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Omalizumab for asthma in adults and children (Review)

Normansell R, Walker S, Milan SJ, Walters EH, Nair P

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[Intervention Review]

Omalizumab for asthma in adults and children

Rebecca Normansell[1], Samantha Walker[2,3], Stephen J Milan[1], E. Haydn Walters[4], Parameswaran Nair[5,6]

[1]Population Health Sciences and Education, St George's, University of London, London, UK. [2]Asthma UK, London, UK. [3]Centre for Population Health Sciences, University of Edinburgh Medical School, Edinburgh, UK. [4]NHMRC CRE for Chronic Respiratory Disease, School of Medicine, University of Tasmania, Hobart, Australia. [5]Firestone Institute for Respiratory Health, McMaster University, Hamilton, Canada. [6]St Joseph's Healthcare, Hamilton, Canada

Contact: Samantha Walker, Asthma UK, London, UK. swalker@asthma.org.uk.

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ABSTRACT

Background

Asthma is a respiratory (airway) condition that affects an estimated 300 million people worldwide and is associated with significant morbidity and mortality. Omalizumab is a monoclonal antibody that binds and inhibits free serum immunoglobulin E (IgE). It is called an 'anti-IgE' drug. IgE is an immune mediator involved in clinical manifestations of asthma. A recent update of National Institute for Health and Care Excellence (NICE) guidance in 2013 recommends omalizumab for use as add-on therapy in adults and children over six years of age with inadequately controlled severe persistent allergic IgE-mediated asthma who require continuous or frequent treatment with oral corticosteroids.

Objectives

To assess the effects of omalizumab versus placebo or conventional therapy for asthma in adults and children.

Search methods

We searched the Cochrane Airways Group Specialised Register of trials for potentially relevant studies. The most recent search was performed in June 2013. We also checked the reference lists of included trials and searched online trial registries and drug company websites.

Selection criteria

Randomised controlled trials examining anti-IgE administered in any manner for any duration. Trials with co-interventions were included, as long as they were the same in each arm.

Data collection and analysis

Two review authors independently assessed study quality and extracted and entered data. Three modes of administration were identified from the published literature: inhaled, intravenous and subcutaneous injection. The main focus of the updated review is subcutaneous administration, as this route is currently used in clinical practice. Subgroup analysis was performed by asthma severity. Data were extracted from published and unpublished sources.

Main results

In all, 25 trials were included in the review, including 11 new studies since the last update, for a total of 19 that considered the efficacy of subcutaneous anti-IgE treatment as an adjunct to treatment with corticosteroids.

For participants with moderate or severe asthma who were receiving background inhaled corticosteroid steroid (ICS) therapy, a significant advantage favoured subcutaneous omalizumab with regard to experiencing an asthma exacerbation (odds ratio (OR) 0.55, 95% confidence interval (CI) 0.42 to 0.60; ten studies, 3261 participants). This represents an absolute reduction from 26% for participants suffering an exacerbation on placebo to 16% on omalizumab, over 16 to 60 weeks. A significant benefit was noted for subcutaneous omalizumab versus placebo with regard to reducing hospitalisations (OR 0.16, 95% CI 0.06 to 0.42; four studies, 1824 participants), representing an absolute reduction in risk from 3% with placebo to 0.5% with omalizumab over 28 to 60 weeks. No separate data on hospitalisations were available for the severe asthma subgroup, and all of these data were reported for participants with the diagnosis of moderate to severe asthma. Participants treated with subcutaneous omalizumab were also significantly more likely to be able to withdraw their ICS completely than those treated with placebo (OR 2.50, 95% CI 2.00 to 3.13), and a small but statistically significant reduction in daily inhaled steroid dose was reported for omalizumab-treated participants compared with those given placebo (weighted mean difference (WMD) -118 mcg beclomethasone dipropionate (BDP) equivalent per day, 95% CI -154 to -84). However, no significant difference between omalizumab and placebo treatment groups was seen in the number of participants who were able to withdraw from oral corticosteroid (OCS) therapy (OR 1.18, 95% CI 0.53 to 2.63).

Participants treated with subcutaneous omalizumab as an adjunct to treatment with corticosteroids required a small but significant reduction in rescue beta$_2$-agonist medication compared with placebo (mean difference (MD) -0.39 puffs per day, 95% CI -0.55 to -0.24; nine studies, 3524 participants). This benefit was observed in both the moderate to severe (MD -0.58, 95% CI -0.84 to -0.31) and severe (MD -0.30, 95% CI -0.49 to -0.10) asthma subgroups on a background therapy of inhaled corticosteroids; however, no significant difference between subcutaneous omalizumab and placebo was noted for this outcome in participants with severe asthma who were receiving a background therapy of inhaled plus oral corticosteroids. Significantly fewer serious adverse events were reported in participants assigned to subcutaneous omalizumab than in those receiving placebo (OR 0.72, 95% CI 0.57 to 0.91; 15 studies, 5713 participants), but more injection site reactions were observed (from 5.6% with placebo to 9.1% with omalizumab).

To reflect current clinical practice, discussion of the results is limited to subcutaneous use, and trials involving intravenous and inhaled routes have been archived.

Authors' conclusions

Omalizumab was effective in reducing asthma exacerbations and hospitalisations as an adjunctive therapy to inhaled steroids and during steroid tapering phases of clinical trials. Omalizumab was significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their inhaled steroids. Omalizumab was generally well tolerated, although more injection site reactions were seen with omalizumab. Further assessment in paediatric populations is necessary, as is direct double-dummy comparison with ICS. Although subgroup analyses suggest that participants receiving prednisolone had better asthma control when they received omalizumab, it remains to be tested prospectively whether the addition of omalizumab has a prednisolone-sparing effect. It is also not clear whether there is a threshold level of baseline serum IgE for optimum efficacy of omalizumab. Given the high cost of the drug, identification of biomarkers predictive of response is of major importance for future research.

PLAIN LANGUAGE SUMMARY

Omalizumab for chronic asthma in adults and children

Review question

We reviewed the evidence for the effect of omalizumab on people with asthma when compared with placebo. We focused on whether omalizumab is a beneficial but safe treatment for adults and children with asthma.

Background

Asthma is a respiratory condition that affects millions of people worldwide. It is thought that allergy may be an important part of the disease for many people with asthma. Omalizumab is a drug that targets a protein, called IgE, and removes it from free circulation in the body. IgE is centrally involved in allergy. Omalizumab is an expensive drug that is usually given by injection under the skin every two to four weeks. It is licenced for use in asthma sufferers who are not being adequately treated with standard therapy and who require frequent courses or continuous use of oral steroid tablets. We looked for evidence on whether administration of omalizumab is better or worse than giving placebo.

Study characteristics

Twenty-five studies, involving 6382 people, were included in this review. These studies lasted between eight and 60 weeks. All of the people included in the studies had asthma, of different severity. Both men and women were included, and some of the studies included children and young people.

All studies compared omalizumab versus placebo. In keeping with current medical practice, most studies (21 of 25) used omalizumab given by injection under the skin. Some of the older studies used omalizumab injected into a vein or given by inhalation. The evidence presented here is current to June 2013. Most of the studies were sponsored by the pharmaceutical industry.

Key results

We found that people receiving omalizumab were less likely to have a flare-up ('exacerbation') of their asthma. For example, on average, 26 of 100 people who were receiving placebo (over a 16 to 60-week period) had an exacerbation compared with an average of 16 of 100 people receiving omalizumab.

People receiving omalizumab were also more likely to be able to reduce the doses of inhaled steroids. For example, on average, 21 of 100 people with moderate or severe asthma who were receiving placebo were able to completely stop their inhaled steroids (over a 28 to 32-week period) compared with an average of 40 of 100 receiving omalizumab.

People receiving omalizumab also experienced improvement in their asthma symptoms and in their health-related quality of life.

People receiving omalizumab were no more or less likely to have unwanted side effects overall. However, people receiving omalizumab were more likely to have skin reactions at the site of the injection.

Perhaps unfortunately, many of the trials in this review included participants with moderate asthma, and this drug is not licenced for this group. More trials need to focus on whether this drug is effective in people with the most severe asthma; evidence for efficacy in this group is poor, in spite of current guidelines.

Quality of the evidence

The evidence presented in this review is generally of moderate quality. Most of the studies did not clearly explain how investigators decided which people would receive omalizumab and which would receive placebo, and this decision is an important part of well-conducted studies.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid) for asthma in adults and children

Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid) for asthma in adults and children

Patient or population: adults and children with asthma
Settings:
Intervention: subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Subcutaneous omalizumab+ steroid versus placebo + steroid (stable steroid)				
Number of participants with at least one exacerbation **All asthmatic participants (16 to 60 weeks)**	**262 per 1000**	**163 per 1000** (130 to 176)	**OR 0.55** (0.46 to 0.65)	3261 (10 studies)	⊕⊕⊕⊖ **moderate** [1]	
Number of participants with at least one exacerbation **Moderate to severe asthma (16 to 60 weeks)**	**274 per 1000**	**159 per 1000** (137 to 185)	**OR 0.5** (0.42 to 0.6)	2889 (7 studies)	⊕⊕⊕⊖ **moderate** [1]	
Number of participants with at least one exacerbation **Severe asthma (16 to 32 weeks)**	**145 per 1000**	**145 per 1000** (78 to 252)	**OR 1** (0.5 to 1.99)	277 (2 studies)	⊕⊕⊖⊖ **low** [2]	
Mortality **16 to 60 weeks**	**2 per 1000**	**0 per 1000** (0 to 3)	**OR 0.19** (0.02 to 1.67)	4245 (9 studies)	⊕⊕⊖⊖ **low** [3,4]	
Hospitalisations **28 to 60 weeks**	**31 per 1000**	**5 per 1000** (2 to 13)	**OR 0.16** (0.06 to 0.42)	1824 (4 studies)	⊕⊕⊕⊖ **moderate** [5]	

Adverse event—serious **16 to 60 weeks**	**64 per 1000**	**47 per 1000** (37 to 58)	**OR 0.72** (0.57 to 0.91)	5713 (15 studies)	⊕⊕⊕⊖ **moderate** [6]

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]A point was deducted for risk of bias to reflect the fact that most studies scored UNCLEAR on both sequence generation and allocation concealment.
[2]A point was deducted for risk of bias to reflect the fact that only one of the two trials scored LOW on both sequence generation and allocation concealment. The remaining trial scored UNCLEAR on both sequence generation and allocation concealment. An additional point was deducted because of the imprecision of the results.
[3]A point was deducted for risk of bias to reflect the fact that only two of the nine trials scored LOW on both sequence generation and allocation concealment. Most (five) scored UNCLEAR on both sequence generation and allocation concealment.
[4]An additional point was deducted to reflect that a death occurred in only two of the nine trials; therefore, the contribution of most of the trials (seven) was non-estimable.
[5]A point was deducted for risk of bias to reflect the fact that only one of the four trials scored LOW on both sequence generation and allocation concealment.
[6]A point was deducted for risk of bias to reflect the fact that only two of the 15 trials scored LOW on both sequence generation and allocation concealment. Most (10) scored UNCLEAR on both sequence generation and allocation concealment.

Summary of findings 2. Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction) for asthma in adults and children

Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction) for asthma in adults and children

Patient or population: adults and children with asthma
Settings:
Intervention: subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Subcutaneous omalizumab+ steroid versus placebo + steroid (steroid reduction)				
Number of participants achieving complete inhaled steroid withdrawal	**212 per 1000**	**402 per 1000** (350 to 457)	**OR 2.5** (2 to 3.13)	1634 (4 studies)	⊕⊕⊖⊖ **low** [1]	

28 to 32 weeks					
>50% reduction in inhaled steroid usage 28 to 32 weeks	**560 per 1000**	**761 per 1000** (720 to 798)	**OR 2.5** (2.02 to 3.1)	1634 (4 studies)	⊕⊕⊕⊖ **moderate** [2]
Exacerbations requiring hospitalisation **28 weeks**	**20 per 1000**	**3 per 1000** (1 to 11)	**OR 0.11** (0.03 to 0.48)	1405 (3 studies)	⊕⊕⊕⊖ **moderate** [3]

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Point deducted, as only two of the four included studies scored LOW on both sequence generation and allocation concealment in the risk of bas assessment. An additional point was deducted to reflect the level of heterogeneity (I^2 = 35%).
[2]Point deducted as only two of the four included studies scored LOW on both sequence generation and allocation concealment in the risk of bas assessment.
[3]Point deducted as only one of the three included studies scored LOW on both sequence generation and allocation concealment in the risk of bas assessment.

BACKGROUND

Description of the condition

Asthma is an airway disease that currently affects an estimated 300 million people worldwide and is associated with significant mortality and morbidity. It is a heterogenous disease characterised by recurrent dyspnoea, wheezing, cough and chest tightness and usually is associated with reversible airflow obstruction and airway hyperresponsiveness (Pelaia 2011). Active asthma accelerates the development of fixed airflow obstruction (Perret 2013). The mainstay of modern treatment has been the use of inhaled steroids and bronchodilator drugs. Although this approach has been useful in the management of mild and moderate forms of the disease, patients with severe asthma sometimes require oral steroids and other immunosuppressive regimens with their attendant side effects (Thomson 2012). In addition, people with poorly controlled asthma, even in spite of treatment, are at increased risk of hospitalisation and emergency room visits (Chipps 2012). Although this group accounts for only around 5% of people with asthma, it contributes to approximately 80% of the economic costs of asthma; therefore novel therapies have been developed for optimal treatment of these patients. It is estimated that more than 50% of people with poorly controlled asthma have allergic immunoglobulin E (IgE)-mediated asthma and therefore may benefit from treatments targeted at IgE.

It is becoming increasingly apparent that 'asthma' is not a single condition but rather a collection of symptoms caused by different mechanisms (Haldar 2008). This heterogeneity in asthma expression appears to be multi-dimensional, including variability in clinical, physiological, age of onset and pathological parameters. Confirmation of evidence of distinct and different combinations of symptom expression and underlying inflammation may require a different approach to therapeutic intervention that may clarify the role of omalizumab in clinical guidelines in the future.

Description of the intervention

Immunoglobulin E (IgE) plays a central role in the development of allergic diseases, including allergic asthma (Thomson 2012). In atopic (allergic) individuals, initial exposure/sensitisation to an allergen initiates a complex series of events, leading to the production of allergen-specific IgE. The IgE becomes attached to inflammatory cells such as mast cells (in particular), basophils and macrophages via its Fc portion linking with Fc receptors. Further allergen exposure leads to cross-bridging between allergen and IgE on the surface of these effector cells (Spector 1999; Wills-Karp 1999). This results in degranulation of mast cells and basophils, leading to the release of proinflammatory mediators such as histamine, prostaglandins, leukotrienes, chemokines and cytokines. In some people with allergic asthma, higher than normal IgE levels may increase persistent airway inflammation and bronchial hyperresponsiveness (Burrows 1989; Sears 1991), presumably through ongoing chronic allergic activation of this complex system. Indeed, the level of circulating IgE to common allergens is a risk factor for emergency admissions with asthma (Thomson 2012). It is these people with high levels of IgE who have been featured in omalizumab studies conducted to date.

Omalizumab has been licenced for use since 2003 in the United States for people with moderate to severe asthma over the age of 12 years whose condition is inadequately controlled by inhaled corticosteroids. The European Medicines Agency followed suit in 2005 and more recently has approved the use of omalizumab in children six years of age and older (Pelaia 2011). In 2006, omalizumab was included as an add-on treatment in Step 5 and above of the Global Initiative for Asthma (GiNA) guidelines (GiNA 2011). In April 2013, updated National Institute for Health and Care Excellence (NICE) guidance suggested that omalizumab can be used in adults and children over six years of age with inadequately controlled severe persistent allergic IgE-mediated asthma who require continuous or frequent treatment with oral corticosteroids (usually accompanied by high-dose inhaled corticosteroid) (NICE 2013). Omalizumab usually is considered only for those with allergic asthma who are sensitised to at least one aeroallergen and have circulating IgE levels within the specified range for determination of dosing.

Omalizumab is recommended to be administered as a subcutaneous injection. The dose and frequency of dosing are guided by a nomogram that is derived from the total serum IgE level and the body mass index. This is based on evidence that total serum IgE is a good predictor of clinical symptoms of asthma and correlates fairly well with the total number of immune cells in the body (tissue and circulation) that have functional cross-linking Fc-epsilon receptors. However, it is not well established whether at least some individuals with low or normal total serum IgE may also respond to treatment with omalizumab. In other words, it is not certain whether the level or the activity of IgE is the better determinant of the clinical efficacy of omalizumab in an individual.

How the intervention might work

Omalizumab (also referred to in the literature as rhuMAb-E25, rhu-Mab or Xolair) is a recombinant humanised IgG1 monoclonal antibody that recognises IgE at the same Fc site as the high-affinity receptor binding site. This anti-IgE antibody forms complexes with free IgE, thus blocking the interaction between IgE and effector cells. Omalizumab treatment also appears to down-regulate the expression of high-affinity IgE receptors on effector cells (Thomson 2012). The complexes of omalizumab and IgE formed as a result of treatment are small and are not thought to be able to trigger complement activation or to give rise to immune complex–mediated pathology. Omalizumab has been shown to reduce serum concentrations of free IgE after a single injection, resulting in significant reductions in early and late asthmatic responses following allergen inhalation and improved asthma symptom control (Milgrom 1997). Recent studies also suggest that treatment with omalizumab may reduce eosinophilic airway inflammation and IgE-bearing cells, although effects on airway hyperresponsiveness and airway wall structural remodelling are less clear (Thomson 2012).

Why it is important to do this review

Omalizumab is a recent addition to the range of treatments available for asthma, but it is much more expensive than alternative asthma treatments. In the UK, national guidance (NICE 2013) states: "Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older: who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year), and only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme." Little

evidence has been found for this recommendation. Indeed, other international guidelines are less proscriptive and recommend this treatment for patients who remain suboptimally controlled after maximal therapy with a combination of inhaled corticosteroids and long-acting bronchodilators and other add-on therapies such as leukotriene antagonists, theophyllines or muscarinic antagonists.

To date, evidence is somewhat lacking about the efficacy of this drug in the more severe asthma population, as many trials include participants with mild or moderate disease. This review seeks to address whether omalizumab is safe and effective but with a particular emphasis on patients with more severe asthma—the group for whom the drug is licensed.

OBJECTIVES

To assess the effects of omalizumab versus placebo or conventional therapy for asthma in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

Only double-blind randomised controlled trials (RCTs) were considered for inclusion. In view of the uncertain washout period for this form of treatment and our interest in inhaled steroid withdrawal and exacerbations, we elected to exclude cross-over studies.

Types of participants

Adults and children with chronic asthma from all referral sources. We included studies in which populations were receiving maintenance therapy and those in which anti-IgE was administered without background therapy. These study populations were analysed separately.

The definitions of chronic asthma varied; both doctor-diagnosed cases and those identified with more objective criteria were considered. Distinctions were made among studies that differed in their definition, and when possible, subgroup analyses were performed on the basis of severity. We classified the studies according to the stepwise management plans recommended in CTS 2012, GiNA 2011 and BTS/SIGN 2012 guidelines.

Types of interventions

Anti-IgE therapy at any dose or route versus placebo.

Types of outcome measures

Primary outcomes

1. Asthma exacerbations as defined by "events", i.e. hospital admissions, emergency room visits, days lost from work/school, unscheduled doctor visits, increase in medication.
2. Reduction or termination of steroid (inhaled, oral, both) use from baseline or run-in period.

The order of the primary outcomes changed from protocol.

Secondary outcomes

1. Asthma symptoms.
2. Health-related quality of life.
3. Rescue medication use.
4. Measures of lung function: forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF).
5. Adverse events.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group's Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and through handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We searched all records in the CAGR using the search strategy described in Appendix 2.

We searched the Register from its inception to June 2013 with no restriction on language of publication.

Searching other resources

To identify relevant randomised controlled trials (RCTs), we:

1. checked the reference lists of all identified RCTs to identify potentially relevant studies;
2. contacted all pharmaceutical companies producing anti-IgE formulations and made enquiries about published and unpublished studies known to and/or supported by these companies;
3. examined the bibliographies of review articles and other selected articles;
4. sought data from online resources (e.g. www.fda.gov; www.clinicalstudyresults.org; http://www.novctrd.com; www.clinicaltrials.gov);
5. made personal contact with colleagues, collaborators and other trialists working in the field of asthma to identify other published and unpublished relevant studies; and
6. searched abstracts of studies presented at leading respiratory society meetings over the past three years to look for relevant studies.

Data collection and analysis

Selection of studies

Two review authors (SJM and PN) independently assessed abstracts and titles of references from search results. A list of potentially eligible references was agreed between the same two review authors, and these articles were retrieved. References were organised by study and were included or excluded on the basis of required prespecified characteristics.

Data extraction and management

Two independent review authors (SJM and either SW or RN) extracted data using a standard form developed before data were extracted. We sought missing information from study authors whenever possible.

Assessment of risk of bias in included studies

For the 2009 and 2013 updates of the review, we adopted the recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* for assessing the risk of bias in eligible studies (Cochrane Handbook). We judged the risk of bias (low, high or unclear) for each of the following potential sources of bias within each included study.

1. Allocation sequence generation.
2. Allocation concealment.
3. Blinding (all outcomes).
4. Handling of missing data (such as intention-to-treat analysis).
5. Selective reporting bias.
6. Other bias.

Previous methods are detailed in Differences between protocol and review.

Measures of treatment effect

For dichotomous variables, we calculated a fixed-effect odds ratio (OR) with 95% confidence interval (CI) for individual studies. We pooled dichotomous data from similar studies using fixed-effect ORs and 95% CIs. If significant heterogeneity ($P < 0.1$) was observed in continuous or dichotomous outcomes, we used random-effects modelling. For statistically significant ORs, we pooled control group event rates to generate a baseline risk (%). Control event rates and corresponding expected rates with omalizumab are shown in Summary of findings for the main comparison and Summary of findings 2 and are illustrated as Cates plots in Figure 1, Figure 2, Figure 3, Figure 4 and Figure 5 (generated by Visual Rx; www.nntonline.net).

Figure 1. In the control group, 26 of 100 people with moderate to severe asthma had an asthma exacerbation over a 16- to 60-week period, compared with 16 (95% CI 13 to 18) of 100 for the omalizumab group.

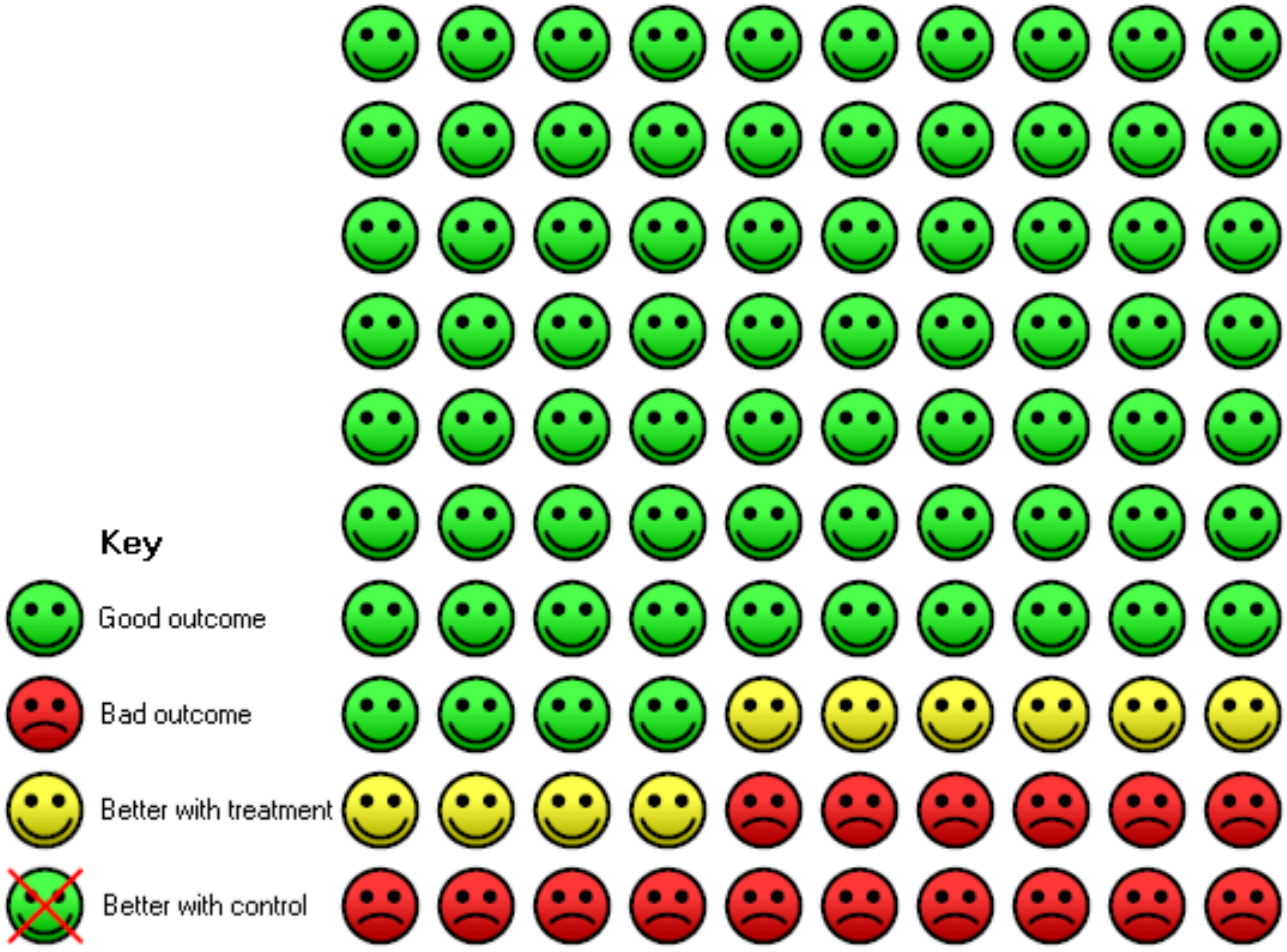


Figure 2. In the control group, three of 100 people with moderate to severe asthma had at least one hospitalisation over a 28- to 60-week period, compared with one (95% CI 0 to 1) of 100 for the omalizumab group.

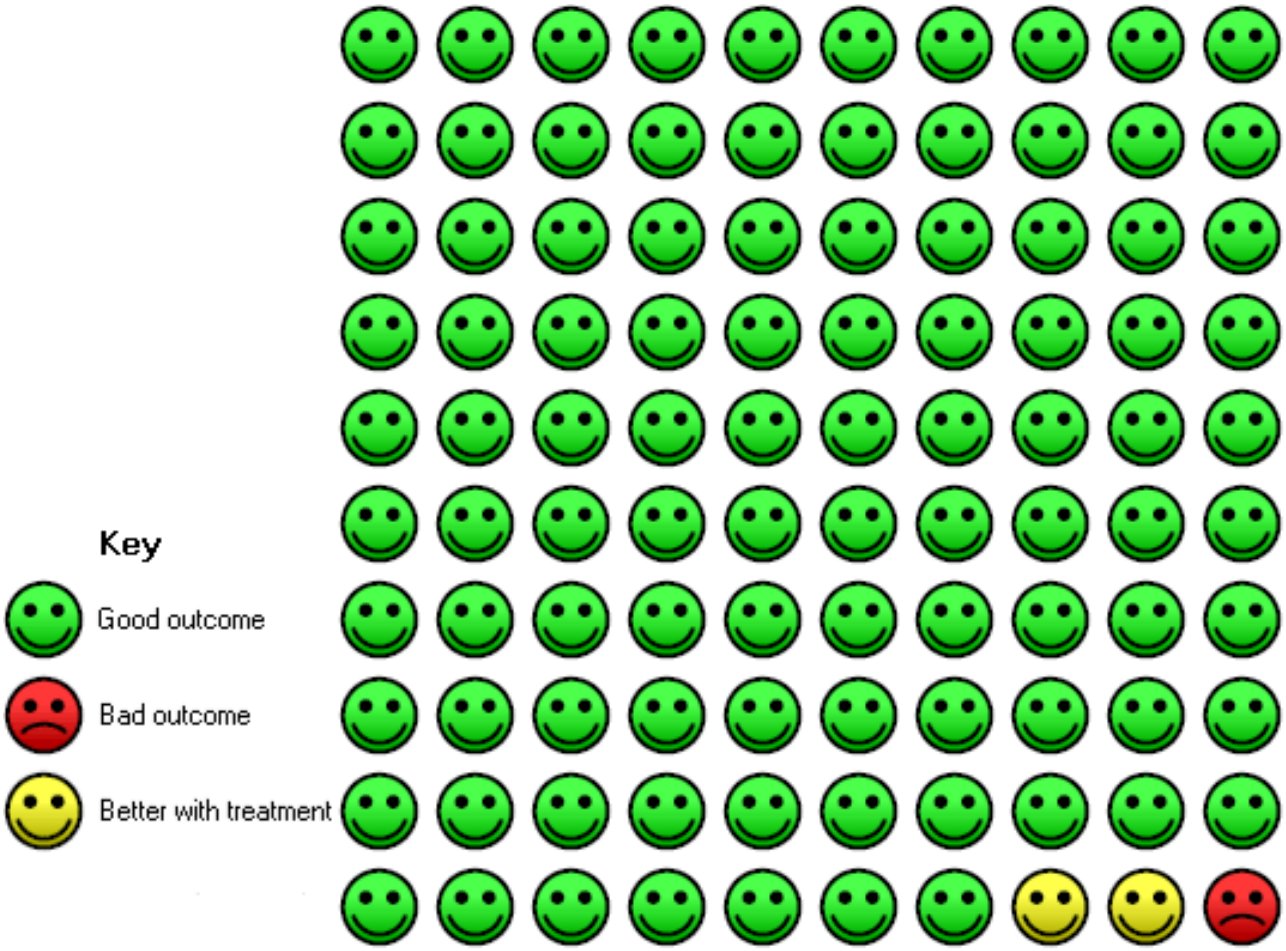


Figure 3. In the control group, 21 of 100 people with moderate or severe asthma were able to withdraw from treatment with inhaled corticosteroids completely (over a 28- to 32-week period) compared with 40 (95% CI 35 to 46) of 100 for the omalizumab group with tapering corticosteroids.

Figure 4. In the control group, six of 100 people with moderate to severe, or severe, asthma had at least one serious adverse event over a 16- to 60-week period compared with five (95% CI 4 to 6) of 100 for the omalizumab group.

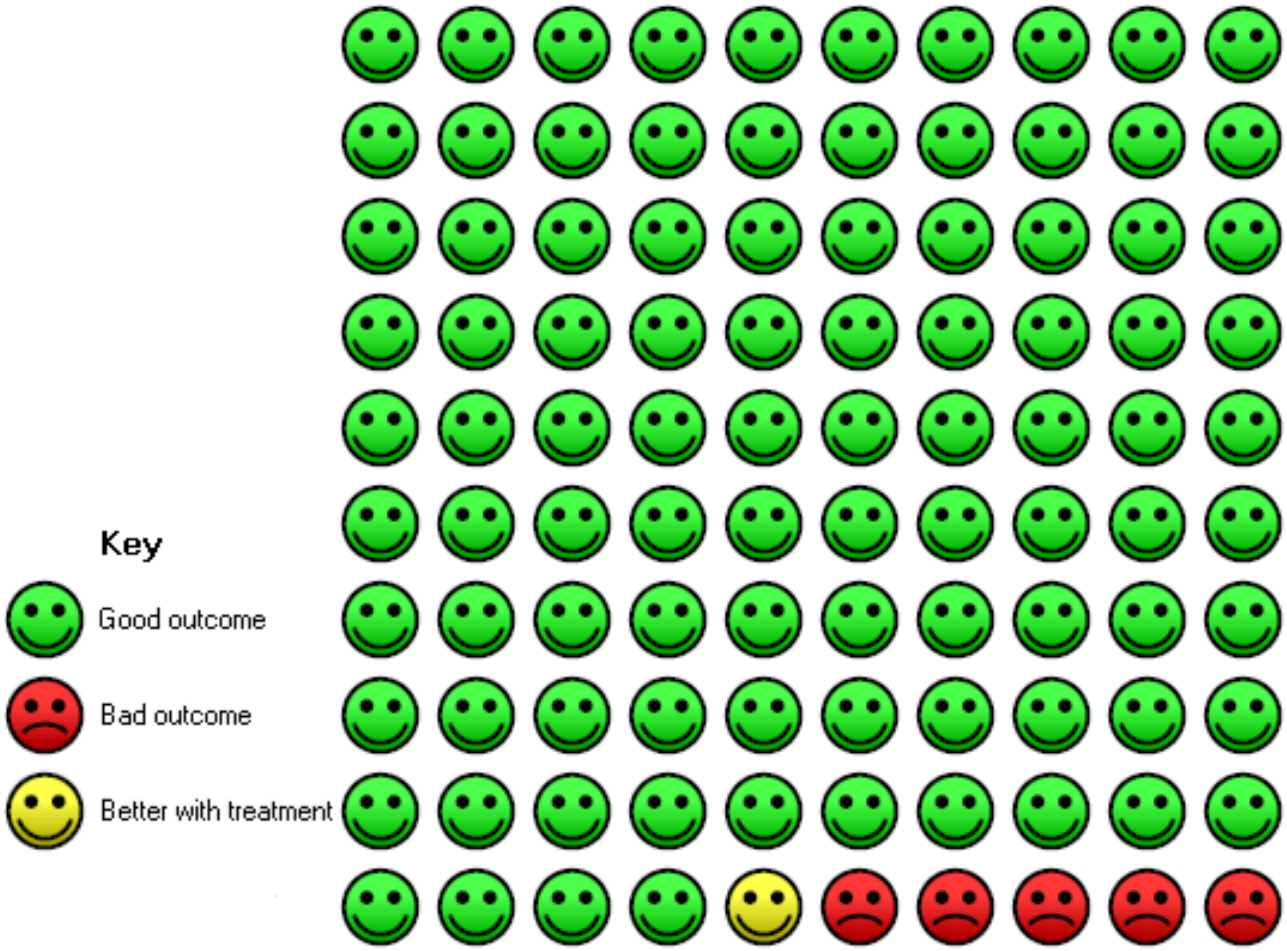
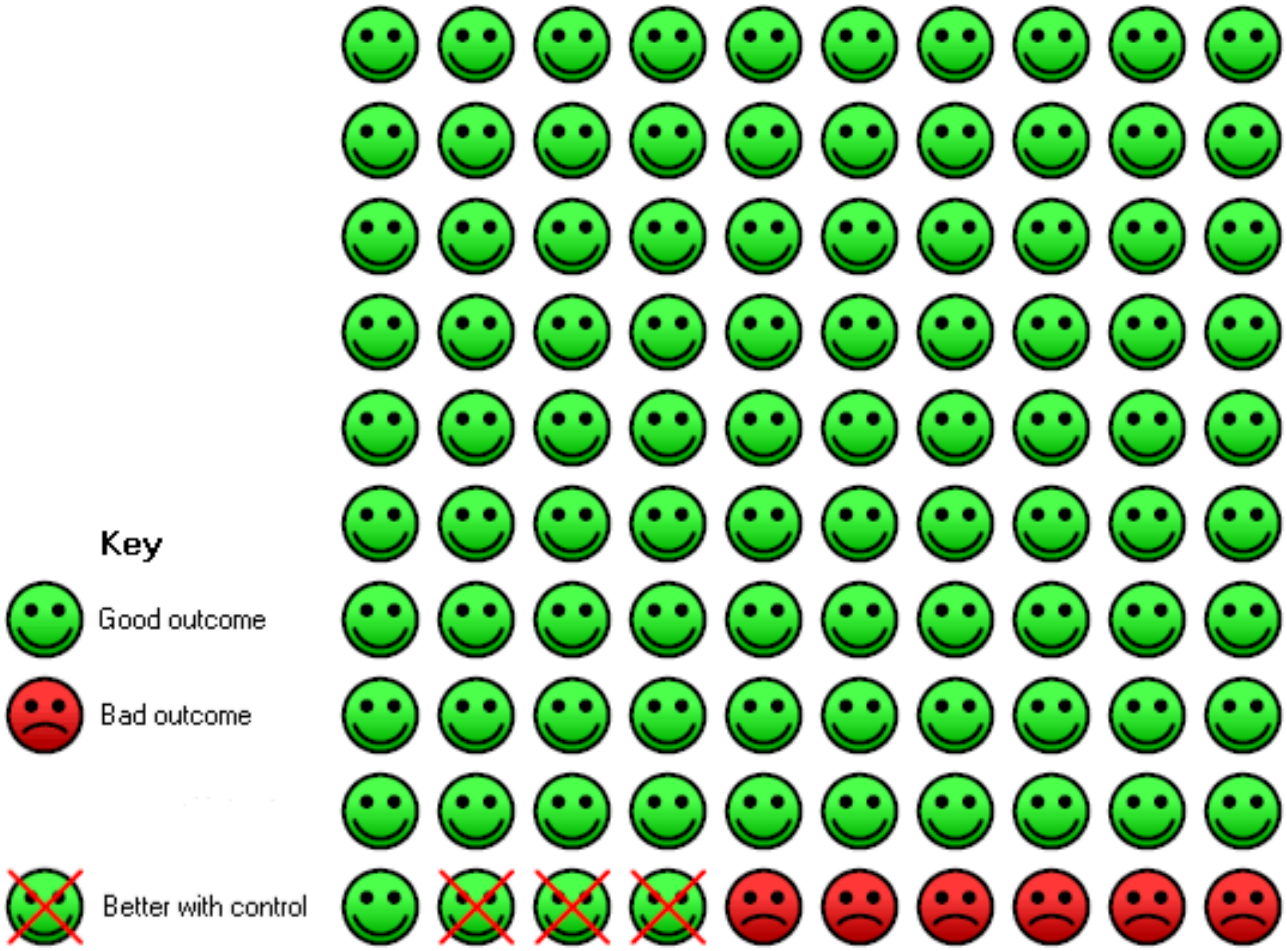


Figure 5. In the control group, six of 100 people with moderate to severe, or severe, asthma had an injection site reaction over a 16- to 60-week period compared with nine (95% CI 7 to 12) of 100 for the omalizumab group.



We identified dichotomous and continuous outcome measures in the trial reports. If primary outcomes were reported as dichotomous variables, we sought from trialists continuous data as means and standard deviations (SDs) or as medians and ranges, and analysed these as appropriate. For the 2013 update of the review, we included analysis of exacerbation rates per participant and analysed these as rate ratios.

Unit of analysis issues

The unit of analysis was the participant.

Dealing with missing data

If outcome data or information on trial design was missing, we attempted to contact authors for clarification.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of forest plots. I^2 was considered and interpreted in relation to the following guidance.

1. 0% to 40%: might not be important.
2. 30% to 60%: may represent moderate heterogeneity.
3. 50% to 90%: may represent substantial heterogeneity.
4. 75% to 100%: may represent considerable heterogeneity (Higgins 2011).

The Chi^2 test was similarly considered (P value < 0.10). We regarded I^2 as our primary measure of heterogeneity.

Assessment of reporting biases

We planned to perform funnel plots for our primary outcomes when the number of studies contributing data was greater than 10.

Data synthesis

We used RevMan 5.2 (RevMan 2012) to analyse data. For continuous variables, we calculated a fixed-effect mean difference (MD) (for variables reported or transformed to the same scale) or standardised mean difference (SMD) (when different scales were pooled) with 95% CIs for each study. We pooled continuous data from similar studies using fixed-effect MDs and 95% CIs.

Subgroup analysis and investigation of heterogeneity

We explored reasons for statistical heterogeneity. When I^2 exceeded 50%, we undertook random-effects modelling to assess whether adjustment for within- and between-study variations impacted the summary estimate. A priori subgroup analyses consisted of:

1. age (children or adults);
2. trial medication;
3. asthma severity;
4. asthma diagnostic entry criteria; and
5. duration of treatment.

