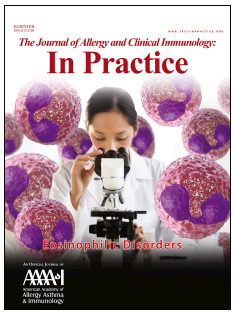
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Real-world effectiveness of omalizumab in severe allergic asthma: a meta-analysis of observational studies

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Real-world effectiveness of omalizumab in severe allergic asthma: a meta-analysis of observational studies

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Xavier Jaumont and Pascal Pfister are employees of Novartis Pharma AG, Basel, Switzerland.

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Abstract

Background: Assessment of clinical outcomes in the real-world corroborates findings from randomized controlled trials (RCTs).

Objective: This meta-analysis evaluated real-world data of omalizumab on treatment response, lung function, exacerbations, oral corticosteroid (OCS) use, patient-reported outcomes (PROs), healthcare resource utilization (HCRU), and school/work absenteeism at 4, 6 and 12 months post-treatment.

Methods: Observational studies in severe allergic asthma patients (≥6 years) treated with omalizumab for ≥16 weeks, published from January 2005 to October 2018 were retrieved from PubMed, Embase and Cochrane. A random effects model was used to assess heterogeneity.

Results: In total, 86 publications were included. Global evaluation of treatment effectiveness (GETE) was good/excellent in 77% patients at 16 weeks (risk difference: 0.77; 95% CI: 0.70–0.84; I^2=96%) and in 82% patients at 12 months (0.82, 0.73–0.91; 97%). The mean improvement in FEV_1 was 160, 220 and 250 mL at 16 weeks, 6 months and 12 months, respectively. There was a decrease in ACQ score at 16 weeks (−1.14), 6 months (−1.56) and 12 months (−1.13) following omalizumab therapy. Omalizumab significantly reduced annualized rate of severe exacerbations (risk ratio [RR]: 0.41, 95% CI: 0.30–0.56; I^2=96%), proportion of patients receiving OCS (RR: 0.59, 95% CI: 0.47–0.75; I^2=96%), and number of unscheduled physician visits (mean difference: −2.34, 95% CI: −3.54–−1.13; I^2=98%) at 12 months versus baseline.

Conclusion: The consistent improvements in GETE, lung function and PROs, and reductions in asthma exacerbations, OCS use and HCRU with add-on omalizumab in real-life confirms and complements the efficacy data of RCTs.

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Highlights

What is already known about this topic?

Omalizumab, an anti-IgE monoclonal antibody has been shown to be effective and safe in patients with moderate-to-severe allergic asthma in both randomized and real-world studies.

What does this article add to our knowledge?

Add-on omalizumab consistently improved treatment effectiveness, lung function and patient-reported outcomes, and reduced the rate of severe exacerbations, OCS use, healthcare resource utilization, and school/workdays absenteeism in real-life settings.

How does this study impact current management guidelines

This meta-analysis of real-world data demonstrated the effectiveness of omalizumab in the real-life practice.

Keywords: omalizumab; severe allergic asthma; real-world evidence; meta-analysis; global evaluation of treatment effectiveness; severe exacerbations; lung function; healthcare resource utilization; patient-reported outcomes

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Abbreviations

ACQ, asthma control questionnaire

ACT, asthma control test

AQLQ, asthma quality of life questionnaire

CI, confidence interval

ER, emergency room

FEV_1, forced expiratory volume in 1 second

GETE, global evaluation of treatment effectiveness

HCRU, healthcare resource utilization

ICS, inhaled corticosteroid

IgE, immunoglobulin E

IV, inverse variance

LABA, long-acting β_2-agonist

MD, mean difference

OCS, oral corticosteroid

PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis

PROs, patient-reported outcomes

RCTs, randomized controlled trial

RR, rate ratio

RWD, real-world data

RD, risk difference

SD, standard deviation

SAA, severe allergic asthma

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Introduction

Omalizumab, the recombinant monoclonal antibody against immunoglobulin E was approved for patients with moderate-to-severe allergic asthma uncontrolled despite treatment with high-dose controller medications. Although several randomized controlled trials (RCTs) have demonstrated the efficacy and safety of omalizumab,[1-6] they were performed under optimized conditions and stringent inclusion and exclusion criteria, which do not reflect medical practice in the real-world settings. Moreover, RCTs enroll a narrow, smaller subset of patients limiting the extrapolation of the findings to the more heterogeneous patient population encountered in routine clinical practice.[7] Further, medication adherence, the key pillar for treatment effectiveness is closely monitored in RCTs, which is not always the case in real-world settings.[7] Therefore, alternative designs such as pragmatic open-label RCTs and observational studies are needed to address these gaps between RCTs and real-world evidence.

Following the approval of omalizumab, several real-world studies[8] have been initiated which led to its wide use with more than 1.3 million patient-years of exposure.[9] A systematic review of 24 real-world observational studies in adult patients with severe allergic asthma (SAA) has shown the short- and long-term efficacy of omalizumab by improving lung function, asthma symptoms and quality of life, and reduced co-medication, severe exacerbations, school/workdays lost, and healthcare resource utilization (HCRU) with benefits extending up to 2–4 years following therapy.[8] A meta-analysis conducted on these noncontrolled studies demonstrated the real-life pharmacotherapeutic effectiveness of omalizumab, and complemented the efficacy data from RCTs.[10] More recently, a systematic review of 42 real-world studies of omalizumab in patients over 12 years confirmed the long-term effectiveness beyond 4 years.[11] However, to date, no meta-analysis has summarized the real-world effectiveness of omalizumab in patients ≥6 years in terms of global evaluation of treatment effectiveness (GETE), lung function, asthma exacerbations, OCS use, patient-reported outcomes (PROs), HCRU and school/work

absenteeism. The aim of this analysis was to assess the efficacy of omalizumab based on these outcome measures in patients with SAA.

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Methods

Information sources and study selection

A systematic literature search was conducted in the PubMed, EMBASE and Cochrane Controlled Trials Register (CENTRAL) databases, to identify publications of observational studies on omalizumab in patients aged ≥6 years with SAA, published from January 2005 to October 2018. The medical subject headings and search terms used were: "omalizumab" OR "Xolair" AND "asthma"; with studies filtered by clinical trial, publication type and language. Additionally, a search for relevant unpublished studies was performed using the same search terms in ClinicalTrials.gov, the Novartis clinical trials database (www.novartisclinicaltrials.com) and the clinical trial databases of GSK https:/www.gsk-studyregister.com), Pfizer (https://www.pfizerpro.com/clinical-trials) and AstraZeneca (https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Search). Publications and studies identified were manually reviewed, using specific inclusion criteria presented below. Other potential studies were identified through manual searching of the eligible studies.

- Population: Patients aged ≥6 years with SAA and a minimum of 12 months pre-omalizumab data and 16 weeks to 1-year post-treatment data
- Intervention: Omalizumab for treatment of SAA
- Comparator: Omalizumab effectiveness was compared to 12 months pre-omalizumab data
- Outcomes: Studies with at least one of the following outcomes were included: physician-rated treatment effectiveness [by GETE], lung function, annualized rate of severe exacerbations, OCS use, PROs (asthma control questionnaire [ACQ], asthma control test [ACT] and asthma quality-of-life questionnaire [AQLQ]), HCRU (asthma-related hospital admissions, emergency room (ER) visits and unscheduled physician visits) and school or work absenteeism
- Study design: Observational studies

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174

175 **Data extraction**

176 Two reviewers independently assessed each study based on the predefined eligibility criteria
177 and extracted data from eligible studies. Patient demographics and clinical characteristics
178 (including age, gender, race, smoking status, body weight, and duration of asthma) and
179 outcomes data were extracted from all included studies. Literature search and meta-analysis
180 were performed in accordance with the Preferred Reporting Items for Systematic Reviews and
181 Meta-analysis (PRISMA) guidelines.[12]

182

183 **Outcomes**

184 The primary outcome of interest in this meta-analysis was physicians' GETE, a validated PRO,
185 which measures the overall response to treatment on a five-point scale of excellent, good,
186 moderate, poor or worsening. GETE responders were defined as those with an excellent or
187 good response, while non-responders were those with moderate, poor or worsening response
188 (Online Repository). The secondary outcomes reported were the mean change in forced
189 expiratory volume in 1 second (FEV_1), annualized rate of severe exacerbations, OCS use,
190 PROs (ACQ, ACT, and AQLQ), HCRU (hospitalizations, ER visits and unscheduled physician
191 visits), and school or work absenteeism, each evaluated after 16 weeks, 6 months, and 12
192 months following omalizumab therapy.
193 Quality and risk of bias of individual studies was not assessed in this meta-analysis. Further, no
194 sensitivity or subgroup analysis was performed.

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Summary measures and synthesis of results

Binary outcomes were presented as risk difference (RD) or risk ratio (RR) and 95% confidence intervals (CI), while continuous outcomes were presented as mean difference (MD) and 95% CI. To make optimal use of extracted data and to avoid effect size selection bias, the effect measures in the analysis were analyzed using random-effects model for all outcomes, as the included studies differed in the mixes of participants and to address the clinical heterogeneity variation across studies. Also, as the included studies differed in treatment duration, we analyzed the effect measures as 16 weeks/4 months, and 6 and 12 months to normalize the effect sizes. Heterogeneity was assessed and quantified using I^2 statistics with upper limits of 25%, 50% and 75% representing low, moderate, and high heterogeneity, respectively.[13] Studies were weighted using the DerSimonian and Laird random-effects model.[14]

The effect estimate for the primary outcome of interest (GETE) obtained in the meta-analysis of observational studies was also compared with the response rate for GETE in the individual RCTs (EXALT[15], EXTRA[16] and INNOVATE[4]). A generalized linear mixed model was applied assuming a binomial distribution for GETE responders across the RCTs and the GETE responder rate from meta-analysis, to observe whether the 95% CI for the response rates overlaps, which would indicate that the response rate for GETE obtained in RCT vs. meta-analysis are comparable. The model accounted for overdispersion, which may occur due to differences in studies/population/other intrinsic factors by using a non-parametric random residual approach. The model provided an estimate of the pooled (average) response which was then compared with the results of individual RCT and the meta-analysis estimate, to assess whether GETE response rates are comparable across the RCTs vs. meta-analysis. Analysis was performed using R software (version 3.4.1, Meta package).[17]

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Results

Study selection

A total of 2019 publications were identified from the databases. Of these, 626 duplicate publications were excluded. One thousand three hundred ninety-three publications were retained and screened manually, of which 651 were rejected based on language restrictions, because they were conference abstracts, or due to disease, and relevancy. Of the remaining 742 publications, 614 were excluded based on study design (most of these were RCTs, reviews, letters, post-hoc analysis); and a further 52 publications were ineligible based on outcomes. Seventy-six eligible studies therefore remained. A further 10 studies were identified by manual review of these articles and a total of 86 publications were included in this meta-analysis.[1, 15, 18-101] Eighty-four studies were identified from the literature databases, and two unpublished studies were identified from the clinicaltrials.gov and manufacturer databases (**Figure 1**).

Baseline demographics and clinical characteristics

Baseline demographic are presented in **Table E1**. Most studies were observational in nature, but four randomized, open-label studies were also included as these studies mirrored real-life clinical practice. The studies included patients across age groups (≥6 years) and gender. While majority of studies included White/Caucasian population, few studies also included Black, Asians and other races.

Global evaluation of treatment effectiveness

GETE data were available from 15 publications with 5976 patients after 16 weeks of therapy, two studies with 1052 patients after 6 months, and 10 studies with 3410 patients after 12 months. On average, 77% patients achieved a good or excellent GETE response after 16 weeks (RD, 0.77, 95% CI, 0.70–0.84; $P<0.01$, $I^2 = 96\%$) and the effect continued with 82% of patients at 12 months (RD, 0.82, 95% CI, 0.73–0.91; $P<0.01$), with considerable heterogeneity

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(I^2 = 97%; **Figure 2**). Despite this heterogeneity, the GETE responses were consistently positive (**Figure 2**).

Forced expiratory volume in 1 second

Data on FEV_1 were available from five studies with 548 patients after 16 weeks, three studies with 217 patients after 6 months and five studies with 260 patients after 12 months of treatment (**Figure 3**). Omalizumab significantly improved FEV_1 with mean change from baseline of 160 mL at 16 weeks (95% CI, 0.04–0.28; *P*<0.01, I^2 = 25%), 220 mL at 6 months (95% CI, 0.08–0.36; *P*<0.01, I^2 = 0%) and 250 mL at 12 months (95% CI, 0.03–0.48; *P*=0.02, I^2 = 50%) with moderate heterogeneity.

