0.86 to 1.31)	53 of 80 (40%)
SAEs (24 wk)	NR	NR	NR
SAEs (40 wk)	5 of 87[a] (3%) 0.92(0.28 to 3.06)	2 of 81 (0%) 0.40 (0.08 to 1.98)	5 of 80 (5%)
Adverse events leading to discontinuation (24 wk)	NR	NR	NR
Adverse events leading to discontinuation (40 wk)	4 of 87[a] (5%) 0.53 (0.16 to 1.73)	2 of 81 (2%) 0.28 (0.06 to 1.32)	7 of 80 (9%)
Mortality (24 wk)	NR	NR	NR
Mortality (40 wk)	0 of 87[a] (0%)	0 of 81 (0%)	0 of 80 (0%)
Staubach et al., 2016[61]; Staubach et al., 2018[62]; X-ACT; NCT01723072			
	Omalizumab 300 mg	NA	Placebo
Total adverse events (12 wk)	30 of 44 (68%) 0.94 (0.72 to 1.23)	NA	34 of 47 (72%)
Total adverse events (36 wk)	NR	NA	NR
SAEs (12 wk)	NR	NA	NR

Safety Outcomes (time point)	Intervention Group 1 Number Events of Total Number (%) Calculated RR (95% CI)	Intervention Group 2 Number Events of Total Number (%) Calculated RR (95% CI)	Comparator Group Number Events of Total Number (%)
SAEs (36 wk)	4 of 44 (9%) 2.14 (0.41 to 11.09)	NA	2 of 47 (4%)
Adverse events leading to discontinuation (12 wk)	NR	NA	NR
Adverse events leading to discontinuation (36 wk)	NR	NA	NR
Mortality (12 wk)	NR	NA	NR
Mortality (36 wk)	NR	NA	NR

Notes. [a] *Includes 7 patients that were initially randomized to the 75-mg dosage group but that received at least 1 dose of 150 mg. Abbreviations. CI: confidence interval; NA: not applicable; NR: not reported; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; wk: week.*