Sensitivity analysis

We planned to conduct sensitivity analyses, if necessary, based on methodological quality and fixed-effect versus random-effects modelling.

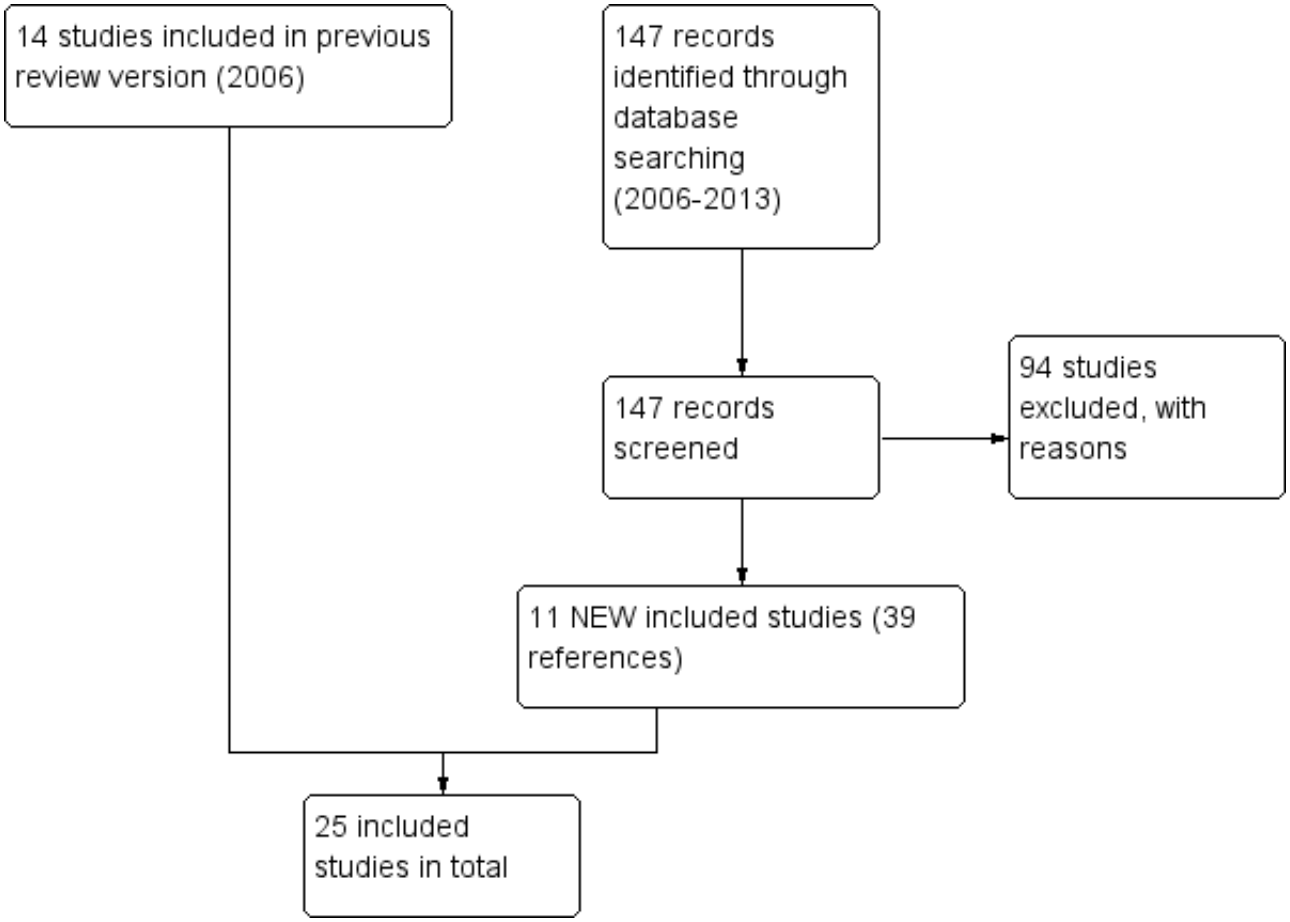
RESULTS

Description of studies

Results of the search

A total of 147 references were identified through electronic searches conducted in June 2013, producing 11 new studies eligible for inclusion. In addition to studies identified in previous versions of the review, this brought the total number of included studies up to 25 randomised, placebo-controlled clinical trials involving 6382 people with asthma (see Figure 6 for study flow diagram). Twenty-one studies involved omalizumab given by the subcutaneous route. For details of previous search results, please see Table 1.

Figure 6. Study flow diagram.



Included studies

Study design and duration

All trials were randomised and double-blind and of parallel-group design. Twenty-two were reported in full; details of two of the remaining trials were available as clinical trial reports on the clinicaltrials.gov system (NCT00096954; NCT01007149), and one was reported as a conference abstract (Garcia 2012). Study duration ranged from eight to 60 weeks. The trials fall broadly into three categories: those in which the background medication (referred to as 'steroid stable' if the background medication included a steroid) was unchanged, those with a steroid stable period followed by an attempt to reduce the background steroid dose ('steroid reduction') and those that sought to demonstrate a reduction in airway responsiveness to allergens after treatment with omalizumab.

Nineteen studies examined the efficacy of subcutaneous anti-IgE treatment as an adjunct to treatment with corticosteroids (Bardelas 2012; Busse 2001; Busse 2011; Chanez 2010; Garcia 2012; Gevaert 2012; Hanania 2011; Holgate 2004a; Holgate 2004b; INNOVATE; Lanier 2009; Massanari 2010; Milgrom 1999; Milgrom 2001; NCT00096954; NCT01007149; Ohta 2009; SOLAR; Solèr 2001). Beclomethasone dipropionate (BDP) was used as the background inhaled steroid in Busse 2001, Milgrom 2001 and Solèr 2001; two studies used high-dose fluticasone propionate (FP) (Holgate 2004a; Holgate 2004b), and another used budesonide (BUD) (SOLAR). In

Bardelas 2012; Busse 2011; Chanez 2010; Hanania 2011; INNOVATE; Lanier 2009; Massanari 2010; Milgrom 1999; NCT01007149 and Ohta 2009, participants remained on their current maintenance inhaled steroid. One study recruited a subgroup of oral steroid–dependent asthmatic participants (Holgate 2004b) for which data were published separately. Details of the background inhaled steroid used in Garcia 2012; Gevaert 2012 and NCT00096954 were not included in the trial report.

In ten studies, no changes were made to background inhaled corticosteroid (ICS) dosage (Bardelas 2012; Busse 2011; Chanez 2010; Hanania 2011; INNOVATE; Massanari 2010 NCT00096954; NCT01007149; Ohta 2009; SOLAR).

In five studies, participants received a stable dose of oral or inhaled corticosteroids for between 12 and 28 weeks; this was followed by an attempt to reduce the corticosteroid dose (Busse 2001; Holgate 2004a; Lanier 2009; Milgrom 2001; Solèr 2001). In earlier updates, in which data on ICS usage were reported, values were transformed to BDP equivalent values. Data on oral corticosteroid (OCS) usage were sought as mean dose or as dichotomised data related to the number of participants who had succeeded in reducing OCS use. Holgate 2004b reported data on OCS tapering only.

Boulet 1997; Djukanovic 2004; Fahy 1997; Fahy 1999; Prieto 2006 and van Rensen 2009 assessed the effects of omalizumab in the absence of any need for background steroid therapy.

Individual steroid doses are detailed in the table Characteristics of included studies.

Most of the included studies were sponsored by the pharmaceutical industry.

Route of administration

Three routes of drug administration were identified: inhaled, one trial (Fahy 1999); intravenous, three trials (Boulet 1997; Fahy 1997; Milgrom 1999); and subcutaneous injection, 21 trials (Bardelas 2012; Busse 2001; Busse 2011; Chanez 2010; Djukanovic 2004; Garcia 2012; Gevaert 2012; Hanania 2011; Holgate 2004a; Holgate 2004b; INNOVATE; Lanier 2009; Massanari 2010; Milgrom 2001; NCT00096954; NCT01007149; Ohta 2009; Prieto 2006; SOLAR; Solèr 2001; van Rensen 2009).

In all studies, anti-IgE was compared with placebo, although doses of omalizumab differed. The study using intravenous omalizumab in moderate to severe asthma compared high (5.8 mcg/kg/ng IgE/mL) and low (2.5 mcg/kg/ng IgE/mL) doses versus placebo (Milgrom 1999); in the two studies that considered intravenous omalizumab in mild asthma, the comparison was 1.0 mg/kg versus placebo (Boulet 1997) and 0.5 mg/kg versus placebo (Fahy 1997). Inhaled omalizumab was given at doses of 1 mg or 10 mg, and subcutaneous omalizumab at doses of 0.016 mg/kg/IU/mL every two to four weeks (Fahy 1999).

To reflect current clinical practice, discussion of the results is limited to subcutaneous use; trials involving intravenous and inhaled routes have been archived and can be found in Appendix 3.

Asthma severity and type

Participants with a diagnosis of allergic asthma were recruited in all trials, with the exception of Garcia 2012 (in which participants with severe non-allergic asthma were studied).

Adult and adolescent populations were assessed in Bardelas 2012; Busse 2001; Busse 2011; Hanania 2011; Holgate 2004a; Holgate 2004b; INNOVATE; Milgrom 1999; NCT00096954; Solèr 2001 and SOLAR, whereas Lanier 2009 and Milgrom 2001 recruited paediatric participants. Only adult participants were involved in Chanez 2010; Gevaert 2012; Massanari 2010; NCT01007149 and Ohta 2009. In Prieto 2006 and van Rensen 2009, the age of participants was unclear. SOLAR recruited participants with co-existing asthma and rhinitis. Adults with mild asthma were recruited to Boulet 1997; Djukanovic 2004; Fahy 1997 and Fahy 1999. Allergic and non-allergic patients with nasal polyps and asthma participated in Gevaert 2012.

Asthma severity varied within and between studies. Subgroup analyses were performed according to asthma severity (severe, moderate/severe and mild asthma) as defined by the review authors (Table 2). Data on asthma severity according to author and review author classification are shown in Table 2. Primary indicators of asthma severity were FEV_1 and baseline therapy. Our classification of severity is based on the stepwise guide to asthma management recommended in the BTS 2005 and BTS/SIGN 2012 guidelines. We examined baseline steroid requirements and FEV_1 (percentage predicted) to determine whether participants were largely mildly (step one of BTS 2005 and BTS/SIGN 2012), moderately (step two), moderately/severely (mixed population samples, step two/three) or severely asthmatic (step four and above). Following analysis of one participant population (Busse 2001), the review authors reclassified severity as moderate to severe (step two/three of BTS/SIGN 2012).

Studies deemed to include participants with mild asthma were Boulet 1997; Djukanovic 2004; Fahy 1997; Fahy 1999; Prieto 2006 and van Rensen 2009; with moderate/severe (step two/three) disease: Busse 2001; Busse 2011; Lanier 2009; Massanari 2010; Milgrom 1999; Milgrom 2001; NCT00096954; Ohta 2009; Solèr 2001 and SOLAR; and with severe (step four) disease: Bardelas 2012; Chanez 2010; Garcia 2012; Hanania 2011; Holgate 2004a; INNOVATE and NCT01007149. All of these studies recruited severe high-dose inhaled steroid–dependent participants. Holgate 2004b recruited participants who required high-dose ICS plus OCS to maintain asthma control and were classified as most severe (step five). We have undertaken analyses of exacerbations that both include and exclude the Holgate 2004b study. Allergic and non-allergic patients with nasal polyps and asthma participated in Gevaert 2012, but details of participant severity were not reported.

Entry criteria for all studies included positive skin tests to common aeroallergens. Threshold ranges of IgE levels were a stated inclusion criterion in all studies with the exception of Boulet 1997; Garcia 2012; Milgrom 1999 and NCT01007149. Baseline IgE levels are presented in Table 3.

Outcome measures

Outcome measures reported ICS or OCS withdrawal, mortality, asthma exacerbations, rescue medication use, lung function, quality of life, global evaluation of treatment effectiveness and adverse events. For each outcome, results are presented separately for any steroid stable phase (omalizumab given as adjunctive

therapy to inhaled corticosteroids) and steroid reduction phase (omalizumab given during steroid reduction).

Subgroup analysis

It was not possible to use the a priori subgroups as planned. Many studies included adults and children over 12 years of age but did not present results separately for the children. Only three studies focused exclusively on a paediatric or adolescent population (Lanier 2009 and Milgrom 2001 included children six to 12 years of age, and Busse 2011 included participants six to 20 years of age). Subgroups were analysed separately for route of delivery of the trial medication, but to reflect clinical practice, we have moved the results of the intravenous and inhaled subgroups to Appendix 3. An attempt was made to analyse the results according to asthma severity; this is discussed under each outcome, when possible. Asthma diagnostic entry criteria did not prove to be a useful subgroup, as all studies, with the exception of Garcia 2012, enrolled only participants with proven allergic asthma and IgE levels within the specified range. We did not attempt subgroup analysis for duration of treatment.

Excluded studies

One hundred ten studies failed to meet the eligibility criteria for our review. They are listed in Characteristics of excluded studies.

Forty-two (38%) of the excluded studies did not compare omalizumab versus placebo, a further 24 (22%) were non-randomised, 13 (12%) were not focused on participants with asthma, 10 (9%) were pooled analyses of trials, nine (8%) were review articles, six (5%) were open-label studies, three (3%) were not completed, two (2%) were cross-over trials and one (1%) was a letter.

Risk of bias in included studies

Allocation

Seven studies (29%) (Busse 2001; Djukanovic 2004; Hanania 2011; Holgate 2004a; Holgate 2004b; Ohta 2009; Solèr 2001) were assessed as having low risk of selection bias. The remaining 18 studies were categorised as having unclear risk (Figure 7).

Figure 7. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

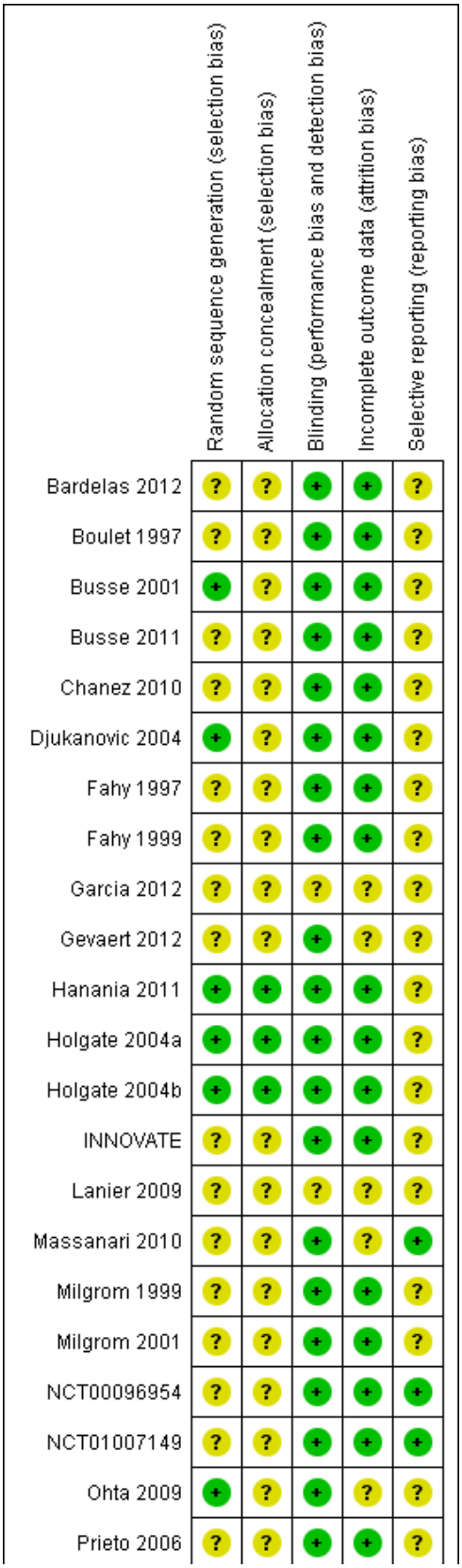
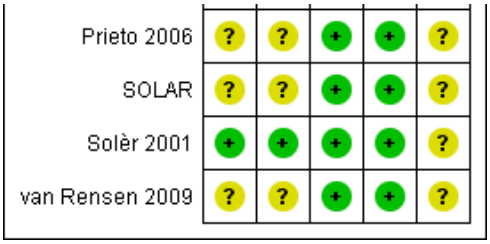


Figure 7. (Continued)



Blinding

Only four studies (17%) (Hanania 2011; Holgate 2004a; Holgate 2004b; Solèr 2001) were judged as having low risk of performance and detection bias. The remaining 21 studies were assessed as having unclear risk.

Incomplete outcome data

Twenty-three studies (96%) were viewed as having low risk of attrition bias, and only Lanier 2009 and Garcia 2012 were judged to be in the unclear category

Selective reporting

Three studies (13%) (Massanari 2010; NCT00096954; NCT01007149) were assessed as having low risk of reporting bias. The remaining 22 studies were categorised as having unclear risk.

Effects of interventions

See: **Summary of findings for the main comparison** Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid) for asthma in adults and children; **Summary of findings 2** Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction) for asthma in adults and children

Primary outcomes

1. Asthma exacerbations

Treatment with omalizumab resulted in fewer exacerbations overall. This effect was maintained during the steroid stable and steroid reduction phases of the included trials but with much greater uncertainty when only participants with severe disease were considered.

Steroid stable phase

Odds ratio of having one or more exacerbations

Overall, treatment with subcutaneous omalizumab resulted in a significant reduction in the odds of having one or more exacerbations when compared with placebo in the steroid stable trials (OR 0.55, 95% CI 0.46 to 0.65; ten studies, 3261 participants). This represents an absolute reduction from 26% for participants suffering an exacerbation with placebo to 16% with omalizumab, over 16 to 60 weeks, as shown in Figure 1.

In analyses based on asthma severity, we found that in participants with moderate/severe asthma and in those who were receiving background inhaled steroid therapy, a significant reduction in the odds of having an asthma exacerbation favoured subcutaneous omalizumab (OR 0.50, 95% CI 0.42 to 0.60; seven studies, 1889 participants; Analysis 1.1).

However, little effect, but with wide confidence intervals, was noted for omalizumab versus placebo in participants who were diagnosed with severe asthma and who were receiving background inhaled steroid therapy (OR 1.00, 95% CI 0.50 to 1.99; two studies, 277 participants; Analysis 1.1), nor for those who were diagnosed with severe asthma who were receiving background inhaled plus oral steroid therapy (OR 1.65, 95% CI 0.66 to 4.13; one study, 95 participants; Analysis 1.1). We are therefore much less certain of any positive impact of omalizumab on exacerbations in patients with more severe asthma.

Exacerbation rate ratio

With regard to exacerbations requiring oral steroids, the clearest benefit in favour of subcutaneous omalizumab was again observed in participants with moderate/severe asthma (rate ratio 0.52, 95% CI 0.37 to 0.73; two studies, 1038 participants; Analysis 1.2). For participants with severe asthma, only one study (Hanania 2011) found significant benefit in favour of subcutaneous omalizumab for those who were receiving background therapy of both inhaled corticosteroids and long-acting beta$_2$-agonists, but again, more uncertainty surrounds those receiving a background therapy of inhaled plus oral corticosteroids. However, it should be noted that these findings are drawn from a single study, and no significant differences were noted between these subgroups.

Hospitalisations

Significant benefit was seen for omalizumab versus placebo with regard to reducing the number of people experiencing one or more hospitalisation (OR 0.16, 95% CI 0.06 to 0.42; four studies, 1824 participants; Analysis 1.3), representing an absolute reduction in risk from 3% with placebo to 0.5% with omalizumab (Figure 2). No data were available for the severe asthma subgroup; data were reported for all participants with the diagnosis of moderate to severe asthma.

Steroid tapering phase

Odds ratio of having one or more exacerbations

During the steroid tapering phase, participants treated with subcutaneous omalizumab were less likely to experience an asthma exacerbation compared with those treated with placebo (OR 0.46, 95% CI 0.36 to 0.59; four trials, 1631 participants). With data added for the subgroup of oral steroid users, the OR was 0.49 (95% 0.39 to 0.62; five trials, 1726 participants; Analysis 2.1). Again, we were less certain of the benefit of omalizumab when the data from participants with severe asthma were considered alone (OR 0.59, 95% CI 0.30 to 1.16).

Hospitalisations

A significant reduction was observed in the odds of hospitalisation in participants with moderate asthma treated with omalizumab compared with those treated with placebo (OR 0.11, 95% CI 0.03 to 0.48; three studies, 1408 participants; Analysis 2.2). This represents an absolute reduction from 20% with placebo to 3% with omalizumab, as shown in Summary of findings 2. No trials included participants with severe asthma that contributed to this outcome.

2. Steroid withdrawal/reduction

Participants treated with omalizumab were significantly more likely to be able to reduce and completely withdraw their inhaled corticosteroids. For the subset of participants receiving oral corticosteroids, we remain uncertain whether benefit is derived from omalizumab over placebo for those withdrawing or reducing their steroid treatment.

Inhaled steroid withdrawal

Participants treated with subcutaneous omalizumab were significantly more likely to be able to withdraw their ICS completely than those treated with placebo (OR 2.50, 95% CI 2.00 to 3.13; four trials, 529 participants; Analysis 2.3). This represents an absolute reduction from 40% in the placebo group to 21% in the omalizumab group, as shown in Figure 3. Most of the evidence comes from trials in participants with moderate to severe asthma, and considerable uncertainty remains about whether benefit is seen in the severe asthma subgroup (OR 1.55, 95% CI 0.80 to 2.98; one trial, 45 participants).

In a trial extension of 32 weeks, 34% (85/254) of moderate to severe participants in the omalizumab-treated group were able to achieve complete steroid withdrawal compared with 14% (31/229) in the control group (Solèr 2001; P < 0.001).

Inhaled steroid reduction

Change from baseline in ICS dose

A small but statistically significant reduction in daily steroid dose was seen among omalizumab-treated participants compared with those given placebo (WMD -118 mcg BDP equivalent per day, 95%CI -154 to -84; three studies, 1188 participants; Analysis 2.4). Although a high degree of heterogeneity was observed (I^2 = 67.2%), random-effects modelling did not alter the direction of the effect but widened the confidence interval (MD -141.24 mcg, 95% CI -221 to -61). The reduction in ICS dose was greater in the trial with severe asthma than in the two trials with moderate to severe asthma, although this difference did not reach statistical significance (test for subgroup differences: Chi^2 = 3.33, df = 1 (P = 0.07), I^2 = 70.0%).

In paediatric participants (Milgrom 2001), median BDP dose reduction was 100% in the omalizumab-treated group compared with 66.7% in the placebo group (P = 0.001).

Likelihood of achieving 50% reduction in ICS dose

Participants treated with omalizumab were significantly more likely to be able to reduce their inhaled steroid dose by greater than 50% (OR 2.50, 95% CI 2.02 to 3.10; four studies, 1098 participants; Analysis 2.5).

Oral steroid withdrawal

No significant difference was noted in the number of participants who were able to withdraw from oral steroid therapy between omalizumab and placebo treatment (OR 1.18, 95% CI 0.53 to 2.63; one study, 95 participants; Analysis 3.1).

Oral steroid reduction

No significant difference in the median reduction of daily oral steroid dose was noted between omalizumab- and placebo-treated participants in Holgate 2004b (69% vs 75%; P = 0.675).

Secondary outcomes

1. Asthma symptoms

Treatment with omalizumab generally improved asthma symptom scores in both steroid stable and steroid reduction phases.

Steroid stable phase

End of treatment symptom scores

A significant difference favouring omalizumab was observed with regard to symptom scores for moderate to severe participants in four of the seven studies reporting data on this outcome (Busse 2001; Busse 2011; Lanier 2009; Solèr 2001), and a significant difference favouring omalizumab was reported for severe participants in two out of four studies (Hanania 2011 and Holgate 2004a). In view of the heterogeneity among different approaches to assessing symptom scores, we have avoided statistical aggregation of these data (Analysis 1.10).

Change from baseline in symptom scores

Significant reductions in symptom scores from baseline in favour of omalizumab were reported in two trials (SOLAR, -1.8, P = 0.023; INNOVATE, P = 0.039, no mean scores presented).

Steroid reduction phase

Change from baseline in symptom scores

Busse 2001 reported that mean change in symptom scores between baseline and the end of steroid reduction was greater in the omalizumab group than in the placebo group (-1.93 vs -1.44, respectively; P < 0.001), and Milgrom 2001 reported that median nocturnal symptom scores were unchanged in either treatment group for the duration of the study, although mean scores were lower in the treatment group at all evaluations (no P values reported). No difference between groups in daytime symptom scores was detected until week 22 during steroid reduction phase: median value 0.36 versus 0.54 for the treatment and control groups, respectively; P value not reported); this reduction in daytime symptom scores then persisted until the end of the study.

2. Health-related quality of life

In most trials reporting quality of life, a significant benefit of omalizumab over placebo was reported during both steroid stable and steroid reduction phases.

Steroid stable phase

Change from baseline in quality of life scores

Significantly greater improvement in the overall Asthma Quality of Life Questionnaire (AQLQ) favoured omalizumab (MD 0.31, 95% CI 0.23 to 0.39; six studies, 2981 participants; Analysis 1.12), but this

finding did not reach the validated clinically relevant effect size of 0.5 (Juniper 1994).

Assessment of asthma control

Participants' global asthma control was significantly better when taking omalizumab than placebo (OR 2.12, 95% CI 1.67 to 2.68; four studies, 1136 participants; Analysis 1.13); however, the very high degree of heterogeneity in this analysis (I^2 = 69%) indicates that findings warrant especially careful interpretation, although it is clear that a significant advantage for subcutaneous omalizumab versus placebo was observed in the moderate to severe (OR 3.32, 95% CI 2.19 to 5.05) and to a lesser extent in the severe (OR 1.69, 95% CI 1.26 to 2.26) subgroup.

Steroid reduction phase

Change from baseline in quality of life scores

Unpublished data were obtained from Holgate 2004a: Overall change was 0.68 (SD 1.02) for omalizumab versus 0.26 (SD 0.96) for placebo (no P values available). In severe participants, a significant difference can be seen in the numbers of participants who achieved clinically relevant improvement in their overall quality of life (an increase of at least 0.5 above baseline) in the omalizumab group (57.5%) compared with the placebo group (38.6%; P < 0.01). A greater number of participants in the omalizumab group (16%) than in the placebo group (5.9%) also reported clinically relevant improvement in their overall quality of life (P < 0.05).

Assessment of asthma control

Moderate to severe participants in two studies were more likely to rate treatment as good or excellent when treated with omalizumab than with placebo (OR 2.72, 95% CI 2.04 to 3.62; two studies, 842 participants).

3. Rescue medication use

Participants were more likely to be able to reduce their rescue medication when using omalizumab.

Steroid stable phase

Participants treated with subcutaneous omalizumab required significantly less rescue $beta_2$-agonist medication compared with those given placebo (nine studies, 3524 participants; Analysis 1.14). This benefit was observed in both moderate to severe (MD -0.58, 95% CI -0.84 to -0.31) and severe (MD -0.30, 95% CI -0.49 to -0.10) asthma subgroups, with the latter receiving a background therapy of inhaled corticosteroids; however, much more uncertainty remains about the difference between subcutaneous omalizumab and placebo for this outcome in severe asthma participants who were receiving a background therapy of inhaled plus oral corticosteroids. No statistically significant difference was seen in results from the three subgroups.

Steroid reduction phase

Change from baseline in rescue medication use

Omalizumab treatment enabled participants to use significantly less rescue medication than placebo (WMD -0.74 puffs per day, 95% CI -1.05 to -0.43; four studies, 1373 participants; Analysis 2.10). Baseline levels were approximately 4.5 puffs per day for these studies, so the effect size was quite small.

4. Measures of lung function

Improvements in lung function were inconsistent across the trials analysed, and the range of different measures presented in the trials prevented meaningful meta-analysis.

End of treatment AM PEF

Differences were very small, and no overall significant difference was reported between participants treated with subcutaneous omalizumab and those given placebo (MD 3.56 L/min, 95% CI -5.05 to 12.18; four studies, 1651 participants; Analysis 1.5).

Change from baseline in AM PEF

A small but statistically significant benefit for subcutaneous omalizumab versus placebo was observed in participants with moderate to severe asthma (MD 11.00 L/min, 95% CI 4.51 to 17.49; one study, 405 participants; Analysis 1.6), and no benefit was observed in severe participants (MD -0.60 L/min, 95%CI -29.77 to 28.57; one study, 31 participants; Analysis 1.6). Given the small effect size and the small numbers of studies and participants contributing to this analysis (especially in the severe asthma subgroup), we recommend that any interpretation of these data be reserved until additional study findings become available.

End of treatment FEV_1 (mL)

No significant difference in FEV_1 was noted in moderate to severe adolescent and adult participants (MD 68.31 mL, 95% CI -23.45 to 160.07; two studies, 1071 participants; Analysis 1.7).

Change from baseline in FEV_1 (mL)

Small but significant improvements from baseline were observed in the moderate to severe subgroup (MD 67.29 mL, 95% CI 23.75 to 110.83; two studies, 732 participants; Analysis 1.8). Considerable heterogeneity was seen between the two studies in the severe subgroup in this analysis (I^2 = 89%); in particular, uncertainties are described regarding the data from NCT01007149, for which baseline values were unavailable in the study report, and the change score in the placebo group was reported as 0.00 L; we have not received clarification on this point from the pharmaceutical company sponsoring this study. In Garcia 2012, the abstract reported that the placebo-adjusted absolute change in FEV_1 with omalizumab was larger, at +250 mL (P = 0.032).

Change from baseline in FEV_1 % predicted

A significant benefit for subcutaneous omalizumab versus placebo was observed (MD 2.15, 95% CI 1.01 to 3.30; four studies, 1079 participants; Analysis 1.9).

Subcutaneous omalizumab (in participants not receiving ICS)

No significant differences between placebo and omalizumab were reported in terms of FEV_1 % predicted. Baseline imbalances between groups at baseline meant that data on FEV_1 could not be reliably analysed. Prieto 2006 and van Rensen 2009 reported no significant differences in the mean change in methacholine responsiveness between omalizumab and placebo. van Rensen 2009 reported a significant difference in late asthmatic response (LAR) in favour of omalizumab (P < 0.05).

5. Adverse events including withdrawals and mortality

Participants receiving subcutaneous omalizumab experienced significantly fewer serious adverse events compared with those given placebo. However, they also experienced significantly more injection site reactions. No significant difference in mortality was detected.

Mortality

No significant difference between subcutaneous omalizumab and placebo with respect to mortality was observed (OR 0.19, 95% CI 0.02 to 1.67; Analysis 1.4). In the nine studies contributing data to this analysis, among 4245 participants, only four deaths were reported—all in the placebo group. Two deaths occurred during the study period and two more than six weeks after discontinuation of the study. None were reported to be asthma-related. Three of the four deaths occurred in the severe asthma subgroup.

Adverse event—serious

Significantly fewer serious adverse events occurred in participants assigned to subcutaneous omalizumab than in those given placebo (OR 0.72, 95% CI 0.57 to 0.91; 15 studies, 5713 participants; Analysis 1.16), and the level of heterogeneity among these studies (I^2 = 7%) was very low. This represents an absolute reduction from 6% receiving placebo to 4% taking omalizumab, as shown in Figure 4.

Adverse event—any

In terms of all adverse events, no significant difference was seen between subcutaneous omalizumab and placebo (OR 0.92, 95% CI 0.81 to 1.06; 14 studies, 5167 participants; Analysis 1.15). However, the level of heterogeneity among these studies (I^2 = 22%) was pronounced.

Adverse event—injection site reactions

Significantly more injection site reactions were reported among participants assigned to subcutaneous omalizumab than among those receiving placebo (OR 1.72, 95% CI 1.33 to 2.24; nine studies, 3577 participants; Analysis 1.17), and the level of heterogeneity among these studies (I^2 = 42%) was considerable. This represents an absolute increase from 6% on placebo to 9% on omalizumab, as shown in Figure 5.

No differences were reported in headache, urticaria, number of participants with any adverse events or number of withdrawals due to adverse events.

Withdrawals

Withdrawals were infrequent in studies using subcutaneous omalizumab. Among adult participants, Busse 2001 reported two withdrawals from the treatment group due to adverse events. Neither was considered drug-related. Solèr 2001 reported five withdrawals from that study—all were from the placebo group. In the paediatric study (Milgrom 2001), five of 225 (2.2%) treated children withdrew from the trial—four because of pain or fear of injection and one because of mild to moderate urticaria on two occasions. In the study placebo group, two of 109 (1.8%) children withdrew because of pain and/or fear of injection, and one child was withdrawn because of prolonged hospitalisation for hip fracture. Two participants withdrew from the severe adult population (Holgate 2004a), both from the placebo group.

DISCUSSION

Summary of main results

We have reviewed the use of omalizumab in 25 randomised, placebo-controlled clinical trials involving 6382 people with differing asthma severity, with most suffering from moderate to severe disease. The trials reviewed varied in design, as described earlier. Treatment duration ranged between 8 and 60 weeks, and some studies included a steroid reduction phase between 8 and 16 weeks in duration. Most of the studies (21, n = 5975) used a subcutaneous route to deliver the drug. Currently, omalizumab is delivered exclusively by the subcutaneous route in clinical practice; for this reason, discussion of results from older studies of inhaled and intravenous administration has been moved to the appendices.

Primary outcomes

Exacerbations

Omalizumab reduced exacerbations when assessed both as an adjunctive treatment and as a steroid-sparing agent in moderate to severe asthma. However, in the subgroup of participants with more severe asthma, including those requiring oral steroids, omalizumab had no significant effect on asthma exacerbations. The results presented here also suggest a reduction in hospitalisations for participants with moderate to severe asthma using omalizumab compared with those given placebo, but no data in this area are available for the more severe subgroup independently.

Steroid sparing effects

Some people with more severe asthma depend on high doses of inhaled or oral corticosteroids to control their disease. Long-term oral steroid use is associated with many unwanted side effects, including hypertension, reduction in bone density, bruising, immune suppression, cataracts, growth failure and hyperglycaemia, among many others. Agents that allow asthma sufferers to reduce their daily steroid dose are therefore of great interest.

The reduction in daily inhaled steroid dose following treatment with omalizumab was clinically modest but statistically significant. The amount of variation in this outcome could be attributable to the higher doses of BDP equivalent inhaled steroid in Holgate 2004a in relation to Busse 2001 and Solèr 2001. It is noteworthy that participants treated with placebo were also able to reduce their intake of ICS by a significant amount, probably because of better adherence to the prescribed doses. The presentation of dichotomous data in the published studies and of unpublished continuous data in the FDA report has enabled us to look at the significance of both methods of measuring effects (Table 4). Treatment with omalizumab increased the likelihood of steroid reduction, but variable baseline steroid doses and a modest mean outcome difference in steroid consumption between treatment and placebo groups bring into question the true size of the steroid sparing effect of omalizumab.

Not all participants across the studies benefited from omalizumab treatment. Approximately 16% of severe participants achieved less than 25% reduction in daily inhaled steroid use over the steroid reduction phase. In the study involving paediatric participants, nine of 225 omalizumab-treated participants appeared to have needed the same amount or an increased amount of steroid therapy

(reported as < 0% reduction in steroid use) (Milgrom 2001). It was not obvious whether these children had more severe asthma. These results confirm the need to better define which patients will benefit most from omalizumab treatment. It is important to note that not all asthmatic patients at the severe end of the spectrum who may benefit most from steroid reduction will respond to omalizumab treatment; this may reflect the heterogeneity of asthma aetiology and pathology, especially in this group (Walker 2006).

Secondary outcomes

Asthma symptoms

Asthma symptom scores were not reported by all included studies. Participants with moderate to severe and severe asthma receiving omalizumab were more likely to experience an improvement in their asthma symptoms, but this difference only reached significance in seven out of the eleven studies reporting this outcome.The heterogeneity of methods for assessing asthma severity prevented meaningful meta-analysis.

Health-related quality of life

Significant improvements in health-related quality of life were observed with omalizumab compared with placebo.

A statistically significant improvement was noted in steroid stable studies of subcutaneous omalizumab for AQLQ scores in the treatment group compared with the placebo group, but this difference did not reach the validated clinically relevant effect size. In addition, Global Asthma Control scores improved significantly in the treatment group compared with the placebo group, but with a high level of heterogeneity.

Further evidence of positive participant perception of omalizumab treatment was ascertained from pooled analysis of the results for global effectiveness of treatment from two trials involving subcutaneous omalizumab. Once again, improvements in global treatment efficacy and overall quality of life noted among control participants suggest that the basic trial design, which included close medical monitoring, might have contributed to a large placebo or more likely Hawthorne effect, mediated through improved adherence to medication.

Rescue medication use

Participants receiving omalizumab were significantly more likely to be able to reduce their use of short-acting bronchodilators or 'rescue medication'. This was true for participants with both moderate and severe disease but was not found for the relatively small number of more severely affected participants receiving oral as well as inhaled corticosteroid as background therapy.

Measures of lung function

Pooled results showed consistent but very modest improvements in the treatment group when compared with the placebo group for the change from baseline FEV_1 predicted and morning PEF.

This is consistent with studies reporting no relationship between reduced hospital admissions and improved lung function (Qureshi 1998) and a poor association between lung function and health-related quality of life (Wijnhoven 2001). It is not yet clear how such small improvements in lung function may equate to clinically relevant findings. The relationship between asthma disease severity and lung function requires further investigation. Given the context in which omalizumab has been assessed in this review, optimising background adherence to inhaled therapy may be more important than adding extra medication to achieve these modest improvements in lung function.

Adverse events

It appears that participants receiving omalizumab were less likely to experience a serious adverse event than those receiving placebo, with a low level of heterogeneity (I^2 = 7%). Injection site reactions were more common in the omalizumab group, but this result also had a considerable degree of heterogeneity (I^2 = 42%). Although no significant difference was seen between groups in the low mortality rates encountered, any advantage favoured omalizumab, as all four deaths occurred among participants receiving placebo (at least two not asthma-related, with no details provided regarding the other two).

Use of a humanised anti-IgE antibody has raised theoretical concerns about immune complex–mediated pathology and abnormal immune responses to parasitic infection. Administration of parenteral anti-IgE results in the formation of small immune complexes (< 10 KDa), which are cleared through the kidney (Arshad 2001). No reports have described immune complex–mediated side effects over up to 60 weeks of administration. Additionally, antibodies to omalizumab did not develop in participants treated with subcutaneous or intravenous omalizumab, although they occurred transiently in one participant who received inhaled anti-IgE therapy.

Further information is needed on the safety profile of the drug after long-term use and in different populations such as those with endemic parasitism. There is a theoretical potential that anti-IgE therapy may lead to increased risk of cancer because of the role of IgE in the immune response to neoplasia; again, longer studies are needed to further explore this possibility.

Overall completeness and applicability of evidence

An important question is the place of omalizumab in the treatment of asthma according to current guidelines. NICE guidance recommends use only in patients with inadequately controlled severe persistent allergic IgE-mediated asthma who require continuous or frequent treatment with oral corticosteroids (i.e. step five of the BTS guidelines for asthma management in children and adults) (BTS/SIGN 2012; NICE 2013). However, this is not strongly supported by the evidence. Few studies recruited only participants with severe disease, and thus our subgroups may not have been adequately powered to detect different responses. Moreover, the current data available in relation to participants on oral steroids (Holgate 2004b; 95 participants) are not sufficient to justify the extrapolation of our main findings to this group. Additional trials limited to this severe oral steroid–dependent population are required to determine whether they would benefit from omalizumab therapy.

Our own classification of the studies included in this review failed to identify a consistently different response to therapy for participants with differing disease severity, with the exception of participants experiencing one or more exacerbations in the steroid stable treatment group who were treated with subcutaneous omalizumab. In this important analysis, it appears that participants

with more severe disease actually benefit less from omalizumab treatment, with a significant difference detected between the subgroups.