Severe exacerbations

Data for annualized rate of severe exacerbations were available from seven publications with 4135 patients after 12 months of therapy. Omalizumab reduced the risk by 81% (RR [95% CI]: 0.19 [0.09–0.41]; *P*<0.01, I^2 = 87%), and 59% (RR [95% CI]: 0.41 [0.30–0.56]; *P*<0.01, I^2 = 96%) following treatment for 16 weeks, and 12 months, respectively (**Figure 4**). Data on change in the mean number of severe exacerbations were available from seven publications with a total of 1208 patients after 16 weeks, 6 publications with a total of 1190 patients after 6 months, and 19 publications with a total of 4286 patients after 12 months of omalizumab therapy. The number of severe exacerbations decreased significantly with MD of 2.13 (MD [95% CI]: −2.13 [−2.94–−1.32]; *P*<0.01, I^2 = 97%), 2.75 (MD [95% CI]: −2.75 [−3.74–−2.02]; *P*<0.01, I^2 = 82%), and 2.75 (MD [95% CI]: −2.75 [−3.46–−2.04]; *P*<0.01, I^2 = 98%) at 16 weeks, 6 months and 12 months, respectively, following initiation of treatment compared with baseline (**Figure 5)**.

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OCS-sparing effect

Data on OCS sparing effect were available from seven studies with a total of 4706 patients after 16 weeks, and from 18 studies with a total of 8279 patients after 12 months of therapy. Treatment with omalizumab significantly reduced the proportion of patients receiving OCS by 32% (RR [95% CI]: 0.68 [0.57–0.82]; $P<0.01$, $I^2 = 83\%$), 41% (RR [95% CI]: 0.59 [0.47–0.75]; $P<0.01$, $I^2 = 95\%$) at 16 weeks and 12 months, respectively, compared with baseline (**Figure 6**). Of the patients treated with omalizumab, a reduction of ≥20% in OCS dose from baseline was observed in 50% patients at 16 weeks, 43% at 6 months and 57% at 12 months (**Figure E1**). The mean daily OCS dose reduced by 6.64 mg/day (MD [95% CI]: −6.64 [−8.11–−5.17]; $P<0.01$, $I^2 = 19\%$) and 5.45 mg/day (MD [95% CI]: −5.45 [−9.91–−0.98]; $P=0.02$, $I^2 = 90\%$) following treatment for 16 weeks and 12 months, respectively (**Figure E2**).

Asthma control and patient-reported outcomes

Asthma control questionnaire

ACQ data were available from five publications with a total of 565 patients at 16 weeks, five publications with a total of 623 patients at 6 months and three publications with a total of 194 patients at 12 months of therapy. A decrease in ACQ score was observed at 16 weeks (MD [95% CI]: −1.14 [−1.40–−0.89]; $I^2 = 74\%$), 6 months (MD [95% CI]: −1.56 [−1.66–−1.45]; $I^2 = 0\%$) and 12 months (MD [95% CI]: −1.13 [−1.47–−0.79]; $I^2 = 67\%$) following omalizumab therapy ($P<0.01$ at all time points; **Figure 7**).

Asthma control test

ACT score were available from eight publications with a total of 582 patients at 16 weeks, six publications with a total of 1047 patients at 6 months and 22 publications with a total of 2669 patients at 12 months following omalizumab therapy. ACT score significantly improved following omalizumab treatment at 16 weeks (MD [95% CI]: 4.44 [3.55–5.34]; $I^2 = 71\%$), 6 months (MD [95% CI]: 3.98 [2.74–5.23]; $I^2 = 82\%$) and 12 months (MD [95% CI]: 6.47 [4.76–8.18]; $I^2 = 98\%$; **Figure E3**).

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Asthma quality of life questionnaire

Data on AQLQ score were available from five studies with a total of 333 patients at 16 weeks, 454 patients at 6 months and 375 patients at 12 months following omalizumab treatment. The change in AQLQ score from baseline was 1.10 at 16 weeks (MD [95% CI]: 1.10 [0.85–1.36]; I^2 = 40%), 1.13 at 6 months (MD [95% CI]: 1.13 [0.73–1.54]; I^2 = 85%) and 1.44 at 12 months (MD [95% CI]: 1.44 [1.16–1.72]; I^2 = 64%) following omalizumab therapy (P<0.01 at all time points; **Figure E4**)**.** These data demonstrate improved asthma control as well as quality of life following omalizumab therapy in patients with SAA.

School or work absenteeism

Data on school or work absenteeism were available from six publications and a total of 3997 patients after 12 months of therapy (**Figure E5**). The missed school or workdays were numerically reduced by 2.12 days upon treatment with omalizumab at 12 months MD; [95% CI]: −2.12 [−4.79–0.55]; P=0.12).

Healthcare resource utilization

Hospitalizations

Hospitalization data were available from thirteen publications with a total of 7793 patients at 12 months of omalizumab therapy. The mean number of hospitalizations reduced by 0.52 days (MD [95% CI]: −0.52 [−0.79–−0.25]; I^2 = 28%), 1.09 days (MD [95% CI]: −1.09 [−1.59–−0.60]; I^2 = 17%) and 0.63 days (MD [95% CI]: −0.63 [−0.85–−0.41]; I^2 = 99%) at 16 weeks, 6 months and 12 months following omalizumab treatment respectively (P<0.01 for all time points; **Figure E6**). Likewise, the risk of hospitalization decreased by 69%, 81%, and 85% following omalizumab treatment for 16 weeks, 6 months, and 12 months, respectively (**Figure E6**)

Emergency room visits

Data on ER visits were available from eleven publications with a total of 6670 patients at 12 months. The mean number of ER visits significantly reduced by 0.76 days following 12 months of omalizumab therapy (MD [95% CI]: −0.76 [−0.94–−0.58]; P<0.01, I^2 = 98%). The risk of ER

318 visits significantly reduced by 54% and 81% following 16 weeks and 6 months of omalizumab
319 therapy, respectively (P<0.01 for both time points; **Figure E7**).

320 ***Unscheduled physician visits***

321 Data on unscheduled physician visits were available from eleven publications and a total of
322 5261 patients after 12 months (**Figure 8**). Treatment with omalizumab for 12 months
323 significantly reduced the number of unscheduled physician visits compared with baseline, with a
324 MD of 2.34 visits (MD [95% CI]: −2.34 [−3.54–−1.13]; P<0.01, I^2 = 98%).

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Discussion

Summary of evidence

This meta-analysis on data from observational/open-label studies showed that omalizumab was associated with an improvement in GETE, lung function (FEV_1), asthma control, PROs (ACQ, ACT and AQLQ) and reduction in severe exacerbations, OCS use, HCRU (hospitalizations, ER visits and unscheduled physician visits), and school absenteeism across all time points.

This is the first meta-analysis to report investigator GETE ratings from real-world data (RWD) in a large patient pool with over 5900 severe asthmatic patients. We observed that 77% of patients achieved an excellent or good GETE response at Week 16 after the start of therapy. The proportion of responders increased after 12 months of therapy, with an average of 82% of patients achieving an excellent or good GETE response. This was in accordance with the results of the EXALT study, in which 72.8% and 76.8% of adolescents and adults patients receiving omalizumab achieved excellent/good responses at Weeks 16 and 32[15], and 91.4% of responder patients at Week 16 continued to respond to treatment at Week 32.[15] The INNOVATE trial reported that 60.5% of patients treated with omalizumab achieved good/excellent responses, compared with 42.8% in the placebo group at Week 28.[4] In the EXTRA study,[16] 65.2%, 68.1% and 71.1% of patients responded to treatment at Weeks 16, 32 and 48, respectively (unpublished data). Further analysis of GETE responders in the RCTs: INNOVATE,[4] EXALT[15] and EXTRA[16] with this meta-analysis showed that the proportion of responders was comparable (**Figure E8**). On average, 65.5% of patients receiving omalizumab showed good or excellent GETE response (95% CI: 53.9%–75.5%) in the pooled analysis of RCTs, with an overdispersion parameter of 2.4 indicating a slight variability across the trials. The findings from the current meta-analysis and these previously reported RCTs (INNOVATE,[4] EXALT[15] and EXTRA[16]) show the persistency of response to omalizumab therapy in severe asthmatic population. In this meta-analysis, the effect estimate for GETE remained consistent across all time points, despite the significant heterogeneity between the included studies.

Patients with severe asthma often experience a significant decline in lung function, and the RCTs-INNOVATE[4] and EXALT[15] have demonstrated that treatment with omalizumab improves FEV_1 in patients with uncontrolled asthma: 94 mL in the INNOVATE study,[4] 110 mL at Week 16 and 130 mL at Week 32 in the EXALT.[15] In the long-term, multicenter, randomized, open-label study (ETOPA), omalizumab added to best standard care therapy (medium- to high-dose ICS with or without long-acting bronchodilator; systemic corticosteroids) resulted in an improvement in morning FEV_1 by a MD of 200 mL, compared with best standard care therapy alone, at the end of study period.[1] The improvement in FEV_1 observed in omalizumab-randomized studies was similar in magnitude to mepolizumab,[102-104] benralizumab,[105, 106] reslizumab,[107, 108] and dupilumab.[109, 110] In this meta-analysis, omalizumab treatment improved FEV_1 by an absolute MD of 160 mL at 16 weeks compared with baseline and the improvements continued throughout the treatment period with a MD of 220 mL and 250 mL from baseline at 6 and 12 months, respectively.

Severe asthma is associated with frequent exacerbations that interfere with social and professional life and emotional health of patients.[111] Several pivotal Phase III studies[2, 5,112,113] have shown that omalizumab reduced the rate of severe exacerbations. The proportion of patients experiencing an exacerbation significantly decreased following treatment with omalizumab versus placebo during the steroid stable (14.6% vs. 23.3%; *P*=0.009) and steroid reduction (21.3% vs. 32.3%; *P*=0.004) phases.[2] In another randomized Phase III study, patients in the omalizumab group had 58% and 52% fewer exacerbations during the steroid stable phase and steroid reduction phase, respectively, compared with placebo.[5] In a pediatric 52-week RCT, omalizumab reduced the rate of clinically significant asthma exacerbations by 31% and 43% versus placebo, following treatment for 24 weeks and 52 weeks.[112] In another pediatric RCT, omalizumab reduced the proportion of patients experiencing an exacerbation that requires treatment with double-dose of ICS or systemic steroids versus placebo (18.2% vs. 38.5%)

during the steroid-reduction phase.[113] All Phase III studies demonstrated that omalizumab reduced the rate of severe exacerbations compared with placebo similar to other biologics including mepolizumab[104] reslizumab[108] benralizumab[105, 114] and dupilumab.[109] This meta-analysis is in line with RCTs as omalizumab reduced the risk of severe exacerbations by approximately 60% following 12 months of treatment compared with baseline. Further, in this study, the proportion of patients receiving OCS decreased by 41% following 12 months of treatment; which is similar to the reductions observed in the RCTs.[115, 116]

Severe asthma is also associated with a substantial financial burden due to the direct costs and indirect costs due to loss of work productivity.[117] In RCTs, omalizumab was found to reduce the number of days of school absenteeism and unscheduled medical visits in children.[113, 118] In the EXALT study, the rate of hospitalizations and ER visits were significantly decreased in patients receiving omalizumab compared to those receiving optimized asthma therapy.[15] Similar results were observed in the ICATA study.[118] In INNOVATE, ER visits for asthma were reduced by 44% in the omalizumab group compared with placebo.[4] Further, the pooled analysis of three Phase III RCTs [2, 5, 113] including children and adolescents, demonstrated that the rate of unscheduled, asthma-related doctor visits was reduced by 40% in patients treated with omalizumab compared with those treated with placebo.[119] In this study, the mean number of asthma-related unscheduled physician visits significantly reduced following 12 months of treatment, with a MD of –2.34 *(P*<0.01) visits compared with baseline; while only numerical improvement of 2.12 days in the number of missed school or work days was observed.

