

Anti-IgE for chronic asthma in adults and children (Review)

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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	2
CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW	2
SEARCH METHODS FOR IDENTIFICATION OF STUDIES	3
METHODS OF THE REVIEW	3
DESCRIPTION OF STUDIES	4
METHODOLOGICAL QUALITY	5
RESULTS	5
DISCUSSION	10
AUTHORS' CONCLUSIONS	12
POTENTIAL CONFLICT OF INTEREST	12
ACKNOWLEDGEMENTS	12
SOURCES OF SUPPORT	12
REFERENCES	13
TABLES	17
Characteristics of included studies	17
Characteristics of excluded studies	24
ADDITIONAL TABLES	24
Table 01. Asthma severity	24
Table 02. Baseline IgE levels	27
Table 03. Responder analyses	28
Table 04. Reported safety profile - Soler 2001 (extension phase)	30
Table 05. Reported safety profile - Milgrom 2001	30
Table 06. Reported safety profile - Milgrom 1999	31
Table 07. Reported safety profile - Busse 2001	31
Table 08. Safety profile - Holgate 2004	32
Table 09. Summary of clinical outcomes - steroid stable	32
Table 10. Summary of clinical outcome - steroid reduction phase or end of study	33
Table 11. Exacerbation rate data (continuous and dichotomous data)	34
Table 12. Corticosteroid use during steroid-tapering phase	34
Table 13. Search history	35
Table 14. What's New History	36
Table 15. Analysis of pooled estimates for exacerbations	36
Table 16. Paediatric populations	36
ANALYSES	37
Comparison 01. Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)	37
Comparison 02. High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid)	37
Comparison 03. Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction)	38
Comparison 04. High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction)	38
Comparison 05. Subcutaneous Omalizumab + steroid versus placebo + steroid (trial extension)	39
Comparison 06. Low dose aerosolized Omalizumab versus placebo	39
Comparison 07. High dose aerosolized Omalizumab versus placebo	39
Comparison 08. Intravenous Omalizumab versus placebo	39
Comparison 09. Subcutaneous Omalizumab versus placebo (without inhaled corticosteroids)	40
Comparison 10. Subcutaneous Omalizumab versus placebo (safety)	40
Comparison 11. Subcutaneous Omalizumab + ICS& OCS versus placebo + ICS & OCS steroid (steroid reduction)	40
INDEX TERMS	40
COVER SHEET	40
GRAPHS AND OTHER TABLES	42

Figure 01. Graphic to show that in order to prevent one person experiencing an exacerbation of their asthma, 11 people would need to be treated with Anti-IgE therapy over a 12-16 week period.	42
Figure 02. Graphic to show that in order for one person to be able to withdraw steroid therapy, 6 people would need to be treated with Omalizumab	43
Figure 03. Graphic to demonstrate that in order for one person to be able to reduce therapy by at least 50%, 5 people would need to be treated with Omalizumab. This assumes that around 56% of people would be able to reduce their inhaled steroid by 50% on placebo.	44
Figure 04. Graphic to demonstrate that in order to prevent one exacerbation from a sample of patients embarked on a steroid tapering protocol, 8 would need to be treated with Omalizumab	45
Figure 05. Graph to show that for every 57 participants treated with Omalizumab, one will not have an exacerbation leading to hospital admission.	46
Figure 06. Graphic to demonstrate that for every five people treated with Omalizumab, one person more will rate their asthma control as good or excellent.	47
Figure 07. Graphic to demonstrate that in order for one person to develop an injection site reaction, approximately 21 would need to be treated with Omalizumab for between 28-32 weeks.	48
Analysis 01.01. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 01 Number of patients with at least one exacerbation (ICS & OCS users)	49
Analysis 01.02. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 02 Exacerbations	50
Analysis 01.03. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 03 Mean exacerbations per participant	50
Analysis 01.04. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 04 Asthma exacerbations per patient	51
Analysis 01.05. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 05 Rescue medication (puffs per day)	52
Analysis 01.06. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 06 Rescue medication usage (imputed values)	53
Analysis 01.07. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 07 FEV1 (mL)	54
Analysis 01.08. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 08 Change in FEV1 (mL)	55
Analysis 01.09. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 09 Change in FEV1 predicted	55
Analysis 01.10. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 10 Peak expiratory flow rate (am)	56
Analysis 01.11. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 11 Change in am PEF	57
Analysis 01.12. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 12 Symptom scores	57
Analysis 01.13. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 13 Mean change in Wasserfallen asthma score	58
Analysis 01.14. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 14 Mean change in AQLQ scores	58
Analysis 01.15. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 15 Quality of life - change from baseline in AQLQ scores	59
Analysis 01.16. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 16 Global evaluation rated good to excellent	60
Analysis 02.01. Comparison 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 01 Rescue medication usage	61
Analysis 02.02. Comparison 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 02 FEV1	61
Analysis 02.03. Comparison 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 03 Morning PEF	62

Analysis 02.04. Comparison 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 04 Symptom scores	62
Analysis 02.05. Comparison 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 05 Quality of life	63
Analysis 02.06. Comparison 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 06 Number of participants with >50% reduction in symptom score	63
Analysis 03.01. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 01 Number of patients achieving complete inhaled steroid withdrawal	64
Analysis 03.02. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 02 >50% reduction in inhaled steroid usage	65
Analysis 03.03. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 03 Mean steroid dose at end of reduction phase	66
Analysis 03.04. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 04 Mean change in steroid consumption (BDP equivalent)	66
Analysis 03.05. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 05 Rescue medication (puffs per day)	67
Analysis 03.06. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 06 Number of participants with exacerbation	68
Analysis 03.07. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 07 Asthma exacerbations per participant	69
Analysis 03.08. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 08 Exacerbations requiring hospitalisation	70
Analysis 03.09. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 09 Quality of Life - change from baseline	71
Analysis 03.10. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 10 Numbers of participants achieving clinically relevant improvement in Quality of Life (>0.5)	71
Analysis 03.11. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 11 Global evaluation rated good to excellent	72
Analysis 03.13. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 13 Asthma exacerbations per participant	73
Analysis 04.01. Comparison 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 01 Number of patients achieving complete inhaled steroid withdrawal	73
Analysis 04.02. Comparison 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 02 >50% reduction in inhaled steroid usage	74
Analysis 04.03. Comparison 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 03 Symptom score	74
Analysis 04.04. Comparison 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 04 Number of patients with >50% reduction in symptom scores	75
Analysis 04.05. Comparison 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 05 Number of participants with exacerbations	75
Analysis 05.01. Comparison 05 Subcutaneous Omalizumab + steroid versus placebo + steroid (trial extension), Outcome 01 Number of patients achieving complete inhaled steroid withdrawal	76
Analysis 05.02. Comparison 05 Subcutaneous Omalizumab + steroid versus placebo + steroid (trial extension), Outcome 02 Participants with one or more exacerbation	76
Analysis 05.03. Comparison 05 Subcutaneous Omalizumab + steroid versus placebo + steroid (trial extension), Outcome 03 Hospitalisations	77
Analysis 05.04. Comparison 05 Subcutaneous Omalizumab + steroid versus placebo + steroid (trial extension), Outcome 04 Number of participants with any adverse event	78
Analysis 06.01. Comparison 06 Low dose aerosolized Omalizumab versus placebo, Outcome 01 FEV1 (litres)	78
Analysis 06.02. Comparison 06 Low dose aerosolized Omalizumab versus placebo, Outcome 02 Area under curve for fall in FEV1 (% x minutes) - early response (0-1 hours)	79
Analysis 06.03. Comparison 06 Low dose aerosolized Omalizumab versus placebo, Outcome 03 Area under curve for fall in FEV1 (% x minutes) - late response (3-7 hours)	79

Analysis 06.04. Comparison 06 Low dose aerosolized Omalizumab versus placebo, Outcome 04 Peak Expiratory Flow (am) (L/min)	80
Analysis 07.01. Comparison 07 High dose aerosolized Omalizumab versus placebo, Outcome 01 FEV1 (litres)	80
Analysis 07.02. Comparison 07 High dose aerosolized Omalizumab versus placebo, Outcome 02 Area under the curve for % fall in FEV1 (early response - 0-1 hours)	81
Analysis 07.03. Comparison 07 High dose aerosolized Omalizumab versus placebo, Outcome 03 Area under the curve for % fall in FEV1 (late response - 3-7 hours)	81
Analysis 07.04. Comparison 07 High dose aerosolized Omalizumab versus placebo, Outcome 04 Peak Expiratory Flow (am) (L/min)	82
Analysis 08.01. Comparison 08 Intravenous Omalizumab versus placebo, Outcome 01 Rescue medication use (one week after end of treatment)	82
Analysis 08.02. Comparison 08 Intravenous Omalizumab versus placebo, Outcome 02 FEV1 (litres)	83
Analysis 08.03. Comparison 08 Intravenous Omalizumab versus placebo, Outcome 03 Fall in FEV1 after allergen challenge (%) (0-1 hours)	83
Analysis 08.04. Comparison 08 Intravenous Omalizumab versus placebo, Outcome 04 Fall in FEV1 after allergen challenge (%) (2-7 hours)	84
Analysis 08.05. Comparison 08 Intravenous Omalizumab versus placebo, Outcome 05 Peak expiratory flow (am)	84
Analysis 08.06. Comparison 08 Intravenous Omalizumab versus placebo, Outcome 06 Symptom scores	85
Analysis 09.01. Comparison 09 Subcutaneous Omalizumab versus placebo (without inhaled corticosteroids), Outcome 01 FEV1 (Litres)	85
Analysis 09.02. Comparison 09 Subcutaneous Omalizumab versus placebo (without inhaled corticosteroids), Outcome 02 FEV1 (% predicted)	86
Analysis 09.03. Comparison 09 Subcutaneous Omalizumab versus placebo (without inhaled corticosteroids), Outcome 03 Change in PC 20	86
Analysis 10.01. Comparison 10 Subcutaneous Omalizumab versus placebo (safety), Outcome 01 Side effects	87
Analysis 11.01. Comparison 11 Subcutaneous Omalizumab + ICS& OCS versus placebo + ICS & OCS steroid (steroid reduction), Outcome 01 Number of patients achieving complete oral steroid withdrawal	88
Analysis 11.02. Comparison 11 Subcutaneous Omalizumab + ICS& OCS versus placebo + ICS & OCS steroid (steroid reduction), Outcome 02 Number of participants with exacerbation	89

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ABSTRACT

Background

Omalizumab is a recombinant humanised monoclonal antibody directed against immunoglobulin E (anti-IgE) to inhibit the immune system's response to allergen exposure. Omalizumab is directed against the binding site of IgE for its high affinity Fc receptor. It prevents free serum IgE from attaching to mast cells and other effector cells and prevents IgE mediated inflammatory changes.

Objectives

To determine the efficacy of anti-IgE compared with placebo in patients with allergic asthma

Search strategy

We searched the Cochrane Airways Group Asthma trials register for potentially relevant studies (February 2006).

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 reviewers independently assessed study quality and extracted and entered data. Three modes of administration were identified from the published literature (inhaled, intravenous and subcutaneous injection). Subgroup analysis was performed by asthma severity. Data were extracted from published and unpublished sources.

Main results

Fourteen trials (15 group comparisons) were included in the review, contributing a total of 3143 mild to severe allergic asthmatic participants with high levels of IgE. Treatment with intravenous and subcutaneous Omalizumab significantly reduced free IgE compared with placebo. Omalizumab led to a significant reduction in inhaled steroid (ICS) consumption compared with placebo (-119 mcg/day (95% CI -154 to -83, three trials)). There were significant increases in the number of participants who were able to reduce ICS by over 50% (odds ratio (OR) 2.50, 95% confidence interval (CI) 2.02 to 3.10 (four trials)); or completely withdraw their daily ICS intake (OR 2.50 (95%CI 2.00 to 3.13; four trials)). Participants treated with Omalizumab were less likely to suffer an asthma exacerbation with treatment as an adjunct to ICS (OR 0.52, 95%CI 0.41 to 0.65, five trials), or as an ICS tapering agent (OR 0.47, 95% CI 0.37 to 0.60, four trials).

Authors' conclusions

Omalizumab was significantly more effective than placebo at increasing the numbers of patients who were able to reduce or withdraw their inhaled steroids, but the clinical value of the reduction in steroid consumption has been considered in the light of the high cost of Omalizumab. The impressive placebo effects observed in control groups bring into question the true effect of Omalizumab. Omalizumab was effective in reducing asthma exacerbations as an adjunctive therapy to inhaled steroids, and during steroid tapering phases of clinical trials. Omalizumab was generally well tolerated, although there were more injection site reactions with Omalizumab. Patient and physician assessments of the drug were positive. Further assessment in paediatric populations is necessary, as is direct double-dummy comparison with ICS.

PLAIN LANGUAGE SUMMARY

Allergic people produce Immunoglobulin E (IgE) when exposed to environmental allergens, and IgE binds to mast cells in the airways. Acute exposure to the allergen causes mast cells to release chemicals (such as histamine) causing itching, sneezing, blocked nose, wheezing, shortness of breath and cough. This review of trials found that anti-IgE, a treatment developed to remove IgE from the circulation, led to a reduction, and in some cases, withdrawal of regular inhaled steroid use and a reduction in asthma exacerbations. Compared with placebo, effects were relatively modest. Side effects were few and mild-moderate in the short term; longer term evaluation is needed. Patient and physician assessment of the effectiveness of therapy were positive.

BACKGROUND

Immunoglobulin E (IgE) plays a central role in the development of allergic diseases. In atopic (allergic) individuals exposure to 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, 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 pro-inflammatory 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 hyper responsiveness (Burrows 1989; Sears 1991), presumably through ongoing chronic allergic activation of this complex system. It is these people who have featured in the studies conducted to date.

Omalizumab (also referred to as rhuMAB-E25, rhu-Mab or Xolair in the literature) is a recombinant humanised 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. The complexes of Omalizumab and IgE formed as a result of treatment are small and not thought to be able to trigger complement activation or give rise to immune complex mediated pathology. Omalizumab has been shown to reduce serum concentrations of free IgE after one injection, resulting in significant reductions in early and late asthmatic responses following allergen inhalation and improved asthma symptom control (Milgrom 1997).

Asthma currently affects an estimated 300 million people worldwide and is associated with significant mortality and morbidity. The mainstay of modern treatment has been the use of inhaled steroids and bronchodilator drugs. While this approach has been useful in the management of mild and moderate forms of the disease, patients with severe asthma often require oral steroids and other immunosuppressive regimens with their attendant side effects. Recent reports have confirmed the safety of Omalizumab and have shown reductions in asthma symptoms and ICS requirement in asthmatic adults and children (Milgrom 1999; Milgrom 2001). The use of anti-IgE antibodies may represent a potentially

promising approach to the treatment of allergic diseases such as asthma although its role in overall asthma management is not yet clear.

Only the results of one drug (Omalizumab) have been reported in detail. This drug currently has a restricted license (USA, Australia, Brazil, Canada, Dominican Republic, Guatemala, Israel, New Zealand, Venezuela and throughout the European Union), and is much more expensive than alternate asthma treatments.

OBJECTIVES

The objective of this review was to compare the clinical outcomes in studies that have compared anti-IgE monoclonal antibodies with placebo or other conventional therapy in the treatment of chronic asthma.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Only randomised controlled trials (RCT) were considered for inclusion.

Types of participants

Adults and children with chronic asthma from all referral sources. The definitions of chronic asthma varied, both doctor diagnosis and objective criteria were considered. Distinctions were made among studies that differed in their definition and where possible subgroup analyses were performed on the basis of severity if possible. We classified the studies according to the stepwise management plans recommended in the BTS guidelines (BTS 2005).

Types of intervention

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

Types of outcome measures

In principle all outcome measures were considered. Outcomes of primary significance were:

Primary outcomes:

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

Secondary outcomes:

- (1) Asthma symptoms
- (2) Health-related quality of life
- (3) Rescue medication use
- (4) Measures of lung function: fixed expiratory flow in one second (FEV1), peak expiratory flow (PEF)
- (5) Adverse events

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Airways Group methods used in reviews.

We searched the Cochrane Airways Group Asthma and Wheeze trials register in asthma using the following terms:

anti-IgE OR anti-immunoglobulin E OR anti-IgE antibody OR anti-immunoglobulin E antibody OR Omalizumab OR rhuMab-E25

Electronic searches were up to date as of February 2006.

We did not place any restrictions on the language of publication.

To identify relevant randomised controlled trials (RCTs):

we reviewed and classified each abstract as either a randomised controlled trial (RCT), clearly not an RCT or unclear;
we obtained and reviewed the full text publication of references classified as RCT or potentially relevant RCT;
we checked the reference lists of all identified RCTs to identify potentially relevant studies;
we contacted all pharmaceutical companies producing anti-IgE formulations and made enquiries about published and unpublished studies known to and/or supported by these companies;
we examined the bibliographies of review articles and other selected articles;
we sought data from online resources (www.fda.gov; <http://www.clinicalstudyresults.org>; www.clinicalstudyresults.org).

We also made personal contact with colleagues, collaborators and other trialists working in the field of asthma to identify other published and unpublished relevant studies.

We searched abstracts of studies presented at the leading respiratory society meetings in the last three years for relevant studies.

METHODS OF THE REVIEW

Two reviewers independently assessed the methodological quality of the eligible RCTs with 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:

- (a) Was the study described as randomised? (1 = Yes 0 = No)
- (b) Was the study described as being double-blind? (1 = Yes 0 = No)
- (c) Was there a description of withdrawals and dropouts? (1 = Yes 0 = No)
- (d) Was the method of randomisation well described and appropriate? (1 = Yes 0 = No)
- (e) Was the method of double-blinding well described and appropriate? (1 = Yes 0 = No)
- (f) Deduct one point if methods for randomisation or blinding were inappropriate

We resolved any disagreements by consensus.

Two reviewers also independently ranked quality of allocation concealment by two reviewers using the Cochrane approach:

Grade A: adequate concealment

Grade B: uncertain

Grade C: clearly inadequate concealment

Data extraction & analysis

Two independent reviewers extracted data using a standard form developed prior to data extraction. We sought missing information from authors wherever possible. We used Cochrane Review Manager 4.2 to analyse data. For continuous variables, we calculated a fixed effect mean difference (MD) (for variables reported or transformed on to the same scale) or standardised mean difference (SMD) (where different scales were pooled) with 95% confidence interval (CI) for each study. We pooled continuous data from similar studies using fixed effects WMD/SMD and 95% CIs.

For dichotomous variables, we calculated a fixed effects odds ratio (OR) with 95% CI for individual studies. We pooled dichotomous data from similar studies using fixed effects OR 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 calculated the number needed to treat (benefit or harm); (NNT(b)/NNT(h)) with 95% CI (see: www.nntonline.net). Control group event rates were pooled to generate a baseline risk (%). NNTs are reported in the text and presented graphically.

We identified dichotomous and continuous outcome measures in the trial reports. If the primary outcomes were reported as dichotomous variables, we sought continuous data as either means

and standard deviations (SD), or medians and ranges, from trialists and analysed these as appropriate.

We explored reasons for statistical heterogeneity and, wherever possible, performed sensitivity analysis on the basis of methodological quality and random effects versus fixed effects modelling. Where I^2 exceeded 0%, we undertook random effects modelling to assess whether adjustment for within and between study variation impacted upon the summary estimate. A priori subgroup analyses were:

- (a) age (children or adults);
- (b) trial medication;
- (c) asthma severity;
- (d) asthma diagnostic entry criteria;
- (e) length of treatment.

We were unable to perform funnel plot tests to identify evidence of publication bias due to the insufficient number of studies.

DESCRIPTION OF STUDIES

For details of search results please see Table 13. Descriptions of each study are contained in 'Characteristics of included studies'.

Update search results January 2004-February 2006

Electronic searches yielded a total of 48 new references from the Airways Group register. Following the exclusion of duplicates, a total of eight studies were retrieved for further scrutiny. Of these, six met the inclusion criteria (Bruno 2005; Djukanovic 2004; Hanf 2005; Humbert 2005; van Rensen 2005; Vignola 2004). Details of studies which failed to meet the inclusion criteria are in 'Characteristics of excluded studies'.

Fourteen trials now meet the inclusion criteria of the review. One study recruited a subgroup of oral steroid dependent asthmatics (Holgate 2004a) which were published separately. Therefore we have included 15 group comparisons (3143 participants) in the review.

Study design & duration

All trials were randomised, double-blind and of parallel group design.

Seven studies examined the efficacy of anti-IgE monoclonal antibodies as an adjunct to treatment with inhaled and oral corticosteroids (Busse 2001; Holgate 2004; Holgate 2004a; Humbert 2005; Milgrom 1999; Milgrom 2001; Vignola 2004; Soler 2001). Beclomethasone dipropionate (BDP) was used as the background inhaled steroid in the majority of studies ($n = 4$) although two studies used high dose fluticasone propionate (FP) (Holgate 2004; Holgate 2004a), and another used budesonide (BUD) (Vignola 2004). In two studies no changes were made to background ICS dosage (Humbert 2005; Vignola 2004). Individual steroid doses are detailed in the table 'Characteristics of Included Studies'. Fol-

lowing a run-in phase to establish symptom control using the lowest steroid dose, Omalizumab was administered as an adjunctive therapy to inhaled or oral corticosteroids for 12 to 28 weeks (stable steroid phase). With the exception of Vignola 2004 and Humbert 2005, participants were then enrolled in a second phase of the study in which attempts were made to reduce the corticosteroid dose. Where data on ICS usage were reported, we transformed them to BDP equivalent values. We sought data on OCS usage as either mean dose or dichotomised data relating to the number of patients who had succeeded in reducing OCS use. Holgate 2004a reported data on OCS tapering only.

Boulet 1997; Bruno 2005; Djukanovic 2004; Fahy 1997; Fahy 1999; Hanf 2005; van Rensen 2005 assessed the effects of Omalizumab without background steroid therapy.

Route of administration

Three routes of drug administration were identified: inhaled (Fahy 1999), intravenous (Boulet 1997; Fahy 1997; Milgrom 1999) and subcutaneous injection (Bruno 2005; Busse 2001; Djukanovic 2004; Hanf 2005; Holgate 2004; Holgate 2004a; Humbert 2005; Milgrom 2001; van Rensen 2005; Vignola 2004; Soler 2001). In all studies anti-IgE was compared with placebo, although doses of Omalizumab differed. The study using intravenous Omalizumab compared high (5.8 mcg/kg/ng IgE/ml) and low (2.5 mcg/kg/ng IgE/ml) doses with placebo (Fahy 1999; Milgrom 1999). 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 2-4 weeks.

Asthma severity and type

Participants with a diagnosis of allergic asthma were recruited. Busse 2001; Holgate 2004; Holgate 2004a; Humbert 2005; Milgrom 1999; Soler 2001; Vignola 2004 assessed Omalizumab in adult and adolescent populations, whereas Milgrom 2001 recruited paediatric participants. Vignola 2004 recruited participants with co-existing asthma and rhinitis. Adults with mild asthma were recruited to Boulet 1997; Djukanovic 2004; Fahy 1997; Fahy 1999. In Bruno 2005; Hanf 2005; van Rensen 2005, the age of participants was unclear.

The severity of the participants varied within and between the studies. Subgroup analyses were performed according to asthma severity (severe, moderate/severe and mild asthma) as defined by the reviewers (Table 01). Data on asthma severity according to author and reviewer classification are also shown in Table 01. Primary indicators of asthma severity were FEV1 and daily inhaled corticosteroid dose required to maintain stable clinical state at baseline. Our classification of severity is based upon the stepwise guide to asthma management recommended in the BTS 2005. We examined baseline steroid consumption and FEV1 (percentage predicted) in order to determine whether participants were largely mild (step 1 of BTS 2005), moderate (step 2), moderate/severe (mixed population samples step 2/3) or severely asthmatic (step 4 and above). Following analysis of one patient population (Busse

2001), the reviewers reclassified severity as moderate to severe (step 2/3).

Studies deemed to include participants with mild asthma were Boulet 1997; Bruno 2005; Djukanovic 2004; Fahy 1997; Fahy 1999; Hanf 2005; van Rensen 2005, moderate/severe (2/3) disease were: Busse 2001; Milgrom 1999; Milgrom 2001; Solèr 2001 and Vignola 2004; severe (4) Holgate 2004 and Humbert 2005 recruited severe high dose steroid-dependent participants. Holgate 2004a recruited participants requiring high dose ICS and OCS to maintain asthma control and was classified severe (5). We have undertaken analyses that include and exclude Holgate 2004a study for exacerbations.

Entry criteria for all the studies included positive skin tests to common aero-allergens. Threshold ranges of IgE levels were a stated inclusion criterion in Boulet 1997; Busse 2001; Fahy 1997; Fahy 1999; Humbert 2005; Milgrom 2001; Solèr 2001 and Vignola 2004. Baseline IgE levels are presented in Table 02.

Outcome measures

Outcome measures reported were serum free IgE levels, ICS or OCS withdrawal or reduction asthma exacerbations, rescue medication use, lung function parameters, quality of life or global evaluation of treatment effectiveness assessment and safety. For each outcome, results are presented separately from stable steroid phase (Omalizumab given as an adjunctive therapy to inhaled corticosteroids) and steroid reduction phase (Omalizumab given during steroid reduction).

METHODOLOGICAL QUALITY

Methodological quality of included studies was fair to high when internal validity was considered. Jadad scores were as follows: three studies scored five (Holgate 2004; Holgate 2004a; Solèr 2001) (following correspondence with Acumed on methodological conduct), three studies scored four (Boulet 1997; Fahy 1997; Fahy 1999), six scored three (Busse 2001; Djukanovic 2004; Humbert 2005; Milgrom 1999; Milgrom 2001; Vignola 2004). Three unpublished conference abstracts scored two (Bruno 2005; Hanf 2005; van Rensen 2005). Allocation concealment was deemed adequate where information were reported. Withdrawals were well described.

RESULTS

A summary of outcomes for each study are given in Table 09; Table 10.

Free serum IgE

There were significant reductions in serum free IgE ranging from 89% to 99% in all trials with intravenous or subcutaneous administration of Omalizumab. These large reductions occurred regardless of different dosing regimens. Serum free IgE concentrations

dropped rapidly following initial administration of Omalizumab and low levels persisted during treatment (analysis of IgE levels was not available beyond the length of the clinical trials reported here).

(1) Omalizumab versus placebo as add on therapy to inhaled or oral corticosteroids (stable steroid phase): Busse 2001; Holgate 2004; Holgate 2004a; Humbert 2005; Milgrom 1999; Milgrom 2001; Solèr 2001; Vignola 2004.

Asthma exacerbations

Subcutaneous Omalizumab

Pooled Odds Ratios

There was a significant reduction in the odds of a patient having an asthma exacerbation in favour of subcutaneous Omalizumab (OR 0.55, 95% CI 0.45 to 0.69; six studies, 2151 participants). There was a high level of statistical heterogeneity across the studies (I^2 : 57.1%). Random effects modelling also gave a significant effect (OR 0.60 (95% CI 0.42 to 0.86)). The different definition of outcome in the Holgate 2004 protocol, and the greater severity of asthma in Holgate 2004a could both contribute to the amount of variation in this outcome. When both data sets from this study were removed from the analysis the I^2 was 36%. Assuming a baseline risk of 25%, the number needed to treat to prevent one exacerbation was 10 (95% CI 8 to 14; Figure 01). This is derived from evidence lasting between 12-28 weeks.

Rate ratio

Patients with severe asthma (Humbert 2005) treated with subcutaneous Omalizumab had a significantly lower risk of having an asthma exacerbation (adjusted Rate Ratio = 0.74 (95% CI 0.552 to 0.998, P = 0.042), adjusted for imbalances in exacerbation history at baseline.

Exacerbations per participant

When exacerbation rates were expressed as means, there were fewer asthma exacerbations per patient in favour of Omalizumab (-0.18 exacerbations (95% CI -0.1 to -0.25; seven studies, 2570 participants). Although there was a moderate level of heterogeneity (I^2 34.1%) random effects modelling did not change the point estimate (95% CI -0.08 to -0.27). The data reflect evidence from trial phases conducted over 16-28 weeks. Baseline exacerbation rates were not available.

Duration of exacerbations

Omalizumab treatment resulted in shorter duration of asthma exacerbations in one study of moderate to severe adults (Busse 2001), with a mean length of exacerbation of 7.8 days compared with 12.7 days in the control group (P < 0.001). In the paediatric study for this subgroup (Milgrom 2001) there was no significant difference in duration of asthma exacerbation between Omalizumab and control (10.2 days in the treatment group compared with 14 days in the placebo group (P = 0.97)). Although the length of these exacerbations appear to vary between the studies, Milgrom

2001 did not report a significant difference in exacerbation rates between treatment and control until the steroid reduction phase.

Intravenous Omalizumab

Odds Ratios

There were fewer participants with exacerbations compared with placebo treatment in Milgrom 1999 (Omalizumab: 32/106 versus placebo: 47/105, $P = 0.01$).

Rescue medication

Subcutaneous Omalizumab

Moderate to severe adolescent and adult participants treated with subcutaneous Omalizumab required significantly less rescue beta-2 agonist medication compared with placebo (-0.63 puffs/d (95% CI -0.90 to -0.36; six studies, 2223 participants)). (NB Because standard deviations were not available for two trials (Vignola 2004; Humbert 2005), we based an estimate of variance for them upon the most conservative SDs available for the other studies).

Intravenous Omalizumab

There was a significant reduction in rescue medication use 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 to 10% (0.8 puffs per day) in the placebo group ($P = 0.02$) (Milgrom 1999).

Lung function

Subcutaneous Omalizumab

End of treatment am PEF

There was no overall significant difference between patients treated with subcutaneous Omalizumab and placebo (MD 3.56 ml, 95% CI -5.05 to 12.18; four studies, 1651 participants).

End of treatment FEV1

There was no significant difference in FEV1 in moderate to severe adolescent and adult participants (MD 68.31 mls (95% CI, -23.45 to 160.07; Busse 2001; Soler 2001).

Change from baseline in FEV1

Small but significant improvements from baseline FEV1 were observed in two trials (Vignola 2004: 73 ml, $P = 0.032$; Humbert 2005: 2.8% predicted, $P = 0.043$).

Intravenous Omalizumab

Change from baseline in am PEF

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

End of treatment FEV1

In participants who received intravenous IV Omalizumab, there was also no significant difference in FEV1 (Milgrom 1999).

Symptom scores

Subcutaneous Omalizumab

End of treatment symptom scores

Moderate/severe and severe participants receiving Omalizumab had significantly lower asthma symptom scores during stable steroid phases (MD -0.46 (95% CI: -0.75 to -0.29, Busse 2001; Soler 2001; Holgate 2004). This represents a reduction of just over 10% from baseline values. There were no significant changes in asthma symptoms in the paediatric study (median nocturnal asthma scores were 0 in both groups throughout the study, Milgrom 2001).

Change from baseline in symptom scores

There were significant reductions in symptom scores from baseline in favour of Omalizumab in two trials (Vignola 2004 (-1.8, $P = 0.023$); Humbert 2005 ($P = 0.039$, no mean scores presented).

Intravenous Omalizumab

Asthma symptom scores were significantly lower in the active group compared with placebo. 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).

Quality of life/global evaluation of treatment effectiveness

Subcutaneous Omalizumab

Change from baseline in quality of life scores

There was a significantly greater improvement in overall AQLQ in favour of Omalizumab of 0.32 (95% CI 0.22 to 0.43; five studies, 2131 participants), which did not reach the validated clinically relevant effect size of 0.5 (Juniper 1994).

Assessment of asthma control

A significantly greater number of investigators rated participants' asthma control on Omalizumab as good or excellent compared with placebo (one trial (Vignola 2004): 59% versus 41%, $P < 0.001$).

Participants were more likely to rate asthma control as good or excellent when they were treated with Omalizumab compared with when they were treated with placebo (OR 2.58 (95% CI 1.94 to 3.43; two studies, $n=824$, $P < 0.00001$).

Intravenous Omalizumab

In patients 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 versus own baseline $P < 0.001$; placebo versus own baseline P value not published). Paediatric results were similar (values not presented).

(2) Omalizumab + steroid versus placebo + steroid (steroid tapering phase): Busse 2001; Holgate 2004; Holgate 2004a; Milgrom 1999; Milgrom 2001; Soler 2001)

Inhaled steroid withdrawal

Subcutaneous Omalizumab

Patients 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; Busse 2001; Holgate 2004; Milgrom 2001; Soler 2001). In order to achieve complete steroid withdrawal in one person, 6 people would need to be treated with Omalizumab (NNT = 6 (95% CI 5 to 8) Figure 02). This statistic is derived from steroid tapering phases of between 12 and 16 weeks, and assumes a pooled control group risk of 23%.

In a trial extension of 32 weeks 34% (85/254) moderate to severe participants in the Omalizumab treated group were able to maintain complete steroid withdrawal compared to 14% (31/229) in the control group (Soler 2001, $P < 0.001$).

Intravenous Omalizumab

Following IV Omalizumab there was no significant difference 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).

Inhaled steroid reduction

Subcutaneous Omalizumab

Change from baseline in ICS dose

There was a small but statistically significant reduction in daily steroid dose in Omalizumab-treated patients compared to placebo (WMD -118 mcg BDP equivalent per day (95%CI -154 to -84)) (Busse 2001; Soler 2001; Holgate 2004). Although a high degree of heterogeneity was observed (I^2 67.2%), Random Effects modelling did not alter the direction of the effect.

In paediatric participants (Milgrom 2001) median BDP 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

Patients 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) (Busse 2001; Holgate 2004; Milgrom 2001; Soler 2001). This translates to a NNT(b) of 5 (Figure 03).

Intravenous Omalizumab

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, $P = 0.05$).

Oral steroid withdrawal

Subcutaneous Omalizumab

There was no significant difference in the number of patients able to withdraw from oral steroid therapy between Omalizumab and placebo treatment (OR 1.18 (95% CI 0.53 to 2.63); Holgate 2004a).

Oral steroid reduction

Subcutaneous Omalizumab

There was no significant difference in the median reduction of daily oral steroid dose between Omalizumab and placebo-treated patients (Holgate 2004a: 69% versus 75% ($P = 0.675$)).

Rescue medication

Subcutaneous Omalizumab

Change from baseline in rescue medication use

Omalizumab treatment enabled participants to use significantly less rescue medication than placebo ((WMD -0.74, 95% CI -1.05 to -0.43; Busse 2001; Holgate 2004; Holgate 2004a; Soler 2001). Baseline levels were approximately 4.5 puffs per day for these studies.

Intravenous Omalizumab

In the intravenous study, 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).

Asthma exacerbations

Subcutaneous Omalizumab

Pooled Odds Ratios

During the steroid tapering phase, patients 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, 0.62; five trials, 1726 participants).

Assuming an overall control group event rate of 32%, 8 participants needed treatment with Omalizumab in order to prevent one exacerbation (NNT(b) = 8, 95% CI 7 to 11, see Figure 04). This statistic is derived from evidence from steroid tapering protocols of between 12 and 16 weeks.