Appendix C. Bibliography of Included Studies

Asthma Studies

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CSU Studies

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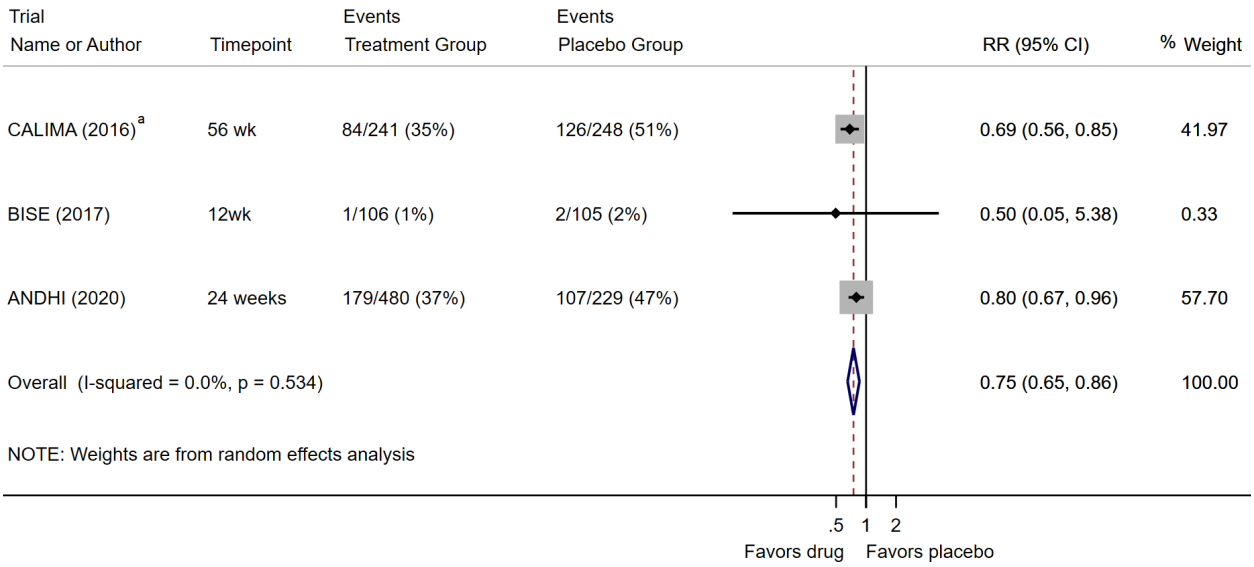
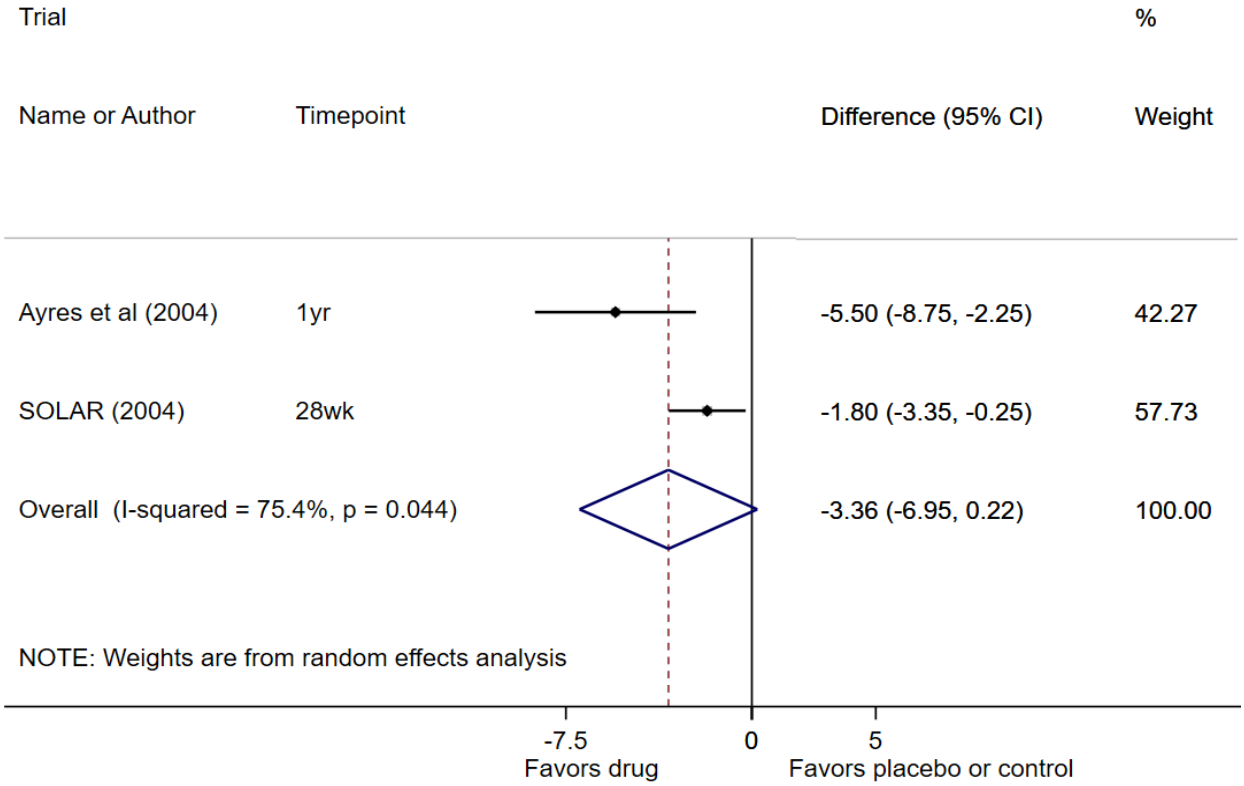
Appendix D. Additional Meta-Analysis Figures

Figure D1. Benralizumab vs. Placebo, Incidence of Exacerbations, Add-on Efficacy RCTs.