The PROs including ACQ, ACT and AQLQ are the validated questionnaires to assess asthma control and health status[120]; and omalizumab has shown to significantly improve asthma control and HRQoL in several studies.[3, 6, 15, 16, 121] EXALT study demonstrated a significantly greater reduction in the ACQ score from baseline following omalizumab treatment compared with

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optimized asthma therapy at Week 16 and Week 32.[15] Moreover, omalizumab treatment for 48 weeks improved the proportion of patients achieving minimal clinically important difference (MCID) of the AQLQ overall score compared with placebo in the EXTRA study.[16] Similar results in terms of the proportion of patients who achieved MCID for AQLQ score were observed in RCTs (omalizumab vs. placebo: 78.8% vs. 69.8%; P=0.050[6] and 58% vs. 39%; P<0.01).[3] In this study, omalizumab treatment significantly decreased the ACQ score, and improved the ACT and AQLQ scores starting from 16 weeks with effects maintained until 12 months following therapy, demonstrating the efficacy of omalizumab in improving the PROs in accordance with RCTs. Although safety was not assessed as a part of this meta-analysis, long-term studies have indicated that omalizumab was well-tolerated.[20-22]

Use of random effects model, and analyzing the effect measures as 16 weeks/4 months, and 6 and 12 months to normalize the effect sizes can be considered strengths of this meta-analysis. The authors also acknowledge few limitations. There was a substantial heterogeneity amongst the studies in terms of the outcomes observed. The risk of bias assessment, and quality of individual studies included in the meta-analysis were not evaluated. To limit the bias in analysis, we have considered within group comparison though the included RWE studies were either Phase IV PMS, observational studies with control group, or uncontrolled studies (before and after). The meta-regression for estimation of dependent effect sizes was out of the scope of analysis and was not performed. However, despite the methodologies weakness, the effectiveness results are showing consistent positive results.

Conclusions

This meta-analysis of real-world data provides consistent evidence on the treatment effectiveness of omalizumab in patients with SAA. It emphasized that the effectiveness of omalizumab did not decrease with time, and even demonstrated important changes in full

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asthma management with 82% achieving GETE asthma control, 250 mL increase in FEV_1 and 59% reduction in severe exacerbations after 12 months of treatment. Regardless of the observed heterogeneity between the included studies, we found that add-on omalizumab is also associated with improvement in PROs, and reduced OCS use, hospitalizations, ER and unscheduled doctor visits. This quantitative synthesis of observational studies confirms, complements and extends the efficacy findings observed in RCTs in patients with SAA.

Data Sharing:

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com

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Figure Legends

Figure 1: PRISMA flow diagram

**The core and extension studies by Odajima H, et al. were considered as two separate publications bringing the total number of publications to 86*

Figure 2: The proportion of GETE responders after 16 weeks, 6 months and 12 months of omalizumab treatment in the real-world meta-analysis of observational studies

CI, confidence interval; df, degrees of freedom; GETE, global evaluation of treatment effectiveness; IV, inverse variance; MH, Mantel-Haenszel

I^2 indicates heterogeneity between the included studies

Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate

Figure 3: Change in FEV_1 following 16 weeks, 6 months and 12 months of omalizumab treatment in patients with severe allergic asthma

CI, confidence interval; df, degrees of freedom; FEV_1, forced expiratory volume in 1 second; IV, inverse variance; SD, standard deviation

I^2 indicates heterogeneity between the included studies

Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate

Figure 4: Omalizumab treatment reduced severe exacerbations in patients with severe allergic asthma

CI, confidence interval; df, degrees of freedom; IV, inverse variance; MH, Mantel-Haenszel

I^2 indicates heterogeneity between the included studies

Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate

Figure 5: The mean number of severe exacerbations decreased following treatment with omalizumab in patients with severe allergic asthma

CI, confidence interval; df, degrees of freedom; IV, inverse variance; SD, standard deviation

I^2 indicates heterogeneity between the included studies

Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate

Figure 6: OCS use reduced following omalizumab treatment in patients with severe allergic asthma

CI, confidence interval; df, degrees of freedom; IV, inverse variance; OCS, oral corticosteroid

I^2 indicates heterogeneity between the included studies

Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate

Figure 7: ACQ score decreased following omalizumab treatment in patients with severe allergic asthma

ACQ, asthma control questionnaire; CI, confidence interval; df, degrees of freedom; IV, inverse variance

I^2 indicates heterogeneity between the included studies

Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate

Figure 8: Change in the number of unscheduled physician visits following 12 months of omalizumab treatment in patients with severe allergic asthma

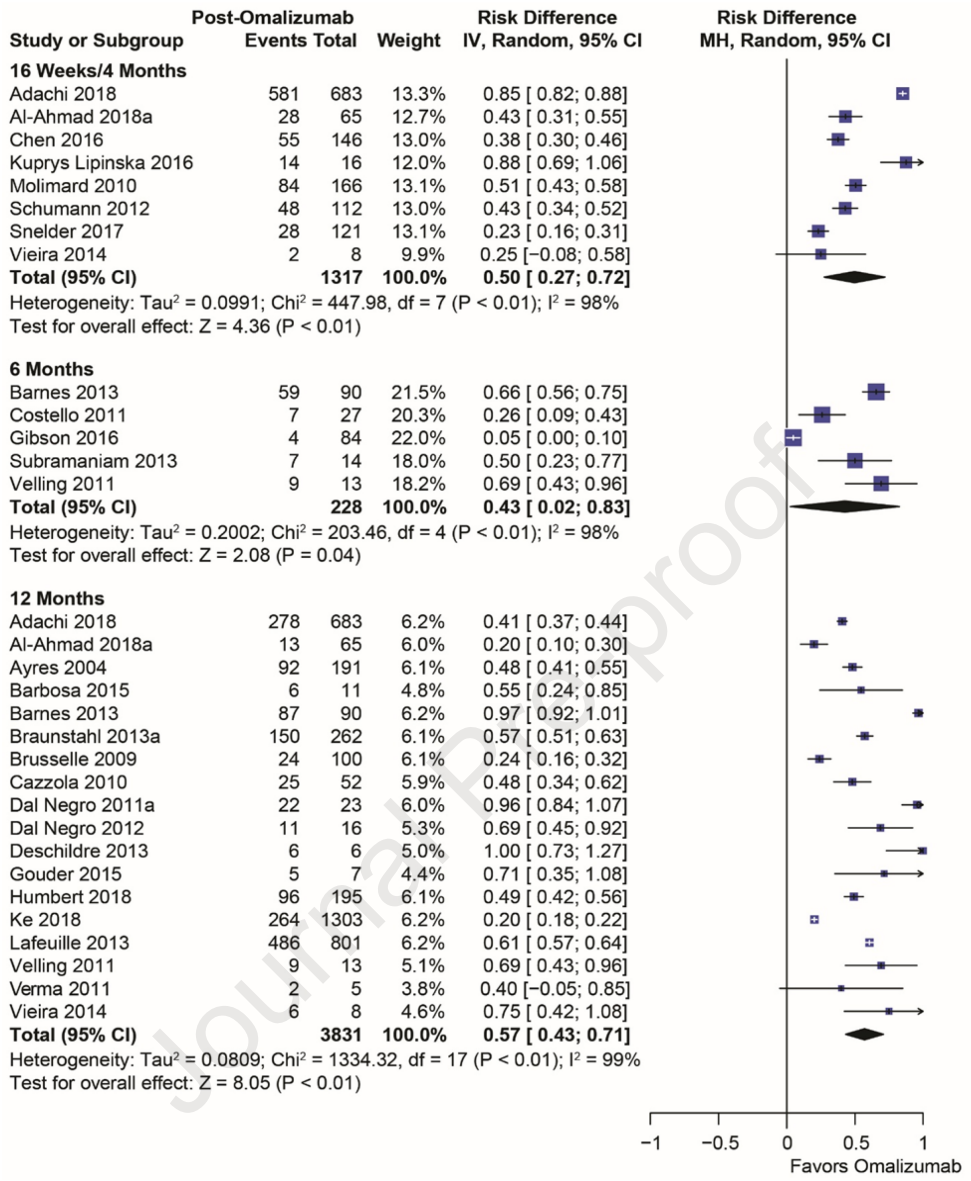
CI, confidence interval; df, degrees of freedom; IV, inverse variance; SD, standard deviation

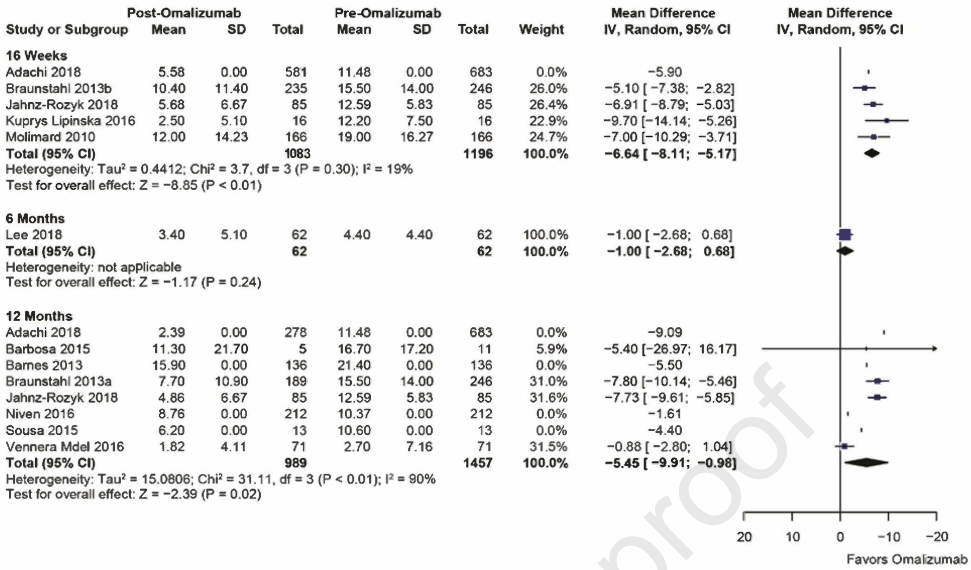
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I^2 indicates heterogeneity between the included studies

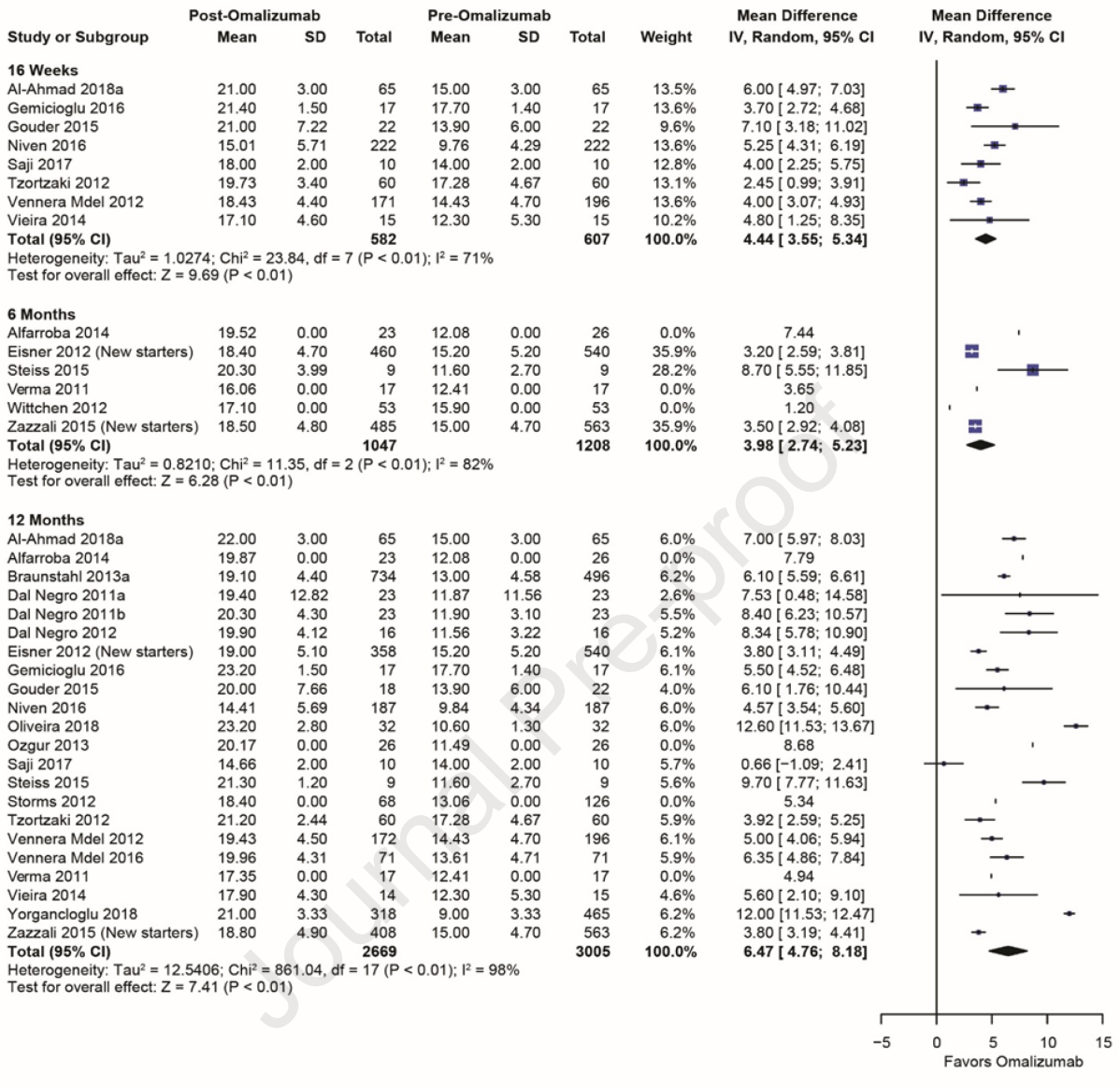
Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate

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Post-Omalizumab
Study or Subgroup Events Total Weight
Risk Difference
IV, Random, 95% CI
Risk Difference
MH, Random, 95% CI
16 Weeks/4 Months
Adachi 2018 581 683 13.3% 0.85 [0.82; 0.88]
Al-Ahmad 2018a 28 65 12.7% 0.43 [0.31; 0.55]
Chen 2016 55 146 13.0% 0.38 [0.30; 0.46]
Kuprys Lipinska 2016 14 16 12.0% 0.88 [0.69; 1.06]
Molimard 2010 84 166 13.1% 0.51 [0.43; 0.58]
Schumann 2012 48 112 13.0% 0.43 [0.34; 0.52]
Snelder 2017 28 121 13.1% 0.23 [0.16; 0.31]
Vieira 2014 2 8 9.9% 0.25 [−0.08; 0.58]
Total (95% CI) 1317 100.0% 0.50 [0.27; 0.72]
Heterogeneity: Tau² = 0.0991; Chi² = 447.98, df = 7 (P < 0.01); I² = 98%
Test for overall effect: Z = 4.36 (P < 0.01)
6 Months
Barnes 2013 59 90 21.5% 0.66 [0.56; 0.75]
Costello 2011 7 27 20.3% 0.26 [0.09; 0.43]
Gibson 2016 4 84 22.0% 0.05 [0.00; 0.10]
Subramaniam 2013 7 14 18.0% 0.50 [0.23; 0.77]
Velling 2011 9 13 18.2% 0.69 [0.43; 0.96]
Total (95% CI) 228 100.0% 0.43 [0.02; 0.83]
Heterogeneity: Tau² = 0.2002; Chi² = 203.46, df = 4 (P < 0.01); I² = 98%
Test for overall effect: Z = 2.08 (P = 0.04)
12 Months
Adachi 2018 278 683 6.2% 0.41 [0.37; 0.44]
Al-Ahmad 2018a 13 65 6.0% 0.20 [0.10; 0.30]
Ayres 2004 92 191 6.1% 0.48 [0.41; 0.55]
Barbosa 2015 6 11 4.8% 0.55 [0.24; 0.85]
Barnes 2013 87 90 6.2% 0.97 [0.92; 1.01]
Braunstahl 2013a 150 262 6.1% 0.57 [0.51; 0.63]
Brusselle 2009 24 100 6.1% 0.24 [0.16; 0.32]
Cazzola 2010 25 52 5.9% 0.48 [0.34; 0.62]
Dal Negro 2011a 22 23 6.0% 0.96 [0.84; 1.07]
Dal Negro 2012 11 16 5.3% 0.69 [0.45; 0.92]
Deschildre 2013 6 6 5.0% 1.00 [0.73; 1.27]
Gouder 2015 5 7 4.4% 0.71 [0.35; 1.08]
Humbert 2018 96 195 6.1% 0.49 [0.42; 0.56]
Ke 2018 264 1303 6.2% 0.20 [0.18; 0.22]
Lafeuille 2013 486 801 6.2% 0.61 [0.57; 0.64]
Velling 2011 9 13 5.1% 0.69 [0.43; 0.96]
Verma 2011 2 5 3.8% 0.40 [−0.05; 0.85]
Vieira 2014 6 8 4.6% 0.75 [0.42; 1.08]
Total (95% CI) 3831 100.0% 0.57 [0.43; 0.71]
Heterogeneity: Tau² = 0.0809; Chi² = 1334.32, df = 17 (P < 0.01); I² = 99%
Test for overall effect: Z = 8.05 (P < 0.01)
−1
−0.5
0
0.5
1
Favors Omalizumab

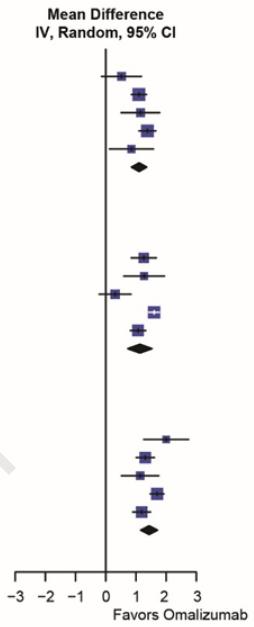


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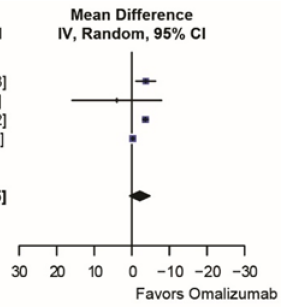
Study or Subgroup	Post-Omalizumab Mean	SD	Total	Pre-Omalizumab Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
16 Weeks								
Gawlewicz-Mroczka 2016	3.97	1.14	15	3.45	0.66	15	15.1%	0.52 [−0.15; 1.19]
Jahnz-Rozyk 2018	4.20	0.88	85	3.10	0.82	85	28.4%	1.10 [0.84; 1.36]
Kuprys Lipinska 2016	4.15	1.11	16	3.00	0.71	16	15.6%	1.15 [0.50; 1.80]
Niven 2016	4.65	1.55	192	3.27	1.29	192	27.4%	1.38 [1.09; 1.67]
Tajiri 2016	4.95	1.37	25	4.10	1.40	30	13.5%	0.85 [0.12; 1.58]
Total (95% CI)			**333**			**338**	**100.0%**	**1.10 [0.85; 1.36]**
Heterogeneity: $Tau^2 = 0.0316$; $Chi^2 = 6.72$, df = 4 (P = 0.15); $I^2 = 40\%$								
Test for overall effect: Z = 8.50 (P < 0.01)								
6 Months								
Gibson 2016	4.78	1.26	67	3.52	1.24	67	19.5%	1.26 [0.84; 1.68]
Hew 2016 (Above-dose range)	4.48	1.21	23	3.21	1.14	23	12.8%	1.27 [0.59; 1.95]
Hew 2016 (Within-dose range)	4.41	1.35	45	4.10	1.21	45	16.4%	0.31 [−0.22; 0.84]
Korn 2009	4.50	1.20	241	2.90	0.90	280	26.7%	1.60 [1.42; 1.78]
Maltby 2017	4.66	0.17	78	3.59	1.17	78	24.5%	1.07 [0.81; 1.33]
Total (95% CI)			**454**			**493**	**100.0%**	**1.13 [0.73; 1.54]**
Heterogeneity: $Tau^2 = 0.1670$; $Chi^2 = 26.37$, df = 4 (P < 0.01); $I^2 = 85\%$								
Test for overall effect: Z = 5.47 (P < 0.01)								
12 Months								
Barbosa 2015	5.10	1.50	22	3.10	1.10	28	11.8%	2.00 [1.25; 2.75]
Braunstahl 2013a	5.58	1.06	92	4.27	1.27	132	23.8%	1.31 [1.00; 1.62]
Gawlewicz-Mroczka 2016	4.59	1.04	15	3.45	0.66	15	14.4%	1.14 [0.52; 1.76]
Jahnz-Rozyk 2018	4.80	0.73	85	3.10	0.82	85	26.0%	1.70 [1.47; 1.93]
Niven 2016	4.39	1.48	161	3.20	1.27	161	24.0%	1.19 [0.89; 1.49]
Total (95% CI)			**375**			**421**	**100.0%**	**1.44 [1.16; 1.72]**
Heterogeneity: $Tau^2 = 0.0589$; $Chi^2 = 11.09$, df = 4 (P = 0.03); $I^2 = 64\%$								
Test for overall effect: Z = 10.05 (P < 0.01)								



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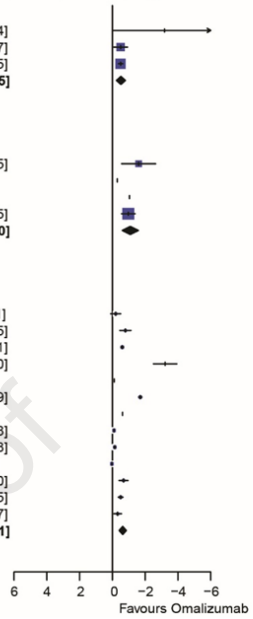
Study or Subgroup	Post-Omalizumab Mean	SD	Total	Pre-Omalizumab Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
12 Months (Days off school or work)								
Adachi 2018	0.60	9.38	3593	4.30	79.67	3593	28.1%	−3.70 [−6.32; −1.08]
Ayres 2004	14.00	60.66	191	10.00	60.83	206	8.0%	4.00 [−7.96; 15.96]
Barbosa 2015	0.70	1.60	54	4.30	2.60	62	31.8%	−3.60 [−4.38; −2.82]
CIGE0250011E3	0.22	1.44	118	0.46	2.22	118	32.1%	−0.24 [−0.72; 0.24]
Dal Negro 2011a	0.00	0.00	23	17.60	70.40	23	0.0%	−17.60
Dal Negro 2012	0.00	0.00	18	19.00	21.00	18	0.0%	−19.00
Total (95% CI)			**3997**			**4020**	**100.0%**	**−2.12 [−4.79; 0.55]**

Heterogeneity: $Tau^2 = 5.2591$; $Chi^2 = 56.56$, df = 3 ($P < 0.01$); $I^2 = 95\%$
Test for overall effect: $Z = -1.55$ ($P = 0.12$)