Hospitalisations

There was a significant reduction in the odds of hospitalisation in participants treated with Omalizumab compared with treatment with placebo (OR 0.11 (95% CI 0.03 to 0.48), Busse 2001; Milgrom 2001; Soler 2001). This translates to a NNT(b) of 57 (see Figure 05).

Exacerbations per participant

When exacerbations were recorded as continuous data, participants treated with Omalizumab experienced fewer exacerbations compared with those treated with placebo (MD -0.27 (95% CI -0.37 to -0.16, Busse 2001; Holgate 2004; Milgrom 2001; Soler 2001; Holgate 2004a). Although there was no significant difference between severe participants treated with Omalizumab and placebo, when pooled with data from moderate to severe patients the resultant summary statistic was significant in favour of Omalizumab. Random effects modelling did not alter the point estimate or confidence intervals.

Intravenous Omalizumab

Asthma exacerbations were also reduced following treatment with intravenous Omalizumab or placebo, with 30.2% participants in the actively treated group having at least one exacerbation during the steroid reduction phase versus 44.8% controls ($P = 0.03$) (Milgrom 1999).

Symptom scores

Subcutaneous Omalizumab

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 compared with placebo (-1.93 versus -1.44 respectively, $P < 0.001$), whilst 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 in daytime symptom scores was detected between the groups 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). The reduction in daytime symptom scores which occurred after week 22 persisted until the end of the study.

Intravenous Omalizumab

There was a small (but statistically significant) reduction in mean asthma symptom scores in participants treated with IV Omalizumab at the end of 20 weeks (2.7 (SD 1.01) compared with placebo 2.9 (SD 1.0) ($P < 0.05$) (Milgrom 1999).

Quality of life

Subcutaneous Omalizumab

Change from baseline in quality of life scores

Unpublished data were used for Holgate 2004: 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 there was a significant difference in the numbers of patients who achieved a 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 patients in the Omalizumab group (16%) than in the placebo group (5.9%) also reported a 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 compared with placebo (OR of 2.72 (95% CI 2.04 to 3.62). This translates to a NNT(b) of 5 (Figure 06).

Safety

We pooled safety data from all the available studies regardless of whether they had conducted a steroid tapering phase. We considered that data pertaining to safety could be pooled from different study protocols as the dose of Omalizumab remained stable

throughout the trials, and they were all between 28 and 32 weeks in duration.

There was no difference in headache, urticaria, number of participants with any adverse events, and withdrawals due to adverse events. Omalizumab led to significantly greater injection site reactions compared with placebo (OR: 2 (95% CI 1.37 to 2.92), CER: 5.5%). This corresponds to a NNT(h) of 21 (Figure 07).

Withdrawals

Withdrawals were infrequent in studies using subcutaneous Omalizumab. In adult participants Busse 2001 reported two withdrawals from the treatment group due to adverse events. Neither was considered drug-related. Soler 2001 reported five withdrawals from the study - all were from the placebo group. In the paediatric study (Milgrom 2001), 5/225 (2.2%) treated children withdrew from the trial; four of these because of pain or fear of injection and one child was withdrawn because of mild to moderate urticaria on two occasions. In the placebo group 2/109 (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 2004), both from the placebo group.

In the intravenous study in moderate-severe participants, withdrawals were similar in the actively treated population (3/106 (Omalizumab) versus 5/105 (placebo); no reported P values, but obviously not significant) Milgrom 1999.

(3) Aerosolised Omalizumab versus placebo (in patients not receiving ICS step 1) (Fahy 1999)

Serum free IgE

Aerosolised administration of Omalizumab did not cause a decrease in serum free IgE levels and there was no significant difference noted in free IgE concentrations in treated participants or controls.

Exacerbations

No data were reported on exacerbation rates.

Rescue medication usage

No data were reported on rescue medication usage.

Lung function

There were no significant differences found in FEV1 or morning PEF between Omalizumab treated and placebo treated participants (FEV1: $P = 0.12$; PEF: $P = 0.3$).

Bronchial allergen challenge

There was no significant difference in area under the curve values at zero to one hour after allergen challenge between low dose Omalizumab treated patients (-842 (percentage fall in FEV1*mins) $\pm$ 527 (mean $\pm$ SD)), high dose Omalizumab (-880 (percentage fall in FEV1*mins) $\pm$ 653) and placebo (-874 (percentage fall in FEV1*mins) $\pm$ 407) (no P values reported). Similarly, there were no significant differences in late airway responses in any of the treatment groups.

Safety

There were more complaints of headache among aerosolised Omalizumab treated participants compared with placebo subjects (9/12 subjects receiving low dose Omalizumab, 8/10 subjects on high dose Omalizumab and 3/11 placebo treated participants). However, these differences did not achieve statistical significance. One subject 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 the completion of the study.

4) Intravenous Omalizumab versus placebo (in patients not receiving ICS) (Boulet 1997; Fahy 1997)

Serum free IgE

Intravenous administration of Omalizumab resulted in decreases in serum free IgE from baseline concentrations compared with placebo treated participants. Fahy 1997 presented these data graphically. Values for free IgE post-treatment imputed from the graphs were 12 ± 6.32 IU/L in the treatment group and 96 ± 12.9 IU/L in the control group ($P < 0.00001$). Boulet 1997 reported data on serum free IgE at baseline and at one week after the completion of the trial as geometric mean and standard errors. Free IgE decreased from 287.8 ± 124 ng/ml to 30 ± 10.7 ng/ml in the treatment group ($P < 0.001$). No change in serum free IgE was reported in the control group.

Asthma exacerbations

No data were reported for exacerbation rates.

Rescue medication

There was no significant difference in rescue medication between treatment with intravenous Omalizumab or placebo (Boulet 1997; Fahy 1997) ($P = 0.67$).

Lung function

No statistically significant differences were detected in FEV1 or PEF at the end of study protocols (no P values reported in published papers). A pooled analysis of FEV1 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 mls (95% CI -26.53 to 91.5).

Bronchial challenge

The fall in FEV1 following allergen challenge was significantly greater in mild populations treated with placebo compared with the Omalizumab group. During the early asthmatic response (EAR) there was a maximal fall of 34% (SD 4) in FEV1 in placebo treated subjects compared with an 18% (SD 8) fall in Omalizumab group ($P < 0.02$) (Fahy 1997). Similarly, placebo treated participants experienced an 18% (SD 17) fall in FEV1 during the allergen-induced late phase response (LAR) compared with 9% (SD 10) in actively treated participants ($P < 0.02$). There was a significant decrease in allergen-specific bronchial hyper responsiveness in the Omalizumab group which was not observed in the placebo group (Boulet 1997). Compared with baseline values measured at three different time points, actively treated participants consistently

required over 2 doubling doses more of allergen to produce a 15% fall in FEV1 (PC 15). In contrast, placebo treated participants showed no change in PC 15 against Omalizumab ($P < 0.002$).

Symptom scores

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

Safety

Few adverse events were noted in participants with mild asthma who received intravenous Omalizumab and these events were not significantly different from side effects observed in placebo treated participants. All side effects were mild. Among the 20 randomised participants in the trials conducted by Boulet 1997, one participant from the Omalizumab treated group was withdrawn because of a transient generalised urticarial rash that occurred after the first dose of Omalizumab. This rash responded to treatment with oral anti-histamine. One Omalizumab treated participant was also withdrawn from the trial conducted by Fahy 1997 at week four. This participant developed an asthma exacerbation which was preceded by symptoms of an upper respiratory tract infection. No participants treated with intravenous Omalizumab developed detectable antibodies to Omalizumab.

5) Subcutaneous Omalizumab versus placebo (in patients not receiving ICS) (Djukanovic 2004; Bruno 2005; Hanf 2005; van Rensen 2005)

Serum free IgE

All participants treated with Omalizumab in Djukanovic 2004 and Hanf 2005 had significantly lower free IgE levels compared with placebo (data not shown).

Exacerbations

No data were presented on exacerbations

Rescue medication usage

No data were presented on rescue medication usage.

Lung function

No significant differences between placebo and Omalizumab were reported in terms of FEV1 % predicted. Baseline imbalances between groups at baseline meant that data on FEV1 could not be reliably analysed. Bruno 2005 and van Rensen 2005 reported no significant difference in the mean change in methacholine response between Omalizumab and placebo. van Rensen 2005 reported a significant difference in favour of Omalizumab in LAR ($P < 0.05$).

Symptoms

No data were reported on symptoms

DISCUSSION

We have reviewed the use of Omalizumab in 15 randomised, placebo controlled clinical trials involving 3143 asthmatic patients of differing severity; the majority suffering from moderate/severe disease. The trials reviewed were of similar design with steroid reduction phases of 8 to 16 weeks. However, longer clinical trials will be required for full evaluation of long term efficacy and safety of Omalizumab.

Efficacy & Safety

Subcutaneous Omalizumab reduced asthma exacerbations when used as either an adjunctive or steroid-sparing therapy. Omalizumab was shown to be superior to placebo in allowing participants to withdraw their inhaled steroid treatment following monthly or fortnightly subcutaneous or intravenous administration of the drug. There were significant improvements in health related quality of life with Omalizumab compared with placebo. There was no consistent effect of Omalizumab on lung function. Side effects following treatment with Omalizumab were mild to moderate and did not differ significantly from placebo with the exception of injection site reactions.

This review had two primary outcomes; exacerbations and steroid use. Omalizumab reduced exacerbations when assessed as both an adjunctive treatment and as a steroid-sparing agent in moderate to severe asthma. However, in the subgroup of patients requiring oral steroids, Omalizumab had no significant effect on asthma exacerbations or reduction in daily oral steroid dose (Holgate 2004a). These data, therefore, do not support the extrapolation of the positive effects of Omalizumab in patients on step 2/3 of the guidelines to patients with oral steroid dependent asthma at step 5. Additional trials in this severe oral steroid dependent population are required to determine whether they would benefit from Omalizumab therapy.

The reduction in daily inhaled steroid dose following treatment with Omalizumab was modest but significant. The amount of statistical variation in this outcome could be attributable to the higher doses of BDP equivalent steroids in Holgate 2004 in relation to Busse 2001 and Soler 2001. It is noteworthy that participants treated with placebo were also able to reduce their intake of ICS by significant amounts, possibly because of better adherence to the prescribed doses. The presentation of dichotomous data in the published studies and unpublished continuous data in the FDA report has enabled us to look at the significance of both methods of measuring effects. Table 11 and Table 12 show the effects of Omalizumab treatment in terms of dichotomous and continuous outcome. Treatment with Omalizumab increased the likelihood of steroid reduction. However, the baseline steroid doses, the impressive effects of placebo treatment, and the mean difference in steroid consumption between treatment and placebo, bring in to 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 patients achieved less than 25% reduction in daily inhaled steroid use over the steroid reduction phase. In the study involving paediatric patients, nine Omalizumab treated participants out of 225 appeared to have needed the same amount or increased steroid therapy (reported as < 0% reduction in steroid use) (Milgrom 2001). It was not obvious whether or not these children had more severe asthma. These results confirm the need to better define which patients will benefit most from Omalizumab treatment. Unfortunately, not all asthmatics at the severe end of the spectrum who may benefit most from steroid reduction will respond to Omalizumab treatment, which may reflect the heterogeneity of asthma aetiology and pathology, especially in this group.

The end of trial data on quality of life suggested an important placebo effect. Further evidence of positive patient perception of Omalizumab treatment was ascertained from pooled analysis of the results for global effectiveness of treatment from two trials involving subcutaneous Omalizumab. The improvements in global treatment efficacy and overall quality of life noted in control subjects suggest that the basic trial design which included close medical monitoring, might have contributed to a large placebo or Hawthorne effect.

The effect of Omalizumab on lung function was inconsistent, with several studies reporting significant changes from baseline in FEV₁ and peak flow (Vignola 2004; Humbert 2005), but pooled estimates from data recorded as final values were not significantly different. This is in line with studies which report 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 improvements in lung function 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, one might not anticipate perceptible increases in lung function, particularly with optimised background inhaled therapy.

Use of a humanised anti-IgE antibody has raised theoretical concerns about immune-complex mediated pathology and abnormal immune responses to parasitic infection. The chimeric antibody could also induce antibodies to mouse epitopes. Administration of parenteral anti-IgE results in the formation of small immune complexes (< 10 KDa) which are cleared through the kidney (Arshad 2001). There were no reports of immune complex-mediated side effects in up to 16 weeks of administration. Aerosolised Omalizumab showed no significant effects on allergen induced early and late asthmatic responses. Many of the observed side effects were similar in adults and children though pruritus was reported only in children. Omalizumab associated adverse events did not differ significantly from placebo. Additionally, antibodies to Omalizumab did not develop in participants treated with subcutaneous or intravenous Omalizumab though these occurred tran-

siently in one participant who received inhaled anti-IgE therapy. There remains need for further information on the safety profile of the drug following long term use and in different populations such as those with endemic parasitism. Finally, it is possible that Omalizumab may have clinical efficacy in IgE-mediated diseases impacting other organ systems such as eosinophilic oesophagitis, dermatitis and anaphylaxis. Further work in these areas would be justified.

Trial methodology, generalisability and responder analyses

Entry criteria for the studies required evidence of sensitivity to aero allergens and raised levels of serum IgE which may not be representative of the asthmatic population in general. The high number of screening failures in several studies are noteworthy (Busse 2001: 525 entered/1117 screened; Solèr 2001: 546 entered/1356 screened; Milgrom 2001: 334 entered/501 screened; Holgate 2004 & Holgate 2004a: 365 entered/706 screened). 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 patients who demonstrated little or no response to Omalizumab. It is not clear from studies published so far why some patients respond and some do not, and it is therefore difficult to extrapolate some of the positive findings of this review to the general asthmatic population.

The cost of treatment with subcutaneous Omalizumab in the UK ranges from 3,330 to 16,650 GBP per annum. Given the time consuming and costly nature of the treatment and in order to target patients who are most likely to benefit, it is important that future studies focus on methods of identifying potential responders. Four responder analyses with varying definitions of 'at risk' or 'severe' asthmatics have been conducted (Babu 2001; Holgate 2001; Wenzel 2002; Bousquet 2004). Bousquet 2004 reported that patients are more likely to respond to treatment if characterised by one or more of: low FEV₁, frequent hospitalisation and high ICS dose. The number of patients who fall into such a category represented 36% of the overall number of patients recruited in to the two trials analysed (for additional information on these analyses see Table 03). Although such studies utilised results of prospective trials, they used *post-hoc* clinically plausible hypotheses to explain variations in response, but which also restrict generalisability of the responders even further. The 'predictors of response' generated by these studies may be used to determine who receives the treatment, rather than to set future research priorities in which entry criteria should reflect the disposition of this small group of responders. Our own classification of the studies included in this review failed to identify a consistently different response to therapy in Holgate 2004; Holgate 2004a and Humbert 2005 and those of the other studies. Given the imbalances between the smaller sample size of these studies and the bigger samples recruited in the other studies, our subgroups may not have been adequately powered to detect different responses. Moreover the current data available in relation to patients on oral steroids (Holgate 2004a) is not sufficient to justify the extrapolation of the findings to this group. It is of

note that the characteristics of the populations suggest that the recommendations are aimed at a subset of particularly severe participants, namely those with documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta-2 agonist (EMA 2005). Such characteristics most closely resemble those recruited to Humbert 2005.

Future clinical studies should have more realistic clinical designs which could be more readily generalised to a routine asthma clinic and the licensed indication for Omalizumab. Current trials included twice daily patient evaluation of peak flow and asthma symptoms and fortnightly medical assessment. Such close monitoring, with resulting better compliance with ICS may have contributed to the large placebo effect noted for all clinical outcomes.

Most participants were adults or adolescents with only one trial recruiting paediatric participants between five and 12 years of age. Most of the 'adult' studies included patients from 12 to 17 years, although this group of participants represented only a small percentage of the overall sample (between 6% and 8%, see Table 16). One paediatric trial included patients as young as five years. Confirmation of these effects in paediatric populations is also required, especially since 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. While results from the paediatric trial were generally similar to those reported for trials involving adult and adolescent participants, there were some differences, notably in exacerbation data during the stable steroid phase, suggesting the need for further evaluation of Omalizumab in exclusively paediatric study populations

The long-term clinical efficacy of Omalizumab has been assessed in extension phases from some of the core studies reviewed in this analysis. Complete data from the extension phase in Solèr 2001 have now been published. It is possible that longer term use of Omalizumab would enable patients to maintain reductions in steroid use and exacerbate less frequently than control (Solèr 2001). Studies with steroid reduction phases of substantially more than 16 weeks would be required to investigate the long-term efficacy of anti-IgE therapy. Discontinuation of Omalizumab treatment is associated with increases in circulating free-IgE to pre-baseline values within eight weeks (Casale 1997). This implies that treatment would need to be continued long term in order for efficacy to persist, which has significant cost implications.

Further investigations into the cost-effectiveness of Omalizumab will be required to identify its role in the management of IgE-mediated airways disease, and future studies should include comparisons with other available treatment options at step two of the asthma guidelines. Study design should try and overcome the confounding effect of improved adherence to ICS therapy which was evident in the studies reviewed, due to the intensity of study monitoring. This could be achieved by optimising steroid doses before entering treatment phases in order to determine the extent to

which participants are able to reduce steroid doses before control of their asthma deteriorates.

Stepwise asthma guidelines and Omalizumab

The steroid-sparing effects of Omalizumab 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. However, the effects observed in the studies reviewed were generally small. Such modest steroid-sparing effects of Omalizumab in moderately severe asthmatics have to be balanced against the cost of anti-IgE treatment. An important question is the place of Omalizumab in the treatment of asthma according to current guidelines. Global Initiatives for Asthma (GINA) guidelines define patients requiring regular inhaled corticosteroids as being of step 2 or more asthma severity (GINA 2002). Such patients usually require daily doses of inhaled steroids, often in combination with long acting beta agonists. In the majority of studies included in this review Omalizumab was assessed as an add-on therapy to inhaled corticosteroids. While Omalizumab proved useful as an adjunctive treatment, it is important to determine whether or not it is any more clinically beneficial or cost effective than other medications such as long-acting beta agonists, anti-leukotriene agents or PDEIs. Comparative studies performed against these drugs have yet to be performed.

AUTHORS' CONCLUSIONS

Implications for practice

Omalizumab is a novel approach to the management of chronic asthma. Data from Phase III trials have shown that the drug has an inhaled steroid-sparing effect. The clinical significance of the magnitude of reduction remains open to interpretation. Omalizumab was more effective than placebo at reducing exacerbations and improved health-related quality of life. In patients on oral steroids, there was no significant impact of Omalizumab on either exacerbations or oral steroid dose. If these patients are to receive this treatment, more evidence is required to justify such an approach. Since Omalizumab is an expensive treatment option, it will be important to determine which patients would benefit most from its use. In order to justify treatment with anti-IgE, the amount of steroid which 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 exposure to steroids. The cost benefit ratio for less severe patients requires assessment. The drug has only been evaluated in one paediatric trial and it would seem unlikely to be recommended for use in children based on the results of this one trial.

Implications for research

There is a need for further research into the role of Omalizumab as a treatment for chronic asthma. Specifically, there is need for:

- clinical trials which assess the long term use of Omalizumab
- more studies assessing the steroid-sparing effect in severe asthma
- more clinical assessment in the paediatric population
- clinical assessment of the effects of Omalizumab in patients with multiple allergic diseases e.g. allergic asthma and eczema
- trials that assess the cost-benefit ratio of anti-IgE therapy in severe and moderate/severe chronic asthma
- double dummy 'head to head' comparison of Omalizumab versus other potential steroid-sparing agents

POTENTIAL CONFLICT OF INTEREST

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* Indicates the major publication for the study

TABLES

Characteristics of included studies

Study	Boulet 1997
Methods	Randomised, double-blind, parallel group placebo controlled trial.
Participants	N = 20. Mean age 27 +/- 8.06. Eight females. Mild asthmatics were recruited. Inclusion criteria: stable, mild asthma, requiring only an inhaled beta-2 agonist on demand to control. At least 1 highly positive allergy skin prick test to at least one aeroallergen, early asthmatic response, FEV1 > 70%, methacoline provocative concentration causing 20% fall in FEV1. Exclusion criteria: history of anaphylaxis, recently unstable asthma (ER visit in previous 6 weeks), respiratory infection or aeroallergen exposure (other than HDM) within 4weeks, smoking within 12months, women of child bearing age and a lack of effective contraception. Baseline characteristics: FEV1: 92 +/- 11, IgE: placebo: 1808/- 3382, Omalizumab: 616 +/- 487.

Characteristics of included studies (Continued)

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	Jadad score: 4
Allocation concealment	A – Adequate

Study Bruno 2005

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
Allocation concealment	B – Unclear

Study Busse 2001

Methods	Randomised, double-blind, parallel group placebo controlled trial. Randomisation by computer-generated random number sequences.
Participants	N = 525. Age range 12-75, 215 males. Treatment group: N = 268, control group: N = 257. Participants with moderate to severe asthma were recruited. Inclusion criteria: Asthma diagnosed for more than one year, positive response to skin prick to one common allergen, total IgE serum > 30 IU/mL and < 700 IU/mL, FEV1 reversibility of 12%
Interventions	Subcutaneous Omalizumab (0.016 mg/kg IgE (IU/mL) per 4 weeks. Participants received 150 or 300 mg every 4 weeks or 225, 300 or 375 mg every 2 weeks, or placebo. Initial phase of the trial was a stable steroid phase of 16 week duration, followed by a 12 week steroid reduction phase.
Outcomes	No. participants with exacerbations, mean no. exacerbation per patient, mean no. days per exacerbation, adverse events, reduction in ICS, rescue medication usage, global evaluation, serum IgE levels.
Notes	Jadad score: 4 Trial 008
Allocation concealment	B – Unclear

Study Djukanovic 2004

Methods	Randomised, double-blind, parallel group placebo controlled trial. Methods of allocation/blinding not reported.
Participants	N = 46. Median age: 26 (range 19-48); Treatment group: 22; control group: 23. Gender: M/F: 22/24; FEV1 (% predicted): Omalizumab: 84; Placebo: 86 Inclusion criteria: stable, mild to moderate asthma (NHLBI definition); treatment with inhaled beta-agonists only; exacerbation-free 6 weeks prior to study entry; age 18-50 years; total serum IgE 30-700IU/ml; +ve skin prick test to >=1 allergen; airway hyperresponsiveness as defined by PC20 <= 8mg/ml; sputum eosinophilia 2% or more of nonsquamous cells
Interventions	Subcutaneous Omalizumab (0.016mg/kg per IgE (IU/ml) versus placebo

Characteristics of included studies (Continued)

	Study duration: 16 weeks
Outcomes	Methacholine challenge; FEV1; Serum free IgE levels
Notes	Jadad score: 3
Allocation concealment	B – Unclear

Study	Fahy 1997
Methods	Randomised, double-blind, parallel group placebo controlled trial.
Participants	N = 19. Mean age 31.5 +/- 4.87, Gender not reported. FEV1: 94.5% predicted +/- 16.72, PC20 mg/ml: 0.62 +/- 0.77, IgE IU/L: 141 +/- 119. Mild asthmatics were recruited. Inclusion criteria: FEV1 > 70%, bronchial hyperactivity to methacoline, positive skin prick test to HDM, cat pelt/rye grass, serum IgE level < 500 IU/ml. Exclusion criteria: Use of corticosteroids in previous 6 weeks, U/L RTI in previous 6 weeks, tobacco use/history of significant medical illness.
Interventions	Intravenous infusion of rhuMAb-E25 5mg/ml (0.5 mg/kg) for nine visits versus placebo. Treatment lasted nine weeks.
Outcomes	FEV1, PEF (am and pm), asthma symptoms, albuterol use, total serum IgE, induced sputum, PC20, percentage fall in FEV1 during early and late response, blood eosinophil percentage.
Notes	Jadad score: 4
Allocation concealment	A – Adequate

Study	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 randomised to receive E25 1 mg, 10 participants were randomised to receive E25 10 mg and 11 were randomised to receive placebo. Two participants dropped out of the placebo group. All had mild asthma. Inclusion criteria: FEV1 > 70% predicted, bronchial hyperactivity to methacoline, serum IgE < 300 IU/ml, positive skin prick test to aeroallergen. Exclusion criteria: Corticosteroids in previous 6 weeks, symptoms of upper/lower RTI in previous 6 weeks, history of tobacco use. Baseline characteristics: FEV1 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	FEV1, PEF(am), PC20, Serum IgE levels.
Notes	Jadad score: 4
Allocation concealment	A – Adequate

Study	Hanf 2005
Methods	Randomised, double-blind, parallel group placebo controlled trial.
Participants	N = 19. Mean age unclear. Treatment group: 9; control group: 10 Concomitant therapy unclear Inclusion criteria: participants with allergic asthma.
Interventions	They were treated with subcutaneous omalizumab 0.016 mg/kg/IgE [IU/ml] every 4 weeks or placebo Study duration: 12 weeks

Characteristics of included studies (Continued)

Outcomes	Serum analyses
Notes	Unpublished conference abstract Jadad score: 2
Allocation concealment	B – Unclear

Study	Holgate 2004
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 (2 withdrawals due to keratitis and dysphonia - communication from Acumed). Mean age (placebo): 40.5 (12-71), treatment group: 41.1 (12-75). Female/Male percentage: placebo; 57.5/42.5, treatment; 64.3/35.7. Severe asthmatics optimally controlled, requiring high dose fluticasone. FP dose: between 1000 and 2000 mcg/day. Inclusion criteria: male/females 12-75 years, severe asthma according to ATS guidelines, allergic response (> 1 positive skin prick test to one or more aeroallergens, mean total daily symptom score ≥ 4 over 7 days prior to randomisation, $\geq 12\%$ reversibility FEV1 within 30 minutes of salbutamol in 12 months prior to or at randomisation, stable medication 4 weeks prior to randomisation; IgE between 30 and 700 IU/mL. Exclusion criteria: females for whom current or future pregnancy could not be excluded, evidence/history of drug or alcohol abuse, history of non-compliance to 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 atopia (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/day): placebo; 1362.5 (+/-359.2), treatment; 1375 (+/-361.6). Participants taking LABA: placebo 52 (43%), treatment 62 (49%). Mean FEV1 (percentage predicted): placebo; 66 (+/-20.2), treatment, 62.9 (+/-17.5). Mean FEV1 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 bodyweight versus placebo. Four phase study. 6-10 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 participants achieving > 50% reduction in inhaled fluticasone (subgroup according to LABA consumption), exacerbations, PEFr, QoL.
Notes	Jadad score: 5 Trial 011
Allocation concealment	A – Adequate

Study	Holgate 2004a
Methods	Identical to Holgate 2004 (ICS)
Participants	N = 95 (Treatment: 50; control: 45). Mean age: not specified (likely to be similar to Holgate 2004). FEV1 (% 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 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)

Characteristics of included studies (Continued)

Trial 011	
Allocation concealment	A – Adequate
Study	Humbert 2005
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. FEV1: 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 ≥ 1 aeroallergen; Serum IgE: 30-700IU/ml; severe persistent asthma requiring >1000 BDP or equivalent and LABA treatment; FEV1 40-80%; FEV1 reversibility $\geq -12\%$ post SABA; ≥ 2 exacerbations requiring OCS in previous 12 months or 1 severe exacerbation resulting in hospitalisation Exclusion criteria: Smokers/smoking history of ≥ 10 pack years; treatment for exacerbation 4 weeks prior to randomisation; use of methotrexate/gold salts/troleandomycin/cyclosporin within 3 months of 1st visit; prior omalizumab treatment
Interventions	Subcutaneous omalizumab (0.016mg/kg per IU/ml) (plus usual care) versus placebo (plus usual care). Study duration: 28 weeks; run-in phase: 7 day screening period; 8 week run-in phase. Follow-up: 16 week (data not presented). During initial 4 weeks of run-in phase, medicines adjusted to achieve best control. No further adjustments permitted in last 4 weeks of run-in.
Outcomes	Exacerbations (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. There was a greater instance of exacerbations requiring oral steroids in Omalizumab group compared with placebo. Adjusted data were extracted and entered.
Allocation concealment	B – Unclear
Study	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. FEV1 71% predicted, ICS dose: 800 mcg, OCS dose 10 mg/day (35 participants), inhaled beta agonist dose: 7 puffs/day, IgE 273-374 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/day), positive skin prick tests, < 1785 IU/mL serum IgE Exclusion criteria: symptom score < 2.5, poorly reversible airway obstruction, treatment does 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 a stable steroid phase lasted for 12 weeks, followed by 8 weeks of steroid reduction. Follow up was 10 weeks.
Outcomes	FEV1, PEF, QoL, withdrawals, asthma exacerbations, daily total symptom score, beta agonist use, mean decrease in CS use, adverse effects.
Notes	Jadad score: 3
Allocation concealment	A – Adequate

Characteristics of included studies (Continued)

Study	Milgrom 2001
Methods	Randomised, double-blind, parallel group placebo controlled trial.
Participants	N = 334 (501 screened). Age range: 6-12 years. Treatment group: N = 225, control group: N = 109. 231 males. Mean PEFr (L/min): treatment group: 261 (101-408); control group: 264 (140-407). Mean FEV1 (percentage predicted) treatment group: 84 (49-129); control group: 85 (43-116). Number hospitalised for asthma in past year: treatment group: N = 18, control group: N = 9. Mean BDP dose: treatment group: 284 (168-672); control group: 267 (168-504). Mean albuterol use (per day): treatment group: 1.1, control group: 1.4. Inclusion criteria: i) diagnosis of allergic asthma of at least 1 year's duration, ii) positive skin prick test to one of: dermatophagoides farinae, dermatophagoides pteronyssinus, cockroach, dog or cat, iii) total serum IgE level between 30 and 1300 IU/mL, iv) body weight < 90kg, v) baseline FEV1 > 60% of predicted normal value, vi) at least 12% increase in FEV1 over baseline within 30 minutes of taking 1 or 2 puffs of albuterol (90 mcg/puff), vii) stable asthma, defined as no significant change in the regular asthma medication and no acute asthma exacerbation requiring corticosteroid rescue for at least 4 weeks before enrollment. Exclusion criteria: i) previous treatment with Omalizumab, ii) known hypersensitivity to any study drug, iii) history of acute infectious sinusitis or respiratory tract infection or active lung disease other than allergic asthma within 1 month or any other significant systemic disease within 3 months of visit 1, iv) clinically significant abnormalities in electrocardiogram, chest x-ray, or lab values, or elevated serum IgE levels for reasons other than atopy, v) children requiring doses of more than 750 mg per 4 weeks, based on total serum IgE and body weight consideration (0.016 mg/IgE in IU/mL x body weight in kg).
Interventions	Subcutaneous administration of Omalizumab (0.016 mg/kg/IgE(IU/mL), equivalent to 150 or 300mg every 4 weeks or 225, 300 or 375 mg every 2 weeks depending on participant's body weight. Run-in phase lasted 4-6 weeks with stabilisation on BDP, there then followed 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 - FEV1 + PEFr, global evaluation of treatment, pharmacoeconomics, pharmacodynamics, adverse events, withdrawals
Notes	Jadad score: 3
Allocation concealment	B – Unclear
Study	Solèr 2001
Methods	Randomised, double-blind, parallel group placebo controlled trial. Randomisation by random number sequences. Participants randomised at visit three. Independent personnel were responsible for allocation.
Participants	N = 546 (1356 screened). Age range 12-75, 268 male participants. Asthma diagnosed according to ATS guidelines. Inclusion criteria: asthma diagnosed for more 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 FEV1 > 40% and < 80% predicted, increasing by > 12% within 30 minutes of taking salbutamol, mean total daily symptom score > 3 (max 9) during 14 days prior to randomisation, treatment with ICS 200 mcg BDP per day for > 3 months prior to 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 > 1 month prior to 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 4-6 weeks with stabilisation of BDP. Stable and reduction phases of BDP followed randomisation. Trial extension phase lasted 32 weeks.

Characteristics of included studies (Continued)

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
Allocation concealment	A – Adequate

Study Vignola 2004

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: 12-75 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: FEV1 reversibility $\geq 12\%$; IgE level ≥ 30 to ≤ 1300 IU/mL; +ve skin-prick test to 1 or more indoor allergen; co-existing moderate - severe perennial rhinitis; ≥ 400 mcg/d ICS; ≥ 2 unscheduled medical visits for asthma in past year; score of $\geq 64/192$ in AQLQ. Exclusion criteria: Patients on 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 $\leq 130 \times 10^9/l$
Interventions	Subcutaneous Omalizumab 0.016 mg/kg/IgE [IU/ML] every 4 weeks versus placebo, in addition to ICS therapy and other stable pre-existing drug regimens (e.g/ LABAs, nasal steroids). 4 week run-in phase - participants switched to BUD equivalent Turbuhaler, dose was kept stable for at least 4 weeks prior to 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 (FEV1, FVC am PEF), ICS use
Notes	Jadad score: 3
Allocation concealment	B – Unclear

Study van Rensen 2005

Methods	Randomised, double-blind, parallel group placebo controlled trial.
Participants	N = 25. Mean age unclear. Treatment group: Inclusion criteria: mild persistent asthma
Interventions	Subcutaneous Omalizumab versus placebo (dosing levels unclear) Study duration: 12 weeks
Outcomes	PC20 methacholine, sputum and allergen challenge followed by a bronchoscopy at 24h; Changes in PC20, sputum eosinophils, max fall in FEV1 during late asthmatic response (LAR), post-allergen eosinophils (EG2) and mast cells (AA1)
Notes	Unpublished conference abstract. Jadad score: 2
Allocation concealment	B – Unclear

ATS: American Thoracic Society; BDP: Beclomethasone; CS: Corticosteroid; E25/rhu-MAb E25/Xolair/Omalizumab: anti-IgE; FEV1: forced expiratory volume; HDM: House dust mite; ICS: Inhaled CS; IgE: Immunoglobulin E; LABA: Long acting beta agonists; OCS: Oral corticosteroid; PC20: Bronchial challenge; PEF: peak flow; QoL: Quality of life; RTI: respiratory tract infection

Characteristics of excluded studies

Study	Reason for exclusion
Anonymous 2000	Review article reporting data from Milgrom 1999.
Anonymous 2000b	German language review article with summary of Milgrom 1999.
Ayres 2004	Inadequate control (best standard care without placebo)
Babu 2001	Review article.
Berger 2002	Review article.
Bisberg 1996	Single blind placebo controlled study. No randomisation reported - pharmacokinetic and pharmacodynamic profiles were analysed.
Buhl 2001	Meta-analysis of data drawn from included studies.
Demoly 1997	Review article.
Emmrich 2001	German language summary of the Milgrom 1999 study.
Fernandez 2005	Non-randomised safety study
Frew 1998	Review article.
Holgate 2001	Review article.
Hughes 2000	Review article.
Moulton 2000	Journal letter.
Ong 2005	Study not concerned with asthma; volunteers with atopy
Study Q2143G	Inadequate control (best standard care without placebo)

ADDITIONAL TABLES

Table 01. Asthma severity

Study ID	FEV1 (incl criteria)	B/line FEV1 mean	Symptom freq	OCS rx	ICS rx	Author opinion	BTS step
Boulet 1997	> 70% pred	91.89 +/- 11.03 (range: 83-106)	No indication reported	No	No	Mild	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 0-9, 9 indicating most severe). Limited physical activity in 482/525 participants.	No	Yes - mean BDP dose: 569 mcg/day (range: 336-1008)	Severe	2. Range in baseline FEV1 extends to above 80% predicted and range of BDP extends below stated criteria.