In addition, the steroid sparing effects of omalizumab, which could be important in severe asthmatic patients, who are at risk of serious side effects from daily use of high-dose inhaled steroids or oral steroids, were generally small. Such modest steroid sparing effects of omalizumab in moderately severe asthmatic patients have to be balanced against the cost of anti-IgE treatment. Studies with a steroid sparing phase of considerably longer than 16 weeks will be required to answer this question more definitively. Discontinuation of omalizumab treatment is associated with increases in circulating free IgE to prebaseline values within eight weeks (Casale 1997). This implies that treatment would need to be continued long term for efficacy to persist, which has significant cost implications.

The cost of omalizumab ranges from approximately £1665 per patient per year for a 75-mg dose administered every four weeks to approximately £26,640 per patient per year for a 600-mg dose administered every two weeks (NICE 2013). Given the time-consuming and costly nature of the treatment and importance of targeting patients who are most likely to benefit, it is essential that future studies focus on methods of identifying potential responders. One of the challenges when treatment with omalizumab is considered is that to date, there is no reliable way of identifying those people before treatment is started. Four responder analyses with varying definitions of 'at risk' or 'severe' asthmatic participants have been conducted (Babu 2001; Bousquet 2004; Holgate 2001; Wenzel 2002). Bousquet 2004 reported that participants were more likely to respond to treatment if characterised by one or more of the following: low FEV_1, frequent hospitalisation and high ICS dose (for additional information on these analyses, see Table 5).

A recent logistic regression analysis from the EXTRA (Hanania 2011) trial did not entirely support this previous work on clinical predictions of efficacy. In contrast, these trial authors suggested that preserved FEV_1 (> 65% predicted) with no intubations for asthma in the preceding year but higher numbers of exacerbations requiring oral steroids in the preceding year was predictive of a better response. These authors speculate that this may indicate that omalizumab is most effective in individuals with uncontrolled disease but in whom irreversible airway remodelling has not yet occurred. Further work in this area would be justified. Hanania 2011 also attempted to identify biomarkers that would allow prospective prediction of likely response to omalizumab and suggested that elevated fractional exhaled nitric oxide (FeNO), blood eosinophilia and serum periostin may predict a better response to omalizumab when compared with placebo.

Another study included in this review (Busse 2011) carried out a rather different prespecified subgroup analysis to investigate potential responders. This study showed that omalizumab had a significant impact on asthma control and exacerbations in an inner city population of children and young adults with severe asthma but also suggested that it was more effective in those who are both sensitized and exposed to cockroach allergen. Compared with those who were neither sensitised nor exposed to cockroach allergen, people receiving omalizumab had bigger reductions in inhaled corticosteroid dose (P = 0.03) and asthma exacerbations (P = 0.06) and increased odds of not having an asthma exacerbation (P = 0.06). This may represent the beginning of an alternative approach to selecting patients for treatment with omalizumab that allows prior identification of likely responders, although, it is important to note, it is not clear from the paper or the supplementary appendices how many people in this study were actually both sensitised and exposed to cockroach allergen (Walker 2011). Further validation of this approach is required.

Entry criteria for the studies in our review required evidence of sensitivity to aeroallergens and raised levels of serum IgE, which may not be representative of the asthmatic population in general. To date, most trials have excluded patients who do not have proven sensitivity to aeroallergens (i.e. non-atopic individuals), thereby raising questions about the generalisability of study findings to the asthmatic population as a whole. It is estimated that up to 50% of severe asthmatic patients are non-atopic. However, a recent small study (Garcia 2012; n = 41) that enrolled non-atopic participants with severe asthma suggests that omalizumab may be effective in this population; larger studies are now required to confirm this finding,

The high number of screening failures in several studies is also noteworthy (e.g. Busse 2001: 1117 screened, 525 enrolled; Lanier 2009: 1433 screened, 628 enrolled; Solèr 2001: 1356 screened, 546 enrolled). IgE levels outside the range of those set as entry criteria were the most common reason for screening failure. Even within this selected stratum, there were participants who demonstrated little or no response to omalizumab. It is still not clear from studies published so far why some patients respond and others do not; it is therefore difficult to extrapolate some of the positive findings of this review to the general asthmatic population. Gevaert 2012 suggested that 'local tissue' IgE may have a significant role in mediating airway symptoms in asthma, and therefore serum IgE, or sensitivity to aeroallergens, may not be a good predictor of response to treatment.

Most participants were adults or adolescents, with only two trials (Lanier 2009 and Milgrom 2001; n = 962) recruiting paediatric participants between five and 12 years of age. Most of the 'adult' studies included some participants from 12 to 17 years of age, although this group of participants represented only a small percentage of the overall sample (between 6% and 8%; see Table 6). Confirmation of these effects in paediatric populations is also required, especially because compliance with monthly injections of medication may prove more challenging in paediatric patients. Milgrom 2001 reported a small number of withdrawals in children due to pain and fear of injection.

Future clinical studies should have more realistic clinical designs that could be more readily generalised to a routine asthma clinic and the licenced indication for omalizumab. One such observational 'real-life' study, EXCELS, is currently under way (Chen 2012) and may go some way toward reducing the strong Hawthorne effect that we have seen in the current analyses.

Quality of the evidence

On the whole, the quality of the included studies, with respect to our risk of bias assessment, was variable. Only seven studies (29%) were categorised as low in relation to risk of selection bias, whereas the risk of selection bias in the remaining 18 studies was viewed as unclear. Only four studies (17%) were evaluated as having low risk of performance and detection bias, and the remaining 21 studies

were assessed as unclear. The risk of reporting bias was also viewed as a concern, as just three studies (13%) were assessed as having low risk of reporting bias, with the remaining 24 studies in the unclear category. However, 23 studies (96%) were viewed as having low risk of attrition bias, and only Lanier 2009 and Garcia 2012 were judged to be in the unclear category.

Potential biases in the review process

We believe that we have identified a very significant proportion of the research addressing this clinical question through the use of a comprehensive systematic search, conducted by a highly experienced information specialist who has also provided considerable support in the identification of unpublished studies. At the same time, we acknowledge that there is a possibility of publication bias in this review, in that through failure to identify unpublished negative trials, the positive effects of omalizumab may be overestimated and, conversely, any failure to have identified unpublished positive trials may have reduced our estimate of the therapeutic benefit. However, these are concerns with most systematic reviews.

In addition, we acknowledge the possibility of study selection bias; however, all studies were independently evaluated by two review authors, and we are confident that studies excluded from the analyses were assessed on the basis of consistent and appropriate criteria.

Agreements and disagreements with other studies or reviews

We have added 11 new clinical trials to the 14 reported in Walker 2006. Our emphasis has shifted to primarily the subcutaneous route of administration of omalizumab (18 studies in total) to maintain consistency between the focus of the review and current clinical treatment. The 11 new clinical trials added to the review all focus on subcutaneous omalizumab versus placebo; therefore the conclusions pertaining to inhaled and intravenous omalizumab are unchanged, although our assessment of the quality, with respect to risk of bias, of the inhaled and intravenous omalizumab trials has been updated to reflect developments in Cochrane methodology. In broad terms, our conclusions related to subcutaneous omalizumab are similar to those of Walker 2006, although we have added to the update outcomes that consider mortality, hospitalisations and adverse events to sharpen the applicability of the review. The most consistent finding from Walker 2006 that subcutaneous omalizumab reduces the likelihood of asthma exacerbations, when compared with placebo, is strengthened by this current update.

AUTHORS' CONCLUSIONS

Implications for practice

Data from the included trials have shown that omalizumab is both effective and safe in patients with moderate to severe asthma that is uncontrolled on moderate to high doses of inhaled steroids with or without long-acting beta$_2$-agonists. Insufficient evidence of benefit has been found in participants specifically with severe OCS-dependent asthma. Very few studies have explored efficacy in children with moderate to severe asthma. Although the drug does enable a modest reduction in the dose of inhaled steroids, it is not clear whether this outcome would justify the cost of this expensive treatment. Because omalizumab is an expensive treatment option, it will be important to determine which people would benefit most from its use. To justify treatment with anti-IgE, the amount of steroid that asthma sufferers are able to forego as a result of therapy would need to result in meaningful advantages in terms of lower risk derived from reduced exposure to steroids. The effect of the drug in participants with extreme values of serum IgE have not been evaluated. Finally, direct comparisons with other controller medications such as leukotriene antagonists or the novel anti-interleukin (IL)-5 therapies or biomarker-based (e.g. sputum eosinophil count) treatment strategies have not been evaluated. Thus, omalizumab remains one of the therapeutic options in patients with atopic asthma whose condition remains uncontrolled despite optimum therapy with high levels of inhaled corticosteroids and long-acting bronchodilators, and in those for whom this therapy can be afforded.

Implications for research

Further research is needed to examine the role of omalizumab as a treatment for chronic asthma. Specifically, the following are needed.

1. Clinical trials that assess the long-term use of omalizumab, how and when to reduce or stop treatment and whether benefits continue after discontinuation.
2. More studies assessing the steroid sparing effect in the most severe asthma group.
3. Further clinical assessment in the paediatric population.
4. Clinical assessment of the effects of omalizumab in participants with multiple allergic diseases (e.g. allergic asthma and eczema).
5. Efficacy in participants with extremes of serum IgE (i.e. very high IgE, as in conditions such as allergic bronchopulmonary aspergillosis (ABPA)) and with low IgE (modest atopy or non-atopic individuals).
6. Direct comparison with other newer controller medications and management strategies.
7. Research to identify clinical, biochemical and genetic markers predictive of response.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bardelas 2012

Methods	Multi-centre, randomised, double-blind, placebo-controlled study
Participants	Treatment group: 136. Age: 41.9 (14.6). Males: 43 (31.6%). Baseline lung function: mean % predicted FEV_1 (SD): 74.4 (17.5) Control group: 135. Age: 40.7 (14.9). Males: 48 (35.6%). Baseline lung function: mean % predicted FEV_1 (SD): 76.5 (17.0) Inclusion criteria stated as: males and females; 12 years or over; inadequately controlled persistent allergic asthma (ACT score equal to or less than 19) and positive skin prick test; on step 4 or above of NHLBI maintenance treatment (ICS + LABA/leukotriene receptor antagonist/theophylline/zileuton); total serum IgE 30 to 700 IU/mL. One or more of the following with four weeks of screening phase: symptoms > 2 days/wk; night-time awakenings ≥ 1 time/wk; use of SABA > 2 days/wk; FEV_1 ≤ 80% predicted Exclusion criteria stated as: body weight > 150 kg; current smoker or ex-smoker within last year, or pack-year history ≥ 10 years; history of intubation for asthma or anaphylaxis; systemic steroids within last four weeks; active lung disease other than asthma; current or anticipated use of beta-blockers or methotrexate, gold, cyclosporine or troleandomycin within three months of enrolment; elevated serum IgE levels for reasons other than atopy or a combination of serum IgE levels and weight requiring doses of omalizumab greater than 750 mg per four weeks Location(s): USA
Interventions	Omalizumab subcutaneous based on body weight and serum IgE; 150 or 300 mg every four weeks or 225, 300 or 375 mg every two weeks versus placebo with same inactive ingredients as study drug Background inhaled steroid dose: at least 250 mcg fluticasone twice daily or 320 mcg budesonide twice daily
Outcomes	Change from baseline in ACT scores, Investigator's Global Evaluation of Treatment Effectiveness (IGETE), Work productivity and activity impairment questionnaire–asthma (WPAI-A), e-diaries, spirometric measurements, use of rescue corticosteroids, safety assessment
Notes	Two-week screening period. 24 weeks Co-medication: background asthma maintenance therapy continued unchanged (e.g. step four or above of NHLBI maintenance treatment (ICS + LABA/leukotriene receptor antagonist/theophylline/zileuton). Oral or IV rescue steroids were allowed if required for an exacerbation

Bardelas 2012 *(Continued)*

	This study is identified as NCT00267202 in the Methods section of Bardelas 2012. However, it has been confirmed by Dr Marc Vaillancourt at Novartis that NCT00267202 relates to Massanari 2010, and that the Bardelas 2012 study is in fact NCT00870584 Authors are employees/stockholders of sponsoring pharmaceutical company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled—placebo contained same inactive ingredients as active preparation. Most outcome data recorded by participants themselves, but not specified whether those analysis data were also blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Balanced dropout from groups, all participants clearly accounted for in flow chart
Selective reporting (reporting bias)	Unclear risk	All outcome measures reported However, subgroup analysis was ad hoc and produced the only significant results

Boulet 1997

Methods	Randomised, double-blind, parallel-group placebo-controlled trial
Participants	N = 20. Mean age: 27 ± 8.06. Eight females. Mild asthmatic participants were recruited Inclusion criteria: stable, mild asthma, requiring only an inhaled beta$_2$-agonist on demand to control; at least one highly positive allergy skin prick test to at least one aeroallergen; early asthmatic response; FEV_1 > 70%; methacholine provocative concentration causing 20% fall in FEV_1 Exclusion criteria: history of anaphylaxis; recently unstable asthma (ER visit in previous six weeks); respiratory infection or aeroallergen exposure (other than HDM) within four weeks; smoking within 12 months; women of child-bearing age and lacking effective contraception. Baseline characteristics: FEV_1: 92 ± 11; IgE: placebo: 1808 ± 3382, omalizumab: 616 ± 487
Interventions	Intravenous rhuMAb-E25 (2.0 mg/kg) or placebo at day 0. Six subsequent injections of 1.0 mg per kg versus placebo. Treatment lasted for 10 weeks
Outcomes	Tolerance and safety, allergen PC15, methacholine responsiveness, serum rhuMab-E25 and IgE levels, respiratory symptoms and pulmonary function, cutaneous responses to allergen
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Boulet 1997 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Details not included in study report
Allocation concealment (selection bias)	Unclear risk	Details not included in study report
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	One of the 20 participants did not complete the trial
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

Busse 2001

Methods	Randomised, double-blind, parallel-group, placebo-controlled trial. Randomisation by computer-generated random number sequences
Participants	N = 525. Age range: 12 to 75, 215 males. Treatment group: N = 268. Control group: N = 257. Participants with moderate to severe asthma were recruited Inclusion criteria: asthma diagnosed for longer than one year; positive response to skin prick to one common allergen; total IgE serum > 30 IU/mL and < 700 IU/mL; FEV_1 reversibility of 12%
Interventions	Subcutaneous omalizumab (0.016 mg/kg IgE (IU/mL) per four weeks). Participants received 150 or 300 mg every four weeks or 225, 300 or 375 mg every two weeks, or placebo. Initial phase of the trial was a stable steroid phase of 16 weeks' duration, followed by a 12-week steroid reduction phase
Outcomes	Number of participants with exacerbations, mean number of exacerbations per participant, mean number of days per exacerbation, adverse events, reduction in ICS, rescue medication usage, global evaluation, serum IgE levels
Notes	Jadad score: 4 Trial 008

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by computer-generated random number sequences
Allocation concealment (selection bias)	Unclear risk	Details not included in study report
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias)	Low risk	Details of participants not completing are included in trial report

Busse 2001 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

Busse 2011

Methods	Randomised, double-blind, parallel-group trial
Participants	Treatment group: 208. Age: 10.9 ± 3.6. Males: 122 (59%). Baseline lung function: mean % predicted FEV_1 (SD): 92.9 ± 18.7 Control group: 211. Age: 10.8 ± 3.4. Males: 120 (57%). Baseline lung function: mean % predicted FEV_1 (SD): 92.2 ± 17.6 73% of participants had moderate/severe asthma according to NAEPP guidelines Inclusion criteria stated as: males and females between the ages of 6 and 20 years; both body weight and total serum IgE suitable for omalizumab dosing (more information about this criterion can be found in the protocol); diagnosis of asthma made by a physician more than one year before study entry OR diagnosis of asthma made less than one year before study entry but asthma symptoms for longer than 1 year before study entry; receiving long-term asthma control therapy OR symptoms consistent with persistent asthma OR evidence of uncontrolled disease; positive prick skin test to at least one perennial allergen (e.g. dust mite, cockroach, mold, cat, dog, rat, mouse); live in a preselected zip code area; able to perform spirometry measurements; willing to sign informed consent or parent or guardian willing to provide informed consent; previously had chicken pox or received varicella (chicken pox) vaccine; some form of healthcare insurance that covers costs of medications Exclusion criteria stated as: if participant meets any of these criteria, not eligible at that time but may be reassessed: systemic prednisolone (or equivalent) during the two weeks before visit two; systemic prednisolone (or equivalent) for more than 30 of the 60 days before study entry; pregnancy or breastfeeding; acute sinusitis or chest infection requiring antibiotics within one month of study screening; currently participating in another asthma-related clinical trial or previously participated in an another asthma-related trial within one month of study entry; does not sleep at least four nights per week in one home; lives with a foster parent; does not have access to a phone; plans to move during the study; previously treated with anti-IgE therapy within one year of study entry; currently receiving or received hyposensitisation therapy to any allergen in the year before study entry; previously received hyposensitisation therapy to dust mite, Alternaria or cockroach for longer than six months in the three years before study entry. If participant meets any of these criteria, he or she is not eligible for the study and may not be reassessed: significant medical illness. More information on this criterion can be found in the protocol: certain medications within four weeks of study screening. More information on this criterion can be found in the protocol: known hypersensitivity to any ingredients of omalizumab or related drugs; diagnosis of cancer; being investigated for possible cancer, or history of cancer; will not allow study physician to manage asthma; does not primarily speak English (or Spanish at centres with Spanish-speaking staff); history of severe anaphylactoid or anaphylactic reaction(s) Location(s): eight centres in USA
Interventions	Stated as: Subcutaneous injections of omalizumab will be administered every two or four weeks, along with standardised asthma care for 60 weeks, beginning with the randomisation visit. Dosage is dependent on participant's individual characteristics. Injection dose of omalizumab (75 to 375 mg) was calculated on the basis of individual weight and total serum IgE level to ensure a minimum monthly dose of 0.016 mg per kilogram of body weight per international unit of IgE per mL versus placebo Background inhaled corticosteroid dose: at least 180 µg budesonide once a day
Outcomes	Primary outcome measures stated as: maximum number of asthma symptom days (recorded monthly throughout study)

Busse 2011 *(Continued)*

	Secondary outcome measures stated as: economic outcomes (recorded monthly throughout study); asthma-related medical care resource utilisation (recorded monthly throughout study); asthma exacerbations (recorded monthly throughout study); pulmonary function and exhaled nitric oxide (recorded at various visits throughout the study); asthma control test or childhood asthma control test (recorded monthly throughout study); number of missed school/work days (recorded monthly throughout study); asthma-specific quality of life (QOL) (recorded at various visits throughout study); asthma medication use, rescue beta-agonist and inhaled corticosteroid (ICS) use (recorded at various visits throughout the study); safety (recorded at every study visit)
Notes	60-Week trial Co-medication: oral prednisolone for exacerbations

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of sequence generation not included in trial report
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not included in trial report
Blinding (performance bias and detection bias) All outcomes	Low risk	Reported as double-blind. Nurses giving Rx aware of Rx allocation; all other staff and participants blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	90% (386) included in primary outcome analysis 272 missed, 25% of Rx visits
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Chanez 2010

Methods	Randomised, double-blind, placebo-controlled study
Participants	Treatment group: 20 (17 completed). Age: 45.7 ± 13.30. Males: 6 (30%). Baseline lung function: mean % predicted FEV_1 (SD): 61.3 (14.83) Control group: 11 (8 completed). Age: 50.6 ± 16.31. Males: 6 (54.5%). Baseline lung function: mean % predicted FEV_1 (SD): 66.6 (11.38) Inclusion criteria stated as: adults aged ≥ 18 years; participants with severe persistent allergic asthma with the following characteristics: FEV_1 < 80% of predicted; frequent daily symptoms (≥ four days/wk on average) or nocturnal awakening (≥ one/wk on average); multiple severe asthma exacerbations: either ≥ two severe asthma exacerbations requiring an unscheduled medical intervention with systemic corticosteroid in the past year, or hospitalisation (including emergency room treatment) for an asthma exacerbation in the past year, despite a high-dose inhaled corticosteroid > 1000 mg beclomethasone dipropionate or equivalent and inhaled long-acting $beta_2$-agonist; an allergy to a perennial allergen demonstrated with convincing criteria (i.e. positive prick skin test or in vitro reactivity to a perennial aeroallergen (RAST)); total serum IgE level ≥ 30 to ≤ 700 IU/mL and suitable serum total IgE level; weight according to Xolair dosing tablets

Chanez 2010 *(Continued)*

	Exclusion criteria stated as: age < 18 years; smoking history > 20 pack-years; asthma exacerbation during the four weeks before randomisation; history of food- or drug-related severe anaphylactoid or anaphylactic reaction; elevated serum IgE levels for reasons other than allergy (e.g. parasite infections, hyperimmunoglobulin E syndrome, Wiskott-Aldrich Syndrome, allergic bronchopulmonary aspergillosis); patients with active cancer, suspicion of cancer or any history of cancer; pregnant women; known hypersensitivity to omalizumab or to one of its components; previous treatment with omalizumab (indeed previous treatment with omalizumab could have modified the FceRI expression); participated in a clinical trial in the past three months Location(s): France
Interventions	Omalizumab injected subcutaneously every two weeks or every four weeks for 16 weeks (dose and dosing interval determined on the basis of participant body weight and pretreatment serum IgE level) versus placebo Background inhaled corticosteroid dose: at least 1000 mcg beclomethasone dipropionate or equivalent daily. Mean dose/d 3556 mcg ± 1157.8 BDP equivalent/d Participants receiving maintenance OCS at baseline = 7 (22%)
Outcomes	Primary outcome measures stated as: change (%) from baseline in FcεRI (high-affinity IgE receptor) expression on blood basophils and dendritic cells after 16 weeks of treatment with omalizumab as compared with placebo (time frame: baseline and week 16); change (%) from baseline in mean fluorescence intensity of FcεRI after 16 weeks of treatment with omalizumab as compared with placebo (time frame: baseline and week 16) Secondary outcome measures stated as: change (%) from baseline in percent of basophils and dendritic cells expressing FcεRI after 4, 8, 12 and 16 weeks of treatment (time frame: baseline, weeks 4, 8, 12 and 16); change (%) from baseline in mean fluorescence intensity of FcεRI after 4, 8, 12 and 16 weeks of treatment (time frame: baseline, weeks 4, 8, 12 and 16); change from baseline in the number of days with asthma symptoms per week (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of puffs of rescue medication per week (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of nights with awakenings per week (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of days with impairment in daily activities per week (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of days with absence from school or work due to asthma symptoms (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of days with hospitalisations (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of unscheduled clinic visits (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in morning daily peak expiratory flow (PEF) (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); physician's overall assessment of treatment effectiveness (time frame: after 16 weeks of treatment)
Notes	16-Week trial Co-medication: steroids and LABA (all), oral corticosteroids three and four, theophylline one and one, montelukast eight and four, anticholinergics six and six

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified by centre and ratio of 2:1. Details of sequence generation not reported

Chanez 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Six participants did not complete the trial (three in each group); reasons for their withdrawal are included in trial report
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Djukanovic 2004

Methods	Randomised, double-blind, parallel-group placebo-controlled trial Methods of allocation/blinding not reported
Participants	N = 46. Median age: 26 (range 19 to 48), Treatment group: 22; control group: 23. Gender: M/F: 22/24, FEV_1 (% predicted): omalizumab: 84; placebo: 86 Inclusion criteria: stable, mild to moderate asthma (NHLBI definition); treatment with inhaled beta-agonists only; exacerbation-free six weeks before study entry; age 18 to 50 years; total serum IgE 30 to 700 IU/mL; +ve skin prick test to ≥ one allergen; airway hyperresponsiveness as defined by PC20 ≤ 8 mg/mL; sputum eosinophilia 2% or more of nonsquamous cells
Interventions	Sucutaneous omalizumab (0.016 mg/kg per IgE (IU/mL)) versus placebo Study duration: 16 weeks
Outcomes	Methacholine challenge; FEV_1; serum free IgE levels
Notes	Jadad score: 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Details not included in study report
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants were withdrawn, and details are included in trial report
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

Fahy 1997

Methods	Randomised, double-blind, parallel-group, placebo-controlled trial
Participants	N = 19. Mean age: 31.5 ± 4.87. Gender not reported. FEV_1: 94.5% predicted ± 16.72; PC20 mg/mL: 0.62 ± 0.77; IgE IU/L: 141 ± 119. Mild asthmatics were recruited Inclusion criteria: FEV_1 > 70%, bronchial hyperreactivity to methacholine, positive skin prick test to HDM, cat pelt/rye grass; serum IgE level < 500 IU/mL. Exclusion criteria: use of corticosteroids in previous six weeks, U/L RTI in previous six weeks, tobacco use/history of significant medical illness
Interventions	Intravenous infusion of rhuMAb-E25 5 mg/mL (0.5 mg/kg) for nine visits versus placebo. Treatment lasted nine weeks
Outcomes	FEV_1, PEF (am and pm), asthma symptoms, albuterol use, total serum IgE, induced sputum, PC20, percentage fall in FEV_1 during early and late response, blood eosinophil percentage
Notes	Jadad score: 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not included in study report
Allocation concealment (selection bias)	Unclear risk	Details not included in study report
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant did not complete the trial and was withdrawn after week four
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

Fahy 1999

Methods	Randomised, multi-centre, double-blind, parallel-group, placebo-controlled study with identical matching placebo
Participants	N = 33. Mean age: 28.64 ± 6.6; 21 male participants. Twelve participants were randomly assigned to receive E25 1 mg, 10 participants were randomly assigned to receive E25 10 mg and 11 were randomly assigned to receive placebo. Two participants dropped out of the placebo group. All had mild asthma Inclusion criteria: FEV_1 > 70% predicted; bronchial hyperreactivity to methacholine; serum IgE < 300 IU/mL; positive skin prick test to aeroallergen

Fahy 1999 *(Continued)*

	Exclusion criteria: corticosteroids in previous six weeks; symptoms of upper/lower RTI in previous six weeks; history of tobacco use. Baseline characteristics: FEV_1 81.96% predicted ± 15.92; IgE 243.61 ± 149.5
Interventions	Aerosolised rhuMAb-E25 (1 mg or 10 mg) versus placebo via inhaler device. Treatment lasted for eight weeks with a four-week follow-up period
Outcomes	FEV_1, PEF (am), PC20, serum IgE levels
Notes	Jadad score: 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified according to late-phase response to allergen during the screening phase. Details of sequence generation not included in study report
Allocation concealment (selection bias)	Unclear risk	Details not included in study report
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants did not complete the trial; reasons for their withdrawal are included in trial report
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

Garcia 2012

Methods	Randomised parallel-group placebo-controlled study
Participants	Reported as 41 participants with severe non-atopic asthma uncontrolled despite daily high-dose inhaled corticosteroids (with or without maintenance oral corticosteroids) plus a long-acting $beta_2$-agonist
Interventions	Randomly assigned to receive omalizumab or placebo in a 1:1 ratio 16-Week study
Outcomes	Reported as the following: The primary endpoint was change in expression of high-affinity IgE receptor FceRI on blood basophils and plasmacytoid dendritic cells (pDC2) after 16 weeks. Impact on lung function and clinical parameters was also assessed
Notes	Funded by Novartis Pharma SAS

Risk of bias

Bias	Authors' judgement	Support for judgement

Garcia 2012 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Details not provided (conference abstract)
Allocation concealment (selection bias)	Unclear risk	Details not provided (conference abstract)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Details not provided (conference abstract)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not provided (conference abstract)
Selective reporting (reporting bias)	Unclear risk	Not possible to assess from conference abstract

Gevaert 2012

Methods	Randomised double-blind placebo-controlled study
Participants	Treatment group: 16. Control group: eight. Details of trial are very limited—reported as conference abstract Allergic and non-allergic participants with nasal polyps and asthma
Interventions	Stated as: Participants received four to eight (subcutaneous) doses of omalizumab or placebo, depending on serum IgE concentrations (30 to 700 kU/L) and body weight No details given of background steroid dose
Outcomes	Stated as: Primary endpoint was reduction in total nasal endoscopic polyp score after 16 weeks. Secondary endpoints included a change in the following: sinus CT scan, nasal and asthma symptoms, validated questionnaires (SF-36, RSOM-31 and AQLQ) and serum/nasal secretion biomarkers
Notes	Limited details reported (conference abstract)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details not provided (conference abstract)
Allocation concealment (selection bias)	Unclear risk	Details not provided (conference abstract)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not provided (conference abstract)

Gevaert 2012 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Hanania 2011

Methods	Randomised, multi-centre, parallel-group, double-blind, placebo-controlled trial
Participants	Treatment group: 427 (427 completed). Age: 43.7 (14.3). Males: 165 (38.6%). Baseline lung function: mean % predicted FEV_1 (SD): 65.4 (15.2) Control group: 423 (421 completed). Age: 45.3 (13.9). Males: 126 (29.9%). Baseline lung function: mean % predicted FEV_1 (SD): 64.4 (13.9) Inclusion criteria stated as: The study included participants 12 to 75 years of age with a history of severe allergic asthma for at least one year before screening. Participants received a diagnosis of asthma from physician investigators at each site on the basis of criteria specified by the NAEPP guidelines. Patients whose asthma was not well controlled despite treatment with high-dose ICS and LABAs with or without other controllers (including OCS) were enrolled. Asthma was considered not well controlled if participants had persistent asthma symptoms with current therapy, defined as an average of one or more night-time awakenings per week and daytime asthma symptoms requiring the use of rescue medication for two or more days per week during the four weeks before screening and for two consecutive weeks up to four weeks before randomisation. In addition, participants were required to have at least one documented asthma exacerbation during the previous 12 months, defined as increased asthma symptoms requiring treatment with systemic corticosteroid rescue therapy. High-dose ICS was given at a minimum dose of 500 mcg of fluticasone dry powder inhaler twice daily or its similar ex-valve dose for at least eight weeks before screening. Long-acting $beta_2$-agonist treatment could consist of salmeterol 50 mcg twice daily or formoterol 12 mcg twice daily for at least eight weeks before screening. Patients were also required to have objective evidence of allergy to a relevant perennial aeroallergen, defined as a positive skin test result or in vitro response (radioallergosorbent test) to dog, cat, cockroach, *Dermatophagoides farinae* (dust mite) or *D. pteronyssinus* documented in the 12 months before screening. Consistent with earlier pivotal studies, participants were also required to have baseline pre-bronchodilator FEV_1 of 40% to 80% of predicted values, serum IgE level of 30 to 700 IU/mL and body weight of 30 to 150 kg Exclusion criteria stated as: Persons were excluded if they had an asthma exacerbation requiring intubation in the 12 months before screening or an exacerbation requiring treatment with systemic corticosteroids (or an increase in the baseline dose of OCS) in the 30 days before screening. Other exclusion criteria included active lung disease other than asthma, treatment with omalizumab in the 12 months before screening, elevated serum IgE levels for reasons other than allergy (e.g. parasite infections, hyperimmunoglobulin E syndrome, Wiskott–Aldrich syndrome, bronchopulmonary aspergillosis) or smoking history of 10 or more pack-years Location(s): 193 sites in the United States and four sites in Canada
Interventions	Minimum dose of 0.008 mg/kg of body weight per IgE (IU/mL) every two weeks or 0.016 mg/kg per IgE (IU/mL) every four weeks versus placebo Background inhaled corticosteroid dose—at least 500 mcg of fluticasone dry powder inhaler (or its equivalent) twice daily Participant using long-term OCS at baseline = 60 (7.1%)
Outcomes	Stated as: The primary endpoint was the rate of protocol-defined exacerbations over the study period. Secondary efficacy endpoints included the change from baseline to week 48 in mean daily number of puffs of albuterol, mean total asthma symptom score and mean overall score on the standardised version of the Asthma Quality of Life Questionnaire (AQLQ[S]). Safety endpoints included the frequency and severity of treatment-emergent adverse events

Hanania 2011 *(Continued)*

Notes	48-Week trial Co-medication stated as: All participants received albuterol as rescue medication throughout the study. In addition, one or more of the following controller medications were allowed: leukotriene modifiers, including montelukast and zafirlukast; zileuton; oral, inhaled or nasal anticholinergic therapy; mast cell stabilisers, including cromolyn and nedocromil; specific immunotherapy; theophylline; and long-term maintenance OCS. Long-term OCS use consisted of a minimum dose of oral prednisolone (or comparable dose of another corticosteroid) of two to 40 mg/d or five to 80 mg every other day for at least four weeks immediately before the screening visit. Participants were classified in the M3 subgroup if they were long-term OCS users at baseline or had at least four asthma exacerbations during the previous year requiring treatment with OCS. Participants were not permitted to receive levalbuterol, gold salts, macrolide antibiotics, methotrexate, cyclosporine, intravenous immunoglobulin or immunosuppressants during the run-in and treatment periods In trial report, NCT number is provided as 00314575. However, on inspection of NCT registry, it appears to be NCT00314574

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stated as: Randomisation was stratified by using a generalisation of the hierarchical dynamic randomisation scheme to achieve approximate overall balance between treatment groups and within each stratum by using the following hierarchy: overall balance, study drug dosing regimens, baseline asthma controller medication group and centre
Allocation concealment (selection bias)	Low risk	Stated as: Only the interactive voice response system provider and the unbinding statistician had access to the unbinding code during the study, for randomisation and safety purposes; neither was involved in adjudication of study outcomes
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	83 discontinued in omalizumab group 94 discontinued in placebo group
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Holgate 2004a

Methods	Randomised, double-blind, parallel-group multi-centre placebo-controlled trial. Randomisation by computer-generated randomisation after run-in. Allocation by independent personnel. Scratch cards given to investigators to be broken in case of emergency
Participants	N = 246. Treatment group: 126; control group: 120 (two withdrawals due to keratitis and dysphonia—communication from Acumed). Mean age (placebo): 40.5 (12 to 71); treatment group: 41.1 (12 to 75). Female/Male percentage: placebo: 57.5/42.5; treatment: 64.3/35.7. Severe asthmatic participants optimally controlled, requiring high-dose fluticasone. FP dose: between 1000 and 2000 mcg/d Inclusion criteria stated as: male/females 12 to 75 years of age, severe asthma according to ATS guidelines, allergic response (> one positive skin prick test to one or more aeroallergens, mean total daily symptom score ≥ four over seven days before randomisation, ≥ 12% reversibility, FEV_1 within 30 min-

Holgate 2004a *(Continued)*

	utes of salbutamol in 12 months before or at randomisation, stable medication four weeks before randomisation, IgE between 30 and 700 IU/mL Exclusion criteria stated as: females for whom current or future pregnancy could not be excluded, evidence/history of drug or alcohol abuse, history of non-compliance with medical regimens, those considered potentially unreliable, known sensitivity to study drugs (omalizumab, corticosteroids, salbutamol and terbutaline), those using theophylline, those suffering from live/kidney disease, haematological abnormality, anaphylaxis, near-fatal asthma exacerbation in last three years, elevated serum IgE for reasons other than atopy (parasitic infections, etc). Baseline data: mean duration of disease: placebo: 22.3 years; treatment: 22.6 years. Never smoked/ex-smokers: placebo: 91/29; treatment: 99/27. Mean serum total IgE levels (IU/mL): placebo: 265.7 (±190.2); treatment: 266.8 (±218.0). Mean fluticasone dose (mcg/d): placebo: 1362.5 (±359.2); treatment: 1375 (±361.6). Participants taking LABA: placebo: 52 (43%); treatment: 62 (49%). Mean FEV_1 (percentage predicted): placebo: 66 (±20.2); treatment: 62.9 (±17.5). Mean FEV_1 reversibility: placebo: 20.6; treatment: 18.6. PEFR: placebo: 385.2; treatment: 371.9
Interventions	Subcutaneous omalizumab (0.016 mg/kg/IgE (IU/mL) at two- or four-weekly intervals depending on body weight versus placebo. Four-phase study. SIx- to 10-week run-in phase, 16-week steroid stable phase, 16-week steroid reduction phase, 12-week follow-up
Outcomes	Percentage reduction from baseline in inhaled FP, number of participants achieving > 50% reduction in inhaled fluticasone (subgroup according to LABA consumption), exacerbations, PEFR, QoL
Notes	Jadad score: 5 Trial 011

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by computer-generated randomisation after run-in
Allocation concealment (selection bias)	Low risk	Allocation by independent personnel
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	18 participants did not complete the trial, and reasons for withdrawal are included in the trial report
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

Holgate 2004b

Methods	Identical to Holgate 2004 (ICS)
Participants	N = 95 (treatment: 50; control: 45). Mean age: not specified (likely to be similar to Holgate 2004). FEV_1 (% predicted): treatment: 60; control: 57. Overnight hospital admission in last year: treatment: 23%; placebo: 23%; prednisolone dose (mg/d): treatment: 10; control: 10.6; ICS dose: (mcg/d): treatment: 1490; control: 1411

Holgate 2004b *(Continued)*

	Inclusion criteria: identical to Holgate 2004 (ICS)
Interventions	Identical to Holgate 2004 (ICS)
Outcomes	Identical to Holgate 2004 (ICS)
Notes	Unpublished data on oral corticosteroid users from Holgate 2004a (source: FDA report) Trial 011

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by computer-generated randomisation after run-in
Allocation concealment (selection bias)	Low risk	Allocation by independent personnel
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	18 participants did not complete the trial, and reasons for withdrawal are included in the trial report
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

INNOVATE

Methods	Randomised, double-blind, parallel-group, multi-centre, placebo-controlled trial. Blinding: matched placebo. Methods of allocation not reported. Randomisation stratified by concomitant asthma treatment and country of origin
Participants	N = 482. Mean age: omalizumab: 43.4; placebo: 43.3. FEV_1: omalizumab: 61; placebo: 61.6; rescue medication usage: omalizumab: 6.6; placebo: 5.5. Overall AQLQ: 3.9 (both groups); serum total IgE: omalizumab: 197.6; placebo: 189.6; ICS dose (BDP equivalent, mcg/d): omalizumab: 2359; placebo: 2301. All participants receiving high-dose ICS + LABA. 22% receiving maintenance oral steroids Inclusion criteria: +ve skin prick test to ≥ one aeroallergen; serum IgE: 30 to 700 IU/mL; severe persistent asthma requiring > 1000 BDP or equivalent and LABA treatment; FEV_1 40% to 80%; FEV_1 reversibility ≥ 12% post SABA; ≥ two exacerbations requiring OCS in previous 12 months or one severe exacerbation resulting in hospitalisation Exclusion criteria: smokers/smoking history of ≥ 10 pack-years; treatment for exacerbation four weeks before randomisation; use of methotrexate/gold salts/troleandomycin/cyclosporin within three months of first visit; prior omalizumab treatment
Interventions	Subcutaneous omalizumab (0.016 mg/kg per IU/mL) (plus usual care) versus placebo (plus usual care). Study duration: 28 weeks; run-in phase: seven-day screening period; eight-week run-in phase. Follow-up: 16-week (data not presented). During initial four weeks of run-in phase, medicines adjusted to achieve best control. No further adjustments permitted in last four weeks of run-in

INNOVATE *(Continued)*

Outcomes	Exacerbatrions (requiring OCS); hospitalisation; emergency room treatment; lung function; AQLQ; adverse events
Notes	Jadad score: 4. Imbalance between groups at baseline for primary outcome in the trial. Greater instance of exacerbations requiring oral steroids in omalizumab group compared with placebo group. Adjusted data were extracted and entered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation stratified by concomitant asthma treatment and country of origin
Allocation concealment (selection bias)	Unclear risk	Methods of allocation not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	52 participants did not complete the trial, and reasons for withdrawal are included in the trial report
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