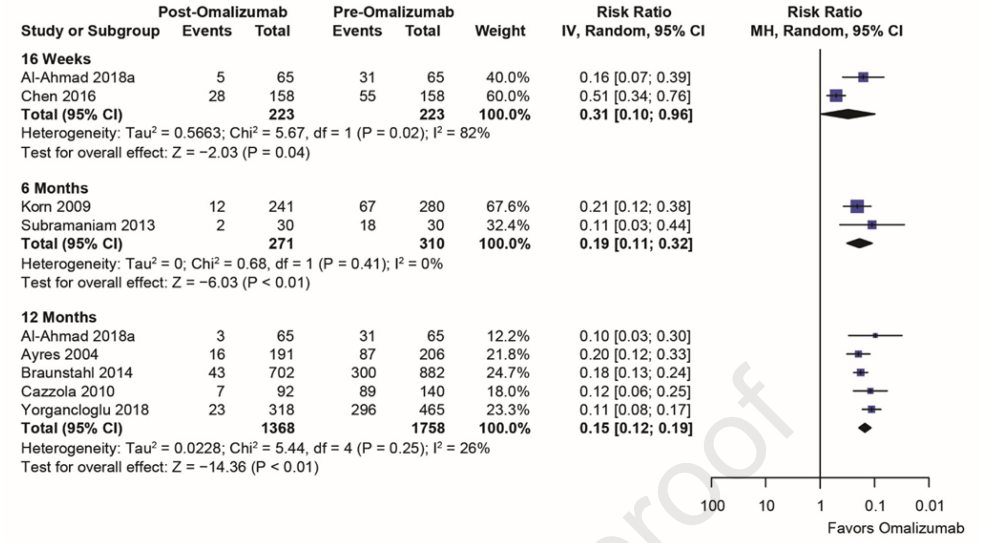


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Study or Subgroup	Post-Omalizumab Mean	SD	Total	Pre-Omalizumab Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
16 Weeks/4 Months								
Chen 2016	2.75	12.02	158	5.93	16.16	158	2.3%	−3.18 [−6.32; −0.04]
Molimard 2010	0.50	2.17	160	1.00	1.75	158	40.6%	−0.50 [−0.93; −0.07]
Vennera Mdel 2012	0.10	0.30	266	0.60	1.20	266	57.1%	−0.50 [−0.65; −0.35]
Total (95% CI)			**584**			**582**	**100.0%**	**−0.52 [−0.79; −0.25]**
Heterogeneity: Tau² = 0.0212; Chi² = 2.79, df = 2 (P = 0.25); I² = 28%								
Test for overall effect: Z = −3.74 (P < 0.01)								
6 Months								
Costello 2011	0.80	3.00	63	2.40	3.00	63	27.4%	−1.60 [−2.65; −0.55]
Lee 2018	0.20	0.00	62	0.50	0.00	62	0.0%	−0.30
Odajima 2015	0.29	0.00	38	1.33	0.00	38	0.0%	−1.04
Subramaniam 2013	0.10	0.40	30	1.07	1.10	30	72.6%	−0.97 [−1.39; −0.55]
Total (95% CI)			**193**			**193**	**100.0%**	**−1.09 [−1.59; −0.60]**
Heterogeneity: Tau² = 0.0328; Chi² = 1.2, df = 1 (P = 0.27); I² = 17%								
Test for overall effect: Z = −4.36 (P < 0.01)								
12 Months								
Adachi 2018	0.40	7.38	2490	0.60	3.12	2490	8.3%	−0.20 [−0.51; 0.11]
Barnes 2013	0.51	1.10	136	1.30	1.73	136	8.0%	−0.79 [−1.13; −0.45]
Braunstahl 2014	0.10	0.43	702	0.70	1.33	882	10.2%	−0.60 [−0.69; −0.51]
Cazzola 2010	1.23	0.49	92	4.45	4.31	140	4.5%	−3.22 [−3.94; −2.50]
Gouder 2015	0.17	0.00	18	0.28	0.00	18	0.0%	−0.11
Humbert 2018	0.20	0.60	706	1.90	1.50	872	10.2%	−1.70 [−1.81; −1.59]
Jahnz-Rozyk 2018	0.26	0.00	85	0.88	0.00	85	0.0%	−0.62
Ke 2018	0.00	0.15	1564	0.10	0.32	1564	10.5%	−0.10 [−0.12; −0.08]
Lafeuille 2012	0.21	0.59	644	0.36	0.77	644	10.3%	−0.15 [−0.22; −0.08]
Lafeuille 2013	0.13	0.40	801	0.10	0.30	3044	10.4%	0.03 [0.00; 0.06]
Niven 2016	0.56	1.33	218	1.24	1.64	218	8.7%	−0.68 [−0.96; −0.40]
Vennera Mdel 2012	0.10	0.40	266	0.60	1.20	266	9.9%	−0.50 [−0.65; −0.35]
Vennera Mdel 2016	0.13	0.57	71	0.45	0.89	71	9.0%	−0.32 [−0.57; −0.07]
Total (95% CI)			**7793**			**10430**	**100.0%**	**−0.63 [−0.85; −0.41]**
Heterogeneity: Tau² = 0.1224; Chi² = 1140.81, df = 10 (P < 0.01); I² = 99%								
Test for overall effect: Z = −5.62 (P < 0.01)								

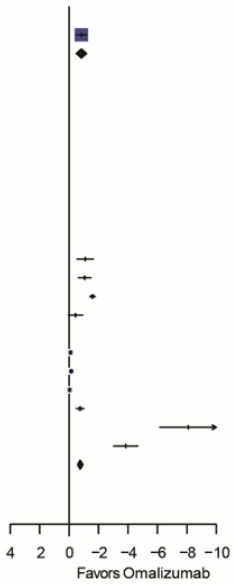


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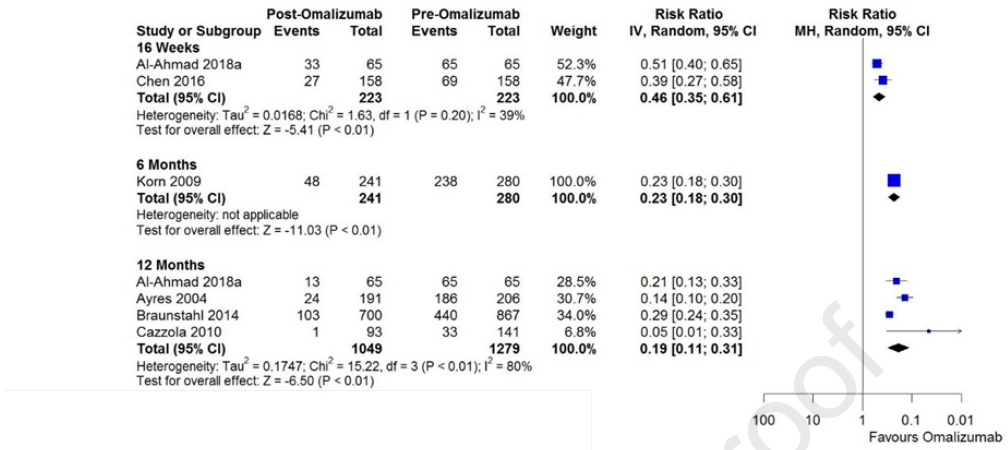


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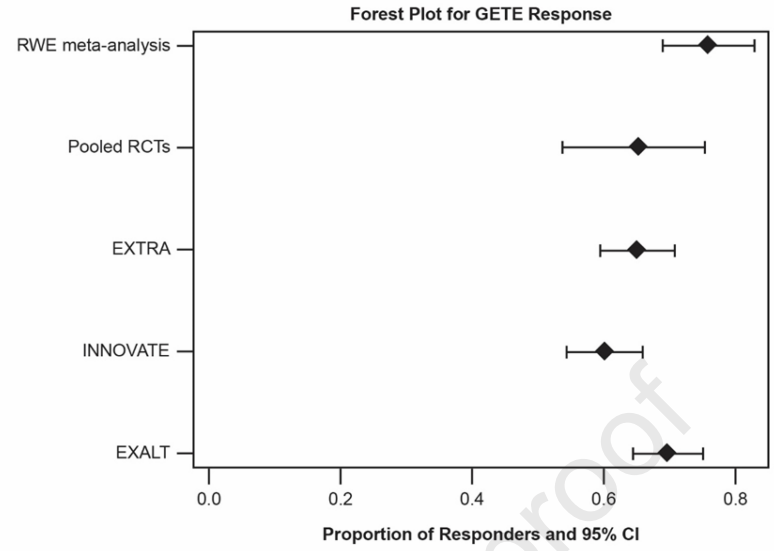
Study or Subgroup	Post-Omalizumab Mean	SD	Total	Pre-Omalizumab Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
16 Weeks/4 Months								
Chen 2016	0.29	0.830	158	1.13	2.040	158	100.0%	−0.84 [−1.18; −0.50]
Total (95% CI)			**158**			**158**	**100.0%**	**−0.84 [−1.18; −0.50]**
Heterogeneity: not applicable								
Test for overall effect: Z = −4.79 (P < 0.01)								
6 Months								
Odajima 2015	0.46	0.000	38	0.68	0.000	38	−−	−0.22
Total (95% CI)			**38**			**38**	**100.0%**	
Heterogeneity: not applicable								
Test for overall effect: Z = NA (P = NA)								
12 Months								
Adachi 2018	0.90	8.650	2425	2.00	11.100	2425	6.9%	−1.10 [−1.66; −0.54]
Barnes 2013	0.46	1.420	136	1.52	2.190	136	8.7%	−1.06 [−1.50; −0.62]
Braunstahl 2014	0.20	0.630	700	1.80	2.800	867	13.5%	−1.60 [−1.79; −1.41]
Dal Negro 2012	0.25	0.310	16	0.69	0.950	16	7.9%	−0.44 [−0.93; 0.05]
Jahnz-Rozyk 2018	0.15	0.000	85	0.97	0.000	85	0.0%	−0.82
Ke 2018	0.00	0.170	1564	0.10	0.320	1564	15.4%	−0.10 [−0.12; −0.08]
Lafeuille 2012	0.20	0.720	644	0.35	0.960	644	14.9%	−0.15 [−0.24; −0.06]
Lafeuille 2013	0.06	0.300	801	0.10	0.500	3044	15.4%	−0.04 [−0.07; −0.01]
Niven 2016	0.37	0.910	218	1.12	1.710	218	12.2%	−0.75 [−1.01; −0.49]
Saji 2017	1.20	0.400	10	9.30	3.100	10	1.0%	−8.10 [−10.04; −6.16]
Vennera Mdel 2016	1.45	2.040	71	5.30	2.900	71	4.2%	−3.85 [−4.67; −3.03]
Total (95% CI)			**6670**			**9080**	**100.0%**	**−0.76 [−0.94; −0.58]**
Heterogeneity: $Tau^2 = 0.0544$; $Chi^2 = 455.7$, df = 9 (P < 0.01); $I^2 = 98\%$								
Test for overall effect: Z = −8.14 (P < 0.01)								



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1 **Table E1: Patient's baseline demographics and clinical characteristics**

Study ID	Age (years)	Gender, male/female (N)	Race (N)	Smoking status (N)	Body weight (kg)	BMI (kg/m^2)	Duration of asthma (years)
Adachi 2018 [E4]	59.3 ± 16.1	1287/2333	-	Ex-smoker (1098)	-	-	18.9 ± 14.5
Al-Ahmad 2018a [E5]	46.7 ± 11.6	22/43	-	Ex-smoker (6)	-	30.6 ± 5.7[§]	-
Al-Ahmad 2018b [E6]	45.8 ± 13.5[§]	9/26	-	-	-	30.3 ± 5.8[§]	-
Alfarroba 2014 [E7]	53 ± 13.6	7/19	Caucasian (26)	Non-smoker (23) Ex-smoker (3)	81.5 ± 15.1	-	28 ± 13.1
Ancochea 2014 [E8]	48.2 ± 17.7	65/149	-	Current smoker (6)	71.1 ± 13.9	-	21.6 ± 13.2
Ayres 2004 [E9]	37.5 (12–73)*	58/148	-	-	-	-	-
Barbosa 2015	49.2 ± 15.0	19/43	Caucasian (60)	Non-smoker	72.5 ± 16.9	-	24.3 ± 13.8

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E10			Black (1) Other (1)	(49) Ex-smoker (10) Current smoker (3)			
Barnes 2013 E11	41.3 ± 14.5	43/93	-	Non-smoker (89) Ex-smoker (24) Current smoker (3) Not recorded (20)	81.2 ± 20.6[a]	-	26.4 ± 14.3[b]
Bousquet 2011 E12	45.6 ± 13.0	89/183	-	-	-	-	-
Braunstahl 2013a[$]/2013b/ 2014 E13- E15	45.0 ± 15.0	325/600	Caucasian (855) Asian (32) Black (21) Native	Non-smoker (719) Ex-smoker (173) Current	75.5 ± 17.7	-	19.4 ± 13.6

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			American (2) Other (15)	smoker (30)			
Brusselle 2009 E16	48.2 ± 17.2	73/85	Caucasian (150) Other (8)	Non-smoker (109) Ex-smoker (33) Current smoker (16)	71.5 ± 16.5	-	-
Caminati 2014 E17	45.6 ±11.5	29/30	-	Non-smoker (40) Ex-smoker (18) Current smoker (1)	Men: 77.7 ± 17.0 Women: 63.6 ± 11.5	-	18.2 ± 15.4
Casale 2018 E18	47.3 ± 17.4	294/512	White (567)	-	-		-
Cazzola 2010 E19	49.6 ± 4.1	70/72	-	-	70.3 ± 13.3		-
Chen 2016 E20	51.3 ± 17.2	161/121	-	-	-		-

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CIGE0250011 E1 [E21]	43.6 ± 15.0	84/138	Caucasian (215) Black (4) Oriental (1) Other (2)	-	75.3 ± 16.4		-
CIGE0250011 E3 [E22]	45.8 ± 14.5	48/70	Caucasian (117) Other (1)	-	75.8 ± 16.4		-
Costello 2011 [E23]	48 ± 21	31/32	-	Non-smoker (41)	-	-	-
Dal Negro 2011a [E24]	46.5 (27–70)‡	9/14	-	Non-smoker (16) Ex-smoker (5) Current smoker (2)	30–150	25.75 (19.8–37.5)‡	12
Dal Negro 2011b [E25]	47.3 ± 12	9/14	-	Non-smoker (23)	-	25.8 ± 9.6	-
Dal Negro	45.4 (31–64)‡	8/8	-	Non-smoker	-	25.2	-

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2012 [E26]				(12) Ex-smoker (4)		(19.8–37.5)[‡]	
Deschildre 2013[$ E27]	11.9 ± 3.1[¶]	60/44	-	-	-	-	9.1 (4.07)[¶]
Di Domenico 2010 [E28]	50.5 ± 9.0[#]	4/2	-	-	84.5 ± 36.5[#]	-	3
Eisner 2012 [E29]	New starters: 44.3 ± 16 Established users: 44.5 ± 16.6[c]	New starters: 195/354 Established users: 1596/2825	New starters: White (430) Black or African-American (77) Asian or Pacific Islander (17) Other (25) Established users: White (3493)	New starters: Non-smoker (351) Ex-smoker (161) Current smoker (37) Established users: Non-smoker (2904) Ex-smoker	-	New starters: 32.2 ± 18.4[e] Established users: 31 ± 11.8[f]	-

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			Black or African-American (632) Asian or Pacific Islander (102) Other (193)[c]	(1310) Current smoker (205)[d]			
Gawlewicz-Mroczka 2016 E30	47 ± 10.6	4/11	-	-	-	-	28.1 ± 12.8
Gemicioglu 2016 E31	48.3 ± 16.4	4/13	-	-	-	-	-
Gibson 2007 E32	22–75	5/7	-	-	-	-	≥1
Gibson 2016 E33	51.4 ± 15	66/114	-	Non-smoker (104) Ex-smoker (39) Current	82 (68.1, 95.7)†	29.1 (25.4, 35.1)†	-