Table 01. Asthma severity *(Continued)*

Study ID	FEV1 (incl criteria)	B/line FEV1 mean	Symptom freq	OCS rx	ICS rx	Author opinion	BTS step
Djukanovic 2004	Not stated	85%	Not stated	No	No	Mild to moderate	1
Fahy 1997	>= 70% pred	94.5 +/- 10.72	No indication reported	No	No	Mild	1
Fahy 1999	>= 70% pred	82.74 +/- 16.09	No indication reported	OCS rx excluded	No	Mild	1
Holgate 2004 (ICS)	Not stated	64.41% (no range given)	Not stated.	No	Optimal control on 1000-2000 mcg/day FP +/- OCS, and long acting β agonist. Mean FP dose: 1368.9	Severe	4
Holgate (ICS & OCS)	Not stated	59%	Not stated	Yes	Optimal control on 1000-2000 mcg/day; mean prednisolone dose: 10.2mcg/d	Severe	5
Humbert 2005	Not stated	61%	Not stated	Yes - 22% receiving maintenance OCS	Yes - 2400mcg/d BDP equivalent	Severe	4
Milgrom 1999	50 to 90% pred	71 (range: 29-129)	Use of β agonist: 8.6 puffs per day (range: 2-37.7), mean symptom score: 4 (range: 1.5-6.5). Inclusion criteria was at least 2.5 on each of 7 days prior to randomisation.	Yes - 35 participants (median: 10mg per day, range: 2.5-40)	Yes - 282 participants, median dose: 800mcg per day (range: 200-4000)	Moderate persistent -severe persistent, defined as: mean FEV1 71% pred value, daily symptom score 4 (0-7 scale, 7 indicating most severe), daily β -agonist use.	2. Although range of FEV1 and symptom scores outside the inclusion criteria suggest that this was a heterogenous population which included some mild persistent participants
Milgrom 2001	FEV1 >= 60% pred.	84.33% (range: 43-	Mean albuterol use:	Not reported	Mean dose of BDP :	Moderate-severe	2

Table 01. Asthma severity (*Continued*)

Study ID	FEV1 (incl criteria)	B/line FEV1 mean	Symptom freq	OCS rx	ICS rx	Author opinion	BTS step
		129).	1.2 puffs per day, mean daytime symptom score: 0.54, mean nocturnal symptom score: 0.22, mean am score: 0.17 (daytime scale: 0-4, nocturnal scale: 0-4 and am scale: 0/1)		278.45mcg/day (range: 168-672).		
Soler 2001	Off bronchodilator, $\geq 40\%$ pred to $\leq 80\%$ pred	69.85 (range: 22-112).	β -agonist on as needed or regular basis. Mean symptom score > 3 , maximum 9.	No	770.54 (Range: 200-2000mcg/day). Inclusion criteria stated inclusion of participants on 500-1200mcg BDP /day.	Moderate-severe. Severe participants: 60 in treatment group and 59 in placebo group defined as baseline FEV1 $\leq 65\%$ pred and mean total symptom score < 4 during last 14 days of run-in period.	2. Majority of participants fall into this category, but judging by baseline FEV1 and BDP dose, there is a possibility of some milder participants being included.
Vignola 2004	Not stated	78.1 (SD 16.61)	QoL scores indicating at least mild symptoms. Mean baseline puffs/day: 2.8	No	870mcg BUD	Moderate-severe	2

Table 02. Baseline IgE levels

Study	IgE level (mean)
Boulet 1997	1152.4 IU/mL (data skewed: SD 2304.5)
Bruno 2005	Unclear
Busse 2001	179.26 IU/mL
Djukanovic 2004	Median: Omalizumab group: 155.5; Placebo group: 141
Fahy 1997	141.5 IU/mL
Fahy 1999	230.1 IU/mL
Hanf 2005	Unclear
Holgate 2004	266.26 IU/mL
Milgrom 1999	441.7 IU/mL
Milgrom 2001	339.85 IU/mL
Solèr 2001	214.38 IU/mL
van Rensen 2005	Unclear
Vignola 2004	Between 30 and 1300 IU/mL (no mean given)

Table 03. Responder analyses

Study	Type of asthma	Definition	Trials analysed	Severe patients (n)	Response
Babu 2001	Severe	Three definitions of severe asthma explored: 1) $\leq 60\%$ baseline FEV1 predicted. 2) $\leq 65\%$ baseline FEV1 predicted 3) $\leq 65\%$ baseline FEV1 + symptom score > 4 (out of 9).	Busse 2001; Milgrom 2001; Soler 2001	22% adult participants; 9% paediatric participants on Omalizumab and 6% on placebo	Median BDP reduction - severe participants reduced consumption by 60-67% versus 80-83% in moderate asthmatics. (These numbers vary depending upon the 'severe' criteria applied).
Bousquet 2004	Moderate to Severe	1. BDP dose $\geq 800\text{mcg/d}$; 2. FEV1 $\leq 65\%$ predicted; 3. History of emergency treatment	Busse 2001; Soler 2001	BDP dose $\geq 800\text{mcg/d}$: 432 FEV1 $\leq 65\%$ predicted: 379 History of emergency treatment: 733	Response to therapy defined as 1) reduction in symptoms of at least 1, with no increase in SABA; reduced use of rescue medication; 2) Reduced usage of SABA (≥ 1 puff per day and no increase in symptoms; 3) Improved lung function (increase in am PEF of $\geq 15\%$); 4) Improvement in QoL (increase in AQLQ of 1 in overall score); 5) Composite of at least of these responses with no asthma exacerbation Odds ratio of composite response according to baseline characteristic indicated that participants more likely to respond with 2 or more variables
Holgate 2001	Participants who were 'at risk' asthmatics	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	Busse 2001; Soler 2001	This sensitivity analysis	Participants who experienced

Table 03. Responder analyses *(Continued)*

Study	Type of asthma	Definition	Trials analysed	Severe patients (n)	Response
		lung function, history of emergency asthma treatment in the last year.		was conducted in order to determine baseline predictors of efficacy	a reduction in symptom scores, reduction in use of rescue medication, improvement in lung function, improvement in quality of life.

Table 04. Reported safety profile - Soler 2001 (extension phase)

Adverse event	Omalizumab (n = 274)	Placebo (n = 272)	p value
Pts with AE	229	232	p = 0.579
Respiratory event	160	173	not reported
Infections and infestations	124	132	not reported
Nervous	99	90	not reported
Muskoloskeletal	86	78	not reported
Body as a whole	78	81	not reported
Digestive	88	69	not reported
Skin and appendages	46	44	not reported
Special senses	35	26	not reported
Urogenital and reproductive	36	33	not reported
Cardiovascular	13	17	not reported

Table 05. Reported safety profile - Milgrom 2001

Adverse event	Omalizumab (n = 225)	Placebo (n = 109)	p value
Whether or not judged study related			
Any	201	95	not reported
Headache	81	33	not reported
Pharyngitis	58	26	not reported
Upper respiratory tract infection	78	39	not reported
Viral infection	56	25	not reported
Fever	39	16	not reported
Sinusitis	38	22	not reported
Coughing	30	19	not reported
Abdominal therapy	28	13	not reported
Rhinitis	24	12	not reported
Otitis media	19	7	not reported
Trauma	17	3	not reported
Vomiting	15	9	not reported
Ear ache	15	4	not reported
Injury	13	1	not reported
Dyspepsia	13	2	not reported

Table 05. Reported safety profile - Milgrom 2001 (*Continued*)

Adverse event	Omalizumab (n = 225)	Placebo (n = 109)	p value
Judged study related			
Any	14	2	not reported
Urticaria	3	0	not reported
Rash maculopapular	1	0	not reported
Flushing	1	0	not reported
Pruritis	1	0	not reported
Pain, arm	1	0	not reported

Table 06. Reported safety profile - Milgrom 1999

Adverse event	Omalizumab (n = 106)	Placebo (n = 105)	p value
Urticaria	8	3	not reported
Anti-IgE antibodies	0	0	not reported
Withdrawal due to adverse events	3	5	not reported
Withdrawals (any reason)	11	16	not reported

Table 07. Reported safety profile - Busse 2001

Adverse event	Omalizumab (n = 268)	Placebo (n = 257)	p value
Any adverse event	239	229	not reported
Upper Respiratory Tract Infection	84	76	not reported
Viral Infection	71	80	not reported
Headache	60	70	not reported
Sinusitis	52	56	not reported
Pharyngitis	39	35	not reported
Pain (back)	38	39	not reported
Arthralgia	26	9	not reported
Rhinitis	22	8	not reported
Coughing	20	23	not reported
Sprains and strains	20	14	not reported
Myalgia	19	17	not reported
Bronchitis	18	25	not reported
Nausea	18	16	not reported
Pain	18	14	not reported
Dyspepsia	17	31	not reported

Diarrhea	14	15	not reported
Insomnia	11	13	not reported
Sinus headache	4	13	not reported

Table 08. Safety profile - Holgate 2004

Adverse event	Omalizumab (n = 126)	Placebo (n = 120)	p value
Serious adverse event	1	5	not provided
Withdrawals due to adverse events	0	2	not provided

Table 09. Summary of clinical outcomes - steroid stable

Clinical outcome	Milgrom 1999	Busse 2001	Milgrom 2001	Soler 2001	Holgate 2004	Humbert 2005	Vignola 2004
Asthma exacerbation (no. participants with 1+ exacerbation)	Not reported	P = 0.0009	P = 0.095	P < 0.001	Not reported	Not analysed (imbalance at baseline - data presented as rate ratio)	P = 0.02
Mean no. exacerbations per participant	Not reported	P = 0.006	P = 0.093	P < 0.001	Evaluated, P value not reported	P = 0.042	P = 0.02
Mean no. days per exacerbation	Not reported	P < 0.001	P = 0.967	Not reported	Not reported	Not reported	Not reported
Unscheduled medical contact	Not reported	Not reported	Evaluated, P value not reported	Not reported	Not reported	Not reported	Not reported
Exacerbations requiring treatment with systemic CS	Not reported	Not reported	Evaluated, P value not reported	Evaluated, P value not reported	Not reported	Not reported	Not reported
Asthma symptom scores	High dose v placebo: P = 0.008	P < 0.001	Evaluated, P value not reported	P < 0.001	Not reported	P = 0.039	P = 0.023
Daily rescue medication use	High dose v placebo: P = 0.02	P < 0.01	Evaluated, P value not reported	P < 0.001	Not reported	0.5 puffs/d less (NS)	Reported, P value not given
Quality of life	High dose v placebo: P < 0.001	Not evaluated	Not evaluated	Not reported	Not reported	LSM - P<0.001	P < 0.05
Global	Not evaluated	Not reported	Not reported	Not reported	Not evaluated	P<0.001	P = 0.009

Table 09. Summary of clinical outcomes - steroid stable (Continued)

Clinical outcome	Milgrom 1999	Busse 2001	Milgrom 2001	Soler 2001	Holgate 2004	Humbert 2005	Vignola 2004
evaluation							
Morning peak flow	High dose v placebo P = 0.007	No P value reported	Evaluated, P value not reported	P < 0.001	Evaluated, P value not reported	P = 0.042	Not reported
FEV1 (L)	High dose v placebo: P = 0.81	P values from < 0.001 to = 0.019	Evaluated, P value not reported	Evaluated, P value not reported	Not reported	Reported, P value not given	P = 0.032

Table 10. Summary of clinical outcome - steroid reduction phase or end of study

Clinical outcome	Milgrom 1999	Busse 2001	Milgrom 2001	Soler 2001	Holgate 2004
>= 50% steroid reduction in ICS	High dose v placebo: p = 0.07 Low dose v placebo: p=0.12	p < 0.001	Not reported	Evaluated, no p value reported	p = 0.001
Complete withdrawal of ICS steroids	High dose v placebo: p = 0.27 Low dose v placebo: p=0.48	p < 0.001	p = 0.004	Evaluated, no p value reported	p = 0.198
Asthma exacerbation (no. participantss with 1+ exacerbation)	High dose v placebo: p = 0.03 Low dose v pacebo: p=0.01	p = 0.0004	p < 0.001	p < 0.001	Evaluated, p value not reported
Mean no. exacerbations per subject	Not evaluated	p = 0.003	p < 0.001	p < 0.001	Not reported
Mean no. days per exacerbation	Not evaluated	p = 0.021	p = 0.329	Not reported	Not reported
Unscheduled medical contacts	Not evaluated	Evaluated, p value not reported	p = 0.001	Not reported	Not reported
Exacerbations requiring treatment with systemic CS	High dose v placebo: p = 0.01 Low dose v placebo: p=0.06	Not reported	Evaluated, no p value reported	Not reported	Not reported
Asthma symptom scores	High dose v placebo: p = 0.048 Low dose v placebo: p=0.14	p < 0.01	Evaluated, no p value reported	p</= 0.01	Not reported
Daily rescue medication use	Evaluated, p value not reported	p < 0.01	p = 0.004	p < 0.001	Not reported
Quality of life	Evaluated, p value not reported	Not evaluated	Not evaluated	Not reported	p < 0.01
Global evaluation	Not evaluated	p < 0.001	p < 0.001	Not evaluated	Not evaluated

Morning peak flow	High dose v placebo: p = 0.02 Low dose v placebo: p=0.046	Evaluated, no p value reported	Evaluated, p value not reported	p < 0.001	Evaluated, p value not reported
FEV1	Evaluated, no p value reported	P values ranging from p<0.001 to =0.019	Evaluated, p value not reported	p < 0.05	Not reported

Table 11. Exacerbation rate data (continuous and dichotomous data)

Study ID	CS stable: means	CS stable: n/N	CS tapering: mean	CS tapering: n/N
Solèr 2001	Anti-IgE: 0.28 (SD 1.09); Placebo: 0.66 (SD 1.43) P < 0.001	Anti-IgE: 35/274 (13%); Placebo: 85/272 (31%)	Anti-IgE: 0.36 (SD 1.01); Placebo: 0.75 (SD 1.43) P < 0.001	Anti-IgE: 43/274 (16%); Placebo: 81/272 (30%) P < 0.001
Busse 2001	Anti-IgE: 0.28 (SD 0.95); Placebo: 0.54 (SD 1.38) Unpublished source	Anti-IgE: 39/268 (15%); Placebo: 60/257 (23%)	Anti-IgE: 0.39 (0.92); Placebo: 0.66 (1.19) Unpublished source	Anti-IgE: 57/268 (21%); Placebo: 83/257 (32%)
Milgrom 2001	Anti-IgE: 0.30 (SD 0.98); Placebo: 0.40 (SD 1.02) P = ns	Anti-IgE: 35/225 (16%); Placebo: 25/109 (23%) P = ns	Anti-IgE: 0.42 (SD 1.08); Placebo: 0.72 (1.2) P < 0.001	Anti-IgE: 41/216 (14%); Placebo: 42/101 (41%) P < 0.001
Holgate 2004	Anti-IgE: 0.15 (SD 0.47); Placebo: 0.23 (SD 0.78) Unpublished source	Anti-IgE: 13/126 (11%); Placebo: 15/120 (13%) Unpublished source	Anti-IgE: 0.19 (SD 0.51); Placebo: 0.34 (SD 0.99) Unpublished source	Anti-IgE: 17/126 (14%); Placebo: 25/120 (21%) Unpublished source
Humbert 2005	Anti-IgE: 0.68 Placebo: 0.91 Published source	Not available	NA	NA
Vignola 2004	Anti-IgE: 0.25 Placebo: 0.4 (P = 0.02) Published source	Anti-IgE: 43/209 (21%); Placebo: 59/196 (30%) Published source	NA	NA
Pooled effect estimates	MD: -0.18 (95%CI: -0.25, -0.10)	OR: 0.49 (95%CI: 0.38, 0.64)	WMD: -0.27 (95%CI: -0.38, -0.17)	OR: 2.50 (95%CI: 2.00, 3.13)

Table 12. 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

Table 12. Corticosteroid use during steroid-tapering phase (*Continued*)

	Solèr 2001	Busse 2001	Milgrom 2001	Holgate 2004	Pooled estimates
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 -119mcg/day [95%CI: -153.72, -84.34]
Median (95%CI) daily ICS dose at end of tapering (Omalizumab/Placebo)	100 (0, 400)/300 (100, 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
No. patients 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, 3.10] NNT 5-7
No. patients 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, 3.13] NNT 5-8

Table 13. 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 hand searching, we retrieved 20 papers and eight studies met the inclusion criteria of the review. One study of subcutaneous anti-IgE recruited adults with severe asthma (Holgate 2004). Four studies examined intravenous

Table 13. Search history (*Continued*)

Date	Search results
	or subcutaneous anti-IgE in adults (Busse 2001; Milgrom 1999; Soler 2001) and children (Milgrom 2001) with moderate/severe asthma and three studies examined aerosolised or intravenous anti-IgE in adults with mild asthma (Boulet 1997; Fahy 1997; Fahy 1999).
Update search results January 2003-04	The 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 (Ayres 2004; Study Q2143G). One further unpublished study in people with co-existing asthma and rhinitis is awaiting assessment (SOLAR 2004).

Table 14. What's New History

Year of update	New detail
January 2004	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 reduction in inhaled steroid consumption for three studies (Busse 2001; Soler 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.

Table 15. Analysis of pooled estimates for exacerbations

Outcome	Method of pooling	Included studies	Result	Heterogeneity (%)
01:17 (Exacerbations)	Fixed Effect OR (data taken from Humbert study: severe exacerbations)	Milgrom 2001; Vignola 2004; Busse 2001; Soler 2001; Holgate 2004 (ICS); Holgate (ICS & OCS)	0.55 (95% CI 0.45, 0.69)	57.1
01:18 (Exacerbations (all studies))	Fixed Effect Rate Ratio (assumed that Rate Ratio and Risk Ratios are similar)	Milgrom 2001; Vignola 2004; Busse 2001; Soler 2001; Holgate 2004 (ICS); Humbert 2005; Holgate (ICS & OCS)	0.66 (95% CI 0.57, 0.77)	50.4

Table 16. Paediatric populations

Trial	Omalizumab	Placebo	%
Holgate 2004& Holgate 2004a (N between 12-17 years)	12/176	9/165	6.5%
Busse 2001	20/268	21/257	7.8%
Soler 2001	18/274	17/272	6.4%

ANALYSES

Comparison 01. Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Number of patients with at least one exacerbation (ICS & OCS users)	6	2151	Odds Ratio (Fixed) 95% CI	0.55 [0.45, 0.69]
02 Exacerbations			Rate ratio (Fixed) 95% CI	Totals not selected
03 Mean exacerbations per participant	7	2570	Exa'ns/pt (Fixed) 95% CI	-0.18 [-0.25, -0.10]
04 Asthma exacerbations per patient	4	1651	Weighted Mean Difference (Fixed) 95% CI	-0.19 [-0.29, -0.09]
05 Rescue medication (puffs per day)	5	1799	Weighted Mean Difference (Fixed) 95% CI	-0.68 [-0.99, -0.36]
06 Rescue medicaton usage (imputed values)	6	2223	Puffs/day (Fixed) 95% CI	-0.63 [-0.90, -0.36]
07 FEV1 (mL)	2	1071	Weighted Mean Difference (Fixed) 95% CI	68.31 [-23.45, 160.07]
08 Change in FEV1 (mL)			mL (Fixed) 95% CI	Totals not selected
09 Change in FEV1 predicted			% (Fixed) 95% CI	Totals not selected
10 Peak expiratory flow rate (am)	4	1651	Weighted Mean Difference (Fixed) 95% CI	3.56 [-5.05, 12.18]
11 Change in am PEF			L/min (Fixed) 95% CI	Totals not selected
12 Symptom scores	3	1317	Weighted Mean Difference (Fixed) 95% CI	-0.46 [-0.63, -0.29]
13 Mean change in Wasserfallen asthma score			Symptoms (Fixed) 95% CI	Totals not selected
14 Mean change in AQLQ scores	5	2131	AQLQ score (Fixed) 95% CI	0.32 [0.22, 0.43]
15 Quality of life - change from baseline in AQLQ scores			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
16 Global evaluation rated good to excellent	2	824	Odds Ratio (Fixed) 95% CI	2.58 [1.94, 3.43]

Comparison 02. High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Rescue medication usage			Standardised Mean Difference (Fixed) 95% CI	Totals not selected
02 FEV1			Standardised Mean Difference (Fixed) 95% CI	Totals not selected
03 Morning PEF			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
04 Symptom scores			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
05 Quality of life			Standardised Mean Difference (Fixed) 95% CI	Totals not selected
06 Number of participants with >50% reduction in symptom score			Odds Ratio (Fixed) 95% CI	Totals not selected

Comparison 03. Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Number of patients achieving complete inhaled steroid withdrawal	4	1634	Odds Ratio (Fixed) 95% CI	2.50 [2.00, 3.13]
02 >50% reduction in inhaled steroid usage	4	1634	Odds Ratio (Fixed) 95% CI	2.50 [2.02, 3.10]
03 Mean steroid dose at end of reduction phase			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
04 Mean change in steroid consumption (BDP equivalent)	3	1188	Weighted Mean Difference (Fixed) 95% CI	-118.76 [-154.38, -83.14]
05 Rescue medication (puffs per day)	4	1373	Weighted Mean Difference (Fixed) 95% CI	-0.74 [-1.05, -0.43]
06 Number of participants with exacerbation	5	1726	Odds Ratio (Fixed) 95% CI	0.49 [0.39, 0.62]
07 Asthma exacerbations per participant	5	1729	Ex'ns/pt (Fixed) 95% CI	-0.27 [-0.37, -0.16]
08 Exacerbations requiring hospitalisation	3	1405	Odds Ratio (Fixed) 95% CI	0.11 [0.03, 0.48]
09 Quality of Life - change from baseline			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
10 Numbers of participants achieving clinically relevant improvement in Quality of Life (>0.5)			Odds Ratio (Fixed) 95% CI	Totals not selected
11 Global evaluation rated good to excellent	2	842	Odds Ratio (Fixed) 95% CI	2.72 [2.04, 3.62]
13 Asthma exacerbations per participant	4	1634	Weighted Mean Difference (Fixed) 95% CI	-0.27 [-0.38, -0.17]

Comparison 04. High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Number of patients achieving complete inhaled steroid withdrawal			Odds Ratio (Fixed) 95% CI	Totals not selected
02 >50% reduction in inhaled steroid usage			Odds Ratio (Fixed) 95% CI	Totals not selected
03 Symptom score			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
04 Number of patients with >50% reduction in symptom scores			Odds Ratio (Fixed) 95% CI	Totals not selected
05 Number of participants with exacerbations			Odds Ratio (Fixed) 95% CI	Totals not selected

Comparison 05. Subcutaneous Omalizumab + steroid versus placebo + steroid (trial extension)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Number of patients achieving complete inhaled steroid withdrawal			Odds Ratio (Fixed) 95% CI	Totals not selected
02 Participants with one or more exacerbation			Odds Ratio (Fixed) 95% CI	Subtotals only
03 Hospitalisations			Odds Ratio (Fixed) 95% CI	Subtotals only
04 Number of participants with any adverse event			Odds Ratio (Fixed) 95% CI	Subtotals only

Comparison 06. Low dose aerosolized Omalizumab versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 FEV1 (litres)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
02 Area under curve for fall in FEV1 (% x minutes) - early response (0-1 hours)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
03 Area under curve for fall in FEV1 (% x minutes) - late response (3-7 hours)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
04 Peak Expiratory Flow (am) (L/min)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected

Comparison 07. High dose aerosolized Omalizumab versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 FEV1 (litres)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
02 Area under the curve for % fall in FEV1 (early response - 0-1 hours)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
03 Area under the curve for % fall in FEV1 (late response - 3-7 hours)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
04 Peak Expiratory Flow (am) (L/min)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected

Comparison 08. Intravenous Omalizumab versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Rescue medication use (one week after end of treatment)	2	39	Standardised Mean Difference (Fixed) 95% CI	0.14 [-0.50, 0.77]
02 FEV1 (litres)	2	39	Standardised Mean Difference (Fixed) 95% CI	0.51 [-0.13, 1.15]
03 Fall in FEV1 after allergen challenge (%) (0-1 hours)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
04 Fall in FEV1 after allergen challenge (%) (2-7 hours)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected

05 Peak expiratory flow (am)	2	39	Standardised Mean Difference (Fixed) 95% CI	0.35 [-0.29, 1.00]
06 Symptom scores	2	39	Standardised Mean Difference (Fixed) 95% CI	-0.33 [-0.96, 0.31]

Comparison 09. Subcutaneous Omalizumab versus placebo (without inhaled corticosteroids)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 FEV1 (Litres)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
02 FEV1 (% predicted)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
03 Change in PC 20			Weighted Mean Difference (Fixed) 95% CI	Totals not selected

Comparison 10. Subcutaneous Omalizumab versus placebo (safety)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Side effects			Odds Ratio (Fixed) 95% CI	Subtotals only

Comparison 11. Subcutaneous Omalizumab + ICS& OCS versus placebo + ICS & OCS steroid (steroid reduction)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Number of patients achieving complete oral steroid withdrawal			Odds Ratio (Fixed) 95% CI	Totals not selected
02 Number of participants with exacerbation			Odds Ratio (Fixed) 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [therapeutic use]; Anti-Asthmatic Agents [therapeutic use]; Antibodies, Anti-Idiotypic [*therapeutic use]; Antibodies, Monoclonal [*therapeutic use]; Asthma [*drug therapy; immunology]; Chronic Disease; Immunoglobulin E [blood; *immunology]; Randomized Controlled Trials

MeSH check words

Adult; Child; Humans

COVER SHEET

Title	Anti-IgE for chronic asthma in adults and children
Authors	Walker S, Monteil M, Phelan K, Lasserson TJ, Walters EH
Contribution of author(s)	SW developed the protocol with input from KP and MM. Editorial support was given by EHW. Studies were selected and appraised by SW and MM. Data were extracted by MM, TL and SW, and then entered by MM and TL. MM and TL developed analysis with input from SW, KJ and EHW. MM and SW developed the discussion, with guidance from KP and EHW. TJL and SW wrote the update of the review, with additional input from EHW, MM and KP
Issue protocol first published	2002/2
Review first published	2003/3

Date of most recent amendment	21 February 2006
Date of most recent SUBSTANTIVE amendment	21 February 2006
What's New	Update 2006 This review includes data from six new trials. Two of these were conducted in large samples of inhaled steroid-dependent asthma patients (Vignola 2004; Humbert 2005) 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.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	01 February 2006
Date authors' conclusions section amended	21 February 2006
Contact address	Dr. Samantha Walker Head of Research National Respiratory Training Centre The Athenaeum 10 Church Street Warwick CV34 4AB UK E-mail: s.walker@educationforhealth.org.uk Tel: 01926 838975 Fax: 01926 493224
DOI	10.1002/14651858.CD003559.pub3
Cochrane Library number	CD003559
Editorial group	Cochrane Airways Group
Editorial group code	HM-AIRWAYS

GRAPHS AND OTHER TABLES

Figure 01. Graphic to show that in order to prevent one person experiencing an exacerbation of their asthma, 11 people would need to be treated with Anti-IgE therapy over a 12-16 week period.

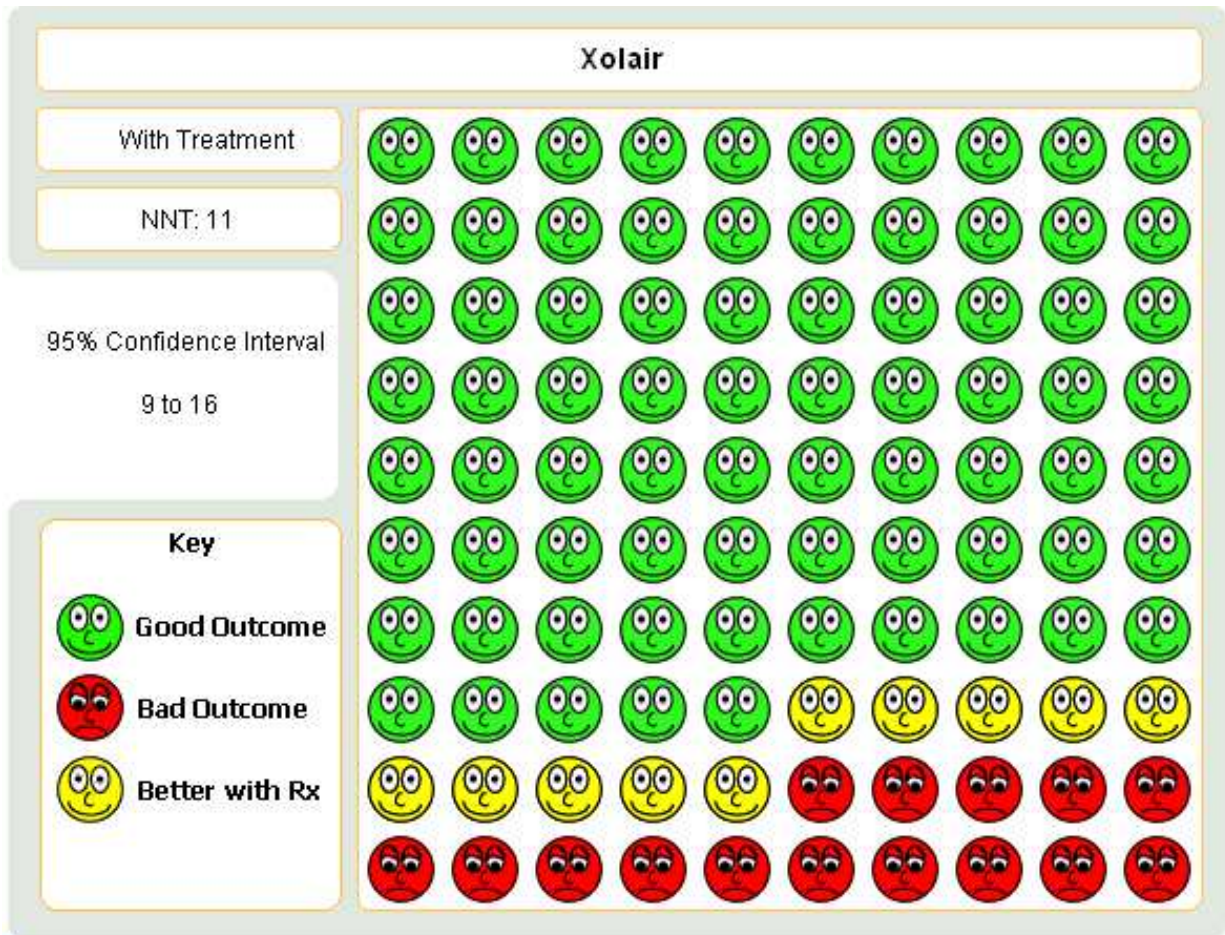


Figure 02. Graphic to show that in order for one person to be able to withdraw steroid therapy, 6 people would need to be treated with Omalizumab

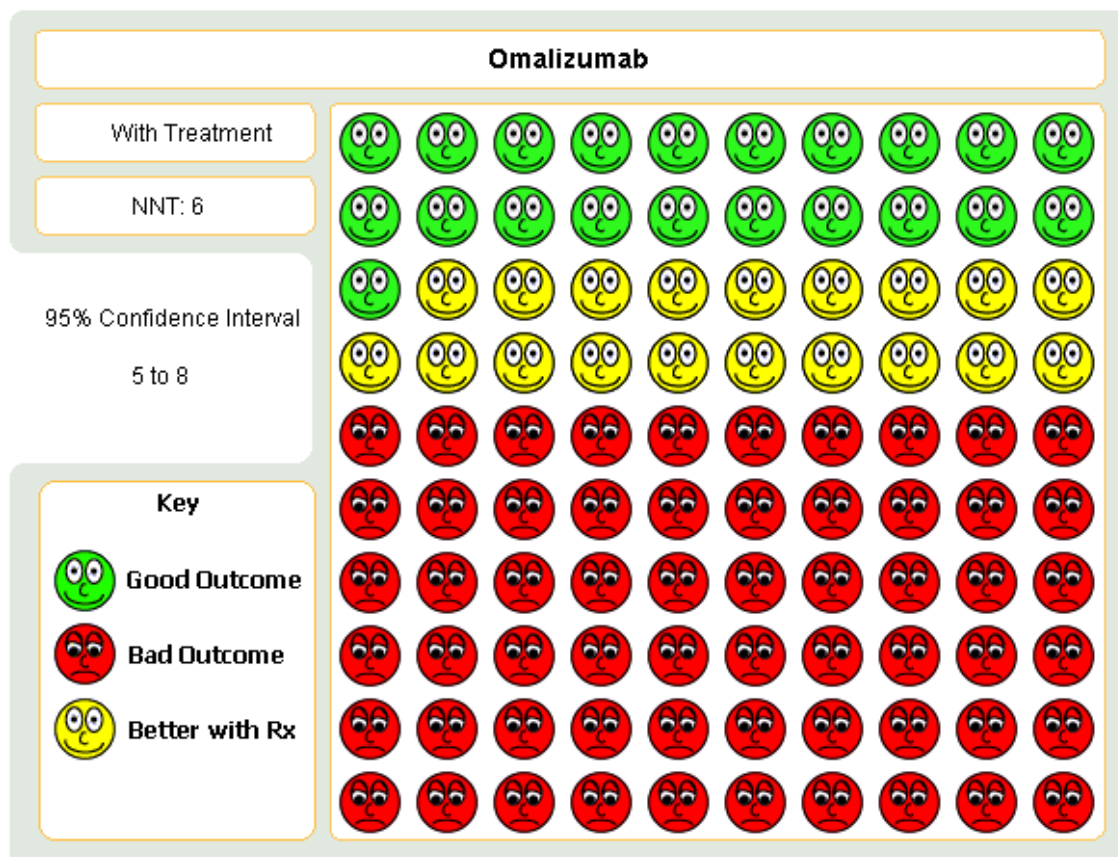


Figure 03. Graphic to demonstrate that in order for one person to be able to reduce therapy by at least 50%, 5 people would need to be treated with Omalizumab. This assumes that around 56% of people would be able to reduce their inhaled steroid by 50% on placebo.