Lanier 2009

Methods	Randomised, multi-centre, double-blind, parallel-group, placebo-controlled study
Participants	Treatment group: 421 (352 completed). Age: 8.7 ± 1.7. Males: 287 (68.2%). Baseline lung function: mean % predicted FEV_1 (SD): 86.0 (17.8) Control group: 206 (175 completed). Age: 8.4 ± 1.7. Males: 138 (66.7%). Baseline lung function: mean % predicted FEV_1 (SD): 87.2 (18.4) Inclusion criteria stated as: Parent or legal guardian was informed of the study procedures and medications and gave written informed consent. Outpatient males and females aged 6 to less than 12 years on study entry, with body weight between 20 and 150 kg. Total serum IgE level ≥ 30 to ≤ 1300 IU. Diagnosis of allergic asthma ≥ one year's duration, according to American Thoracic Society (ATS) criteria, and a screening history consistent with clinical features of moderate or severe persistent asthma according to National Heart Lung and Blood Institute (NHLBI) guidelines. Positive prick skin test to at least one perennial allergen, documented within the past two years or taken at screening. A radioallergosorbent test (RAST) could have been performed for participants with a borderline skin prick test result after consultation with Novartis clinical personnel. Patients with ≥ 12% increase in forced expiratory volume in one second (FEV_1) over starting value within 30 minutes of taking up to four puffs (4 × 100 µg) salbutamol (albuterol) or nebulised salbutamol up to 5 mg (or equivalent of alternative β_2-agonist) documented within the past year, at screening, during the run-in period or before randomisation. Patients were not to take their long-acting β_2-agonist (LABA) medication within 12 hours of reversibility testing. Clinical features of moderate or severe persistent asthma (at least step three) despite therapy at step three or four (at least medium-dose inhaled corticosteroid (ICS) fluticasone dry powder inhaler (DPI) ≥ 200 mg/d or equivalent with or without other controller medications)

Lanier 2009 *(Continued)*

	Documented history of experiencing asthma exacerbations and demonstrated inadequate symptom control during the past four weeks of run-in despite receiving an equivalent dose of fluticasone DPI ≥ 200 mg/d total daily ex-valve dose Exclusion criteria stated as: patients who received systemic corticosteroids for reasons other than asthma, beta-adrenergic antagonists by any route, anticholinergics within 24 hours of screening, methotrexate, gold salts, cyclosporin or troleandomycin, or had received desensitisation therapy with less than three months of stable maintenance doses before screening. Patients with a history of food- or drug-related severe anaphylactoid or anaphylactic reaction, a history of allergy to antibiotics, with aspirin- or other non-steroidal anti-inflammatory drug (NSAID)-related asthma (unless the NSAID could be avoided), with active lung disease or acute sinusitis/chest infection, elevated serum IgE levels for other reasons, presence/history of a clinically significant uncontrolled systemic disease, cancer, abnormal electrocardiogram (ECG) in the previous month, or platelets ≤ 100 × 109/L or clinically significant laboratory abnormalities at screening Location(s): 87 centres in seven countries: Argentina (eight), Brazil (three), Canada (six), Colombia (five), Poland (six), USA (58) and South Africa (one)
Interventions	Stated as: Participants received omalizumab administered by subcutaneous injection every two or four weeks for a duration of 52 weeks. Omalizumab dose was based on participant's body weight and total serum IgE level at screening. The first 24 weeks of the treatment period was a fixed steroid phase, where the steroid dose was maintained constant; in the following 28 weeks, the steroid dose was adjustable, depending on the participant's condition. Following the 52-week treatment period, participants were followed up for an additional 16 weeks Placebo was administered by subcutaneous injection every two or four weeks, depending on the dosing schedule in the protocol for a total of 52 weeks. The first 24 weeks of the treatment period was a fixed steroid phase, where the steroid dose was maintained constant; in the following 28 weeks, the steroid dose was adjustable, depending on the participant's condition. Following the 52-week treatment period, participants were followed up for an additional 16 weeks Matched vials of placebo supplied as sterile powder in a 5-mL vial designed to deliver 150 mg of placebo for s/c administration upon reconstitution with 1.4 mL sterile water Backgound inhaled corticosteroid dose: at least 200 mg/d fluticasone propionate via dry powder inhaler or equivalent, mean ICS dose 515.1 ± 285.4 mcg/d (fluticasone propionate equivalent) Participants using maintenance oral steroids at baseline = 8 (1.3%)
Outcomes	Primary outcome measures stated as: rate of clinically significant asthma exacerbations per participant in the 24-week fixed-dose steroid treatment period (time frame: baseline to end of the fixed-dose steroid treatment period (week 24). Percentage of participants with at least one adverse event (time-frame: baseline to end of the study (week 68)) Secondary outcome measures stated as: change in mean nocturnal asthma symptom score from baseline to the end (last four weeks) of the 24-week fixed-dose steroid treatment period (time frame: baseline to the end (last four weeks) of the 24-week fixed-dose steroid treatment period). Rate of clinically significant asthma exacerbations per participant in the 52-week treatment period (time frame: baseline to end of treatment period (week 52)). Change in mean daily number of puffs of asthma rescue medication from baseline to end (last four weeks) of 24-week fixed-dose steroid treatment period (time-frame: baseline to the end (last four weeks) of 24-week fixed-dose steroid treatment period). Change in Pediatric Asthma Quality of Life Questionnaire (Standardised) (PAQLQ(S)) scores from baseline to end of 24-week fixed-dose steroid treatment period (week 24) (time frame: baseline to end of 24-week fixed-dose steroid treatment period (week 24))
Notes	One-year trial Co-medication: inhaled corticosteroids 24-week fixed-dose and 28-week adjustable-dose

Lanier 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned (two:one) to receive omalizumab or placebo by a randomisation card system
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details of 101 participants who did not complete the trial are reported
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Massanari 2010

Methods	Randomised, double-blind, parallel-group, placebo-controlled study
Participants	Treatment group: 139. Age: 38.2 (9.89). Males: 51 (37%). Baseline lung function: mean % predicted FEV_1 (SD): 86.1 (11.18) (n = 134) Control group: 136. Age: 38.2 (10.02). Males: 37 (27%). Baseline lung function: mean % predicted FEV_1 (SD): 88.1 (11.64) (n = 131) Inclusion criteria stated as: male or female, any race, ages 18 to 55 years, body weight ≥ 20 kg and ≤ 150 kg, total serum IgE concentration ≥ 30 and ≤ 700 IU/mL at visit 0. History of at least moderate persistent allergic asthma of ≥ one year in duration, on a stable asthma treatment regimen including inhaled corticosteroids for the preceding four weeks, an FEV_1 while withholding short-acting beta-agonists for at least six hours and long-acting beta-agonists for at least 12 hours, of ≥ 75% of predicted value at visit 0, reversibility (increase in FEV_1 of ≥ 12% between 20 and 30 minutes after four puffs), positive skin test to at least one perennial allergen (house dust mite, cat or dog), average PEFR variability ≤ 20%, prespecified level of nocturnal asthma symptoms, non-smoker for at least one year before visit 1, with a smoking history of no more than 10 pack-years, good physical and mental health Exclusion criteria stated as: history of intubation for asthma or requiring systemic steroids in last three months, asthma requiring ED visit on admission in the preceding six months, URTI or sinusitis within the preceding four weeks, history of an anaphylactic allergic reaction (except to stinging insects, foods or drugs other than omalizumab), history of treatment with immunotherapy to any allergen within past three years, history of aspirin- or non-steroidal anti-inflammatory drug (NSAID)-related asthma, history of or current malignancy, any clinically significant uncontrolled systemic disease or a history of such disease within the previous three months, clinically significant laboratory abnormalities at visit 1, platelet levels ≤ 130×10^9/L at visit one, pregnant or breast-feeding women or women using inadequate contraception, history of hypersensitivity to the study medication or drugs related to omalizumab (e.g. monoclonal antibodies, polyclonal gammaglobulin), Previous treatment with omalizumab within one year of screening, Considered by investigator to be potentially unreliable or who may not have reliably attended study visits, history of drug or alcohol abuse Location(s): USA

Massanari 2010 *(Continued)*

Interventions	At least 0.016 mg/kg/IgE (IU/mL) omalizumab subcutaneous per four weeks. Study drug administered by subcutaneous injection every two or four weeks according to weight and baseline IgE versus placebo Background inhaled corticosteroid dose—all participants receiving ICS at baseline; no further details given
Outcomes	Primary: systemic allergic reaction to participant-specific allergen. Secondary: severity of the first SAR to SIT, achievement of target maintenance SIT dose, number of visits required to complete the cluster SIT regimen, number of doses of rescue medications for managing SIT reactions
Notes	26-Week study that consisted of four periods: screening (two weeks), treatment with omalizumab or placebo (16 weeks), cluster SIT (four weeks, including three weeks of overlap with omalizumab/placebo) and maintenance SIT (seven weeks) Co-medication: Patients remained on usual asthma treatment. After 13 weeks of omalizumab treatment (or placebo), they were challenged with their specific allergens (SIT)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details of sequence generation. Stratified by allergens
Allocation concealment (selection bias)	Unclear risk	No details of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Because reconstituted placebo vials did not exactly match those containing omalizumab, a study technician not involved with any participant study assessments was responsible for preparing and administering all injections (providing this technician did not divulge information to participants or study staff)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants accounted for but higher drop out in the placebo group (75% vs 61%)
Selective reporting (reporting bias)	Low risk	All stated outcome measures reported

Milgrom 1999

Methods	Randomised, double-blind, parallel-group, placebo-controlled trial
Participants	N = 317 (569 screened). Mean age 30 years, 133 male. High-dose group: N = 106; low-dose group: N = 106; placebo group: N = 105. FEV_1 71% predicted. ICS dose: 800 mcg, OCS dose: 10 mg/d (35 participants), inhaled beta-agonist dose: seven puffs/d, IgE 273 to 374 IU/mL. Five participants dropped out of the placebo group, and two participants withdrew from each of the two treatment groups Inclusion criteria: inhaled triamcinolone, flunisolide or beclomethasone (200 mcg/d), positive skin prick tests, < 1785 IU/mL serum IgE

Milgrom 1999 *(Continued)*

	Exclusion criteria: symptom score < 2.5, poorly reversible airway obstruction, treatment doses projected to be < 1 mL, negative skin prick tests, active disease other than asthma, lack of compliance
Interventions	Twice-weekly intravenous low-/high-dose omalizumab versus placebo. Low dose: 2.5 mcg/kg/ng IgE/mL, high dose: 5.8 mcg/kg/ng IgE/mL. Treatment during stable steroid phase lasted for 12 weeks, followed by eight weeks of steroid reduction. Follow-up was 10 weeks
Outcomes	FEV_1, PEF, QoL, withdrawals, asthma exacerbations, daily total symptom score, beta-agonist use, mean decrease in CS use, adverse effects
Notes	Jadad score: 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of sequence generation not included in trial report
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not included in trial report
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	34 participants did not complete the trial, and reasons for withdrawal are included in the trial report
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

Milgrom 2001

Methods	Randomised, double-blind, parallel-group, placebo-controlled trial
Participants	N = 334 (501 screened). Age range: six to 12 years. Treatment group: N = 225; control group: N = 109. 231 males. Mean PEFR (L/min): treatment group: 261 (101 to 408); control group: 264 (140 to 407). Mean FEV_1 (percentage predicted) treatment group: 84 (49 to 129); control group: 85 (43 to 116). Number hospitalised for asthma in past year: treatment group: N = 18; control group: N = 9. Mean BDP dose: treatment group: 284 (168 to 672); control group: 267 (168 to 504). Mean albuterol use (per day): treatment group: 1.1, control group: 1.4 Inclusion criteria: diagnosis of allergic asthma of at least one year's duration; positive skin prick test to one of: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cockroach, dog or cat; total serum IgE level between 30 and 1300 IU/mL; body weight < 90 kg; baseline FEV_1 > 60% of predicted normal value; at least 12% increase in FEV_1 over baseline within 30 minutes of taking one or two puffs of albuterol (90 mcg/puff); stable asthma, defined as no significant change in regular asthma medication and no acute asthma exacerbation requiring corticosteroid rescue for at least four weeks before enrolment Exclusion criteria: previous treatment with omalizumab; known hypersensitivity to any study drug; history of acute infectious sinusitis or respiratory tract infection or active lung disease other than allergic asthma within one month or any other significant systemic disease within three months of visit one; clinically significant abnormalities in electrocardiogram, chest x-ray or lab values, or elevated serum

Milgrom 2001 *(Continued)*

	IgE levels for reasons other than atopy; children requiring doses greater than 750 mg per four weeks, based on total serum IgE and body weight consideration (0.016 mg/IgE in IU/mL × body weight in kg)
Interventions	Subcutaneous administration of omalizumab (0.016 mg/kg/IgE (IU/mL), equivalent to 150 or 300 mg every four weeks, or 225, 300 or 375 mg every two weeks, depending on participant's body weight. Run-in phase lasted four to six weeks with stabilisation on BDP, followed by a stable steroid phase (16 weeks) and a steroid reduction phase (12 weeks)
Outcomes	BDP dose, asthma symptom score, asthma exacerbation rate, rescue beta-agonist use, pulmonary function—FEV_1 + PEFR, global evaluation of treatment, pharmacoeconomics, pharmacodynamics, adverse events, withdrawals
Notes	Jadad score: 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of sequence generation not included in trial report
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not included in trial report
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Eight participants did not complete the trial, and reasons for withdrawal are included in the trial report
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

NCT00096954

Methods	Randomised, multi-centre, parallel-group, double-blind, placebo-controlled study
Participants	Treatment group: 159. Age: 36.0 (14.7). Males: 47 (30%). Baseline lung function: mean % predicted FEV_1 (SD): not stated Control group: 174. Age: 38.1 (15.1). Males: 55 (32%). Baseline lung function: mean % predicted FEV_1 (SD): not stated Patients with 'difficult to treat atopic asthma' Inclusion criteria stated as: documented history of asthma as well as evidence of ≥ 12% reversibility of FEV_1; baseline FEV_1 ≥ 80% predicted normal value before randomisation; positive skin test (diameter of wheal ≥ 3 mm vs control) or in vitro radioallergosorbent test (RAST(R)) or ImmunoCap(R) to one relevant perennial aeroallergen such as cat or house dust mites documented within the previous year; receiving at least an inhaled corticosteroid dosage of fluticasone dry powder inhaler (DPI) ≥ 200 µg/d or equivalent; during four-week run-in period before randomisation demonstrate evidence of inadequate asthma symptom control; inadequate asthma symptom control defined as at least one of the following reported on the participant diary card during four-week run-in period: daytime asthma symptoms as a score of ≥ one (scale of zero to four) on at least 20 of 28 days (missing data to be treated as a day with no symptoms) and mean symptom score ≥ 1.5 or night-time awakening because of asthma symptoms

NCT00096954 *(Continued)*

	(more than four times during four-week run-in period); meet study drug-dosing table eligibility criteria (serum baseline IgE level ≥ 30 to ≤ 1300 IU/mL and body weight ≥ 20 to ≤ 150 kg); if female of child-bearing potential, using an effective method of contraception Exclusion criteria stated as: received long-term systemic corticosteroids (oral or intravenous) within three months or received a burst of oral corticosteroids within the last two weeks before screening; received Xolair therapy at any time within 12 months before screening; pregnant or lactating; known hypersensitivity to any ingredients of Xolair, including excipients (sucrose, histidine, polysorbate 20); lifetime history of smoking > 10 pack-years; active lung disease other than asthma (e.g. chronic bronchitis, emphysema, cystic fibrosis, chronic obstructive pulmonary disease); history of upper respiratory infection or lower respiratory infection within 30 days before randomisation; diagnosis of aspirin- or nonsteroidal anti-inflammatory drug-induced asthma; immunosuppressants or other investigational drugs within 30 days before screening; significant medical illness other than asthma Location(s): unclear
Interventions	Omalizumab (Xolair) was administered subcutaneously every two or four weeks. Dose (mg) and dosing frequency were determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). Dose of placebo consisting of sucrose, L-histidine, L-histidine hydrochloride monohydrate and polysorbate 20 administered by subcutaneous injection every two or four weeks Background inhaled corticosteroid dose—fluticasone dry powder inhaler (DPI) ≥ 200 µg/d or equivalent
Outcomes	Rate of asthma exacerbations over 24-week treatment period; number of participants experiencing one or more protocol-defined asthma exacerbations during the treatment period; change from baseline in nocturnal and daytime asthma symptom scores at week 24; relative percentage change from baseline in forced expiratory volume in one second (FEV_1) at week 24
Notes	24-Week study (four-week monitoring run-in; baseline therapy not changed) Co-medication too: usual asthma regimen (immunotherapy not allowed)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Information on participants failing to complete included in report. 157 (99%) completed in intervention group and 171 (99%) in control
Selective reporting (reporting bias)	Low risk	All outcome measures clearly reported

NCT01007149

Methods	Randomised, multi-centre, double-blind, placebo-controlled, parallel-group

NCT01007149 *(Continued)*

Participants	Treatment group: 20. Age:55.0 (9.67). Males: seven (35%). Baseline lung function: mean % predicted FEV_1 (SD): not stated Control group: 21. Age: 54.6 (12.78). Males: 8 (38%). Baseline lung function: mean % predicted FEV_1 (SD): not stated Participants with severe persistent asthma (GINA criteria) Inclusion criteria stated as: severe persistent asthma with the following characteristics: uncontrolled according to Global Initiative for Asthma (GINA) 2007 guidelines and at least two exacerbations having required systemic corticosteroid and/or at least one hospitalisation or emergency room visit in the past year; treated with high-dose inhaled corticosteroid (i.e. > 1000 µg beclometasone dipropionate equivalent per day) plus inhaled long-acting β_2-agonist (with or without maintenance oral corticosteroid); non-atopic (i.e. negative blood multi-allergic testing and negative *Aspergillus*-specific IgE-radioallergosorbent blood test and negative skin prick tests to a battery of common aeroallergens Exclusion criteria stated as: current smoker or smoking history stopped for less than three years or > 10 pack-years; asthma exacerbation during the four weeks before randomisation; active lung disease other than non-atopic asthma; patients with an active cancer, a suspicion of cancer or any history of cancer with less than five disease-free years; pregnant or nursing (lactating) women; treatment with omalizumab Location(s): 10 centres in France
Interventions	Intervention: Participants received subcutaneous injections of omalizumab every two weeks or every four weeks; dosage dependent on IgE level and body weight Control: Participants received subcutaneous injections of placebo to omalizumab every two weeks or every four weeks Background inhaled corticosteroid dose > 1000 µg beclometasone dipropionate equivalent per day Patients using oral corticosteroids were included, but no further details were given
Outcomes	Change from baseline in expression of FcεRI receptors of blood basophils; change from baseline in expression of FcεRI receptors of dendritic cells; change in fractional exhaled nitric oxide; change from baseline in induced sputum eosinophil count; change from baseline in score of the shortened version of the Asthma Control Questionnaire; change from baseline in nasal symptom global score and individual components; physician and participant global evaluation of treatment effectiveness; change in forced expiratory volume in one second (FEV_1) from baseline to 16 weeks; number of participants with at least one asthma-related event over 16 weeks
Notes	16-Week trial. Two-week 'screening' period; no run-in described Co-medication: not specifically stated, but all participants had to be using high-dose inhaled steroids plus LABA to be eligible for inclusion

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind

NCT01007149 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	High completion rate. 100% in intervention group and 20 (95%) in control group
Selective reporting (reporting bias)	Low risk	All outcome measures reported

Ohta 2009

Methods	Randomised, double-blind, parallel-group, multi-centre study
Participants	Treatment group: 158. Age: 48.8 (14.88). Males: 74 (46.8%). Baseline lung function: mean % predicted FEV_1 (SD): 74.06 (19.91) Control group: 169. Age: 49.2 (14.42). Males: 70 (42.7%). Baseline lung function: mean % predicted FEV_1 (SD): 75.81 (20.89) Inclusion criteria stated as: males and females with inadequately controlled allergic asthma for > one year (positive skin prick test), 20 to 75 years, weighing 30 to 150 kg, with allergic asthma, IgE level 30 to 700 IU/mL, taking inhaled corticosteroids at a dosage of BDP 800 µg/d (or equivalent) and at least one more drug for managing their asthma at least three months before trial observation (e.g. oral corticosteroids, β_2-agonists (oral, inhaled or patch-type) theophylline, leukotriene-3 antagonists or a thromboxane A2 inhibitor/antagonist) Exclusion criteria stated as: pregnant or breast-feeding, history of severe anaphylactic reaction or anaphylactoid reaction, patients taking unacceptable medications (e.g. > 10 mg of prednisolone-equivalent oral corticosteroids, immunosuppressants), significant underlying medical conditions that could impact interpretation of results Location(s): 73 centres in Japan
Interventions	Subcutaneous dose of omalizumab was based on participant's body weight and total serum IgE level at visit 1 and was at least 0.016 mg/kg/IgE (IU/mL) every four weeks or 0.008 mg/kg/IgE (IU/mL) every two weeks versus placebo Background inhaled corticosteroid dose > 1000 µg beclometasone dipropionate equivalent per day Participants using oral corticosteroids at baseline included but no further details given
Outcomes	Morning peak expiratory flow (PEF) at baseline and at end of treatment, pulmonary function parameters measured by spirometer, frequency of rescue medication use, symptoms score, activities of daily living score, night-time sleep score, adverse events
Notes	Two-week pretreatment phase, 16-week treatment phase and 12-week follow-up Co-medication: doses of ICS and other concomitant asthma medications were kept constant for one month before pretreatment phase and were maintained during treatment phase. Participants were permitted to use rescue medication as needed. If any worsening of asthma occurred, which required additional treatment with a systemic corticosteroid, the participant was discontinued from the study

Risk of bias

Ohta 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stated as: randomised and allocated to receive either omalizumab or placebo using a third party's central registration system
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind but unclear whether blinding continued beyond end of 16-week treatment phase
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unbalanced withdrawals from groups (8.2% from treatment group vs 16.6% from placebo group)
Selective reporting (reporting bias)	Unclear risk	All outcome measures reported with exception of serum IgE levels and correlation with efficacy and other pharmacological measurements

Prieto 2006

Methods	Randomised, double-blind, parallel-group, placebo-controlled trial
Participants	N = 34. Mean age unclear. Treatment group: 18; control group: 16 Inclusion criteria: mild to moderate allergic asthma
Interventions	Subcutaneous omalizumab versus placebo (dosage unclear) Treatment lasted for 12 weeks
Outcomes	Airway responsiveness
Notes	Unpublished conference abstract: Jadad score: 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of sequence generation not included in trial report
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not included in trial report
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Five participants did not complete the trial, and reasons for withdrawal are included in the trial report
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

SOLAR

Methods	Randomised, double-blind, parallel-group, placebo-controlled trial. Method of allocation: not reported
Participants	N = 405 (no data on N screened). Treatment: 209; control: 196. Age range: 12 to 75 years. Mean steroid dose (BUD equivalent mcg/d): treatment: 842; control: 901. Mean exacerbations requiring OCS in past year: treatment: 2.1; control: 2.1 Inclusion criteria: FEV_1 reversibility ≥ 12%; IgE level ≥ 30 to ≤ 1300 IU/mL; +ve skin prick test to one or more indoor allergen; co-existing moderate to severe perennial rhinitis; ≥ 400 mch/d ICS; ≥ two unscheduled medical visits for asthma in past year; score ≥ 64/192 on AQLQ Exclusion criteria: patients taking systemic steroids; long-acting antihistamines; cromolyn sodium, oral beta-agonists; theophylline; leukotriene antagonists; inhaled anticholinergics; methotrexate; gold salts; cyclosporin; allergen-specific immunotherapy; non-allergic rhinitis; pregnancy; platelet count ≤ $130 \times 10^{(9)}$/one
Interventions	Subcutaneous omalizumab 0.016 mg/kg/IgE (IU/mL) every four weeks versus placebo, in addition to ICS therapy and other stable preexisting drug regimens (e.g. LABAs, nasal steroids). Four-week run-in phase; participants switched to BUD equivalent Turbuhaler; dose kept stable for at least four weeks before study entry Study duration: 28 weeks
Outcomes	Asthma exacerbations (defined as worsening of asthma symptoms necessitating treatment with oral steroids/doubling dose of baseline ICS); AQLQ, RQLQ; rescue medication usage; symptoms; lung function (FEV_1, FVC am PEF), ICS use
Notes	Jadad score: 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of sequence generation not included in trial report
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not included in trial report
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	20 participants did not complete the trial, and reasons for withdrawal are included in the trial report
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

Solèr 2001

Methods	Randomised, double-blind, parallel-group, placebo-controlled trial. Randomisation by random number sequences. Participants randomly assigned at visit three. Independent personnel were responsible for allocation

Solèr 2001 *(Continued)*

Participants	N = 546 (1356 screened). Age range: 12 to 75, 268 male participants. Asthma diagnosed according to ATS guidelines Inclusion criteria: asthma diagnosed for longer than one year, positive skin prick test to at least one allergen, serum total IgE level > 30 and < 700 IU/mL-1, body weight < 150 kg, baseline FEV_1 > 40% and < 80% predicted, increasing by > 12% within 30 minutes of taking salbutamol, mean total daily symptom score > 3 (max 9) during 14 days before randomisation, treatment with ICS 200 mcg BDP per day for > three months before randomisation, use of beta-agonists on an as-needed/regular basis Exclusion criteria: unstable asthma, significant alteration to regular medication and acute exacerbation requiring additional corticosteroid treatment > one month before screening visit, oral steroids. 59 participants withdrew from the study (placebo: n = 40; omalizumab: n = 19). Reasons cited were withdrawal of consent (placebo: n = 14; omalizumab: n = 3), unsatisfactory therapeutic effect (placebo: n = 11; omalizumab: n = 8), adverse events (placebo: n = 5; omalizumab: n = 0)
Interventions	Subcutaneous omalizumab ≥ 0.016 mg/kg/IgE (IU/mL) versus placebo over a core 28-week period. Run-in phase was four to six weeks with stabilisation of BDP. Stable and reduction phases of BDP followed randomisation. Trial extension phase lasted 32 weeks
Outcomes	Number of exacerbations, change in serum free IgE, reduction in BDP, symptom score, rescue medication use, morning PEF, safety and tolerability
Notes	Jadad score: 5 Trial 009

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by random number sequences. Participants randomly assigned at visit three
Allocation concealment (selection bias)	Low risk	Independent personnel responsible for allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	20 participants did not complete the trial, and reasons for withdrawal are included in the trial report
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

van Rensen 2009

Methods	Randomised, double-blind, parallel-group, placebo-controlled trial
Participants	N = 25. Mean age: unclear Inclusion criteria: mild persistent asthma
Interventions	Subcutaneous omalizumab versus placebo (dosing levels unclear)

van Rensen 2009 *(Continued)*

	Study duration: 12 weeks
Outcomes	PC20 methacholine, sputum and allergen challenge followed by bronchoscopy at 24 hours; changes in PC20, sputum eosinophils, max fall in FEV_1 during late asthmatic response (LAR), post-allergen eosinophils (EG2) and mast cells (AA1)
Notes	Unpublished conference abstract. Jadad score: 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of sequence generation not included in trial report
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not included in trial report
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant did not complete the trial, and reasons for withdrawal are included in the trial report
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

ATS: American Thoracic Society; BDP: Beclomethasone; CS: Corticosteroid; E25/rhu-MAb E25/Xolair/omalizumab: anti-IgE; FEV_1: forced expiratory volume in one second; HDM: House dust mite; ICS: Inhaled CS; IgE: Immunoglobulin E; LABA: Long-acting beta-agonists; OCS: Oral corticosteroid; PC20: Bronchial challenge; PEFR: peak flow; QoL: Quality of life; RTI: respiratory tract infection.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anonymous 2000	Review article reporting data from Milgrom 1999.
Anonymous 2000b	German language review article with summary of Milgrom 1999.
Anonymous 2003	Not a randomised study
Ayars 2011	Trial focuses on mepolizumab rather than omalizumab.
Ayars 2013	Not Omalizumab Added June 2013
Babu 2001	Review article.
Beeh 2006	Pooled analysis from 4 studies (not identified in conference abstract).
Berger 2002	Review article.

Study	Reason for exclusion
Bisberg 1996	Single blind placebo controlled study. No randomisation reported - pharmacokinetic and pharmacodynamic profiles were analysed.
Blanken 2013	Respiratory syncytial virus and recurrent wheeze in healthy preterm infants Added June 2013
Bousquet 2010	A comparison between different clinical measures
Bousquet 2011	Open label study
Bruselle 2009	Observational study
Buhl 2001	Meta-analysis of data drawn from included studies.
Busse 2013	Not Omalizumab Added June 2013
Castro 2011	Evaluation of bronchial thermoplasty
Chipps 2009	Pooled analysis from 2 studies (not identified in conference abstract).
CIGE025A1305	Study in population with seasonal allergic rhinitis
CIGE025A1306	Study in population with seasonal allergic rhinitis
CIGE025A1307	Non-randomised study
CIGE025A2208	Non-randomized study
CIGE025A2303	Mixed population of patients with asthma and allergic rhinitis
CIGE025AUS23	Study focuses on impact of Xolair on immunotherapy outcomes
Corren 2010	Phase 2 study of AMG 317, an IL-4Ralpha antagonist
Corren 2011	Trial focuses on lebrikizumab rather than omalizumab.
Corren 2011a	This trial focuses on the effect of omalizumab on cat-allergen induced bronchospasm.
Demoly 1997	Review article.
Eckman 2010	Diagnosis is cat-induced allergic rhinitis rather than asthma
Emmrich 2001	German language summary of the Milgrom 1999 study.
ETOPA	Inadequate control (best standard care without placebo)
Fernandez 2005	Non-randomised safety study
Frew 1998	Review article.
Gauvreau 2012	Not Omalizumab Added June 2013
Gauvreau 2012a	Not Omalizumab Added June 2013
Gober 2008	Trial focuses on chronic idiopathic urticaria rather than asthma

Study	Reason for exclusion
Gossage 2010	Trial focuses on subcutaneous (SC) dose study of MEDI-563, a monoclonal antibody
Gossage 2012	Not Omalizumab Added June 2013
Hanania 2011a	Trial focuses on lebrikizumab rather than omalizumab.
Hendeles 2007	Crossover study
Hodsman 2013	Not Omalizumab Added June 2013
Holgate 2001	Review article.
Hoshino 2011	Open label study
Hughes 2000	Review article.
Johansson 2009	Diagnosis is cat-induced allergy rather than asthma
Kamin 2010	Main focus of trial is on allergic rhinitis
Karpel 2010	Pooled analysis from two trials Busse 2001 and Solèr 2001
Kenyon 2011	Trial focuses on L-arginine supplementation
Kopp 2009	Study focuses on impact of Xolair on immunotherapy outcomes
Lanier 2010	Non-randomized study
Leynadier 2004	Target population with latex allergy.
Lobo 2007	Assessment of a quality of life instrument rather than a comparison between two groups
Massanari 2008	Pooled analysis of two studies (not identified in conference abstract).
Massanari 2009	Pooled analysis from two trials Busse 2001 and Solèr 2001
Maykut 2008	Pooled analysis from five trials (not identified in conference abstract)
McClintock 2012	Not Omalizumab Added June 2013
Milgrom 2007	Pooled analysis from four trials (not identified in conference abstract)
Milgrom 2009	Pooled analysis from two trials (not identified in conference abstract)
Milgrom 2011	Pooled analysis from two trials Milgrom 2001 and Lanier 2009
Molfino 2013	Not Omalizumab Added June 2013
Moulton 2000	Journal letter.
NCT00109187	Non-randomized study
NCT00109200	Non-randomized study
NCT00133042	Crossover study

Study	Reason for exclusion
NCT00180011	Non-randomized study
NCT00189228	Non-randomized study
NCT00201097	Open label study
NCT00219323	Non-randomized study
NCT00242359	The study was withdrawn due to problems identifying the target population.
NCT00283504	Non-randomized study
NCT00287378	Study terminated due to difficulties with enrolment
NCT00401596	Open label study
NCT00434434	Trial focuses on the effect of omalizumab on allergen-induced airway responsiveness
NCT00482248	Non-randomized study
NCT00482508	Non-randomized study
NCT00500539	Non-randomized study
NCT00546143	Non-randomized study
NCT00567476	Open label study
NCT00624832	This trial focuses on the effect of omalizumab on allergen-induced bronchospasm
NCT00639691	Non-randomized study
NCT00777764	Non-randomized study
NCT00784485	Terminated due to difficulties with enrolment
NCT00829179	Non-randomized study
NCT01155700	Non-randomized study
NCT01219036	Non-randomized study
Nopp 2010	Non-randomized study
Oh 2010	Trial focuses on Interleukin-9 Monoclonal Antibody (MEDI-528)
Oh 2012	Not Omalizumab Added June 2013
Ong 2005	Study not concerned with asthma; volunteers with atopy
Parker 2010	Trial focuses on Interleukin-9 Monoclonal Antibody (MEDI-528)
Parker 2011	Trial focusing on brain magnetic resonance imaging in adults with asthma

Study	Reason for exclusion
Parker 2011a	Trial focusing on multiple subcutaneous doses of MEDI-528, a humanized anti-interleukin-9 monoclonal antibody
Patel 2009	This trial focuses on the effect of omalizumab on airway hyperresponsiveness
Pavord 2012	Not Omalizumab Added June 2013
Piper 2011	Phase 2 study of tralokinumab
Piper 2013	Not Omalizumab Added June 2013
Q2143G	Inadequate control (best standard care without placebo)
Riviere 2008	Assessment of different preparations of Anti-IgE
Riviere 2009	Bioequivalence study without placebo arm
Riviere 2011	Bioequivalence study without placebo arm
Rubin 2012	Open label study
Scheerens 2011	Trial focuses on lebrikizumab rather than omalizumab.
Stallings 2009	Study focuses on rhinovirus colds
Tajiri 2013	Not asthma Added June 2013
Townley 2011	This trial focuses on the effects of omalizumab on bronchial and alveolar airway inflammation as measured by exhaled nitric oxide
Wenzel 2013	Not Omalizumab Added June 2013
Wilson 2008	Bronchial biopsy from patients included in studies already in the review.
Yalcin 2011	Not an RCT and no comparison with placebo
Zaidi 2009	Study focuses on changes in the Fc-epsilonRI-Beta: Fc-epsilonRI-alpha Ratio
Zielen 2009	This trial focuses on the effect of omalizumab on allergen-induced bronchospasm
Zielen 2013	Allergen-induced bronchoconstriction Added June 2013

Characteristics of studies awaiting assessment *[ordered by study ID]*

Creticos 2010

Methods	We have been unable to obtain confirmation that this study is the same trial as NCT00162773 (which is reported as randomised, but for which no data are reported). It is unclear from the trial report (a conference abstract) whether Creticos 2010 was randomised. It is hoped that this issue will be clarified by the next update of this review
Participants	Eight participants in total, with five allocated to intervention and three to control. Details in conference abstract are very limited. Moderate to severe non-allergic asthma

Creticos 2010 *(Continued)*

Interventions	Omalizumab versus placebo
Outcomes	Please see Notes below
Notes	Conference abstract results and conclusions reported as: database/advertising screen of 870+ adult asthmatic patients yielded 85 participants (< 10%) meeting initial criteria, 29 of whom completed screening, with eight (1%) qualifying for enrolment. All participants had negative primary puncture skin test sensitivity/RASTs to perennial allergens (dust mite/cat/ dog/cockroach); two demonstrated secondary reactivity to dust mites. Mechanistically, an expected rise in serum IgE (1.5-/6.4-fold) was observed in two or four subjects four months taking omalizumab. DC and basophils from these participants showed a > 50% decrease in FceRIa. However, low serum IgE levels (<two of eight IU) were not increased in the other two omalizumab participants, nor were changes in FceRIa expression discernible. Placebo participants (n = 53) showed no drop in FceRIa. Finally, no discernible changes were observed in basophil/DC function in any of the omalizumab-treated participants. Conclusions: This study demonstrates the difficulty in identifying a true subset of participants with the disease entity of NAA. Although expected shifts in cellular FceRIa expression were evident, we observed no evidence of clinical benefit (symptoms/lung function/med usage/QOL) in NAA participants treated with omalizumab

NCT00046748

Methods	Randomised, double-blind, parallel-group study
Participants	Adults and adolescents with severe persistent asthma
Interventions	Subcutaneous omalizumab versus placebo
Outcomes	Clinically significant asthma exacerbation Medical resource utilisation Time to first asthma exacerbation Quality of life assessment at baseline, last visit Frequency of asthma rescue medication use Safety/tolerability of omalizumab
Notes	No data available at time of completion of 2012 update of this review

NCT00226200

Methods	Randomised, double-blind, parallel-group study
Participants	Moderate to severe allergic or non-allergic asthmatic patients
Interventions	Omalizumab versus placebo
Outcomes	Measure of sCD23 in plasma CD23 expression on T cell correlated with spirometry, AQLQ and RQLQ
Notes	No data available at time of completion of 2012 update of this review

NCT00329381

Methods	Randomised, parallel-group, placebo-controlled, double-blind, multi-centre
Participants	Treatment group: 139. Age: 38.2 (9.89). Males: 51 (36.7%). Baseline lung function: mean FEV_1 L (SD): 2.93 (0.69) Control group: 136. Age: 38.2 (10.02). Males: 37 (27.2%). Baseline lung function: mean FEV_1 L (SD): 2.84 (0.62) Inclusion criteria stated as: men and women 18 years to 55 years; clinical diagnosis and history of moderate persistent allergic asthma > one year's duration (GINA guidelines); body weight ≥ 20 kg and ≤ 150 kg; total serum IgE ≥ 30 and ≤ 700 IU/mL; on stable asthma treatment including corticosteroids for the preceding four weeks; non-smoker for at least one year before visit one; prebronchodilation FEV_1 at least 75% predicted at first visit; documented (positive skin prick test) sensitivity to at least one of three perennial aeroallergens (house dust mite, dog, cat); judged to be in good physical and mental health and capable of completing the trial Exclusion criteria stated as: history of intubation for asthma or exacerbation requiring systemic steroids within preceding three months or exacerbation requiring hospital treatment within preceding six months; history of immunotherapy to any allergen within the past three years; history of anaphylactic allergic reaction; upper respiratory tract infection within preceding four weeks; history of NSAID- or aspirin-related asthma; history of or current malignancy or other clinically significant uncontrolled systemic medical condition within preceding three months; platelets < 130 × 10^9/L at first visit; pregnant or breast-feeding women, or women not practicing a medically approved contraceptive method; allergy to any of the study medications or components; history of drug or alcohol abuse; inability to complete diary or perform lung function tests; oral, IM, IV or intra-articular steroids within preceding four weeks; beta-agonists within preceding one week; antihistamines within one week before skin prick testing; could then be used for remainder of study; IV gammaglobulin or immunosuppressants within preceding four weeks; tricyclic antidepressants within preceding one week; investigational drugs within preceding four weeks Location(s): 70 centres in the USA
Interventions	Omalizumab 150 to 375 mg SQ every two or four weeks based on body weight and pretreatment IgE level (to ensure receipt of at least 0.016 mg/kg/IgE per four weeks) versus matching placebo administered subcutaneously
Outcomes	Effect of omalizumab on systemic allergic reactions to specific immunotherapy (SIT) in participants with persistent allergic asthma who require treatment with inhaled steroids Severity of first SAR to SIT (grade one to four), achievement of target maintenance SIT dose Number of visits required to complete cluster SIT dosing regimen, number of doses of rescue medication (epinephrine, oral steroids or antihistamines), adverse events
Notes	26-Week trial (period one: screening (two weeks); period two: study drug treatment (16 weeks including three-week overlap with period three); period three: cluster immunotherapy (four weeks); period four: maintenance immunotherapy (seven weeks) Co-medication: oral steroids, epinephrine, antihistamines, $beta_2$-agonists, h_2-agonists and 'other rescue medications' as required

NCT00367016

Methods	Randomised, double-blind, parallel-group study

NCT00367016 *(Continued)*

Participants	Mild or moderate persistent asthma
Interventions	Subcutaneous omalizumab versus placebo
Outcomes	Reduction in FcεRI level on basophils and to examine whether this occurs at a transcriptional level Suppression of IgE production, in addition to sequestration of IgE
Notes	No data available at time of completion of 2013 update of this review

NCT00495612

Methods	Randomised, double-blind, parallel-group study
Participants	Participants eight to 65 years of age with history of cat dander–induced asthma in the three years before randomisation
Interventions	Subcutaneous omalizumab versus placebo
Outcomes	Percentage change in FEV_1 Percentage decrease in FEV_1 Maximum percentage change in FEV_1 Duration of cat chamber exposure Change in chest symptom score Change in nasal and ocular symptom scores
Notes	Above change scores are from baseline to week 16 No data available at time of completion of 2013 update of this review

NCT00670930

Methods	Randomised, double-blind, parallel-group study
Participants	Participants 18 to 60 years of age with moderate to severe persistent allergic asthma
Interventions	Omalizumab at a dose of 0.016 mg/kg/IU/mL versus placebo
Outcomes	Number of subepithelial eosinophils following 78 weeks of treatment, as assessed by biopsy samples Number of subepithelial mast cells following 78 weeks of treatment, as assessed by biopsy samples Number of subepithelial CD4+ T lymphocytes following 78 weeks of treatment, as assessed by biopsy samples Thickness of the lamina reticularis following 78 weeks of treatment, as assessed by biopsy samples Safety and tolerability of 78 weeks of therapy
Notes	Background therapy: inhaled corticosteroids and long-acting beta-agonists.