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				smoker (4)			
Gouder 2015 [E34]	52.7 ± 11	14/8	Caucasian (21) Other (1)	Non-smoker (12) Ex-smoker (10) Current smoker (0)	82 ± 16.4	-	-
Grimaldi-Bensouda 2013 [E35]	49.7 ± 14.6	37/63	-	Non-smoker (61) Ex-smoker (27) Current smoker (12)	-	26.7 ± 6.1	26.5 ± 15.9
Hew 2016 [E36]	Within-dose table range: 52 ± 14.6 Above-dose table range: 50.3 ± 16	Within-dose table range: 49/75 Above-dose table range: 17/38	-	Within-dose table range: Non-smoker (67) Ex-smoker (23)[g]	Within-dose table range: 79.6 (69, 91.7)[†] Above-dose table range: 86 (65.5, 107.9)[†]	Within-dose table range: 29 (25.7, 33.5)[†i] Above-dose table range 32.1 (24.7,	-

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				Current smoker (2) Above-dose table range: Non-smoker (32) Ex-smoker (13) Current smoker (2)[h]		39.8)[†j]	
Huang 2018 [E37]	56.4 ± 2.1	12/11	-	Ex-smoker (5)	-	-	-
Humbert 2018[$] [E38]	44.1 ± 19.7	377/495	-	Non-smoker (583) Ex-smoker (180) Current smoker (67) Missing (42)	70 ± 20.3	-	-

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Jahnz-Rozyk 2018 [E39]	44.9 (13–79)[‡‡]	33/52	-	-	77.4 (34–140) [‡‡]	-	-
Ke 2018[$ E40]	44.9 ± 15.7	598/966	-	-	-	-	-
Kelmenson 2013 [E41]	43.8 ± 8.8[#]	2/2	White (2) Multiple (1) Black Native American (1)	-	-	35.3 ± 1.93[#]	-
Korn 2009 [E42]	43.9 ± 16.3	166/114	-	Non-smoker (209) Ex-smokers (40) Current smoker (13)	73.1 ± 17.2	-	-
Korn 2010[$ E43]	43.8 ± 16.5	188/283	-	Non-smoker and Ex-smoker (351) Continuous smoker (82)	73.7 ± 17.6[α]	-	-

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Kuprys-Lipinska 2016[$] E44	45.8 ± 15.3	20/33	-	-	-	-	13 ± 10.8
Lafeuille 2012 E45	49.9 ± 14.2	263/381	-	-	-	-	-
Lafeuille 2013 E46	48.5 ± 15.7	1146/1898	-	-	-	-	-
Lee 2018 E47	44.5 ± 13.1	26/36	-	Non-smoker (43) Ex-smoker (12) Current smoker (7)	-	-	10.0 ± 7.7
Levy 2015 E48	54 ± 12.7	14/33	-	-	-	-	-
Lopez Tiro 2015 E49	43.5 (15–67)[‡‡]	10/42	-	-	-	-	-
Maltby 2017 E50	50.3 ± 14.9	66/94	-	Non-smoker (92) Ex-Smoker	80.1 (67.0–96.2)[†]	29.0 (25.1–34.3)[†]	20.6 (6.0–40.0)[†]

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				(27) Current smoker (4)			
Mansur 2017 E51	44.9 ± 12.7	8/37	-	-	85.9 ± 21.5	-	-
Menzella 2012 E52	47.5 ± 9.6	7/4	-	Non-smoker (8) Ex-smoker (3)	81.6 ± 12.1	-	-
Menzella 2017 E53	43 ± 9	5/3	-	-	-	-	-
Molimard 2008 E54	46.5 ± 13.6	54/93	-	-	71.3 ± 16.0	-	-
Molimard 2010 E55	46.1 ± 13.9	75/91	-	-	72.4 ± 16.8	-	-
Niven 2016 E56	44.7 ± 14.2	90/168	-	Non-smoker (161) Ex-smoker (83) Current	82.4 ± 20.1	29.9 ± 6.8	25.1 ± 15.1

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				smoker (6) Unknown (8)			
Novelli 2015 [E57]	52 ± 13.7	113/193	-	Non-smoker (211) Ex-smoker (83) Current smoker (12)	-	26.4 (16.7–46.8)*	-
Odajima 2017[$] [E58, E59]	Core study: 10.7 ± 2.5 Extension study: 11.5 ± 2.5	Core study: 23/15 Extension study: 23/15	Core study: Asian (38) Extension study: Asian (38)	-	Core study: 37.0 ± 10.8 Extension study: 40.1 ± 11.1	-	Core study: 8.4 ± 3.05 Extension study: 9.3 ± 3.1
Oliveira 2018 [E60]	52.9 ± 9.6	8/24	-	-	-	30.4 ± 5.8	-
Ozgur 2013 [E61]	47.6 ± 13.9	5/21	-	-	70.6 ± 10.9	-	22.7 ± 10.1
Pace 2011 [E62]	50 ± 8	4/3	-	-	-	-	-
Paganin 2017 [E63]	50.0 ± 15.2	79/128	-	Ex or active smokers (30)	-	26.1 ± 5.3	-

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Pelaia 2011 [E64]	46.1 ± 11.5	4/12	-	-	68.2 ± 13.9	27.5 ± 5.4	-
Rottem 2012 [E65]	50.0 ± 12.2	18/15	-	-	-	-	-
Rubin 2012 [E66]	43.8 ± 13.1	18/60	Caucasian/white (54) Black (13) Other (11)	-	20–150[††]	-	31.7 ± 16.3
Saji 2017 [E67]	58.2 ± 18.6	6/4	-	Non-smokers (9) Ex-smoker (1)	57.8 ± 21.7	-	14 ± 11
Schumann 2012 [E68]	43.6 ± 16.9	78/114	-	Non-smoker (142) Ex-smoker (22) Current smoker (8)	74.4 ± 18.5	-	-
Siergiejko 2011 [E69]	45.2 ± 12.6	19/40	-	-	76.1 ± 19.6	-	-
Snelder 2017[$]	47 ± 15.6	149/253	-	Tried to quit	78.6 ± 17.4	-	-

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[E70]				smoking (101) Did not try to quit smoking (29)			
Sousa 2015 [E71]	52 ± 10	12/36	-	-	-	-	-
Sposato 2016 [E72]	55.3 ± 13.4[§]	33/72	-	Ex-smokers (24) Current smoker (8)	-	27.1 ± 4.6[§]	-
Steiss 2015[$] [E73]	11.3 ± 0.7	3/6	-	-	-	-	-
Storms 2012 [E74]	52 (14–82)[‡‡]	54/113	-	-	194.1 (32–670) [‡‡]	-	-
Subramaniam 2013 [E75]	45.6 (21–75)[‡‡]	14/16	-	Non-smoker (24) Ex-smoker (6) Current	-	-	13.4 (1–40) [‡‡]

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				smoker (0)			
Sweeney 2012 E76	44.8 ± 13.6	127/222	White (315)	Non-smoker (210) Ex-smoker (108) Current smoker (19) Unknown (12)	81.5 ± 20	29.1 ± 6.4	-
Tajiri 2014 E77	55 ± 16	10/21	-	Non-smoker (18) Ex-smoker (13)	-	25.0 ± 5.3	16.2 ± 13.9
Tajiri 2016 E78	55.9 ± 16.3	8/22	-	-	-	25.3 ± 5.8	41.2 ± 18.2
Tat 2016 E79	69.3 ± 5.8	5/14	-	Non-smoker (16) Ex-smoker (2) Current smoker (1)	-	-	19.4 ± 8.6

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Tzortzaki 2012 [E80]	54 ± 14	24/36	-	-	75.3 ± 15.8	-	23.4 ± 13.3
Velling 2011 [E81]	47.5 ± 14.8	10/13	-	-	82.3 ± 22.0	-	-
Vennera Mdel 2012 [E82]	51.0 (13.7)[§§]	83/183	-	-	28.2 (5.6)[§§]	-	28.3 (14.8)[§§]
Vennera Mdel 2016 [E83]	50.6 ± 13.6	29/42	-	Non-smoker (46) Ex-smoker (22) Current smoker (3)	-	27.4 ± 5.0	-
Verma 2011 [E84]	60 (49–85)*	16/1	Black (6) White (6) Hispanic (3) Other (2)	-	-	-	-
Vieira 2014 [E85]	46.5 ± 10.8	2/13	-	Non-smoker (14) Ex-smoker (1)	66.8 ± 10.6	-	36.3 ± 10.8
Wittchen 2012	48.3 ± 13.7	27/26	-	Ex-smoker (20)	-	-	19.7 ± 14.6

E86				Current smoker (3)			
Yorgancloglu 2018 E87	47.7 ± 11.9	112/353	-	Non-smoker (361) Ex-smoker (49) Current smoker (18)	75 (43–129)†	-	13 (1–48)†
Zazzali 2015 E88	44.4 ± 16.6	1784/3146	White (3884) Black (710) Asian (91) Other (244)	Non-smoker (3241) Ex- smoker (1447) Current smoker (240)	-	-	-
Zierau 2017 E89	Men: 37 (43)* Women: 37 (43)*	25/29	-	-	-	-	-

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*Median (range); †Median (IQR); ‡Mean (min-max); §Combined mean and SD (data were reported as two separate groups); ¶SD was calculated from 95% CI; #Data were reported for individual patients – converted to mean and SD; ††Reported in range; ‡‡Mean (range); §§Median (SD)

$Studies including children

The sample size varies for the following studies. Barnes 2013: [a]132; [b]120. Eisner 2012: [c]4420; [d]4419; [e]547; [f]4414. Hew 2016: [g]92; [h]47; [i]121; [j]53

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Real-world effectiveness of omalizumab in severe allergic asthma: a meta-analysis of observational studies

(Online Repository Text)

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Global evaluation of treatment effectiveness (GETE)

GETE is a validated tool that reflects clinical outcomes and health-related quality of life in patients with asthma. It measures response to therapy on a five-point scale: excellent, good, moderate, poor and worsening of asthma. In clinical trials of omalizumab, GETE has been frequently used in patients with allergic moderate-to-severe or severe persistent asthma as a measure of treatment effectiveness.[E1 , E2]. The score of excellent or good on GETE is an index of responsiveness, and rationale for continuing omalizumab therapy. [E2]. The early stopping rule for omalizumab states that physicians should assess GETE following 16 weeks, and treatment should be continued in patients who showed marked improvement in asthma symptoms following omalizumab therapy. [E3] It is also important to measure GETE response over time in omalizumab treated patients as it is its efficacy measure per label.

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Figure Legends

Figure E1: Reduction in OCS dose by ≥20% post-omalizumab treatment in patients with severe allergic asthma

CI, confidence interval; df, degrees of freedom; IV, inverse variance; OCS, oral corticosteroid

I^2 indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate

Figure E2: The change in the mean daily OCS dose following omalizumab treatment in patients with severe allergic asthma

CI, confidence interval; df, degrees of freedom; IV, inverse variance; OCS, oral corticosteroid; SD, standard deviation

I^2 indicates heterogeneity between the included studies

Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate

Figure E3: ACT score improved following omalizumab treatment in patients with severe allergic asthma

ACT, asthma control test; CI, confidence interval; df, degrees of freedom; IV, inverse variance

I^2 indicates heterogeneity between the included studies

Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate

Figure E4: AQLQ score improved following omalizumab treatment in patients with severe allergic asthma

AQLQ, asthma quality of life questionnaire; CI, confidence interval; df, degrees of freedom; IV, inverse variance

I^2 indicates heterogeneity between the included studies

Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate

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Figure E5: Mean change in school or work absenteeism following 12 months of omalizumab therapy in patients with severe allergic asthma

CI, confidence interval; df, degrees of freedom; IV, inverse variance; SD; standard deviation

I^2 indicates heterogeneity between the included studies

Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate

Figure E6: A) The mean number of hospital admissions decreased following omalizumab treatment in patients with severe allergic asthma

B) Omalizumab treatment decreased the hospitalization rate in patients with severe allergic asthma

CI, confidence interval; df, degrees of freedom; IV, inverse variance. I^2 indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate

Figure E7: A) The mean number of emergency room visits decreased following omalizumab treatment in patients with severe allergic asthma

B) Emergency room visits decreased following omalizumab treatment in patients with severe allergic asthma

CI, confidence interval; df, degrees of freedom; IV, inverse variance

I^2 indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate

Figure E8: Comparison of GETE responders from a pooled analysis of randomized controlled trials and meta-analysis of real-world observational studies