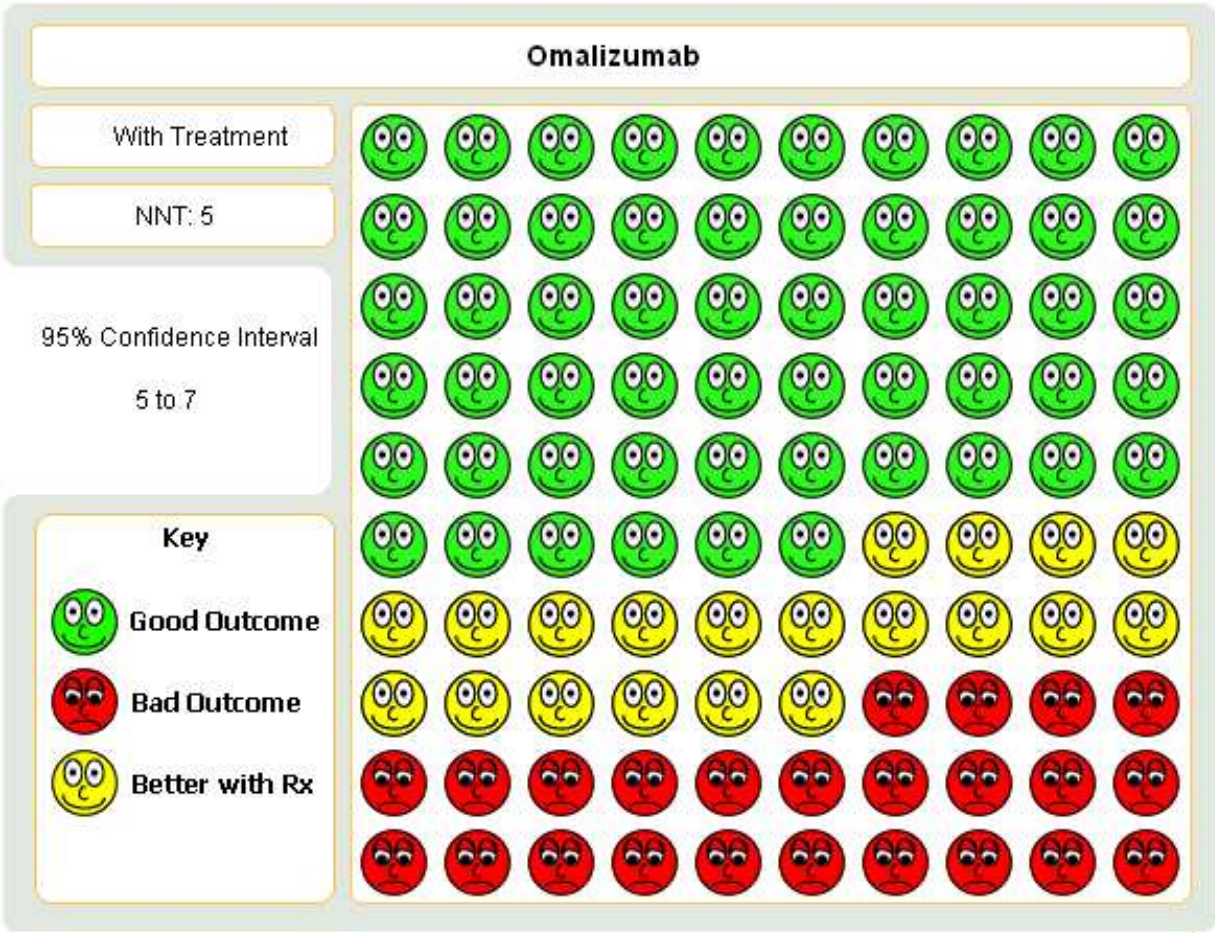


Figure 04. Graphic to demonstrate that in order to prevent one exacerbation from a sample of patients embarked on a steroid tapering protocol, 8 would need to be treated with Omalizumab

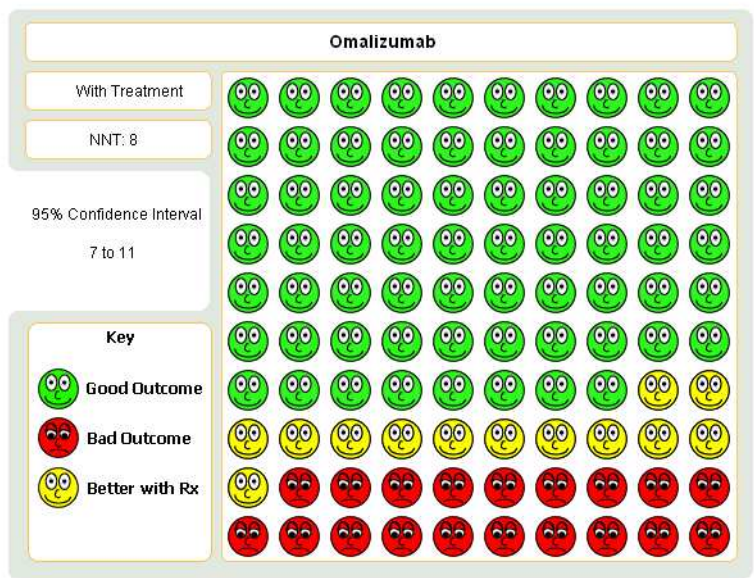


Figure 05. Graph to show that for every 57 participants treated with Omalizumab, one will not have an exacerbation leading to hospital admission.

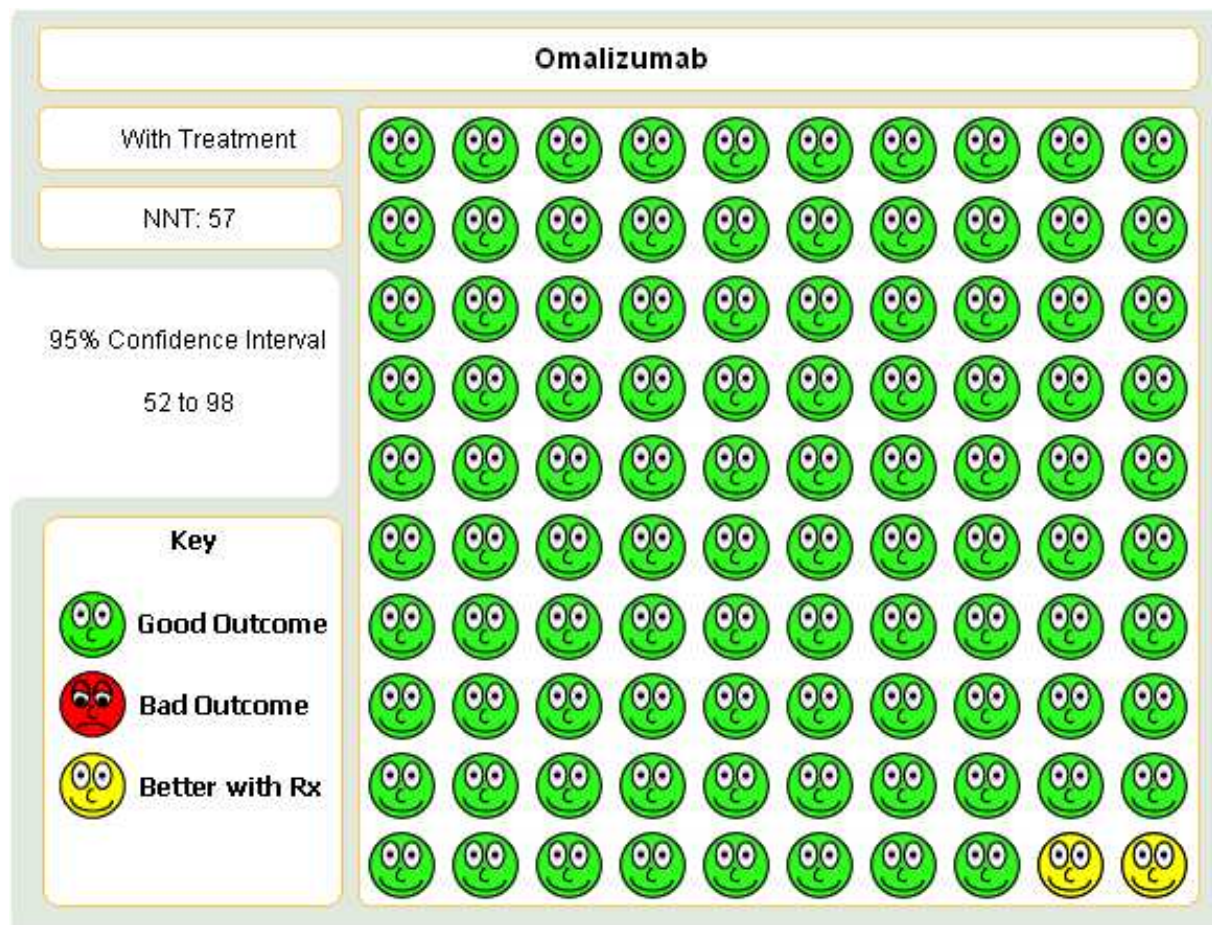


Figure 06. Graphic to demonstrate that for every five people treated with Omalizumab, one person more will rate their asthma control as good or excellent.

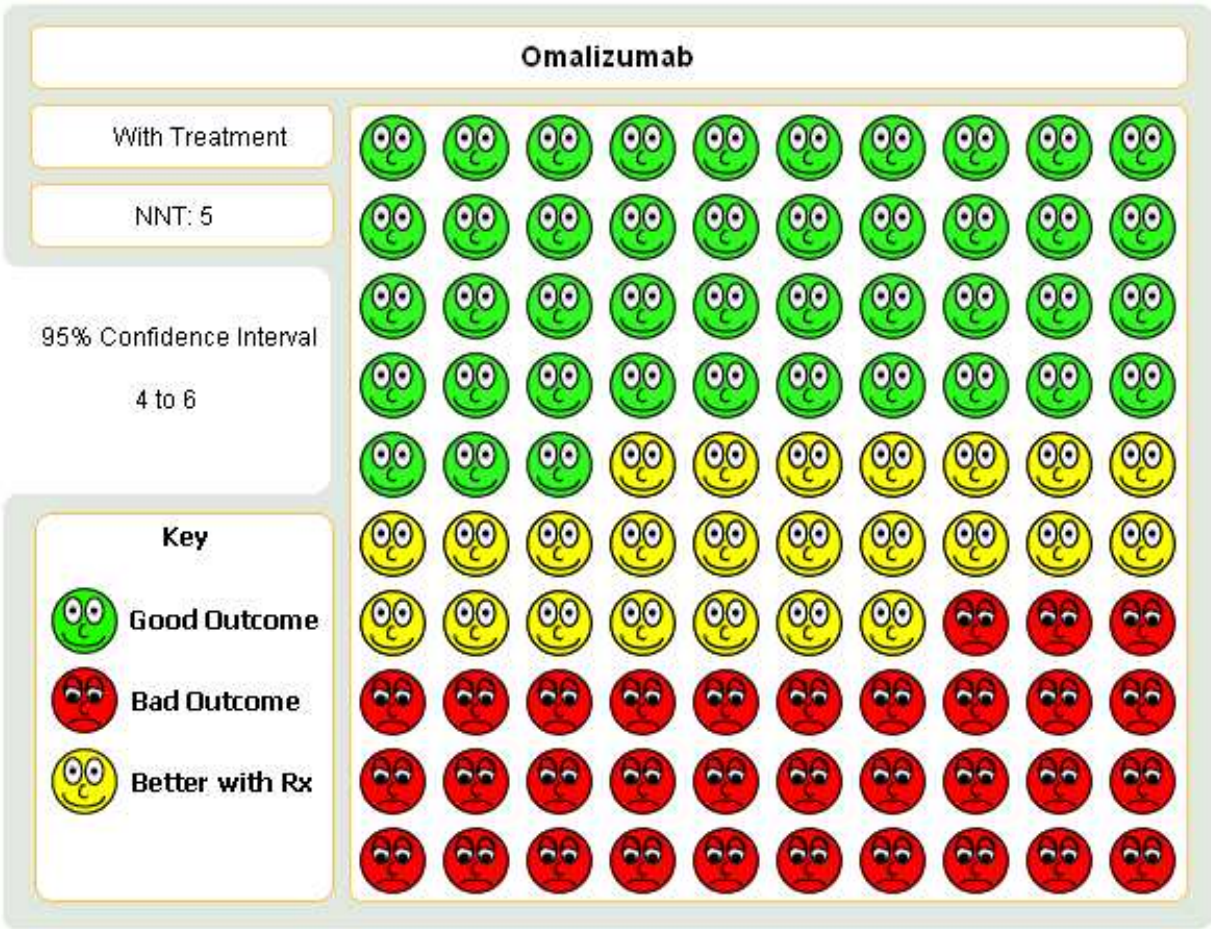
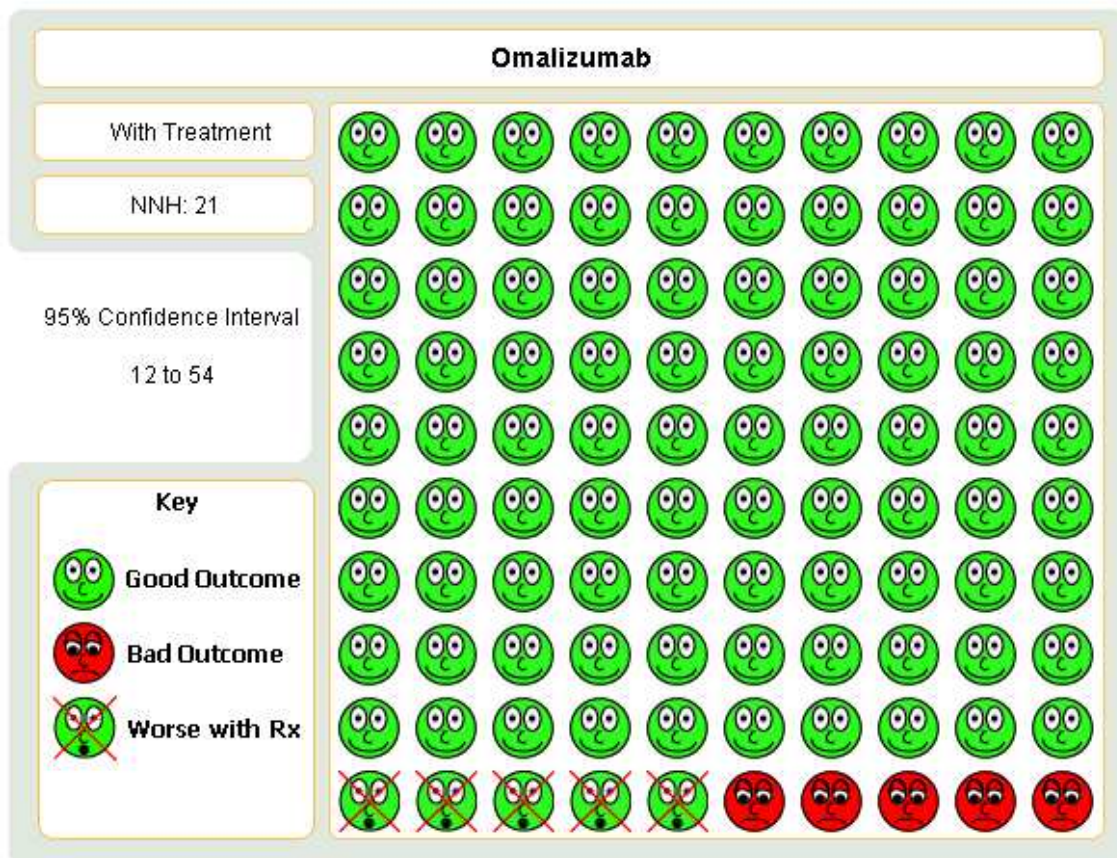


Figure 07. Graphic to demonstrate that in order for one person to develop an injection site reaction, approximately 21 would need to be treated with Omalizumab for between 28-32 weeks.

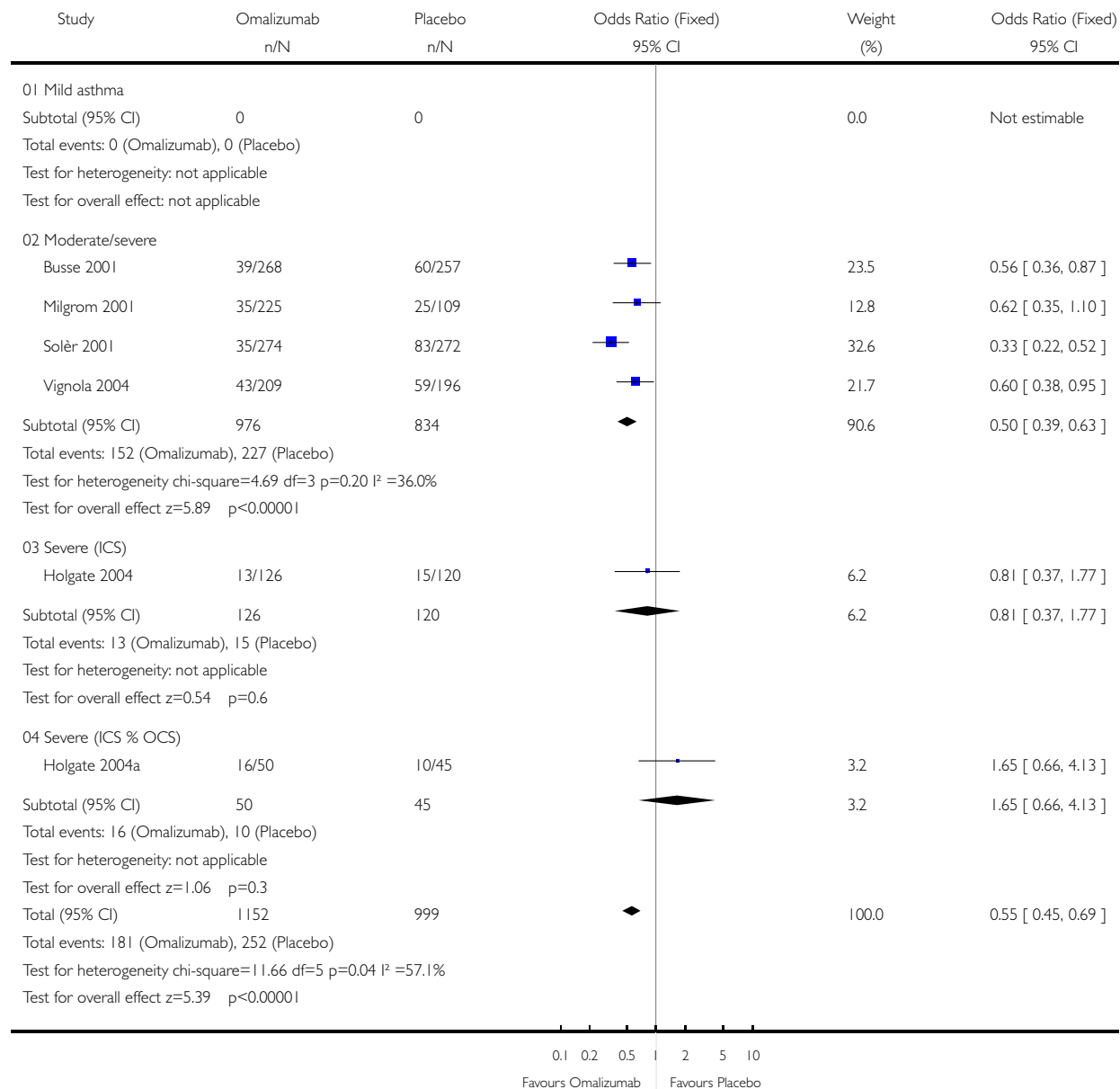


Analysis 01.01. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 01 Number of patients with at least one exacerbation (ICS & OCS users)

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 01 Number of patients with at least one exacerbation (ICS % OCS users)

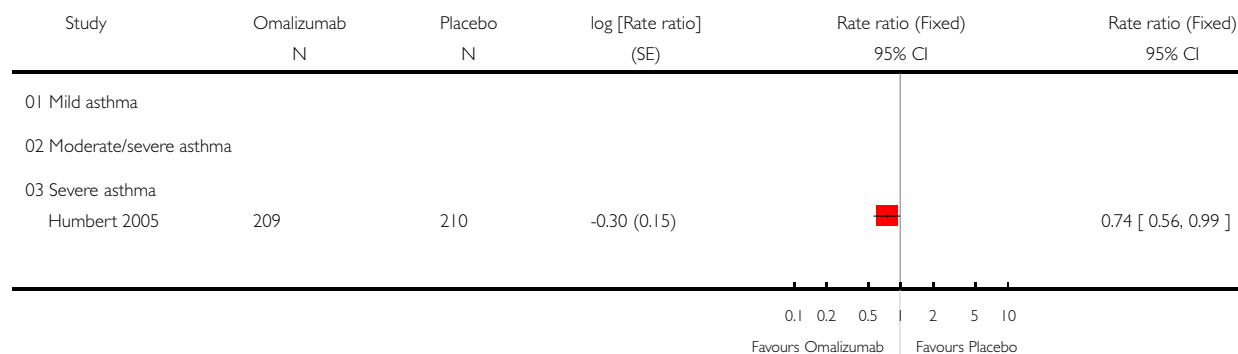


Analysis 01.02. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 02 Exacerbations

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 02 Exacerbations

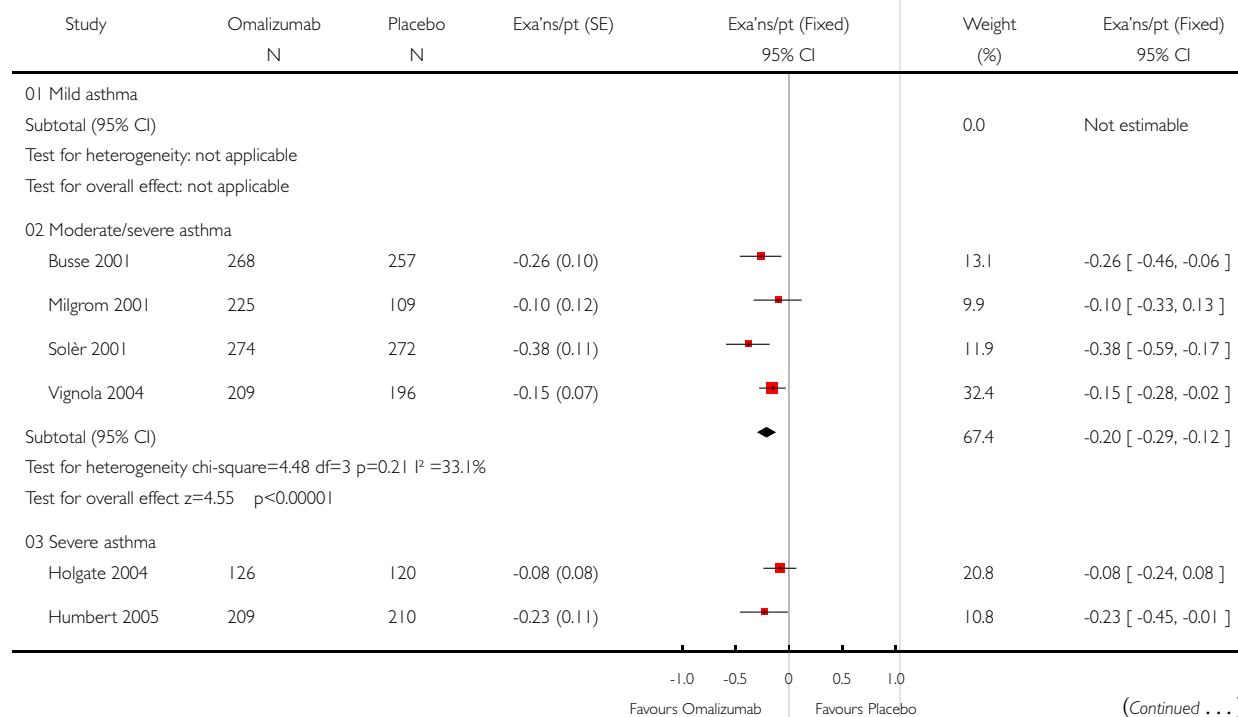


Analysis 01.03. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 03 Mean exacerbations per participant

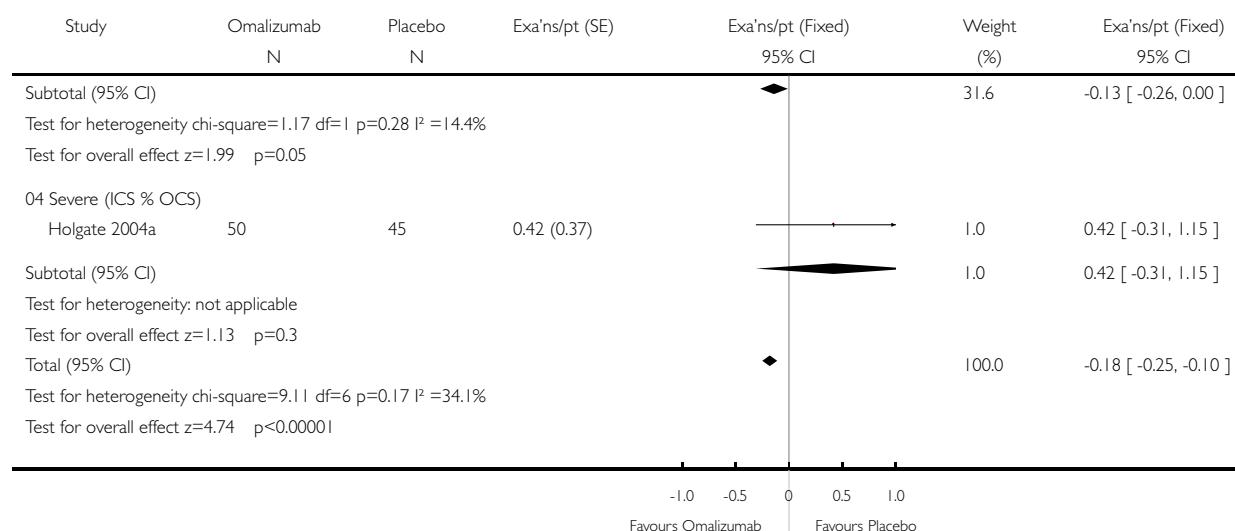
Review: Anti-IgE for chronic asthma in adults and children

Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 03 Mean exacerbations per participant



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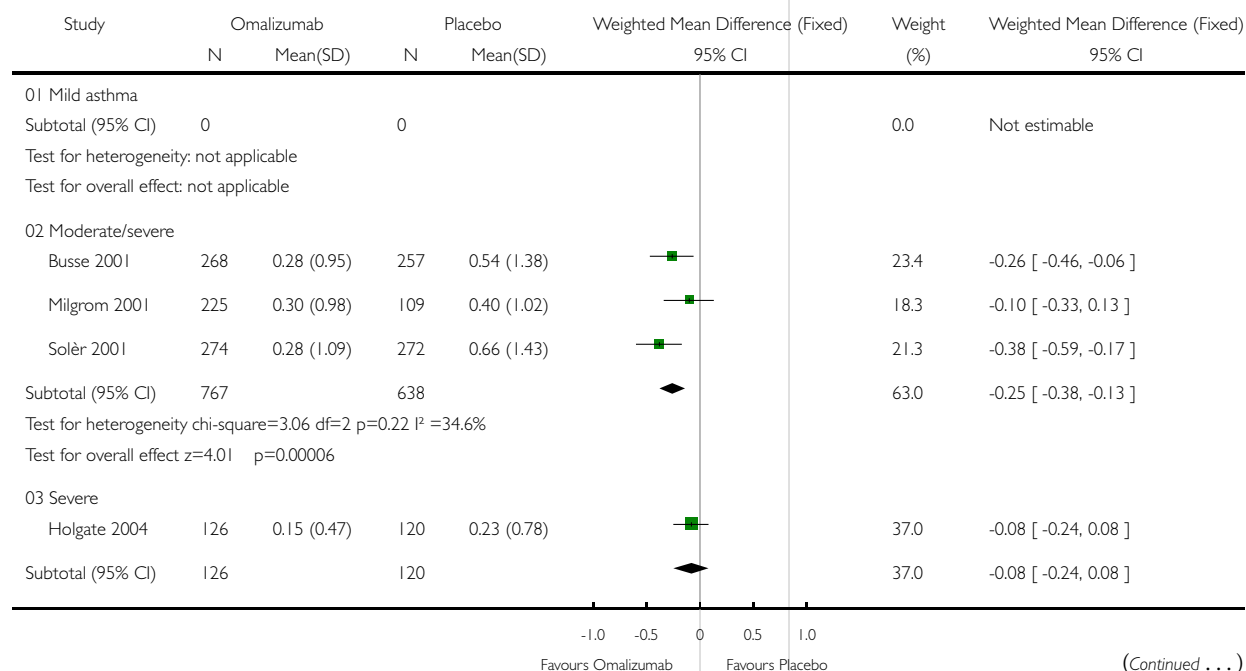


Analysis 01.04. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 04 Asthma exacerbations per patient

Review: Anti-IgE for chronic asthma in adults and children

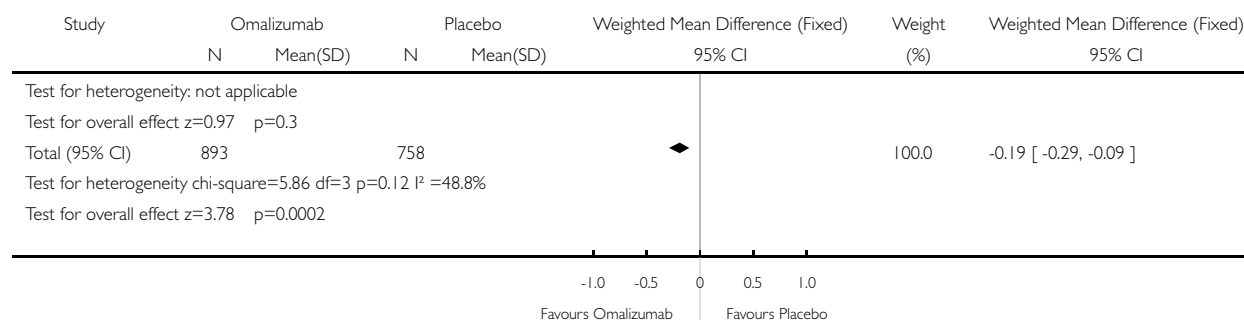
Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 04 Asthma exacerbations per patient



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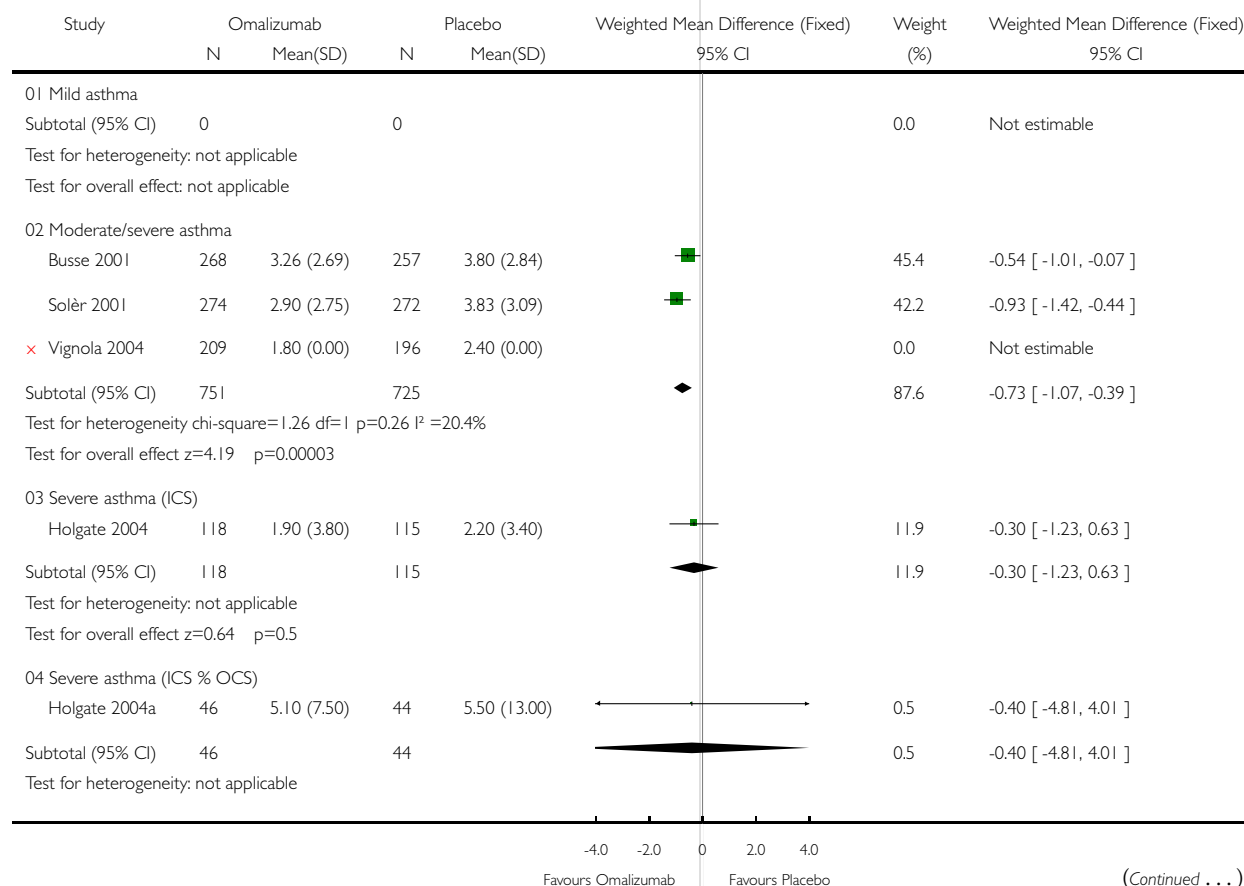


Analysis 01.05. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 05 Rescue medication (puffs per day)

Review: Anti-IgE for chronic asthma in adults and children

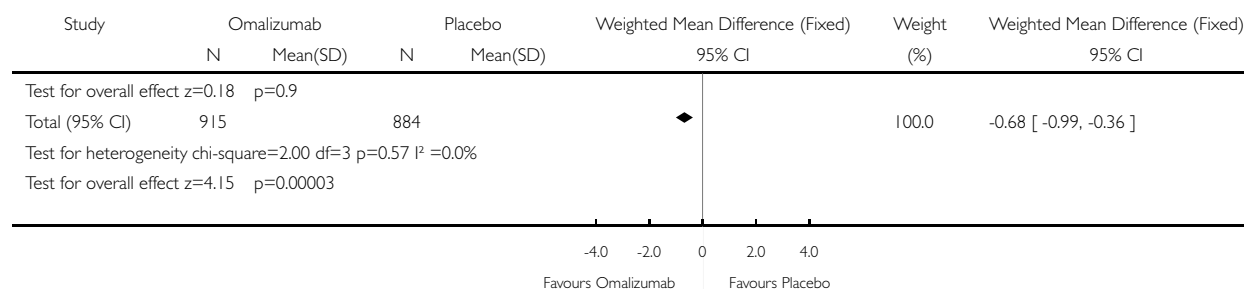
Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 05 Rescue medication (puffs per day)