NCT00670930 *(Continued)*

	No data available at time of completion of 2013 update of this review

NCT00691873

Methods	Randomised, double-blind, parallel-group study
Participants	Patients with at least moderate persistent allergic asthma inadequately controlled with inhaled corticosteroids
Interventions	Xolair 150 to 375 mg SQ every two or four weeks based on body weight and pretreatment IgE level versus placebo
Outcomes	Effect of omalizumab on systemic allergic reactions to specific immunotherapy (SIT) in participants with persistent allergic asthma who require treatment with inhaled steroids
Notes	No data available at time of completion of 2013 update of this review

NCT01393340

Methods	Randomised, double-blind, parallel-group study
Participants	Patients at least 18 years of age with a diagnosis of asthma for longer than two years
Interventions	Xolair(R) will be administered subcutaneously in a dose of 75 to 375 mg every two to four weeks. Doses (mg) and dosing frequency are determined by total serum IgE level (IU/mL) measured at the start of treatment and body weight (kg). During this 20-week trial, participants will receive four or eight doses of omalizumab
Outcomes	Effect of omalizumab on nasal polyp size and evolution of nasal polyps Nasal examination at all visits by endoscopy of each nasal fossa Daytime and night-time symptom scores Morning and evening peak flows Exhaled nitric oxide Total dosage of rescue $beta_2$-agonists Total symptom-free days Quality of life scores Markers of airway remodelling and inflammation Local IgE synthesis in the bronchial mucosa and its expression
Notes	No data available at time of completion of 2013 update of this review

Scripps 2009

Methods	Double-blind, randomised, parallel-group trial

Scripps 2009 *(Continued)*

Participants	Inclusion criteria: aspirin-exacerbated respiratory disease, allergic asthma Exclusion criteria: pregnant females, starting immunotherapy in the past three months, prior treatment with Xolair, negative allergy skin tests, unable to participate in lung function tests, unable to complete data forms, low platelets, serum IgE greater than 700 IU, cancer, another uncontrolled medical condition, unacceptable concomitant medication, younger than 18 years of age Protocol: '40/60 patients will receive omalizumab injections every month for the next 4 months and the other 20 patients, via a random program, will receive placebo injections' and '60 patients with aspirin-exacerbated respiratory disease will be screened to determine if they also have allergic respiratory tract disease as a co-morbid complication. This will involve history, allergy skin tests and a serum IgE level. They must also have been desensitised to aspirin and be taking aspirin 325 or 650 mg morning and night'.
Interventions	Omalizumab versus placebo
Outcomes	Primary: respiratory index score. Secondary: FEV_1, nasal flow rates, nasal smell scores, quality of life scores for rhinitis and asthma
Notes	Four-month trial. No data available at time of completion of 2013 update of this review

Characteristics of ongoing studies *[ordered by study ID]*

NCT00139152

Trial name or title	Non-invasive ways to evaluate lung disease after treatment with Xolair
Methods	Randomised, double-blind, parallel-group study
Participants	People with stable asthma. 12 years of age and older
Interventions	Xolair 0.016 mg/kg IgE, SQ versus saline placebo
Outcomes	Levels of pH, nitrate/nitrite in exhaled breath condensate before and after four months of treatment
Starting date	September 2005
Contact information	http://clinicaltrials.gov/ct2/show/NCT00139152
Notes	

NCT00208234

Trial name or title	Effect of Xolair on airway hyperresponsiveness
Methods	Randomised, double-blind, parallel-group study
Participants	Steroid-naive allergic asthma patients 19 to 50 years
Interventions	Omalizumab 0.016 mg/kg IgE versus placebo
Outcomes	Changes in PC20 values to methacholine bronchoprovocation challenges and/or PC15 values to hypertonic saline-induced bronchoprovocation challenges in a time-dependent manner

NCT00208234 *(Continued)*

	Exhaled NO and sputum eosinophilia
Starting date	January 2004
Contact information	http://www.clinicaltrials.gov/ct2/show/NCT00208234
Notes	

NCT00555971

Trial name or title	Therapeutic utility of Xolair in patients undergoing aspirin desensitisation
Methods	Randomised, double-blind, parallel-group study
Participants	Patients with aspirin-exacerbated respiratory disease 18 years of age or older
Interventions	Dosage (150 to 375 mg) based on IgE levels; administered subcutaneously every two to four weeks for 16 weeks versus placebo
Outcomes	FEV_1 and changes in serum and urinary markers of eosinophil activation during desensitisation and change in urinary LTE4 during bronchospasm
Starting date	May 2006
Contact information	http://clinicaltrials.gov/ct2/show/NCT00555971
Notes	

NCT01113437

Trial name or title	Omalizumab in non-atopic asthma
Methods	Randomised, double-blind, parallel-group study
Participants	Patients 18 to 60 years of age with moderate or severe non-atopic asthma
Interventions	Omalizumab or placebo by subcutaneous injections, at four-weekly or two-weekly intervals versus placebo
Outcomes	Prebronchodilator FEV_1 Before reduction of existing antiasthma therapy (first 12 weeks of study): pre-bronchodilator FEV_1 Disease exacerbation
Starting date	April 2010
Contact information	http://clinicaltrials.gov/ct2/show/record/NCT01113437
Notes	Dr Chris Corrigan (PI) has confirmed that trial is still blinded and will be until April 2013 at the earliest

NCT01125748

Trial name or title	A study evaluating the persistency of response with or without Xolair after long-term therapy (XPORT)
Methods	Randomised, double-blind, parallel-group study
Participants	Patients with allergic asthma 17 to 70 years of age
Interventions	Omalizumab versus placebo
Outcomes	Severe exacerbation
Starting date	May 2010
Contact information	http://clinicaltrials.gov/ct2/show/NCT01125748
Notes	

NCT01202903

Trial name or title	Omalizumab in patients with moderate to severe persistent allergic asthma not adequately controlled despite GINA (2009) step four therapy
Methods	Randomised, double-blind, parallel-group study
Participants	18- to 75-year-old Chinese patients with moderate to severe persistent allergic asthma
Interventions	Omalizumab versus placebo
Outcomes	Change from baseline in mean morning peak expiratory flow (PEF) following 24-week treatment period FEV_1 percent predicted, PEF, overall score of the standardised AQLQ, ACQ, investigators' and participants' GETE, total nocturnal, daytime and morning asthma symptom scores
Starting date	September 2010
Contact information	http://clinicaltrials.gov/ct2/show/NCT01202903
Notes	

NCT01430403

Trial name or title	Preventative omalizumab or step-up therapy for severe fall exacerbations (PROSE)
Methods	Randomised, double-blind, parallel-group study
Participants	Children with asthma six to 17 years
Interventions	Three arms: omalizumab, fluticasone and placebo
Outcomes	Exacerbation requiring systemic corticosteroid therapy or hospitalisation

NCT01430403 *(Continued)*

Starting date	September 2011
Contact information	http://clinicaltrials.gov/ct2/show/NCT01430403
Notes	

NCT01544348

Trial name or title	Phase 1, randomised, placebo-controlled, dose escalation safety study of MEDI4212 in allergic subjects (MEDI42121085)
Methods	Randomised, double-blind, parallel-group study
Participants	Allergic asthma Allergic dermatitis Allegic rhinitis
Interventions	Omalizumab, MEDI4212 and placebo
Outcomes	Safety and tolerability
Starting date	January 2012
Contact information	http://clinicaltrials.gov/ct2/show/NCT01544348
Notes	

DATA AND ANALYSES

Comparison 1. Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid)

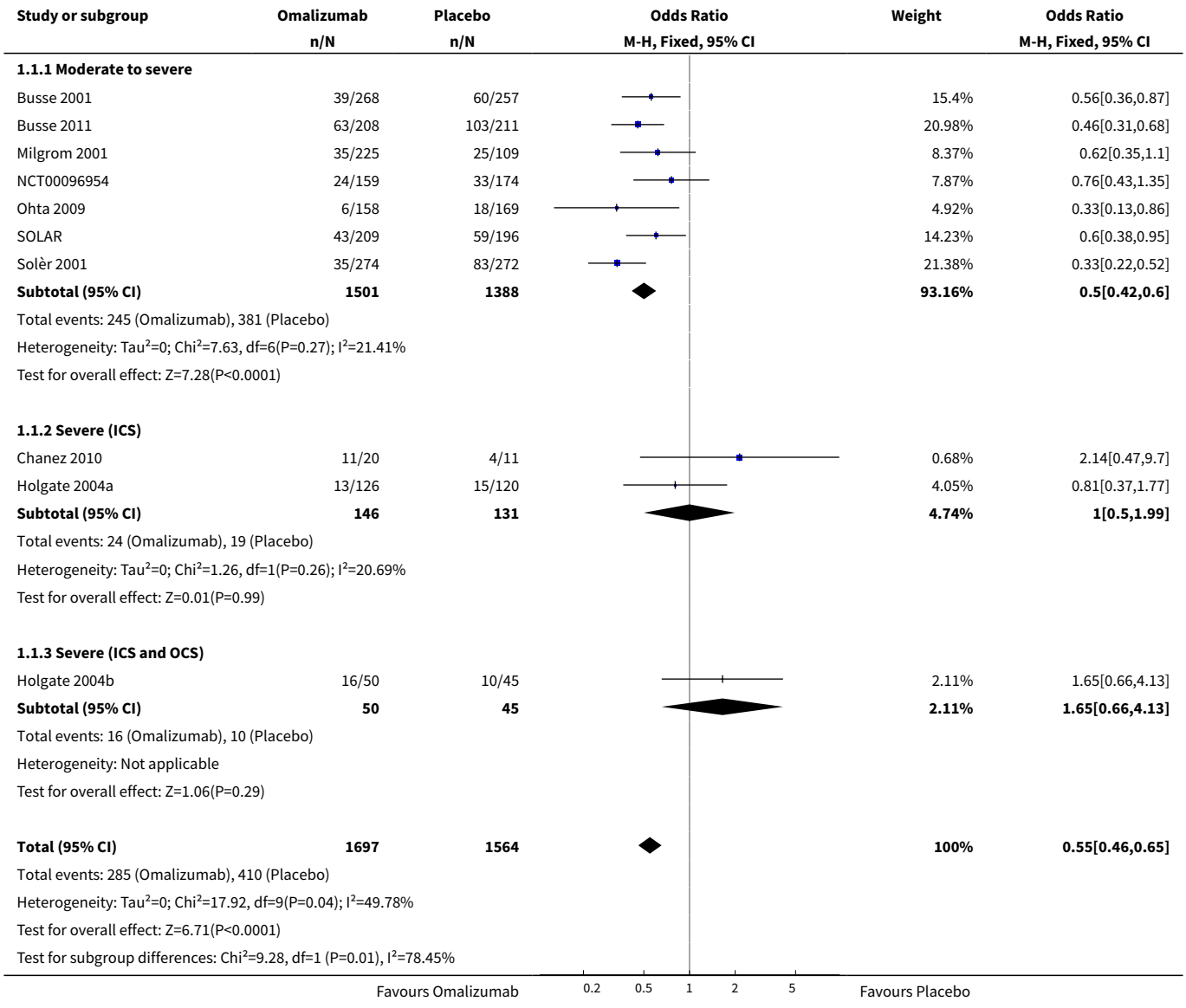
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with at least one exacerbation (ICS and OCS users)	10	3261	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.46, 0.65]
1.1 Moderate to severe	7	2889	Odds Ratio (M-H, Fixed, 95% CI)	0.50 [0.42, 0.60]
1.2 Severe (ICS)	2	277	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.50, 1.99]
1.3 Severe (ICS and OCS)	1	95	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [0.66, 4.13]
2 Exacerbations requiring oral steroids	3		Rate Ratio (Fixed, 95% CI)	Subtotals only
2.1 Moderate to severe asthma (ICS + mixed treatments)	2		Rate Ratio (Fixed, 95% CI)	0.52 [0.37, 0.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Severe asthma (ICS + LABA)	1		Rate Ratio (Fixed, 95% CI)	0.66 [0.45, 0.97]
2.3 Severe asthma (ICS + LABA + other treatment)	1		Rate Ratio (Fixed, 95% CI)	0.72 [0.53, 0.98]
2.4 Severe asthma (ICS and OCS)	1		Rate Ratio (Fixed, 95% CI)	0.95 [0.63, 1.43]
3 Hospitalisations	4	1824	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.06, 0.42]
3.1 Moderate to severe asthma	4	1824	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.06, 0.42]
3.2 Severe asthma	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Mortality	9	4245	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.02, 1.67]
4.1 Moderate to severe asthma	7	3124	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.85]
4.2 Severe asthma	2	1121	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.73]
5 Peak expiratory flow rate (am)	4	1651	Mean Difference (IV, Fixed, 95% CI)	3.56 [-5.05, 12.18]
5.1 Moderate to severe asthma	3	1405	Mean Difference (IV, Fixed, 95% CI)	4.93 [-4.11, 13.97]
5.2 Severe asthma	1	246	Mean Difference (IV, Fixed, 95% CI)	-9.90 [-38.27, 18.47]
6 Change in am PEF	2		Mean Difference (Fixed, 95% CI)	Totals not selected
6.1 Moderate to severe asthma	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Severe asthma	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
7 FEV_1 (mL)	2	1071	Mean Difference (IV, Fixed, 95% CI)	68.31 [-23.45, 160.07]
7.1 Moderate to severe	2	1071	Mean Difference (IV, Fixed, 95% CI)	68.31 [-23.45, 160.07]
7.2 Severe	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Change in FEV_1 (mL)	5	1463	Mean Difference (Fixed, 95% CI)	56.39 [16.82, 95.96]
8.1 Moderate to severe asthma	2	732	Mean Difference (Fixed, 95% CI)	67.29 [23.75, 110.83]
8.2 Severe asthma	3	731	Mean Difference (Fixed, 95% CI)	4.68 [-90.16, 99.52]
9 Change in FEV_1 predicted	4	1498	Mean Difference (Fixed, 95% CI)	2.15 [1.01, 3.30]

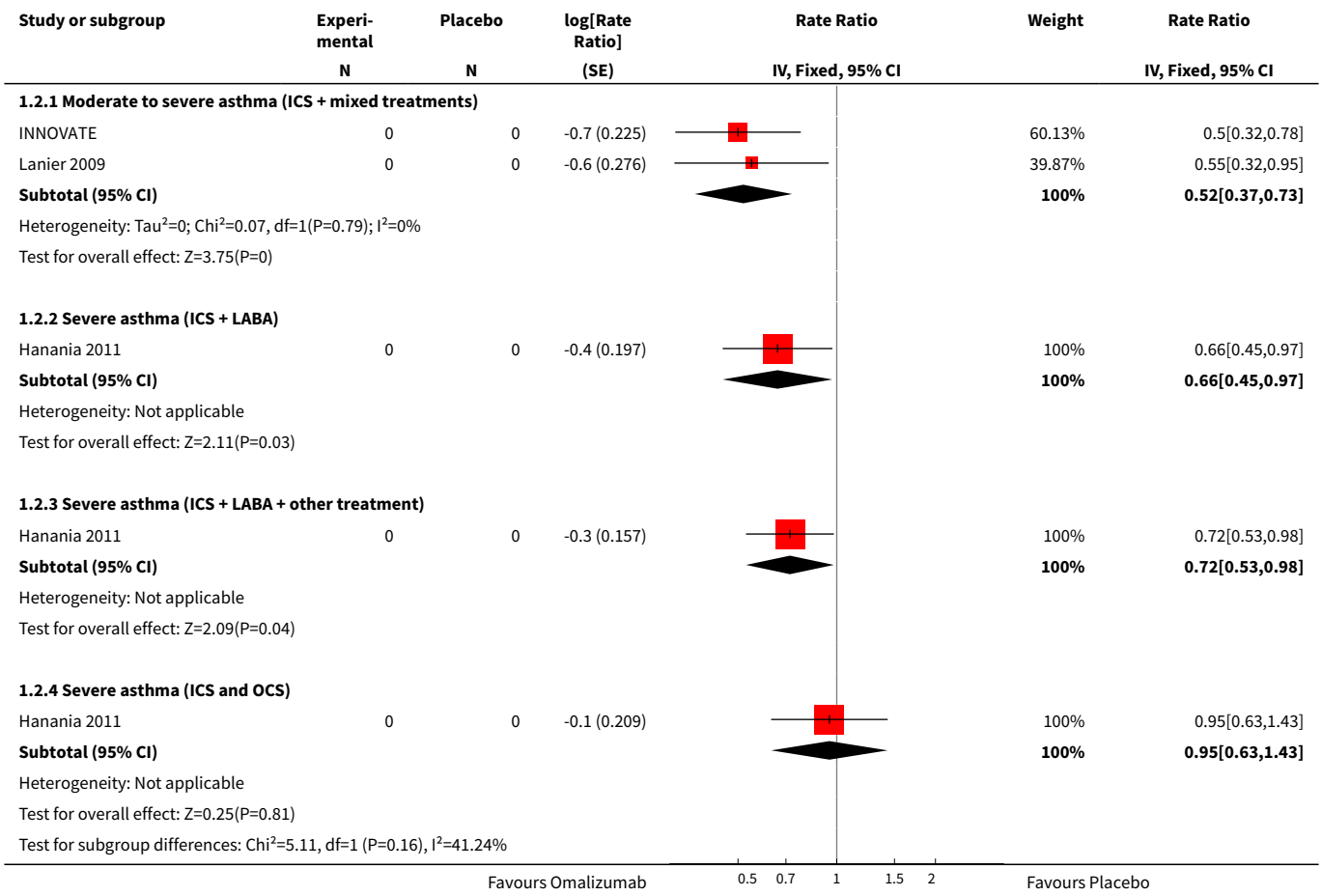
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Moderate to severe asthma	3	1079	Mean Difference (Fixed, 95% CI)	2.01 [0.76, 3.27]
9.2 Severe asthma	1	419	Mean Difference (Fixed, 95% CI)	2.8 [0.10, 5.50]
10 Symptom scores	10		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Moderate to severe asthma	6		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Severe asthma	4		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Mean change in Wasserfallen asthma score	1		Symptoms (Fixed, 95% CI)	Totals not selected
11.1 Moderate to severe asthma	1		Symptoms (Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Quality of life—change from baseline in AQLQ scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Moderate to severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Severe asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Global evaluation rated good to excellent	4	1136	Odds Ratio (M-H, Fixed, 95% CI)	2.12 [1.67, 2.68]
13.1 Moderate to severe asthma	1	405	Odds Ratio (M-H, Fixed, 95% CI)	3.32 [2.19, 5.05]
13.2 Severe asthma	3	731	Odds Ratio (M-H, Fixed, 95% CI)	1.69 [1.26, 2.26]
14 Rescue medication	9		Mean Difference (Fixed, 95% CI)	Subtotals only
14.1 Moderate to severe asthma	4		Mean Difference (Fixed, 95% CI)	-0.58 [-0.84, -0.31]
14.2 Severe asthma (ICS)	4		Mean Difference (Fixed, 95% CI)	-0.30 [-0.49, -0.10]
14.3 Severe asthma (ICS and OCS)	1		Mean Difference (Fixed, 95% CI)	-0.4 [-4.81, 4.01]
15 Adverse event—any	14	5167	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.81, 1.06]
15.1 Moderate to severe asthma	8	3246	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.09]
15.2 Severe asthma	6	1921	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.76, 1.16]
16 Adverse event—serious	15	5713	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.57, 0.91]
16.1 Moderate to severe asthma	9	3792	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.48, 0.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.2 Severe asthma	6	1921	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.56, 1.05]
17 Injection site reactions	9	3577	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [1.33, 2.24]
17.1 Moderate to severe asthma	6	2001	Odds Ratio (M-H, Fixed, 95% CI)	1.79 [1.31, 2.43]
17.2 Severe asthma	3	1576	Odds Ratio (M-H, Fixed, 95% CI)	1.57 [0.96, 2.57]

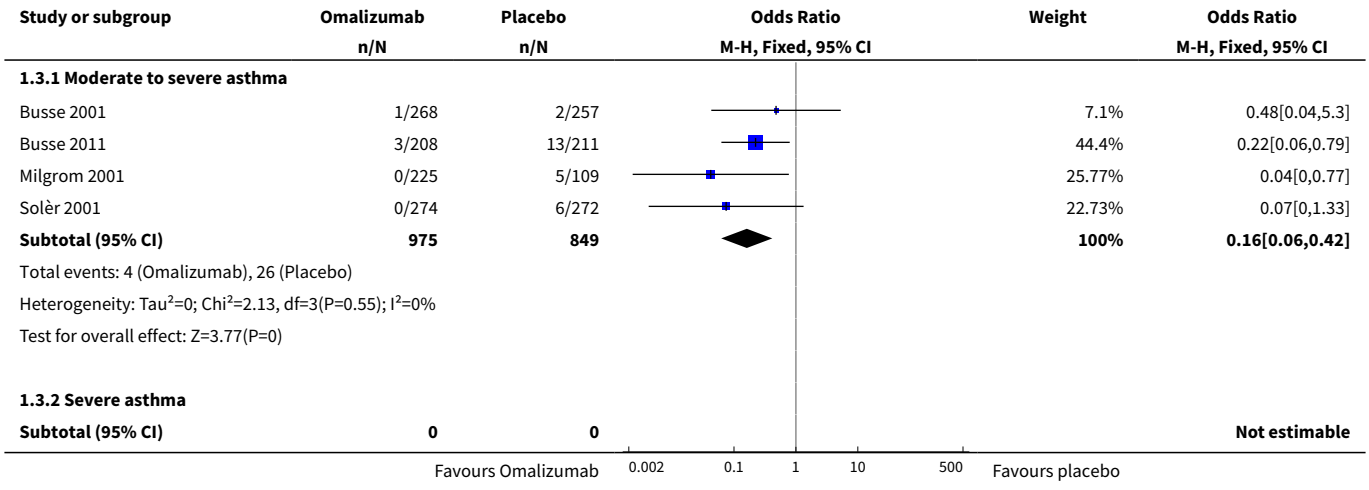
Analysis 1.1. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 1 Number of participants with at least one exacerbation (ICS and OCS users).

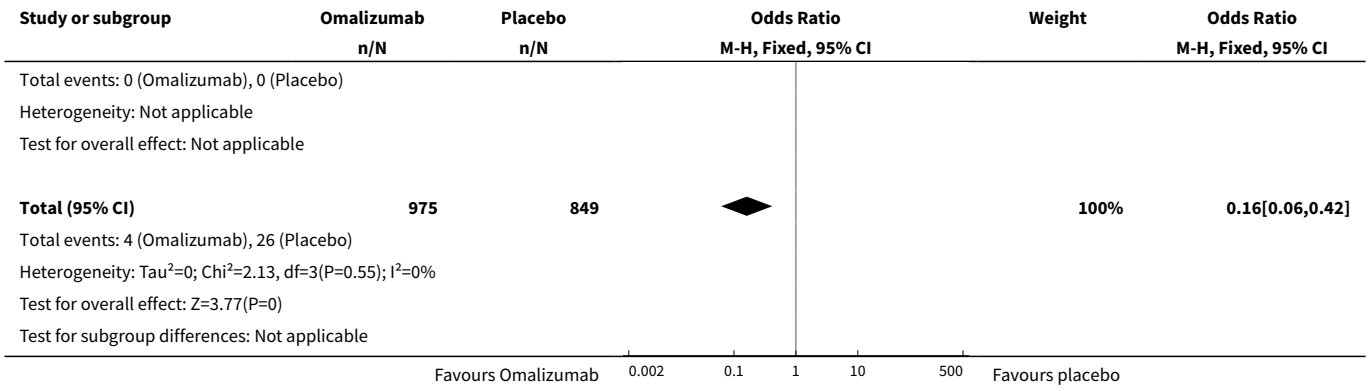


Analysis 1.2. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 2 Exacerbations requiring oral steroids.

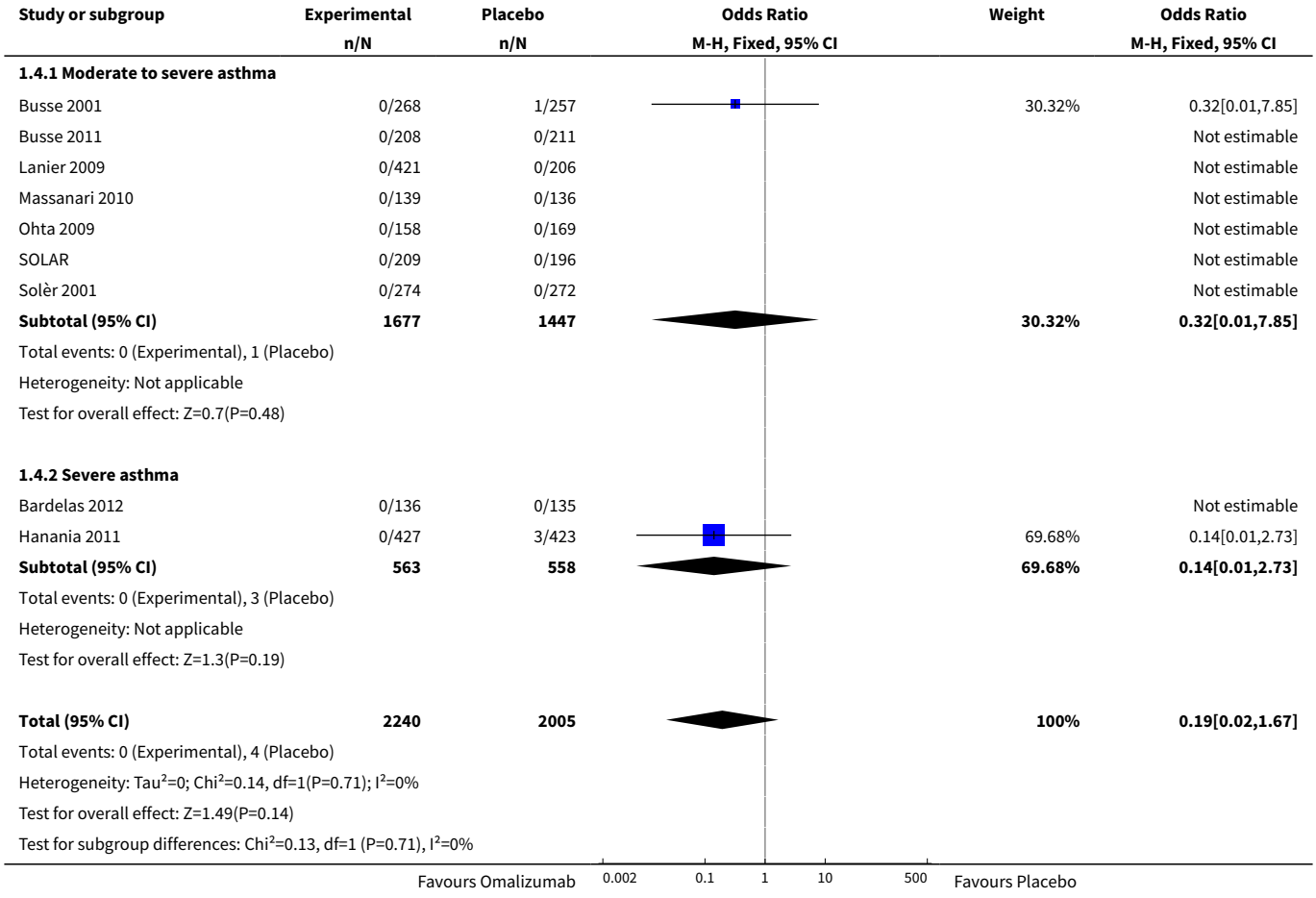


Analysis 1.3. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 3 Hospitalisations.



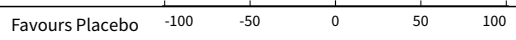


Analysis 1.4. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 4 Mortality.



Analysis 1.5. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 5 Peak expiratory flow rate (am).

Study or subgroup	Omliazumab N	Omliazumab Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.5.1 Moderate to severe asthma							
Busse 2001	268	338.5 (90.3)	257	334.1 (93.7)		29.89%	4.4[-11.35,20.15]
Milgrom 2001	225	268.7 (62.6)	109	269.2 (65.2)		34.25%	-0.5[-15.22,14.22]
Solèr 2001	274	395.5 (94.2)	272	383 (104.5)		26.65%	12.5[-4.19,29.19]
Subtotal ***	**767**		**638**			**90.78%**	**4.93[-4.11,13.97]**
Heterogeneity: Tau²=0; Chi²=1.32, df=2(P=0.52); I²=0%							
Test for overall effect: Z=1.07(P=0.29)							
1.5.2 Severe asthma							
Holgate 2004a	126	384.5 (113.3)	120	394.4 (113.7)		9.22%	-9.9[-38.27,18.47]
Subtotal ***	**126**		**120**			**9.22%**	**-9.9[-38.27,18.47]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.68(P=0.49)							
Total ***	**893**		**758**			**100%**	**3.56[-5.05,12.18]**
Heterogeneity: Tau²=0; Chi²=2.27, df=3(P=0.52); I²=0%							
Test for overall effect: Z=0.81(P=0.42)							
Test for subgroup differences: Chi²=0.95, df=1 (P=0.33), I²=0%							

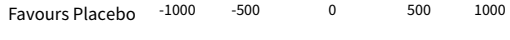


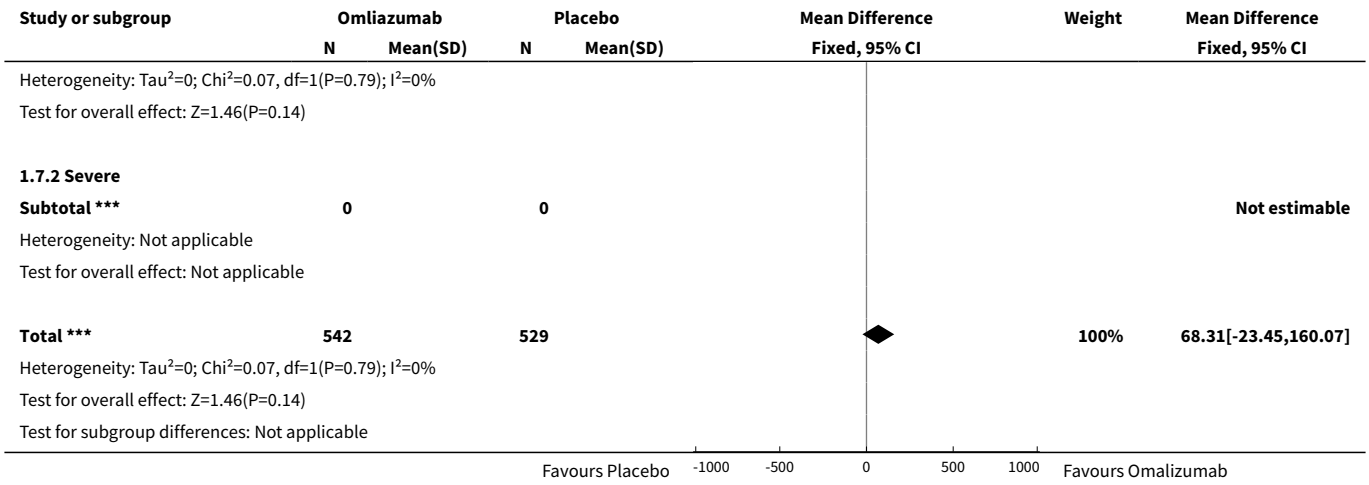
Analysis 1.6. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 6 Change in am PEF.

Study or subgroup	Omalizumab N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.6.1 Moderate to severe asthma					
SOLAR	209	196	11 (3.31)		11[4.51,17.49]
1.6.2 Severe asthma					
Chanez 2010	20	11	-0.6 (14.884)		-0.6[-29.77,28.57]

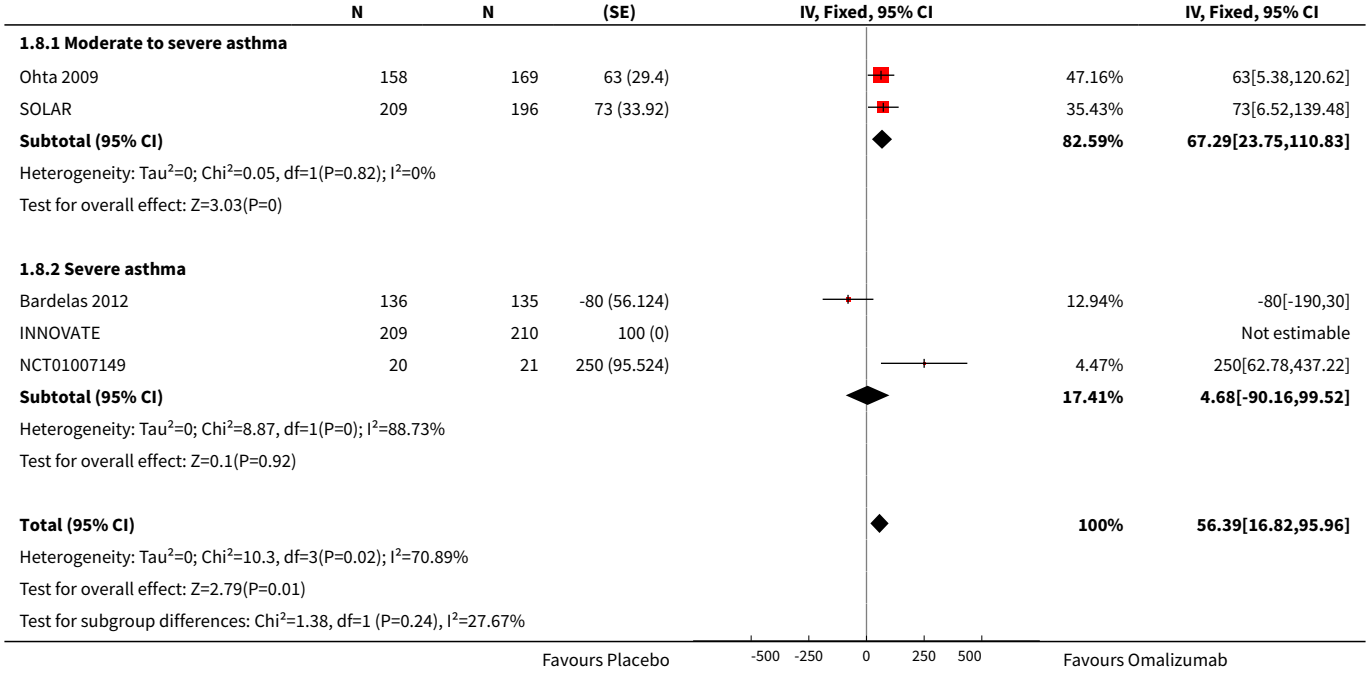
Analysis 1.7. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 7 FEV_1 (mL).

Study or subgroup	Omliazumab N	Omliazumab Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.7.1 Moderate to severe							
Busse 2001	268	2460.6 (718.1)	257	2381 (729.8)		54.85%	79.6[-44.3,203.5]
Solèr 2001	274	2633.3 (795.3)	272	2578.7 (832.1)		45.15%	54.6[-81.95,191.15]
Subtotal ***	**542**		**529**			**100%**	**68.31[-23.45,160.07]**



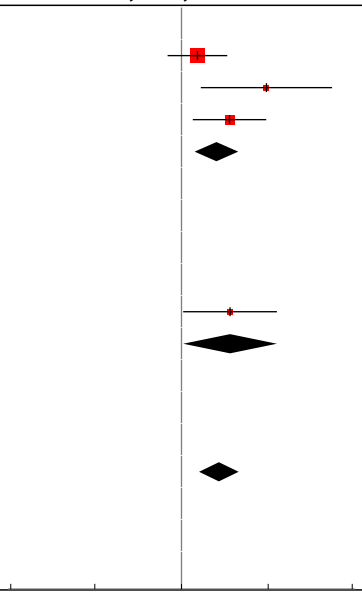


Analysis 1.8. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 8 Change in FEV_1 (mL).



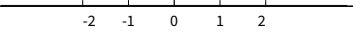
Analysis 1.9. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 9 Change in FEV_1 predicted.

Study or subgroup	Omalizumab N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 Moderate to severe asthma						
Busse 2011	208	211	0.9 (0.878)		44.02%	0.92[-0.8,2.64]
NCT00096954	159	174	4.9 (1.931)		9.09%	4.9[1.12,8.68]
Ohta 2009	158	169	2.8 (1.08)		29.06%	2.77[0.65,4.89]
Subtotal (95% CI)					**82.17%**	**2.01[0.76,3.27]**
Heterogeneity: Tau^2=0; Chi^2=4.28, df=2(P=0.12); I^2=53.24%						
Test for overall effect: Z=3.14(P=0)						
1.9.2 Severe asthma						
INNOVATE	209	210	2.8 (1.379)		17.83%	2.8[0.1,5.5]
Subtotal (95% CI)					**17.83%**	**2.8[0.1,5.5]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.03(P=0.04)						
Total (95% CI)					**100%**	**2.15[1.01,3.3]**
Heterogeneity: Tau^2=0; Chi^2=4.54, df=3(P=0.21); I^2=33.98%						
Test for overall effect: Z=3.7(P=0)						
Test for subgroup differences: Chi^2=0.27, df=1 (P=0.61), I^2=0%						



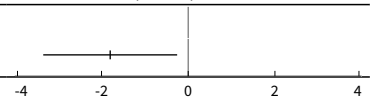
Analysis 1.10. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 10 Symptom scores.

Study or subgroup	Omalizumab N	Omalizumab Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.10.1 Moderate to severe asthma						
Busse 2001	268	2.5 (1.6)	257	2.9 (1.4)		-0.44[-0.7,-0.18]
Busse 2011	208	1.5 (1.4)	211	2 (1.5)		-0.48[-0.76,-0.2]
Lanier 2009	421	-0.6 (0.7)	207	-0.5 (0.7)		-0.13[-0.25,-0.01]
NCT00096954	159	-0.5 (0.8)	174	-0.5 (0.7)		0.01[-0.15,0.17]
Ohta 2009	158	-2.1 (8.6)	169	-0.4 (8.6)		-1.73[-3.6,0.14]
Solèr 2001	274	2.5 (1.7)	272	3.1 (1.8)		-0.53[-0.82,-0.24]
1.10.2 Severe asthma						
Bardelas 2012	136	-1.7 (2.4)	135	-1.5 (2.4)		-0.25[-0.81,0.31]
Hanania 2011	427	-1.6 (1.9)	423	-1.4 (1.9)		-0.25[-0.5,0]
Holgate 2004a	126	1 (1.7)	120	1.4 (1.1)		-0.4[-0.75,-0.05]
NCT01007149	20	-0.6 (1.3)	21	-0.9 (1.7)		0.3[-0.64,1.24]



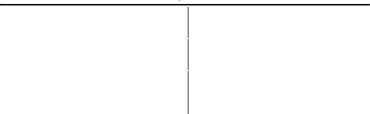
Analysis 1.11. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 11 Mean change in Wasserfallen asthma score.