CI, confidence interval; GETE, global evaluation of treatment effectiveness; RCT, randomized controlled trial; INNOVATE[E1]; EXALT[E12]; EXTRA[E90]

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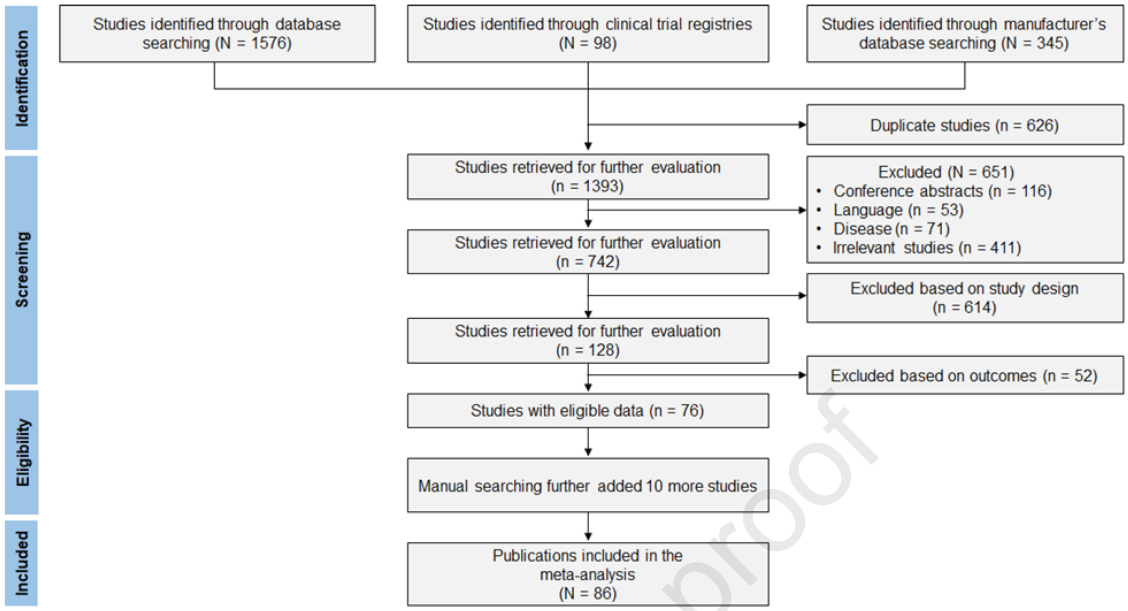
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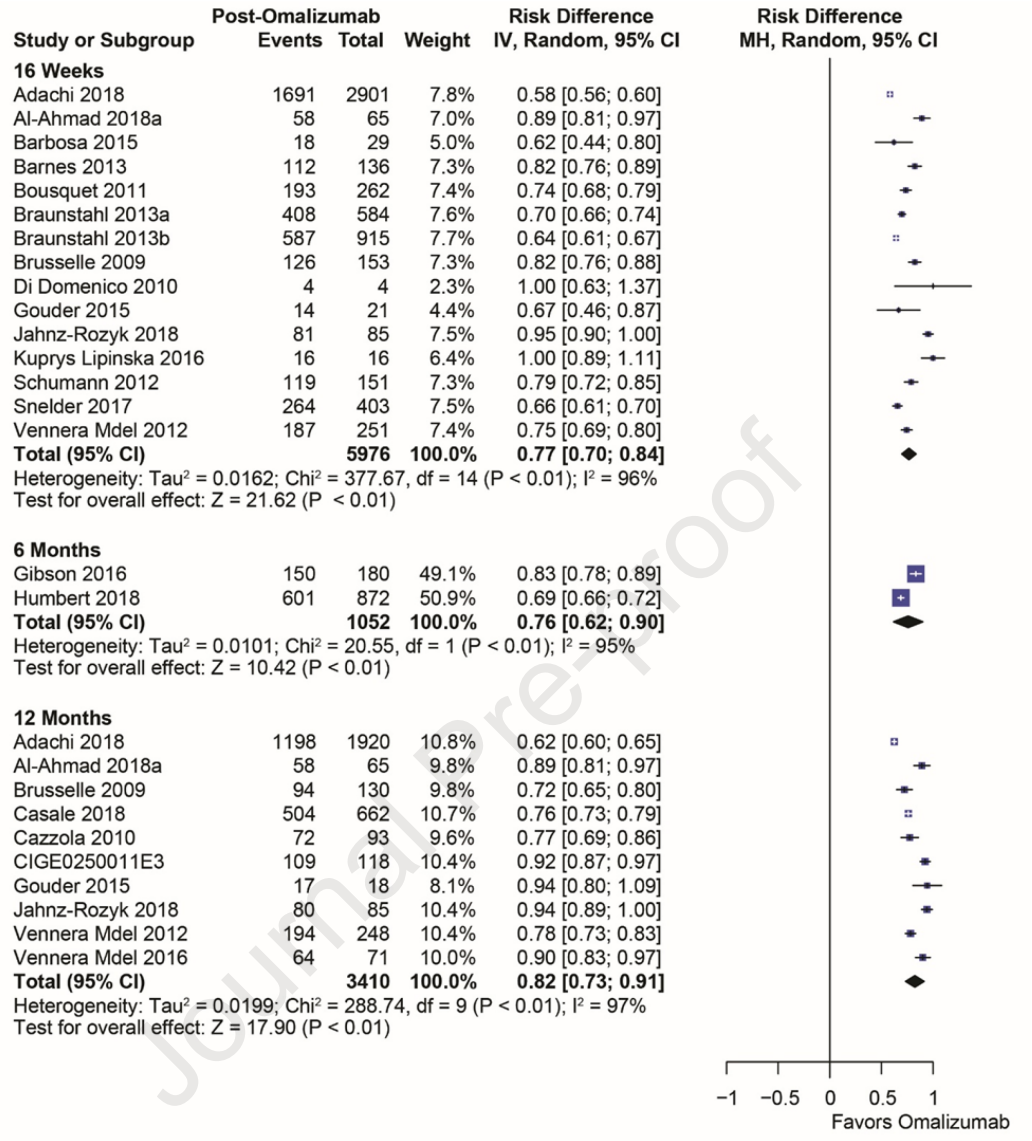
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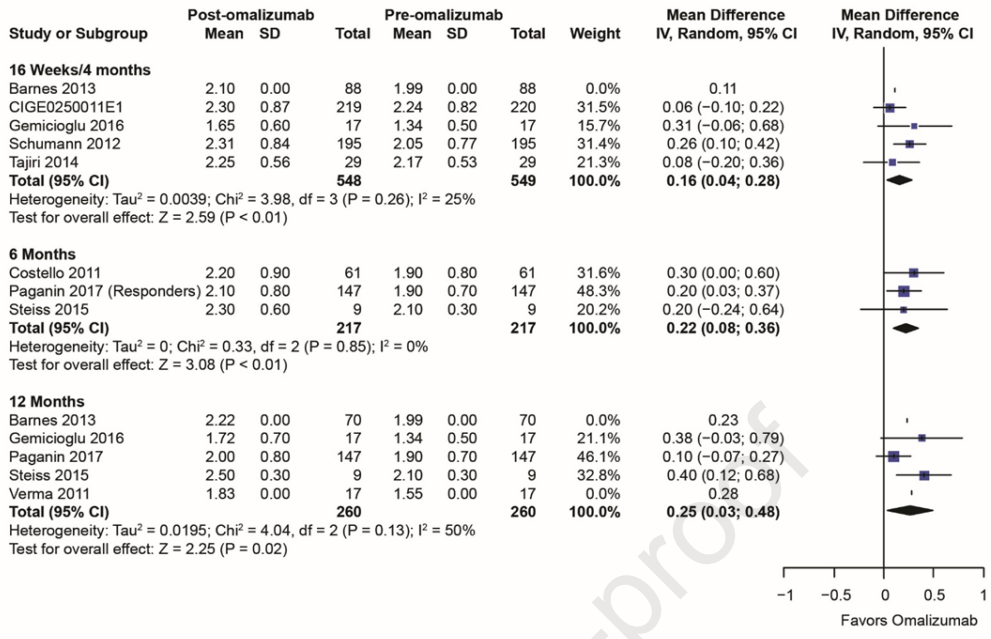
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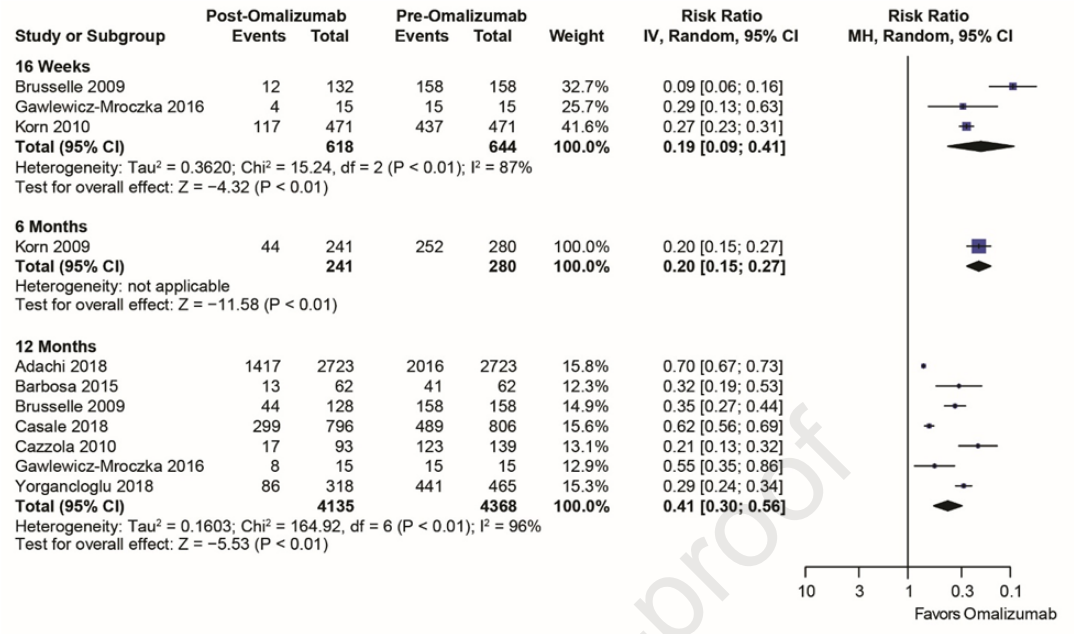
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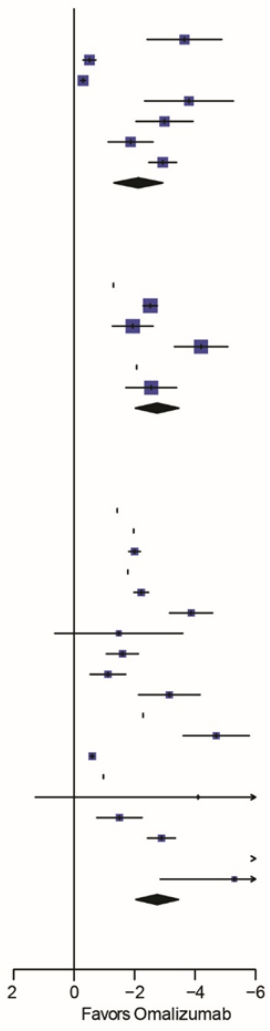