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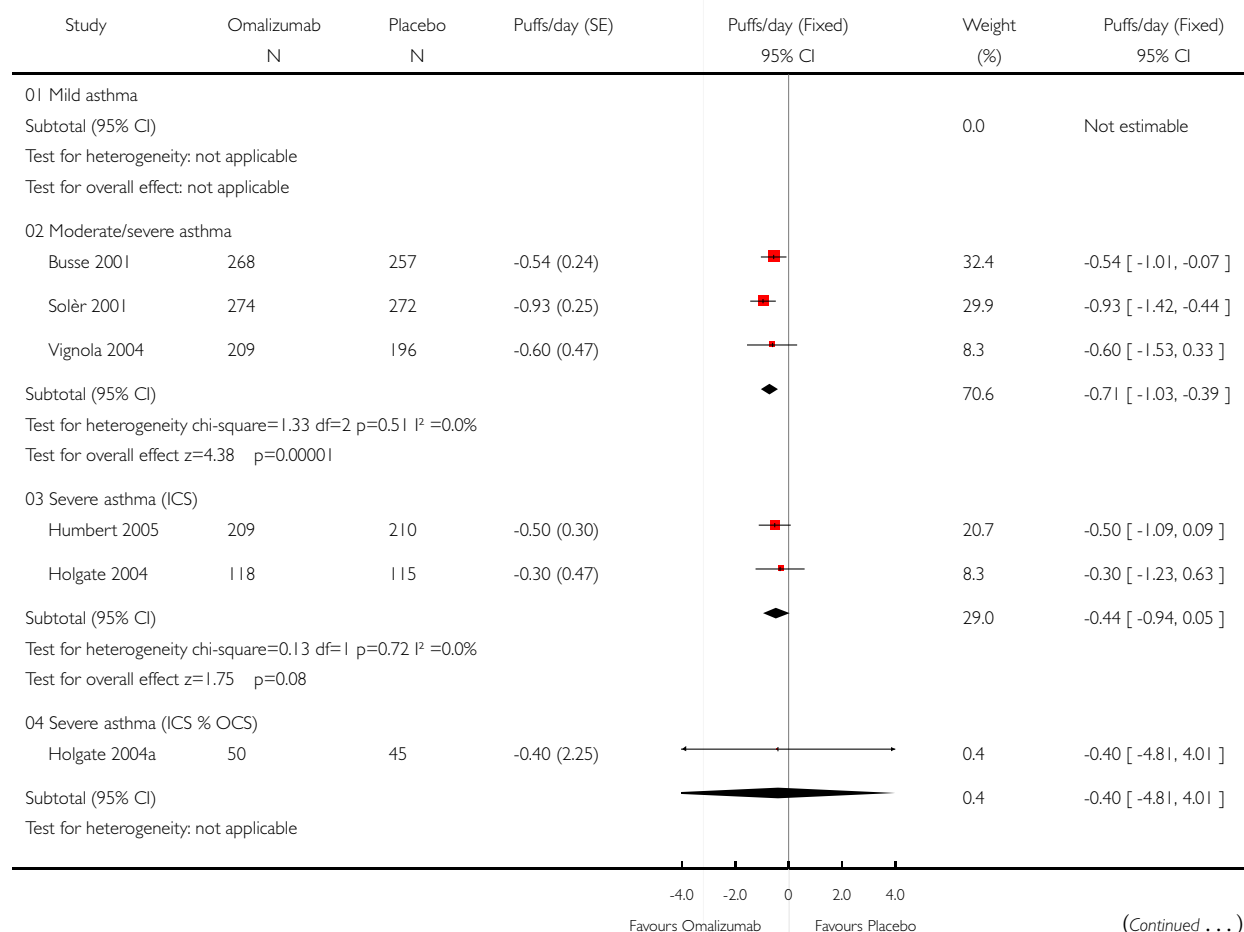


Analysis 01.06. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 06 Rescue medication usage (imputed values)

Review: Anti-IgE for chronic asthma in adults and children

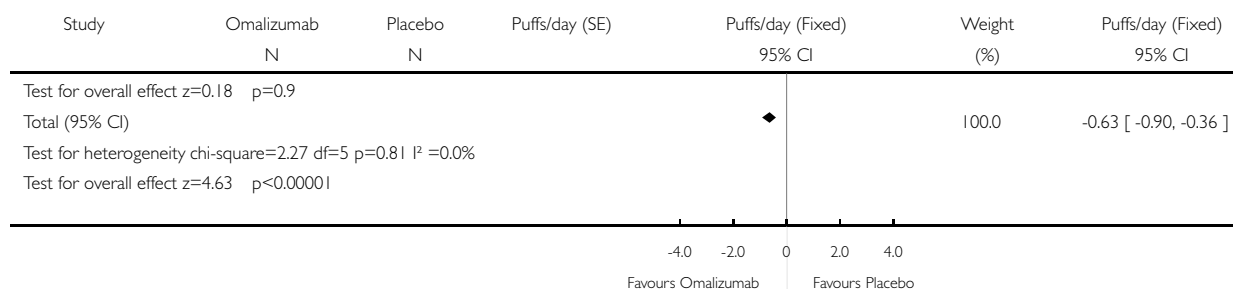
Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 06 Rescue medication usage (imputed values)



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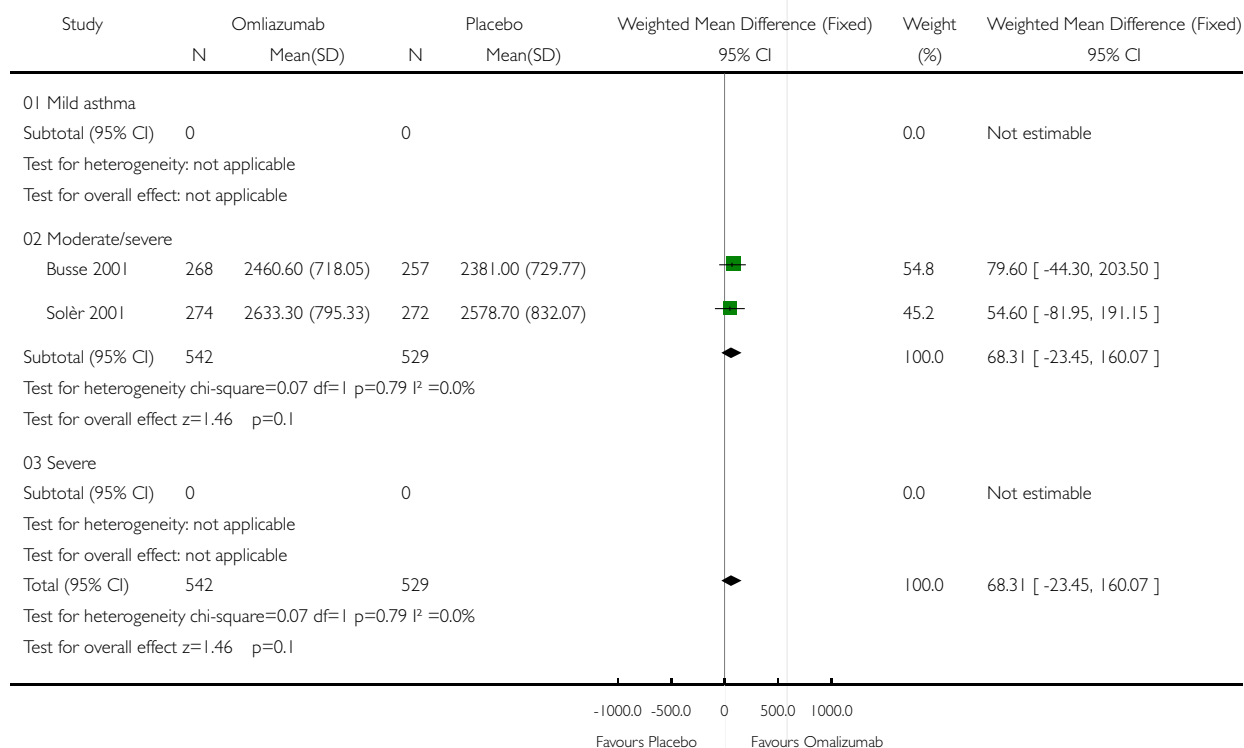


Analysis 01.07. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 07 FEV1 (mL)

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 07 FEV1 (mL)

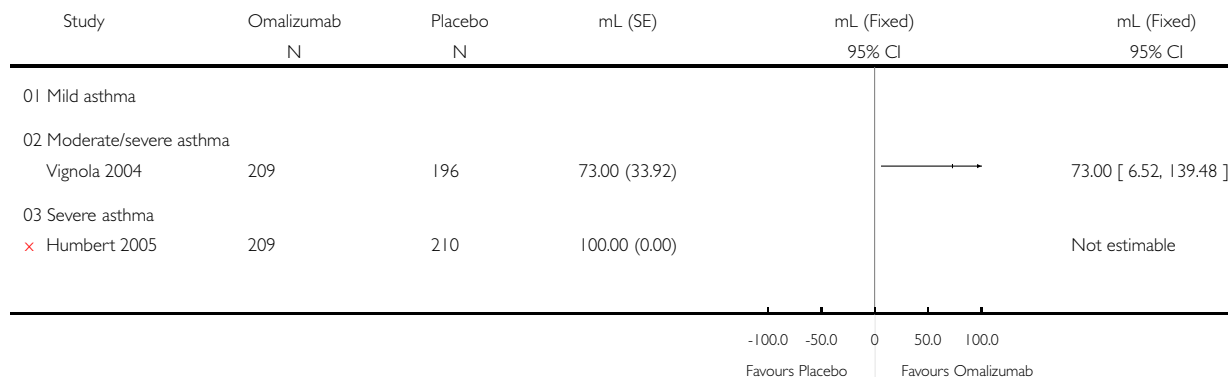


Analysis 01.08. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 08 Change in FEV1 (mL)

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 08 Change in FEV1 (mL)

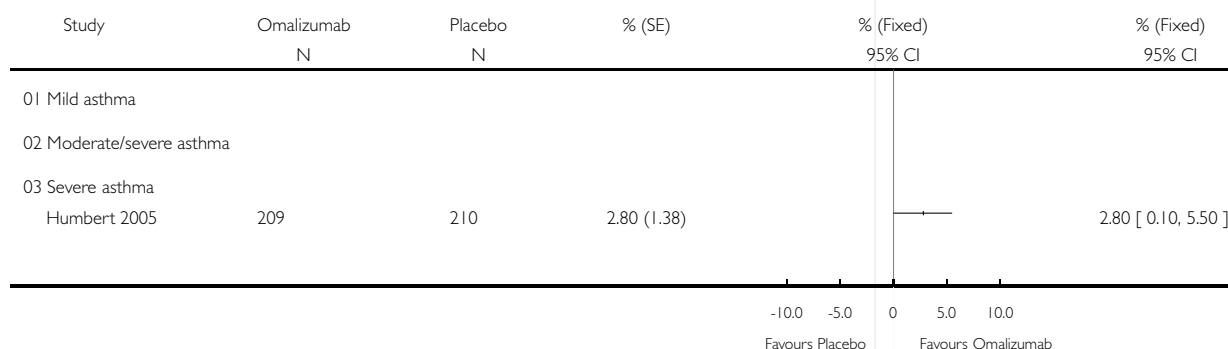


Analysis 01.09. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 09 Change in FEV1 predicted

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 09 Change in FEV1 predicted

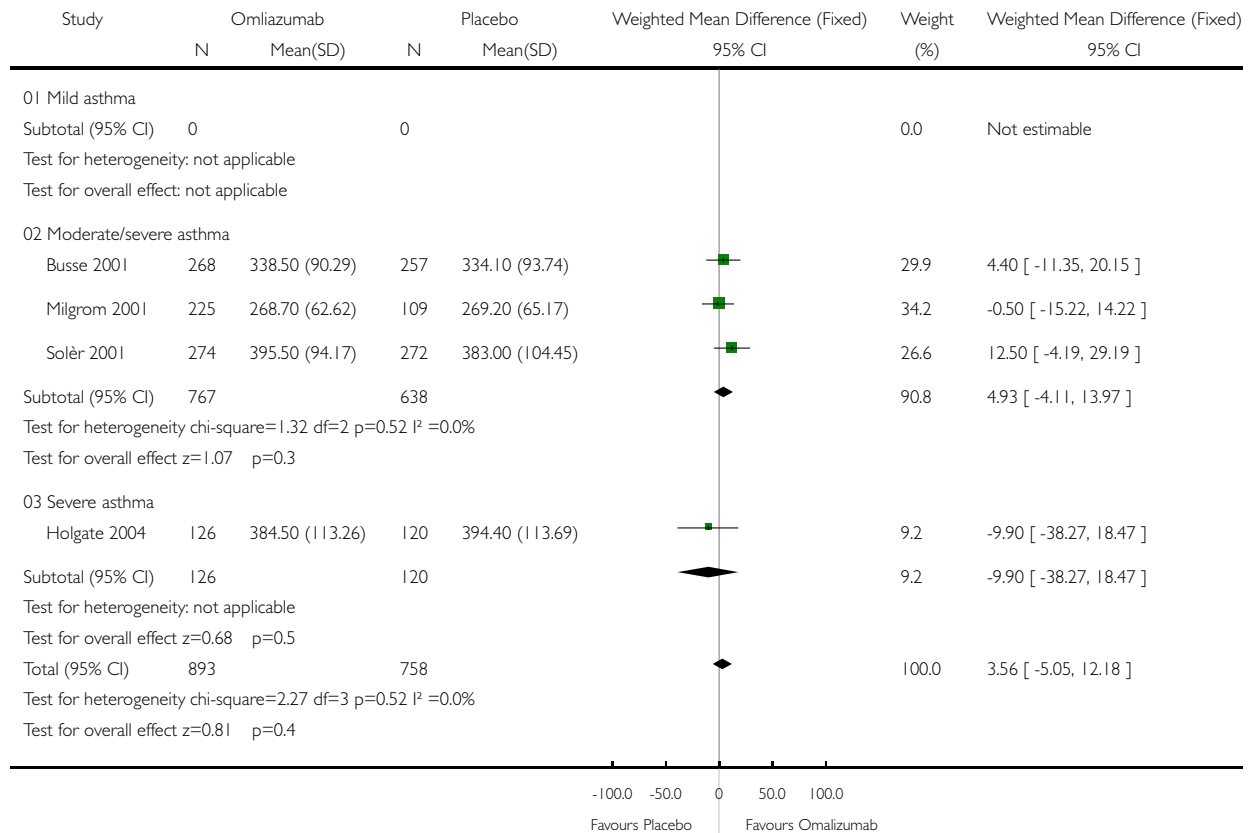


Analysis 01.10. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 10 Peak expiratory flow rate (am)

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 10 Peak expiratory flow rate (am)

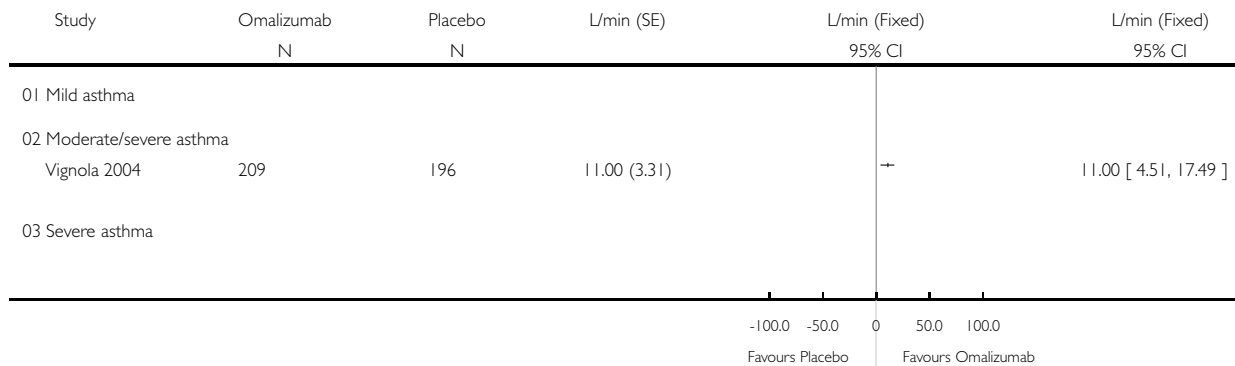


Analysis 01.11. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 11 Change in am PEF

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 11 Change in am PEF

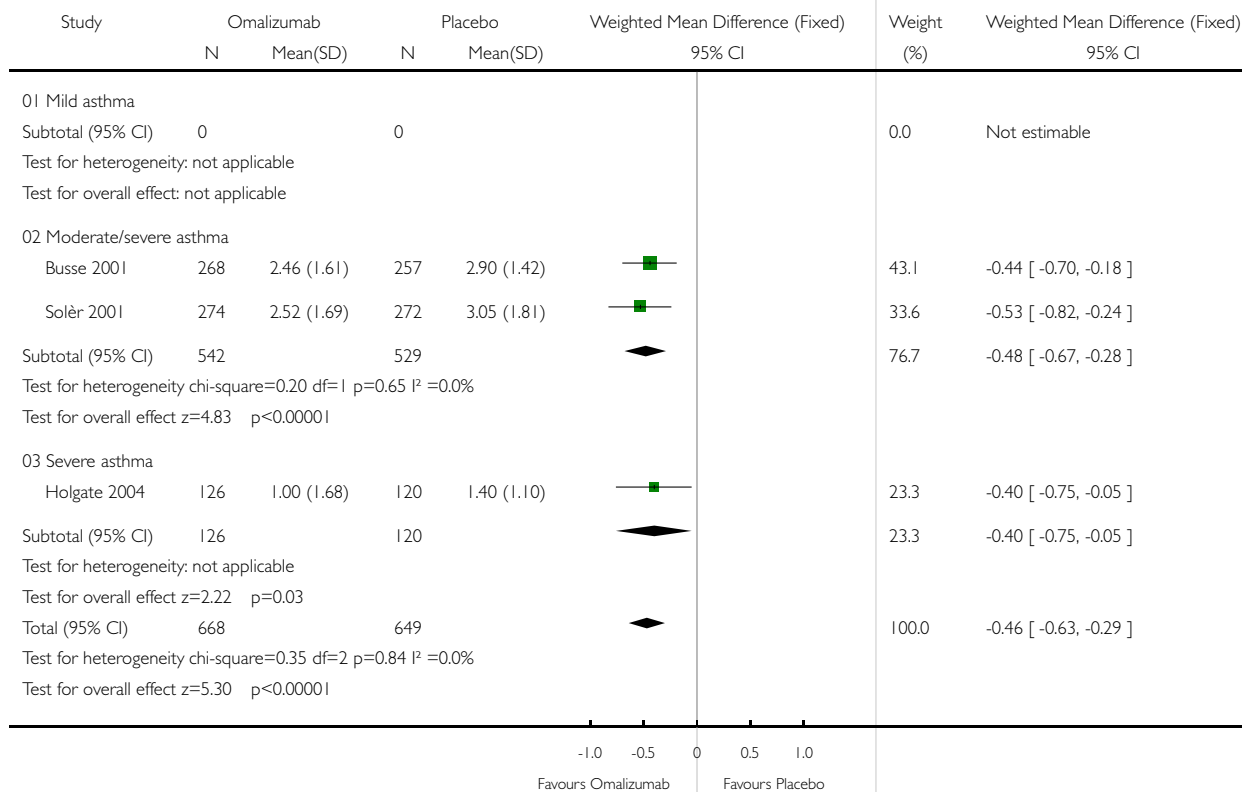


Analysis 01.12. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 12 Symptom scores

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 12 Symptom scores

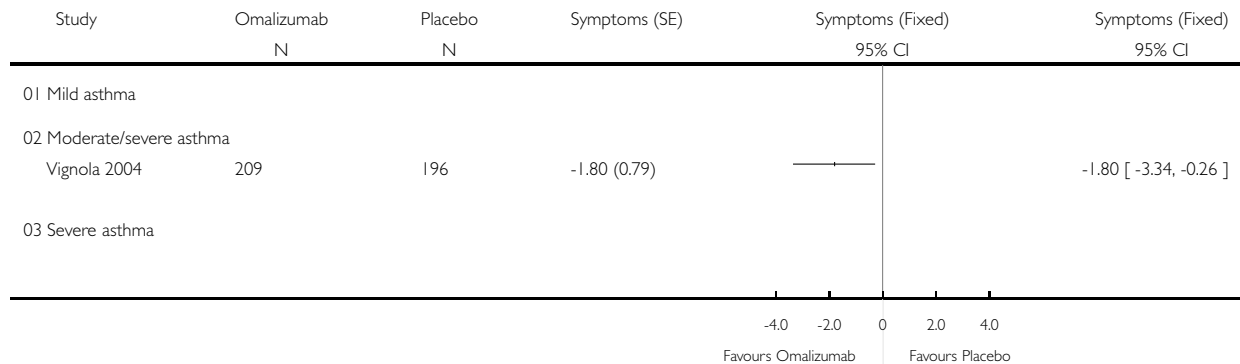


Analysis 01.13. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 13 Mean change in Wasserfallen asthma score

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 13 Mean change in Wasserfallen asthma score

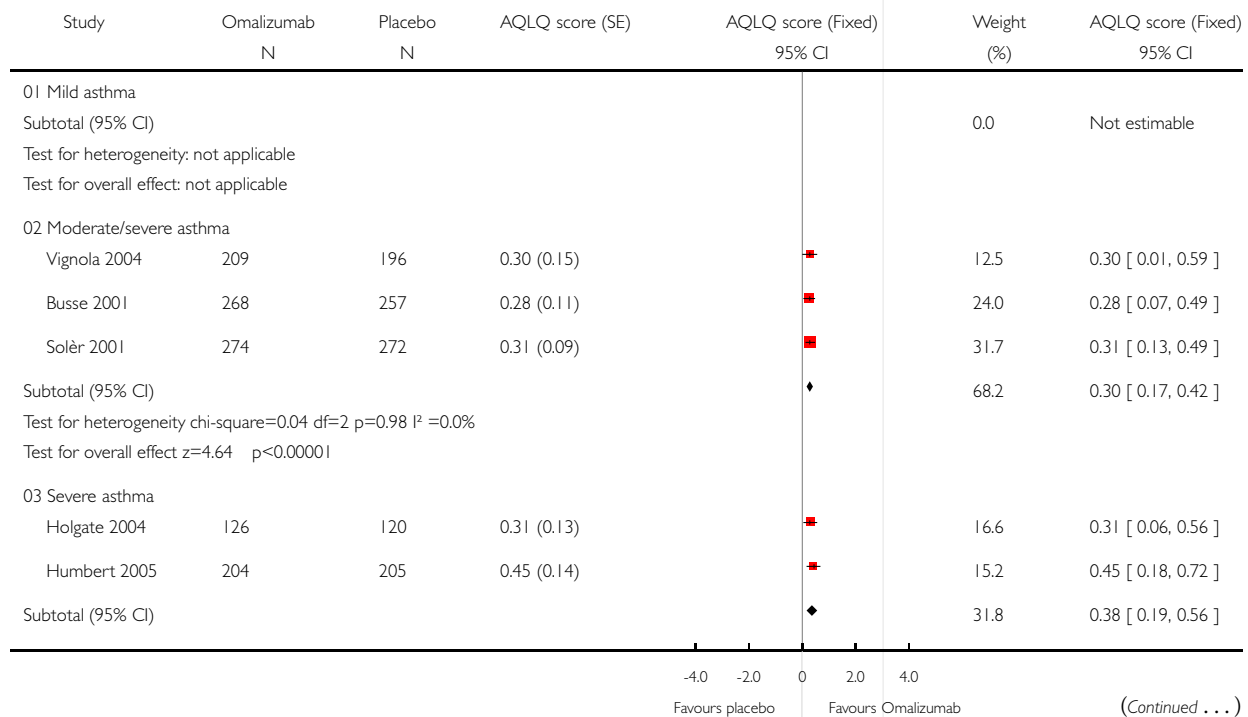


Analysis 01.14. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 14 Mean change in AQLQ scores

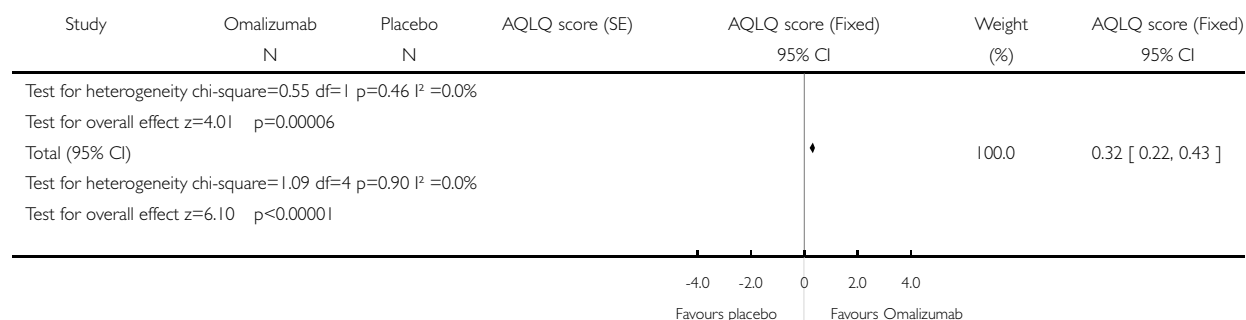
Review: Anti-IgE for chronic asthma in adults and children

Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 14 Mean change in AQLQ scores



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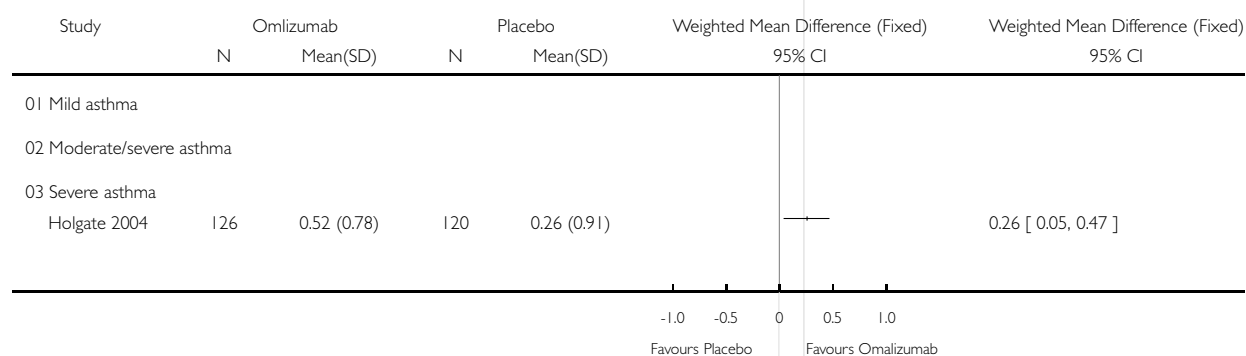


Analysis 01.15. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 15 Quality of life - change from baseline in AQLQ scores

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 15 Quality of life - change from baseline in AQLQ scores

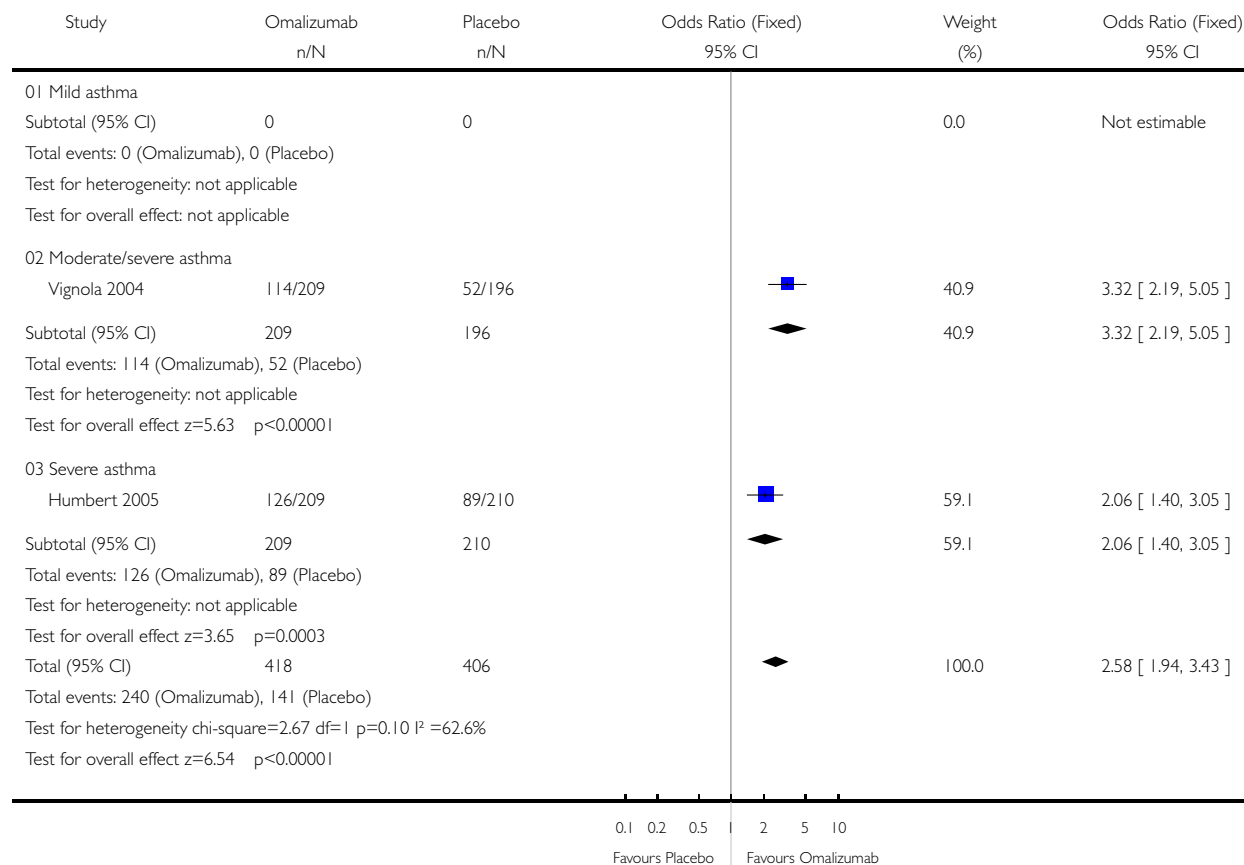


Analysis 01.16. Comparison 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 16 Global evaluation rated good to excellent

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 01 Subcutaneous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 16 Global evaluation rated good to excellent

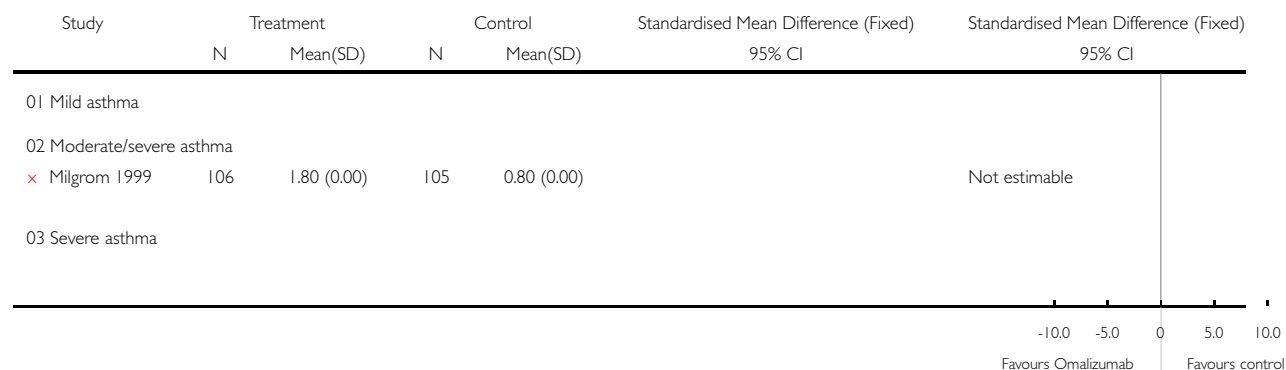


Analysis 02.01. Comparison 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 01 Rescue medication usage

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 01 Rescue medication usage

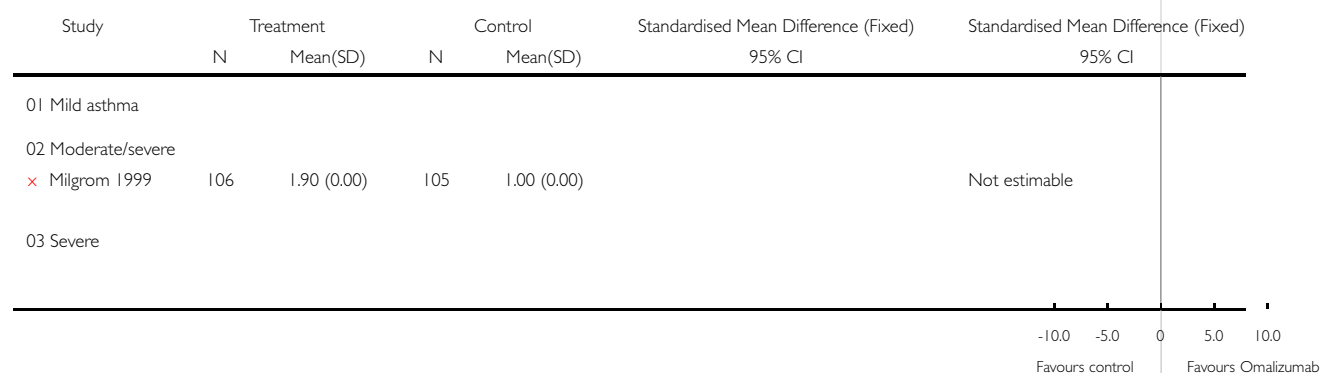


Analysis 02.02. Comparison 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 02 FEV1

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 02 FEV1

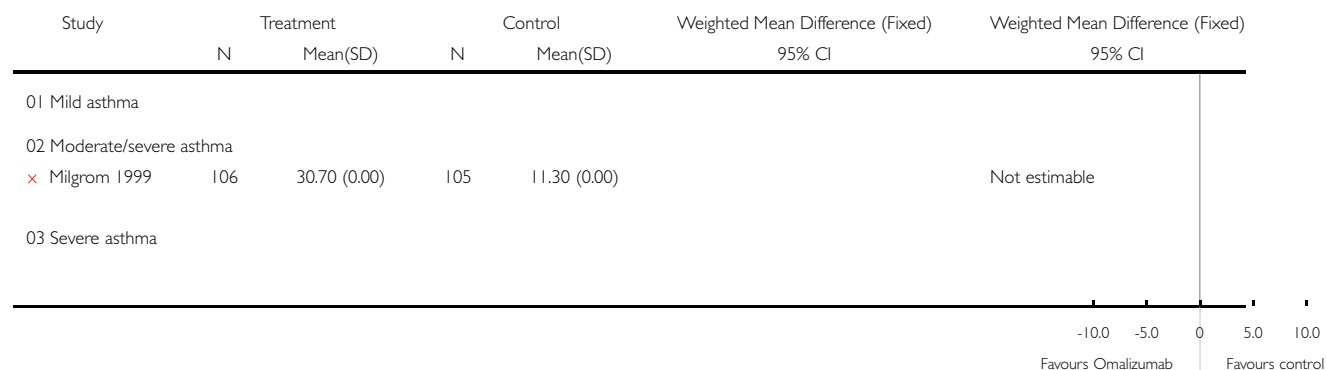


Analysis 02.03. Comparison 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 03 Morning PEF