Study or subgroup	Omalizumab N	Placebo N	Symptoms (SE)	Symptoms IV, Fixed, 95% CI	Symptoms IV, Fixed, 95% CI
1.11.1 Moderate to severe asthma					
SOLAR	209	196	-1.8 (0.788)		-1.8[-3.34,-0.26]



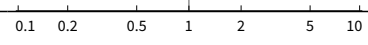
Analysis 1.12. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 12 Quality of life—change from baseline in AQLQ scores.

Study or subgroup	Omlizumab N	Omlizumab Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.12.1 Moderate to severe asthma						
1.12.2 Severe asthma						
Holgate 2004a	126	0.5 (0.8)	120	0.3 (0.9)		0.26[0.05,0.47]



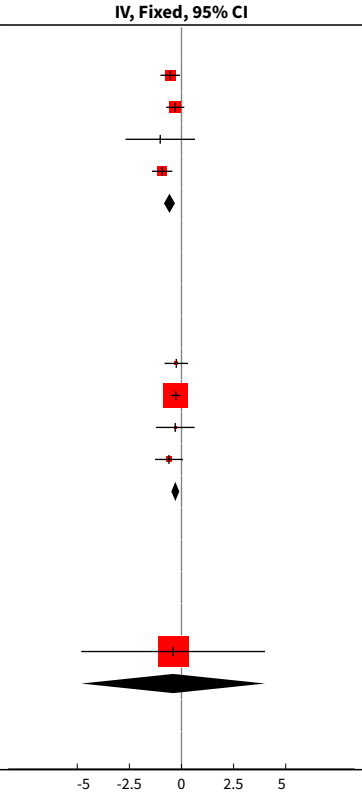
Analysis 1.13. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 13 Global evaluation rated good to excellent.

Study or subgroup	Omalizumab n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.13.1 Moderate to severe asthma					
SOLAR	114/209	52/196		26.16%	3.32[2.19,5.05]
Subtotal (95% CI)	**209**	**196**		**26.16%**	**3.32[2.19,5.05]**
Total events: 114 (Omalizumab), 52 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=5.63(P<0.0001)					
1.13.2 Severe asthma					
Bardelas 2012	70/136	63/135		32.9%	1.21[0.75,1.95]
INNOVATE	126/209	89/210		37.81%	2.06[1.4,3.05]
NCT01007149	8/20	5/21		3.14%	2.13[0.56,8.19]
Subtotal (95% CI)	**365**	**366**		**73.84%**	**1.69[1.26,2.26]**
Total events: 204 (Omalizumab), 157 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.99, df=2(P=0.22); I^2=33.17%					
Test for overall effect: Z=3.5(P=0)					
Total (95% CI)	**574**	**562**		**100%**	**2.12[1.67,2.68]**
Total events: 318 (Omalizumab), 209 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=9.74, df=3(P=0.02); I^2=69.2%					
Test for overall effect: Z=6.16(P<0.0001)					
Test for subgroup differences: Chi^2=6.77, df=1 (P=0.01), I^2=85.23%					



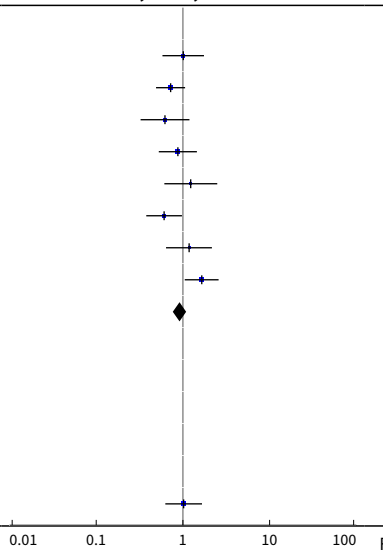
Analysis 1.14. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 14 Rescue medication.

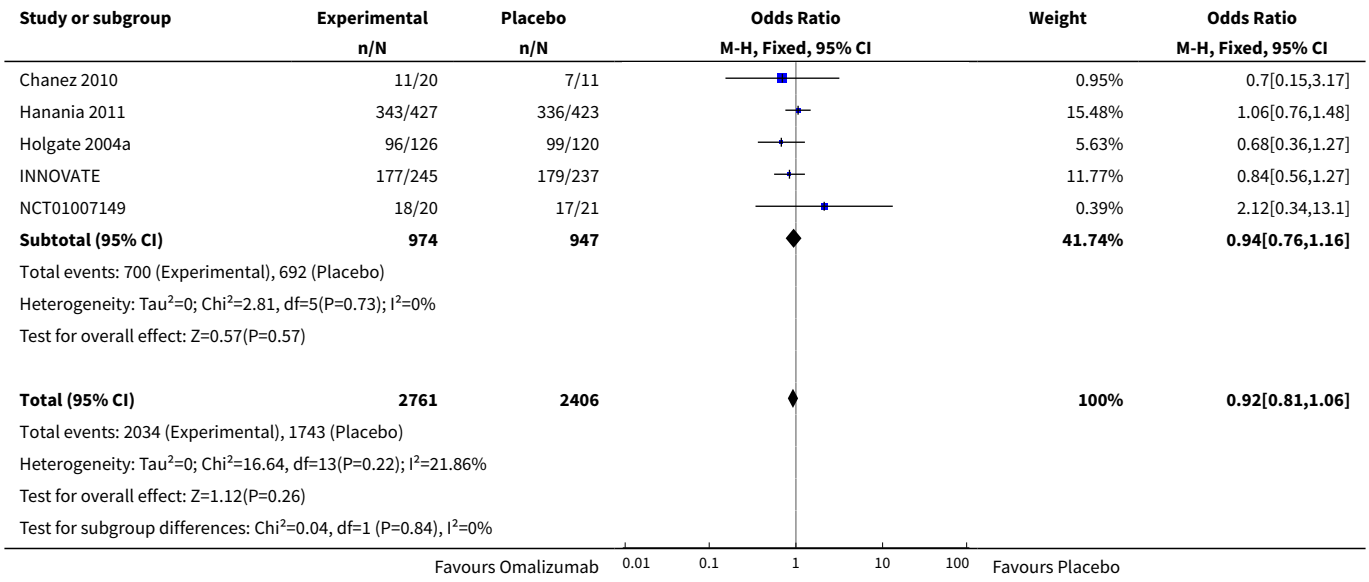
Study or subgroup	Omalizumab N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
1.14.1 Moderate to severe asthma						
Busse 2001	268	257	-0.5 (0.24)		31.57%	-0.54[-1.01,-0.07]
Lanier 2009	421	207	-0.3 (0.222)		36.83%	-0.3[-0.74,0.14]
Ohta 2009	158	169	-1 (0.85)		2.52%	-1.02[-2.69,0.65]
Solèr 2001	274	272	-0.9 (0.25)		29.09%	-0.93[-1.42,-0.44]
Subtotal (95% CI)					**100%**	**-0.58[-0.84,-0.31]**
Heterogeneity: Tau^2=0; Chi^2=3.84, df=3(P=0.28); I^2=21.94%						
Test for overall effect: Z=4.28(P<0.0001)						
1.14.2 Severe asthma (ICS)						
Bardelas 2012	136	135	-0.2 (0.286)		11.7%	-0.25[-0.81,0.31]
Hanania 2011	427	423	-0.3 (0.112)		75.85%	-0.27[-0.49,-0.05]
Holgate 2004a	118	115	-0.3 (0.474)		4.25%	-0.3[-1.23,0.63]
NCT01007149	20	21	-0.6 (0.341)		8.21%	-0.6[-1.27,0.07]
Subtotal (95% CI)					**100%**	**-0.3[-0.49,-0.1]**
Heterogeneity: Tau^2=0; Chi^2=0.87, df=3(P=0.83); I^2=0%						
Test for overall effect: Z=3.03(P=0)						
1.14.3 Severe asthma (ICS and OCS)						
Holgate 2004b	50	45	-0.4 (2.25)		100%	-0.4[-4.81,4.01]
Subtotal (95% CI)					**100%**	**-0.4[-4.81,4.01]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.18(P=0.86)						



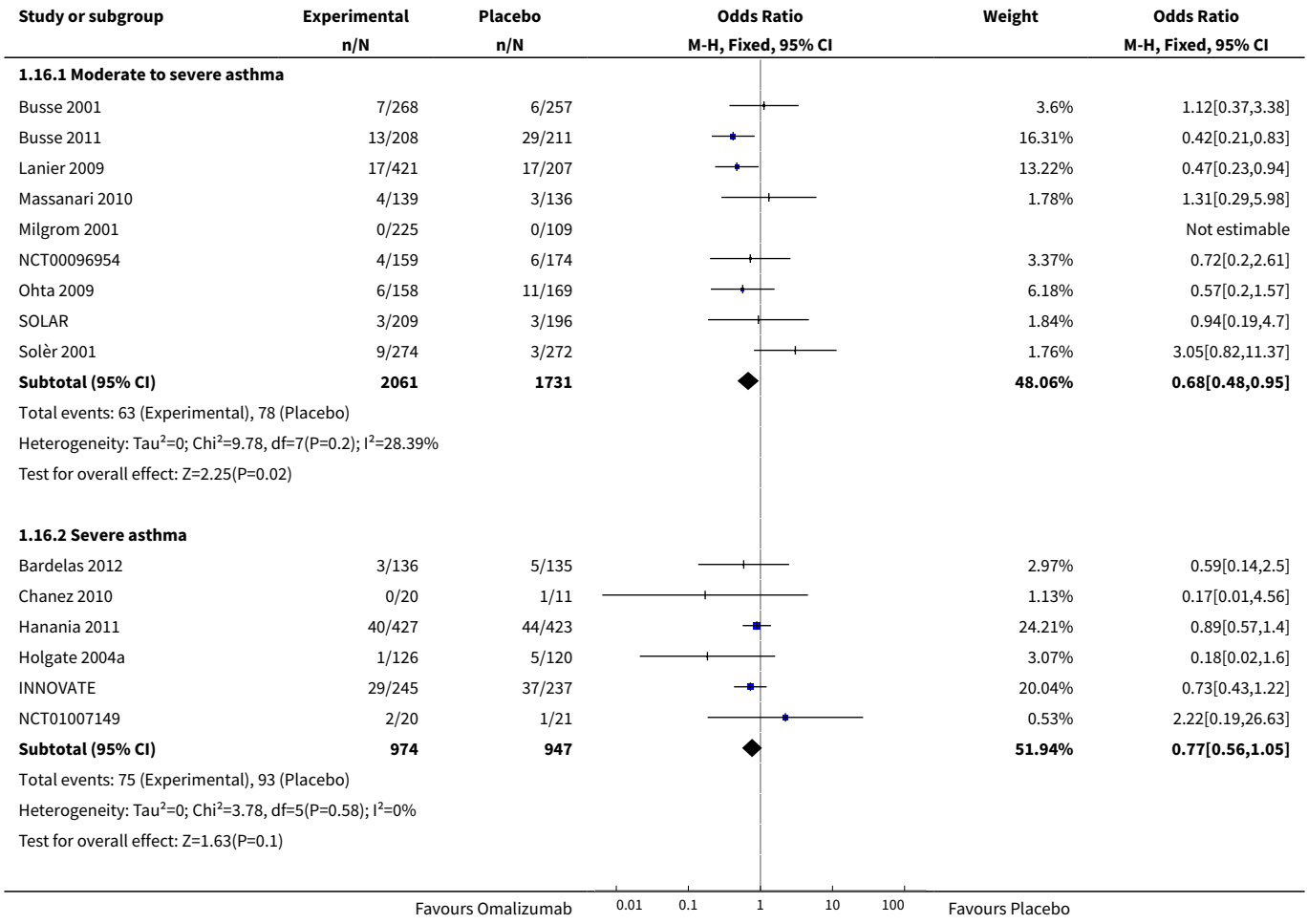
Analysis 1.15. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 15 Adverse event—any.

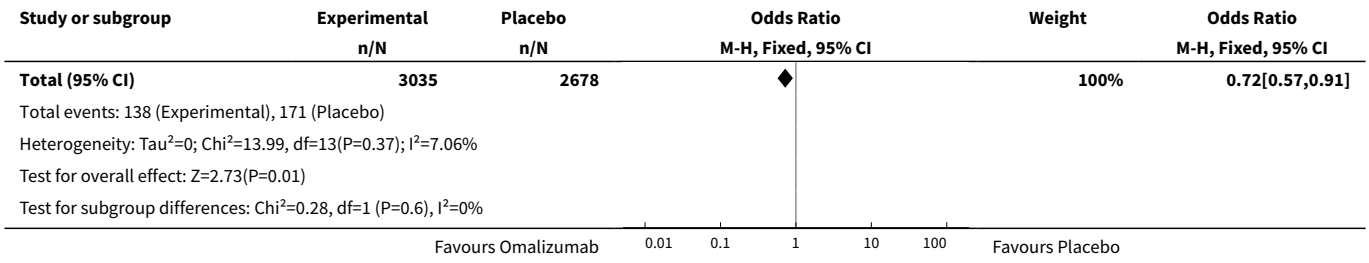
Study or subgroup	Experimental n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.15.1 Moderate to severe asthma					
Busse 2001	239/268	229/257		5.9%	1.01[0.58,1.75]
Busse 2011	82/208	100/211		14.02%	0.72[0.49,1.06]
Lanier 2009	380/421	194/207		5.9%	0.62[0.33,1.19]
Massanari 2010	92/139	94/136		7.49%	0.87[0.53,1.45]
Milgrom 2001	201/225	95/109		3.18%	1.23[0.61,2.49]
NCT00096954	40/159	62/174		10.33%	0.61[0.38,0.98]
Ohta 2009	136/158	142/169		4.45%	1.18[0.64,2.16]
SOLAR	164/209	135/196		6.99%	1.65[1.05,2.58]
Subtotal (95% CI)	**1787**	**1459**		**58.26%**	**0.91[0.76,1.09]**
Total events: 1334 (Experimental), 1051 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=13.8, df=7(P=0.05); I^2=49.27%					
Test for overall effect: Z=0.99(P=0.32)					
1.15.2 Severe asthma					
Bardelas 2012	55/136	54/135		7.52%	1.02[0.63,1.66]



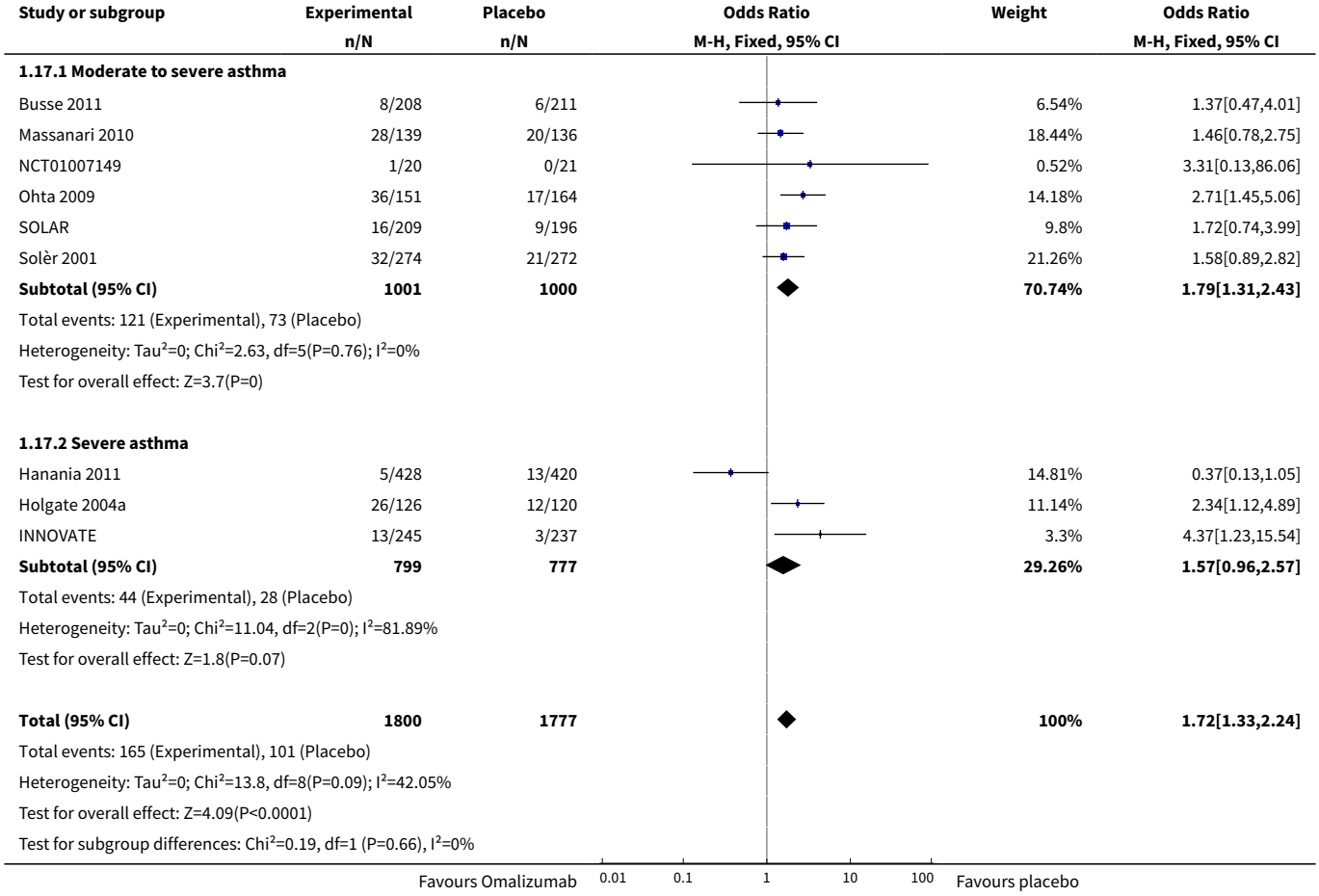


Analysis 1.16. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 16 Adverse event—serious.





Analysis 1.17. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 17 Injection site reactions.



Comparison 2. Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction)

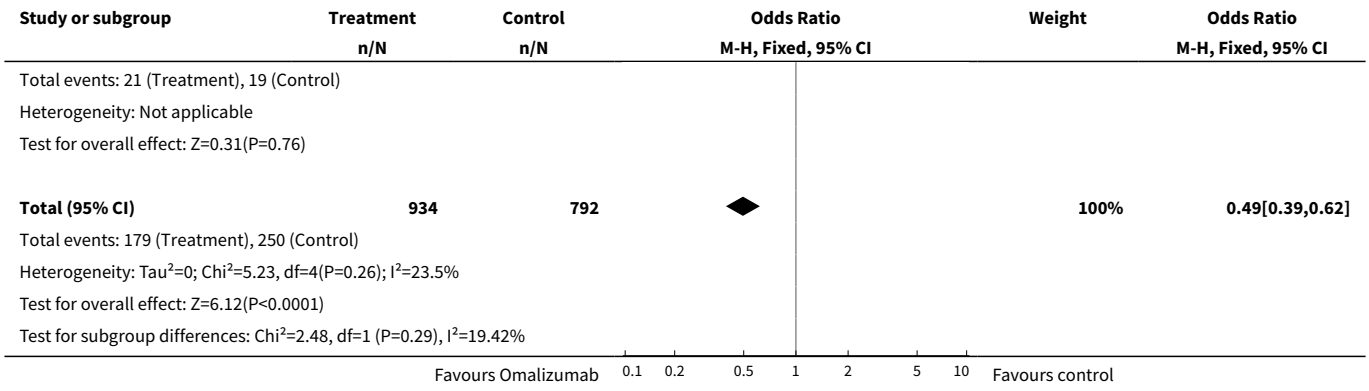
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with exacerbation	5	1726	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.39, 0.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Moderate to severe asthma	3	1388	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.36, 0.59]
1.2 Severe asthma	1	246	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.30, 1.16]
1.3 Severe (ICS and OCS users)	1	92	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.38, 2.01]
2 Exacerbations requiring hospitalisation	3	1405	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.03, 0.48]
2.1 Moderate asthma	3	1405	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.03, 0.48]
2.2 Severe asthma	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Number of participants achieving complete inhaled steroid withdrawal	4	1634	Odds Ratio (M-H, Fixed, 95% CI)	2.50 [2.00, 3.13]
3.1 Moderate to severe	3	1388	Odds Ratio (M-H, Fixed, 95% CI)	2.67 [2.10, 3.39]
3.2 Severe	1	246	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.80, 2.98]
4 Mean change in steroid consumption (BDP equivalent)	3	1188	Mean Difference (IV, Fixed, 95% CI)	-118.76 [-154.38, -83.14]
4.1 Moderate to severe asthma	2	942	Mean Difference (IV, Fixed, 95% CI)	-114.08 [-150.03, -78.13]
4.2 Severe asthma	1	246	Mean Difference (IV, Fixed, 95% CI)	-372.0 [-636.43, -107.57]
5 > 50% reduction in inhaled steroid usage	4	1634	Odds Ratio (M-H, Fixed, 95% CI)	2.50 [2.02, 3.10]
5.1 Moderate to severe asthma	3	1388	Odds Ratio (M-H, Fixed, 95% CI)	2.44 [1.93, 3.08]
5.2 Severe asthma	1	246	Odds Ratio (M-H, Fixed, 95% CI)	2.84 [1.66, 4.86]
6 Mean steroid dose at end of reduction phase	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Moderate to severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Severe asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Quality of life—change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Moderate to severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Severe asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

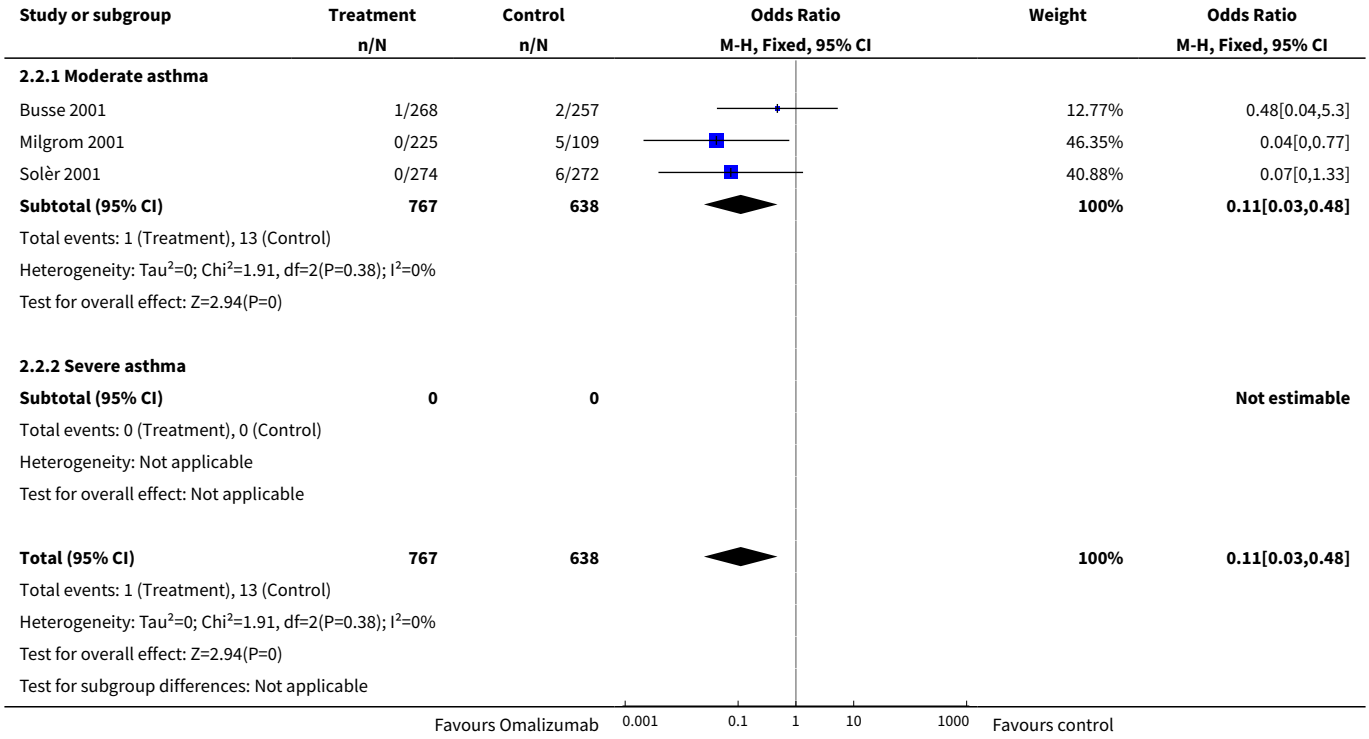
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Numbers of participants achieving clinically relevant improvement in quality of life (> 0.5)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 Severe asthma	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Global evaluation rated good to excellent	2	842	Odds Ratio (M-H, Fixed, 95% CI)	2.72 [2.04, 3.62]
9.1 Moderate to severe asthma	2	842	Odds Ratio (M-H, Fixed, 95% CI)	2.72 [2.04, 3.62]
9.2 Severe asthma	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Rescue medication (puffs per day)	4	1373	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-1.05, -0.43]
10.1 Moderate to severe asthma	2	1071	Mean Difference (IV, Fixed, 95% CI)	-0.73 [-1.06, -0.40]
10.2 Severe asthma (ICS)	1	220	Mean Difference (IV, Fixed, 95% CI)	-0.7 [-1.65, 0.25]
10.3 Severe asthma (ICS and OCS)	1	82	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-7.40, 1.80]

Analysis 2.1. Comparison 2 Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 1 Number of participants with exacerbation.

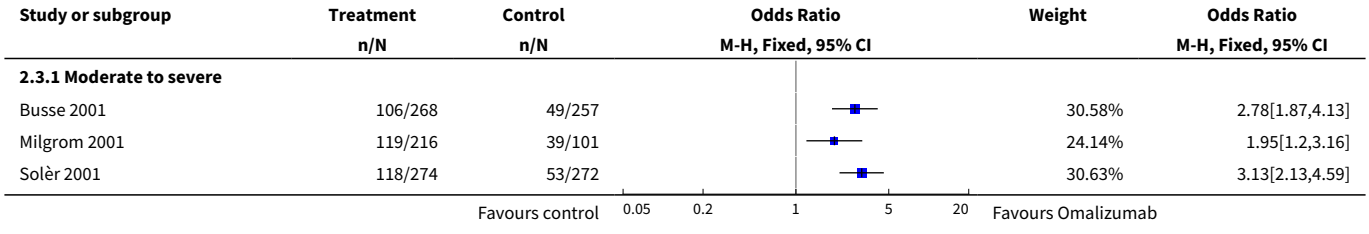
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Moderate to severe asthma					
Busse 2001	57/268	83/257		30.92%	0.57[0.38,0.84]
Milgrom 2001	41/216	42/101		21.49%	0.33[0.2,0.55]
Solèr 2001	43/274	81/272		31.77%	0.44[0.29,0.67]
Subtotal (95% CI)	**758**	**630**		**84.18%**	**0.46[0.36,0.59]**
Total events: 141 (Treatment), 206 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.71, df=2(P=0.26); I^2=26.07%					
Test for overall effect: Z=6.11(P<0.0001)					
2.1.2 Severe asthma					
Holgate 2004a	17/126	25/120		10.27%	0.59[0.3,1.16]
Subtotal (95% CI)	**126**	**120**		**10.27%**	**0.59[0.3,1.16]**
Total events: 17 (Treatment), 25 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.52(P=0.13)					
2.1.3 Severe (ICS and OCS users)					
Holgate 2004b	21/50	19/42		5.55%	0.88[0.38,2.01]
Subtotal (95% CI)	**50**	**42**		**5.55%**	**0.88[0.38,2.01]**

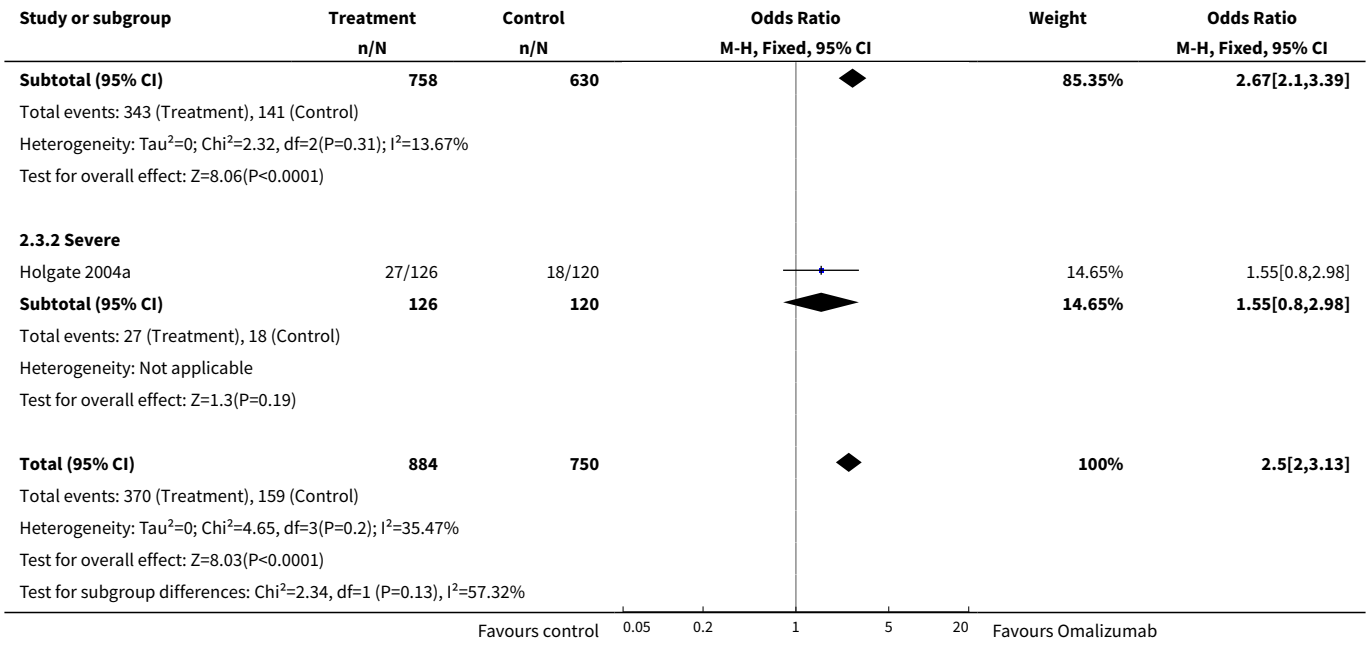


Analysis 2.2. Comparison 2 Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 2 Exacerbations requiring hospitalisation.

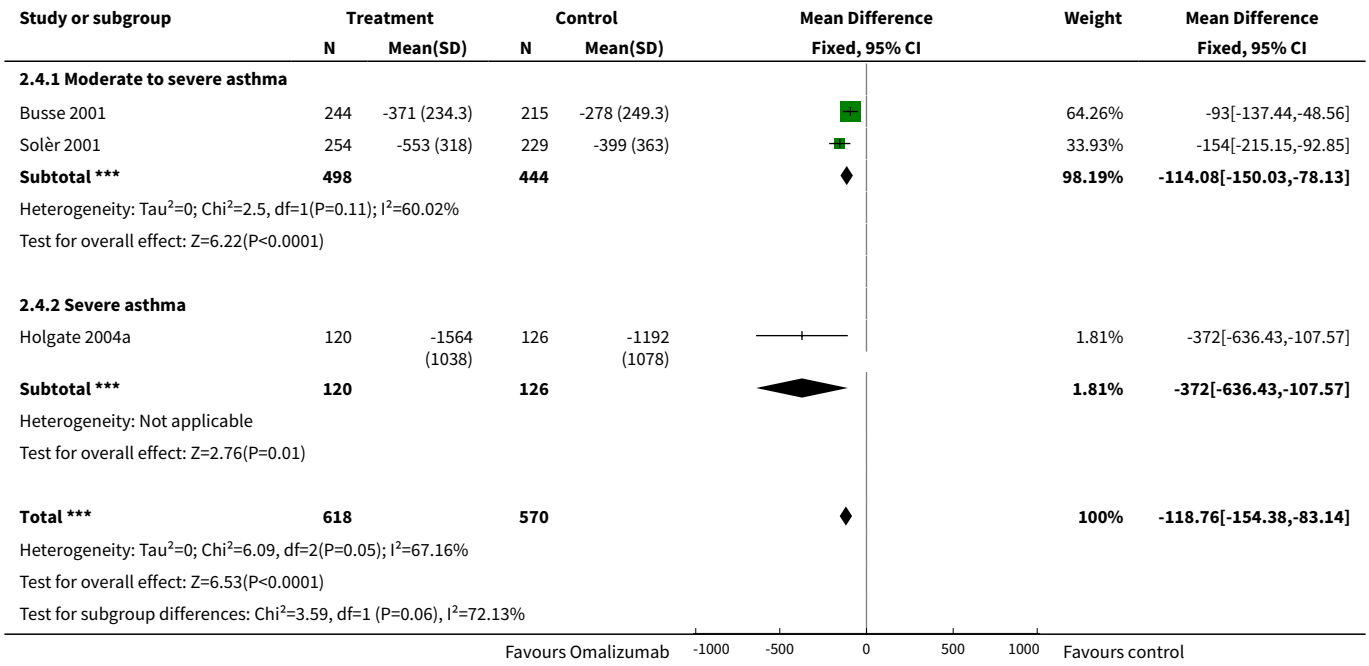


Analysis 2.3. Comparison 2 Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 3 Number of participants achieving complete inhaled steroid withdrawal.



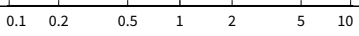


Analysis 2.4. Comparison 2 Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 4 Mean change in steroid consumption (BDP equivalent).



Analysis 2.5. Comparison 2 Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 5 > 50% reduction in inhaled steroid usage.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.5.1 Moderate to severe asthma					
Busse 2001	194/268	141/257		37.67%	2.16[1.5,3.1]
Milgrom 2001	174/216	68/101		17.08%	2.01[1.18,3.43]
Solèr 2001	216/274	150/272		30.21%	3.03[2.08,4.41]
Subtotal (95% CI)	**758**	**630**		**84.96%**	**2.44[1.93,3.08]**
Total events: 584 (Treatment), 359 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.22, df=2(P=0.33); I^2=9.81%					
Test for overall effect: Z=7.47(P<0.0001)					
2.5.2 Severe asthma					
Holgate 2004a	94/126	61/120		15.04%	2.84[1.66,4.86]
Subtotal (95% CI)	**126**	**120**		**15.04%**	**2.84[1.66,4.86]**
Total events: 94 (Treatment), 61 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.81(P=0)					
Total (95% CI)	**884**	**750**		**100%**	**2.5[2.02,3.1]**
Total events: 678 (Treatment), 420 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.49, df=3(P=0.48); I^2=0%					
Test for overall effect: Z=8.37(P<0.0001)					
Test for subgroup differences: Chi^2=0.26, df=1 (P=0.61), I^2=0%					

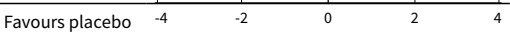


Analysis 2.6. Comparison 2 Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 6 Mean steroid dose at end of reduction phase.

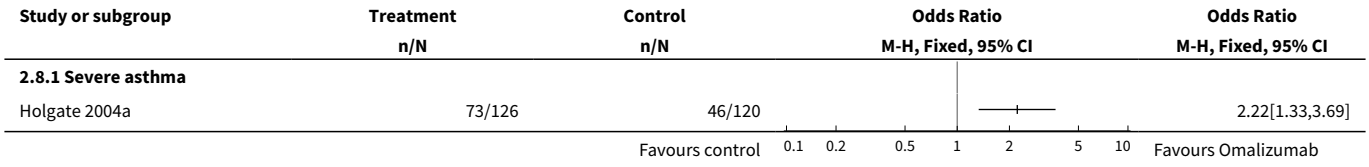
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.6.1 Moderate to severe asthma						
2.6.2 Severe asthma						
Holgate 2004a	115	506.5 (493.9)	109	690.4 (507.9)		-183.85[-315.15,-52.55]

Analysis 2.7. Comparison 2 Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 7 Quality of life—change from baseline.

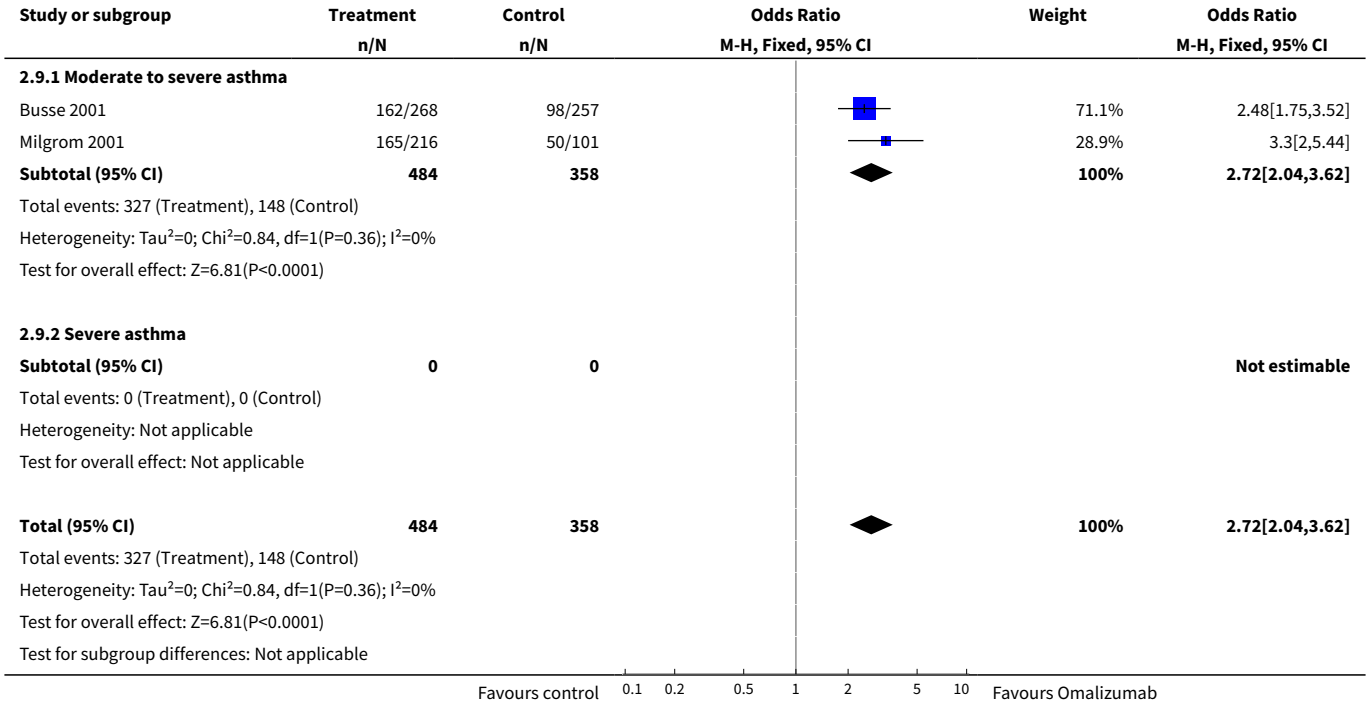
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.7.1 Moderate to severe asthma						
2.7.2 Severe asthma						
Holgate 2004a	126	0.7 (1)	120	0.3 (1)		0.42[0.17,0.67]



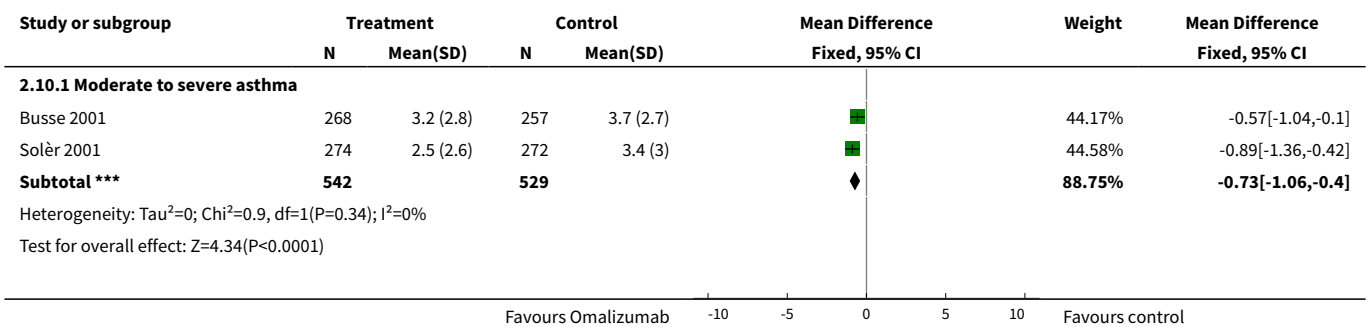
Analysis 2.8. Comparison 2 Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 8 Numbers of participants achieving clinically relevant improvement in quality of life (> 0.5).