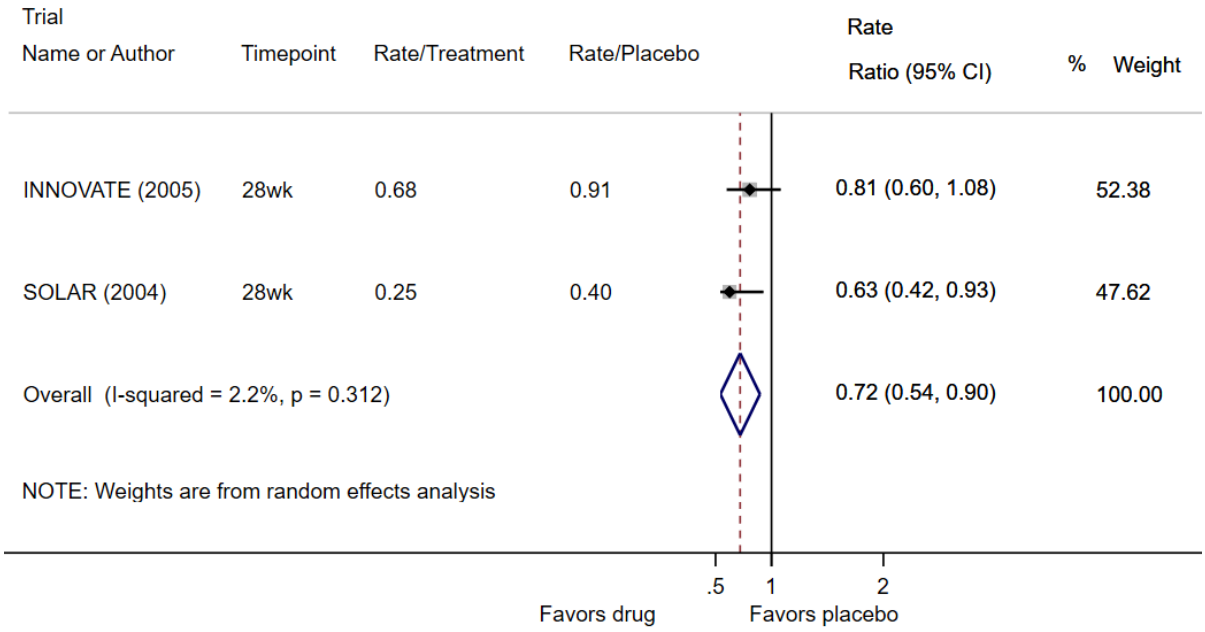
Note. [a] *Represents the every 4 week dosing option; RR for every 8 week dosing option is 0.79 (95% CI, 0.64 to 0.95). Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; wk: week.*

Figure D2. Omalizumab vs. Placebo, Change in Wasserfallen Asthma Symptom Score, Add-on Efficacy RCTs



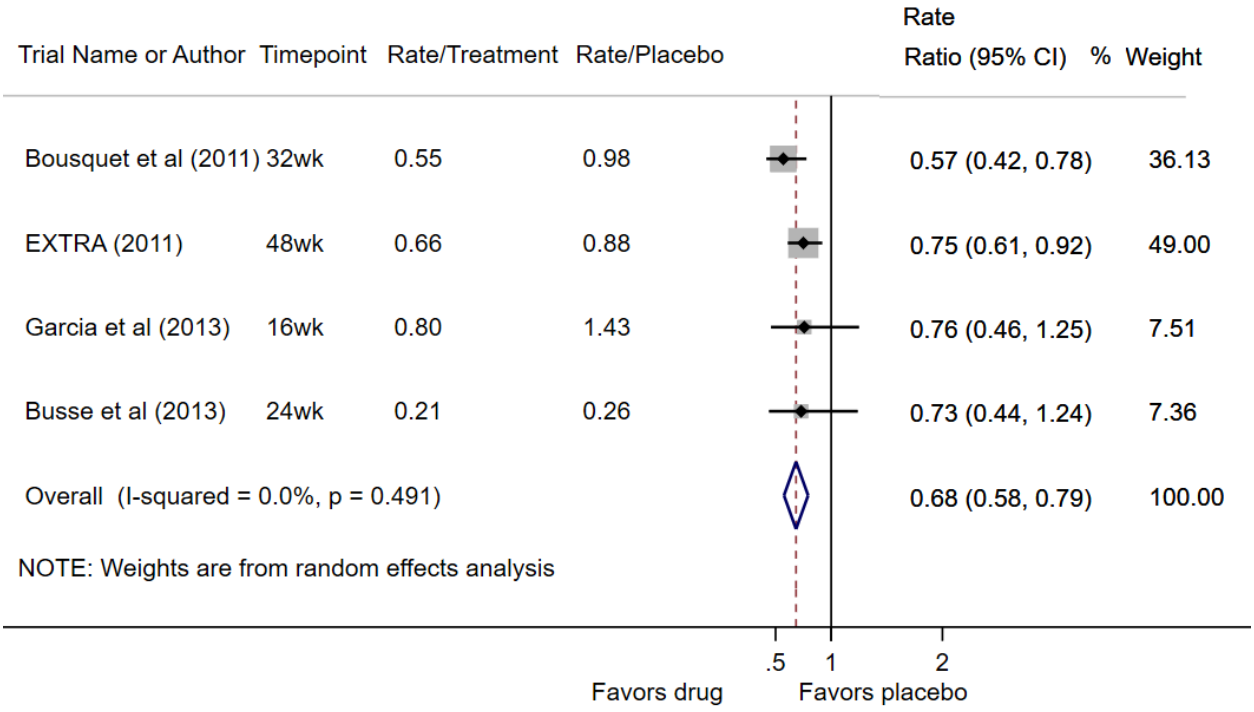
Abbreviations. CI: confidence interval; RCT: randomized controlled trial; wk: week; yr: year.

Figure D3. Omalizumab vs. Placebo, Annualized Exacerbation Rate, Add-on Efficacy RCTs



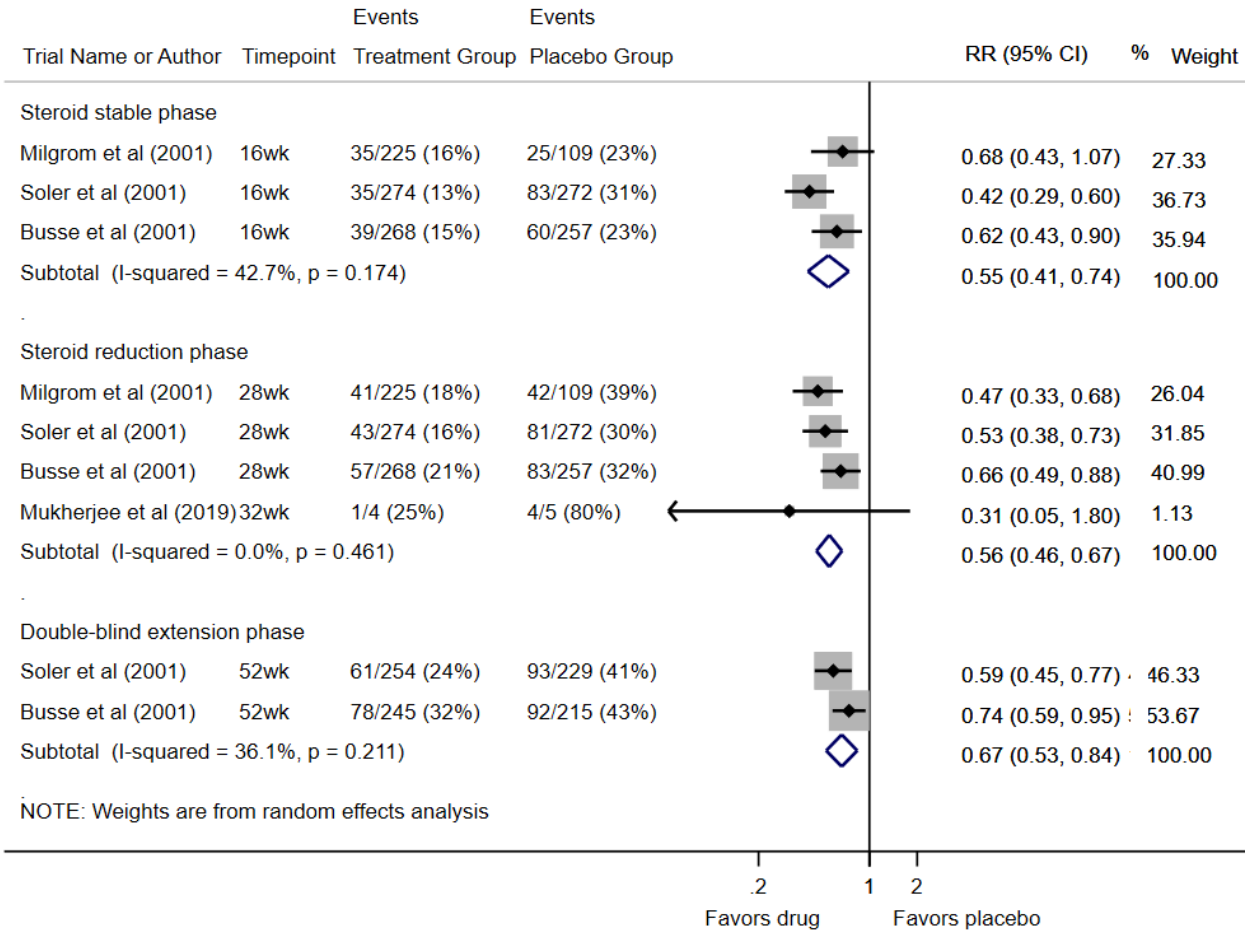
Abbreviations. CI: confidence interval; RCT: randomized controlled trial; wk: week.

Figure D4. Omalizumab vs. Placebo, Exacerbation Rate, Add-on Efficacy RCTs



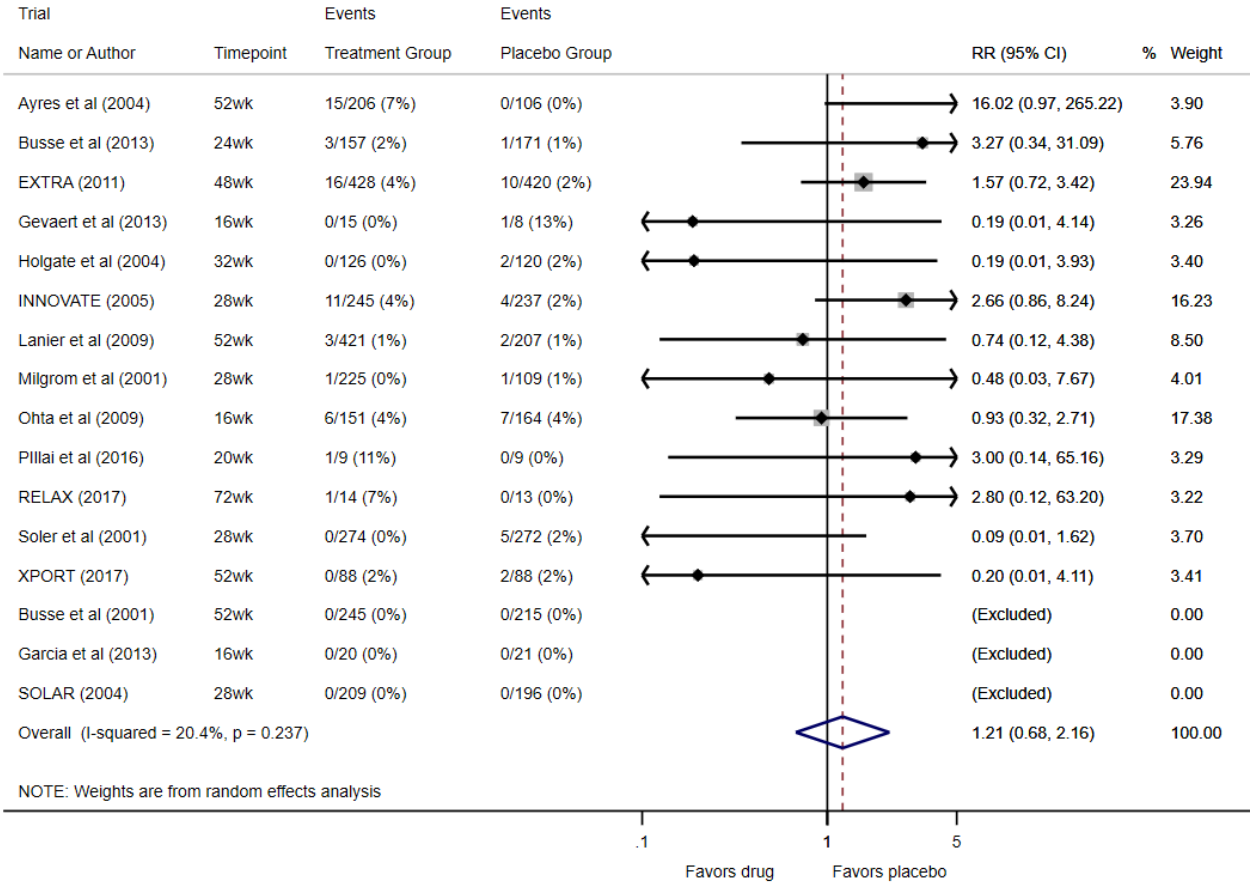
Note. [a] *Enrolled participants with nonatopic asthma.*
Abbreviations. CI: confidence interval; RCT: randomized controlled trial; wk: week.

Figure D5. Omalizumab vs. Placebo, Incidence of Exacerbation, Steroid-Sparing RCTs



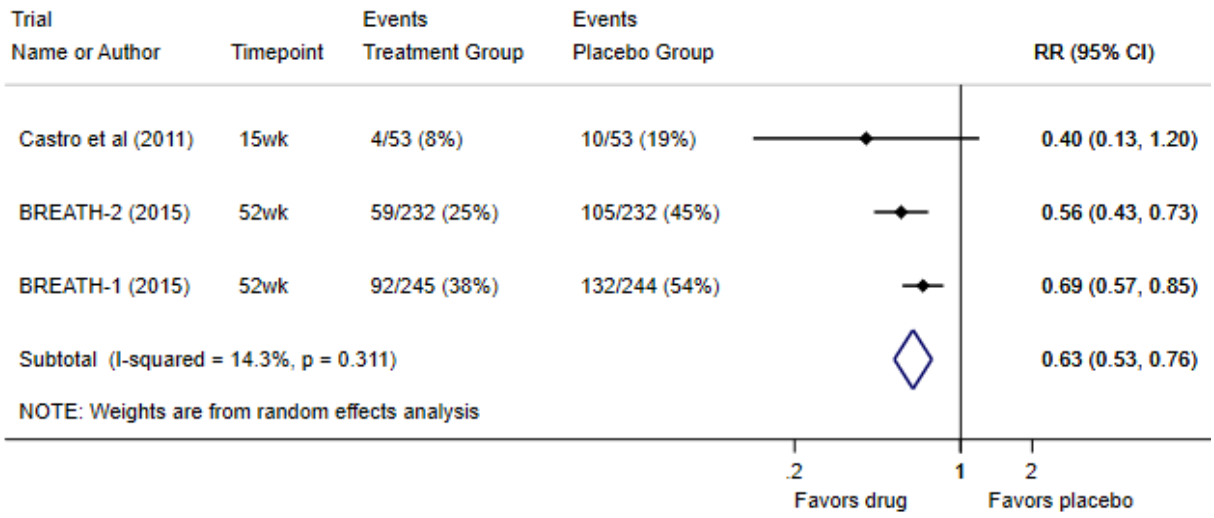
Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; wk: week.

Figure D6. Omalizumab vs. Placebo, Adverse Events Leading to Discontinuation



Abbreviations. CI: confidence interval; RR: risk ratio; wk: week.

Figure D7. Reslizumab vs. Placebo, Incidence of Exacerbation, Add-on Efficacy Trials



Abbreviations. CI: confidence interval; RR: risk ratio; wk: week.

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