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 03 Morning PEF

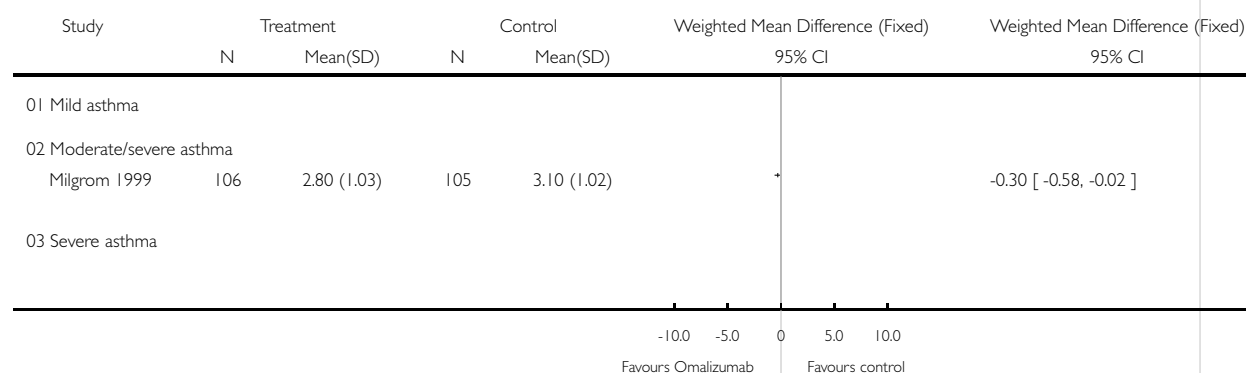


Analysis 02.04. Comparison 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 04 Symptom scores

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 04 Symptom scores

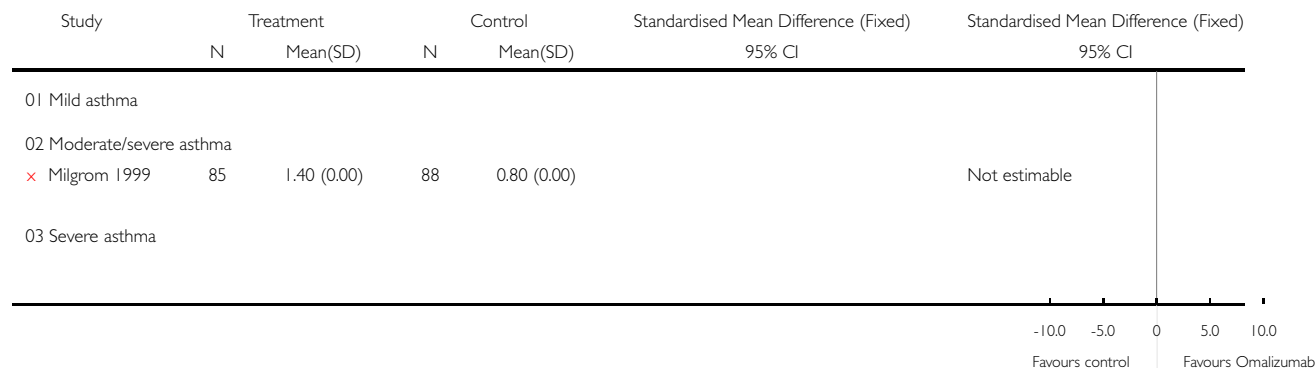


Analysis 02.05. Comparison 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 05 Quality of life

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 05 Quality of life

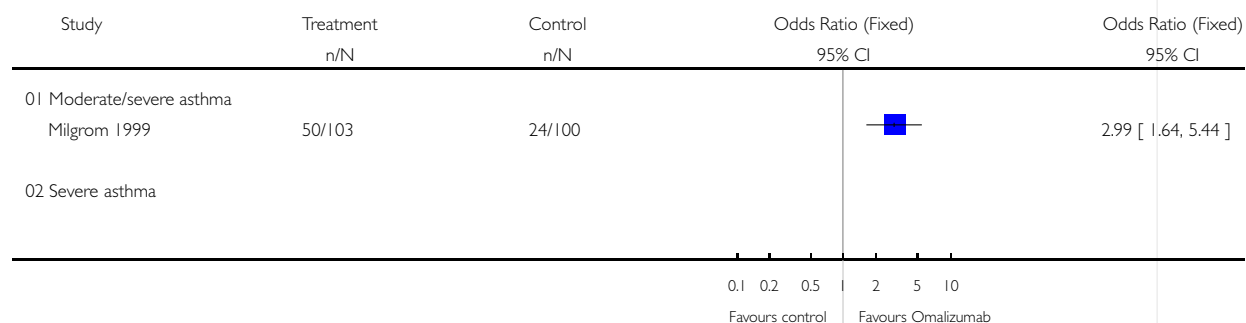


Analysis 02.06. Comparison 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 06 Number of participants with >50% reduction in symptom score

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 02 High dose intravenous Omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 06 Number of participants with >50% reduction in symptom score

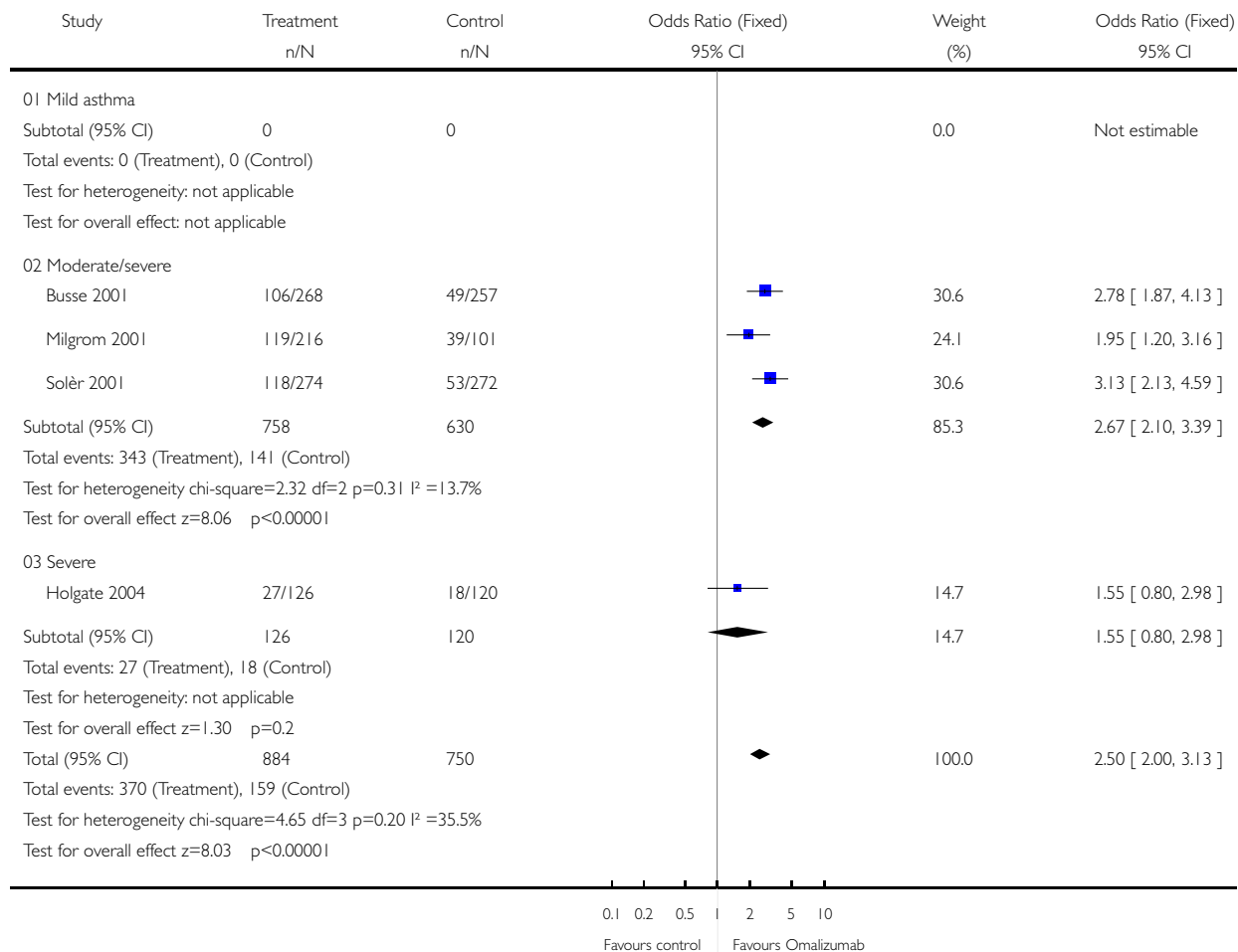


Analysis 03.01. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 01 Number of patients achieving complete inhaled steroid withdrawal

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 01 Number of patients achieving complete inhaled steroid withdrawal

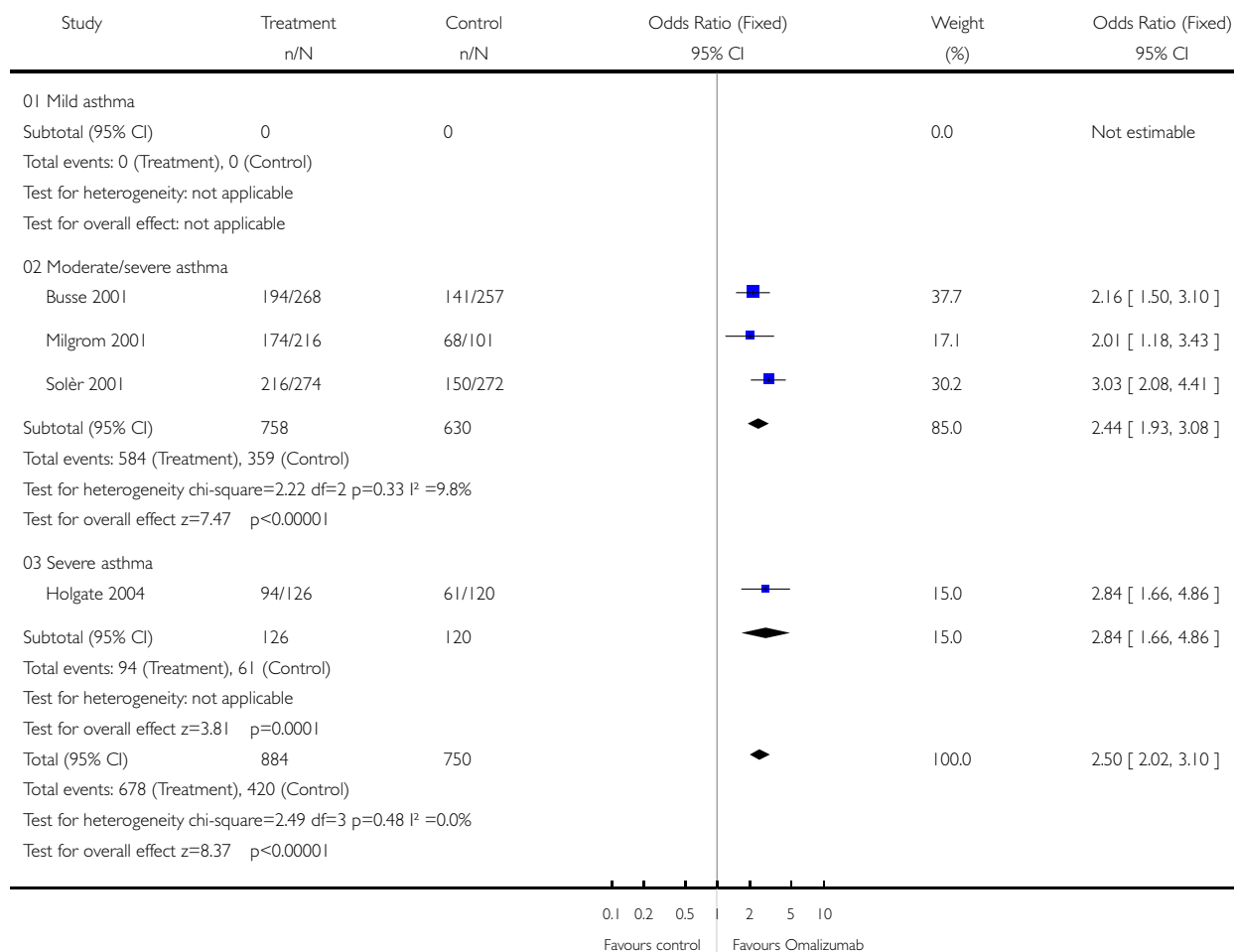


Analysis 03.02. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 02 >50% reduction in inhaled steroid usage

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 02 >50% reduction in inhaled steroid usage

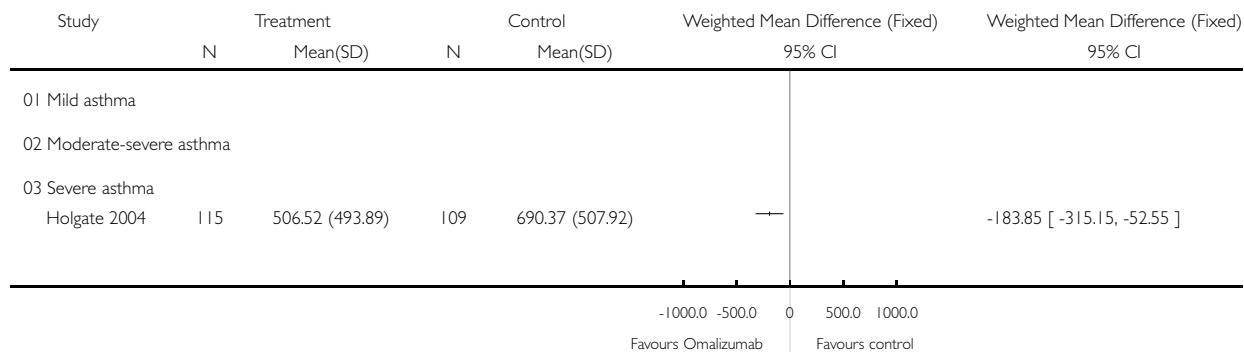


Analysis 03.03. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 03 Mean steroid dose at end of reduction phase

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 03 Mean steroid dose at end of reduction phase

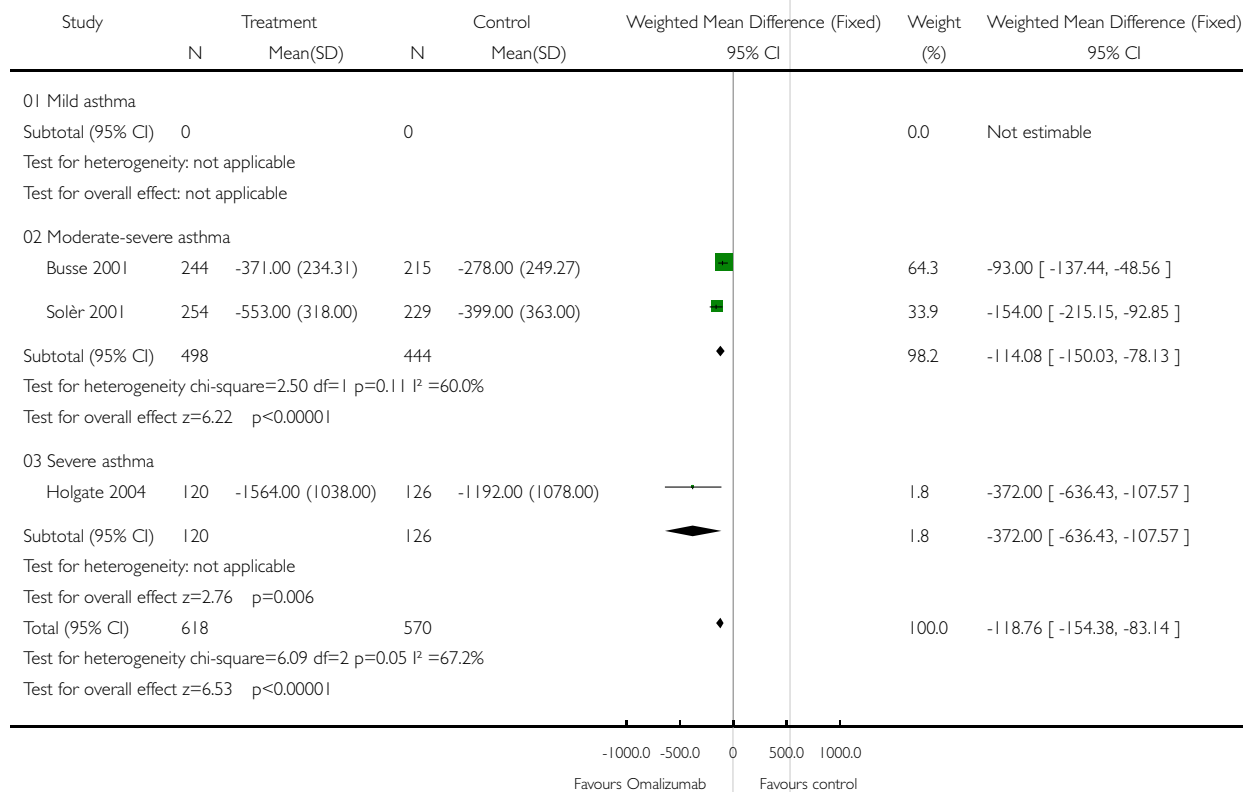


Analysis 03.04. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 04 Mean change in steroid consumption (BDP equivalent)

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 04 Mean change in steroid consumption (BDP equivalent)

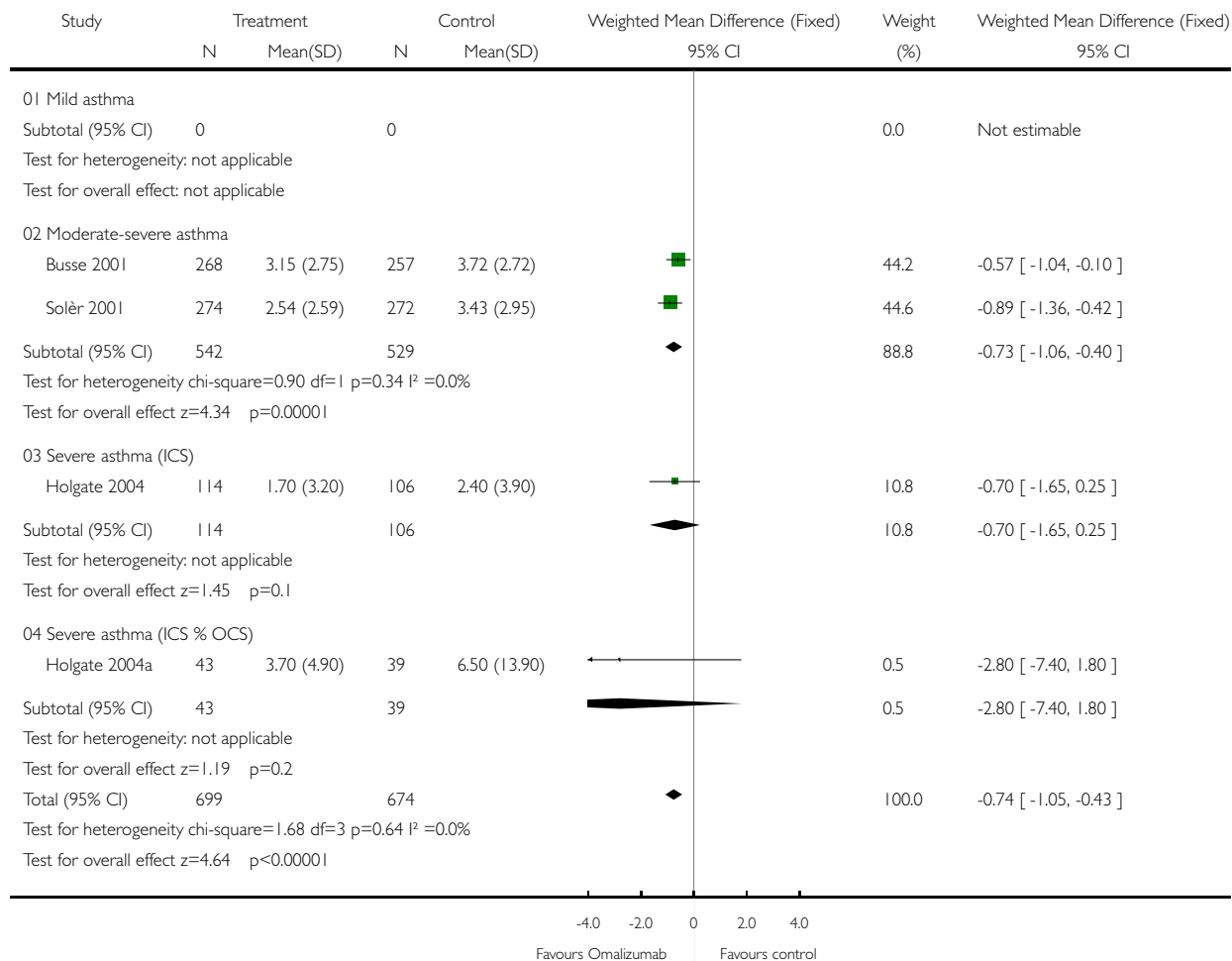


Analysis 03.05. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 05 Rescue medication (puffs per day)

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 05 Rescue medication (puffs per day)

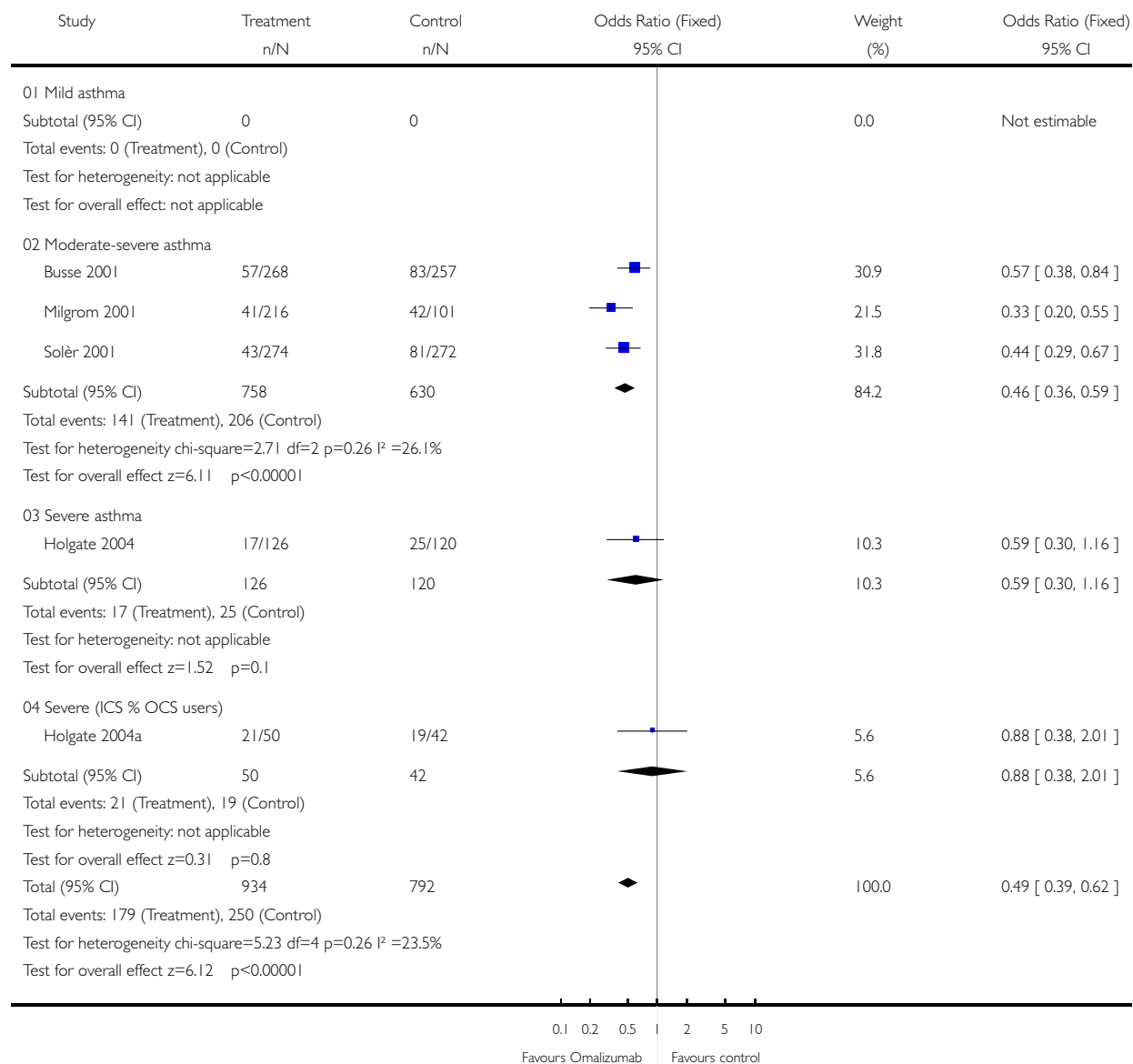


Analysis 03.06. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 06 Number of participants with exacerbation

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 06 Number of participants with exacerbation

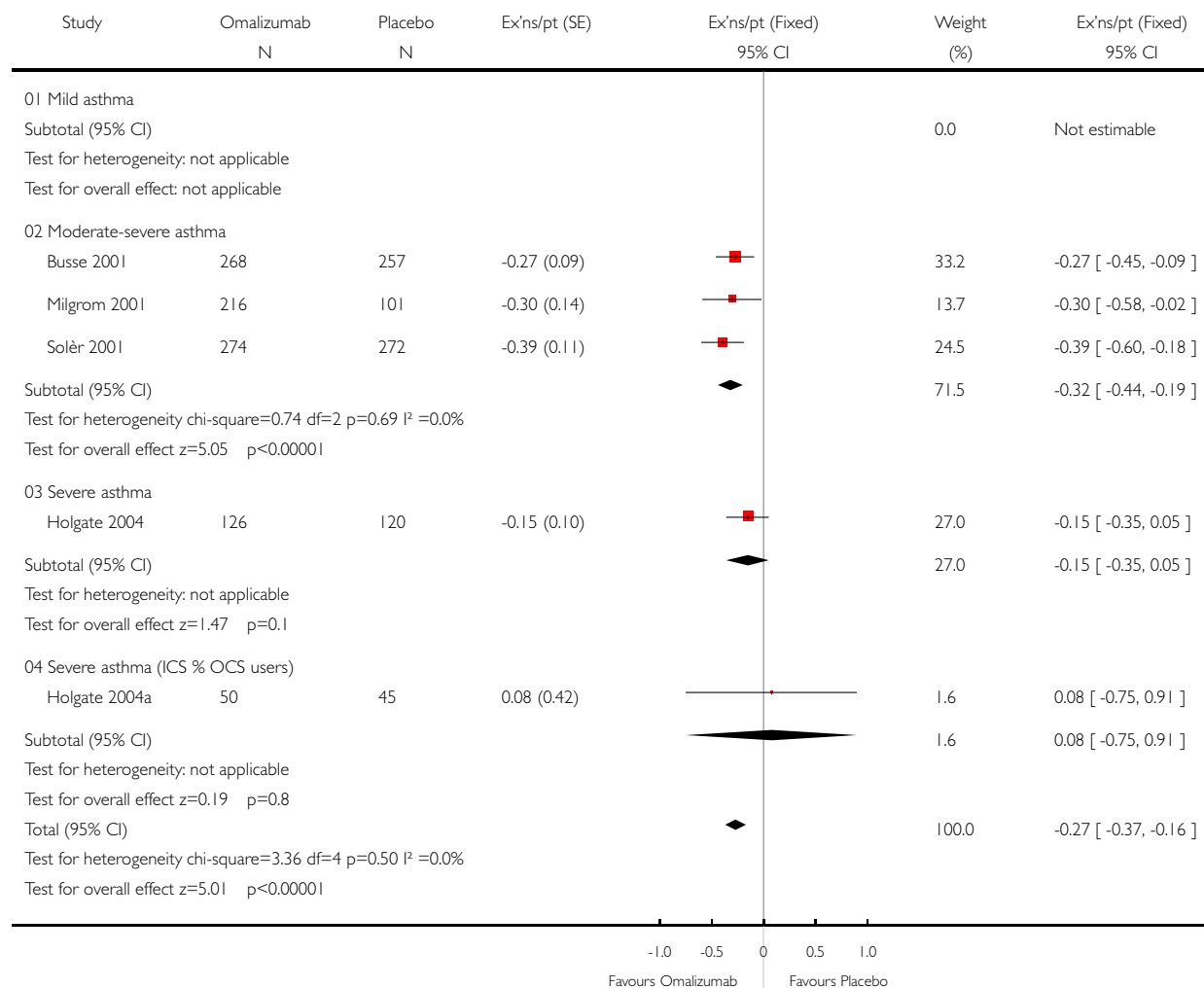


Analysis 03.07. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 07 Asthma exacerbations per participant

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 07 Asthma exacerbations per participant

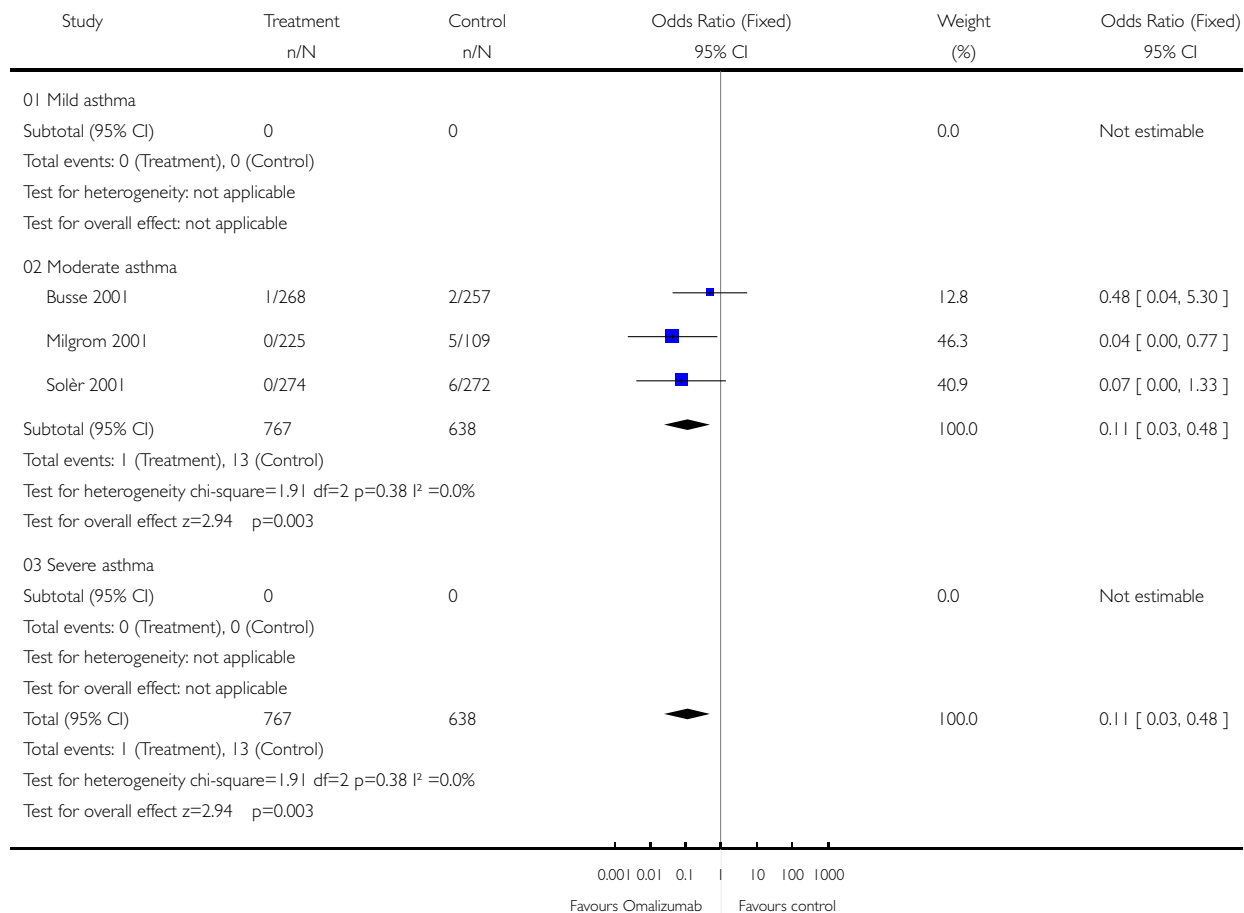


Analysis 03.08. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 08 Exacerbations requiring hospitalisation

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 08 Exacerbations requiring hospitalisation

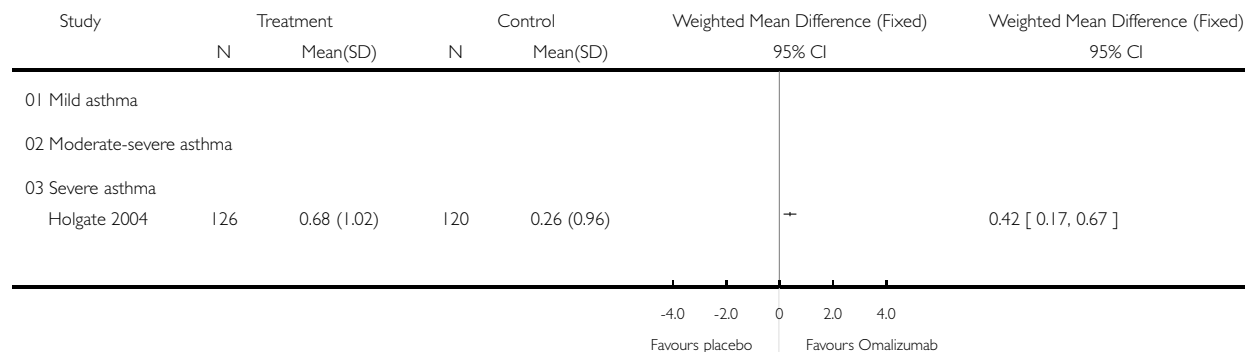


Analysis 03.09. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 09 Quality of Life - change from baseline

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 09 Quality of Life - change from baseline

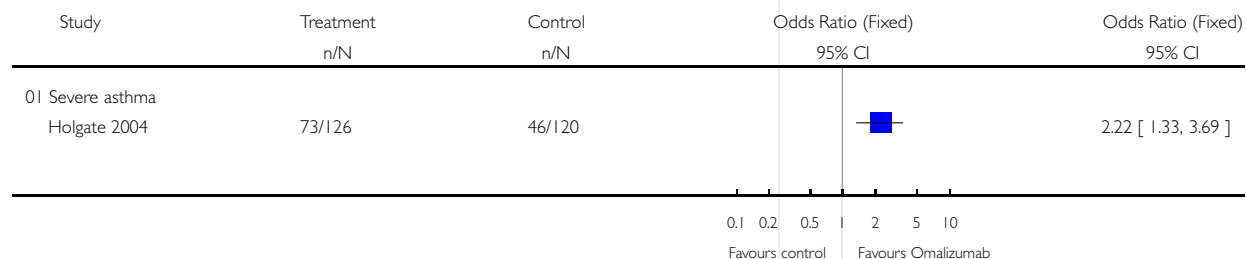


Analysis 03.10. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 10 Numbers of participants achieving clinically relevant improvement in Quality of Life (>0.5)

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 10 Numbers of participants achieving clinically relevant improvement in Quality of Life (>0.5)

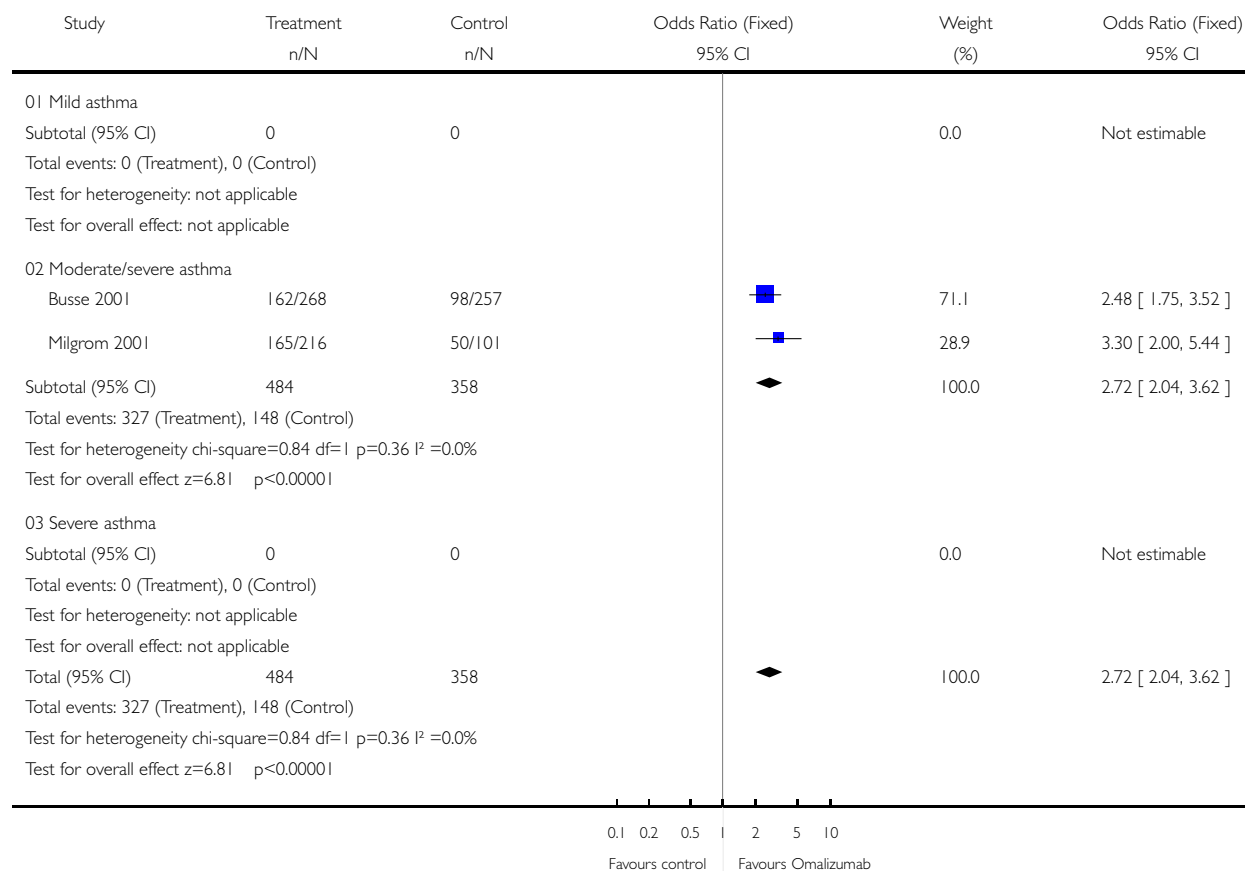


Analysis 03.11. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 11 Global evaluation rated good to excellent

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 11 Global evaluation rated good to excellent

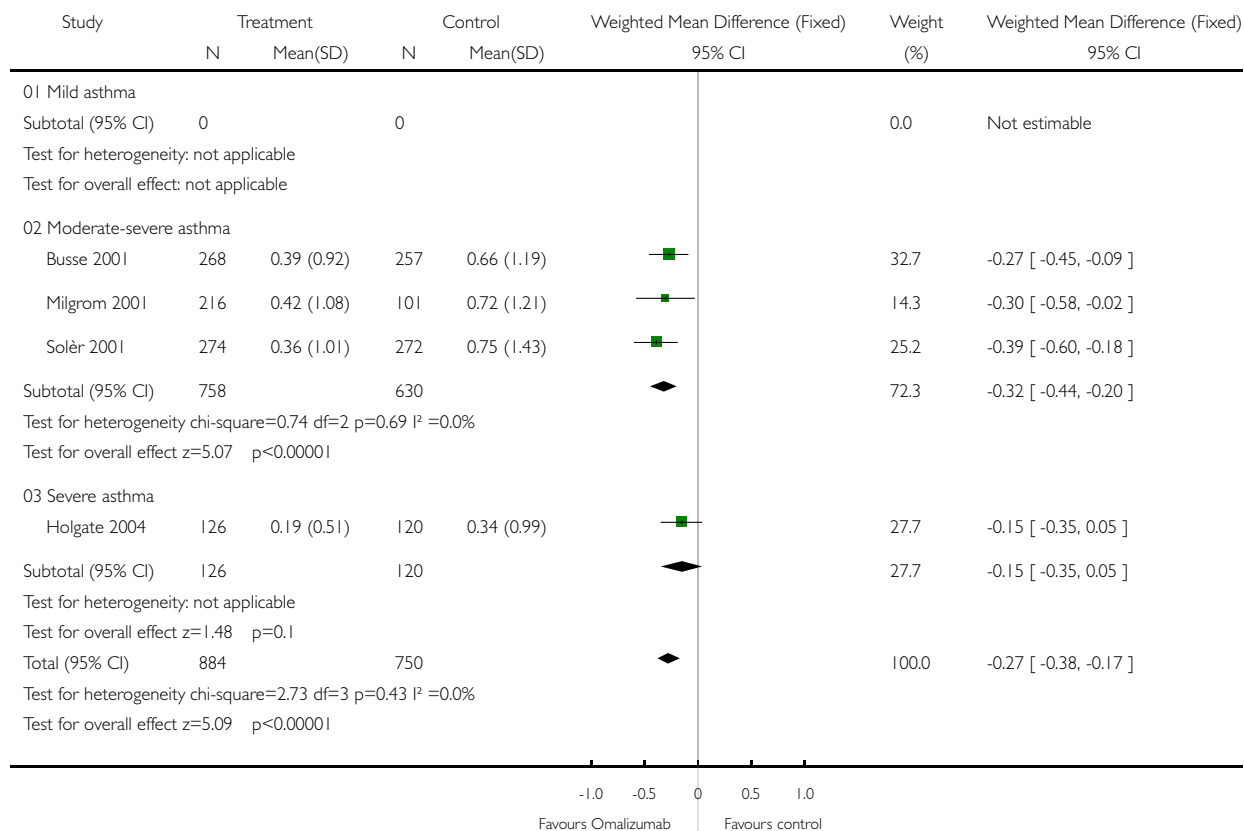


Analysis 03.13. Comparison 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 13 Asthma exacerbations per participant

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 03 Subcutaneous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 13 Asthma exacerbations per participant

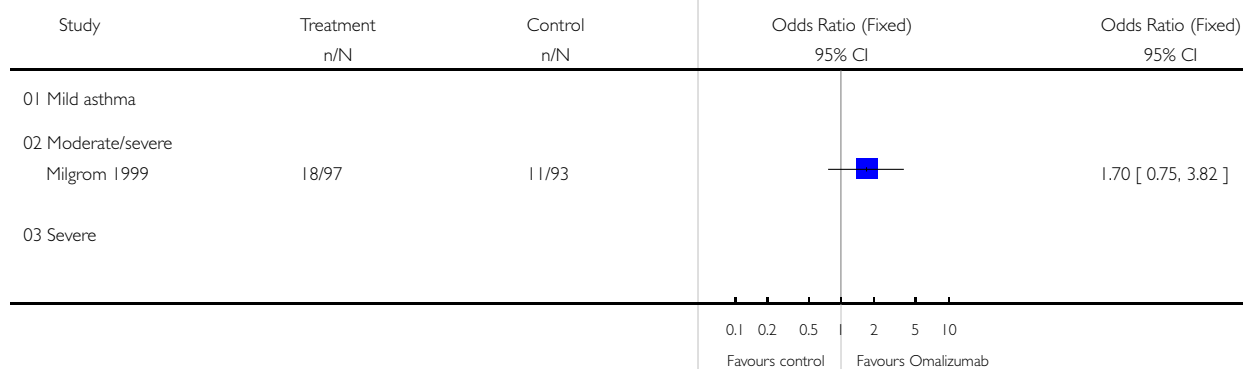


Analysis 04.01. Comparison 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 01 Number of patients achieving complete inhaled steroid withdrawal

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 01 Number of patients achieving complete inhaled steroid withdrawal

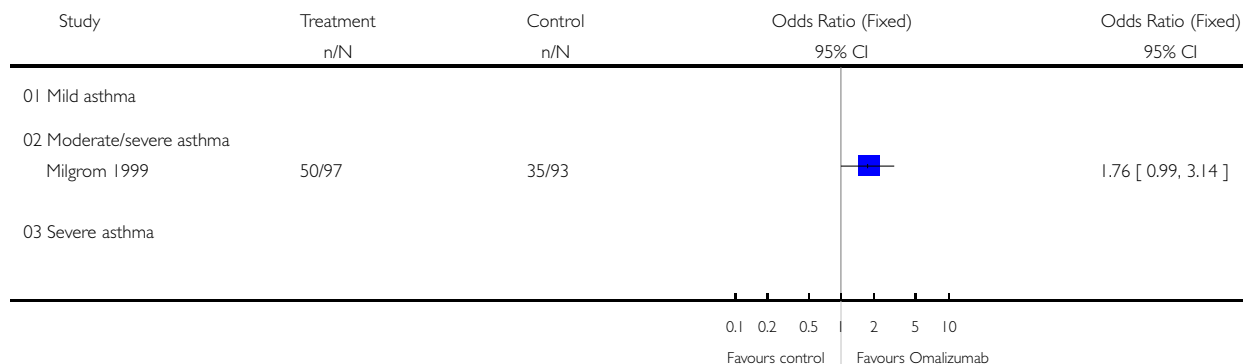


Analysis 04.02. Comparison 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 02 >50% reduction in inhaled steroid usage

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 02 >50% reduction in inhaled steroid usage

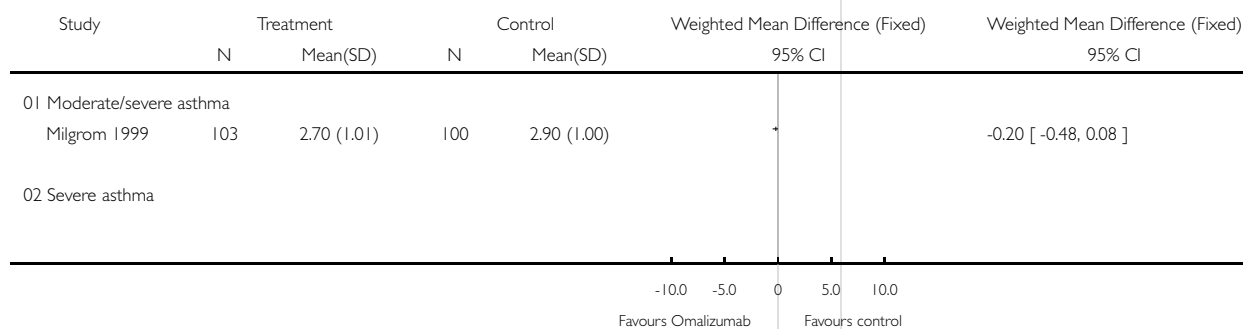


Analysis 04.03. Comparison 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 03 Symptom score

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 03 Symptom score

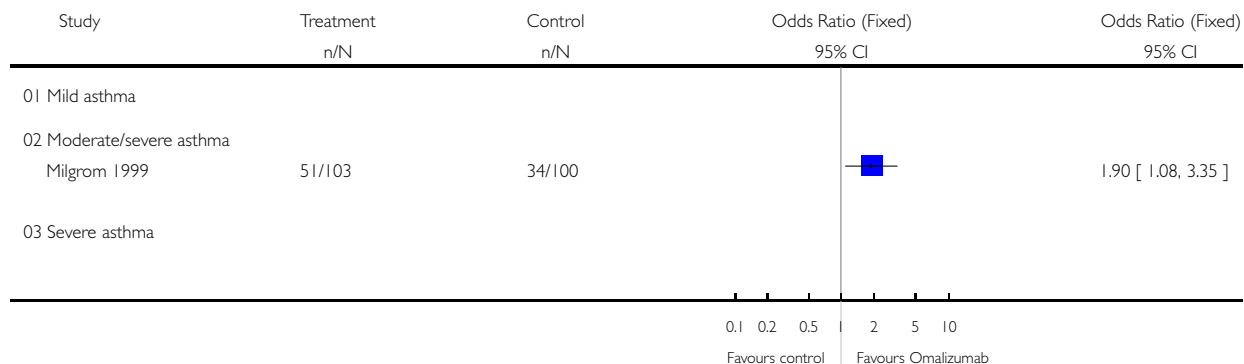


Analysis 04.04. Comparison 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 04 Number of patients with >50% reduction in symptom scores

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 04 Number of patients with >50% reduction in symptom scores

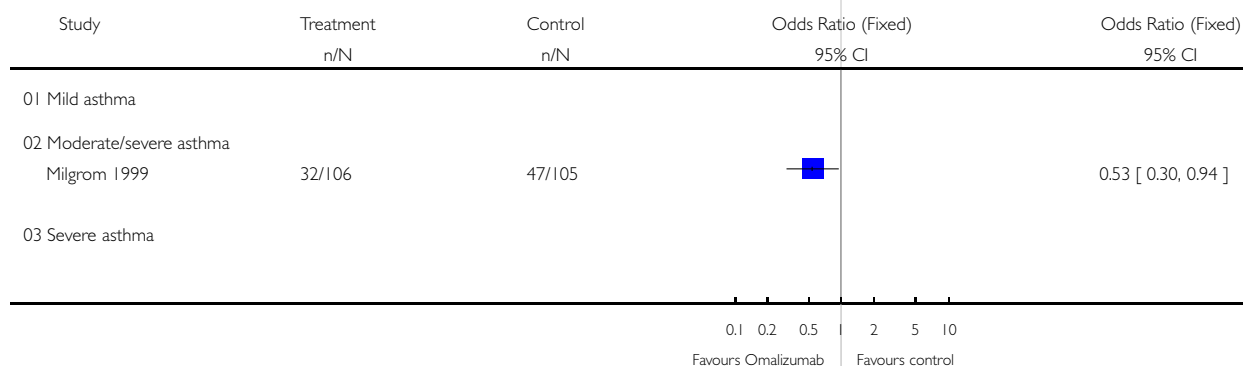


Analysis 04.05. Comparison 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction), Outcome 05 Number of participants with exacerbations

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 04 High dose intravenous Omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 05 Number of participants with exacerbations

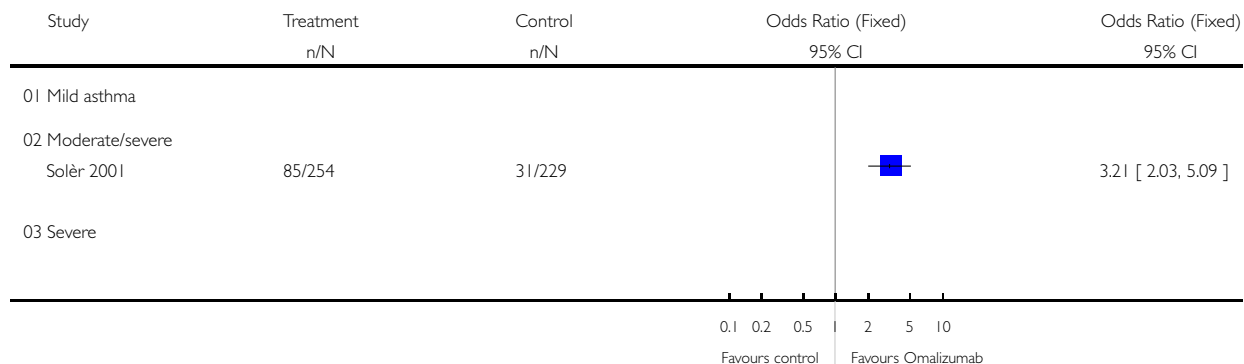


Analysis 05.01. Comparison 05 Subcutaneous Omalizumab + steroid versus placebo + steroid (trial extension), Outcome 01 Number of patients achieving complete inhaled steroid withdrawal

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 05 Subcutaneous Omalizumab + steroid versus placebo + steroid (trial extension)

Outcome: 01 Number of patients achieving complete inhaled steroid withdrawal

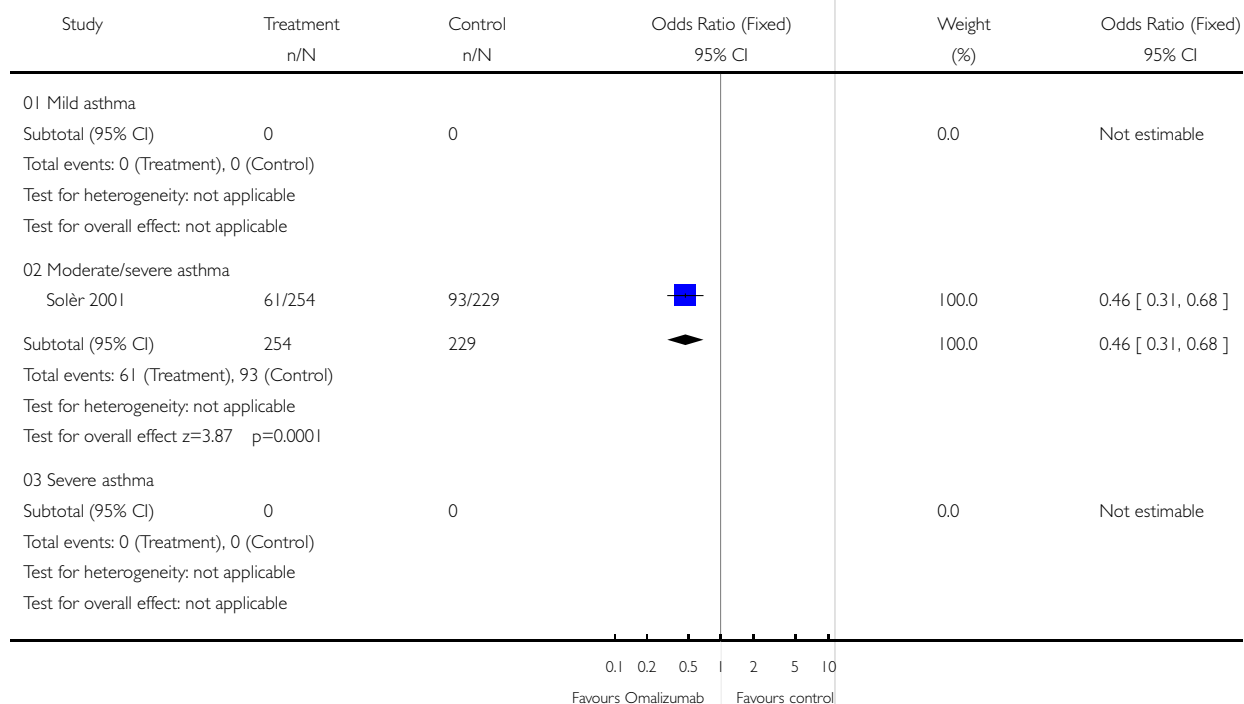


Analysis 05.02. Comparison 05 Subcutaneous Omalizumab + steroid versus placebo + steroid (trial extension), Outcome 02 Participants with one or more exacerbation

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 05 Subcutaneous Omalizumab + steroid versus placebo + steroid (trial extension)

Outcome: 02 Participants with one or more exacerbation

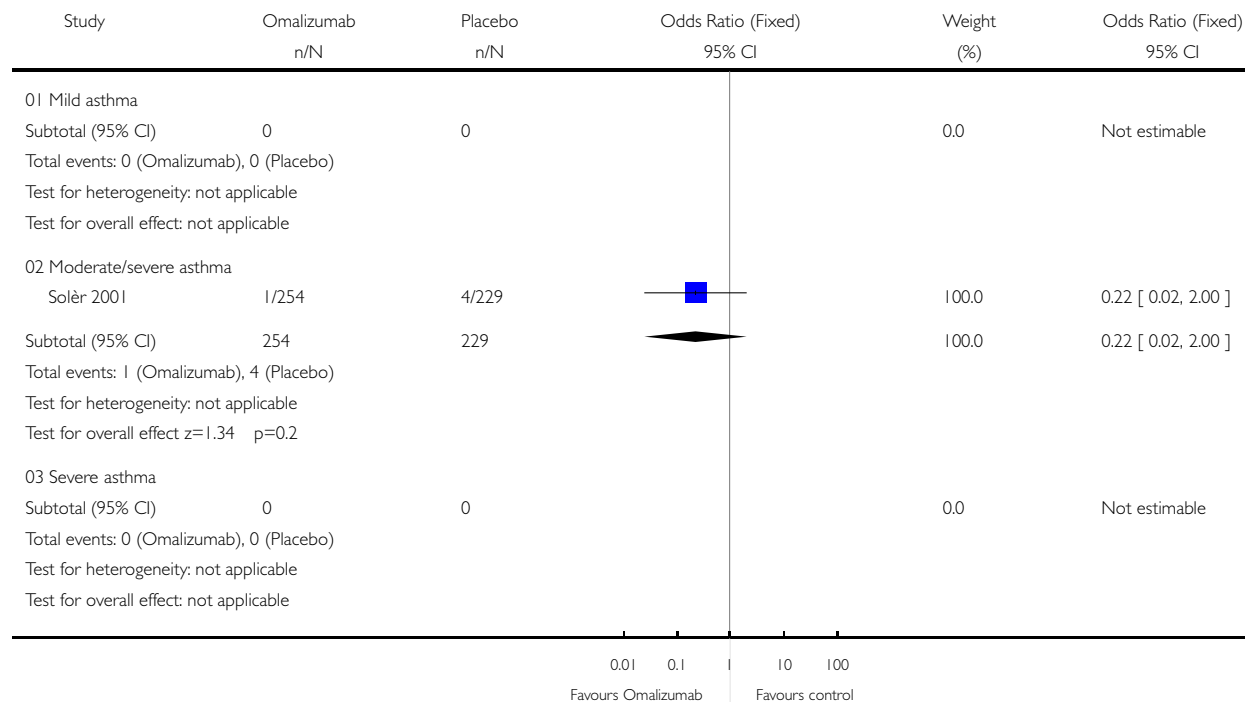


Analysis 05.03. Comparison 05 Subcutaneous Omalizumab + steroid versus placebo + steroid (trial extension), Outcome 03 Hospitalisations

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 05 Subcutaneous Omalizumab + steroid versus placebo + steroid (trial extension)

Outcome: 03 Hospitalisations

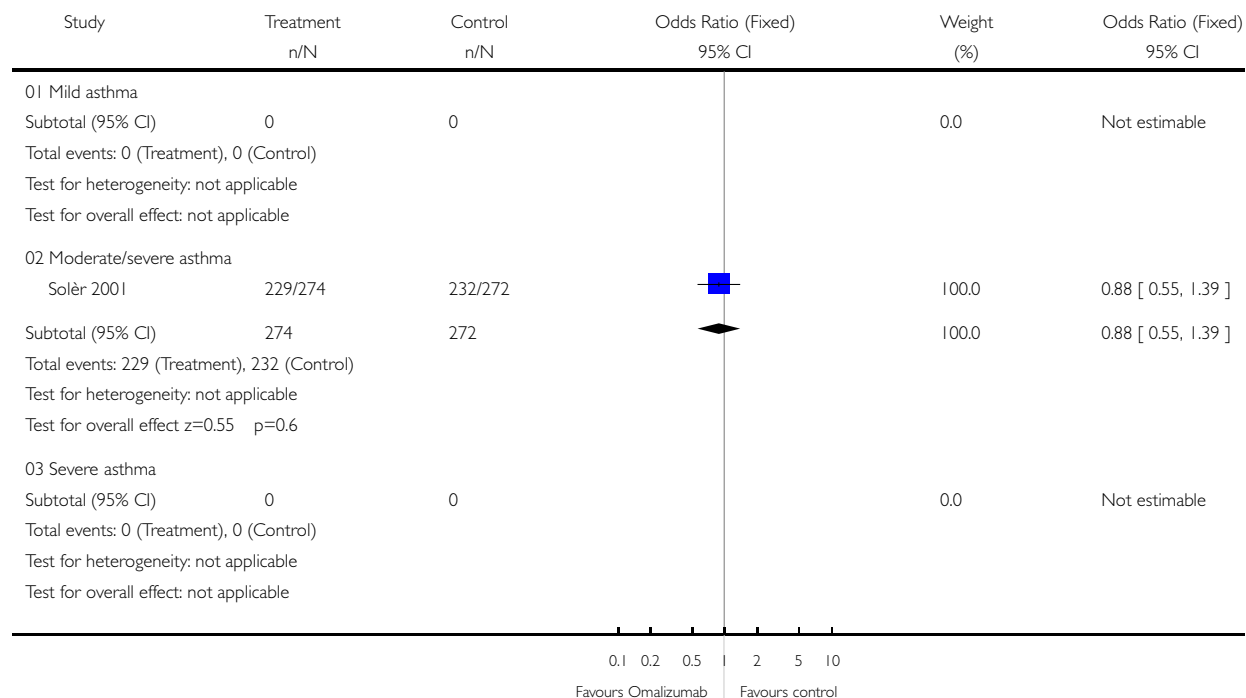


Analysis 05.04. Comparison 05 Subcutaneous Omalizumab + steroid versus placebo + steroid (trial extension), Outcome 04 Number of participants with any adverse event

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 05 Subcutaneous Omalizumab + steroid versus placebo + steroid (trial extension)

Outcome: 04 Number of participants with any adverse event

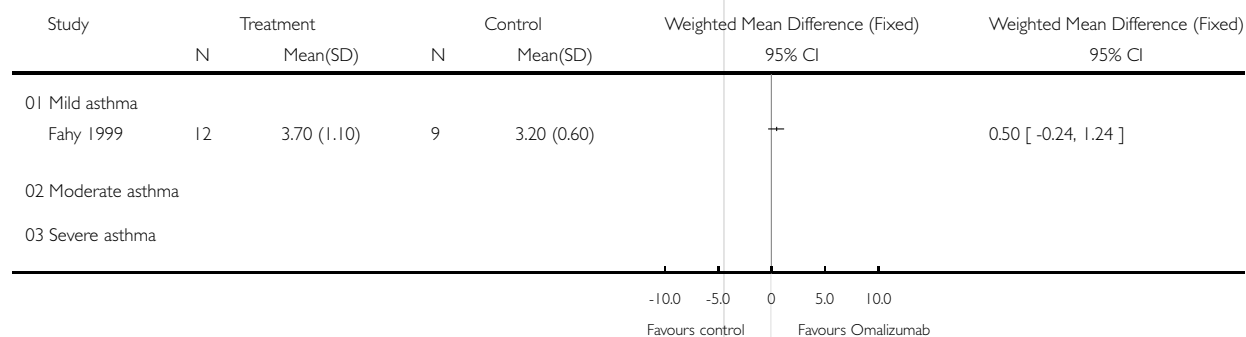


Analysis 06.01. Comparison 06 Low dose aerosolized Omalizumab versus placebo, Outcome 01 FEV1 (litres)

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 06 Low dose aerosolized Omalizumab versus placebo

Outcome: 01 FEV1 (litres)

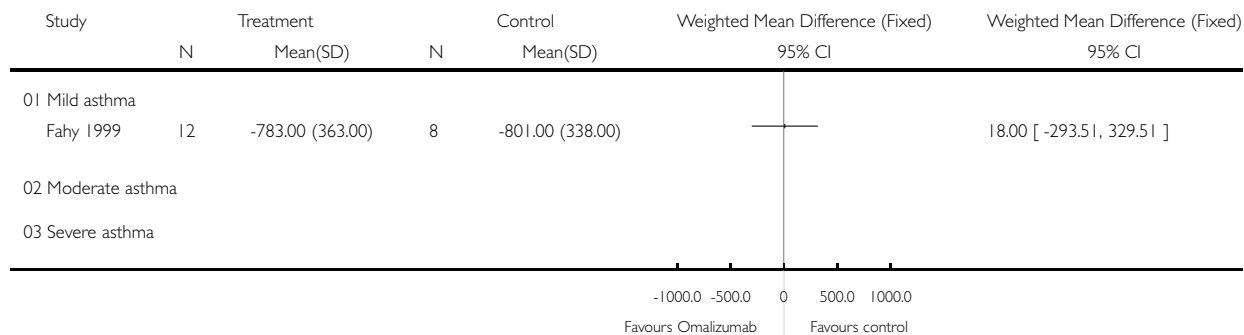


Analysis 06.02. Comparison 06 Low dose aerosolized Omalizumab versus placebo, Outcome 02 Area under curve for fall in FEV1 (% x minutes) - early response (0-1 hours)

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 06 Low dose aerosolized Omalizumab versus placebo

Outcome: 02 Area under curve for fall in FEV1 (% x minutes) - early response (0-1 hours)

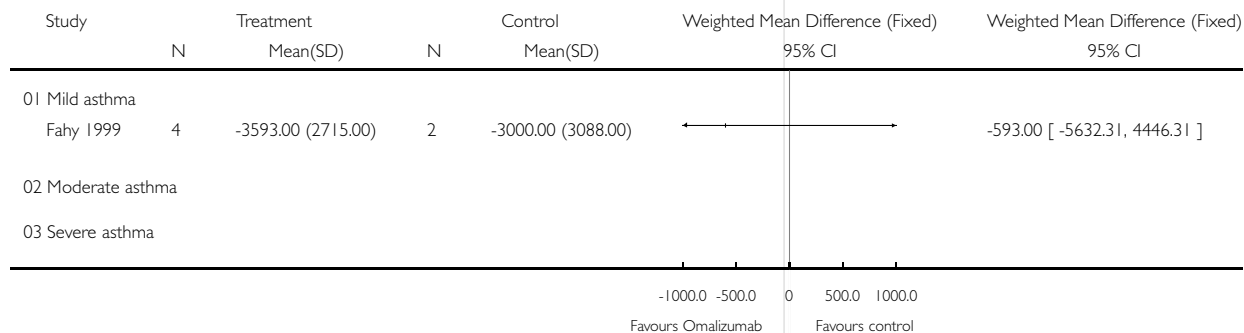


Analysis 06.03. Comparison 06 Low dose aerosolized Omalizumab versus placebo, Outcome 03 Area under curve for fall in FEV1 (% x minutes) - late response (3-7 hours)

Review: Anti-IgE for chronic asthma in adults and children

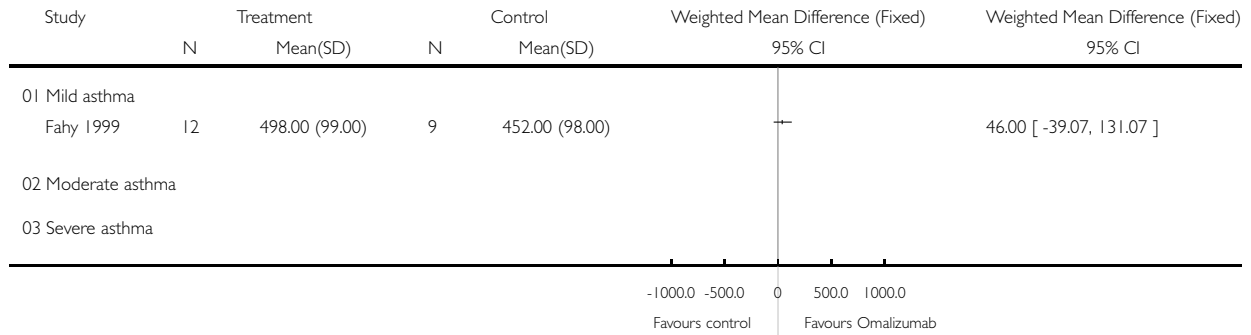
Comparison: 06 Low dose aerosolized Omalizumab versus placebo

Outcome: 03 Area under curve for fall in FEV1 (% x minutes) - late response (3-7 hours)



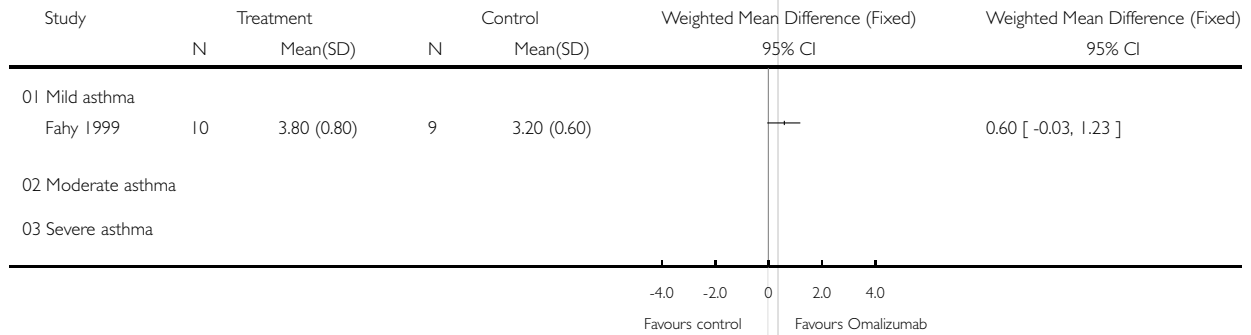
Analysis 06.04. Comparison 06 Low dose aerosolized Omalizumab versus placebo, Outcome 04 Peak Expiratory Flow (am) (L/min)

Review: Anti-IgE for chronic asthma in adults and children
 Comparison: 06 Low dose aerosolized Omalizumab versus placebo
 Outcome: 04 Peak Expiratory Flow (am) (L/min)