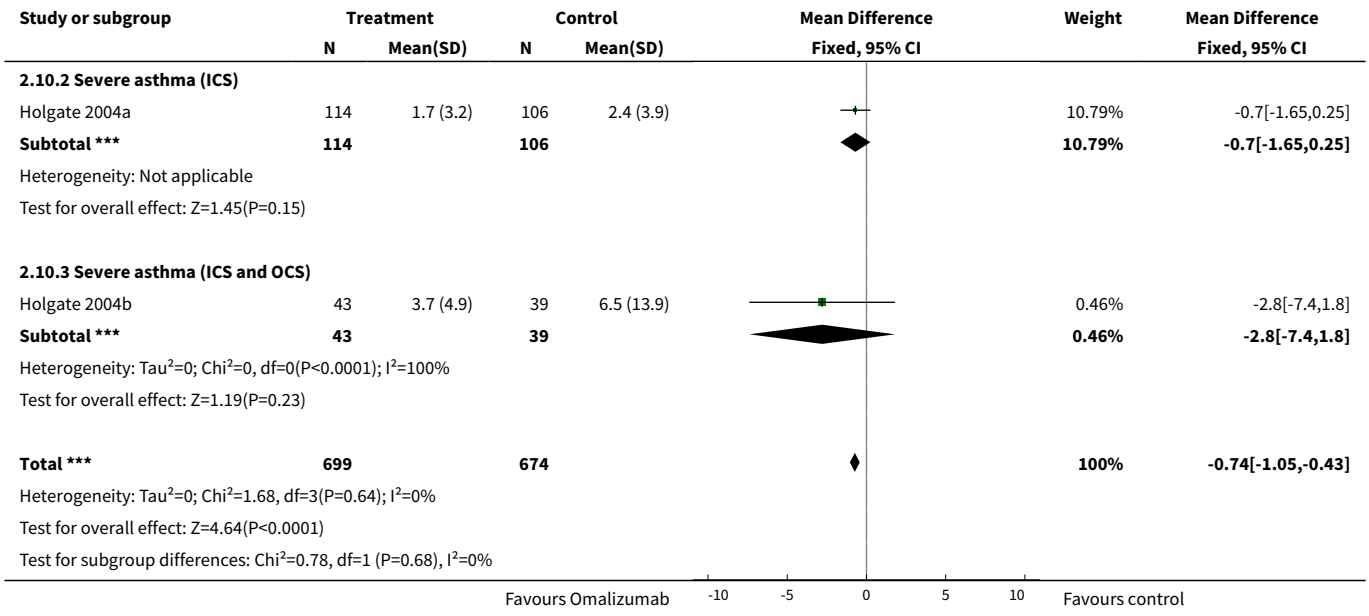


Analysis 2.9. Comparison 2 Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 9 Global evaluation rated good to excellent.



Analysis 2.10. Comparison 2 Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 10 Rescue medication (puffs per day).

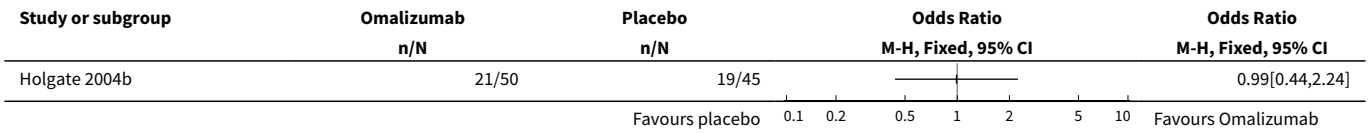




Comparison 3. Subcutaneous omalizumab + ICS and OCS versus placebo + ICS and OCS steroid (steroid reduction)

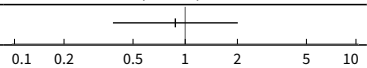
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants achieving complete oral steroid withdrawal	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Number of participants with exacerbation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Mean change in AQLQ scores	6		Mean Difference (Fixed, 95% CI)	0.31 [0.23, 0.39]
3.1 Moderate to severe asthma	3		Mean Difference (Fixed, 95% CI)	0.30 [0.17, 0.42]
3.2 Severe asthma	3		Mean Difference (Fixed, 95% CI)	0.32 [0.21, 0.43]

Analysis 3.1. Comparison 3 Subcutaneous omalizumab + ICS and OCS versus placebo + ICS and OCS steroid (steroid reduction), Outcome 1 Number of participants achieving complete oral steroid withdrawal.



Analysis 3.2. Comparison 3 Subcutaneous omalizumab + ICS and OCS versus placebo + ICS and OCS steroid (steroid reduction), Outcome 2 Number of participants with exacerbation.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Holgate 2004b	21/50	19/42		0.88[0.38,2.01]



Favours Omalizumab | Favours control

Analysis 3.3. Comparison 3 Subcutaneous omalizumab + ICS and OCS versus placebo + ICS and OCS steroid (steroid reduction), Outcome 3 Mean change in AQLQ scores.

Study or subgroup	Omalizumab N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.3.1 Moderate to severe asthma						
Busse 2001	268	257	0.3 (0.108)		15.51%	0.28[0.07,0.49]
SOLAR	209	196	0.3 (0.15)		8.04%	0.3[0.01,0.59]
Solèr 2001	274	272	0.3 (0.094)		20.47%	0.31[0.13,0.49]
Subtotal (95% CI)					**44.01%**	**0.3[0.17,0.42]**
Heterogeneity: Tau^2=0; Chi^2=0.04, df=2(P=0.98); I^2=0%						
Test for overall effect: Z=4.64(P<0.0001)						
3.3.2 Severe asthma						
Hanania 2011	427	423	0.3 (0.071)		35.48%	0.29[0.15,0.43]
Holgate 2004a	126	120	0.3 (0.13)		10.69%	0.31[0.06,0.56]
INNOVATE	204	205	0.5 (0.136)		9.82%	0.45[0.18,0.72]
Subtotal (95% CI)					**55.99%**	**0.32[0.21,0.43]**
Heterogeneity: Tau^2=0; Chi^2=1.1, df=2(P=0.58); I^2=0%						
Test for overall effect: Z=5.66(P<0.0001)						
Total (95% CI)					**100%**	**0.31[0.23,0.39]**
Heterogeneity: Tau^2=0; Chi^2=1.22, df=5(P=0.94); I^2=0%						
Test for overall effect: Z=7.32(P<0.0001)						
Test for subgroup differences: Chi^2=0.08, df=1 (P=0.78), I^2=0%						

Favours placebo | Favours Omalizumab

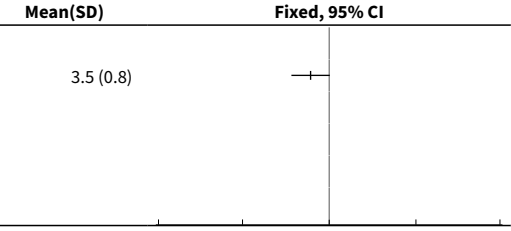
Comparison 4. Subcutaneous omalizumab versus placebo (without inhaled corticosteroids)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV_1 (litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Mild asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Moderate asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 FEV_1 (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Change in PC20	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

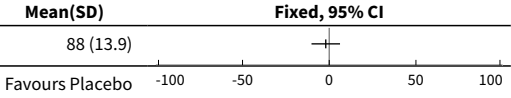
Analysis 4.1. Comparison 4 Subcutaneous omalizumab versus placebo (without inhaled corticosteroids), Outcome 1 FEV_1 (litres).

Study or subgroup	Omalizumab N	Omalizumab Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.1.1 Mild asthma						
Djukanovic 2004	21	3 (0.6)	22	3.5 (0.8)		-0.43[-0.87,0.01]
4.1.2 Moderate asthma						
4.1.3 Severe asthma						



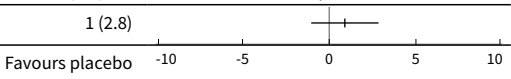
Analysis 4.2. Comparison 4 Subcutaneous omalizumab versus placebo (without inhaled corticosteroids), Outcome 2 FEV_1 (% predicted).

Study or subgroup	Omliazumab N	Omliazumab Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Djukanovic 2004	21	86 (13.6)	22	88 (13.9)		-2[-10.22,6.22]



Analysis 4.3. Comparison 4 Subcutaneous omalizumab versus placebo (without inhaled corticosteroids), Outcome 3 Change in PC20.

Study or subgroup	Omalizumab N	Omalizumab Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Prieto 2006	18	1.9 (3)	16	1 (2.8)		0.9[-1.04,2.84]



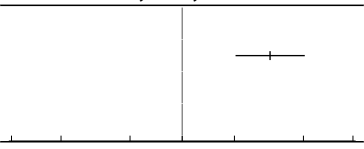
Comparison 5. Subcutaneous omalizumab + steroid versus placebo + steroid (trial extension)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants achieving complete inhaled steroid withdrawal	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Moderate to severe	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Severe	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Participants with one or more exacerbation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Moderate to severe asthma	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Severe asthma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Hospitalisations	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Moderate to severe asthma	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Severe asthma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Number of participants with any adverse event	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Moderate to severe asthma	1	546	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.55, 1.39]
4.2 Severe asthma	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

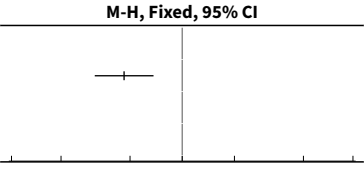
Analysis 5.1. Comparison 5 Subcutaneous omalizumab + steroid versus placebo + steroid (trial extension), Outcome 1 Number of participants achieving complete inhaled steroid withdrawal.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
5.1.1 Moderate to severe				
Solèr 2001	85/254	31/229		3.21[2.03,5.09]
5.1.2 Severe				

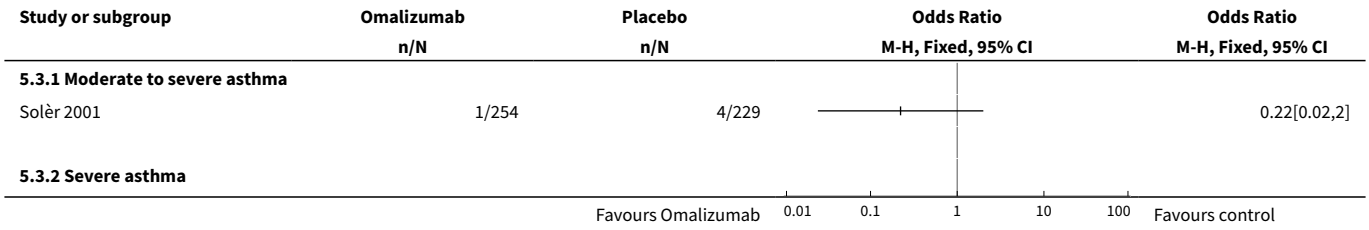


Analysis 5.2. Comparison 5 Subcutaneous omalizumab + steroid versus placebo + steroid (trial extension), Outcome 2 Participants with one or more exacerbation.

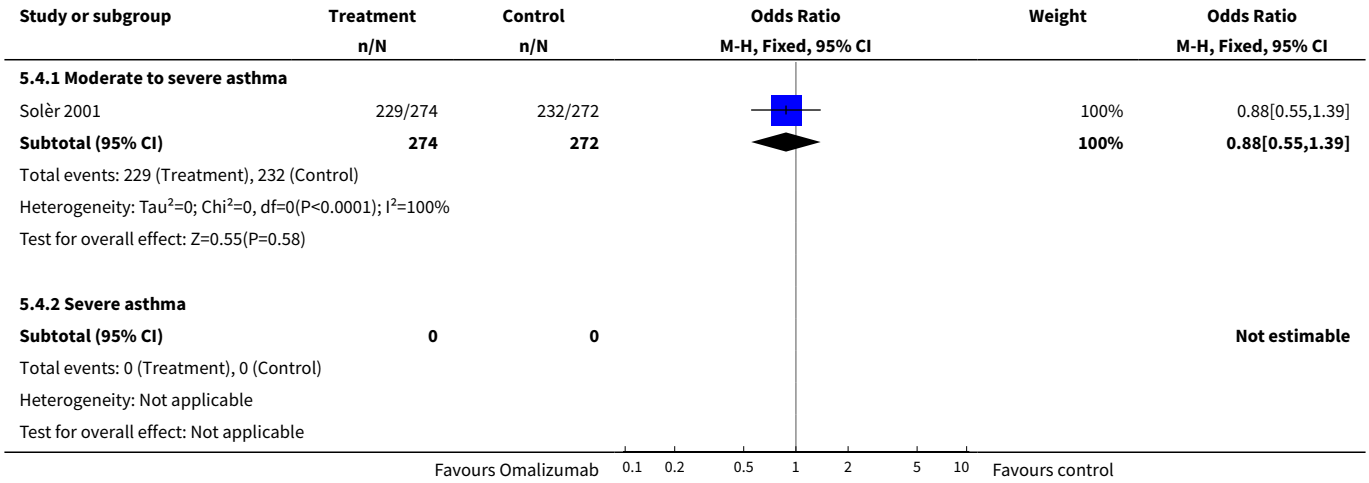
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
5.2.1 Moderate to severe asthma				
Solèr 2001	61/254	93/229		0.46[0.31,0.68]
5.2.2 Severe asthma				



Analysis 5.3. Comparison 5 Subcutaneous omalizumab + steroid versus placebo + steroid (trial extension), Outcome 3 Hospitalisations.



Analysis 5.4. Comparison 5 Subcutaneous omalizumab + steroid versus placebo + steroid (trial extension), Outcome 4 Number of participants with any adverse event.



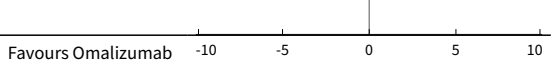
Comparison 6. High-dose intravenous omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rescue medication usage	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Mild asthma	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Moderate to severe asthma	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Severe asthma	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Morning PEF	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Mild asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Moderate to severe asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Moderate to severe	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Symptom scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Mild asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Moderate to severe asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Quality of life	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Mild asthma	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Moderate to severe asthma	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Severe asthma	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Number of participants with > 50% reduction in symptom score	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Moderate to severe asthma	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Severe asthma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

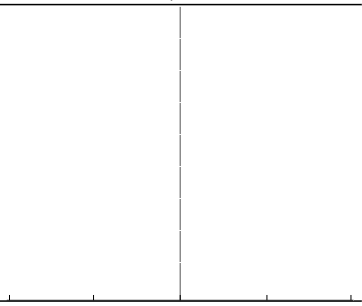
Analysis 6.1. Comparison 6 High-dose intravenous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 1 Rescue medication usage.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
6.1.1 Mild asthma						
6.1.2 Moderate to severe asthma						
Milgrom 1999	106	1.8 (0)	105	0.8 (0)		Not estimable
6.1.3 Severe asthma						



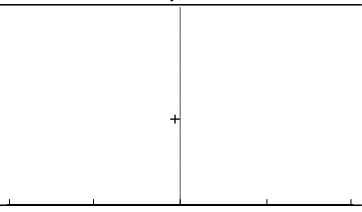
Analysis 6.2. Comparison 6 High-dose intravenous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 2 Morning PEF.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.2.1 Mild asthma						
6.2.2 Moderate to severe asthma						
Milgrom 1999	106	30.7 (0)	105	11.3 (0)		Not estimable
6.2.3 Severe asthma						
6.2.4 Moderate to severe						
Milgrom 1999	106	1.9 (0)	105	1 (0)		Not estimable



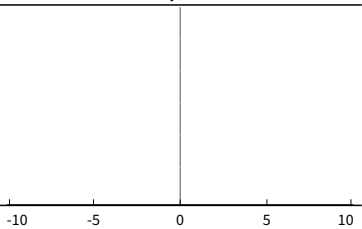
Analysis 6.3. Comparison 6 High-dose intravenous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 3 Symptom scores.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.3.1 Mild asthma						
6.3.2 Moderate to severe asthma						
Milgrom 1999	106	2.8 (1)	105	3.1 (1)		-0.3[-0.58,-0.02]
6.3.3 Severe asthma						



Analysis 6.4. Comparison 6 High-dose intravenous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 4 Quality of life.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
6.4.1 Mild asthma						
6.4.2 Moderate to severe asthma						
Milgrom 1999	85	1.4 (0)	88	0.8 (0)		Not estimable
6.4.3 Severe asthma						



Analysis 6.5. Comparison 6 High-dose intravenous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 5 Number of participants with > 50% reduction in symptom score.

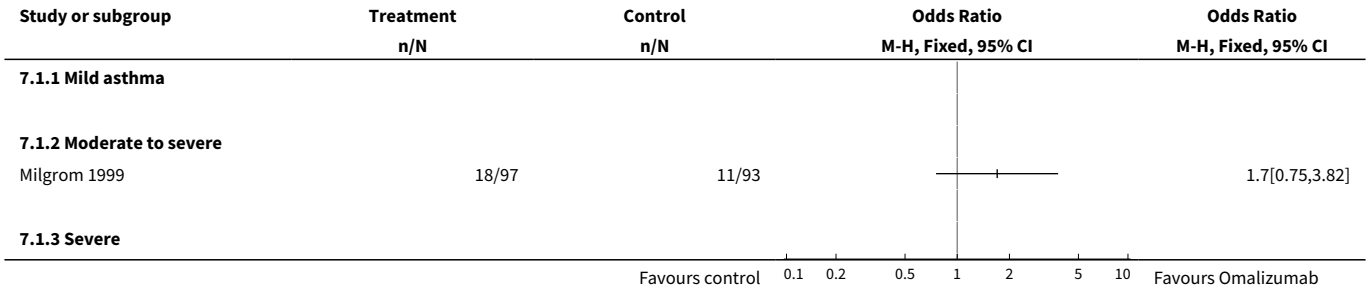
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.5.1 Moderate to severe asthma				
Milgrom 1999	50/103	24/100		2.99[1.64,5.44]
6.5.2 Severe asthma				

Comparison 7. High-dose intravenous omalizumab + steroid versus placebo + steroid (steroid reduction)

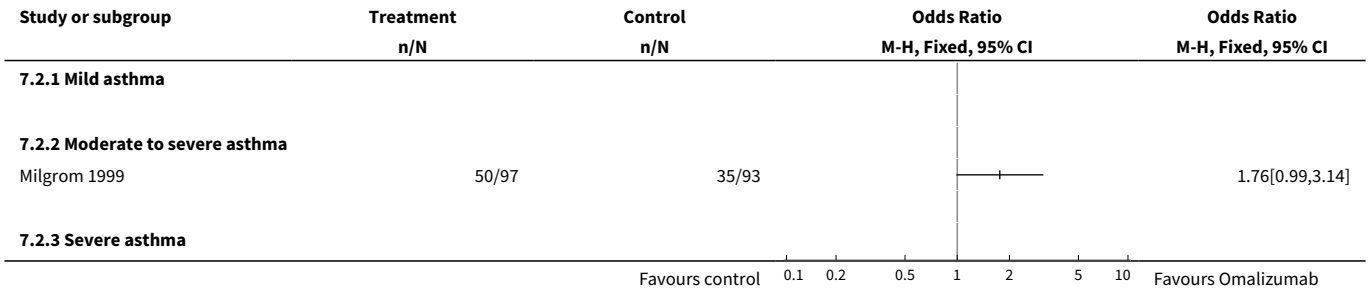
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants achieving complete inhaled steroid withdrawal	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Mild asthma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Moderate to severe	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Severe	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 > 50% reduction in inhaled steroid usage	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Mild asthma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Moderate to severe asthma	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Severe asthma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Symptom score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Moderate to severe asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Number of participants with > 50% reduction in symptom scores	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Mild asthma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Moderate to severe asthma	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Severe asthma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Number of participants with exacerbations	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Mild asthma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Moderate to severe asthma	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Severe asthma	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

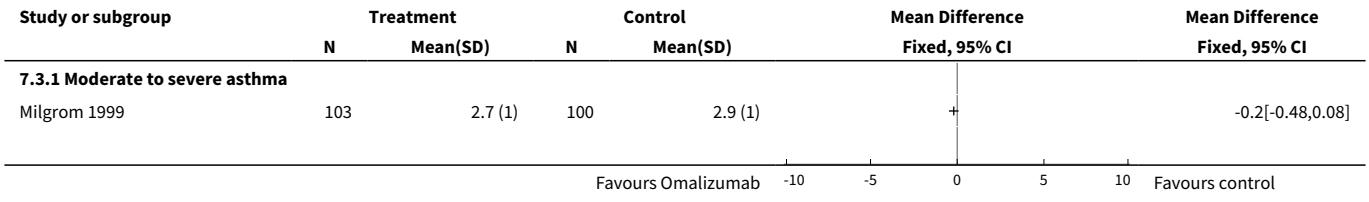
Analysis 7.1. Comparison 7 High-dose intravenous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 1 Number of participants achieving complete inhaled steroid withdrawal.

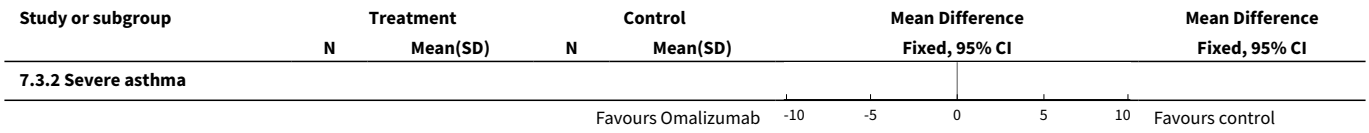


Analysis 7.2. Comparison 7 High-dose intravenous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 2 > 50% reduction in inhaled steroid usage.

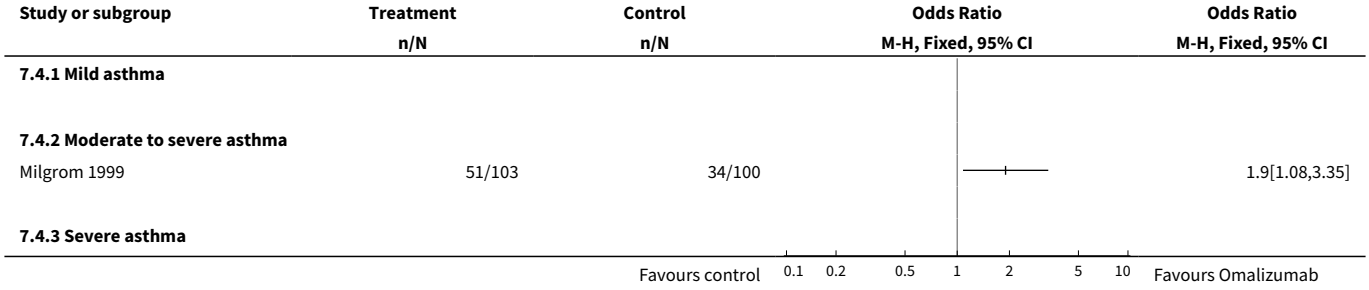


Analysis 7.3. Comparison 7 High-dose intravenous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 3 Symptom score.

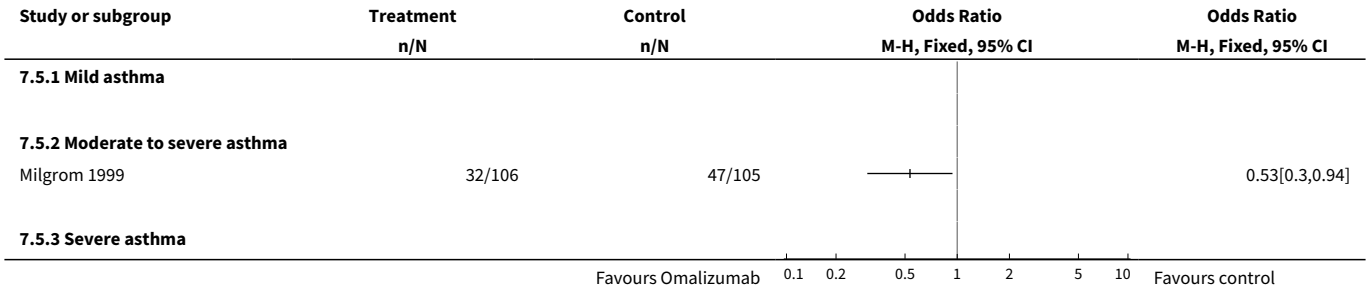




Analysis 7.4. Comparison 7 High-dose intravenous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 4 Number of participants with > 50% reduction in symptom scores.



Analysis 7.5. Comparison 7 High-dose intravenous omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 5 Number of participants with exacerbations.



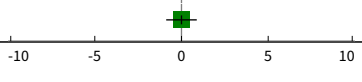
Comparison 8. Intravenous omalizumab versus placebo

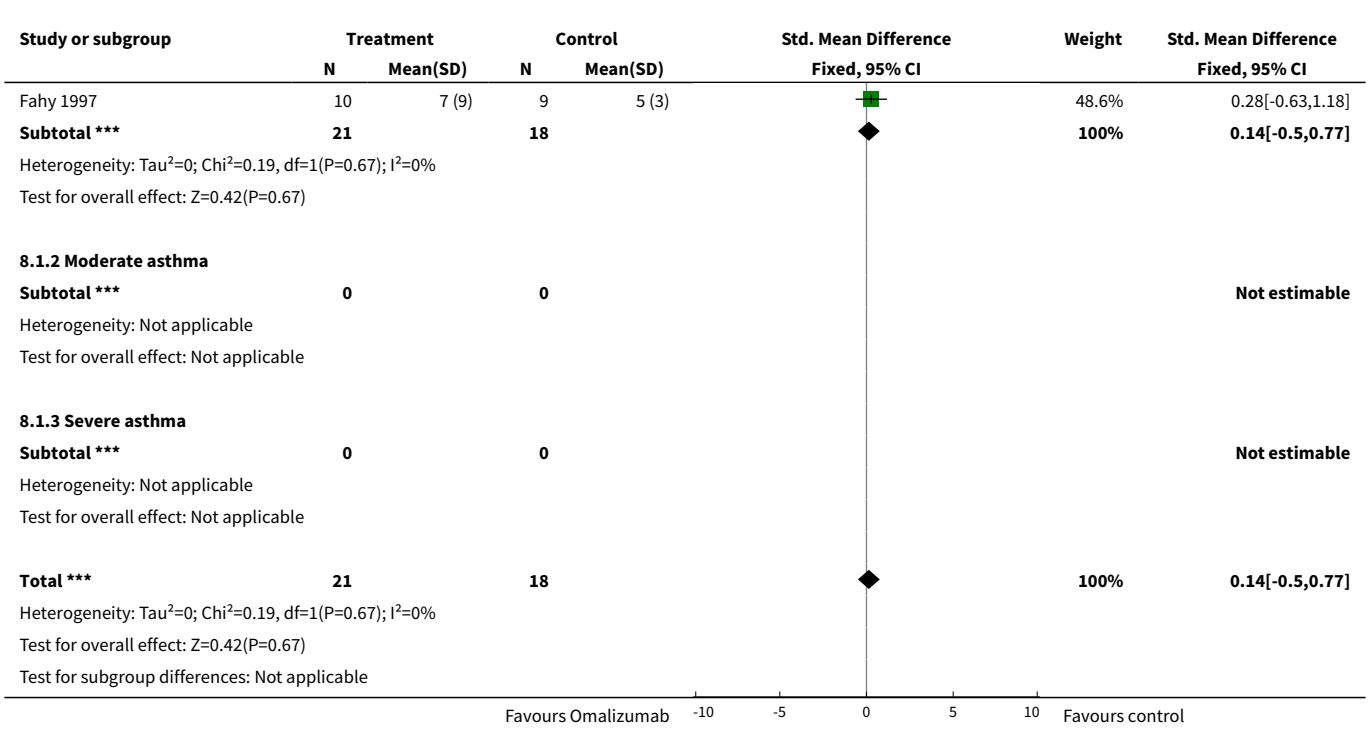
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rescue medication use (one week after end of treatment)	2	39	Std. Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.50, 0.77]
1.1 Mild asthma	2	39	Std. Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.50, 0.77]
1.2 Moderate asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Severe asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 FEV_1 (litres)	2	39	Std. Mean Difference (IV, Fixed, 95% CI)	0.51 [-0.13, 1.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Mild asthma	2	39	Std. Mean Difference (IV, Fixed, 95% CI)	0.51 [-0.13, 1.15]
2.2 Moderate asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Severe asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Fall in FEV_1 after allergen challenge (%) (zero to one hour)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Mild asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Moderate asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Fall in FEV_1 after allergen challenge (%) (two to seven hours)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Mild asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Moderate asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Peak expiratory flow (am)	2	39	Std. Mean Difference (IV, Fixed, 95% CI)	0.35 [-0.29, 1.00]
5.1 Mild asthma	2	39	Std. Mean Difference (IV, Fixed, 95% CI)	0.35 [-0.29, 1.00]
5.2 Moderate asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Severe	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Symptom scores	2	39	Std. Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.96, 0.31]
6.1 Mild asthma	2	39	Std. Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.96, 0.31]
6.2 Moderate asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Severe asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

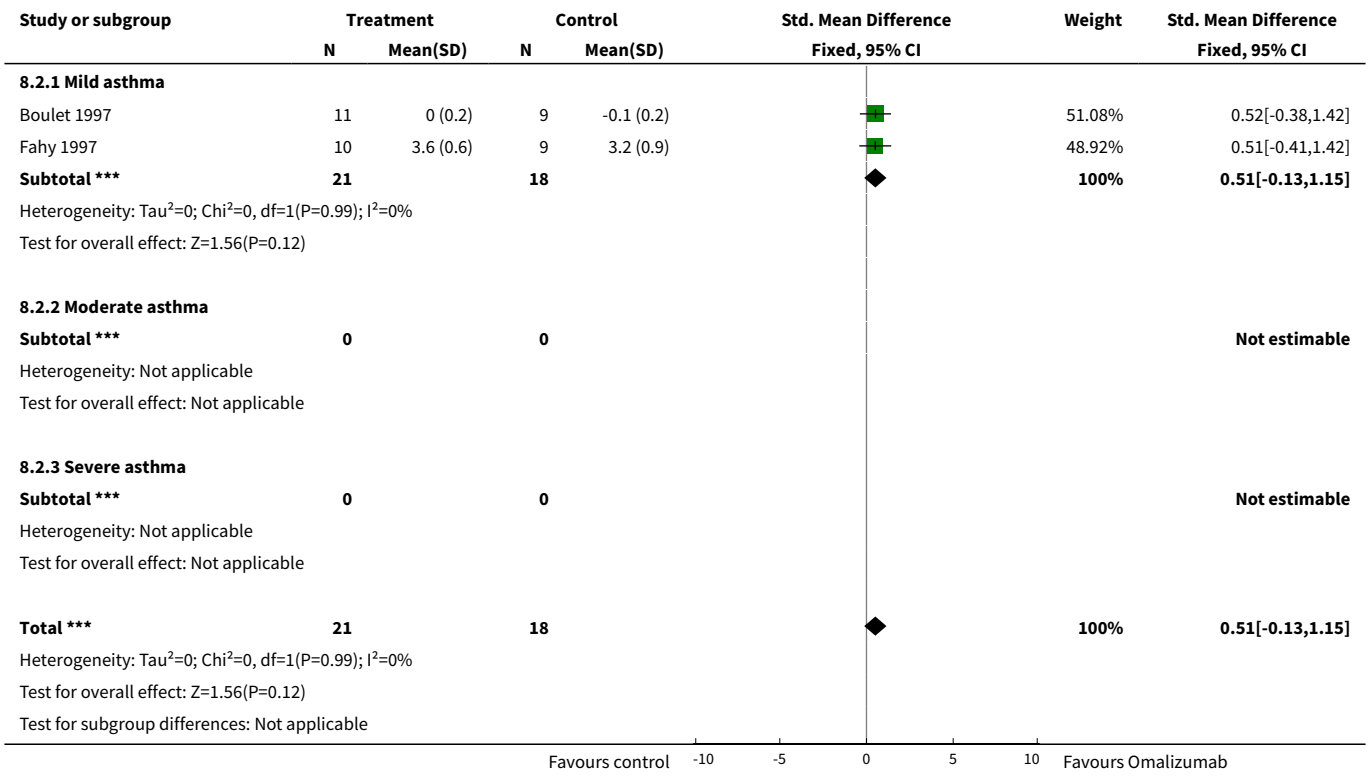
Analysis 8.1. Comparison 8 Intravenous omalizumab versus placebo, Outcome 1 Rescue medication use (one week after end of treatment).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.1.1 Mild asthma							
Boulet 1997	11	-0.4 (0.9)	9	-0.4 (1)		51.4%	0[-0.88,0.88]



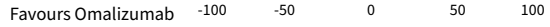


Analysis 8.2. Comparison 8 Intravenous omalizumab versus placebo, Outcome 2 FEV_1 (litres).



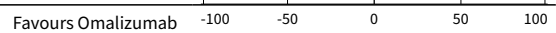
Analysis 8.3. Comparison 8 Intravenous omalizumab versus placebo, Outcome 3 Fall in FEV_1 after allergen challenge (%) (zero to one hour).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
8.3.1 Mild asthma						
Fahy 1997	10	18 (8)	9	34 (4)		-16[-21.6,-10.4]
8.3.2 Moderate asthma						
8.3.3 Severe asthma						



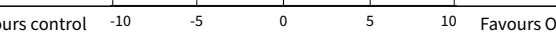
Analysis 8.4. Comparison 8 Intravenous omalizumab versus placebo, Outcome 4 Fall in FEV_1 after allergen challenge (%) (two to seven hours).

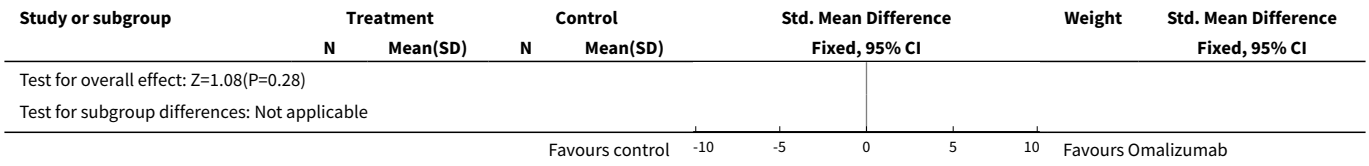
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
8.4.1 Mild asthma						
Fahy 1997	10	9 (10)	9	18 (17)		-9[-21.72,3.72]
8.4.2 Moderate asthma						
8.4.3 Severe asthma						



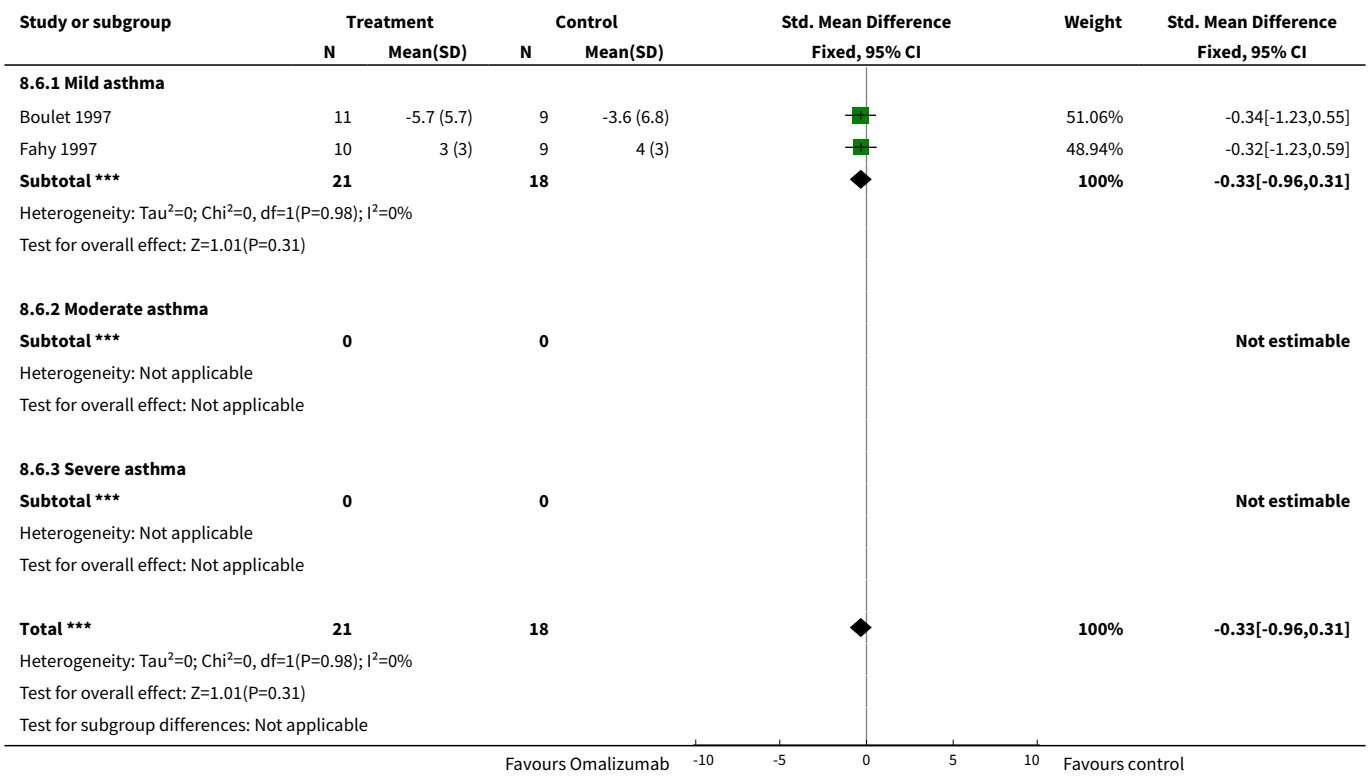
Analysis 8.5. Comparison 8 Intravenous omalizumab versus placebo, Outcome 5 Peak expiratory flow (am).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.5.1 Mild asthma							
Boulet 1997	11	17.9 (29.1)	9	16.5 (29.4)		52.95%	0.05[-0.84,0.93]
Fahy 1997	10	482 (102)	9	414 (81)		47.05%	0.7[-0.23,1.64]
Subtotal ***	**21**		**18**			**100%**	**0.35[-0.29,1]**
Heterogeneity: $Tau^2=0$; $Chi^2=1$, df=1(P=0.32); $I^2=0\%$							
Test for overall effect: Z=1.08(P=0.28)							
8.5.2 Moderate asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.5.3 Severe							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**21**		**18**			**100%**	**0.35[-0.29,1]**
Heterogeneity: $Tau^2=0$; $Chi^2=1$, df=1(P=0.32); $I^2=0\%$							





Analysis 8.6. Comparison 8 Intravenous omalizumab versus placebo, Outcome 6 Symptom scores.