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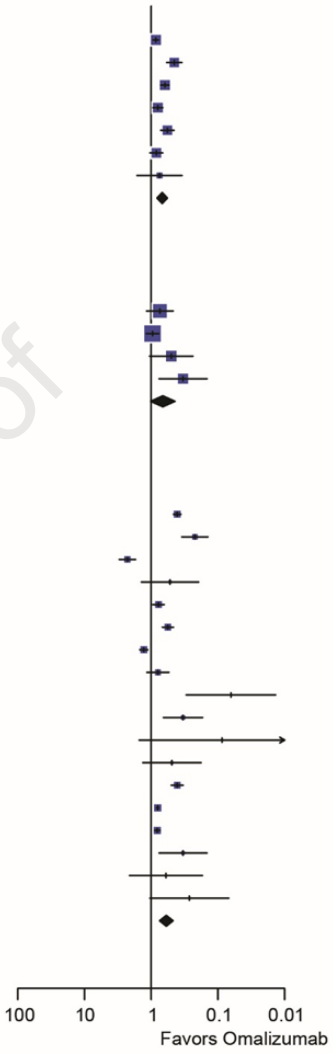
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Study or Subgroup	Post-Omalizumab Mean	SD	Total	Pre-Omalizumab Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
16 Weeks								
Jahnz-Rozyk 2018	2.98	3.25	85	6.63	4.83	85	13.4%	−3.65 [−4.89; −2.41]
Korn 2010	0.51	1.26	471	1.02	2.03	471	15.2%	−0.51 [−0.73; −0.29]
Kuprys Lipinska 2016	0.06	0.11	16	0.36	0.14	16	15.2%	−0.30 [−0.39; −0.21]
Molimard 2010	1.90	3.88	152	5.70	8.28	148	12.7%	−3.80 [−5.27; −2.33]
Schumann 2012	1.00	1.87	195	3.99	6.49	195	14.1%	−2.99 [−3.94; −2.04]
Tzortzaki 2012	0.40	0.81	60	2.27	2.82	60	14.5%	−1.87 [−2.61; −1.13]
Vennera Mdel 2012	0.67	1.20	229	3.60	3.60	263	14.9%	−2.93 [−3.39; −2.47]
Total (95% CI)			**1208**			**1238**	**100.0%**	**−2.13 [−2.94; −1.32]**
Heterogeneity: Tau² = 1.0238; Chi² = 209.49, df = 6 (P < 0.01); I² = 97%								
Test for overall effect: Z = −5.14 (P < 0.01)								
6 Months								
Alfarroba 2014	1.83	0.00	23	3.13	0.00	26	0.0%	−1.30
Casale 2018	0.48	0.96	795	3.00	3.28	804	26.0%	−2.52 [−2.76; −2.28]
Costello 2011	1.24	1.50	63	3.18	2.30	63	25.1%	−1.94 [−2.62; −1.26]
Korn 2009	0.30	0.80	241	4.50	7.50	280	24.4%	−4.20 [−5.08; −3.32]
Odajima 2015	0.92	0.00	38	2.99	0.00	38	0.0%	−2.07
Subramaniam 2013	0.93	0.83	30	3.48	2.20	30	24.5%	−2.55 [−3.39; −1.71]
Total (95% CI)			**1190**			**1241**	**100.0%**	**−2.75 [−3.47; −2.02]**
Heterogeneity: Tau² = 0.4232; Chi² = 16.54, df = 3 (P < 0.01); I² = 82%								
Test for overall effect: Z = −7.45 (P < 0.01)								
12 Months								
Alfarroba 2014	1.70	0.00	23	3.13	0.00	26	0.0%	−1.43
Barnes 2013	1.70	0.00	136	3.67	0.00	136	0.0%	−1.97
Braunstahl 2013a	0.20	0.60	691	2.20	2.81	842	8.3%	−2.00 [−2.20; −1.80]
Brusselle 2009	0.95	0.00	130	2.73	0.00	130	0.0%	−1.78
Casale 2018	0.78	1.37	796	3.00	3.28	804	8.3%	−2.22 [−2.47; −1.97]
Cazzola 2010	1.00	1.29	93	4.87	4.00	139	7.9%	−3.87 [−4.58; −3.16]
Dal Negro 2011a	0.52	3.67	23	2.00	3.67	23	5.9%	−1.48 [−3.60; 0.64]
Dal Negro 2011b	0.50	0.70	23	2.10	1.10	23	8.1%	−1.60 [−2.13; −1.07]
Dal Negro 2012	0.94	0.46	16	2.06	1.12	16	8.0%	−1.12 [−1.71; −0.53]
Deschildre 2013	1.25	3.42	92	4.40	3.87	104	7.6%	−3.15 [−4.17; −2.13]
Gemicioglu 2016	0.29	0.00	17	2.57	0.00	17	0.0%	−2.28
Jahnz-Rozyk 2018	1.93	1.83	85	6.63	4.83	85	7.5%	−4.70 [−5.80; −3.60]
Ke 2018	0.60	0.75	1564	1.20	1.14	1564	8.3%	−0.60 [−0.67; −0.53]
Niven 2016	0.69	0.00	218	1.66	0.00	218	0.0%	−0.97
Steiss 2015	0.40	1.50	9	4.50	8.10	9	2.3%	−4.10 [−9.48; 1.28]
Tzortzaki 2012	0.77	0.94	60	2.27	2.82	60	7.9%	−1.50 [−2.25; −0.75]
Vennera Mdel 2012	0.71	1.30	225	3.60	3.60	263	8.1%	−2.89 [−3.36; −2.42]
Vennera Mdel 2016	3.05	4.12	71	10.77	5.94	71	6.6%	−7.72 [−9.40; −6.04]
Vieira 2014	2.20	1.50	14	7.50	4.60	15	5.3%	−5.30 [−7.76; −2.84]
Total (95% CI)			**4286**			**4545**	**100.0%**	**−2.75 [−3.46; −2.04]**
Heterogeneity: Tau² = 1.4598; Chi² = 593.72, df = 13 (P < 0.01); I² = 98%								
Test for overall effect: Z = −7.61 (P < 0.01)								

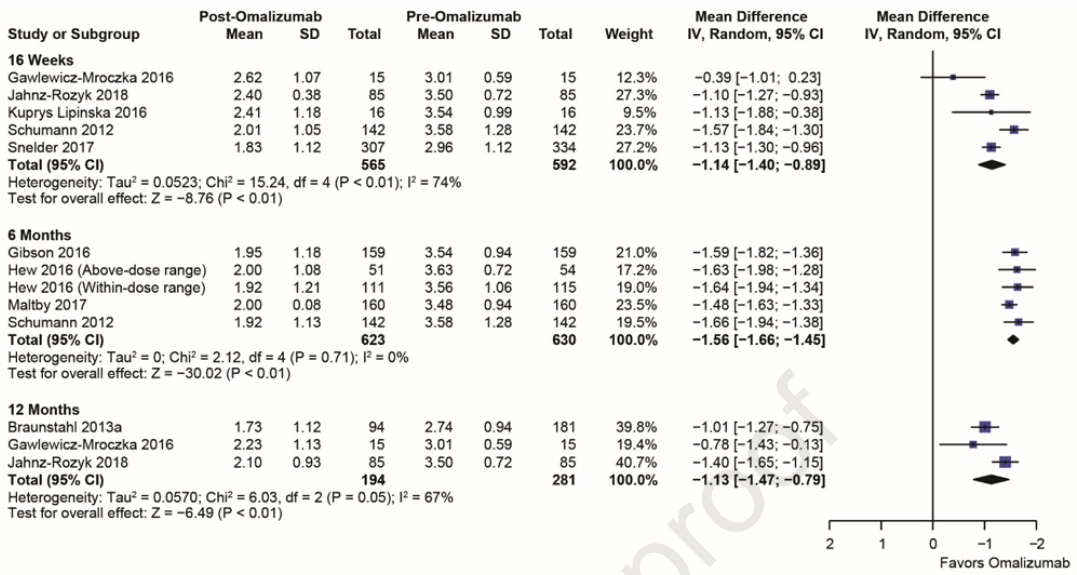


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Study or Subgroup	Post-Omalizumab Events	Total	Pre-Omalizumab Events	Total	Weight	Risk Ratio IV, Random, 95% CI
16 Weeks/4 Months						
Adachi 2018	581	3593	683	3593	16.5%	0.85 [0.77; 0.94]
Al-Ahmad 2018a	29	65	65	65	14.5%	0.45 [0.34; 0.59]
Chen 2016	91	158	146	158	16.1%	0.62 [0.54; 0.72]
Molimard 2010	132	346	166	346	15.8%	0.80 [0.67; 0.95]
Schumann 2012	64	195	112	195	15.0%	0.57 [0.45; 0.72]
Snelder 2017	93	334	121	364	15.1%	0.84 [0.67; 1.05]
Vieira 2014	6	15	8	15	7.0%	0.75 [0.34; 1.64]
Total (95% CI)		**4706**		**4736**	**100.0%**	**0.68 [0.57; 0.82]**
Heterogeneity: $Tau^2 = 0.0430$; $Chi^2 = 34.93$, df = 6 (P < 0.01); $I^2 = 83\%$						
Test for overall effect: Z = −4.14 (P < 0.01)						
6 Months						
Costello 2011	20	63	27	63	28.1%	0.74 [0.47; 1.17]
Gibson 2016	80	168	84	168	37.7%	0.95 [0.76; 1.19]
Subramaniam 2013	7	30	14	30	18.1%	0.50 [0.24; 1.06]
Velling 2011	4	13	12	13	16.1%	0.33 [0.15; 0.76]
Total (95% CI)		**274**		**274**	**100.0%**	**0.67 [0.44; 1.02]**
Heterogeneity: $Tau^2 = 0.1067$; $Chi^2 = 8.21$, df = 3 (P = 0.04); $I^2 = 63\%$						
Test for overall effect: Z = −1.88 (P = 0.06)						
12 Months						
Adachi 2018	278	3593	683	3593	8.8%	0.41 [0.36; 0.46]
Al-Ahmad 2018a	14	65	65	65	6.2%	0.22 [0.14; 0.35]
Ayres 2004	99	191	47	206	7.7%	2.27 [1.71; 3.02]
Barbosa 2015	5	54	11	62	2.8%	0.52 [0.19; 1.41]
Barnes 2013	70	136	90	136	8.3%	0.78 [0.64; 0.95]
Braunstahl 2013a	118	734	262	916	8.4%	0.56 [0.46; 0.68]
Brusselle 2009	106	130	100	158	8.7%	1.29 [1.12; 1.49]
Cazzola 2010	27	93	52	142	6.8%	0.79 [0.54; 1.16]
Dal Negro 2011a	1	23	23	23	1.4%	0.06 [0.01; 0.30]
Dal Negro 2012	5	16	16	16	4.4%	0.33 [0.17; 0.66]
Deschildre 2013	0	92	6	104	0.5%	0.09 [0.00; 1.52]
Gouder 2015	4	20	9	22	2.7%	0.49 [0.18; 1.34]
Humbert 2018	99	723	243	723	8.3%	0.41 [0.33; 0.50]
Ke 2018	1039	1564	1303	1564	9.1%	0.80 [0.76; 0.83]
Lafeuille 2013	315	801	1479	3044	8.9%	0.81 [0.74; 0.89]
Velling 2011	4	13	12	13	3.5%	0.33 [0.15; 0.76]
Verma 2011	3	17	5	17	1.9%	0.60 [0.17; 2.12]
Vieira 2014	2	14	8	15	1.7%	0.27 [0.07; 1.05]
Total (95% CI)		**8279**		**10819**	**100.0%**	**0.59 [0.47; 0.75]**
Heterogeneity: $Tau^2 = 0.1627$; $Chi^2 = 335.71$, df = 17 (P < 0.01); $I^2 = 95\%$						
Test for overall effect: Z = −4.45 (P < 0.01)						



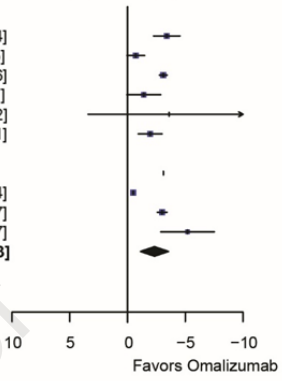
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Study or Subgroup	Post-Omalizumab Mean	SD	Total	Pre-Omalizumab Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
12 Months								
Adachi 2018	2.00	12.14	2398	5.40	26.23	2398	12.0%	−3.40 [−4.56; −2.24]
Barnes 2013	3.82	3.25	136	4.54	3.27	136	12.7%	−0.72 [−1.49; 0.05]
Braunstahl 2014	0.70	1.48	684	3.80	4.73	823	13.3%	−3.10 [−3.44; −2.76]
Brusselle 2009	3.72	6.09	105	5.13	4.77	105	11.3%	−1.41 [−2.89; 0.07]
Dal Negro 2011a	0.14	1.90	23	3.74	17.06	23	2.6%	−3.60 [−10.62; 3.42]
Dal Negro 2012	1.42	0.67	16	3.38	2.03	16	12.3%	−1.96 [−3.01; −0.91]
Gouder 2015	6.90	0.00	18	21.60	0.00	18	0.0%	−14.70
Jahnz-Rozyk 2018	1.84	0.00	85	4.95	0.00	85	0.0%	−3.11
Ke 2018	0.50	0.73	1564	1.00	1.06	1564	13.4%	−0.50 [−0.56; −0.44]
Niven 2016	1.60	2.07	218	4.60	2.48	218	13.2%	−3.00 [−3.43; −2.57]
Vieira 2014	0.90	1.30	14	6.10	4.40	15	9.2%	−5.20 [−7.53; −2.87]
Total (95% CI)			**5261**			**5401**	**100.0%**	**−2.34 [−3.54; −1.13]**

Heterogeneity: $Tau^2 = 2.8059$; $Chi^2 = 378.22$, df = 8 ($P < 0.01$); $I^2 = 98\%$
Test for overall effect: $Z = -3.79$ ($P < 0.01$)



Journal Pre-proof