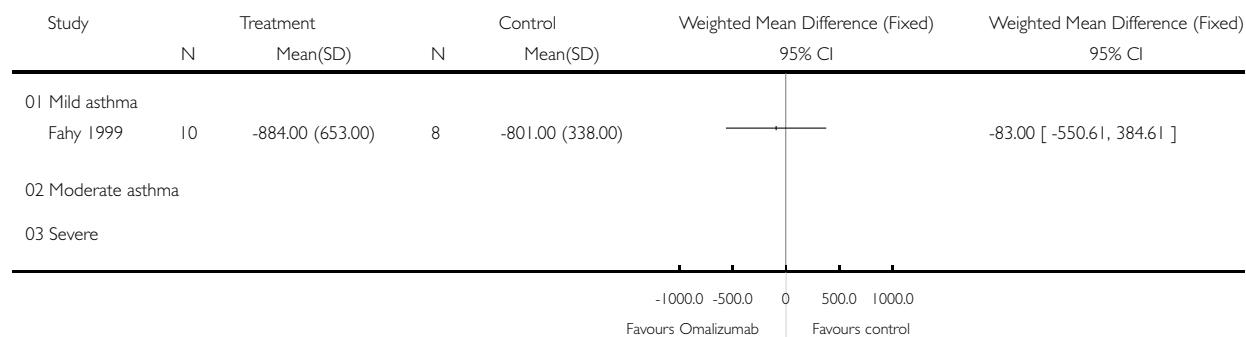
Analysis 07.01. Comparison 07 High dose aerosolized Omalizumab versus placebo, Outcome 01 FEV1 (litres)

Review: Anti-IgE for chronic asthma in adults and children
 Comparison: 07 High dose aerosolized Omalizumab versus placebo
 Outcome: 01 FEV1 (litres)



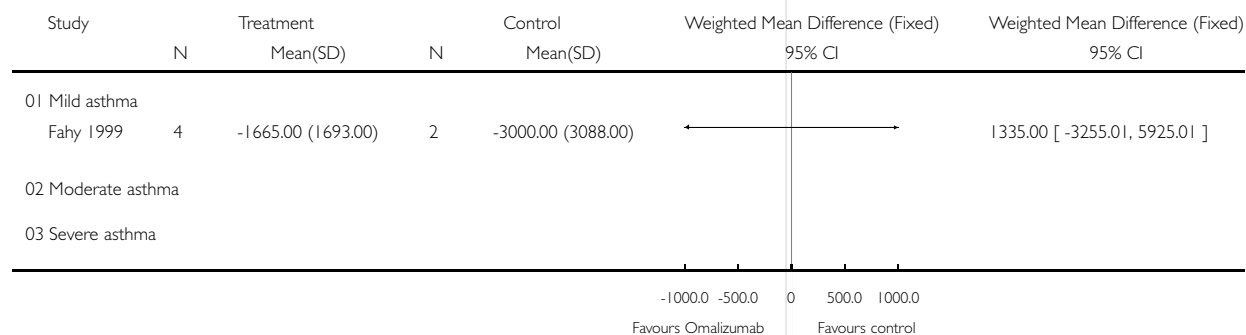
Analysis 07.02. Comparison 07 High dose aerosolized Omalizumab versus placebo, Outcome 02 Area under the curve for % fall in FEV1 (early response - 0-1 hours)

Review: Anti-IgE for chronic asthma in adults and children
 Comparison: 07 High dose aerosolized Omalizumab versus placebo
 Outcome: 02 Area under the curve for % fall in FEV1 (early response - 0-1 hours)



Analysis 07.03. Comparison 07 High dose aerosolized Omalizumab versus placebo, Outcome 03 Area under the curve for % fall in FEV1 (late response - 3-7 hours)

Review: Anti-IgE for chronic asthma in adults and children
 Comparison: 07 High dose aerosolized Omalizumab versus placebo
 Outcome: 03 Area under the curve for % fall in FEV1 (late response - 3-7 hours)

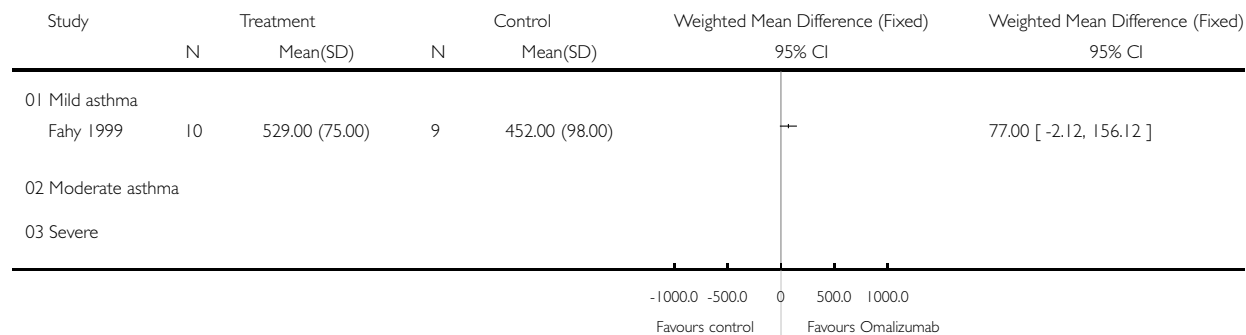


Analysis 07.04. Comparison 07 High dose aerosolized Omalizumab versus placebo, Outcome 04 Peak Expiratory Flow (am) (L/min)

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 07 High dose aerosolized Omalizumab versus placebo

Outcome: 04 Peak Expiratory Flow (am) (L/min)

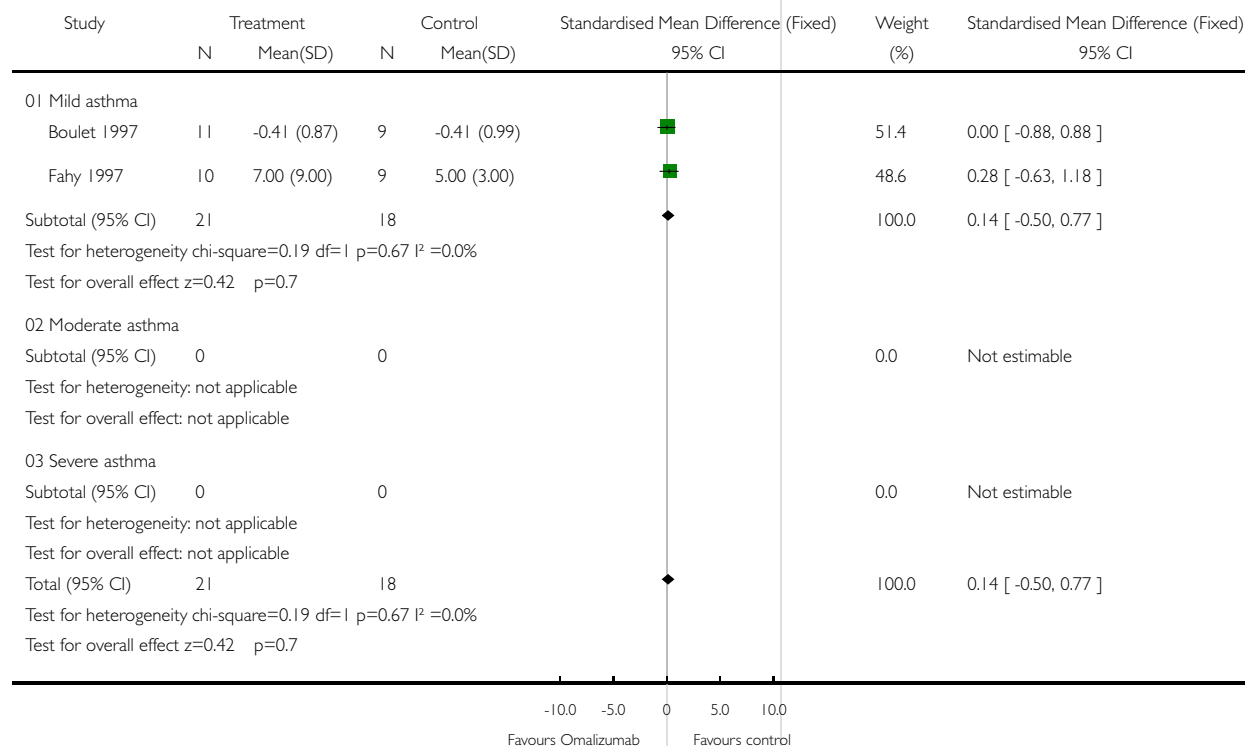


Analysis 08.01. Comparison 08 Intravenous Omalizumab versus placebo, Outcome 01 Rescue medication use (one week after end of treatment)

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 08 Intravenous Omalizumab versus placebo

Outcome: 01 Rescue medication use (one week after end of treatment)

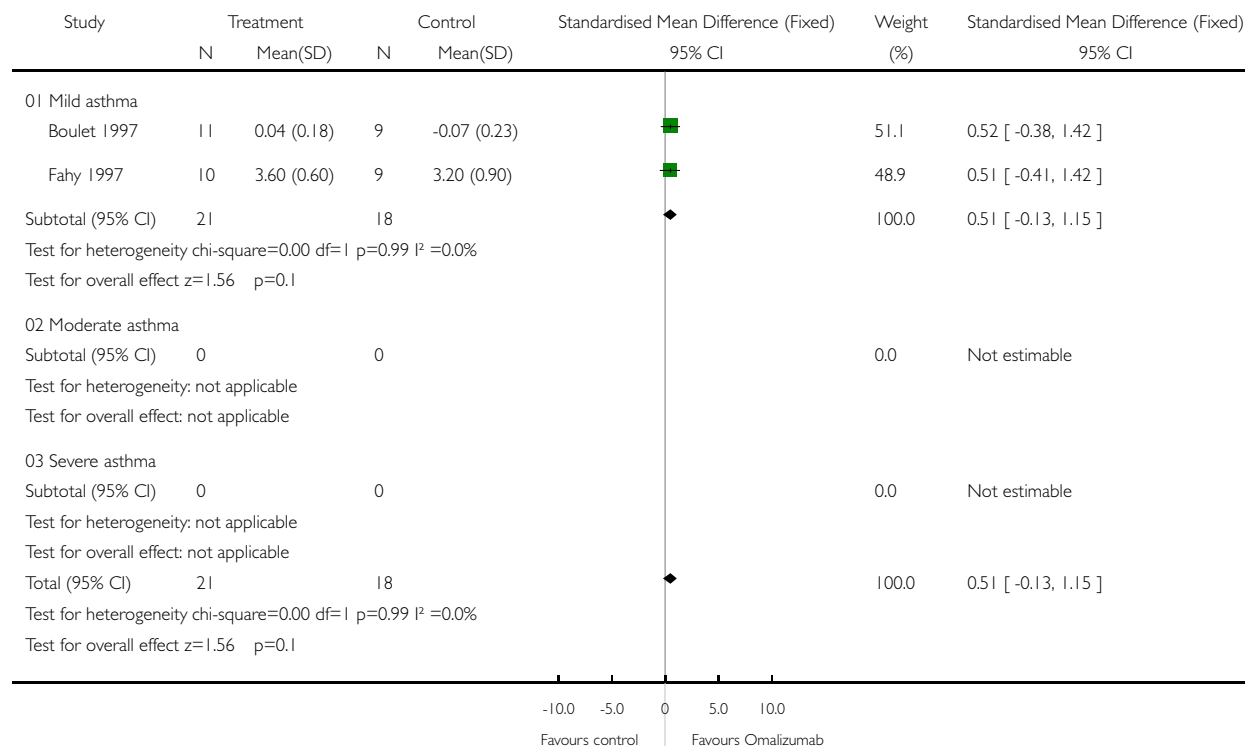


Analysis 08.02. Comparison 08 Intravenous Omalizumab versus placebo, Outcome 02 FEV1 (litres)

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 08 Intravenous Omalizumab versus placebo

Outcome: 02 FEV1 (litres)

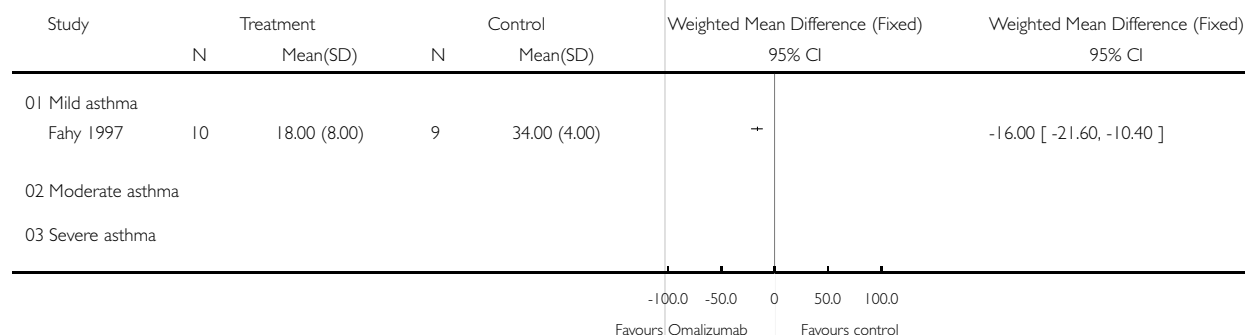


Analysis 08.03. Comparison 08 Intravenous Omalizumab versus placebo, Outcome 03 Fall in FEV1 after allergen challenge (%) (0-1 hours)

Review: Anti-IgE for chronic asthma in adults and children

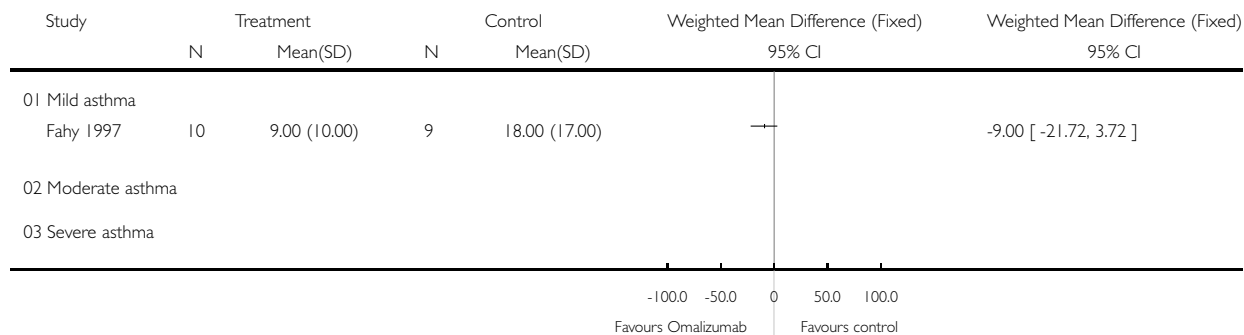
Comparison: 08 Intravenous Omalizumab versus placebo

Outcome: 03 Fall in FEV1 after allergen challenge (%) (0-1 hours)



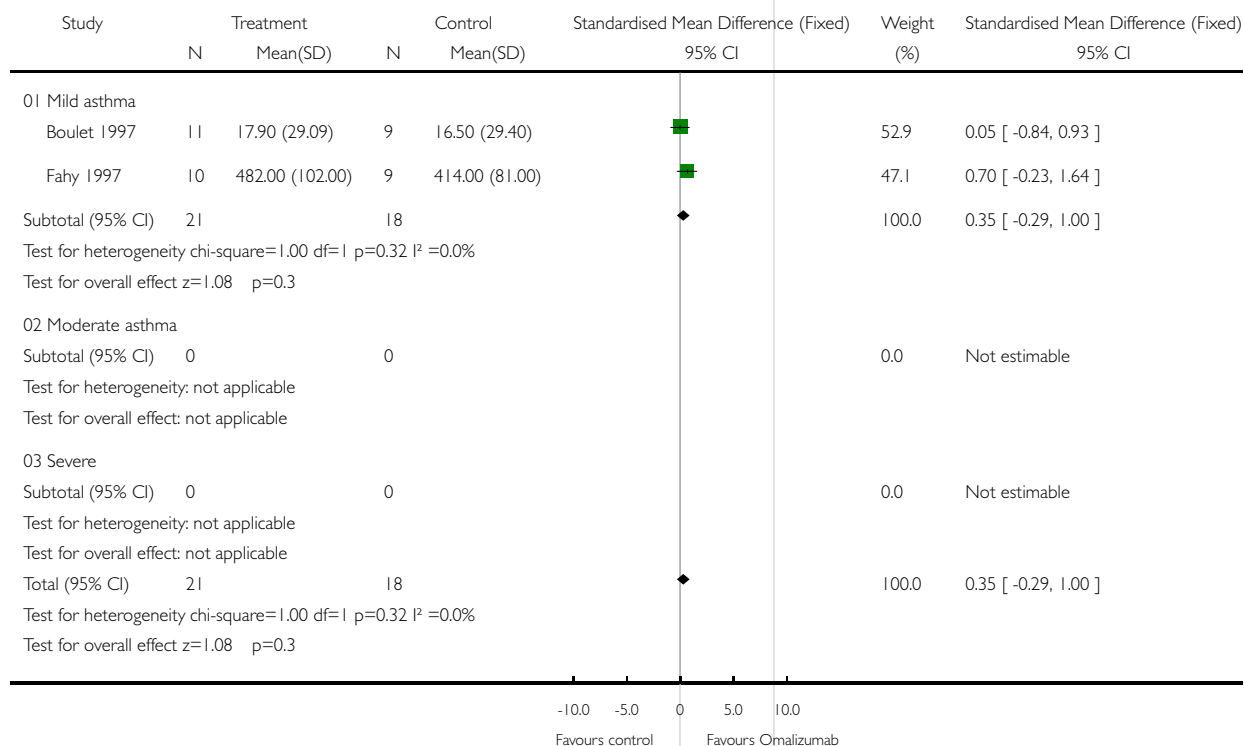
Analysis 08.04. Comparison 08 Intravenous Omalizumab versus placebo, Outcome 04 Fall in FEV1 after allergen challenge (%) (2-7 hours)

Review: Anti-IgE for chronic asthma in adults and children
 Comparison: 08 Intravenous Omalizumab versus placebo
 Outcome: 04 Fall in FEV1 after allergen challenge (%) (2-7 hours)



Analysis 08.05. Comparison 08 Intravenous Omalizumab versus placebo, Outcome 05 Peak expiratory flow (am)

Review: Anti-IgE for chronic asthma in adults and children
 Comparison: 08 Intravenous Omalizumab versus placebo
 Outcome: 05 Peak expiratory flow (am)

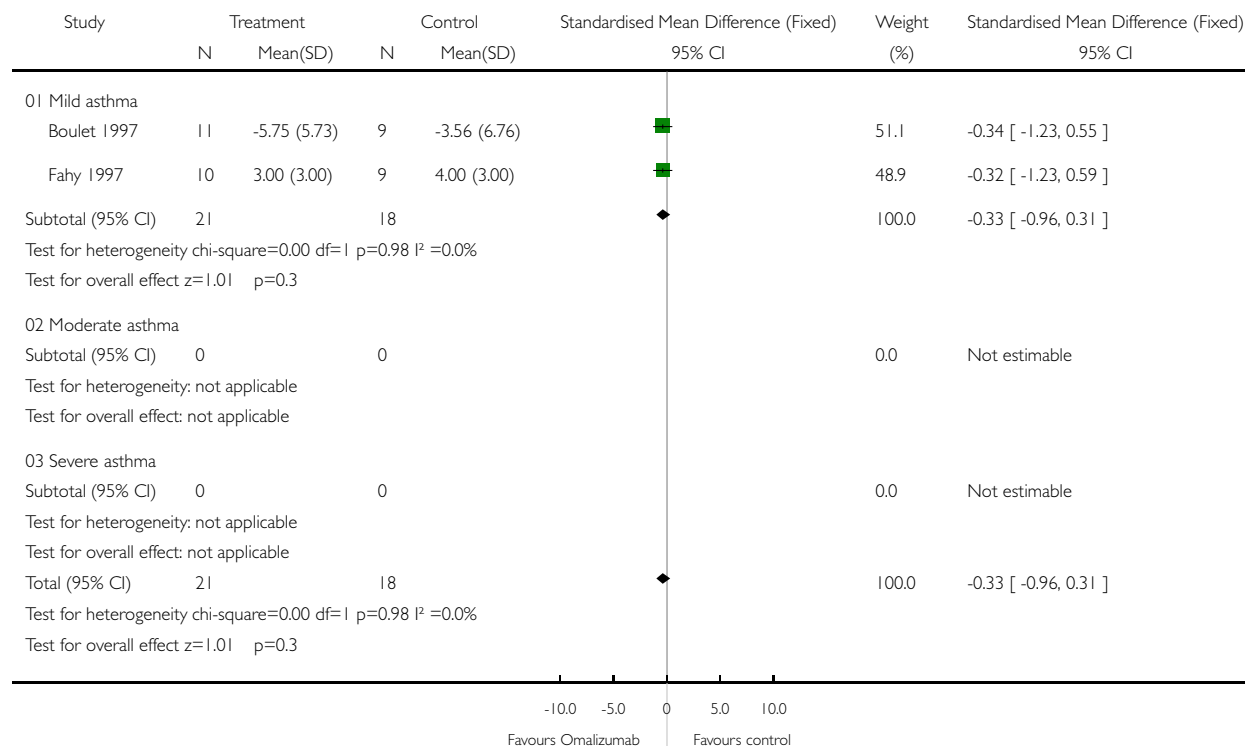


Analysis 08.06. Comparison 08 Intravenous Omalizumab versus placebo, Outcome 06 Symptom scores

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 08 Intravenous Omalizumab versus placebo

Outcome: 06 Symptom scores

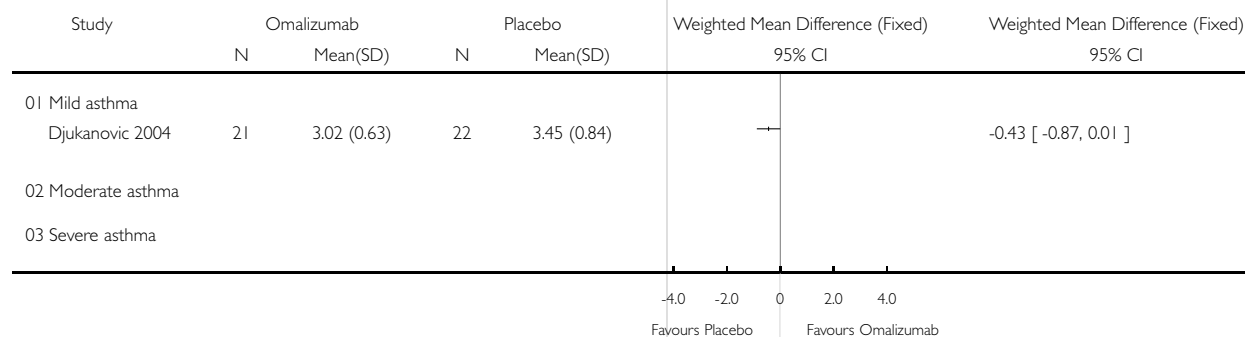


Analysis 09.01. Comparison 09 Subcutaneous Omalizumab versus placebo (without inhaled corticosteroids), Outcome 01 FEV1 (Litres)

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 09 Subcutaneous Omalizumab versus placebo (without inhaled corticosteroids)

Outcome: 01 FEV1 (Litres)

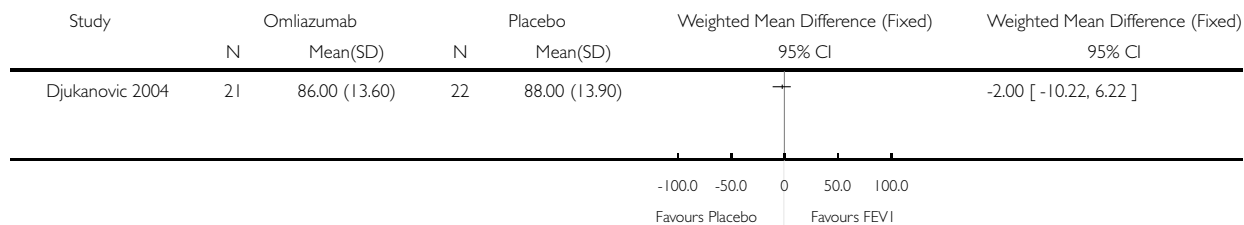


Analysis 09.02. Comparison 09 Subcutaneous Omalizumab versus placebo (without inhaled corticosteroids), Outcome 02 FEV1 (% predicted)

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 09 Subcutaneous Omalizumab versus placebo (without inhaled corticosteroids)

Outcome: 02 FEV1 (% predicted)

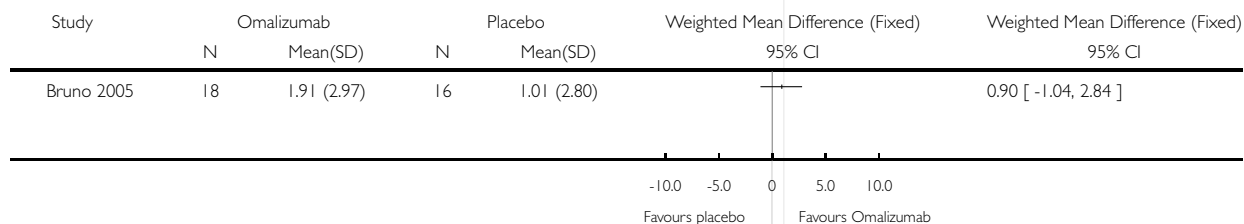


Analysis 09.03. Comparison 09 Subcutaneous Omalizumab versus placebo (without inhaled corticosteroids), Outcome 03 Change in PC 20

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 09 Subcutaneous Omalizumab versus placebo (without inhaled corticosteroids)

Outcome: 03 Change in PC 20

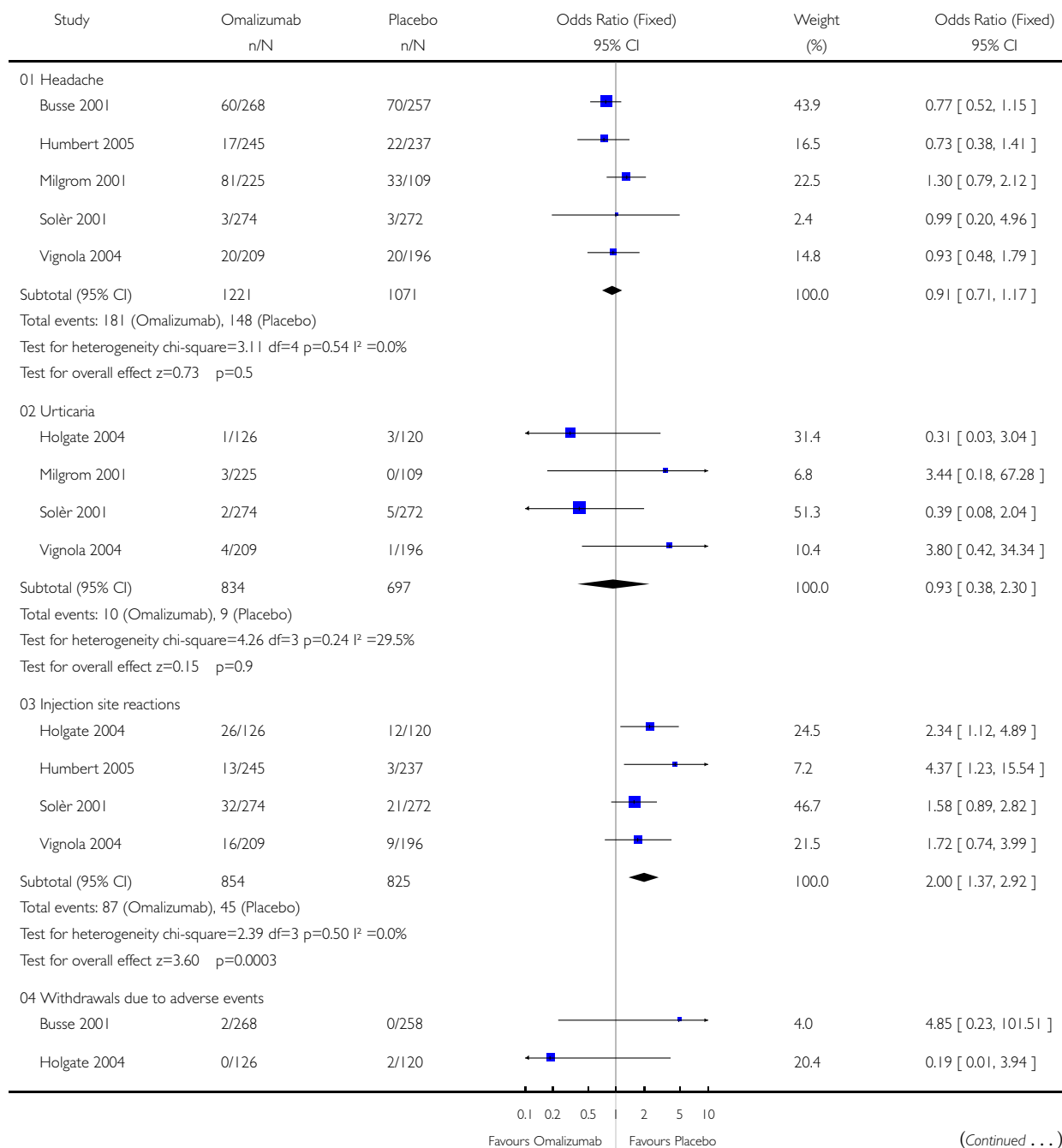


Analysis 10.01. Comparison 10 Subcutaneous Omalizumab versus placebo (safety), Outcome 01 Side effects

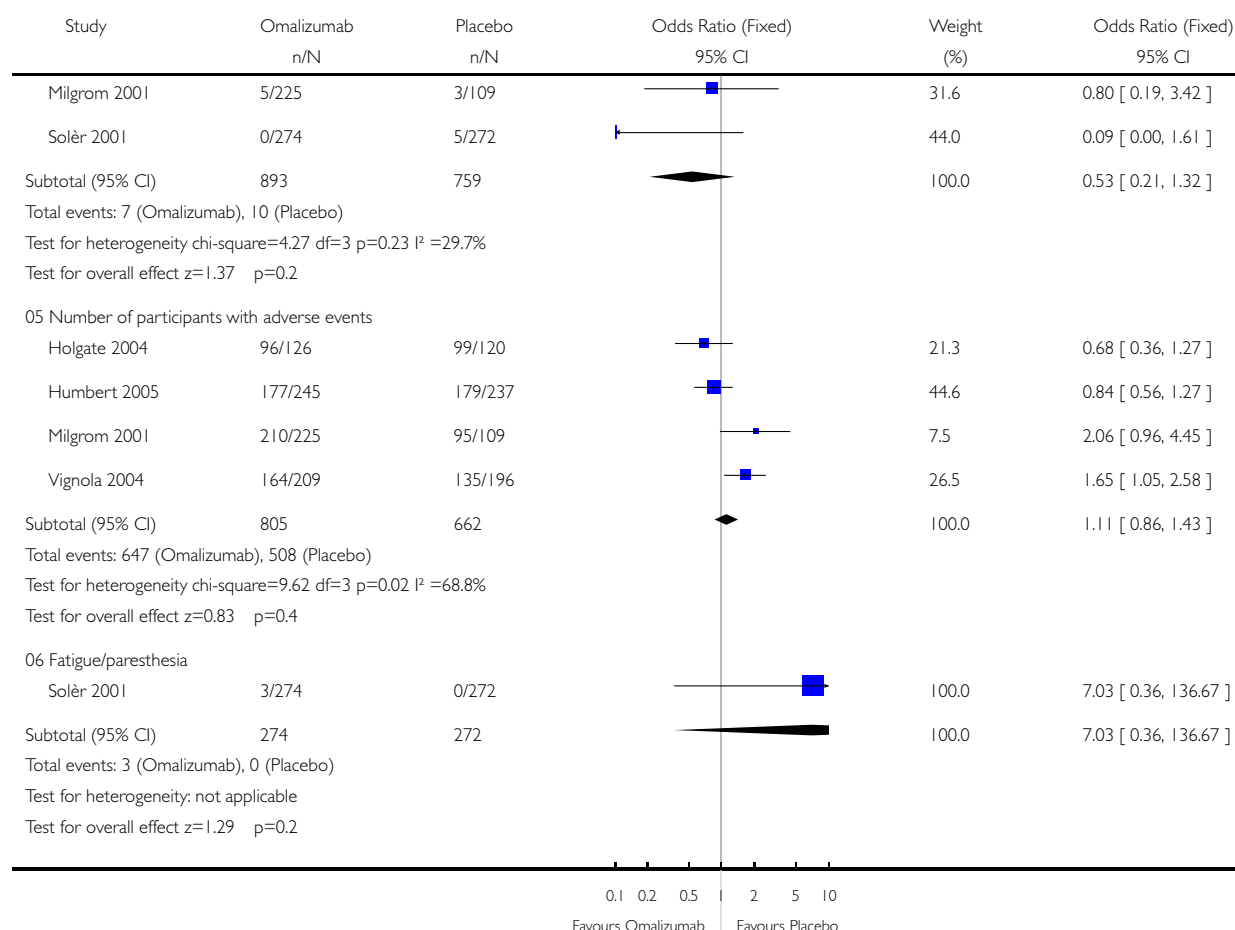
Review: Anti-IgE for chronic asthma in adults and children

Comparison: 10 Subcutaneous Omalizumab versus placebo (safety)

Outcome: 01 Side effects



(... Continued)

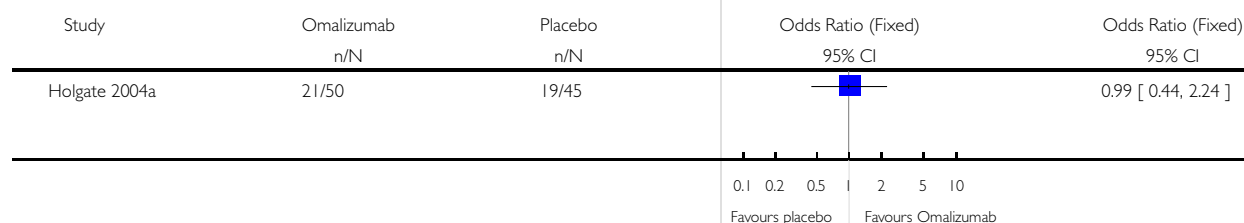


Analysis 11.01. Comparison 11 Subcutaneous Omalizumab + ICS& OCS versus placebo + ICS & OCS steroid (steroid reduction), Outcome 01 Number of patients achieving complete oral steroid withdrawal

Review: Anti-IgE for chronic asthma in adults and children

Comparison: 11 Subcutaneous Omalizumab + ICS% OCS versus placebo + ICS % OCS steroid (steroid reduction)

Outcome: 01 Number of patients achieving complete oral steroid withdrawal



Analysis 11.02. Comparison 11 Subcutaneous Omalizumab + ICS& OCS versus placebo + ICS & OCS steroid (steroid reduction), Outcome 02 Number of participants with exacerbation

Review: Anti-IgE for chronic asthma in adults and children
Comparison: 11 Subcutaneous Omalizumab + ICS% OCS versus placebo + ICS % OCS steroid (steroid reduction)
Outcome: 02 Number of participants with exacerbation