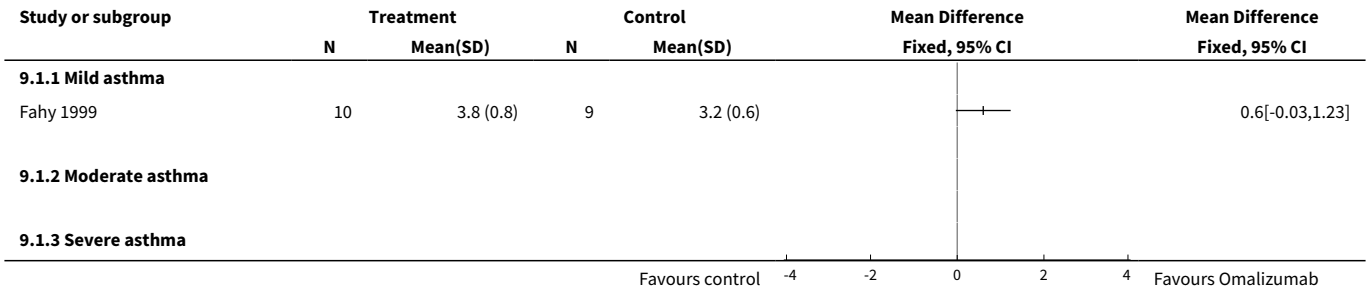


Comparison 9. High-dose aerosolised omalizumab versus placebo

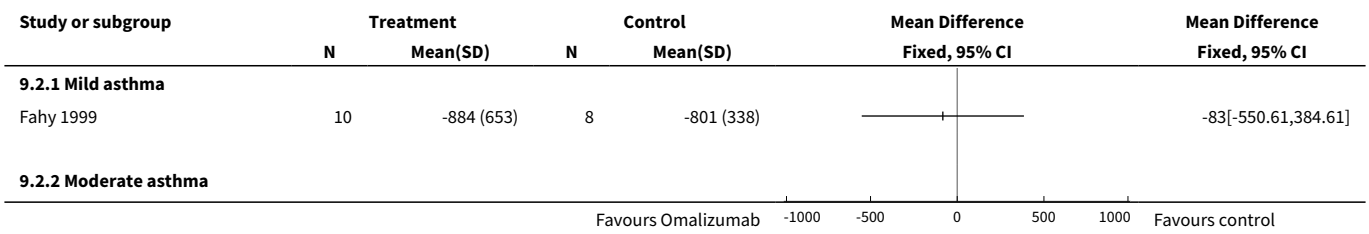
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV_1 (litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Mild asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Moderate asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Area under the curve for % fall in FEV_1 (early response: zero to one hour)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

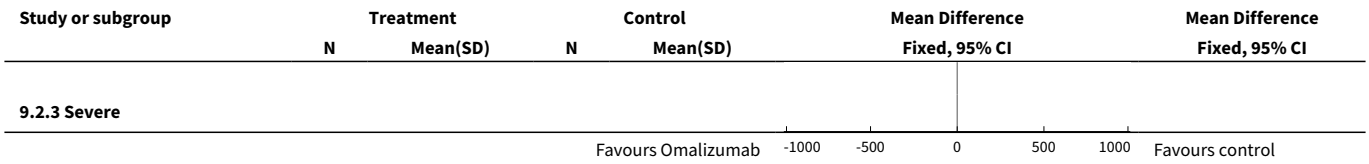
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Mild asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Moderate asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Severe	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Area under the curve for % fall in FEV_1 (late response: three to seven hours)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Mild asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Moderate asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Peak expiratory flow (am) (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Mild asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Moderate asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Severe	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 9.1. Comparison 9 High-dose aerosolised omalizumab versus placebo, Outcome 1 FEV_1 (litres).

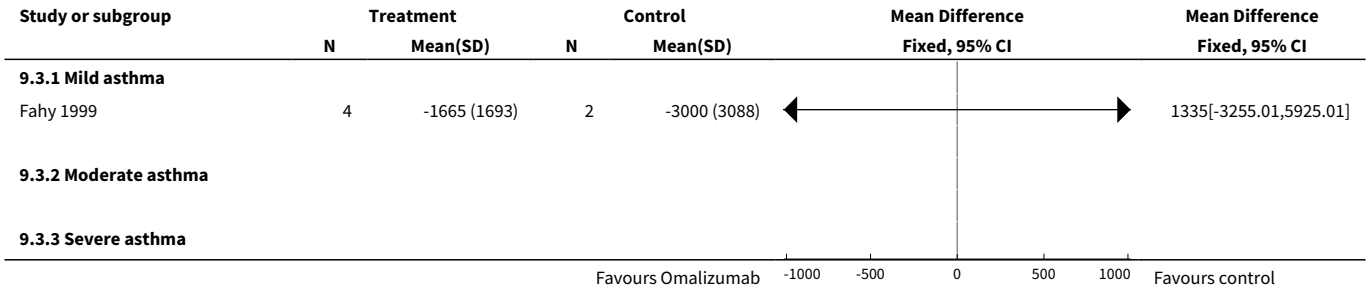


Analysis 9.2. Comparison 9 High-dose aerosolised omalizumab versus placebo, Outcome 2 Area under the curve for % fall in FEV_1 (early response: zero to one hour).

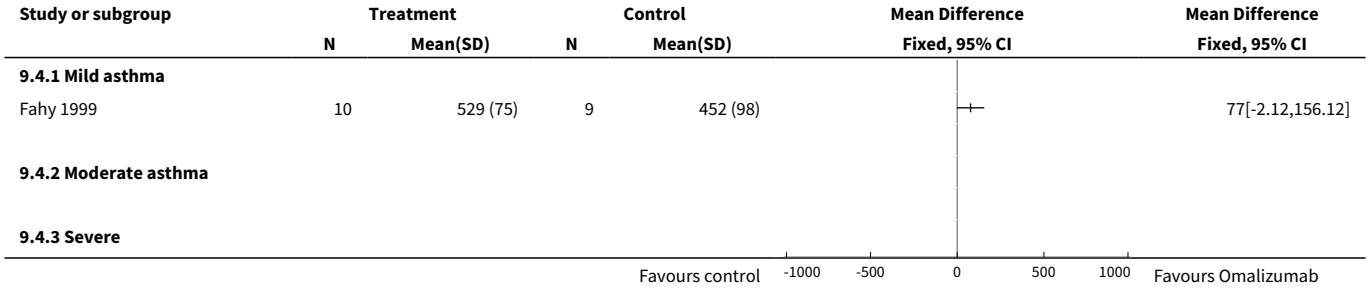




Analysis 9.3. Comparison 9 High-dose aerosolised omalizumab versus placebo, Outcome 3 Area under the curve for % fall in FEV_1 (late response: three to seven hours).



Analysis 9.4. Comparison 9 High-dose aerosolised omalizumab versus placebo, Outcome 4 Peak expiratory flow (am) (L/min).



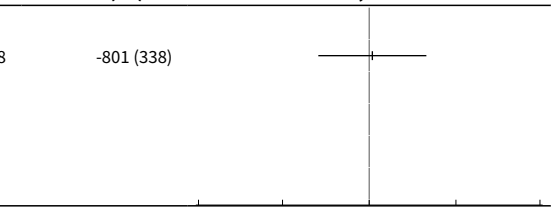
Comparison 10. Low-dose aerosolised omalizumab versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Area under curve for fall in FEV_1 (% × minutes)—early response (zero to one hour)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Mild asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Moderate asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Area under curve for fall in FEV_1 (% × minutes)—late response (three to seven hours)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Mild asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Moderate asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Peak expiratory flow (am) (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Mild asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Moderate asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 FEV_1 (litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Mild asthma	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Moderate asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Severe asthma	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

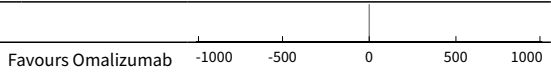
Analysis 10.1. Comparison 10 Low-dose aerosolised omalizumab versus placebo, Outcome 1 Area under curve for fall in FEV_1 (% × minutes)—early response (zero to one hour).

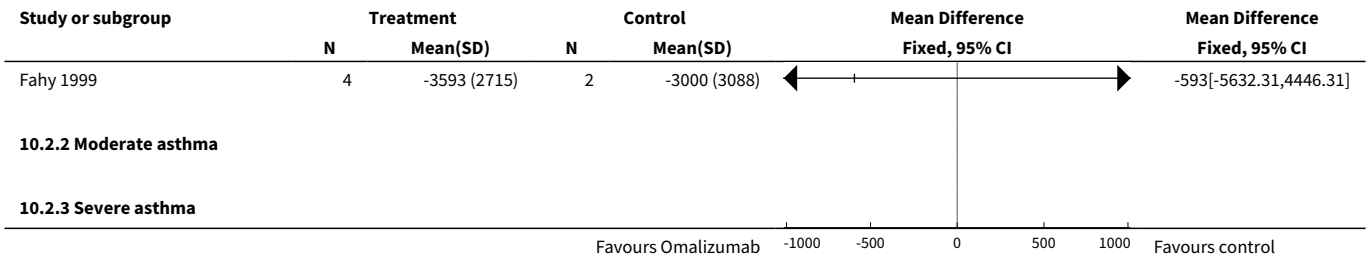
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
10.1.1 Mild asthma						
Fahy 1999	12	-783 (363)	8	-801 (338)		18[-293.51,329.51]
10.1.2 Moderate asthma						
10.1.3 Severe asthma						



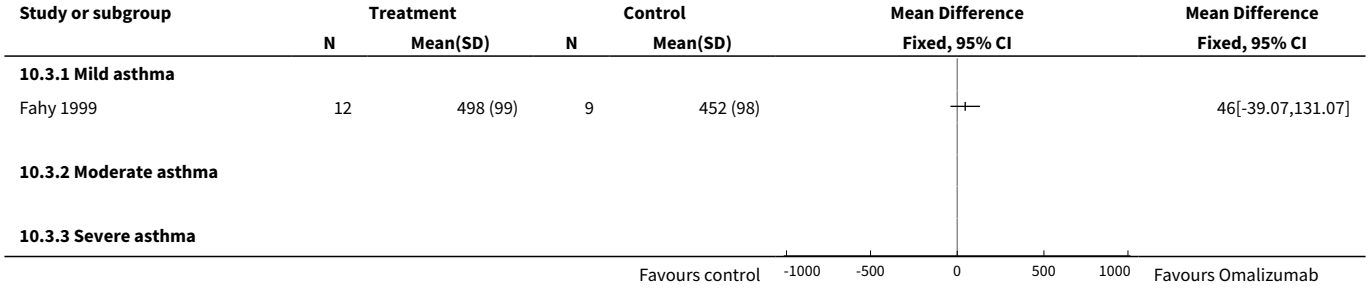
Analysis 10.2. Comparison 10 Low-dose aerosolised omalizumab versus placebo, Outcome 2 Area under curve for fall in FEV_1 (% × minutes)—late response (three to seven hours).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
10.2.1 Mild asthma						

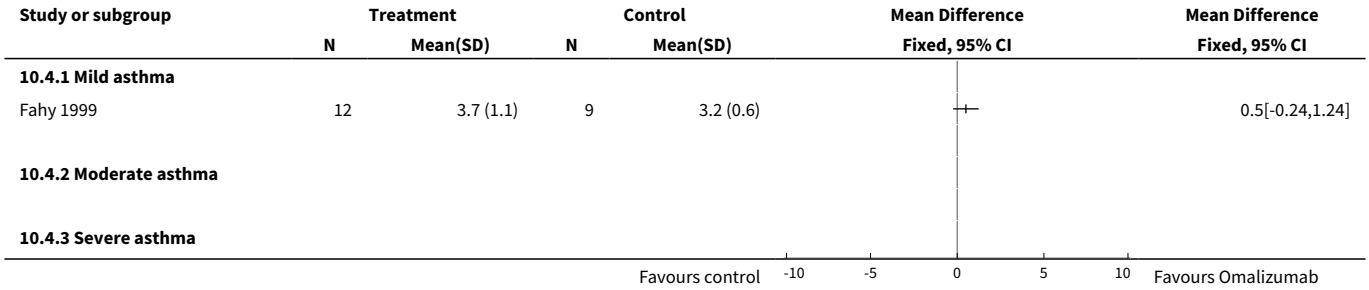




Analysis 10.3. Comparison 10 Low-dose aerosolised omalizumab versus placebo, Outcome 3 Peak expiratory flow (am) (L/min).



Analysis 10.4. Comparison 10 Low-dose aerosolised omalizumab versus placebo, Outcome 4 FEV_1 (litres).



ADDITIONAL TABLES

Table 1. Search history

Date	Search results
Initial version of the review (all years to January 2003)	From a total of 169 references identified by electronic searches and handsearching, we retrieved 20 papers and eight studies that met the inclusion criteria of the review. One study of subcutaneous anti-IgE recruited adults with severe asthma (Holgate 2004a). Four studies examined intravenous or subcutaneous anti-IgE in adults (Busse 2001; Milgrom 1999; Solèr 2001) and children (Milgrom 2001) with moderate to severe asthma, and three studies examined aerosolised or intravenous anti-IgE in adults with mild asthma (Boulet 1997; Fahy 1997; Fahy 1999)

Table 1. Search history *(Continued)*

Update search results (January 2003 to 2004)	Publication of a critical review of the efficacy of omalizumab from published and unpublished clinical trials has prompted this update. For details of this publication, please see http://www.fda.gov. Two unpublished studies were identified from this report (ETOPA; Q2143G). One further unpublished study in people with co-existing asthma and rhinitis is awaiting assessment (SOLAR)
Update search results (January 2004 to February 2006)	Electronic searches yielded a total of 48 new references from the Airways Group register. After exclusion of duplicates, a total of eight studies were retrieved for further scrutiny. Of these, five met the inclusion criteria (Prieto 2006; Djukanovic 2004; INNOVATE; van Rensen 2009; SOLAR). Details of studies that failed to meet the inclusion criteria are found in Characteristics of excluded studies
Update search results (June 2013)	147 new references were identified by the Aiways Group register, producing an additional 11 studies that met the inclusion criteria: Bardelas 2012; Busse 2011; Chanez 2010; Garcia 2012; Gevaert 2012; Hanania 2011; Lanier 2009; Massanari 2010; NCT00096954; NCT01007149; Ohta 2009. Studies that did not meet the inclusion criteria are listed in Characteristics of excluded studies

Table 2. Asthma severity

Study ID	FEV_1 (incl criteria)	B/line FEV_1 mean	Symptom freq	OCS rx	ICS rx	Author opinion	BTS step
Bardelas 2012	≤ 80% pred (or symptoms > 2 days/wk, ≥1 night-time wakening/wk or > 2 SABA use/wk	75.5% pred ± 17.25	Asthma control test mean score = 13.8	No	Yes—at least 250 mcg fluticasone bd or 320 mcg budesonide bd	Severe	Step 4 and above
Boulet 1997	> 70% pred	91.89 ± 11.03 (range 83 to 106)	No indication reported	No	No	Mild	Step 1
Busse 2001	≥ 40% to ≤ 80%	67.95 ± 14.59	Puffs of medication per day 4.85 ± 2.6; asthma score: 4.27 ± 1.17 (scale 0 to 9, with 9 indicating most severe). Limited physical activity in 482/525 participants	No	Yes—mean BDP dose: 569 mcg/d (range 336 to 1008)	Severe	Step 2. Range in baseline FEV_1 extends to above 80% predicted, and range of BDP extends below stated criteria
Busse 2011	Not stated	92.1% pred ± 17.1	Astham control test mean score = 19 or less Asthma-related symptoms—number of days in two weeks preceding visit = 3.1 ± 3.6 (placebo group); 3.0 ± 3.5 (treatment group)	No	Yes—at least 180 µg budesonide once a day	Mild, moderate and severe	Steps 1 to 6 (26.5% steps 1 and 2, 54% steps 4 to 6)
Chanez 2010	FEV_1 < 80% pred	63.2% pred ± 13.75	Absenteeism from school or work in previous year (days): mean 33.8 ± 100.22	Yes; seven (22%) participants receiving maintenance OCS	Yes—at least 1000 mcg beclometasone dipropionate or equivalent daily mean dose/d 3556 mcg ± 1157.8 BDP equivalent/d	Severe	Step 4 and above
Djukanovic 2004	Not stated	85%	Not stated	No	No	Mild to moderate	Step 1

Table 2. Asthma severity *(Continued)*

Fahy 1997	≥ 70% pred	94.5 ± 10.72	No indication reported	No	No	Mild	Step 1
Fahy 1999	≥ 70% pred	82.74 ± 16.09	No indication reported	OCS rx excluded	No	Mild	Step 1
Garcia 2012	Not stated	Not stated	Not stated	Not stated	Not stated	Severe	Not specifically stated but likely step 4 and above
Gevaert 2012	Not stated	FEV_1 (% predicted), median (IQR) OMA 88.5 (71.0 to 114.8); placebo 99.5 (73.5 to 110.3)	Not stated	During the study, participants were not permitted to use systemic corticosteroids	During the study, participants were not permitted to use an inhaled corticosteroid (doses of greater than 1000 mg/d beclomethasone dipropionate or equivalent)	Total serum IgE levels between 30 and 700 kU/mL	Not stated
Hanania 2011	FEV_1 40% to 80% pred	64.9% pred ± 14.6	Mean total asthma symptom severity score = 3.9 ± 1.8 Mean AQLQ(S) score 4.0 ± 1.1 Mean puffs of rescue medication per day 4.0 ± 2.9 (treatment group) and 4.1 ± 3.2 (placebo group)	Yes, 60 (7.1%) of participants using long-term OCS at baseline	Yes, minimum dose of 500 mcg of fluticasone dry powder inhaler (or its equivalent) twice daily	Severe	Step 4 and above
Holgate 2004 (ICS)	Not stated	64.41% (no range given)	Not stated	No	Optimal control on 1000 to 2000 mcg/d FP ± OCS, and long-acting β-agonist. Mean FP dose: 1368.9	Severe	Step 4
Holgate (ICS & OCS)	Not stated	59%	Not stated	Yes	Optimal control on 1000 to 2000 mcg/d; mean prednisolone dose: 10.2 mcg/d	Severe	Step 5
INNOVATE	Not stated	61%	Not stated	Yes—22% receiving maintenance OCS	Yes—2400 mcg/d BDP equivalent	Severe	Step 4

Table 2. Asthma severity *(Continued)*

Lanier 2009	Not stated	86.4% pred ± 18.0	Mean normal number of daily puffs of short-acting β_2-agonist at baseline 2.8 ± 2.6	Yes, 1.3% of participants were using maintenance oral steroids at baseline	Yes, mean ICS dose, mg/d (fluticasone propionate equivalent): 515.1 ± 285.4	Intermittent to severe persistent (99% of participants moderate to severe)	Steps 1 to 6
Massanari 2010	FEV_1 ≥ 75% pred	87.1% pred ± 11.43	Average total asthma symptom score = 1.16 ± 0.90 Average daily number of rescue puffs of β-agonist = 0.98 ± 1.12	No	Yes, all participants receiving ICS at baseline; no further details given	Moderate to severe (however, participants with unstable asthma excluded)	Steps 2 to 4
Milgrom 1999	50% to 90% pred	71 (range 29 to 129)	Use of β-agonist: 8.6 puffs per day (range 2 to 37.7), mean symptom score: 4 (range 1.5 to 6.5). Inclusion criteria at least 2.5 on each of seven days before randomisation	Yes—35 participants (median: 10 mg per day, range: 2.5 to 40)	Yes—282 participants, median dose: 800 mcg per day (range 200 to 4000)	Moderate persistent to severe persistent, defined as: mean FEV_1 71% pred value, daily symptom score 4 (0 to 7 scale, 7 indicating most severe), daily β-agonist use	Step 2. Although range of FEV_1 and symptom scores outside the inclusion criteria suggest that this was a heterogenous population that included some mild persistent participants
Milgrom 2001	FEV_1 ≥ 60% pred	84.33% (range 43 to 129)	Mean albuterol use: 1.2 puffs per day, mean daytime symptom score: 0.54, mean nocturnal symptom score: 0.22, mean am score: 0.17 (daytime scale: 0 to 4, nocturnal scale: 0 to 4 and am scale: 0/1)	Not reported	Mean dose of BDP: 278.45 mcg/d (range 168 to 672)	Moderate to severe	Step 2
NCT00096954	FEV_1 ≥ 80% predicted	Not stated	"Evidence of inadequate asthma symptom control despite inhaled corticosteroids with or without other controller asthma medications"	No	Yes, fluticasone dry powder inhaler (DPI) ≥ 200 µg/d or equivalent	Mild to severe	Step 2 and above

Table 2. Asthma severity *(Continued)*

NCT01007149	FEV_1 < 80% pred	Not stated	"Uncontrolled according to Global Initiative for Asthma (GINA) 2007 guidelines and at least 2 exacerbations having required systemic corticosteroid and/or at least 1 hospitalisation or emergency room visit in the past year"	Yes, but no details of numbers receiving maintenance OCS	Yes, > 1000 µg beclometasone dipropionate equivalent per day	Severe	Step 4 and above
Ohta 2009	FEV_1 or mean PEF 40% to 80% pred (or another marker of poor control; see paper for details)	Treatment group = 74.06% ± 19.912; placebo group = 75.81% ± 20.888	Hospitalisation due to asthma in previous year = 10.1% of participants; ER visits due to asthma in previous year = 19.7% of participants	Yes; 9.5% receiving maintenance OCS at baseline	Yes, ≥ 800 mcg/d beclomethasone (or equivalent). Mean dose = 1169 mcg/d	Moderate to severe	Step 3 and above
Solèr 2001	Off bronchodilator, ≥ 40% pred to ≤ 80% pred	69.85 (range 22 to 112)	β-Agonist on as-needed or regular basis. Mean symptom score > 3, maximum 9	No	770.54 (range 200 to 2000 mcg/d). Inclusion criteria stated inclusion of participants on 500 to 1200 mcg BDP/d	Moderate to severe. Severe participants: 60 in treatment group and 59 in placebo group defined as baseline FEV_1 ≤ 65% pred and mean total symptom score < 4 during last 14 days of run-in period	Step 2. Most participants fall into this category, but judging by baseline FEV_1 and BDP dose, some milder participants may be included
SOLAR	Not stated	78.1 (SD 16.61)	QoL scores indicating at least mild symptoms. Mean baseline puffs/d: 2.8	No	870 mcg BUD	Moderate to severe	Step 2

Table 3. Baseline IgE levels

Study	IgE level (mean)
Bardelas 2012	180 IU/mL ± 130.5
Boulet 1997	1152.4 IU/mL (data skewed: SD 2304.5)
Busse 2001	179.26 IU/mL
Busse 2011	Unclear
Chanez 2010	220.2 IU/mL ± 151.96
Djukanovic 2004	Median: omalizumab group: 155.5; placebo group: 141
Fahy 1997	141.5 IU/mL
Fahy 1999	230.1 IU/mL
Garcia 2012	Not stated
Gevaert 2012	Not stated
Hanania 2011	176.9 IU/mL
Holgate 2004	266.26 IU/mL
INNOVATE	Between 30 and 1300 IU/mL (no mean given)
Lanier 2009	469.7 IU/mL ± 338.0
Massanari 2010	176.63 IU/mL ± 138.018
Milgrom 1999	441.7 IU/mL
Milgrom 2001	339.85 IU/mL
NCT00096954	≥ 30 to ≤ 1300 IU/mL; no mean given
NCT01007149	Unclear
Ohta 2009	508.1 IU/mL
Prieto 2006	199.2 IU/mL
SOLAR	193.6 IU/mL
Solèr 2001	214.38 IU/mL
van Rensen 2009	Unclear

Table 4. Corticosteroid use during steroid-tapering phase

	Solèr 2001	Busse 2001	Milgrom 2001	Holgate 2004	Pooled estimates
Baseline mean ICS dose (omalizumab/placebo)	766/777	564/522	284/267	1407/1376	N/A
Length of study (weeks)	52	28	28	32	N/A
Length of tapering phase	12	12	12	16	N/A
Mean daily ICS dose at end of tapering phase (omalizumab/placebo)	213/378 Source: FDA website	193/274 Source: FDA website	N/A	506/690 Source: unpublished data (Acumed)	N/A
Change in CS dose (omalizumab/placebo), mcg	Mean change (ICS): -553/-399 Source: FDA website	Mean change (ICS): -371/-278 Source: FDA website	N/A	Mean change (ICS): -782/-596 Source: published paper	Busse 2001/Solèr 2001/Holgate 2004: WMD -119 mcg/d (95% CI -153.72 to -84.34)
Median (95% CI) daily ICS dose at end of tapering (omalizumab/placebo)	100 (0 to 400)/300 (100 to 600)	N/A	N/A	N/A	N/A
Change (%) (omalizumab/placebo)	72/51	66/50	Median change (ICS): 100/67 P = 0.001	Median change (ICS): 60/50 P = 0.003 Source: FDA website Median change (OCS): 69%/75% P = 0.7	N/A
Number of participants achieving > 50% reduction in ICS dose (n/N) (omalizumab/placebo)	216/274 150/272	194/268 141/257	174/216 68/101	94/126 61/120	OR 2.5 (95% CI 2.02 to 3.10) NNTB five to seven
Number of participants achieving complete ICS withdrawal (omalizumab/placebo)	118/274 53/272	106/268 49/257	119/216 39/101	27/126 18/120	OR 2.5 (95% CI 2.0 to 3.13) NNTB five to eight

Table 5. Responder analyses

Study	Type of asthma	Definition	Trials analysed	Severe participants (n)	Response
Babu 2001	Severe	Three definitions of severe asthma explored:	Busse 2001; Milgrom 2001; Solèr 2001	22% adult participants; 9% paedi-	Median BDP reduction: Severe participants reduced consumption by 60% to 67% versus 80% to 83% in moderate

Table 5. Responder analyses *(Continued)*

		1. ≤ 60% baseline FEV_1 predicted 2. ≤ 65% baseline FEV_1 predicted 3. ≤ 65% baseline FEV_1 + symptom score > 4 (out of 9)		atric participants taking omalizumab and 6% given placebo	asthmatic participants. (These numbers vary depending upon the 'severe' criteria applied.)
Bousquet 2004	Moderate to severe	1. BDP dose ≥ 800 mcg/d 2. FEV_1 ≤ 65% predicted 3. History of emergency treatment	Busse 2001; Solèr 2001	BDP dose ≥ 800 mcg/d: 432 FEV_1 ≤ 65% predicted: 379 History of emergency treatment: 733	Response to therapy defined as (1) reduction in symptoms of at least one, with no increase in SABA; reduced use of rescue medication; (2) reduced usage of SABA (≥one puff per day and no increase in symptoms; (3) improved lung function (increase in am PEF ≥ 15%); (4) improvement in QoL (increase in AQLQ of 1 in overall score); (5) composite of at least one four responses with no asthma exacerbation Odds ratio of composite response according to baseline characteristic indicated that participants more likely to respond with two or more variables
Holgate 2001	'At-risk' asthmatic participants	Intubation at some point prior to screening/ hospitalised in the past year	Busse 2001; Soler 2001; Chung 2002	254	N = 34 experienced exacerbations in omalizumab treated group versus N = 42 in placebo
Wenzel 2002	Severe	High dose BDP, poor lung function, history of emergency asthma treatment in the last year.	Busse 2001; Soler 2001	This sensitivity analysis was conducted in order to determine baseline predictors of efficacy	Participants who experienced a reduction in symptom scores, reduction in use of rescue medication, improvement in lung function, improvement in quality of life.

Table 6. Paediatric populations

Trial	Omalizumab	Placebo	%
Bardelas 2012	Footnote[1]		
Busse 2001	20/268	21/257	7.8%
Busse 2011	Footnote[2]		
Hanania 2011	23/427	16/421	4.6%
Holgate 2004 and Holgate 2004a (N between 12 and 17 years)	12/176	9/165	6.5%
Lanier 2009	421/421	206/206	100%

Table 6. Paediatric populations *(Continued)*

Milgrom 2001	225/225	109/109	100%
NCT00096954	Footnote[3]		
Solèr 2001	18/274	17/272	6.4%

[1] Bardelas 2012 included participants from 12 years of age. However, no details are provided in the study report on the proportion of paediatric participants in the sample (mean ages: omalizumab 41.9 ± 14.60 and placebo 40.7 ± 14.85).
[2] Busse 2011 included participants from six to 20 years of age. However, no details are provided in the study report on the proportion of paediatric participants in the sample (mean ages: omalizumab 10.8 ± 3.4 and placebo 10.9 ± 3.6).
[3] NCT00096954 included participants from 12 years of age. However, no details are provided in the study report on the proportion of paediatric participants in the sample (mean ages: omalizumab 36.0 ± 14.7 and placebo 38.1 ± 15.1).

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*The Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards

(Continued)

European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy for the Cochrane Airways Group Register of Trials

Strategy used for 2013 update

#1 AST:MISC1

#2 MeSH DESCRIPTOR Asthma Explode All

#3 asthma*:ti,ab

#4 #1 or #2 or #3

#5 anti-IgE

#6 "anti-immunoglobulin E"

#7 omalizumab

#8 rhuMAb-E25

#9 Xolair

#10 "monoclonal antibody"

#11 #5 or #6 or #7 or #8 or #9 or #10

#12 #4 and #11

[In search line #1, MISC1 denotes the field where the reference has been coded for condition, in this case, asthma]

Strategy used for previous versions

anti-IgE OR "anti-immunoglobulin E" OR "anti-IgE antibody" OR "anti-immunoglobulin E antibody" OR Omalizumab OR rhuMAb-E25 or Xolair

[Limited to asthma records in the register]

Appendix 3. Archived results from trials of intravenous and inhaled omalizumab

Primary outcomes

1. Exacerbations

Intravenous omalizumab

Odds ratio of having one or more exacerbations

Fewer participants had exacerbations compared with placebo treatment in Milgrom 1999 (omalizumab: 32/106 vs placebo: 47/105; P = 0.01) during the steroid stable phase.

During the steroid reduction phase, asthma exacerbations were also reduced following treatment with intravenous omalizumab, with 30.2% of participants in the actively treated group having at least one exacerbation versus 44.8% of controls (P = 0.03) (Milgrom 1999).

2. Steroid reduction/withdrawal

Intravenous omalizumab

Following IV omalizumab, no significant difference was noted between the numbers of participants in treated (18.6%, 18/97) and control (11.8%, 11/93) groups who achieved complete withdrawal of daily ICS (Milgrom 1999).

Intravenous high-dose omalizumab also resulted in more treated participants (50/97, 51.6%) achieving a greater than 50% reduction than control participants (35/93, 37.6%) (Milgrom 1999; P = 0.05).

Secondary outcomes

1. Symptom scores

Intravenous omalizumab

Asthma symptom scores were significantly lower in the active group compared with the placebo group during the steroid stable phase. Mean asthma scores at 12 weeks were 2.8 (SD 1.01) in the high-dose treatment group compared with 3.1 (SD 1.02) in the control group (P = 0.008) (Milgrom 1999).

A small (but statistically significant) reduction in mean asthma symptom scores was noted in participants treated with IV omalizumab at the end of 20 weeks, after the steroid reduction phase (2.7 (SD 1.01)) compared with placebo 2.9 (SD 1.0; P < 0.05) (Milgrom 1999).

Intravenous omalizumab versus placebo (in participants not receiving ICS)

Pooled analysis of symptom scores in mild asthmatic participants who received intravenous omalizumab did not show a treatment effect in favour of omalizumab (SMD -0.33, 95% CI -0.96 to 0.31).

2. Health-related quality of life

Intravenous omalizumab

In participants treated with IV omalizumab, one study (Milgrom 1999) showed a mean increase of 1.4 in the high-dose group versus 0.8 in the placebo group on the Asthma Quality of Life Questionnaire for adults (scale 1 to 7) (omalizumab group vs own baseline P < 0.001; placebo vs own baseline P value not published). Paediatric results were similar (values not presented).

3. Rescue medication use

Intravenous omalizumab

A significant reduction in rescue medication use was noted following treatment with IV high-dose omalizumab. At the end of the stable steroid phase, participants reduced their albuterol use by 14% (1.2 puffs per day) from baseline in the actively treated group compared with 10% (0.8 puffs per day) in the placebo group (P = 0.02) (Milgrom 1999).

Statistically significant changes in rescue medication usage in favour of omalizumab achieved at 12 weeks apparently continued during the steroid reduction phase (P values not available; Milgrom 1999).

Intravenous omalizumab versus placebo (in patients not receiving ICS)

No significant difference in rescue medication was observed between treatment with intravenous omalizumab or placebo (Boulet 1997; Fahy 1997) (P = 0.67).

4. Lung function

Intravenous omalizumab

Change from baseline in am PEF

A significant increase in morning PEF of 30.7 L/min was reported in actively treated participants compared with 11.3 L/min in the control group (P = 0.007; Milgrom 1999).

End of treatment FEV_1

In participants who received intravenous IV omalizumab, no significant difference in FEV_1 was reported (Milgrom 1999).

Aerosolised omalizumab

No significant differences were found in FEV_1 or morning PEF between omalizumab-treated and placebo-treated participants (FEV_1: P = 0.12; PEF: P = 0.3).

Intravenous omalizumab (in participants not receiving ICS)

No statistically significant differences were detected in FEV_1 or PEF at the end of study protocols (no P values reported in published papers). A pooled analysis of FEV_1 was non-significant (SMD 0.51, 95% CI -0.13 to 1.15). Pooled analysis of PEF was also non-significant (SMD 0.35, 95% CI -0.29 to 1.00). This represents a difference of 32 mL (95% CI -26.53 to 91.5).

5. Adverse events

Aerosolised omalizumab

More complaints of headache were seen among aerosolised omalizumab-treated participants compared with placebo participants (nine of 12 participants receiving low-dose omalizumab, eight of 10 participants receiving high-dose omalizumab and three of 11 placebo-treated

participants). However, these differences did not achieve statistical significance. One participant developed IgG and IgA anti-omalizumab antibodies during the treatment phase of the trial. These antibodies were not detected at follow-up 11 weeks after completion of the study.

Intravenous omalizumab (in participants not receiving ICS)

Few adverse events were noted among participants with mild asthma who received intravenous omalizumab, and these events were not significantly different from side effects observed in placebo-treated participants.

In the intravenous study in moderate to severe participants, withdrawals were similar in the actively treated population (three of 106 (omalizumab) vs five of 105 (placebo); no reported P values, but obviously not significant) (Milgrom 1999).

WHAT'S NEW

Date	Event	Description
13 June 2013	New citation required and conclusions have changed	Title changed and inclusion criteria limited to omalizumab. 11 new trials of subcutaneous omalizumab included: Bardelas 2012; Busse 2011; Chanez 2010; Garcia 2012; Gevaert 2012; Hanania 2011; Lanier 2009; Massanari 2010; NCT00096954; NCT01007149; Ohta 2009. New risk of bias, summary of findings table added, new author team and complete re-write of text.
13 June 2013	New search has been performed	New literature search run

HISTORY

Protocol first published: Issue 2, 2002
Review first published: Issue 3, 2003

Date	Event	Description
10 February 2010	New search has been performed	Literature search re-run
30 June 2008	Amended	Converted to new review format.
21 February 2006	New citation required and conclusions have changed	This review includes data from six new trials. Two of these were conducted in large samples of inhaled steroid-dependent asthma patients (SOLAR; INNOVATE) and the remainder were conducted in mild, non-steroid dependent asthma patients (Djukanovic 2004; Bruno 2005; van Rensen 2005; Hanf 2005). One of these studies assessed the effects of treatment in particularly severe adult and adolescent asthma patients. The data from these studies have improved the precision of our summary effect estimates. Assessment of this drug in children remains a priority.
30 January 2004	New search has been performed	This review has been updated with additional data that were not available when the initial version of the review was published. These data were obtained from the Food and Drug Administration's medical officer's review of clinical trial data. One unpublished study has since been published as a full article (Holgate 2004). The outcomes enhanced by these new data were exacerbations (for steroid stable and tapering phases), and also mean reduc-

Date	Event	Description
		tion in inhaled steroid consumption for three studies (Busse 2001; Solèr 2001; Holgate 2004). One study published in abstract form has come to the attention of the reviews (SOLAR 2003). This placebo-controlled study recruited people with co-existent asthma and rhinitis.

CONTRIBUTIONS OF AUTHORS

Original version of review: SW developed the protocol with input from K Phelan (KP) and M Monteil (MM). Editorial support was given by EHW. Studies were selected and appraised by SW and MM. Data were extracted by MM, T Lasserson (TL) and SW, and then were entered by MM and TL. MM and TL developed the analysis with input from SW, KP and EHW. MM and SW developed the discussion, with guidance from KP and EHW.

TL and SW wrote the update of the review, with additional input from EHW, MM and KP.

In the 2013 update, SW and PN updated the Background section with input from EHW, and SJM updated the Methods section. Studies were selected and appraised by SW and PN, and data were extracted by SJM, SW, and RN, and then were entered by SJM. The risk of bias of the included studies was assessed by SJM, RN, SW and PN. SJM conducted the analysis with input from SW, PN and RN. The Results section was written by SJM with input from SW, PN and RN. The summary of findings tables were completed by SJM and RN. The Discussion and Conclusions sections were written by SW and PN with input from RN, SJM and EHW.

DECLARATIONS OF INTEREST

2013 update:

SW has received travel grants from AstraZeneca, GlaxoSmithKline, Schering-Plough, Aventis Pharma and 3M.

SM has received support with travel costs and conference attendance from Novartis.

EHW has received research support from GlaxoSmithKline, AstraZeneca, Novartis, Boehringer and Schering-Plough in the past but none in recent years.

PN has received research grants from GSK, AZ and Schering, and honoraria or travel grants from GSK, AZ, Merck, Novartis, Teva, BI and Cipla.He is listed on a patent for a sputum filtration device and has provided scientific advice for a university spin-off company, Cellometrics Inc.

RN: none known.

Original version of the review: Michele Monteil has received travel grants from GlaxoSmithKline and Merck Sharpe & Dohme.

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Internal sources

- NHS Research and Development, UK.

External sources

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- The Thriplow Charitable Trust, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Study assessment

We have adopted the risk of bias assessment tool as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Handbook). The previous method of assessing study quality was not applied to the studies in this updated review. Our original method for assessing study quality was as follows.

Two review authors independently assessed the methodological quality of eligible RCTs using the five-point scoring instrument proposed by Jadad 1996. This instrument evaluated the reported quality of randomisation, blinding and description of withdrawals and dropouts. Each study was scored according to the following criteria.

1. Was the study described as randomised? (1 = Yes, 0 = No).
2. Was the study described as double-blind? (1 = Yes, 0 = No).
3. Was there a description of withdrawals and dropouts? (1 = Yes, 0 = No).
4. Was the method of randomisation well described and appropriate? (1 = Yes, 0 = No).
5. Was the method of double-blinding well described and appropriate? (1 = Yes, 0 = No).
6. Deduct one point if methods used for randomisation or blinding were inappropriate.

We resolved any disagreements by consensus.

Two review authors also independently ranked quality of allocation concealment using the Cochrane approach.

1. Grade A: adequate concealment.
2. Grade B: uncertain concealment.
3. Grade C: clearly inadequate concealment.

2. NNT calculations

We have used a Summary of findings table to express the results of the meta-analysis in absolute terms and to provide a summary assessment of the overall quality of the evidence. The number needed to treat for an additional beneficial outcome (NNTB) results have been replaced by natural frequencies of events on control treatment and omalizumab, which is in keeping with the Summary of findings tables.

3. 2013 update

In the 2013 update, we have brought greater clarity to the decision that only double-blind trials should be included in the review. All previously included studies were double-blind, but the inclusion criteria had not explicitly addressed this point in earlier versions of the review. The order of the primary outcomes changed from protocol.

4. Generic inverse variance

This method has been used to carry out meta-analyses of adjusted outcomes (such as exacerbation rates) in the 2013 update.

The Jadad scoring system used in previous versions of the review has been replaced by a Cochrane risk of bias assessment for each included trial.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [therapeutic use]; Anti-Asthmatic Agents [administration & dosage] [*therapeutic use]; Antibodies, Anti-Idiotypic [administration & dosage] [*therapeutic use]; Antibodies, Monoclonal, Humanized [administration & dosage] [*therapeutic use]; Asthma [*drug therapy] [immunology]; Chronic Disease; Immunoglobulin E [blood] [*immunology]; Injections, Subcutaneous; Omalizumab; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans