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Anti-interleukin-13 and anti-interleukin-4 agents versus placebo, anti-interleukin-5 or anti-immunoglobulin-E agents, for people with asthma (Review)

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[Intervention Review]

Anti-interleukin-13 and anti-interleukin-4 agents versus placebo, anti-interleukin-5 or anti-immunoglobulin-E agents, for people with asthma

Andrew Gallagher[1], Michaela Edwards[2], Parameswaran Nair[3], Stewart Drew[4], Aashish Vyas[5], Rashmi Sharma[6], Paul A Marsden[5,7,8], Ran Wang[9,10], David JW Evans[11]

[1]Lancaster Medical Practice, Lancaster, UK. [2]Nottingham Business School, Nottingham Trent University, Nottingham, UK. [3]Firestone Institute for Respiratory Health, McMaster University & St Joseph`s Healthcare, Hamilton, Canada. [4]Children's Physiotherapy Service, Lancashire Care NHS Foundation Trust, Preston, UK. [5]Department of Respiratory Medicine, Lancashire Teaching Hospitals Trust, Preston, UK. [6]Department of Microbiology, BTH NHS Foundation Trust, Blackpool, UK. [7]North West Lung Centre, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK. [8]Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, University of Manchester, Manchester, UK. [9]Department of Respiratory Medicine, Manchester University NHS Foundation Trust, Manchester, UK. [10]Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, University of Manchester, Manchester, UK. [11]Lancaster Medical School, Lancaster University, Lancaster, UK

Contact: David JW Evans, david.jw.evans@hotmail.co.uk.

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ABSTRACT

Background

Targeting the immunoglobulin E pathway and the interleukin-5 pathway with specific monoclonal antibodies directed against the cytokines or their receptors is effective in patients with severe asthma. However, there are patients who have suboptimal responses to these biologics. Since interleukin-4 and interleukin-13, signalling through the interleukin-4 receptor, have multiple effects on the biology of asthma, therapies targeting interleukin-4 and -13 (both individually and combined) have been developed.

Objectives

To assess the efficacy and safety of anti-interleukin-13 or anti-interleukin-4 agents, compared with placebo, anti-immunoglobulin E agents, or anti-interleukin-5 agents, for the treatment of children, adolescents, or adults with asthma.

Search methods

We identified studies from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group and through searches of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform. The search was carried out on the 16 October 2020.

Selection criteria

We included parallel-group randomised controlled trials that compared anti-interleukin-13 or -4 agents (or agents that target both interleukin-13 and interleukin-4) with placebo in adolescents and adults (aged 16 years or older) or children (younger than 16 years), with a diagnosis of asthma; participants could receive their usual short- or long-acting medications (e.g. inhaled corticosteroids (ICS), long-acting beta adrenoceptor agonists (LABA), long-acting muscarinic antagonists (LAMA), and/or leukotriene receptor antagonists) provided that they were not part of the randomised treatment.

Data collection and analysis

We used standard methods expected by Cochrane.

Main results

We identified and included 41 RCTs. Of these, 29 studies contributed data to the quantitative analyses, randomly assigning 10,604 people with asthma to receive an anti-interleukin-13 (intervention) or anti-interleukin-4 agent (intervention), or placebo (comparator). No relevant studies were identified where the comparator was an anti-immunoglobulin agent or an anti-interleukin-5 agent. Studies had a duration of between 2 and 52 (median 16) weeks. The mean age of participants across the included studies ranged from 22 to 55 years. Only five studies permitted enrolment of children and adolescents, accounting for less than 5% of the total participants contributing data to the present review. The majority of participants had moderate or severe uncontrolled asthma. Concomitant ICS use was permitted or required in the majority (21 of 29) of the included studies. The use of maintenance systemic corticosteroids was not permitted in 19 studies and was permitted or required in five studies (information not reported in five studies). Regarding the most commonly assessed anti-interleukin-13/-4 agents, four studies evaluated dupilumab (300 mg once every week (Q1W), 200 mg once every two weeks (Q2W), 300 mg Q2W, 200 mg once every four weeks (Q4W), 300 mg Q4W, each administered by subcutaneous (SC) injection); eight studies evaluated lebrikizumab (37.5 mg Q4W, 125 mg Q4W, 250 mg Q4W each administered by SC injection); and nine studies (3259 participants) evaluated tralokinumab (75 mg Q1W, 150 mg Q1W, 300 mg Q1W, 150 mg Q2W, 300 mg Q2W, 600 mg Q2W, 300 mg Q4W, each administered by SC injection; 1/5/10 mg/kg administered by intravenous (IV) injection); all anti-interleukin-13 or-4 agents were compared with placebo.

The risk of bias was generally considered to be low or unclear (insufficient detail provided); nine studies were considered to be at high risk for attrition bias and three studies were considered to be at high risk for reporting bias.

The following results relate to the primary outcomes. The rate of exacerbations requiring hospitalisation or emergency department (ED) visit was probably lower in participants receiving tralokinumab versus placebo (rate ratio 0.68, 95% CI 0.47 to 0.98; moderate-certainty evidence; data available for tralokinumab (anti-interleukin-13) only). In participants receiving an anti-interleukin-13/-4 agent, the mean improvement versus placebo in adjusted asthma quality of life questionnaire score was 0.18 units (95% CI 0.12 to 0.24; high-certainty evidence); however, this finding was deemed not to be a clinically relevant improvement. There was likely little or no difference between groups in the proportion of patients who reported all-cause serious adverse events (anti-interleukin-13/-4 agents versus placebo, OR 0.91, 95% CI 0.76 to 1.09; moderate-certainty evidence).

In terms of secondary outcomes, there may be little or no difference between groups in the proportion of patients who experienced exacerbations requiring oral corticosteroids (anti-interleukin-13/-4 agents versus placebo, rate ratio 0.98, 95% CI 0.72 to 1.32; low-certainty evidence). Anti-interleukin-13/-4 agents probably improve asthma control based on asthma control questionnaire score (anti-interleukin-13/-4 agents versus placebo, mean difference -0.19; 95% CI -0.24 to -0.14); however, the magnitude of this result was deemed not to be a clinically relevant improvement. The proportion of patients experiencing any adverse event was greater in those receiving anti-interleukin-13/-4 agents compared with those receiving placebo (OR 1.16, 95% CI 1.04 to 1.30; high-certainty evidence); the most commonly reported adverse events in participants treated with anti-interleukin-13/-4 agents were upper respiratory tract infection, nasopharyngitis, headache and injection site reaction. The pooled results for the exploratory outcome, the rate of exacerbations requiring oral corticosteroids (OCS) or hospitalisation or emergency department visit, may be lower in participants receiving anti-interleukin-13/-4 agents versus placebo (rate ratio 0.71, 95% CI 0.65 to 0.77; low-certainty evidence).

Results were generally consistent across subgroups for different classes of agent (anti-interleukin-13 or anti-interleukin-4), durations of study and severity of disease. Subgroup analysis based on category of T helper 2 (TH2) inflammation suggested greater efficacy in patients with higher levels of inflammatory biomarkers (blood eosinophils, exhaled nitric oxide and serum periostin).

Authors' conclusions

Based on the totality of the evidence, compared with placebo, anti-interleukin-13/-4 agents are probably associated with a reduction in exacerbations requiring hospitalisation or ED visit, at the cost of increased adverse events, in patients with asthma. No clinically relevant improvements in health-related quality of life or asthma control were identified. Therefore, anti-interleukin-13 or anti-interleukin-4 agents may be appropriate for adults with moderate-to-severe uncontrolled asthma who have not responded to other treatments. These conclusions are generally supported by moderate or high-certainty evidence based on studies with an observation period of up to one year.

PLAIN LANGUAGE SUMMARY

Anti-interleukin-13 or anti-interleukin-4 agents versus placebo, anti-interleukin-5 or anti-immunoglobulin-E agents, for children and adults with asthma

Review question

We assessed the efficacy and safety of anti-interleukin-13 or anti-interleukin-4 agents, compared with placebo, anti-immunoglobulin E agents, or anti-interleukin-5 agents, for the treatment of children, adolescents, or adults with asthma.

Background

Immunoglobulin E and interleukin-5 are chemicals in the body that promote allergy (or an allergic response) in the airways and cause the symptoms of asthma. Some people with severe asthma take drugs that target immunoglobulin E or interleukin-5, but these drugs don't work for everyone. Since interleukin-4 and interleukin-13 are also chemicals in our body that promote allergy (or an allergic response) in the airways, we looked at whether drugs that target interleukin-4 and interleukin-13 are safe and effective (compared with placebo - a substance that has no therapeutic effect) for improving the symptoms or quality of life of people with asthma.

Study characteristics

We found 41 studies that compared anti-interleukin-4 or anti-interleukin-13 agents (or agents that target both interleukin-13 and interleukin-4) with placebo in people with asthma. No relevant studies were identified where anti-interleukin-4 or -13 agents were compared with either anti-interleukin-5 or anti-immunoglobulin agents. Twenty-nine of the included studies (10,604 participants) reported information that fed into this review. The evidence presented is current up to October 2020. Most of the people who took part in the included studies had moderate or severe, uncontrolled asthma and the average age of people in each study ranged from 22 to 55 years. Only four studies allowed recruitment of children and adolescents and participants in this age group accounted for less than 5% of those contributing data to his review. Most studies tested whether dupilumab, an interleukin-4 agent (four studies), or the anti-interleukin-13 agents lebrikizumab (eight studies) or tralokinumab (nine studies), were better than placebo.

Key results

When we pooled the information provided by the 29 studies, we showed that these drugs reduced the number of people having asthma attacks and improved lung function to a level where a person would feel the benefit. Small improvements in health-related quality of life and asthma control were also seen, but the size of these effects was not great enough for a person with asthma to feel the benefit. A 16 per cent reduction in the dose of oral corticosteroids was also observed, although our confidence in this finding is low. Although no increase in serious side effects was found (i.e. any untoward medical occurrence that results in death; is life threatening; requires hospitalisation; results in persistent or significant disability/incapacity; or is a birth defect), the number of people who had any side effect was increased compared with people who took placebo. The most commonly reported side effects in participants treated with anti-interleukin-13/-4 agents were upper respiratory tract infections, colds, headaches or injection site reactions. The results also showed that information about blood markers (blood eosinophils and serum periostin) and the exhaled nitric oxide levels may help predict the efficacy of these medications in an individual with asthma. In summary, these drugs are likely helpful for some people with severe or uncontrolled asthma when other treatments have not worked and the purpose of the treatment is to reduce the number of asthma attacks experienced.

Quality of the evidence

The included studies were generally well designed and well reported. People in the studies and those performing the research did not know which treatment people were receiving, which ensures a fair evaluation of the treatments. Overall, we can be confident in the conclusions of this review.

SUMMARY OF FINDINGS

Summary of findings 1. Anti-IL13 or anti-IL4 agents compared to placebo for children and adults with asthma

Anti-IL13 of anti-IL4 agents compared to placebo for children and adults with asthma

Patient or population: children and adults with asthma
Setting: community
Intervention: anti-IL13 of anti-IL4 agents
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with anti-IL13 of anti-IL4 agents				
Exacerbation requiring hospitalisation or ED visit **Follow-up:** 52 weeks	The mean AAER in the placebo group was 0.075[1]	The AAER in the intervention group was 0.024 lower (0.002 lower to 0.04 lower)	Rate ratio 0.68 (0.47 to 0.98)	2039 (2 RCTs)	⊕⊕⊕⊖ MODERATE[2]	
Health-related quality of life (AQLQ) **Scale:** 1 to 7 (higher is better) **Follow-up:** 12 weeks to 52 weeks	Where reported, the mean change in the placebo group ranged from 0.64 to 0.88	MD 0.18 higher (0.12 higher to 0.24 higher)	-	4960 (7 RCTs)	⊕⊕⊕⊕ HIGH	MCID = 0.5; the treatment effect was not clinically relevant.
Serious adverse events **Follow-up:** 3 to 52 weeks	81 per 1000	74 per 1000 (63 to 87)	OR 0.91 (0.76 to 1.09)	7739 (22 RCTs)	⊕⊕⊕⊖ MODERATE[3]	
Exacerbation requiring OCS (rate ratio) **Follow-up:** 52 weeks	The mean AAER in the placebo group was 0.90	The AAER in the intervention group was 0.08 lower (0.27 lower to 0.29 higher)	RR 0.98 (0.72 to 1.32)	452 (1 RCT)	⊕⊕⊖⊖ LOW[2,3]	
Change from baseline in ACQ score **Scale:** 0 to 6 (higher is worse) **Follow-up:** 12 to 52 weeks	Where reported, the mean change from baseline in ACQ score in the placebo group ranged from -1.30 (SE 0.06) to -0.27 (error NR)	MD 0.19 lower (0.24 lower to 0.14 lower)	-	6251 (14 RCTs)	⊕⊕⊕⊖ MODERATE[4]	MCID = 0.4; the treatment effect was not clinically relevant.
Adverse events (any)	707 per 1000	737 per 1000	OR 1.16	7419	⊕⊕⊕⊕	

Follow-up: 10 days to 52 weeks		(715 to 759 participants per 1000)	(1.04 to 1.30)	(18 RCTs)	HIGH	
Time off work or study	-	-	-	-	-	No studies reported data for this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AAER: adjusted annualised exacerbation rate; **ACQ:** asthma control questionnaire; **AQLQ:** asthma quality of life questionnaire; **CI:** Confidence interval; **ED:** emergency department; **MCID**: minimally clinically important difference; **MD:** mean difference; **OCS:** oral corticosteroids; **RR:** Risk ratio; **OR:** Odds ratio; **SD:** standard deviation; **RCT:** randomised controlled trial; **SE:** standard error.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Mean of the AAER in the placebo group of the two studies: 0.07 and 0.08
[2]Downgraded once for indirectness (low number of studies of a single agent)
[3]Downgraded once for imprecision as the 95% confidence intervals for the treatment effect crossed 1.0
[4] Downgraded once for inconsistency (moderate heterogeneity of 30% to 60%)
[6]Downgraded twice for inconsistency (substantial heterogeneity of 50% to 90% or considerable heterogeneity of 75% to 100%)

Summary of findings 2. Other secondary and post hoc exploratory outcomes

Anti-IL13 of anti-IL4 agents compared to placebo for children and adults with asthma

Patient or population: children and adults with asthma
Setting: community
Intervention: anti-IL13 of anti-IL4 agents
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with anti-IL13 of anti-IL4 agents				
Change from baseline in pre-bronchodilator FEV1	Where reported, the mean change from baseline in FEV1 in the placebo	MD 0.1 L higher	-	4829 (13 RCTs)	⊕⊕⊕⊖ MODERATE[2]	These changes were borderline

Follow-up: 12 to 52 weeks	groups ranged from -0.02 L (SE 0.03) to 0.21 L (SE 0.02)	(0.08 higher to 0.12 higher)				clinically relevant (MCID is approximately 0.1 to 0.2 L).
Change from baseline in FENO (ppb) **Follow-up:** 10 days to 52 weeks	Where reported, the mean change from baseline in FENO in the placebo groups ranged from -31.1 to 23.8 ppb	MD 14.68 ppb lower (16.56 lower to 12.8 ppb lower)	-	3577 (11 RCTs)	⊕⊕⊕⊖ MODERATE[2]	
Change from baseline in blood eosinophils (cells x 10*9/L) **Follow-up:** 12 to 52 weeks	Where reported, the mean change from baseline in blood eosinophil count in the placebo groups ranged from -0.048 (SD 0.347) to 0.003 (SD 0.313) cells x 10^9/L	MD 0.06 cells x 10^{*9}/L higher (0.04 higher to 0.09 cells x 10^{*9}/L higher)	-	2598 (6 RCTs)	⊕⊕⊕⊕ HIGH	
Change from baseline in Periostin (ng/mL) **Follow-up:** 12 to 52 weeks	Where reported, the mean change from baseline in periostin concentration in the placebo groups ranged from -5.05 (SD 27.89) to -0.3 (SD 1.0) ng/mL	MD 9.04 ng/mL lower (10.92 lower to 7.17 ng/mL lower)	-	2106 (2 RCTs)	⊕⊕⊖⊖ LOW[3]	
Percentage reduction from baseline in maintenance OCS dose **Follow-up:** 24 to 40 weeks	Where reported, the mean reduction from baseline in OCS dose in the placebo groups ranged from -29.85 (SE 4.98) to -41.9 (SE 4.6)%	MD 15.58% lower (23.3% lower to 7.85% lower)	-	350 (2 RCTs)	⊕⊕⊖⊖ LOW[3]	
Post hoc exploratory endpoint: Exacerbation requiring hospitalisation/ED/OCS (rate ratio) **Follow-up:** 24 weeks to 52 weeks	The mean AAER in the placebo groups was 1.00 (range 0.60 to 2.31)[1]	The AAER in the intervention groups was 0.29 lower (0.35 lower to 0.23 lower)	Rate ratio 0.71 (0.65 to 0.77)	6998 (7 RCTs)	⊕⊕⊖⊖ LOW[3]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AAER, adjusted annualised exacerbation rate; **CI:** Confidence interval; **ED**, emergency department; **FENO**, fractional exhaled nitric oxide; **FEV1**, forced expiratory volume in 1 second; **MD**, mean difference; **OCS**, oral corticosteroids; **ppb**, parts per billion; **RR:** Risk ratio; **SD**, standard deviation; **RCT**, randomised controlled trial; **SE**, standard error

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Mean of the AAER in the placebo groups of the seven studies (1 study had two placebo arms): 2.31, 0.60, 0.82, 0.94, 0.61, 0.87, 0.97, 0.897
[2] Downgraded once for inconsistency (moderate heterogeneity of 30% to 60%)
[3]Downgraded twice for inconsistency (substantial heterogeneity of 50% to 90% or considerable heterogeneity of 75% to 100%)

BACKGROUND

Description of the condition

Asthma is a prevalent, noncommunicable, heterogeneous disease, typically characterised by chronic airway inflammation (GINA 2020). Common symptoms include wheezing, chest tightness, a cough, and shortness of breath, and they are frequently worse early in the morning or late at night (GINA 2020). Airflow limitation and symptoms vary over time and in intensity, and are known to be triggered by viral respiratory infections, changing weather, irritant and allergen exposure, and exercise (GINA 2020). Symptoms and airflow limitation can be absent for periods of weeks or months.

Asthma may affect up to 334 million individuals worldwide (Global Asthma Network 2014), and has been highlighted as one of the forum of international respiratory societies' 'Big 5' respiratory diseases (ERS 2017). It is noted as "the most common chronic condition in children, and is more severe in children in non-affluent countries" (ERS 2017). Asthma is known to affect "1 to 18% of the population in different countries" (GINA 2020), and can carry a particularly serious burden in low- or middle-income countries, which find it more difficult to afford the associated costs (Global Asthma Network 2014).

The goal of asthma treatment is to maintain good activity levels and control symptoms (GINA 2020). In addition, the use of maintenance medication can reduce the future risk of exacerbations (GINA 2020). Individuals should also be assessed for any relevant comorbidities (e.g. obstructive sleep apnoea, depression and anxiety, obesity, rhinosinusitis, rhinitis, and gastroesophageal reflux), which may contribute to asthma symptoms and poor control of asthma (GINA 2020).

It is increasingly accepted that asthma is a heterogeneous condition, with distinct clinical phenotypes. One of the better characterised phenotypes is that of eosinophilic asthma, where eosinophils infiltrate the bronchial mucosa and airways, and cause inflammation. Eosinophilic infiltration is a hallmark of both childhood-onset allergic asthma and late-onset non-allergic asthma. In both cases, the cytokines interleukin-4, -5, and -13 play a central role in the pathophysiology (De Groot 2015). Immunoglobulin E (IgE) also plays a role, and treatment with anti-IgE therapies can reduce airway and blood eosinophils, and associated inflammation. However, some patients with uncontrolled asthma do not respond to anti-IgE therapies, and continue to exhibit inflammation. Therefore, therapies targeting interleukin-4, -5, and -13, have been developed; the evidence around anti-interleukin-5 therapies has recently been synthesised elsewhere (De Groot 2015; Farne 2017); anti-interleukin-5 agents were evaluated as active comparators, as they target the initiation and maintenance of eosinophilic airway inflammation (Ortega 2014).

Description of the intervention

The majority of anti-interleukin-13 and anti-interleukin-4 agents are humanised monoclonal antibodies (i.e. biological therapies) that bind to, and inhibit their respective inflammatory cytokines or their receptors (Bice 2014; Kau 2014). Antibodies targeting the interleukin-13 pathway alone include lebrikizumab, GSK67958, tralokinumab, anrukinzumab, and IMA-026. Antibodies inhibiting the interleukin-4 pathway alone include pascolizumab and altrakincept. Antibodies inhibiting both the interleukin-4 and -13 pathways include pitrakina, AMG-317, and dupilumab (Bice 2014; Kau 2014). All of the agents are administered by subcutaneous injection once every several weeks. However, pitrakina can also be administered by nebulised inhalation.

How the intervention might work

Interleukins are a broad group of proteins, which are important in cell signalling. Interleukin-13 is a pleiotropic cytokine produced by type 2 helper T cells (TH_2), and has been shown to drive airway eosinophilia and increase airway inflammation in asthma. Interleukin-13 contributes to goblet cell metaplasia, subepithelial cell fibrosis, smooth muscle hyperplasia, and stimulation of periostin secretion (Woodruff 2007); periostin is a matricellular protein, which has a role in fibroblast activation and increasing collagen gel elasticity (Sidhu 2010). These pathophysiological processes are hallmarks of asthma. In preclinical models, interleukin-13 has also been shown to increase airway hyper-responsiveness (Chiba 2009). Interleukin-4 is a closely related cytokine, which shares many of the biological and immunoregulatory functions of interleukin-13 (Chomorat 1998). In particular, interleukin-4 plays an important role in maintaining the TH_2 phenotype, leading to further secretion of interleukin-4 and -13 in a positive feedback effect (Bice 2014). Interleukin-4 also promotes B-cell isotype switching, affects the production of chemokines by the airway epithelium, and increases IgE production (Li-Weber 2003). Interleukin-13 and interleukin-4 have been shown to enhance bronchial smooth muscle proliferation (Ynuk 2008).

Anti-interleukin-13 and -4 agents target these pathways with the aim of reducing inflammation and airway remodelling, which are both features of asthma. Furthermore, these agents may be more effective in specific populations of people with asthma, such as those with eosinophilic asthma, where inhibition of these pathways may reduce infiltration of eosinophils into the airways. It is believed that blocking interleukin-13 may reduce very late antigen-4 expression, and thus, reduce the movement of eosinophils from circulation into airway tissue, and subsequently into the lumen (Pelaquini 2011). Glucorticosteroids have diverse effects on the airways, including inhibition of interleukin-13 production; however, some patients with poorly controlled asthma continue to have elevated levels of interleukin-13, despite the use of high-dose inhaled or systemic glucocorticosteroids (Saha 2008). Therefore, direct inhibition of interleukin-13 is a potential therapeutic target in this group of patients, and agents, such as lebrikizumab, have been shown to be effective in reducing interleukin-13 levels following subcutaneous administration (Hanania 2016). Inhibition of the interleukin-4 pathway by dupilumab has also been shown to reduce levels of TH_2-associated inflammatory markers in patients with persistent, moderate to severe asthma, following the withdrawal of treatment with long-acting beta-adrenoceptor agonists (LABA) and glucocorticoid therapy (Wenzel 2013b).

Why it is important to do this review

Whilst severe or difficult to treat asthma represents only 5% to 10% of the total asthma population, these patients carry a disproportionate burden of healthcare, socioeconomic, and personal costs (Sullivan 2007). Around 1200 people die of asthma each year in the UK, and approximately 40% of deaths occur in individuals with severe asthma (BLF 2012; RCoP 2014). Therefore,

it is imperative to find therapies that will offer improvements in disease control for this group of patients.

It is important to synthesise the available evidence on the safety and efficacy of anti-interleukin-13 and anti-interleukin-4 agents, given that data from phase III clinical trials are becoming available (Hanania 2016). Whilst improvements in laboratory markers, such as forced expiratory volume in 1 second (FEV1; (Corren 2011b)), and fraction of exhaled nitric oxide (FENO; (Noonan 2013b)) have been shown, a demonstration of consistent improvement in patient symptoms appear to be more elusive (Corren 2011b; De Boever 2014). Furthermore, some markers, such as elevated periostin levels, may identify a subset of patients who are more likely to have a favourable response. However, trial evidence is again mixed in this respect.

OBJECTIVES

To assess the efficacy and safety of anti-interleukin-13 or anti-interleukin-4 agents, compared with placebo, anti-immunoglobulin E agents, or anti-interleukin-5 agents, for the treatment of children, adolescents, or adults with asthma.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs; parallel-group). Cross-over trials were excluded because the half-life of these agents is in the order of a month, and thus trialists are unlikely to implement a sufficient washout period for eliminating a carry-over effect (i.e. several times the half-life). We included studies reported in full text, those published as an abstract only, and unpublished data. We excluded non-randomised studies.

Types of participants

We included adolescents and adults (aged 16 years or older) and children (younger than 16 years), with a diagnosis of asthma. We excluded participants with other chronic respiratory comorbidities (e.g. COPD, bronchiectasis). If a study included a mixture of patients with COPD and asthma, we used or attempted to obtain data for the subgroup of patients with asthma; if this was not possible, the study was excluded.

If studies in adolescent or adult populations included a proportion of individuals under 16 years, and data were not reported separately, we included the study if the mean age in the intervention and comparator groups was 16 years or older.

Types of interventions

We included studies of adolescents and adults (aged 16 years or older) and studies of children (younger than 16 years) in separate comparisons. In each main comparison, we included studies that compared the following:

1. Anti-interleukin-13 or -4 agents* with placebo.
2. Anti-interleukin-13 or -4 agents* with anti-immunoglobulin E (IgE) agents.
3. Anti-interleukin-13 or -4 agents* with anti-interleukin-5 agents.

*Some agents may inhibit both interleukin-13 and -4, and we also included studies of these agents.

We selected anti-interleukin-5 agents as active comparators, as they target the initiation and maintenance of eosinophilic airway inflammation (Ortega 2014). We selected anti-IgE agents as active comparators, as they target IgE-mediated immune response, thought to be involved in severe allergic asthma (Busse 2001).

Co-interventions were permitted, providing they were not part of the randomised treatment. For example, individuals' usual short- or long-acting medications (e.g. inhaled corticosteroids, long-acting beta adrenoceptor agonists (LABA), long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonists), oral corticosteroids (OCS) or macrolides.

If a study evaluated more than one dose of an anti-interleukin-13 or -4 agent (in separate arms), we considered the most clinically relevant dose. If the clinically relevant dose for a given agent was not clear, we extracted data for both doses, and used the most appropriate dataset for the meta-analysis, based on the doses used in the majority of other included studies.

Types of outcome measures

Primary outcomes

1. Exacerbations requiring hospitalisation or emergency department visit (see section Unit of analysis issues for more details)
2. Quality of life (measured on a validated asthma scale, e.g. Asthma Quality of Life Questionnaire)
3. Serious adverse events (all causes; i.e. any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalisation, results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect)

Secondary outcomes

1. Exacerbations requiring oral corticosteroids
2. Lung function (e.g. change from baseline in forced expiratory volume in 1 second (FEV1; (L)); change from baseline in % predicted FEV1 (%); FEV1 bronchodilator reversibility (%); concentration of methacholine needed to produce a 20% fall in FEV1 from baseline (PC20 methacholine; (mg/mL))
3. Asthma control (measured on a validated scale, e.g. Asthma Control Questionnaire or Asthma Control Test)
4. Time off work or study
5. Adverse events (all causes)
6. Measures of airway inflammation (e.g. blood eosinophil (count - absolute); sputum or bronchoalveolar lavage eosinophil (%); fraction of exhaled nitric oxide (FENO)
7. Reduction in maintenance oral corticosteroid dose

Additionally, we assessed the exploratory outcome "exacerbations requiring hospitalisation, emergency department visit or OCS". When we started to conduct the review, it was clear that the majority of studies reported this endpoint and that important evidence would be lost as a result of its omission from the published protocol. We plan to include this outcome as a primary outcome in future updates to the review.

We extracted data for each outcome at the time point closest to the end of the treatment period. Where multiple outcomes were proposed (i.e. as for lung function and measures of airway inflammation), we extracted data for all available measures.

Reporting one or more of the outcomes listed here in the study was not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We identified studies from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The Cochrane Airways Trials Register contains studies identified from several sources:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies (CRS) inception to October 2020;
2. weekly searches of MEDLINE Ovid SP 1946 to October 2020;
3. weekly searches of Embase Ovid SP 1974 to October 2020;
4. monthly searches of PsycINFO Ovid SP 1967 to October 2020;
5. monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) 1937 to October 2020;
6. monthly searches of AMED EBSCO (Allied and Complementary Medicine) inception to October 2020;
7. handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register were identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We searched the following trials registries:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)
2. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch)

We searched the Cochrane Airways Trials Register and additional sources from inception to 16 October 2020, with no restriction on language of publication.

Searching other resources

We checked the reference lists of all selected studies for additional references. We searched relevant manufacturers' websites for study information.

We searched for errata or retractions from included studies published in full text on PubMed, on 26 February 2021.

Data collection and analysis

Selection of studies

Three review authors (DE, AG, ME) independently screened the titles and abstracts of the search results and coded them as 'retrieve' (eligible, potentially eligible, or unclear) or 'do not retrieve'. We retrieved the full-text study reports of all potentially eligible studies, and three review authors (DE, AG, ME) independently screened them for inclusion, recording the reasons for exclusion of ineligible studies. We resolved any disagreement through discussion or, if required, we consulted a fourth review author (PM). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table (Moher 2009).

Data extraction and management

We used a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. Two review authors (DE, RW) extracted the following study characteristics from included studies:

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, baseline measures of airway inflammation, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention (including dose), comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for studies and notable conflicts of interest of trial authors.

Two review authors (from DE, AG, ME) independently extracted outcome data from the included studies. We noted in the Characteristics of included studies table if outcome data were not reported in a usable way. We resolved disagreements by consensus, or by involving a fourth review author (RS). One review author (DE) transferred data into the Review Manager 5 file (RevMan 2014). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (SD) spot-checked study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (from DE, ME, RW) independently assessed the risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion, or by involving a third author (from DE, ME, RW). We assessed the risk of bias according to the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We judged each potential source of bias as high, low, or unclear, and provided a quote from the study report together with a justification for our judgement in the risk of bias table. We summarised the risk of bias judgements across different studies for each of the

domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the risk of bias table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and justified any deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as odds ratios (OR), and continuous data as rate ratios (RR), mean difference (MD), or standardised mean difference (SMD), which were presented with 95% confidence intervals (CI). If data from rating scales were combined in a meta-analysis, we ensured that they were entered with a consistent direction of effect (e.g. lower scores always indicate improvement).

We undertook meta-analyses only when this was meaningful; that is, if the treatments, doses, participants, and the underlying clinical question were similar enough for pooling to make sense.

Where multiple trial arms were reported in a single study, we included only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) were combined in the same meta-analysis, we either combined the active arms or halved the control group to avoid double-counting.

If adjusted analyses were available (ANOVA or ANCOVA), we used these as a preference in our meta-analyses. If both change from baseline and endpoint scores were available for continuous data, we used change from baseline, unless there was a low correlation between measurements in individuals. If a study reported outcomes at multiple time points, we used the latest available time point (i.e. corresponding to the end of the study) for studies with a duration of one year or less.

We used intention-to-treat (ITT) or 'full analysis set' analyses when they were reported (i.e. when data were imputed for participants who were randomly assigned but did not complete the study), instead of completer or per protocol analyses.

Unit of analysis issues

With the exception of outcomes relating to exacerbations, for dichotomous outcomes, we used participants, rather than events, as the unit of analysis (i.e. number of children admitted to hospital, rather than number of admissions per child). However, if data permitted the calculation of rate ratios, we analysed them on this basis. The majority of patients enrolled in studies of anti-interleukin-13 and anti-interleukin-4 agents had relatively severe or uncontrolled asthma, and experienced at least one exacerbation during the treatment period. Therefore, we synthesised data relating to exacerbations based on the number of exacerbations per patient during the treatment period, using rate ratios. We planned to only meta-analyse data from cluster-RCTs if the available data had been adjusted (or could be adjusted), to account for the clustering; however, no cluster-RCTs were included in the review.

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data when possible (e.g. when a study was identified as an abstract only). If this was not possible, and the missing data were thought to introduce serious bias, we planned to take this into consideration in the GRADE rating for affected outcomes (however, this was not necessary). We did not contact investigators to obtain data for outcomes that were not prespecified in the trial protocols.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the studies in each analysis. An I^2 value of 30% to 60% may represent moderate heterogeneity, a value of 50% to 90% may represent substantial heterogeneity and a value of 75% to 100% may represent considerable heterogeneity. If we identified substantial heterogeneity, we reported it and explored the possible causes by our prespecified subgroup analysis.

Assessment of reporting biases

We did not explore possible small study and publication biases.

Data synthesis

We used a fixed-effects model. We performed a sensitivity analysis with a random-effects model. Rate ratios were combined using the generic inverse variance method.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses for the primary outcomes (for each of the main comparisons in children, and adolescents and adults, respectively):

1. Individual anti-interleukin-13 or anti-interleukin-4 agent (e.g. including but not limited to lebrikizumab, tralokinumab, IMA-026, GSK679586, anrukinzumab, pascolizumab, pitrakina, altrakincept, AMG-317, dupilumab).
2. Agent class (anti-interleukin-13 only versus anti-interleukin-4 only versus drugs that inhibit both interleukin-13 and -4 pathways).
3. Duration of therapy (up to 6 months versus longer than 6 months).
4. Severity of asthma as per Global Initiative for Asthma (GINA) or British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) definitions (mild or moderate versus severe).
5. Category of TH_2 inflammation (high versus low: e.g. as determined by serum IgE concentration (high: ≥ 300 kU/L%), exhaled nitric oxide (eNO; (high: ≥ 50 parts per billion (ppb)), airway eosinophil count (high: sputum eosinophilia ≥ 3%), serum periostin (high: ≥ 50 ng/mL), or direct assay of serum or sputum IL-13 (high: ≥ 10 pg/mL)). Rationale: TH_2 cells play a central role in asthma; interleukin-4 controls the development of TH_2 cells, and interleukin-13 functions during the effector phase of immunity, mediating the physiological response to TH_2-induced inflammation. Patients with greater levels of TH_2 inflammation may respond better to anti-interleukin-13 or -4 therapies than patients with lower levels of TH_2 inflammation.
6. Dose of corticosteroids (including prednisone) at randomisation. Rationale: there is some overlap in the

mechanism of action between corticosteroids and anti-interleukin agents; prior or concomitant corticosteroid use may potentially confound the results, with greater effects of the anti-interleukin agents observed when corticosteroid doses are low. Equally, some patients may not respond to even high doses of corticosteroids, but may respond to anti-interleukin-13 or -4 therapies.

We used the formal test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

We planned to carry out the following sensitivity analyses, removing the following from the primary outcome analyses:

1. Unpublished data.
2. Studies at high risk of bias for blinding of participants and personnel.
3. Studies at high risk for random sequence generation or allocation concealment.

We compared the results from a fixed-effect model with the random-effects model.

Summary of findings and assessment of the certainty of the evidence

We created summary of findings tables using the following outcomes: exacerbations requiring hospitalisation or emergency department visit, quality of life, serious adverse events (all causes), exacerbations requiring oral corticosteroids, asthma control, time off work or study, adverse events (all causes). We used the five considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it related to the studies that contributed data for the prespecified outcomes. We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT). We justified all decisions to downgrade the quality of the evidence using footnotes, and we made comments to aid the reader's understanding of the review, where necessary.

RESULTS

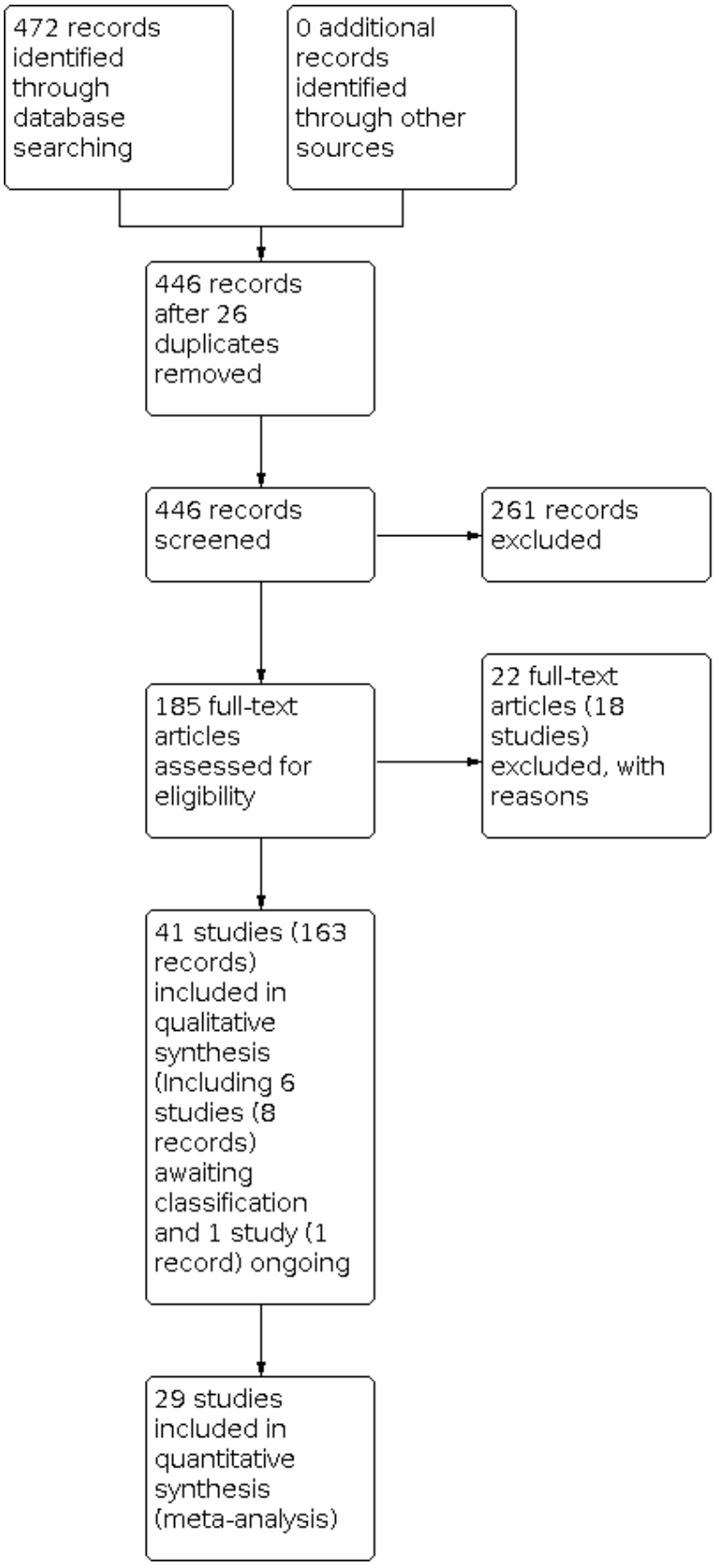
Description of studies

Details of the included studies are presented in the Characteristics of included studies tables and are summarised in Table 1. In the Characteristics of excluded studies table, we report reasons for the exclusion of studies considered during review of full-text articles.

Results of the search

We identified 472 records by conducting electronic searches of bibliographic databases on the 16 October 2020. Of a total of 446 records (26 duplicates removed), we excluded 261 records upon screening titles and abstracts. We examined full-text articles of the remaining 185 records and excluded a further 22 records (reporting 18 studies; see Excluded studies). The remaining 163 records reported the findings of 41 studies, which we included in this review (n = 34 studies included in the narrative analyses; n = 6 studies awaiting classification; n = 1 study ongoing). A total of 29 studies were included in the quantitative analyses. Figure 1 presents the flow of information through this systematic review.

Figure 1. Study flow diagram.



Included studies

A total of 41 studies met the inclusion criteria, of which 29 contributed to the quantitative analyses (Borish 1999; Borish 2001; Brightling 2015; Burgess 2018; Busse 2015; Castro 2018; Corren 2010; Corren 2011; De Boever 2014; Hanania 2011; Hanania 2015a; Hanania 2015b; Hanania 2016a; Hanania 2016b; Hodsman 2013; Korenblat 2018; NCT00425061; NCT00640016; Noonan 2013; Pannetieri 2018A; Pannetieri 2018B; Piper 2013; Rabe 2018; Russell 2018; Singh 2010; Tripp 2017; Wenzel 2010; Wenzel 2013; Wenzel 2016); five were included in qualitative analyses (narrative synthesis only Gauvreau 2011a; Gauvreau 2011b; Scheerens 2014; Wenzel 2007a; Wenzel 2007b), six were awaiting classification (having completed, but no data reported Euctr 2015-001572-22; NCT00024544; NCT01987492; NCT02948959; NCT03112577; NCT03387852); and one was ongoing (NCT03782532). Regarding the replicate studies Hanania 2015a and Hanania 2015b, following the discovery of a host-cell impurity in the study drug material, protocols were amended to convert from phase III to phase IIb. Subsequently, dosing of study medication was discontinued early as a precautionary measure. The data collected for analysis were from a placebo-controlled period of variable duration and pooled across both studies. Therefore, pooled data for the two studies have herein been included under Hanania 2015a.

The studies Hanania 2016a; Hanania 2016b were reported in a single publication, as were the studies Pannetieri 2018A; Pannetieri 2018B.

Methods

All of the 29 included studies contributing to the quantitative analyses were randomised, placebo-controlled trials; eight were phase 3 studies, fifteen were phase 2 studies, and six were phase 1 dose-ranging studies (Borish 1999; Borish 2001; Burgess 2018; Hodsman 2013; Singh 2010; Tripp 2017). The majority (24 of 29) were multi-centre studies. Overall geographical coverage was broad; the majority of studies were performed in Europe, North America and Oceania and several large studies enrolled participants from South America, Russia, Asia, and South Africa (Brightling 2015; Castro 2018; Hanania 2015a; Hanania 2015b; Hanania 2016a; Hanania 2016b; Rabe 2018; Wenzel 2016). Studies had a randomly assigned treatment period ranging from two weeks to 52 weeks (mean 18 weeks; median 16 weeks; mode 12 weeks). The study setting was poorly reported, but appeared, principally, to comprise of academic and clinical research centres.

Additionally, five studies were allergen challenge studies and did not contribute data to the quantitative analyses (Gauvreau 2011a; Gauvreau 2011b; Scheerens 2014; Wenzel 2007a; Wenzel 2007b). Of these studies, all were randomised, controlled trials (phase 1, n = 2; phase 2, n = 3); two were single-centre studies conducted in the UK (Wenzel 2007a; Wenzel 2007b), two studies were conducted at four centres in Canada (Gauvreau 2011a; Gauvreau 2011b) and the number of centres and location was not reported for Scheerens 2014. Four of the studies had a duration of approximately four weeks and one study had a duration of 12 weeks (Scheerens 2014). Where declared, all of the included studies were sponsored by pharmaceutical companies (two studies did not declare the source of funding).

Participants

The 29 studies contributing quantitative data randomised a total of 10,604 participants (Table 1). The majority of studies (23 of 29) enrolled individuals with moderate or severe uncontrolled asthma; four studies enrolled individuals with mild-to-moderate asthma (Korenblat 2018; Noonan 2013; Singh 2010; Tripp 2017) and two enrolled individuals with mild asthma (Burgess 2018; Hodsman 2013). The mean ages of participants across the relevant arms of all included studies ranged from 22 to 55 years. Only five studies permitted enrolment of children/adolescents (defined by the authors as aged between 12 and 18 years)(Busse 2015; Castro 2018; Pannetieri 2018A; Pannetieri 2018B; Rabe 2018); participants in this age group accounted for less than 5% of the total participants contributing data to the present review. In approximately half of the trials, less than 50 per cent of participants were male (range across studies 25% to 63%, with the exception of Burgess 2018 and Hodsman 2013 where all participants were male, and NCT00640016; Singh 2010, and Tripp 2017, where the proportion of males across treatment arms ranged from 0 to 75, 67 to 100 and 75 to 100, respectively). Where reported, post-bronchodilator per cent predicted FEV1 ranged from 55% to 87% (with the exception of Hodsman 2013 where the range was 102 to 105% across groups). ICS were not permitted or discontinued prior to study initiation in six studies; were maintained/permitted in 21 studies; and were tapered during the double-blind period in two studies. The use of maintenance systemic corticosteroids was not permitted in 19 studies and was permitted or required in five studies (this information was not reported in five studies).

The five allergen challenge studies randomised a total of 141 participants to receive either anti-interleukin-13 or anti-interleukin-13/-4 (pitrakinra) agents or placebo. Participants had mild or mild-to-moderate asthma, were aged between 26 and 36 years of age and approximately half were male; post-bronchodilator per cent predicted FEV1 ranged from 82% to 102%.

Intervention

Of the 10,604 participants randomised across the 29 studies contributing quantitative data, a total of 2560 participants were randomised to receive an anti-interleukin-4 agent (soluble IL-4R, dupilumab, pitrakinra), 4401 participants were randomised to receive an anti-interleukin-13 agent (GSK679586, IMA-638 [anrukinzumab], lebrikizumab, RPC4046, tralokinumab, VR492) and 3643 were randomised to receive placebo. The authors noted that pitrakinra and dupilumab also have some interleukin-13 activity. No relevant studies were identified where the comparator was an anti-immunoglobulin agent or an anti-interleukin-5 agent.

Across the 29 studies, four studies (2835 participants) evaluated dupilumab (300 mg once every week (Q1W), 200 mg once every 2 weeks (Q2W), 300 mg Q2W, 200 mg once every 4 weeks (Q4W), 300 mg Q4W, each administered by subcutaneous injection), eight studies (3432 participants) evaluated lebrikizumab (37.5 mg Q4W, 125 mg Q4W, 250 mg Q4W), and nine studies (3259 participants) evaluated tralokinumab (75 mg Q1W, 150 mg Q1W, 300 mg Q1W, 150 mg Q2W, 300 mg Q2W, 600 mg Q2W, 300 mg Q4W, each administered by SC injection; 1/5/10 mg/kg administered by IV injection). Additionally, two studies evaluated a soluble IL-4R (Borish 1999; Borish 2001), two studies evaluated GSK679586 (De Boever 2014; Hodsman 2013), and one study valuated each of IMA-638 (NCT00425061), VR492 (Burgess 2018), RPC4046

(Tripp 2017) and pitrakinra (Wenzel 2010). Concomitant inhaled corticosteroid (ICS) use was permitted or required in most of the included studies, with the exception of five (Borish 1999; Borish 2001; Hodsman 2013; Korenblat 2018; Noonan 2013).

Of the five allergen challenge studies, two evaluated IMA-638 (Gauvreau 2011a; Gauvreau 2011b), two evaluated pitrakinra (Wenzel 2007a; Wenzel 2007b) and one evaluated lebrikizumab (Scheerens 2014).

Outcomes

Most prespecified outcomes were reported by at least seven of the included studies (reporting data for ≥ 4960 participants). The proportion of participants experiencing an exacerbation requiring an emergency department visit or hospitalisation was reported by two large studies (reporting data for 2039 participants) and the proportion of patients experiencing an exacerbation requiring a course of OCS was only reported by one study (reporting data from 452 participants). However, a post hoc exploratory endpoint combining the two prespecified outcomes relating to exacerbations (i.e. the proportion of patients requiring emergency department visit, hospitalisation or OCS) was evaluated by seven studies (reporting data for 6998 participants). Health-related quality of life (measured using the Asthma Quality of Life Questionnaire (AQLQ)) was evaluated by seven studies, lung function (change from baseline in FEV1) was evaluated by 13 studies, asthma control (measured by the Asthma Control Questionnaire (ACQ)-5) was evaluated by 14 studies and adverse events and serious adverse events by 18 and 22 studies, respectively (Summary of findings 1 and Table 2). Time off work or study was not reported by any of the included studies. Changes from baseline in FENO, blood eosinophils and periostin were evaluated by 11, six and two studies, respectively.

Five studies contributed data to the subanalysis of the post hoc outcome 'proportion of patients requiring emergency department visit, hospitalisation or OCS' according to levels of blood eosinophils (Castro 2018; Hanania 2016a; Hanania 2016b; Rabe 2018; Wenzel 2016), FENO (Castro 2018) or periostin (Hanania 2015a; Hanania 2015b; Hanania 2016a; Hanania 2016b).

With the exception of FEV1, the allergen challenge studies did not evaluate prespecified outcomes of interest.

Excluded studies

We excluded 18 studies from the review following examination of full-text reports. Nine studies used a control arm not relevant to this review (i.e. not placebo or a prespecified active comparator) (NCT00339872; NCT00638989; NCT00785668; NCT01592396; NCT02085473; NCT02134028; NCT02546869; NCT02902809; Nsouli 2018); in five studies, the study population was not relevant to this review (e.g. participants had respiratory comorbidities or were healthy volunteers) (Bachert 2016; Bachert 2019; NCT01875003; Oh 2009; Weinstein 2017); in one study, patients received an intervention (omalizumab) not relevant to this review (Djukanovic 2004); in one study patients were not randomised (Banfield 2008); and one study used a sequential study design (Parsey 2004). The CLAVIER study (NCT02099656) was terminated early and drug dosing was terminated and enrolment closed before the planned sample size was achieved; therefore, this study was excluded (as only an article reporting bronchoscopy data from this study was available (Austin 2020)).

Risk of bias in included studies

Please refer to the Characteristics of included studies tables for details on risk of bias and for supporting evidence for each study. Figure 2 provides a summary of risk of bias judgements, presented by study and domain (sequence generation, allocation concealment, blinding, incomplete data, selective reporting and 'other'). Figure 3 depicts the risk of bias for each domain, presented as percentages across all included studies. Across 306 assessments (34 studies, nine risk of bias domains), 23 6 were considered to be at a low risk of bias, 15 at a high risk of bias and 5 5 to have an unclear risk of bias.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

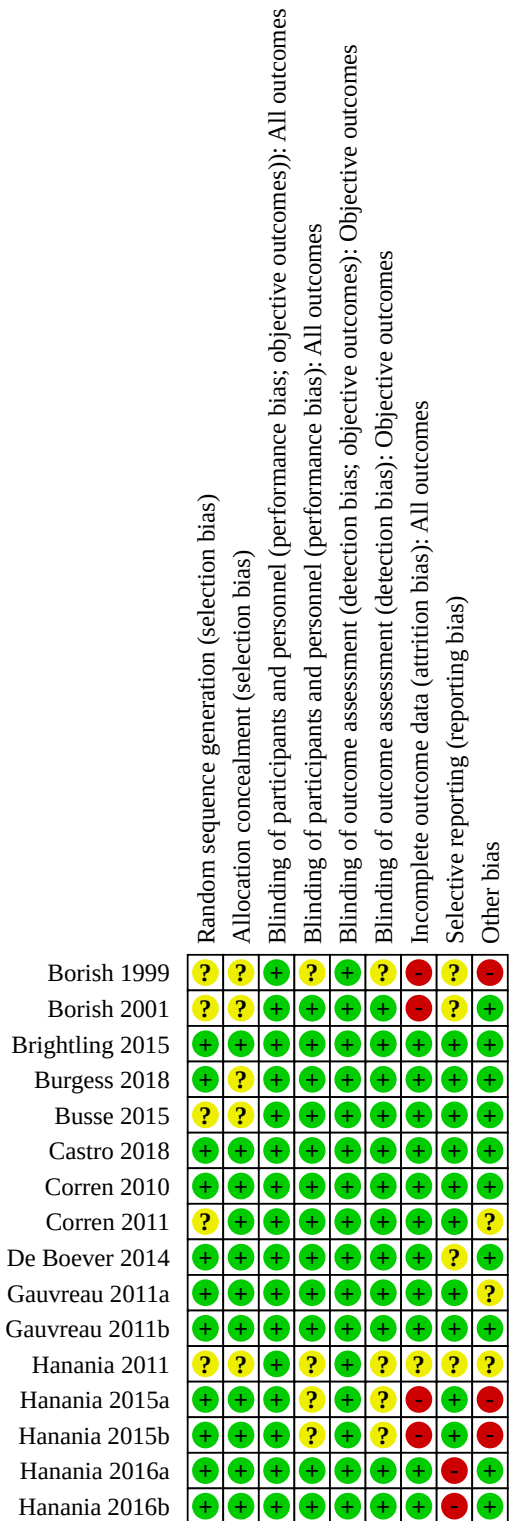


Figure 2. (Continued)

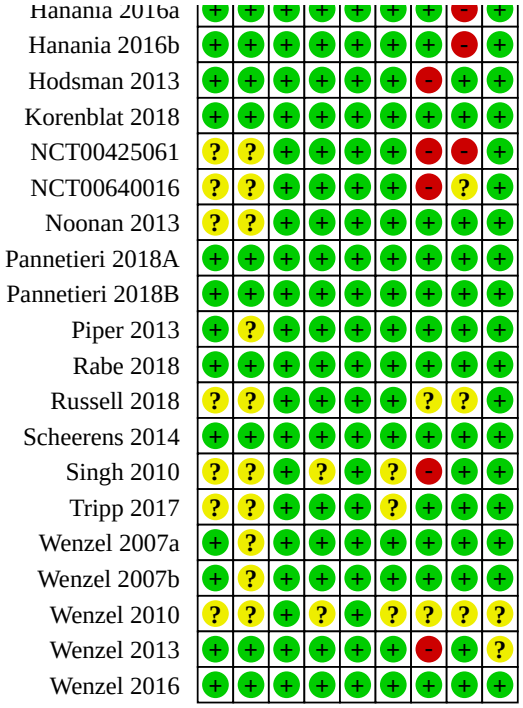
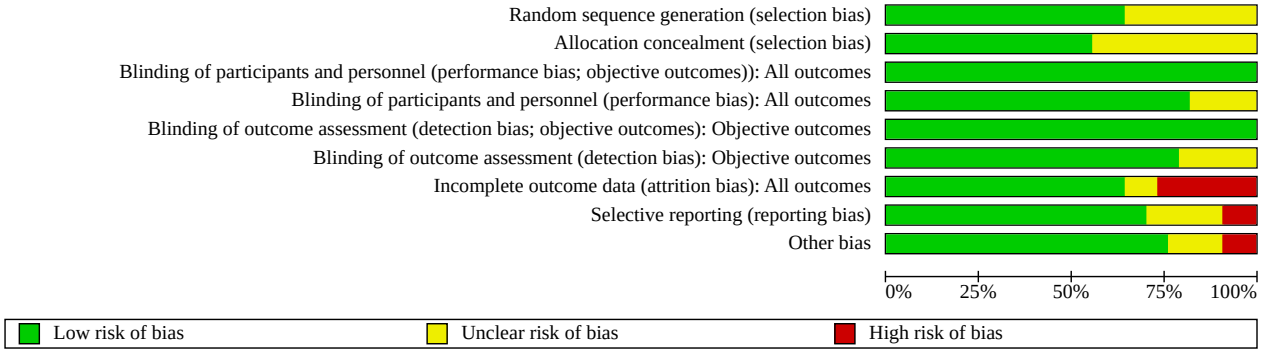


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Approximately a third of the included studies (12 of 34) provided insufficient information regarding methods of random sequence generation and approximately half (15 of 34 studies) provided insufficient information regarding concealment of treatment allocation to allow a judgement on risk of bias; the risk of bias for these studies was rated as unclear. Twenty-two studies employed adequate methods of random sequence generation and were considered to be at low risk of bias, and 19 of 34 studies reported adequate methods of allocation concealment. No studies were considered to have a high risk of selection bias.

Blinding

We considered the risk of performance and detection bias for objective and subjective outcomes separately. For objective outcomes (all-cause mortality, serious adverse events (SAEs), exacerbations, lung function, time off work or study, reduction in corticosteroid dose, Adverse events (AEs) and measures of airway inflammation) we considered that a lack of blinding would not result in a risk of detection or performance bias; therefore, all studies were considered to be at low risk of bias with respect to these outcomes. The only subjective outcomes relevant to this review were health-related quality of life (HRQoL) based on assessment of AQLQ, and asthma control determined by the ACQ; for these outcomes, 28 of 34 studies were considered to be at low risk of performance bias and the risk unclear in the remaining

six studies (Borish 1999; Hanania 2011; Hanania 2015a; Hanania 2015b; Singh 2010; Wenzel 2010). The risk of detection bias for the HRQoL and asthma control outcomes was considered to be low for 2 7 of 34 studies and unclear in the remaining seven studies (Borish 1999; Hanania 2011; Hanania 2015a; Hanania 2015b; Singh 2010; Tripp 2017; Wenzel 2010).

Incomplete outcome data

We considered 22 of 34 studies to be at low risk of attrition bias on the basis of low and balanced rates of participant withdrawal, which were adequately documented in the trial reports. Nine studies (Borish 1999; Borish 2001; Hanania 2015a; Hanania 2015b; Hodsman 2013; NCT00425061; NCT00640016; Singh 2010; Wenzel 2013) were considered to be at high risk for attrition bias based on either a high proportion of withdrawals in one or more treatment arms, an uneven proportion of withdrawals between treatment arms, or both; in some instances, high or imbalanced withdrawal rate arose due to early study termination (Hanania 2015a; Hanania 2015b; Singh 2010). Insufficient information was reported for three studies (Hanania 2011; Russell 2018; Wenzel 2010), resulting in a rating of unclear risk of attrition bias.

Selective reporting

We considered 24 of 34 studies to be at low risk of reporting bias. Three studies were considered to be at high risk of reporting bias; in one instance, the study was stopped early due to futility of the interim efficacy analysis results and the sponsor decided to only analyse safety results and key efficacy data (NCT00425061); and in two instances, outcomes were reported by biomarker level, which was not prespecified in the trial registry (Hanania 2016a; Hanania 2016b). Seven studies (Borish 1999; Borish 2001; De Boever 2014; Hanania 2011; NCT00640016; Russell 2018; Wenzel 2010) provided insufficient information (i.e. comparison of prespecified and reported outcomes was not possible).

Other potential sources of bias

No 'other' sources of bias were identified in 26 of the included studies. Five studies were rated as 'unclear' for other risk of bias, where insufficient information was available (abstract only; Hanania 2011; Wenzel 2010) or it was uncertain how the anomaly would affect the results (lack of formal sample size calculation and lower than planned dose of allergen received [Gauvreau 2011a]; or imbalance in baseline characteristics where the effect on treatment effect was uncertain [Corren 2011; Wenzel 2013]). We considered there to be potential sources of bias present in three of the studies: in one study (Borish 1999) the authors stated that baseline characteristics were balanced, but there appeared to be a trend towards better baseline lung function and fewer symptoms in the placebo group versus IL-4R groups, which would tend to favour placebo with regards to treatment effect; and in two studies (Hanania 2015a; Hanania 2015b), the protocol underwent substantial modification after study initiation because the study drug was found to contain an impurity that required a manufacturing change and the study was downgraded to a phase IIb (from phase III) and planned enrolment was greatly reduced.

Effects of interventions

See: **Summary of findings 1** Anti-IL13 or anti-IL4 agents compared to placebo for children and adults with asthma; **Summary of findings 2** Other secondary and post hoc exploratory outcomes

Structure of the meta-analysis

We performed a meta-analysis only when interventions and outcomes were sufficiently similar to permit the pooling of data. In each forest plot, we subgrouped the data according to type and dose of anti-interleukin-13 or anti-interleukin-4 agent. A number of comparisons should be interpreted with caution due to the relatively small number of trials for each subgroup, heterogeneity in study design (i.e. length of study, and eligibility criteria), or a low number of events (e.g. SAEs).

Structure of the narrative synthesis

In the following sections, we present a narrative summary of the effects of the interventions according to the prespecified outcomes of interest (primary: exacerbations requiring hospitalisation or emergency department visit, respiratory health-related quality of life, SAEs; secondary: exacerbations requiring OCS, lung function, asthma control, time off work or study, AEs, measures of airway inflammation, reduction in OCS dose; exploratory outcome: exacerbation requiring OCS/hospitalisation/emergency department visit). For each outcome, we described the overall effect of the intervention irrespective of anti-interleukin-13/-4 agent or dose, followed by the effect of the intervention in subgroups according to anti-interleukin-13/-4 agent and dose.

Several studies examined the response to anti-interleukin-13/-4 agents following allergen challenge (Gauvreau 2011a; Gauvreau 2011b; Scheerens 2014; Wenzel 2007a; Wenzel 2007b). Data from these studies were not included in the meta-analyses as these studies posed a different clinical question.

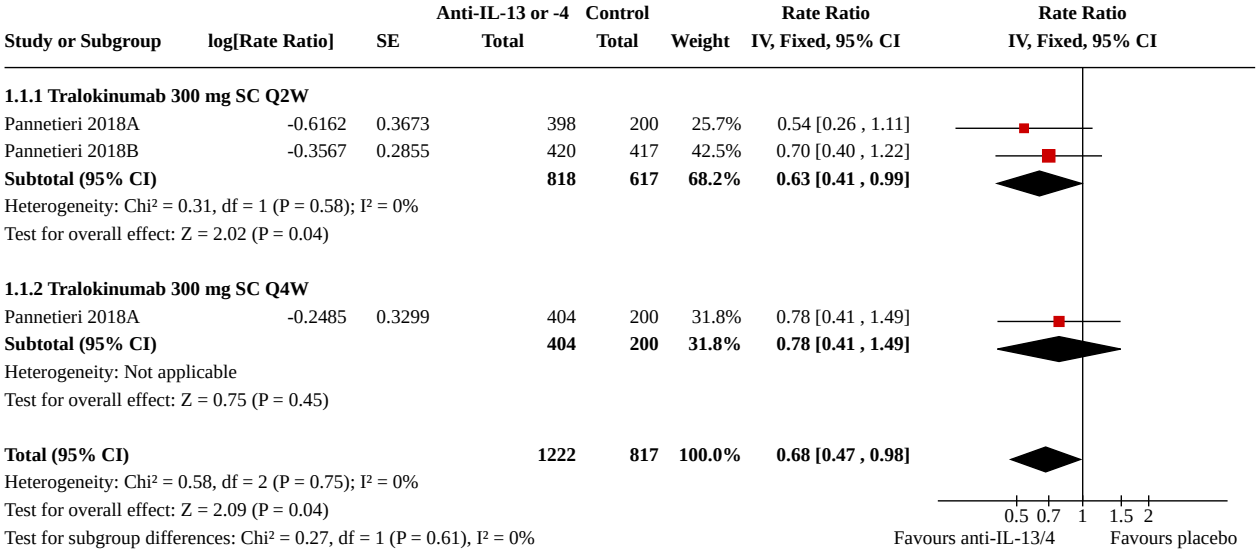
Primary outcomes

Exacerbations requiring hospitalisation or emergency department visit

Two studies (2039 participants) reported exacerbations requiring hospitalisation or emergency department visit; both studies compared tralokinumab with placebo (Pannetieri 2018A; Pannetieri 2018B). The rate of exacerbations requiring hospitalisation or emergency department visit was lower in participants receiving tralokinumab versus placebo (rate ratio 0.68, 95% CI 0.47 to 0.98; Analysis 1.1). The overall certainty of the evidence for this outcome was rated as moderate, having been downgraded once for indirectness (low number studies of a single anti-interleukin-13 agent).

Evaluation of the results by agent and dose showed that a reduction in the rate of exacerbations requiring hospitalisation or emergency department visit was achieved in participants receiving tralokinumab 300 mg subcutaneous (SC) every two weeks (Q2W; rate ratio 0.63, 95% CI 0.41 to 0.99; P = 0.04; n = 2 studies; n = 1435 participants); in participants receiving tralokinumab 300 mg SC Q4W, the 95% confidence intervals included no difference (rate ratio 0.78, 95% CI 0.41 to 1.49; P = 0.45; n = 1 study; n = 604 participants) (Figure 4). The test for subgroup differences was not significant (P = 0.61).

Figure 4. Forest plot of comparison: 1 Anti-interleukin-13 or -4 agents with placebo, outcome: 1.1 Exacerbation requiring hospitalisation or ED visit.



Respiratory health-related quality of life

Seven studies (4960 participants) reported adjusted respiratory HRQoL at the end of treatment (i.e. change from baseline in HRQoL), as assessed using the AQLQ (Brightling 2015; Castro 2018; Corren 2010; Korenblat 2018; Pannetieri 2018A; Pannetieri 2018B; Wenzel 2016). An increase in AQLQ score represents an improvement in quality of life, with a change of 0.5 units considered as the minimally clinically important difference (MCID). In participants receiving an anti-interleukin-13/-4 agent, the mean improvement versus placebo in adjusted AQLQ score was 0.18 (95% CI 0.12 to 0.24; Analysis 1.2); however, this finding did not exceed the MCID and was thus deemed not to be a clinically relevant improvement. The overall certainty of the evidence for this outcome was rated as high.

The results were generally consistent across different anti-interleukin-13/-4 agents and doses, with mean differences versus placebo ranging from 0.11 with tralokinumab 300 mg SC Q2W, to 0.30 with dupilumab 300 mg SC Q4W. Although some statistically significant effects were observed with individual agents (dupilumab 200 mg SC Q2W [MD 0.29, 95% CI 0.16 to 0.42; P < 0.0001; participants = 1111; studies = 2]; dupilumab 300 mg SC Q2W [MD 0.27, 95% CI 0.14 to 0.40; P < 0.0001; participants = 1127; studies = 2]; tralokinumab 300 mg SC Q2W [MD 0.11, 95% CI -0.00 to 0.23; P = 0.06; participants = 1262; studies = 3]), none of the improvements exceeded the MCID and were thus not considered to be clinically relevant (Analysis 1.2). Furthermore, the overall test for subgroup differences was negative (P = 0.17).

Serious adverse events

Twenty-two studies (7739 participants) reported the number of participants experiencing SAEs during the study period; there was probably little or no difference between groups (anti-interleukin-13/-4 agents versus placebo; OR 0.91, 95% CI 0.76 to 1.09; I^2 = 0%; Analysis 1.3). Compared with taking placebo, we estimated that taking an anti-interleukin-13/-4 agent would result in seven fewer people per 1000 experiencing an SAE, but the confidence intervals ranged from 18 fewer to six more people per 1000. The overall certainty of the evidence for this outcome was rated as moderate, having been downgraded once for imprecision (95% CI for the treatment effect crossed 1.0).

The results were consistent across the different anti-interleukin-13/-4 agents and doses, with ORs ranging from 0.16 with lebrikizumab 37.5 mg SC Q4W to 2.59 with IMA-638 IV 200 mg SC (Figure 5); the overall test for subgroup differences was negative (P = 0.99).

Figure 5. Forest plot of comparison: 1 Anti-interleukin-13 or -4 agents with placebo, outcome: 1.2 Health-related quality of life (adjusted mean diff versus placebo). A change of 0.5 is considered the minimum clinically significant difference (MCID).

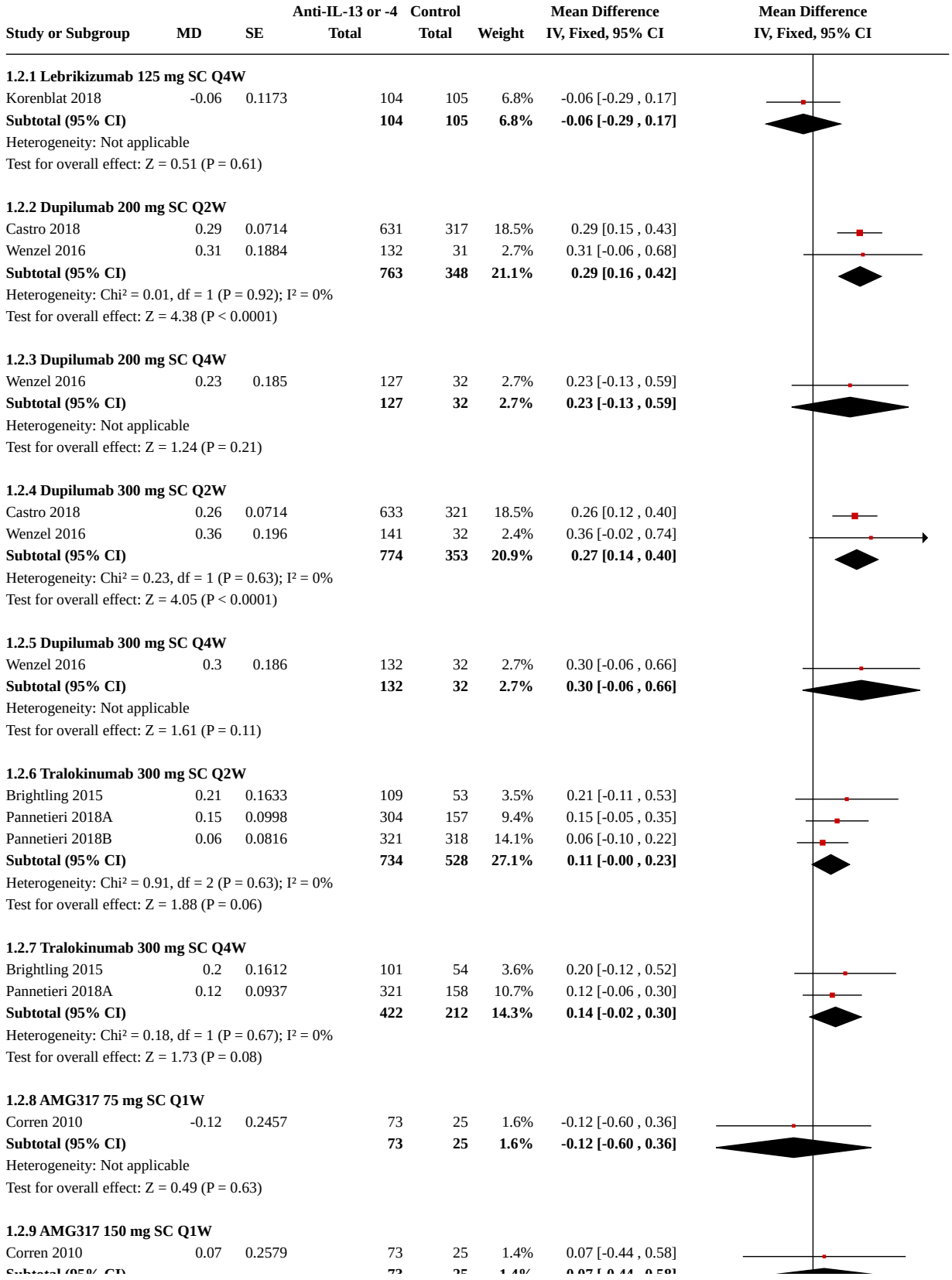
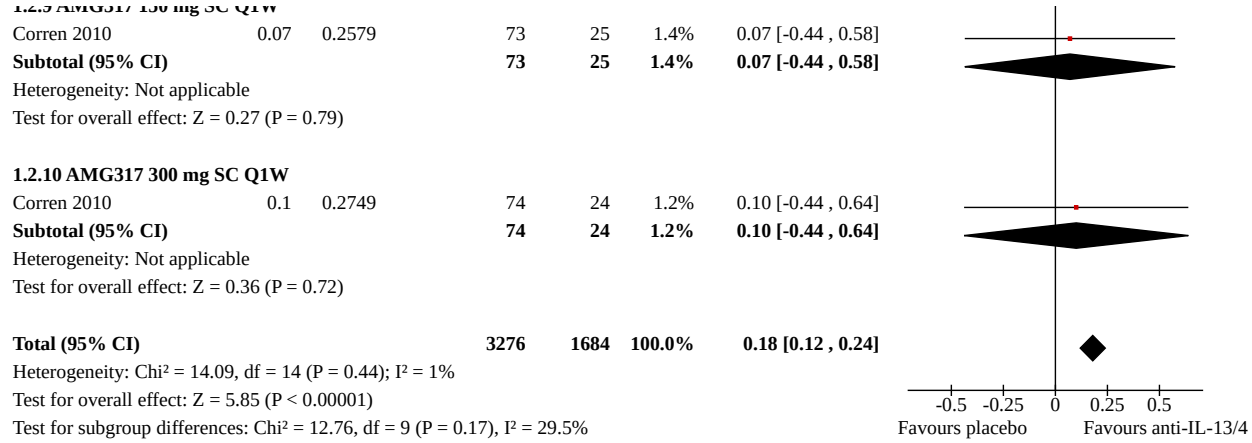


Figure 5. (Continued)



Secondary outcomes

Exacerbations requiring OCS

One study (452 participants) reported annualised rates of exacerbations requiring treatment with OCS (Brightling 2015); compared with placebo, there may be little or no difference in the rate of exacerbations requiring OCS in patients receiving tralokinumab (rate ratio 0.98, 95% CI 0.72 to 1.32; Analysis 1.4). The rate ratio was consistent for both dose regimens of tralokinumab examined (300 mg SC Q2W: rate ratio 0.94, 95% CI 0.62 to 1.42; 300 mg SC Q4W: rate ratio 1.02, 95% CI 0.65 to 1.59) (overall test for subgroup differences was negative (P = 0.79)) . The overall certainty of the evidence for this outcome was rated as low, having been downgraded once for imprecision (95% CI for the treatment effect crossed 1.0) and once for indirectness (low number studies of a single anti-interleukin-13 agent).

Two studies reported the number of participants experiencing an exacerbation requiring treatment with OCS (Corren 2010; NCT00425061) . There was no clear difference in the number of participants experiencing an exacerbation requiring OCS between those receiving an anti-interleukin-13 agent and those receiving placebo (OR 0.93, 95% CI 0.49 to 1.78; participants = 453; I^2 = 29%; Analysis 1.5), although confidence intervals were wide. Acknowledging the small sample sizes per study, this finding was consistent for both agents examined, regardless of dose. Where estimable, the odds ratio versus placebo ranged from 0.47 to 1.14 across doses of AMG317, from 6.38 to 19.29 with SC doses of IMA638, and from 0.09 to 0.33 with IV doses of IMA638. The overall test for subgroup differences was negative (P = 0.20).

Lung function (adjusted trough FEV1)

A total of 13 studies (n = 4829 participants) reported adjusted trough FEV1 at the end of treatment (i.e. change from baseline in FEV1). In participants receiving an anti-interleukin-13/4 agent, the mean difference versus placebo in adjusted trough FEV1 was 0.10 L (95% CI 0.08 to 0.12; I^2 = 36%; Analysis 1.6). The MCID in FEV_1 has not been definitively established for asthma, but it is likely that changes of 100 mL to 200 mL in FEV_1 are clinically important (Santanello 1999). Therefore, improvements in adjusted trough FEV1 observed in participants receiving anti-interleukin-13/4 agents are borderline clinically relevant. The overall certainty of the evidence for this outcome was rated as moderate, having been downgraded once for inconsistency (moderate heterogeneity of 36%).

The results were generally consistent across the different anti-interleukin-13/4 agents and doses examined. An exception to the general trend was observed with GSK679586 10 mg/kg IV Q1W where a statistically significant *decrease* in trough FEV1 was observed (MD -0.10, 95% CI -0.19 to -0.01; participants = 198), although this result was based on a single study and did not exceed the MCID. The overall test for subgroup differences was significant (P = 0.005), largely driven by this outlying result.

Asthma control

Fourteen studies (n = 6251 participants) reported adjusted ACQ scores at the end of treatment (i.e. change from baseline in ACQ score). In participants receiving an anti-interleukin-13/-4 agent versus placebo, there is probably a greater improvement in the mean adjusted ACQ score (MD -0.19, 95% CI -0.24 to -0.14; I^2 = 14%; Analysis 1.7); however, the magnitude of the improvement did not exceed the MCID of 0.40 (Nguyen 2014). The overall certainty of the evidence for this outcome was rated as moderate, having been downgraded once for inconsistency (moderate heterogeneity of 14%).

Results were generally consistent across the different anti-interleukin-13/-4 agents and doses examined, but the effect never exceeded the MCID of 0.40 (Analysis 1.7) (overall test for subgroup differences P = 0.07).

Time off work or study

No studies reported data for this outcome.

Adverse events (all causes)

A total of 18 studies (n = 7419 participants) reported the number of participants reporting any adverse event during the study period. The proportion of patients experiencing any AE was greater in those receiving anti-interleukin-13/-4 agents compared with those receiving placebo (OR 1.16, 95% CI 1.04 to 1.30; participants =

7419; I^2 = 0%; Analysis 1.8). The most commonly reported adverse events in participants treated with anti-interleukin-13/-4 agents were upper respiratory tract infection, nasopharyngitis, headache and injection site reaction. The overall certainty of the evidence for this outcome was rated as high. Examination of the results across different agents and doses (Analysis 1.8) revealed little or no difference versus placebo for all agents and doses, with the exception of tralokinumab 300 mg SC Q2W (OR 1.37, 95% CI 1.11 to 1.69; P = 0.004); the weighting of this subgroup (25.9%) appeared to account for the statistical significance of the pooled effect. The overall test for subgroup differences was negative (P = 0.81).

Measures of airway inflammation

Change from baseline in FENO

Eleven studies (n = 3577 participants) reported adjusted FENO levels at the end of treatment. In participants receiving an anti-interleukin-13/-4 agent, the mean difference versus placebo in adjusted FENO levels at the end of treatment was -14.68 (95% CI -16.56 to -12.80; I^2 = 46%; Analysis 1.9). The overall certainty of the evidence for this outcome was rated as moderate, having been downgraded once for inconsistency (moderate heterogeneity of 46%). This effect was generally consistent across individual agents and doses with the magnitude of the observed difference versus placebo ranging from -40 ppb with GSK679586 10 mg/kg IV Q4W, to -3.8 ppb with VR492 0.5 mg (Analysis 1.9). The relative reduction in FENO was statistically significant for all subgroups with the exception of the lebrikizumab 500 mg SC Q4W, dupilumab 200 mg SC Q4W, VR492 0.5 mg and nebulised soluble IL-4R 500 µg and 1500 µg groups (acknowledging the low number of participants in the soluble IL-R4 and VR492 groups). The overall test for subgroup differences was significant at P = 0.03, but should be interpreted with caution, given the small size and low participant numbers in many of the individual subgroups.

Change from baseline in blood eosinophil count

Six studies (n = 2598 participants) reported data on adjusted blood eosinophil count at the end of treatment (Castro 2018; Corren 2011; De Boever 2014; NCT00425061; Russell 2018; Wenzel 2013). In participants receiving an anti-interleukin-13/-4 agent, the mean difference versus placebo in adjusted blood eosinophil count at the end of treatment was 0.06 x 10*9 cells/L (95% CI 0.04 to 0.09 x 10*9 cells/L; I^2 = 13%; Analysis 1.10); however, this increase is not considered to be clinically relevant. The overall certainty of the evidence for this outcome was rated as high. A consistent effect was observed across agents and doses examined (Analysis 1.10) (overall test for subgroup differences, P = 0.32), with increases from baseline versus placebo ranging from 0.02 x 10*9 cells/L with dupilumab 200 mg SC Q2W, to 0.20 x 10*9 cells/L with IMA-638 0.6 mg/kg IV and 75 mg SC.

Change from baseline in periostin concentration

Two studies (n = 2106 participants) reported data-adjusted periostin levels at the end of treatment (Castro 2018; Korenblat 2018). In participants receiving either lebrikizumab or dupilumab, the mean difference versus placebo in adjusted periostin concentration at the end of treatment was -9.04 ng/mL (95% CI -10.92 to -7.17 ng/mL; I^2 = 92%; Analysis 1.11). The overall certainty of the evidence for this outcome was rated as low, having been downgraded twice for inconsistency (considerable heterogeneity of 92%). The magnitude of the relative reduction in adjusted periostin levels was greater for dupilumab with SC doses of 200 or 300 mg Q2W (MD -14 ng/mL) than with lebrikizumab at a dose of 125 mg Q4W (MD -4.2 ng/mL) (overall test for subgroup differences P < 0.00001).

Reduction in maintenance oral corticosteroid dose

Two studies (350 participants) reported the percentage reduction from baseline in OCS use (Busse 2015; Rabe 2018). In participants receiving either lebrikizumab or dupilumab, the mean reduction in OCS dose versus placebo at end of treatment was -15.58% (95% CI -23.30 to -7.85; I^2 = 84%; Analysis 1.12). The overall certainty of the evidence for this outcome was rated as low, having been downgraded twice for inconsistency (considerable heterogeneity of 84%). In terms of subgroups, one study reported a non-significant 7.8% reduction in OCS dose in patients receiving tralokinumab 300 mg SC Q2W versus placebo (MD -7.77, 95% CI -17.60 to 2.06; participants = 140), whereas a statistically significant 28% reduction in OCS dose was reported in the second study for patients receiving dupilumab 300 mg SC Q2W versus placebo (MD -28.20, 95% CI -40.70 to -15.70; P < 0.00001; participants = 210). However, the overall test for subgroup differences was negative (P = 0.32).

Post hoc exploratory outcome

Exacerbations requiring hospitalisation, emergency department visit or OCS

Seven studies (6998 participants) reported exacerbations requiring OCS or hospitalisation or emergency department visit (Busse 2015; Castro 2018; Hanania 2016a; Hanania 2016b; Pannetieri 2018A; Pannetieri 2018B; Wenzel 2016). The rate of exacerbations requiring OCS or hospitalisation or emergency department visit may be lower in participants receiving anti-13/-4 agents versus placebo (rate ratio 0.71, 95% CI 0.65 to 0.77; participants = 6998; I^2 = 67%; Analysis 1.13). The overall certainty of the evidence for this outcome was rated as low, having been downgraded twice for inconsistency (substantial heterogeneity of 67%).

Evaluation of the results by agent and dose showed that, although a reduction in the rate of exacerbations requiring hospitalisation or emergency department visit was seen for all agents and doses, the magnitude and certainty of this reduction was greater in participants receiving lebrikizumab 37.5 mg SC Q4W (rate ratio 0.68, 95% CI 0.53 to 0.87; n = 2 studies; participants = 1074), lebrikizumab 125 mg SC Q4W (rate ratio 0.74, 95% CI 0.59 to 0.93; n = 2 studies; participants = 1074), dupilumab 200 mg SC Q2W (rate ratio 0.51, 95% CI 0.40 to 0.64; n = 2 studies; participants = 1135) and dupilumab 300 mg SC Q2W (rate ratio 0.52, 95% CI 0.42 to 0.65; n = 2 studies participants = 1144). The reduced rates of exacerbations requiring OCS, hospitalisation or emergency department visit were uncertain with tralokinumab 300 mg SC (either Q2W or Q4W) or with dupilumab SC Q4W (either 200 mg or 300 mg) (Analysis 1.13). This is reflected in the overall test for subgroup differences (P < 0.00001), although cautious interpretation is required due to the small size and low participant numbers in many of the individual subgroups.

Prespecified subgroup analyses

Individual anti-interleukin-13 or anti-interleukin-4 agent

The effect of individual agents is reported in the main analyses of the primary and secondary outcomes (see above).

Agent class

This subgroup analysis evaluated the effect of agents directly targeting IL13 (tralokinumab, lebrikizumab, GSK679-586, IMA-638, RPC-4046) versus the effects of agents directly targeting IL4R (dupilumab, AMG-317, pitrakinra, soluble IL-4R).

For the primary outcome, exacerbations requiring hospitalisation or emergency department (ED) visit, only two studies of tralokinumab, which targets interleukin-13, contributed data to the meta-analysis. Therefore, a comparison between agents directly targeting interleukin-13 and IL-4R, could not be performed for this outcome as no data for agents directly targeting IL-4 were available.

For the primary outcome, health-related quality of life, agents directly targeting interleukin-13 resulted in an improvement in respiratory health-related quality of life versus placebo, as assessed by AQLQ (MD 0.10, 95% CI 0.01 to 0.18; participants = 2105; Analysis 2.2), as did agents directly targeting IL-4R (MD 0.26, 95% CI 0.17 to 0.34; participants = 2855; Analysis 3.1); neither improvement versus placebo exceeded the MCID for AQLQ.

For the primary outcome, SAEs, subgroup analyses by agent class were consistent with the primary analyses (agents directly targeting interleukin-13 versus placebo: OR 0.84, 95% CI 0.67 to 1.05; participants = 4443; Analysis 2.3; agents directly targeting IL4R versus placebo: OR 1.05, 95% CI 0.78 to 1.40; participants = 3296; Analysis 3.2).

Studies of three agents (dupilumab, lebrikizumab, tralokinumab) contributed data to the meta-analyses for the exploratory outcome, exacerbations requiring hospitalisation/ED/OCS. The rate of exacerbations requiring OCS or hospitalisation or emergency department visit was lower in participants receiving agents directly targeting interleukin-13 (tralokinumab or lebrikizumab; rate ratio 0.83, 95% CI 0.74 to 0.92; participants = 4327; Analysis 2.4) compared with placebo. The rate of exacerbations requiring OCS or hospitalisation or emergency department visit was also lower in participants receiving agents directly targeting IL-4R (dupilumab; rate ratio 0.52, 95% CI 0.44 to 0.61; participants = 2671; Analysis 3.3) compared with placebo. The magnitude of the improvement versus placebo appeared to be greater with dupilumab compared with agents directly targeting interleukin-13; however, formal statistical comparison was not performed.

Duration of therapy

This subgroup analysis examined the effect of treatment duration (≤ six months versus > six months).

For the primary outcome, exacerbations requiring hospitalisation or ED visit, only two 52-week studies of tralokinumab contributed data to the meta-analysis. Therefore, a comparison between studies of duration ≤ six months or > six months could not be performed for this outcome.

For the primary outcome, health-related quality of life, considering data from studies with a duration of six months or less demonstrated an improvement in respiratory health-related quality of life versus placebo, as assessed by AQLQ (MD 0.13, 95% CI -0.00 to 0.26; participants = 1162; Analysis 4.1); this was also the case when considering data from studies with a duration greater than six months (MD 0.19, 95% CI 0.13 to 0.26; participants = 3798; Analysis 5.2); neither improvement versus placebo exceeded the MCID for AQLQ.

For the primary outcome, SAEs, subgroup analyses by study duration were consistent with the primary analyses. There was no clear difference between anti-interleukin-13/-4 agents versus placebo, when considering data from studies of duration ≤ six months (OR 1.09, 95% CI 0.73 to 1.63; participants = 2738; Analysis 4.2) or > six months (OR 0.87, 95% CI 0.72 to 1.06; participants = 5001; Analysis 5.3). However, confidence intervals did not exclude an effect.

For the exploratory outcome, exacerbations requiring hospitalisation/ED/OCS, only one of the studies contributing to the primary analyses had a duration of six months or less. Results from this study showed that the rate of exacerbations was lower in participants receiving dupilumab versus placebo (rate ratio 0.43, 95% CI 0.27 to 0.68; participants = 769; Analysis 4.3). Considering data from studies of a duration greater than six months also showed that the rate of exacerbations was lower in participants receiving anti-IL13/-4 agents versus placebo (rate ratio 0.72, 95% CI 0.66 to 0.79; participants = 6229; Analysis 5.4).

Severity of asthma

This subgroup analysis examined the effect of asthma severity (mild-to-moderate versus severe) as per Global Initiative for Asthma (GINA) or British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) definitions. We note that this approach excludes consideration of data from studies that enrolled participants with moderate-to-severe asthma.

The two studies contributing data to the meta-analysis for the primary outcome, exacerbations requiring hospitalisation or ED visit, enrolled participants with severe, uncontrolled asthma (Pannetieri 2018A; Pannetieri 2018B); thus, no subgroup analysis could be performed for this outcome.

For the primary outcome, health-related quality of life, an improvement in respiratory health-related quality of life versus placebo, as assessed by AQLQ, was observed in participants with severe asthma (MD 0.21, 95% CI 0.14 to 0.27; participants = 4457; Analysis 7.2), but was not observed in the relatively small subgroup of participants with mild-to-moderate asthma (MD -0.06, 95% CI -0.29 to 0.17; participants = 209; Analysis 7.1). However, formal statistical comparison was not performed and the MCID for AQLQ was not exceeded in either subgroup.

For the primary outcome, SAEs, subgroup analyses by asthma severity were consistent with the primary analyses. There was no clear difference between anti-interleukin-13/-4 agents versus placebo, in participants with mild or moderate asthma, although confidence intervals were wide (OR 1.41, 95% CI 0.49 to 4.01; participants = 664; Analysis 6.2) or in participants with severe asthma (OR 0.94, 95% CI 0.78 to 1.13; participants = 5946; Analysis 7.3).

For the exploratory outcome, exacerbations requiring hospitalisation/ED/OCS, all of the studies contributing data to the meta-analysis enrolled participants with either severe or moderate-to-severe asthma. Therefore, a subgroup analysis examining this outcome in participants with mild or moderate versus severe asthma could not be performed.

Dose of corticosteroids (including prednisone), at randomisation

To some extent, the dose of corticosteroids at randomisation reflects the severity of asthma experienced (see previous subanalysis). Therefore, we considered the effect of concomitant ICS use versus no concomitant ICS use during the study. Only five of the included studies discontinued ICS prior to study start or enrolled participants who were not previously taking ICS (Borish 1999; Borish 2001; Hodsman 2013; Korenblat 2018; Noonan 2013).

The two studies contributing data to the meta-analysis for the primary outcome, exacerbations requiring hospitalisation or ED visit, permitted participants to receive ICS during the study. Therefore, subgroup analysis by ICS use could not be performed for this outcome.

For the primary outcome, respiratory health-related quality of life, an improvement versus placebo, as assessed by AQLQ, was observed in participants who received concomitant ICS (MD 0.20, 95% CI 0.13 to 0.26; participants = 4751; Analysis 9.2) but was not observed in the single study that prohibited the use of concomitant ICS (MD -0.06, 95% CI -0.29 to 0.17; participants = 209; Analysis 8.1). However, formal statistical comparison was not performed and the MCID for AQLQ was not exceeded in either subgroup.

For the primary outcome, SAEs, subgroup analyses by concomitant ICS use were consistent with the primary analyses. There was no clear difference versus placebo in participants who were not receiving concomitant ICS during the study, although confidence intervals were wide (OR 1.73, 95% CI 0.40 to 7.48; participants = 470; Analysis 8.2) or in those who were permitted to receive concomitant ICS (OR 0.90, 95% CI 0.76 to 1.08; participants = 7269; Analysis 9.3).

All of the studies contributing data to the meta-analysis for the exploratory outcome, exacerbations requiring hospitalisation/ED/OCS, permitted participants to receive ICS during the study. Therefore, subgroup analysis by ICS use could not be performed for this outcome.

Category of TH_2 inflammation

The influence of several markers of TH2 inflammation was examined by a number of the included studies.

Blood eosinophils

No studies reported data subgrouped by patients with high and low blood eosinophil levels for any of the primary outcomes.

Five studies reported data on the rate of exacerbations requiring hospitalisation/ED visit/OCS (exploratory outcome) by high and low blood eosinophil levels (Castro 2018; Hanania 2016a; Hanania 2016b; Rabe 2018; Wenzel 2016) based on the threshold of 300 cells/µL; additionally Castro 2018 reported data for low blood eosinophils > 150 and < 300 cells/µL. The studies reported data for dupilumab 200 mg Q2W, 200 mg Q4W and 300 mg Q2W, all versus placebo (Castro 2018; Rabe 2018), and for lebrikizumab 37.5 mg Q4W and 125 mg Q4W, both versus placebo (Hanania 2016a; Hanania 2016b). Overall, the subanalyses by blood eosinophil levels showed that a reduction in the rate of exacerbations requiring hospitalisation or emergency department visits or OCS was achieved in patients with high blood eosinophil levels (≥ 300 cells/µL: rate ratio 0.47, 95% CI 0.40 to 0.55; participants = 2052; studies = 5; Analysis 10.1) and low blood eosinophil levels (< 300 cells/µL: (rate ratio 0.75, 95% CI 0.65 to 0.87; participants = 1881; studies = 4; Analysis 10.2). For patients with high blood eosinophil levels, treatment with dupilumab 200 mg Q2W and 300 mg Q2W led to a large reduction in the rate of exacerbations requiring hospitalisation or emergency department visits or OCS (rate ratios 0.34, 95% CI 0.24 to 0.47 and (rate ratio 0.46, 95% CI 0.36 to 0.59, respectively). A similar reduction was observed with dupilumab 200 mg Q4W or 300 mg Q4W, but with more uncertainty. Both lebrikizumab doses were superior to placebo (37.5 mg Q4W: rate ratio 0.54, 95% CI 0.38 to 0.76; 125 mg Q4W: rate ratio 0.59, 95% CI 0.42 to 0.83). The overall test for subgroup difference was negative (P = 0.27). For patients with low blood eosinophil levels, all doses and agents resulted in a reduction in the rate of exacerbations compared to placebo, but the size and certainty of the effect varied. The overall test for subgroup differences was negative (P = 0.51).

Airway eosinophils (sputum eosinophilia ≥ 3%)

No studies reported data subgrouped by patients with high and low airway eosinophil levels for any of the primary outcomes, or the exploratory efficacy outcome.

FENO (high: ≥ 50 ppb)

No studies reported data subgrouped by patients with high and low FENO levels for any of the primary outcomes.

One study reported data on the rate of exacerbations requiring hospitalisation/ED visit/OCS (exploratory outcome) by high, medium and low serum FENO levels (Castro 2018). The study reported data for dupilumab 200 mg Q2W and 300 mg Q2W, both versus placebo. Overall, the subanalyses by FENO serum levels showed that a reduction in the rate of exacerbations requiring hospitalisation or emergency department visits or OCS use was achieved in patients with high FENO levels (≥ 50 ppb: rate ratio 0.31, 95% CI 0.22 to 0.45; participants = 389; Analysis 11.1), medium FENO levels (≥ 25 to < 50 ppb: rate ratio 0.42, 95% CI 0.30 to 0.58; participants = 554; Analysis 11.2) and low FENO levels (< 25 ppb: rate ratio 0.77, 95% CI 0.61 to 0.97; participants = 935 Analysis 11.3).

Subgroup data on the rate of exacerbations requiring hospitalisation/ED visit/OCS with tralokinumab were reported by Pannetieri 2018A and Pannetieri 2018B, but could not be used as a threshold of 37 ppb was used to separate the low and high FENO groups, in contrast to the threshold of 50 ppb prespecified in this review.

Periostin (high: ≥ 50 ng/mL)

No studies reported data subgrouped by patients with high and low serum periostin levels for any of the primary outcomes.

Four studies reported data on the rate of exacerbations requiring hospitalisation/ED visit/OCS (exploratory outcome) by high and low serum periostin levels (Hanania 2015a; Hanania 2015b; Hanania 2016a; Hanania 2016b); the results of the two VERSE trials (Hanania 2015a; Hanania 2015b) were reported in combined fashion and are entered into the analyses under Hanania 2015a. The four studies reported data for lebrikizumab 37 mg Q4W and 125 mg Q4W, both versus placebo; two studies also reported data for lebrikizumab 250 mg Q4W. Overall, the subanalyses by periostin serum levels showed that a reduction in the rate of exacerbations requiring hospitalisation or emergency department visits or OCS use was achieved in patients with high serum periostin levels (≥ 50 ng/mL: rate ratio 0.63, 95% CI 0.51 to 0.77; participants = 1499; studies = 3; Analysis 12.1); in patients with low serum periostin

levels the 95% confidence intervals included no difference (< 50 ng/mL: rate ratio 0.87, 95% CI 0.68 to 1.11; participants = 1212; studies = 3; Analysis 12.2). For patients with high serum periostin levels, both the 37.5 mg and 125 mg Q4W doses reduced exacerbation rates compared with placebo (rate ratio 0.59, 95% CI 0.43 to 0.79 and 0.66, 95% CI 0.49 to 0.89, respectively). The difference versus placebo was more uncertain for the 250 mg Q4W dose (rate ratio 0.78, 95% CI 0.27 to 2.24).

Subgroup data on the rate of exacerbations requiring hospitalisation/ED visit/OCS with tralokinumab were reported by Brightling 2015 but were not compatible with the present subgroup analyses as the threshold used to differentiate between low and high serum periostin levels was based on the median periostin levels at baseline (~23 ng/mL), in contrast to the threshold of 50 ng/mL prespecified in this review.

Sensitivity analyses

The following sensitivity analyses were performed for the primary outcomes.

Unpublished data

No unpublished data (i.e. not publicly available) were included in this review, so it was not possible to perform this prespecified sensitivity analysis.

Fixed- versus random-effect models

The results were consistent regardless of choice of analysis model (fixed- versus random-effects model) (Table 2).

Risk of bias assessments

None of the included studies were considered to be at high risk of bias for blinding of participants and personnel, or high risk of bias for random sequence generation or allocation concealments; therefore, these sensitivity analyses could not be conducted.

DISCUSSION

Summary of main results

Twenty-nine studies with a median duration of 16 weeks contributed data to the quantitative analyses in the present review; these studies randomised a total of 10,604 participants to receive either an anti-interleukin-13 agent (n = 4401 participants), an anti-interleukin-4 agent (n = 2560 participants), or placebo (n = 3643 participants). Most participants were adults with moderate or severe uncontrolled asthma. The majority of studies were well designed and considered to be at low risk of bias.

Our findings support a benefit for anti-interleukin-13/-4 agents over placebo in adult patients with asthma. For the primary endpoint "exacerbations requiring hospitalisation or OCS", only data for tralokinumab, an anti-interleukin-13 agent, were available. Compared with placebo, tralokinumab was likely associated with a reduction in the adjusted annualised exacerbation rate (moderate-certainty evidence). For the primary endpoint "health-related quality of life", anti-interleukin-13/-4 agents were associated with a small improvement over placebo; however, the improvement did not exceed the minimal clinically important difference such that the improvement in HRQoL was not considered to be clinically relevant (high-certainty evidence). There was likely little or no difference between groups (anti-interleukin-13/-4 versus placebo) in the proportion of patients experiencing serious adverse events (moderate-certainty evidence).

In terms of secondary endpoints, compared with placebo, there was a likely improvement in lung function with anti-interleukin-13/-4 agents (100 mL measured with trough FEV1) that was borderline clinically relevant (moderate-certainty evidence); a likely improvement in asthma control with anti-interleukin-13/-4 agents that was deemed not to be clinically relevant (moderate-certainty evidence); and there may be a reduction in oral corticosteroid dose (~16%) in participants receiving anti-interleukin-13/-4 agents (low-certainty evidence) driven by the reduction in OCS observed in single study with dupilumab. The proportion of patients experiencing any adverse event was higher in participants receiving anti-interleukin-13/-4 agents compared with those receiving placebo (high-certainty evidence). The most commonly reported adverse events in participants treated with anti-interleukin-13/-4 agents were upper respiratory tract infection, nasopharyngitis, headache and injection site reaction. There may be little or no difference between groups (anti-interleukin-13/-4 versus placebo) in the proportions of patients with exacerbations requiring OCS (low-certainty evidence), and there were no studies that reported data for the outcome "time off work or study". Reductions in inflammatory biomarkers were observed in participants receiving anti-interleukin-13/-4 agents compared with those receiving placebo, including in FENO (moderate-certainty evidence) and periostin concentrations (low-certainty evidence). Notably, treatment with anti-interleukin-13/-4 agents was associated with a small increase in blood eosinophil levels (high-certainty evidence).

We also analysed data for an exploratory (post hoc) endpoint "Exacerbations requiring hospitalisation, emergency department visit or OCS" as this endpoint was reported by a number of the studies, particularly in relation to biomarker levels. As the endpoint essentially combines two of the prespecified endpoints of the review, we deemed it important to examine these data. The rate of exacerbations requiring OCS or hospitalisation or emergency department visit may be lower in participants receiving anti-13/-4 agents versus placebo (low-certainty evidence).

The results of the subgroup analyses by agent class (anti interleukin-13 versus anti-interleukin-4 agent), study duration (up to six months versus six months or longer), disease severity (mild-to-moderate versus severe) and inhaled corticosteroid use at baseline (concomitant use versus non-concomitant use; i.e. a proxy for disease severity), were generally consistent with those of the primary analyses.

Subgroup analyses by category of TH2 inflammation support the notion that anti-interleukin-13/-4 agents provide greater clinical benefit in patients with higher levels of inflammatory biomarkers. Subanalysis by high and low blood eosinophil levels based on the threshold of 300 cells/μL showed that a reduction in the rate of exacerbations requiring hospitalisation/emergency department visit/OCS (post hoc exploratory outcome) was achieved in patients with high blood eosinophil levels (rate ratio 0.47, 95% CI 0.40 to 0.55) and low blood eosinophil levels (rate ratio 0.75, 95% CI 0.65 to 0.87). A similar trend was observed for FENO, where a reduction in the rate of exacerbations requiring hospitalisation or emergency department or OCS use was achieved in patients with high FENO levels (≥ 50 ppb: rate ratio 0.31, 95% CI 0.22 to 0.45), medium FENO levels (≥ 25 to < 50 ppb: rate ratio 0.42, 95% CI 0.30 to 0.58)

and low FENO levels (< 25 ppb: rate ratio 0.77, 95% CI 0.61 to 0.97), with the greatest treatment effect observed in patients with high FENO levels. Finally, subanalyses by periostin serum levels showed that a clear reduction in the rate of exacerbations requiring hospitalisation or emergency department visit or OCS use was only achieved in patients with high serum periostin levels (≥ 50 ng/mL: rate ratio 0.63, 95% CI 0.51 to 0.77) but not in patients with low serum periostin levels (< 50 ng/mL: rate ratio 0.87, 95% CI 0.68 to 1.11), although we did not perform a formal statistical comparison.

The results of the review were consistent regardless of choice of analysis model (fixed- versus random-effects model).

Overall completeness and applicability of evidence

The findings of this review are principally applicable to people with moderate-to-severe, uncontrolled asthma (95 per cent of the participants in the included studies contributing data to the quantitative analyses had moderate or severe asthma). Furthermore, studies evaluating dupilumab, lebrikizumab and tralokinumab accounted for 90 per cent of participants randomised to the studies contributing quantitative data to this review and thus the findings are most relevant to these drugs. At the time of writing, the clinical development of lebrikizumab and tralokinumab for the treatment of patients with asthma has been halted indefinitely.

Quality of the evidence

The certainty of the evidence was generally considered to be moderate or high with the exceptions of the secondary outcomes "exacerbations requiring OCS" and the exploratory outcome "exacerbations requiring emergency department visit, hospitalisation or OCS use" which were both considered to be low certainty.

We downgraded the outcome "exacerbations requiring hospitalisation or ED visit" once for indirectness, "serious adverse events" for imprecision, "exacerbations requiring OCS" for both indirectness and imprecision and "change from baseline in ACQ score" for inconsistency.

Risk of bias in the included studies was generally considered to be low or was unclear due to the lack of necessary information provided in the study reports. Across 306 assessments (34 studies, nine domains each), over three-quarters were considered to be at a low risk of bias, and only 15 were considered to be at a high risk of bias. Risk of bias was considered unclear in the remaining 5 5 assessments. Nine studies were considered to be at high risk for attrition bias based on either a high proportion of withdrawals in one or more treatment arms, an uneven proportion of withdrawals between treatment arms, or both; in some instances, high or imbalanced withdrawal rates arose due to early study termination (Hanania 2015a; Hanania 2015b; Singh 2010). Three studies were considered to be at high risk for reporting bias; in one instance, the study was stopped early due to futility of the interim efficacy analysis results and the sponsor decided to only analyse safety results and key efficacy data (NCT00425061); and in two instances, outcomes were reported by biomarker level, which was not prespecified in the trial registry (Hanania 2016a; Hanania 2016b). We did not examine whether the results were robust to the removal of studies with any domain considered to be at high risk of attrition or reporting bias as this was not a prespecified sensitivity analysis. However, no downgrading of the strength of the evidence (by GRADE) was performed on the basis of risk of bias.

Potential biases in the review process

The review was conducted to the Cochrane's MECIR standards (MECIR 2020) and in accordance with the published protocol (Edwards 2018). In particular, two authors independently screened the search results, determined studies for inclusion, assessed the risk of bias, extracted the relevant data, and performed the GRADE assessment (i.e. all steps involving subjective decisions).

There were three deviations from the protocol (see Differences between protocol and review). First, as few studies reported data on the prespecified primary endpoint for efficacy (exacerbations requiring hospitalisation or ED visit) and more studies reported the rate of exacerbations requiring hospitalisation, ED visit, or OCS use, this outcome was investigated as an exploratory outcome. For future updates of the review, we would suggest that this outcome is selected as a primary efficacy outcome. Additionally, the present review considered patients with any severity of asthma. Given that these agents are only likely to be used clinically in selected patients with uncontrolled asthma, despite the use of other medications, it would perhaps be appropriate to exclude patients with mild asthma from future updates to this review. Second, the main analyses were conducted using a fixed-effect model, and the sensitivity analyses were conducted using a random-effects model; comparison of the data derived using the two models showed no difference in findings for the primary endpoints. Finally, we did not explore possible small study and publication biases, as planned in the original protocol.

It is unlikely that any relevant studies were missed, as a skilled information specialist conducted the main electronic searches. Additionally, the main searches were supplemented by manual searches of reference lists of associated studies and reviews. Finally, this review has undergone editorial and peer review and thus considers the opinions of independent external experts. In summary, the review was conducted in a manner that should ensure that our conclusions fairly and accurately represent the results synthesised during the review process.

Agreements and disagreements with other studies or reviews

Our findings with respect to anti-interleukin-13 agents are consistent with those from a recent systematic review which examined lebrikizumab and tralokinumab for uncontrolled asthma (Li 2019). The authors reported that anti-interleukin-13 treatments were associated with a significant improvement in asthma exacerbations, FEV1 and AQLQ scores, and a reduction in rescue medication use (Li 2019).

Our findings with respect to dupilumab are consistent with three systematic reviews conducted by the European Academy of Allergy and Clinical Immunology task force that evaluated dupilumab (and other biologicals) for the treatment of severe asthma (Agache 2020), severe eosinophilic asthma (Agache 2020b) and severe allergic asthma (Agache 2020). The authors reported high-certainty evidence in patients with severe asthma that dupilumab reduced the rate of severe exacerbations and that the magnitude of the reduction was significantly greater in patients with high levels of eosinophils (≥ 300 cells/μL) or high levels of FENO (≥ 50

ppb) at baseline (Agache 2020). Improvements in asthma control, asthma-related quality of life and lung function and reduced OCS use were also observed but did not exceed the MCID for each measure (Agache 2020). Similar findings were reported with respect to patients with severe eosinophilic asthma where high-certainty evidence showed that dupilumab reduced exacerbation rates and OCS use; observed improvements in asthma control and asthma-related quality of life did not exceed the MCID (Agache 2020b). Similarly, Agache and colleagues reported high-certainty evidence that dupilumab as an add-on to standard of care reduces exacerbation rates for patients aged 12 years and over with severe allergic asthma; again, improvements in asthma control and lung function were demonstrated but did not exceed the MCID (Agache 2020).

Interestingly, anti-interleukin-13/-4 agents were not found to have an anti-eosinophilic effect; in fact, a small, statistically significant increase in blood eosinophils was observed (high-certainty evidence). The direction of this treatment effect (i.e. an increase) was consistent across all agents contributing data (tralokinumab, dupilumab, lebrikizumab, IMA-638) but was not always statistically significant for each contributing study. The effect of anti-interleukin-4 and anti-interleukin-13 inhibitors on blood eosinophil levels may depend on the duration of treatment and time points analysed. A recent analysis of eosinophil kinetics in a large cohort of patients with asthma showed that blood eosinophils increased from baseline by 9.2% at week 4, returned to baseline by week 24, and fell below baseline by week 52 (Wechsler 2021). These findings suggest that the benefit of treatment with anti-interleukin-13 or anti-interleukin-4 agents is mediated through multiple pathways, perhaps particularly on mucus clearing as demonstrated in the EXPEDITION study (NCT02573233).

AUTHORS' CONCLUSIONS

Implications for practice

As the clinical development of lebrikizumab and tralokinumab for the treatment of patients with asthma has been halted indefinitely, the following conclusions focus on the use of dupilumab. The findings of the review support the use of dupilumab in adult patients with moderate-to-severe uncontrolled asthma. Given that the magnitude of the observed effect was relatively small (reduction in exacerbations without a clinically relevant improvement in asthma control, lung function or asthma-related quality of life) the use of dupilumab is likely to be limited to a specific patient set. This is consistent with the approved indication for dupilumab, which is licensed for use in Europe for "adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FENO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment" (EMA 2021) and in the USA "as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma" (FDA 2021).

Implications for research

Given the number of published studies comparing anti-interleukin-13 or anti-interleukin-4 agents with placebo and the number of different agents studied, a future network meta-analysis may be warranted. In this way, more specific clinical advice relating to individual agents and dose regimens could be derived (the present conclusions are relevant to the class of agents as a whole). Future updates of the review should include the outcome 'exacerbations requiring emergency department visit, hospitalisation or OCS use' as a primary outcome. Future updates of the review may also wish to examine the role of demographic characteristics (e.g. age or gender). Importantly, future clinical studies are required to evaluate the safety and efficacy of these agents in children and adolescents, as this population accounted for less than 5% of the participants contributing data to the present review. It is noteworthy that the exacerbation outcomes were poorly measured/analysed/reported in the individual studies. The use of core outcome sets across trials would improve uniformity and enable more powerful synthesis of results. Future studies of anti-interleukin agents should also strive to use unified thresholds of biomarkers to define 'low' and 'high' inflammation groups. Future studies may also wish to include outcomes to examine effects on work or study (i.e. days lost). Future studies may also wish to compare the safety and efficacy of anti-interleukin-13/-4 agents with that of anti-interleukin-5 agents or immunoglobulin-E, in people with asthma.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Borish 1999

Study characteristics	
Methods	**Study ID and dates performed:** No trial registration number reported; December 1996 to May 1997 **Study design:** Randomised, double-blind, placebo-controlled trial **Duration of study:** 1-week run-in; 2-week follow-up (after single dose) **Study setting, location, number of centres:** Single centre, Denver, Colorado, USA **Key inclusion criteria:** Aged ≥ 18 years; moderate atopic asthma (daily ICS requirement of 4 to 8 puffs; atopy confirmed by a positive skin-prick test reaction [wheal diameter > 5 mm] to one or more components of the Colorado allergen panel and by a history of allergic rhinitis; smoking history ≤ 5 pack-years **Key exclusion criteria:** significant intercurrent illness; requirement of maintenance therapy with systemic corticosteroids for > 1 year; experienced an acute asthma exacerbation requiring emergency treatment within 6 weeks or hospitalisation within the 6 months; history of intubation for asthma exacerbation; undergone desensitisation therapy within the 12 months prior to enrolment **Concomitant medications:** ICS treatment withdrawn on the day before study drug was administered. Concomitant therapy with systemic corticosteroids, antihistamines, theophylline, cromolyn, and leukotriene modifiers was not allowed; pre-study use of these agents was also proscribed for periods of 2 to 8 weeks.
Participants	**N randomised:** IL-4R 500 µg: 8; IL-4R 1500 µg: 9; placebo: 8 **Withdrawals, n/N:** IL-4R 500 µg: 3/8; IL-4R 1500 µg: 0/9; placebo: 2/8 **N analysed (safety), n/N (%):** IL-4R 500 µg: 8; IL-4R 1500 µg: 9; placebo: 8

Borish 1999 *(Continued)*

	Median age (range), years: IL-4R 500 µg: 35 (26-52); IL-4R 1500 µg: 38 (26-66); placebo: 38 (25-47) **Gender - male, n (%):** IL-4R 500 µg: 2/8 (25%) ; IL-4R 1500 µg: 5/8 (63%); placebo: 2/8 (25%) **Baseline lung function - mean (SD) % pred FEV1:** IL-4R 500 µg: 80 (13); IL-4R 1500 µg: 79 (16); placebo: 87 (12)
Interventions	**Intervention:** Single nebulised dose of IL-4R at either 500 µg or 1500 µg **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Protocol or trial registry not available **Relevant reported outcomes:** AQLQ; asthma symptom score (based on diary); FEV1; exhaled NO, total eosinophil count; total IgE concentration; safety.
Notes	**Funding for trial; notable author COIs:** Funding from Immunex corporation, who manufacture the IL-4R; several authors employees of Immunex corporation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided ("double-blind")
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Insufficient information provided ("double-blind")
Incomplete outcome data (attrition bias) All outcomes	High risk	Three patients (38%) in the IL-4R 500 µg and two patients (25%) in the placebo group withdrew. Following the ITT principle, data from all patients were analysed, using LOCF method (except for QoL outcomes). Uneven withdrawals between groups noted
Selective reporting (reporting bias)	Unclear risk	No protocol or clear description of aims in the paper with which to compare results
Other bias	High risk	The authors stated that baseline characteristics were balanced, but there seemed to be a trend towards better baseline lung function and fewer symp-

Borish 1999 *(Continued)*

	toms in the placebo group versus IL-14R groups; this would tend to favour placebo with regards to treatment effect.

Borish 2001

Study characteristics	
Methods	**Study ID and dates performed:** Trial registration number not reported; May 1998 to September 1998 **Study design:** Randomised, double-blind, placebo-controlled dose-finding study **Duration of study:** 12-week treatment period **Study setting, location, number of centres:** 4 university- or community-based asthma clinics. **Key inclusion criteria:** Asthma (no definition provided); ICS use for > 6 months and stable moderate doses for ≥ 1 month; FEV1 ≥ 65% of predicted normal values; reversibility ≥ 12% within 30 minutes of albuterol; positive skin prick test responses to ≥ 2 allergen; reactivity to methacholine with a provocative concentration of 20% of ≤ 8 mg/mL; washout of other asthma therapy was required for at least 4 weeks. **Key exclusion criteria:** Allergen immunotherapy within 3 months; oral or parenteral steroids continuously for > 1 year; emergency department treatment within 6 weeks; hospitalisation within 1 year; or intubation for asthma **Concomitant medications:** During screening, subjects underwent one or two 50% reductions in inhaled corticosteroid dose at 2-week intervals; participants were allowed to continue using an albuterol inhaler as needed at ≤ 12 puffs daily.
Participants	**N randomised:** Placebo: 16; IL-4R 0.75 mg: 15; IL4-R 1.5 mg: 16; IL-4R 3.0 mg: 15 **N analysed, n/N (%):** Not reported; patients were withdrawn if they experienced an exacerbation; withdrawal rates were reported by time point. **Median age (range), years:** Placebo: 41 (22-60) ; IL-4R 0.75 mg: 46 (28-59); IL4-R 1.5 mg: 40 (24-72); IL-4R 3.0 mg: 36 (20-64) **Gender - male, n (%):** Placebo: 6/16 (37%); IL-4R 0.75 mg: 4/15 (27%); IL4-R 1.5 mg: 4/16 (25%); IL-4R 3.0 mg: 5/15 (33%) **BL lung function - mean (SD) % pred FEV1:** Placebo: 76 (11); IL-4R 0.75 mg: 76 (12); IL4-R 1.5 mg: 76 (13); IL-4R 3.0 mg: 75 (14)
Interventions	**Intervention:** IL-4R at 0.75, 1.5 or 3.0 mg once weekly by inhalation **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Protocol or trial registry not available **Relevant outcomes reported:** Mean % change from baseline in FEV1 (clinic, am and pm); asthma symptom score (method not validated); safety
Notes	**Funding for trial; notable author COIs:** Funding of study not reported but likely to be Immunex corporation, who manufacture the IL-4R. No author COIs reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Borish 2001 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information provided
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment assignment was blinded to all personnel involved in direct conduct or monitoring of the study.
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Treatment assignment was blinded to all personnel involved in direct conduct or monitoring of the study.
Incomplete outcome data (attrition bias) All outcomes	High risk	The study was designed so that patients were withdrawn once they had experienced an exacerbation meeting predefined criteria; at day 84, 56%, 67%, 69%, and 47% of participants in each group had discontinued. Up to a 22% difference in dropout rates between groups
Selective reporting (reporting bias)	Unclear risk	Protocol or trial registration report not available
Other bias	Low risk	None identified

Brightling 2015

Study characteristics	
Methods	**Study ID and dates performed:** NCT01402986; study dates not reported **Study design:** A phase 2, randomised, double-blind, placebo-controlled, parallel-group, multi-centre, phase 2b study **Duration of study:** 5-week screening/run-in period; 52-week treatment period; 22-week safety follow-up period **Study setting, location, number of centres:** 98 sites in North America, South America, Europe and Asia **Key inclusion criteria:** Aged 18 to 75 years; severe uncontrolled asthma (ERS/ATS definition); receiving high-dose ICS plus LABA ≥ 30 days prior to visit 1 (run-in day -35); 2 to 6 exacerbations in previous 12 months; diagnosis of asthma ≥ 1 year; documented increase in post-BD FEV1 of ≥ 12% or a positive methacholine challenge in the previous 12 years or post-BD FEV1 of ≥ 12% and ≥ 200 mL at visits 1 or 2 **Key exclusion criteria:** Concomitant respiratory disease; current cigarette smoking; known immune deficiency; history of cancer

Brightling 2015 *(Continued)*

	Concomitant medications: All patients received fluticasone 500 µg and salmeterol 50 µg twice daily via dry powder inhaler; patients continued to take any additional pre-study asthma controller drugs.
Participants	**N randomised:** 452 (placebo Q2W: 76; placebo Q4W, 75; TLK Q2W, 150; TLK Q4W, 151) **N completed:** 452 (placebo Q2W: 76; placebo Q4W, 75; TLK Q2W, 150; TLK Q4W, 151; note efficacy [ITT] and safety populations were identical in this study) **N withdrawals, n/N (%):** 452 (placebo Q2W: 9/76; placebo Q4W, 8/75; TLK Q2W, 15/150; TLK Q4W, 21/151) **Median age (SD), years:** placebo: 50.3 (12.9); TLK Q2W: 49.7 (12.2); TLK Q4W: 50.5 (11.8) **Gender - male, n (%):** placebo: 54/151 (36%); TLK Q2W: 50/150 (33%); TLK Q4W: 51/151 (34%) **BL lung function - mean (SD) pre-BD FEV1, %:** placebo: 68.0 (16.2); TLK Q2W: 68.3 (19.6); TLK Q4W: 69.3 (18.6)
Interventions	**Intervention:** Tralokinumab 300 mg SC (either every 2 weeks [Q2W] or every 2 weeks for 12 weeks then every 4 weeks [Q4W]) **Comparator:** Placebo SC
Outcomes	**Relevant prespecified outcomes:** Annual asthma exacerbation rate (AER) (Note: AER appeared to align with outcome "exacerbation requiring OCS"); mean change from baseline in FEV1 at 1 year; mean change from baseline in FVC at 1 year; mean change from baseline in FEV1/FVC ratio at 1 year; change from baseline in ACQ-6 score; change from baseline in AQLQ score; AEs, SAEs; outcomes were also reported by peripheral blood eosinophil count, serum periostin level. **Relevant outcomes reported:** All prespecified relevant outcomes of interest were reported.
Notes	**Funding for trial; notable author COIs:** Trial was funded by Medimmune; 5 authors were employees of Medimmune and 3 authors received financial compensation from MedImmune.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned using an interactive voice response system
Allocation concealment (selection bias)	Low risk	Randomly assigned using an interactive voice response system
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were masked to treatment allocation.
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.

Brightling 2015 *(Continued)*

Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Outcome assessors were masked to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	High rates of completion and reasons for dropouts given. Secondary efficacy data were reported for ~75% to 80% of patients; numbers analysed not reported for primary outcome. Attrition was balanced across treatment groups.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes well reported
Other bias	Low risk	None identified

Burgess 2018

Study characteristics	
Methods	**Study ID and dates performed:** NCT02473939; June 2015-April 2016 **Study design:** A phase 1, randomised, double-blind, placebo-controlled study **Duration of study:** 2-week treatment period (part 2: 10 days plus 4-day follow-up) **Study setting, location, number of centres:** Single site in the UK **Key inclusion criteria:** Male or female (non-childbearing potential); weight > 50 kg; BMI 18.0 to 31.0 kg/m^2; PIF > 60 L/min for at least 2 sec; FEV1/FVC ratio > 0.7 at the screening visit **Key exclusion criteria:** Clinically relevant abnormal history, physical findings, ECG, or laboratory values at the pre-trial screening assessment; presence of acute or chronic illness or history of chronic illness sufficient to invalidate the subject's participation in the trial or make it unnecessarily hazardous (excluding mild asthma in part 2); impaired endocrine, thyroid, hepatic, respiratory (excluding mild asthma in part 2) or renal function, diabetes mellitus, coronary heart disease, cancer, or history of any psychotic mental illness; respiratory tract infection within 4 weeks before the screening visit; history of surgery or medical intervention, or planned surgery or medical intervention; presence or history of severe adverse reaction to any drug, or sensitivity to components of the trial medication; use of a prescription or over-the-counter medicine, with the exception of acetaminophen (paracetamol), during the 7 days before the first dose of trial medication; presence or history of drug or alcohol abuse; evidence of drug abuse on urine testing, or a positive test for alcohol; current smoker; or ex-smokers who (a) gave up less than 1 year ago, or (b) who have a history of more than 10 pack-years; blood pressure and heart rate at the screening examination outside the ranges 90 to 140 mmHg systolic, 40-90 mmHg diastolic; heart rate 40 to 100 bpm; loss of more than 400 mL blood, e.g. as a blood donor, or donation of blood products, during the 3 months before the trial; positive test for hepatitis B, hepatitis C, or HIV; life-threatening asthmatic episode in the past; asthmatic episode or respiratory tract infection requiring steroid treatment in the past 3 months; use of the following medicines within the specified time before screening: LABA (at any time before screening); anti-IgE therapy (6 months); ICS (> 500 µg per day of BDP or equivalent) (8 weeks); oral or injectable steroids (8 weeks); intranasal or topical steroids (4 weeks); LTRA (2 weeks); xanthines (excluding caffeine) or anticholinergics, cromoglycates (1 week) **Concomitant medications:** Inhaled SABA, and ICS (stable dose with at least 2 weeks documented use of ≥ 80% compliance before screening and day -1) were permitted.
Participants	**N randomised:** Placebo: 16; VR492 0.5 mg: 6; VR492 10 mg: 6; VR492 20 mg: 17 **N completed:** Placebo: 16; VR492 0.5 mg: 6; VR492 10 mg: 6; VR492 20 mg: 17 **N withdrawals, n/N (%):** Placebo: 0; VR492 0.5 mg: 0; VR492 10 mg: 0; VR492 20 mg: 0

Burgess 2018 *(Continued)*

	Median age (SD), years: Placebo: 29 (9.3); VR492 0.5 mg: 30 (6.4); VR492 10 mg: 29 (4.7); VR492 20 mg: 30 (7.3) **Gender - male, n (%):** Placebo: 100%; VR492 0.5 mg: 100%; VR492 10 mg: 100%; VR492 20 mg: 100% **BL lung function - mean (SD) pre-BD FEV1, %:** Placebo: 89 (17.1); VR492 0.5 mg: 78 (10.4); VR492 10 mg: 86 (11.7); VR492 20 mg: 77 (13.5)
Interventions	**Intervention:** VR942 (Vectura Ltd, Chippenham, UK) was administered at nominal doses of 0.5 mg (1 × 0.5 mg inhalation), 10 mg (2 × 5.0 mg inhalations), and 20 mg (4 × 5.0 mg inhalations). The formulation was contained in a unit-dose blister and delivered via the multidose F1P dry-powder inhaler (DPI; Vectura Ltd, Chippenham, UK) **Comparator:** Matching placebo
Outcomes	**Relevant prespecified outcomes:** Primary: safety. Secondary: pharmacodynamics of repeated doses in mild asthmatics (change in biomarker levels); pharmacokinetic parameters; number of used blisters and inhalers that do not meet the performance characteristics of the device intended by the manufacturer **Relevant outcomes reported:** All prespecified outcomes reported except device performance measures
Notes	**Funding for trial; notable author COIs:** Study funding and funding for the medical writing and editorial support for preparation of the manuscript were split equally between the two study co-funders (Vectura Ltd and UCB Pharma). Authors declared conflicts of interest as employees of sponsor, or senior partners/owner of the contract research organisations.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All participants were randomised to receive VR942 or placebo based on a randomisation list prepared by an independent statistician using SAS®software (SAS Institute, Cary, NC)
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	All site staff, enrolled participants, and all trial personnel, participants, and the study sponsor were blinded to treatment allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All site staff, enrolled participants, and all trial personnel, participants, and the study sponsor were blinded to treatment allocation.
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	All site staff, enrolled participants, and all trial personnel, participants, and the study sponsor were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	All site staff, enrolled participants, and all trial personnel, participants, and the study sponsor were blinded to treatment allocation.

Burgess 2018 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rates of attrition
Selective reporting (reporting bias)	Low risk	Prespecified outcomes of interest were reported.
Other bias	Low risk	None identified

Busse 2015

Study characteristics	
Methods	**Study ID and dates performed:** NCT02281357 (TROPOS); February 2015 to September 2017 **Study design:** A phase 3, randomised, triple-blind (participant, care provider, investigator) **Duration of study:** 40-week treatment period **Study setting, location, number of centres:** 56 sites in 7 countries (USA, Belgium, France, Germany, Netherlands, Poland, Ukraine) **Key inclusion criteria:** Aged 12 to 75 years; documented physician-diagnosed asthma; documented treatment with ICS at a total daily dose corresponding to ≥ 500 µg fluticasone propionate dry powder formulation and a LABA; participants must have received OCS for the treatment of asthma for 6 months prior to visit 1 and on a stable OCS dose between ≥ 7.5 to ≤ 30 mg daily or daily equivalent for at least one month prior to enrolment (visit 1); pre-BD FEV1 value < 80% (< 90% for patients 12 to 17 yrs of age) of their PNV; post-BD reversibility of ≥ 12% in FEV1 **Key exclusion criteria:** Clinically important pulmonary disease other than asthma; history of anaphylaxis following any biologic therapy; hepatitis B, C or HIV; pregnant or breastfeeding; history of cancer; current tobacco smoking or a history of tobacco smoking for ≥ 10 pack-years; previous receipt of tralokinumab **Concomitant medications:** Participants continued their regular ICS-LABA asthma controller therapy regimen without change, throughout the study.
Participants	**N randomised:** Placebo: 70 TLK: 70 **N completed:** Placebo: 66/70 TLK: 63/70 **N withdrawals, n/N (%):** Placebo: 4/70 TLK: 7/70 **Median age (SD), years:** Placebo: 55.4 (10.26); TLK: 54.0 (11.05) **Gender - male, n (%):** Placebo: 31/70 (44.3%); TLK: 22/70 (31.5%) **BL lung function - mean (SD) pre-BD FEV1, %:** Not reported
Interventions	**Intervention:** Tralokinumab 300 mg (150 mg/mL) SC Q2W **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Per cent change from baseline in final daily average OCS dose at week-40 (while not losing asthma control); number of patients with final daily average OCS dose ≤ 5.0 mg at week-40; number of patients with ≥ 50% reduction in final average daily OCS dose at week-40; AAER up to week-40; safety **Relevant outcomes reported:** All prespecified outcomes reported

Busse 2015 *(Continued)*

Notes	**Funding for trial; notable author COIs:** Study funded by AstraZeneca; data sourced from clinicaltrials.gov

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple masking (participant, care provider, investigator); as reported at https://clinicaltrials.gov/ct2/show/NCT02161757
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Triple masking (participant, care provider, investigator); as reported at https://clinicaltrials.gov/ct2/show/NCT02161757
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low and balanced between groups.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were well reported.
Other bias	Low risk	None identified

Castro 2018

Study characteristics

Methods	**Study ID and dates performed:** NCT02414854; April 2015 to July 2017 **Study design:** A phase 3, randomised, double-blind, placebo-controlled, parallel-group trial **Duration of study:** 52 weeks **Study setting, location, number of centres:** 389 sites in the USA, Argentina, Australia, Brazil, Canada, Chile, Colombia, France, Germany, Hungary, Italy, Japan, Republic of Korea, Mexico, Poland, Russian Federation, South Africa, Spain, Taiwan, Turkey, Ukraine and the United Kingdom

Castro 2018 *(Continued)*

	Key inclusion criteria: Aged ≥ 12 years; physician diagnosis of asthma for ≥ 12 months, based on the GINA 2014 Guidelines and the following criteria: a) Existing treatment with medium to high dose ICS (≥ 250 µg of FP twice daily or equipotent ICS daily dosage to a maximum of 2000 µg/day of FP or equivalent) in combination with a second controller (e.g. LABA, LTRA) for at least 3 months with a stable dose ≥ 1 month prior to visit 1. i) Note for Japan: for participants aged 18 years and older, ICS must be on ≥ 200 µg of fluticasone propionate twice daily or equivalent; for participants aged 12 to 17 years, ICS must be ≥ 100 µg of fluticasone propionate twice daily or equivalent. ii) Participants requiring a third controller for their asthma will be considered eligible for this study, and it should also be used for at least 3 months with a stable dose ≥ 1 month prior to visit 1. **Key exclusion criteria:** Weight < 30 kg; COPD or other lung diseases (e.g. idiopathic pulmonary fibrosis, Churg-Strauss Syndrome, etc.) which may impair lung function; severe asthma exacerbation (defined as a deterioration of asthma that results in emergency treatment, hospitalisation due to asthma, or treatment with systemic steroids at any time from 1 month prior to the screening visit up to and including the baseline visit); evidence of lung disease(s) other than asthma, either clinical evidence or imaging (chest X-ray, CT, MRI) within 12 months of visit 1 or at the screening visit, as per local standard of care; Japan only: chest X-ray should be performed at screening visit if there is no chest imaging (chest X-ray, CT, MRI) available within 3 months prior to screening to exclude participants with suspected active or untreated latent tuberculosis; current smoker or cessation of smoking within 6 months prior to visit 1; previous smoker with a smoking history > 10 pack-years; comorbid disease that may interfere with evaluation of the study drug **Concomitant medications:** See inclusion criteria
Participants	**N randomised:** DUP 200 mg Q2W: 631; matching placebo: 317; DUP 300 mg Q2W: 633; matching placebo: 321 **N completed:** DUP 200 mg Q2W: 631; matching placebo: 317; DUP 300 mg Q2W: 633; matching placebo: 321 **N withdrawals, n/N (%):** DUP 200 mg Q2W: 70; matching placebo: 38; DUP 300 mg Q2W: 85; matching placebo: 35 **Mean age (SD), years:** 47.9 (15.3) **Gender - male, n (%):** 705 (37.1) **BL lung function - mean (SD) pre-BD FEV1, %:** 58.43 (13.52)
Interventions	**Intervention:** Dupilumab 200 mg Q2W or 300 mg Q2W **Comparator:** Matching placebo for each dupilumab dose group
Outcomes	**Relevant prespecified outcomes:** Primary: Annualised rate of severe exacerbation events during 52-week treatment period; absolute change from baseline to week-12 in FEV1. Secondary: Per cent change from baseline to week-12 in FEV1; change from baseline to week-24 in AQLQ score; change from baseline to week-24 in ACQ-5 score; annualised rate of severe exacerbation events resulting in hospitalisation or ED visit during 52-week treatment period; key outcomes examined by prespecified eosinophil levels at baseline **Relevant outcomes reported:** All prespecified outcomes relevant to this review were well reported.
Notes	**Funding for trial; notable author COIs:** The trial was supported by Sanofi and Regeneron Pharmaceuticals. Several authors were employed by the sponsor or declared relevant conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was conducted by means of interactive voice–Web response technology.

Castro 2018 *(Continued)*

Allocation concealment (selection bias)	Low risk	Randomisation was conducted by means of interactive voice–Web response technology.
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple masking (participant, care provider, investigator) – see clinicatrials.gov
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Triple masking (participant, care provider, investigator) – see clinicatrials.gov
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 1902 randomly assigned patients were included in the final analysis.
Selective reporting (reporting bias)	Low risk	Key prespecified primary and secondary outcomes were well reported.
Other bias	Low risk	None identified

Corren 2010

Study characteristics	
Methods	**Study ID and dates performed:** NCT00436670; not reported **Study design:** A phase 2, randomised, double-blind, placebo-controlled, multiple dose phase 2 study **Duration of study:** 12-week treatment period; 4-week follow-up period **Study setting, location, number of centres:** 52 sites in the USA **Key inclusion criteria:** Aged 18 to 65 years; moderate-to-severe asthma; receiving stable doses of ICS (> 200 to < 1000 mg/d fluticasone or equivalent); ACQ score ≥ 1.5 or higher, percentage of predicted FEV1 ≥ 50% to ≤ 80% at screening and ≥ 12% reversibility over baseline FEV1 with ß-agonist inhalation **Key exclusion criteria:** Acute asthma exacerbation within 3 months; history of any chronic pulmonary condition other than asthma **Concomitant medications:** Not reported
Participants	**N randomised:** Placebo: 74; AMG 317 75 mg QW: 73; AMG 317 150 mg QW: 73; AMG 317 300 mg QW: 74 **N completed:** Placebo: 63; AMG 317 75 mg QW: 62 AMG 317 150 mg QW: 61; AMG 317 300 mg QW: 58

Corren 2010 *(Continued)*

	N withdrawals, n/N (%): Placebo: 11; AMG 317 75 mg QW: 11; AMG 317 150 mg QW: 12; AMG 317 300 mg QW: 14 **Mean age (min, max), years:** Placebo: 39.5 (19, 63); AMG 317 75 mg QW: 43.2 (19, 63); AMG 317 150 mg QW: 41.3 (22, 64); AMG 317 300 mg QW: 41.4 (18, 59) **Gender - male, n (%):** Placebo: 33 (44.6); AMG 317 75 mg QW: 28 (38.4); AMG 317 150 mg QW: 29 (39.8); AMG 317 300 mg QW: 34 (45.9) **BL lung function - mean (SE) pre-BD FEV1, %:** Placebo: 67.1 (1.3); AMG 317 75 mg QW: 69.8 (1.5); AMG 317 150 mg QW: 69.0 (1.3); AMG 317 300 mg QW: 67.4 (1.6)
Interventions	**Intervention:** AMG 317 (75 mg, 150 mg or 300 mg) SC QW for 12 weeks **Comparator:** Placebo SC QW for 12 weeks
Outcomes	**Relevant prespecified outcomes:** Primary: change in ACQ symptom scores from baseline to week-12. Secondary: change from baseline in frequency of rescue beta agonist use during week-12; change from baseline PEFR during week-12 (morning/evening, diurnal and inter-day variation); change from baseline in pre- and post-bronchodilator FEV1 at week-12. Safety endpoints: antibodies, adverse events, change from baseline in AQLQ score at week-12 **Relevant outcomes reported:** All prespecified outcomes relevant to this review were well reported.
Notes	**Funding for trial; notable author COIs:** The study was funded by Amgen; a majority of authors were either employees of Amgen or had received grants, honoraria or consultancy fees from Amgen.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment to treatment group was based on a stratified randomisation schedule via an Interactive Voice Response System.
Allocation concealment (selection bias)	Low risk	Assignment to treatment group was based on a stratified randomisation schedule via an Interactive Voice Response System.
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masking was reported as: “Quadruple (participant, care provider, investigator, outcomes assessor)” [www.clinicaltrials.gov].
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Masking was reported as: “Quadruple (participant, care provider, investigator, outcomes assessor)” [www.clinicaltrials.gov].
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low and generally balanced between groups (note: withdrawal rate in AMG 300 mg QW group was 22% but was within 10% of value reported for placebo (13%).

Corren 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	Prespecified outcomes (as per www.clinicaltrials.gov) were well reported.
Other bias	Low risk	None identified. Baseline imbalance in BMI likely not relevant

Corren 2011

Study characteristics	
Methods	**Study ID and dates performed:** NCT00930163; July 2009 to September 2010 **Study design:** A phase 2, randomised, double-blind, placebo controlled trial **Duration of study:** 2-week run-in; 6-month treatment; 8-week follow-up **Study setting, location, number of centres:** Multi-centre **Key inclusion criteria:** Aged 18 to 65 years; asthma diagnosed by a consultant; at least 12% increase in FEV1 after inhalation of short-acting bronchodilator; pre-bronchodilator FEV1 between 40 to 80% inclusive of predicted value; use of ICS for at least 6 months; evidence of uncontrolled asthma on the day of randomisation (ACQ-5) **Key exclusion criteria:** Asthma exacerbation during screening; known malignancy; known immunodeficiency; pre-existing lung disease other than asthma; uncontrolled clinically significant medical disease; current smoker; history of substance abuse that may impair or risk the patient's full participation in the study; prior allergic reaction to a monoclonal antibody; patients (men and women) of reproductive potential who are not willing to use contraception; pregnancy **Concomitant medications:** Inhaled glucocorticoids and any other asthma treatments (e.g. LABA) were not altered during the run-up or 24-week trial.
Participants	**N randomised:** Placebo: 112; LBK: 106 **N completed:** Placebo: 109; LBK: 102 **N withdrawals, n/N (%):** Placebo: 3; LBK: 4 **Mean age (SD), years:** Placebo: 44 (13); LBK: 45 (12) **Gender - male, n (%):** Placebo: 37 (33); LBK: 37 (35) **BL lung function - mean (SD) pre-BD FEV1, %:** Placebo: 66 (10); LBK: 64 (12)
Interventions	**Intervention:** Lebrikizumab 250 mg SC Q4W **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: change in FEV1 from baseline to week-12; change in pre-bronchodilator FEV1 from baseline to week-24. Secondary: change in quality of life and symptom scores from baseline to week-12; change in peak flow from baseline to week-1; rate of asthma exacerbations during the 24-week treatment period; change in rescue medication use from baseline to week-1; frequency and severity of adverse events through study completion or early study discontinuation; incidence of human anti-therapeutic antibodies (ATA) at the end of the follow-up period **Relevant outcomes reported:** Primary: relative change in pre-bronchodilator FEV1 from baseline to week-12. Secondary: rates of protocol-defined exacerbations and severe exacerbations through week 24, morning pre-bronchodilator peak exploratory flow, change in ACQ-5 score from baseline to week-12, asthma symptom score. Post hoc exploratory outcomes included exhaled FENO; weekly fre-

Corren 2011 *(Continued)*

	quency of nocturnal awakening due to asthma; serum CCL13 (MCP-4), CCL17 (TARC), and IgE levels and peripheral-blood eosinophil counts at week-12; and post-bronchodilator FEV1 at week-20
Notes	**Funding for trial; notable author COIs:** Genentech

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	A 'dynamic randomisation process' was employed; insufficient details provided regarding random sequence generation
Allocation concealment (selection bias)	Low risk	Randomisation codes were concealed from all staff members at the investigational sites and from staff members of the sponsor who had access to site information and patient data.
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masking: Double (participants were blinded).
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Masking: Double (participant, investigator). Patients were outcome assessors for subjective outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low and balanced between groups.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes well reported; note that FENO and eosinophil data were declared as post hoc exploratory thus risk of bias could be considered high for those outcomes.
Other bias	Unclear risk	Some imbalances in baseline characteristics – relevance unclear

De Boever 2014

Study characteristics

Methods	**Study ID and dates performed:** NCT00843193; December 2008 to April 2010 **Study design:** A phase 2 randomised, double-blind, placebo-controlled, repeat-dose study **Duration of study:** 4-week run in, 12-week treatment period

De Boever 2014 *(Continued)*

	Study setting, location, number of centres: 34 investigational sites in 8 countries (USA, France, Germany, Netherlands, Norway, Poland, South Africa, UK) **Key inclusion criteria:** Aged 18 to 75 years; history of asthma for ≥ 6 months; taking ICS; non-smoking; baseline (pre-bronchodilator) FEV1 35 to 80% predicted at screening; reversible airways disease as indicated by an increase of FEV1 ≥ 12% from baseline after nebulised salbutamol or albuterol; symptomatic according to the ACQ-7 **Key exclusion criteria:** Acute asthma exacerbation requiring hospitalisation or intubation within 3-6 months; acute respiratory illness within 4 weeks; presence of other respiratory disease or chronic pulmonary condition other than asthma; treatment with omalizumab within 4 months of study; methotrexate, troleandomycin, oral gold, cyclosporine or other experimental anti-inflammatory therapies within 3 months; recent gastrointestinal or respiratory parasitic infestation; 12 or more years of smoking **Concomitant medications:** During the 4-week run-in period, the ICS dose was increased to 1000 mg/d FPE. No changes were made to the ICS dose in patients already taking 1000 mg/d FPE or greater or to other asthma maintenance therapy.
Participants	**N randomised:** Placebo: 99; GSK679586: 99 **N analysed (ITT):** Placebo: 99; GSK679586: 99 **N withdrawals, n/N (%):** Placebo: 8; GSK679586: 11 **Mean age (SD), years:** Placebo: 51 (12); GSK679586: 51 (11) **Gender - male, n (%):** Placebo: 50 (51); GSK679586: 48 (48) **BL lung function - mean (SD) pre-BD FEV1, %:** Placebo: 58 (13); GSK679586: 55 (12)
Interventions	**Intervention:** IV infusion of 10 mg/kg GSK679586 (Q4W) **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: Change from baseline in asthma control questionnaire (ACQ-7) over 12 weeks. Secondary: change from baseline in ACQ-7 over 16 weeks and 24 weeks; change in ACQ-7 over 12 weeks; change in FEV1 over 12 weeks; change from baseline in FEV1 over 16 weeks and 24 weeks; adverse/serious adverse events; number of participants with clinically significant abnormality in vital signs/ECG; number of participants with abnormal haematological parameters/abnormal clinical chemistry parameters/abnormal urinalysis/pharmacokinetic parameters; number of participants with confirmed positive anti-GSK679586 antibody results **Relevant outcomes reported:** Prespecified outcomes were well reported.
Notes	**Funding for trial; notable author COIs:** GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation schedule was generated by Discovery Biometrics (GlaxoSmithKline, King of Prussia, Pa) by using validated in-house software and was stratified by OCS use at baseline with a 1:1 allocation. Patient randomisation numbers and container treatment assignment list numbers were assigned through an in-house interactive voice-response system after a patient's eligibility was confirmed at the completion of the run-in period.
Allocation concealment (selection bias)	Low risk	A computer-generated randomisation schedule was generated by Discovery Biometrics (GlaxoSmithKline, King of Prussia, Pa) by using validated in-house software and was stratified by OCS use at baseline with a 1:1 allocation. Patient randomisation numbers and container treatment assignment list num-

De Boever 2014 *(Continued)*

		bers were assigned through an in-house interactive voice-response system after a patient's eligibility was confirmed at the completion of the run-in period.
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quadruple masking (participant, care provider, investigator, outcomes assessor) Source: Clinicaltrials.gov
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Quadruple masking (participant, care provider, investigator, outcomes assessor) Source: Clinicaltrials.gov
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low and balanced between groups.
Selective reporting (reporting bias)	Unclear risk	Reporting of the data was very confusing. The primary endpoint (ACQ-7 change from BL to 12 weeks) was reported as change from 4-12 weeks (confusion was disparity between abstract statement and Table II). Also, the study claimed to run to 24 weeks but only data to week-12 were reported.
Other bias	Low risk	None identified

Gauvreau 2011a

Study characteristics	
Methods	**Study ID and dates performed:** NCT00410280; April 2007 to March 2008 **Study design:** A phase 1, randomised, placebo-controlled, double-blind trial **Duration of study:** Two doses of 2 mg/kg were administered subcutaneously approximately 1 week apart. Allergen challenges were conducted 14 and 35 days after the first dose. **Study setting, location, number of centres:** Canada; n = 4 centres **Key eligibility criteria:** Healthy, men and women with mild allergic asthma; aged 18 to 60 years; FEV1 > 70% predicted; methacholine PC20 ≤ 16 mg/mL; non-smoking; no other lung disease; no self-reported lower respiratory tract infection or worsening of asthma for 4 weeks before screening, and avoided exposure to sensitising allergens apart from house dust mite; not currently using ICS; no asthma medication with the exception of infrequently inhaled b2-agonist, which was withheld for 8 hours before spirometry **Concomitant medications:** Participants were not currently using inhaled corticosteroids and used no asthma medication with the exception of infrequently inhaled b2-agonist, withheld for 8 hours before spirometry

Gauvreau 2011a *(Continued)*

Participants	**N randomised:** IMA-638: 14; placebo: 13 **N analysed (ITT):** IMA-638: 14; placebo: 13 **N withdrawals, n/N (%):** IMA-638: 0; placebo: 0 **Median age (SE), years:** IMA-638: 26.1 (1.7); placebo: 32.3 (3.2) **Gender - male, n (%):** IMA-638: 7 (50%); placebo: 5 (38%) **BL lung function - mean (SE) pre-BD FEV1, %:** IMA-638: 93.0 (3.4); placebo: 87.1 (2.5)
Interventions	**Intervention:** Subcutaneous IMA-638 (4 mg/kg); two doses of 2 mg/kg were administered subcutaneously approximately 1 week apart. **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Maximum per cent drop from pre-allergen baseline in FEV1 for late-phase asthma response between 3-7 hours at screening; maximum per cent drop from pre-allergen baseline in FEV1 for late-phase asthma response at day 14; maximum per cent drop from pre-allergen baseline in FEV1 for late-phase asthma response at day 35 **Relevant outcomes reported:** Airway hyper-responsiveness (methacholine PC20 values); sputum eosinophils (%); IL-13 levels in serum; eosinophils, total and IgE in blood; safety
Notes	**Funding for trial; notable author COIs:** Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomised sequence of treatment was computer-generated, and treatment kit number was assigned on the day of dosing, using a centralised system.
Allocation concealment (selection bias)	Low risk	The randomised sequence of treatment was computer-generated, and treatment kit number was assigned on the day of dosing, using a centralised system.
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quadruple (participant, care provider, investigator, outcomes assessor); source clinicaltrials.gov
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Quadruple (participant, care provider, investigator, outcomes assessor); source clinicaltrials.gov

Gauvreau 2011a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes are well-reported.
Other bias	Unclear risk	No formal sample size calculations and 11 participants receiving a lower dose of the allergen than initially planned

Gauvreau 2011b

Study characteristics	
Methods	**Study ID and dates performed:** NCT00725582; January 2009 to June 2009 **Study design:** A phase 1, randomised, placebo-controlled, double-blind trial **Duration of study:** Two doses of 2 mg/kg were administered subcutaneously approximately 1 week apart. Allergen challenges were conducted 14 and 35 days after the first dose. **Study setting, location, number of centres:** Canada; n = 4 centres **Key eligibility criteria:** Healthy, men and women with mild allergic asthma; aged 18 to 60 years; FEV1 > 70% predicted; methacholine PC20 ≤ 16 mg/mL; non-smoking; no other lung disease; no self-reported lower respiratory tract infection or worsening of asthma for 4 weeks before screening, and avoided exposure to sensitising allergens apart from house dust mite; not currently using ICS; no asthma medication with the exception of infrequently inhaled b2-agonist, which was withheld for 8 hours before spirometry **Concomitant medications:** Participants were not currently using inhaled corticosteroids and used no asthma medication with the exception of infrequently inhaled b2-agonist, withheld for 8 hours before spirometry.
Participants	**N randomised:** IMA-638: 14; placebo: 15 **N analysed (ITT):** IMA-638: 14; placebo: 15 **N withdrawals, n/N (%):** IMA-638: 0; placebo: 2 **Median age (SE), years:** IMA-638: 33.1 (3.3); placebo: 33.5 (13.0) **Gender - male, n (%):** IMA-638: 7 (50%); placebo: 8 (53%) **BL lung function - mean (SE) pre-BD FEV1, %:** IMA-638: 90.6 (2.8); placebo: 86.5 (9.6)
Interventions	**Intervention:** Subcutaneous IMA-638 (4 mg/kg); two doses of 2 mg/kg were administered subcutaneously approximately 1 week apart. **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Maximum per cent drop from pre-allergen baseline in FEV1 for late-phase asthma response between 3-7 hours at screening; maximum per cent drop from pre-allergen baseline in FEV1 for late-stage asthma response at day 14; maximum per cent drop from pre-allergen baseline in FEV1 for late-phase asthma response at day 35 **Relevant outcomes reported:** Airway hyper-responsiveness (methacholine PC20 values); sputum eosinophils (%); IL-13 levels in serum; eosinophils, total and IgE in blood; safety

Gauvreau 2011b *(Continued)*

Notes	**Funding for trial; notable author COIs:** Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomised sequence of treatment was computer-generated, and treatment kit number was assigned on the day of dosing, using a centralised system.
Allocation concealment (selection bias)	Low risk	The randomised sequence of treatment was computer-generated, and treatment kit number was assigned on the day of dosing, using a centralised system.
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quadruple (participant, care provider, investigator, outcomes assessor); source clinicaltrials.gov
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Quadruple (participant, care provider, investigator, outcomes assessor); source clinicaltrials.gov
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was less than 15% (2/15 participants in the placebo group dropped out).
Selective reporting (reporting bias)	Low risk	Prespecified outcomes are well-reported.
Other bias	Low risk	None identified

Hanania 2011

Study characteristics

Methods	**Study ID and dates performed:** Not reported (abstract only) **Study design:** A phase 2, randomised, placebo-controlled trial **Duration of study:** 24 weeks **Study setting, location, number of centres:** Not reported **Key inclusion criteria:** Adults with asthma inadequately controlled by ICS

Hanania 2011 *(Continued)*

	Key exclusion criteria: Not reported **Concomitant medications:** Not reported
Participants	**N randomised:** LBK: 88; placebo: 92 **N completed:** Not reported **N withdrawals, n/N (%):** Not reported **Median age (SD), years:** Not reported **Gender - male, n (%):** Not reported **BL lung function - mean (SD) pre-BD FEV1, %:** Not reported
Interventions	**Intervention:** LBK (dose not stated) **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: Change in FEV1 from baseline to week-12. Secondary: Change in FEV1 from baseline to week-24; rate of severe exacerbations to week-24; SAEs **Relevant outcomes reported:** Primary: Change in FEV1 from baseline to week-12. Secondary: Change in FEV1 from baseline to week-24; rate of severe exacerbations to week-24; SAEs
Notes	**Funding for trial; notable author COIs:** Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information (abstract only)
Allocation concealment (selection bias)	Unclear risk	Insufficient information (abstract only)
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information (abstract only)
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Insufficient information (abstract only)
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient information (abstract only)

Hanania 2011 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Insufficient information (abstract only)
Other bias	Unclear risk	Insufficient information (abstract only)

Hanania 2015a

Study characteristics	
Methods	**Study ID and dates performed:** NCT01545440 (LUTE; March 2012 to March 2013) **Study design:** A phase 2, randomised, double-blind, placebo-controlled study **Duration of study:** The study was designed to be 52 weeks. However, the trial was terminated early and outcomes were assessed for the duration of the placebo-controlled period. **Study setting, location, number of centres:** 71 study centres in the USA and Australia **Key inclusion criteria:** Patients aged 1 to 75 years with uncontrolled asthma despite daily use of 500 to 2000 µg/day of fluticasone propionate DPI or equivalent and a second asthma controller medication (LABA, LTRA, LAMA, or theophylline); diagnosis of asthma ≥ 12 months; acute bronchodilator response (≥ 12% relative improvement) and pre-bronchodilator FEV1 40 to 80% of predicted. Uncontrolled asthma was defined as an ACQ-5 score ≥ 1.5 and at least one of the following: symptoms > 2 days/week, night-time awakenings ≥ 1 time/week, use of a SABA as rescue medication > 2 days/week or interference with normal daily activities. **Key exclusion criteria:** Receipt of maintenance OCS treatment within the previous three months or treatment with systemic corticosteroids within the previous four weeks for any reason **Concomitant medications:** See eligibility criteria above
Participants	**Note:** A host cell protein impurity (PLBL2)17 was identified after the initiation of the studies. This required manufacturing process changes to the drug product. As a consequence, the studies were no longer considered pivotal studies and the protocols were amended from phase III to phase IIb. Due to early termination of the study, results were pooled with study NCT01545453 (see Hanania 2015b). Pooled data are reported below. **N randomised:** LBK 37.5 mg, 117; LBK 125 mg, 112; LBK 250 mg, 118; placebo, 116 **N completed:** See note above **N withdrawals, n/N (%):** See note above **Median age (SD), years:** LBK 37.5 mg, 48.7 (13.1); LBK 125 mg, 46.8 (13.4); LBK 250 mg, 47.9 (11.9); placebo, 50.0 (13.3) **Gender - male, n (%):** LBK 37.5 mg, 45 (38.5); LBK 125 mg, 52 (46.4); LBK 250 mg, 49 (41.5); placebo, 66 (56.9) **BL lung function - mean (SD) pre-BD FEV1, %:** LBK 37.5 mg, 62.5 (10.2); LBK 125 mg, 62.8 (10.9); LBK 250 mg, 60.9 (10.2); placebo, 62.7 (10.2)
Interventions	**Intervention:** Lebrikizumab 37.5 mg, 125 mg or 250 mg SC Q4W **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: Rate of asthma exacerbations during the placebo-controlled period. Secondary (baseline to end of placebo-controlled period): Change in FEV1; time to first

Hanania 2015a *(Continued)*

	asthma exacerbation; change in FENO; change in AQLQ[S] score; change in asthma rescue medication use; rate of urgent asthma-related health-care utilisation; safety. Analysis of the primary efficacy and all secondary efficacy endpoints were performed separately in periostin-high (≥ 50 ng/mL) and periostin-low (< 50 ng/mL) subgroups. **Relevant outcomes reported:** Prespecified outcomes were reported.
Notes	**Funding for trial; notable author COIs:** The study was sponsored by Genentech. Several authors were employees of Genentech or had received financial support or honoraria from Genentech.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised to the treatment arms through the interactive voice/web-based response system (IxRS) provided by Perceptive Informatics, Inc.
Allocation concealment (selection bias)	Low risk	The IxRS also assigned study treatment kits to patients at each visit.
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided to determine whether personnel or outcome assessors were blinded (participants were blinded).
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Insufficient information provided to determine whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Because dosing was terminated early, not all patients had the opportunity to participate in the placebo-controlled treatment period for the minimum duration (i.e. seven doses of study drug over 28 weeks) as specified in the amended protocols.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were well reported.
Other bias	High risk	The protocol for these studies underwent substantial modification after study initiation – this was because the study drug was found to contain an impurity that required a manufacturing change – study was downgraded to a phase IIb (from phase III) and planned enrolment was greatly reduced.

Hanania 2015b

Study characteristics	
Methods	**Study ID and dates performed:** NCT01545453 (VERSE; March 2012 to July 2013) **Study design:** A phase 2, randomised, double-blind, placebo-controlled study **Duration of study:** The study was designed to be 52 weeks. However, the trial was terminated early and outcomes were assessed for the duration of the placebo-controlled period. **Study setting, location, number of centres:** 64 centres in the USA and Australia **Key inclusion criteria:** See Hanania 2015a **Key exclusion criteria:** See Hanania 2015a **Concomitant medications:** See Hanania 2015a
Participants	**Note:** A host cell protein impurity (PLBL2)17 was identified after the initiation of the studies. This required manufacturing process changes to the drug product. As a consequence, the studies were no longer considered pivotal studies and the protocols were amended from phase III to phase IIb. Due to early termination of the study, results were pooled with study NCT01545453 (see Hanania 2015b). Pooled data were reported in the table of characteristics for Hanania 2015a. **N randomised:** See Hanania 2015a **N completed:** See Hanania 2015a **N withdrawals, n/N (%):** See Hanania 2015a **Median age (SD), years:** See Hanania 2015a **Gender - male, n (%):** See Hanania 2015a **BL lung function - mean (SD) pre-BD FEV1, %:** See Hanania 2015a
Interventions	**Intervention:** Lebrikizumab 37.5 mg, 125 mg or 250 mg SC Q4W **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** See Hanania 2015a **Relevant outcomes reported:** See Hanania 2015a
Notes	**Funding for trial; notable author COIs:** The study was sponsored by Genentech. Several authors were employees of Genentech or had received financial support or honoraria from Genentech.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomised to the treatment arms through the interactive voice/web-based response system (IxRS) provided by Perceptive Informatics, Inc.
Allocation concealment (selection bias)	Low risk	The IxRS also assigned study treatment kits to patients at each visit.
Blinding of participants and personnel (performance bias; objective outcomes))	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.

Hanania 2015b *(Continued)*

All outcomes		
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided to determine whether personnel or were blinded (participants were blinded).
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Insufficient information provided to determine whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Because dosing was terminated early, not all patients had the opportunity to participate in the placebo-controlled treatment period for the minimum duration (i.e. seven doses of study drug over 28 weeks) as specified in the amended protocols.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were well reported.
Other bias	High risk	The protocol for these studies underwent substantial modification after study initiation – this was because the study drug was found to contain an impurity that required a manufacturing change – study was downgraded to a phase IIb (from phase III) and planned enrolment was greatly reduced.

Hanania 2016a

Study characteristics	
Methods	**Study ID and dates performed:** NCT01867125 (LAVOLTA-1; July 2013 to January 2017) **Study design:** A phase 3, randomised, double-blind, placebo-controlled study **Duration of study:** 2-week screening period; 52-week treatment period; 20-week safety follow-up period **Study setting, location, number of centres:** 230 global study sites **Key inclusion criteria:** Aged 18 to 75 years; uncontrolled asthma (ACQ-5 score ≥ 1.5 plus one of the following during the screening period: symptoms for > 2 days/week, night-time awakenings ≥ per week, use of SABA as rescue medication ≥ 2 days/week, or interference with normal daily activities); FEV1 40 to 80% predicted; bronchodilator response ≥ 12%; on stable background of ICS (500 to 2000 µg/day of FP or equivalent for ≥ 6 months; ≥ 1 additional controller medication **Key exclusion criteria:** Current or former smoker (≥ 10 pack-years); pregnancy; parasitic infection within previous 6 months; clinically significant lung disease other than asthma; maintenance OCS treatment within previous 3 months **Concomitant medications:** See eligibility criteria above
Participants	**N randomised:** LBK 37.5 mg, 360; LBK 125 mg, 359; placebo, 362 **N completed:** LBK combined, 656 ; placebo, 320 **N withdrawals, n/N (%):** LBK combined, 63; placebo, 42

Hanania 2016a *(Continued)*

	Median age (SD), years: LBK 37.5 mg, 51.4 (12.9); LBK 125 mg, 51.0 (12.6); placebo, 51.3 (12.3) **Gender - male, n (%):** LBK 37.5 mg, 126 (35); LBK 125 mg, 111 (31); placebo, 131 (36) **BL lung function - mean (SD) pre-BD FEV1, %:** LBK 37.5 mg, 60.6 (10.3); LBK 125 mg, 61.3 (10.5); placebo, 61 (10.6)
Interventions	**Intervention:** Lebrikizumab 37.5 mg or 125 mg SC Q4W **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: Rate of asthma exacerbations during 52-week placebo-controlled period in biomarker high patients (periostin ≥ 50 ng/mL or eosinophils ≥ 300 cells/µL). Secondary (baseline to 52 weeks): absolute change in pre-BD FEV1; time to first asthma exacerbation; rate of urgent asthma-related healthcare; change in AQLQ(S) score; change in asthma rescue medication use; change in asthma control (ACQ-5 score); safety **Relevant outcomes reported:** Prespecified outcomes were well reported.
Notes	**Funding for trial; notable author COIs:** The study was sponsored by Genentech. Several authors were employees of Genentech or had received financial support or honoraria from Genentech.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An interactive voice-web-based response system was used.
Allocation concealment (selection bias)	Low risk	An interactive voice-web-based response system was used.
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, investigators, study site personnel and the funder were masked to treatment assignment during the study.
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Patients, investigators, study site personnel and the funder were masked to treatment assignment during the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low and balanced between groups.
Selective reporting (reporting bias)	High risk	The trial registration site (clinicaltrials.gov) did not state that primary and secondary outcomes would be presented by biomarker groups. It seemed that a greater treatment effect was seen in 'biomarker high' groups but this group was not a prespecified group of interest. However, in the primary report, the

Hanania 2016a *(Continued)*

		primary outcome was stated as rate of exacerbations in the periostin high group.
Other bias	Low risk	None identified

Hanania 2016b

Study characteristics	
Methods	**Study ID and dates performed:** NCT01868061 (LAVOLTA-2; July 2013 to January 2017) **Study design:** A phase 3, randomised, double-blind, placebo-controlled study **Duration of study:** See Hanania 2016a **Study setting, location, number of centres:** 232 global study locations **Key inclusion criteria:** See Hanania 2016a **Key exclusion criteria:** See Hanania 2016a **Concomitant medications:** See Hanania 2016a
Participants	**N randomised:** LBK 37.5 mg, 356; LBK 125 mg, 357; placebo, 354 **N completed:** LBK combined, 642; placebo, 315 **N withdrawals, n/N (%):** LBK combined, 71; placebo, 39 **Median age (SD), years:** LBK 37.5 mg, 50.9 (12.9); LBK 125 mg, 50.2 (12.6); placebo, 49.5 (13.3) **Gender - male, n (%):** LBK 37.5 mg, 154 (43); LBK 125 mg, 120 (34); placebo, 135 (38) **BL lung function - mean (SD) pre-BD FEV1, %:** LBK 37.5 mg, 60.5 (10.5); LBK 125 mg, 60.7 (10.6); placebo, 61.1 (10.6)
Interventions	**Intervention:** Lebrikizumab 37.5 mg or 125 mg SC Q4W **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** See Hanania 2016a **Relevant outcomes reported:** See Hanania 2016a
Notes	**Funding for trial; notable author COIs:** See Hanania 2016a

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	An interactive voice-web-based response system was used. Randomisation was stratified by biomarker levels and a biased coin assignment was used when the imbalance in a stratum had exceeded a specified threshold.
Allocation concealment (selection bias)	Low risk	An interactive voice-web-based response system was used.
Blinding of participants and personnel (perfor-	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.

Hanania 2016b *(Continued)*

mance bias; objective outcomes)) All outcomes		
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, investigators, study site personnel and the funder were masked to treatment assignment during the study.
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Patients, investigators, study site personnel and the funder were masked to treatment assignment during the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low and balanced between groups.
Selective reporting (reporting bias)	High risk	The trial registration site (clinicaltrials.gov) did not state that primary and secondary outcomes would be presented by biomarker groups. It seemed that a greater treatment effect was seen in 'biomarker high' groups but this group was not a prespecified group of interest. However, in the primary report, the primary outcome was stated as rate of exacerbations in the periostin high group.
Other bias	Low risk	None identified

Hodsman 2013

Study characteristics	
Methods	**Study ID and dates performed:** NCT00411814 (November 2006 to February 2008) **Study design:** A phase 1, two-part, randomised, double-blind, placebo-controlled, dose-escalation study **Duration of study:** 84 days **Study setting, location, number of centres:** 2 centres in Australia **Key inclusion criteria:** non-smoking males; aged 18 to 65 years; BMI of 19 to 29.9 kg/m^2; healthy volunteers (part 1); patients with mild bronchial asthma diagnosed at least 6 months prior to screening but otherwise healthy (part 2); pre-bronchodilator FEV1 > 70% but < 90% of predicted at screening with ≥ 12% reversibility after SABA (part 2) **Key exclusion criteria:** A strong family history of Th1 cytokine-related inflammatory disorders, including but not limited to, type I diabetes mellitus, multiple sclerosis, Crohn's disease, rheumatoid arthritis, sarcoidosis; known history of active or latent tuberculosis; history of chronic urogenital infections; any vaccination within 2 months; history of confirmed or active parasitic infection **Concomitant medications:** Intermittent SABA permitted
Participants	Note: this section reports the results in part 2 of the study (patients with mild asthma). **N randomised:** GSK679586 2.5 mg/kg, 6; GSK679586 10 mg/kg, 6; GSK679586 20 mg/kg, 9; placebo, 7

Hodsman 2013 *(Continued)*

	N analysed: GSK679586 2.5 mg/kg, 6; GSK679586 10 mg/kg, 6; GSK679586 20 mg/kg, 9; placebo, 7 **N withdrawals, n/N (%):** GSK679586 2.5 mg/kg, 3; GSK679586 10 mg/kg, 3; GSK679586 20 mg/kg, 3; placebo, 2 **Median age (SD), years:** GSK679586 2.5 mg/kg, 25 (4); GSK679586 10 mg/kg, 32 (11); GSK679586 20 mg/kg, 29 (10); placebo, 29 (6) **Gender - male, n (%):** GSK679586 2.5 mg/kg, 6 (100); GSK679586 10 mg/kg, 6 (100); GSK679586 20 mg/kg, 9 (100); placebo, 7 (100) **BL lung function - mean (SD) pre-BD FEV1, %:** GSK679586 2.5 mg/kg, 105 (9); GSK679586 10 mg/kg, 104 (24); GSK679586 20 mg/kg, 105 (14); placebo, 102 (21)
Interventions	**Intervention:** GSK679586 2.5 mg/kg, 10 mg/kg or 20 mg/kg (2 IV infusions 4 weeks apart) **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: safety. Secondary: Phamacokinetics; lung function; serum antibodies to GSK679586; serum concentrations of IL-13; FENO **Relevant outcomes reported:** Prespecified outcomes were reported.
Notes	**Funding for trial; notable author COIs:** The study was sponsored by GlaxoSmithKline. Several authors were employees of GlaxoSmithKline or had received financial support or honoraria from GlaxoSmithKline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedule generated using a web-based validated randomisation software system (Rand All) at GlaxoSmithKline
Allocation concealment (selection bias)	Low risk	Randomisation schedule generated using a web-based validated randomisation software system (Rand All) at GlaxoSmithKline
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study subjects and all sponsor and site personnel involved in the conduct of the study remained blinded to treatment assignment until study completion.
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	The study subjects and all sponsor and site personnel involved in the conduct of the study remained blinded to treatment assignment until study completion.
Incomplete outcome data (attrition bias) All outcomes	High risk	The attrition rate was 50% in two of the four relevant arms and ~33% in the remaining arms.

Hodsman 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	All prespecified outcomes (www.clintrials.gov) were well reported.
Other bias	Low risk	None identified

Korenblat 2018

Study characteristics	
Methods	**Study ID and dates performed:** NCT02104674 (STRETTO; June 2014 to May 2016) **Study design:** A phase 3, randomised, double-blind, controlled study **Duration of study:** 22 weeks (2-week screening; 12-week treatment period; 8-week safety follow-up) **Study setting, location, number of centres:** 113 study sites in the USA, Brazil, Bulgaria, Canada, Cazech Republic, Georgia, New Zealand, Poland, Puerto Rico, Romania, Russian Federation, Slovakia, South Africa, and the UK **Key inclusion criteria:** Aged 18 to 75 years; asthma diagnosis for ≥ 12 months at screening and a pre-bronchodilator FEV1 of 60 to 85% predicted; demonstrate a bronchodilator response during screening (≥ 15% relative improvement in FEV1 after bronchodilator administration); stable asthma during the screening period, as defined by stable FEV1, PEF, and daily SABA use) **Key exclusion criteria:** Current smoker or former smoker with more than 10 pack-years history; parasitic infection within the preceding 6 months; clinically significant lung disease other than asthma **Concomitant medications:** ICS treatment was not permitted for at least 30 days prior to enrolment and during the 12-week placebo-controlled period; patients treated with ICS must not have been discontinued from ICS therapy expressly to meet study eligibility.
Participants	**N randomised:** LBK, 105; placebo, 106 **N completed:** LBK, 91; placebo, 98 **N withdrawals, n/N (%):** LBK, 7; placebo, 11 **Median age (SD), years:** LBK, 42.9 (13.8); placebo, 44.7 (14.0) **Gender - male, n (%):** LBK, 41 (39.4); placebo, 39 (37.1) **BL lung function - mean (SD) pre-BD FEV1, %:** LBK, 71.81 (6.47); placebo, 72.32 (6.91)
Interventions	**Intervention:** Lebrikizumab 125 mg SC Q4W **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: change in pre-bronchodilator FEV1 from baseline at week-12. Secondary: absolute change in pre-bronchodilator PEF from baseline at week-12; time to treatment failure; change in SABA use; change AQLQ(S) overall score; safety **Relevant outcomes reported:** Prespecified outcomes were reported.
Notes	**Funding for trial; notable author COIs:** The study was sponsored by F. Hoffmann-La Roche Ltd. Author declaration of interests not reported in the article

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Korenblat 2018 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation was performed through an interactive voice/web-based response system (IxRS) using a permuted block design method.
Allocation concealment (selection bias)	Low risk	Randomisation was performed through an interactive voice/web-based response system (IxRS) using a permuted block design method.
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were blinded to treatment.
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	The spirometry technician was blinded to study treatment, and patients were asked not to discuss study treatment assignment with the spirometry technician. Patients were blinded to treatment and completed AQLQ questionnaires.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The rate of attrition was low and balanced across groups.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (as recorded in trial registration on www.clinicaltrials.gov) were well reported. Absolute rather than prespecified relative PEF was reported but did not warrant high risk of bias for selective reporting given that this outcome did not feature in this review.
Other bias	Low risk	None identified

NCT00425061

Study characteristics	
Methods	**Study ID and dates performed:** NCT00425061 (February 2007 to August 2008) **Study design:** A phase 2, randomised, double-blind, placebo-controlled, parallel-group, sequential dose-finding study **Duration of study:** 16 weeks **Study setting, location, number of centres:** 82 centres in the USA **Key inclusion criteria:** Generally healthy men and women with persistent asthma, aged 18 to 70 years of age, with body weight between 50 kg and 115 kg; history of treatment with a medium to high dose of ICS, with or without LABA, for at least 2 months prior to the screening visit and must remain constant during the study; FEV1 ≥ 55% to ≤ 80% predicted and demonstrated improvement in FEV1 with inhaled albuterol (salbutamol) reversibility of ≥ 12% **Key exclusion criteria:** Not reported

NCT00425061 *(Continued)*	**Concomitant medications:** Not reported
Participants	**N randomised:** IMA-638: 98; placebo: 61 **N completed:** IMA-638: 64; placebo: 40 **N withdrawals, n/N (%):** IMA-638: 34; placebo: 21 **Age (range), years:** Not reported **Gender - male, n (%):** IMA-638: 44/98 (44.9%); placebo: 24/61 (39.3%) **BL lung function - mean (SD) pre-BD FEV1, L [range across groups]:** IMA-638: 2.0-2.3 L; placebo: 2.0-2.1 L
Interventions	**Intervention:** IMA-638 (SC injection) **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: change from baseline in morning PEFR at day 112. Secondary: change from baseline in pre-beta agonist FEV1 at days 8, 28, 56, 84 and 112; change from baseline in airway hyperreactivity (PC20) at baseline and on days 28 and 112; change from baseline in ACQ-5 score at days 8, 28, 56, 84 and 112; percentage of participants who required treatment with systemic steroids for clinical exacerbation of asthma to day 112; mean number of puffs of rescue medication used (days 8, 28, 56, 84, 89, 91, 94, 98, 112); FVC on at baseline and on days 8, 28, 56, 84, 112; forced mid-expiratory flow rate 25 per cent (%) to 75% (FEF25-75) at baseline and on days 8, 28, 56, 84, 112; blood eosinophil levels at baseline and on days 8, 28, 56, 84, 112; log 10-transformed serum total immunoglobulin E at baseline and on days 8, 28, 56, 84, 112; serum IL-13 levels at baseline and on days 8, 28, 56, 84, 112; safety **Relevant outcomes reported:** All relevant prespecified outcomes reported
Notes	**Funding for trial; notable author COIs:** The study was sponsored by Pfizer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided (NCT record only)
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided (NCT record only)
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double masking (participant, investigator)". Patients were blinded; therefore, low risk of performance bias for subjective outcomes
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.

NCT00425061 *(Continued)*

Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Insufficient information provided. Double masking (participant, investigator). Patients were outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was uneven between groups and high.
Selective reporting (reporting bias)	High risk	The study was stopped early due to futility of the interim efficacy analysis results. Hence, the sponsor decided to only analyse safety results and key efficacy data. For example, IL-13 level was not reported.
Other bias	Low risk	None identified

NCT00640016

Study characteristics	
Methods	**Study ID and dates performed:** NCT00640016 (January to July 2008) **Study design:** A phase 2, double-blind, placebo-controlled, parallel-group study **Duration of study:** 12 weeks **Study setting, location, number of centres:** 41 centres in Australia, Germany, Netherlands, Poland, UK **Key inclusion criteria:** Women either infertile or who are practicing an acceptable form of birth control; uncontrolled (refractory) asthma despite treatment with ≥ 800 µg BDP or equivalent ICS per day plus ≥ 1 additional controller (e.g. LABA, leukotriene antagonist or theophylline; oral corticosteroids (not parenteral) as additional treatment at any dose are acceptable); FEV1 > 60% predicted normal on airway challenge days; methacholine PC20 < 4 mg/mL; aged 18 to 80 years; weight < 130 kg; normal ECG and laboratory findings **Key exclusion criteria:** Experienced a severe exacerbation within 28 days; onset of uncontrolled seasonal allergy symptoms within 28 days; history of allergic rhinitis, seasonal allergy or oesophagitis must be optimally controlled and remain on a stable treatment regimen during the study; lower respiratory tract infection within 6 weeks; current smokers or ex-smokers (> 10 pack-years); other significant lung disease **Concomitant medications:** See inclusion criteria
Participants	**N randomised:** CAT-354: 11; placebo: 3 **N completed:** CAT-354: 3; placebo: 1 **N withdrawals, n/N (%):** CAT-354: 8; placebo: 2 **Median age range, years:** CAT-354: 34-41; placebo: 34 **Gender - male, n (%):** CAT-354: 3/4 (75%); placebo: 0 **BL lung function - mean pre-BD FEV1, L:** CAT-354: 2.7 L; placebo: 2.6 L
Interventions	**Intervention:** Tralokinumab 1, 5 & 10 mg/kg **Comparator:** Placebo

NCT00640016 *(Continued)*

Outcomes	**Relevant prespecified outcomes:** Primary: change from baseline in doubling concentration of methacholine at day 28. Secondary: change from baseline in doubling concentration of methacholine at days 56, 84 or early discontinuation; FEV1 pre-dose and 30 minutes and 6 hours post-dose on days 0, 56, 84 or early discontinuation; FVC pre-dose and 30 minutes and 6 hours post-dose on days 0, 56, 84 or early discontinuation; FEV1/FVC pre-dose and 30 minutes and 6 hours post-dose on days 0, 56, 84 or early discontinuation; ACQ-5 total score on days 0, 56, 84 or early discontinuation; post-bronchodilator FEV1 on days 0 to 84; number of participants with diary data; number of participants with exacerbations; morning peak flow and peak flow variability (days 0 to 84); adult asthma quality of life questionnaire score (days 0, 28, 84 or early discontinuation); pharmacokinetics; safety **Relevant outcomes reported:** All relevant prespecified outcomes were reported.
Notes	**Funding for trial; notable author COIs:** The study was sponsored by MedImmune LLC.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided (NCT record only)
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided (NCT record only)
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double masking (participant, investigator); participants were blinded; therefore, low risk of performance bias for subjective outcomes
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Double masking (participant, investigator); participants were outcome assessors for subjective outcomes.
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition rates (67-75%)
Selective reporting (reporting bias)	Unclear risk	Some prespecified data were not collected and hence, not analysed because the study was prematurely terminated on the basis of several factors namely, observed low rate of participant randomisation into the study; delay caused by temporary halt of study and potential for expiry date of investigation medicinal product before end of study. But collected data were reported on www.clinicaltrials.gov.
Other bias	Low risk	None identified

Noonan 2013

Study characteristics	
Methods	**Study ID and dates performed:** NCT00971035 (MOLLY; November 2009 to February 2011) **Study design:** A phase 2, randomised, double-blind, placebo-controlled dose-ranging study **Duration of study:** 22 weeks (2-week screening period; 12-week treatment period; 8-week safety period) **Study setting, location, number of centres:** Not reported **Key inclusion criteria:** Asthmatic adults (aged 18-65 years old); not receiving ICS; a bronchodilator response of ≥ 15% and a pre-bronchodilator FEV1 of 60% to 85% of predicted value, with protocol defined disease stability demonstrated during the run-in period; stable asthma (diagnosis of asthma 12 or more months before enrolment, a bronchodilator response, and relative change in pre-bronchodilator FEV1 the week before treatment of less than 15%); pre-bronchodilator PEF also had to be stable before treatment, and daily use of SABA therapy had to be < 10 inhalations or 2 or fewer nonscheduled administrations of nebulised SABA therapy. **Key exclusion criteria:** asthma exacerbation during screening; known malignancy; known immunodeficiency; pre-existing lung disease other than asthma; uncontrolled clinically significant medical disease; current smoker; pregnancy **Concomitant medications:** ICSs or oral or parenteral corticosteroids were not permitted; see also eligibility criteria above.
Participants	**N randomised:** LBK 125 mg, 54; LBK 250 mg, 54; LBK 500 mg, 52; placebo, 52 **N analysed:** LBK 125 mg, 53; LBK 250 mg, 53; LBK 500 mg, 52; placebo, 52 **N withdrawals, n/N (%):** LBK 125 mg, 3; LBK 250 mg, 5; LBK 500 mg, 8; placebo, 10 **Median age (SD), years:** LBK 125 mg, 37.6 (12.4); LBK 250 mg, 40.0 (12.4); LBK 500 mg, 40.6 (11.4); placebo, 40.8 (13.1) **Gender - male, n (%):** LBK 125 mg, 23 (43.4); LBK 250 mg, 17 (32.1); LBK 500 mg, 17 (32.7); placebo, 19 (36.5) **BL lung function - mean (SD) pre-BD FEV1, %:** LBK 125 mg, 72.1 (7.0); LBK 250 mg, 71.7 (7.2); LBK 500 mg, 74.0 (6.2); placebo, 73.7 (7.3)
Interventions	**Intervention:** Lebrikizumab 125 mg, 250 mg or 500 mg SC Q4W **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: change in FEV1 (baseline to week-12). Secondary: change in FEV1 (baseline to week-24); change in quality of life and symptom scores (baseline to week-12); change in peak flow (baseline to week-1); rate of asthma exacerbations to 24 weeks; change in rescue medication use (baseline to week-1); safety (including incidence of anti-therapeutic antibodies) **Relevant outcomes reported:** The majority of relevant prespecified outcomes were reported.
Notes	**Funding for trial; notable author COIs:** The study was supported by F. Hoffmann–La Roche Ltd. Several authors were either employees of Genetech or Roche, or received financial support/honoraria from Genentech or Roche.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Noonan 2013 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information provided
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded to treatment allocation. Participants were blinded; therefore, low risk of performance bias for subjective outcomes
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Participants and investigators were blinded to treatment allocation; participants were outcome assessors for subjective outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low and balanced across groups.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (as per trial registry entry) were well reported.
Other bias	Low risk	None identified

Pannetieri 2018A

Study characteristics	
Methods	**Study ID and dates performed:** NCT02161757; June 2014 to July 2017 **Study design:** A phase 3, randomised, double-blind, placebo-controlled trial **Duration of study:** 4–6-week run-in, followed by a 52-week treatment period, and a 20-week safety follow-up **Study setting, location, number of centres:** International, multi-centre, 243 study sites **Key inclusion criteria:** Age 12 to 75 years; documented physician-diagnosed asthma; documented treatment with ICS at a total daily dose corresponding to ≥ 500µg fluticasone propionate dry powder formulation equivalents) and a LABA; morning pre-BD FEV1 value of ≥ 40 and < 80% value (< 90% for patients 12 to 17 years of age) of their PNV; post-BD reversibility of ≥ 12% and ≥ 200 mL in FEV1; ACQ-6 score ≥ 1.5 **Key exclusion criteria:** Pulmonary disease other than asthma; history of anaphylaxis following any biologic therapy; hepatitis B, C or HIV; pregnant or breastfeeding; history of cancer; current tobacco smoking or a history of tobacco smoking for ≥ 10 pack-years; previously taken tralokinumab

Pannetieri 2018A *(Continued)*

	Concomitant medications: All participants received a stable dose of ICS (≥ 500 µg fluticasone propionate dry powder or equivalent) and a LABA throughout the treatment period.
Participants	**N randomised:** tralokinumab 300 mg Q2W: 401; tralokinumab 300 mg Q4W: 406; placebo: 400 **N analysed:** tralokinumab 300 mg Q2W: 398; tralokinumab 300 mg Q4W: 404; placebo 400 **N withdrawals, n/N (%):** tralokinumab 300 mg Q2W: 66; tralokinumab 300 mg Q4W: 49; placebo 40 **Mean age (SD), years:** tralokinumab 300 mg Q2W: 49.4 (14.3); tralokinumab 300 mg Q4W: 51.1 (13.9); placebo: 51.4 (14.3) **Gender - male, n (%):** tralokinumab 300 mg Q2W: 146 (36.7); tralokinumab 300 mg Q4W: 123 (30.4); placebo: 135 (33.7) **BL lung function - mean (SD) pre-BD FEV1, %:** tralokinumab 300 mg Q2W: 59.8 (12.8); tralokinumab 300 mg Q4W: 60.9 (13.8); placebo 61.5 (13.3)
Interventions	**Intervention:** Tralokinumab 300 mg Q2W or 300 mg Q4W **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: AAER. Secondary: per cent change from baseline to week-52 in pre-dose/pre-BD FEV1; change from baseline to week-52 in total asthma symptom score (bi-weekly means); change from baseline to week-52 in AQLQ(S)+12 total score; change from baseline to week-52 in ACQ-6 score; AAER associated with an ER/UC visit, or a hospitalisation up to week-52; change from baseline in EQ-5D-5L VAS scores at week-52; change from baseline in total asthma rescue medication use at week-52 (bi-weekly means); change from baseline in home PEF (morning and evening) at week-52; change from baseline in night-time awakenings due to asthma requiring rescue medication use at week-52 (bi-weekly means [percentage]); number of patients with ≥ 1 asthma exacerbation up to week-52; WPAI + CIQ: productivity loss at week-52; WPAI + CIQ: activity impairment at week-52; asthma-related healthcare encounters by type up to week-52; hospitalisations; serum trough concentration of tralokinumab during the study period up to week-72; number of patients positive for anti-drug antibodies **Relevant outcomes reported:** Prespecified outcomes were well reported.
Notes	**Funding for trial; notable author COIs:** AstraZeneca. The authors received grants and/or personal fees, or were employees of, AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out in blocks using an Interactive Web or Voice Response System.
Allocation concealment (selection bias)	Low risk	Randomisation was carried out in blocks using an Interactive Web or Voice Response System.
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple (participant, care provider, investigator). Tralokinumab and placebo are visually distinct and so were administered by an unblinded team member not involved in the management of the participants to maintain blinding. The

Pannetieri 2018A *(Continued)*

		participants and trial site personnel assessing outcomes were unaware of the treatment allocation.
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Triple (participant, care provider, investigator). Tralokinumab and placebo are visually distinct and so were administered by an unblinded team member not involved in the management of the participants to maintain blinding. The participants and trial site personnel assessing outcomes were unaware of the treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low and even rates of attrition across arms
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (per trial registry) were well reported.
Other bias	Low risk	None identified

Pannetieri 2018B

Study characteristics	
Methods	**Study ID and dates performed:** NCT02194699 (October 2014 to September 2017) **Study design:** A phase 3, randomised, double-blind, placebo-controlled trial **Duration of study:** 4 to 6-week run-in, followed by a 52-week treatment period, and a 20-week safety follow-up **Study setting, location, number of centres:** International, multi-centre, 243 study sites **Key inclusion criteria:** Age 12 to 75 years; documented physician-diagnosed asthma; documented treatment with ICS at a total daily dose corresponding to ≥ 500 µg fluticasone propionate dry powder formulation equivalents) and a LABA; morning pre-BD FEV1 value of ≥ 40 and < 80% value (< 90% for patients 12 to 17 years of age) of their PNV; post-BD reversibility of ≥ 12% and ≥ 200 mL in FEV1; ACQ-6 score ≥ 1.5 **Key exclusion criteria:** Pulmonary disease other than asthma; history of anaphylaxis following any biologic therapy; hepatitis B, C or HIV; pregnant or breastfeeding; history of cancer; current tobacco smoking or a history of tobacco smoking for ≥ 10 pack-years; previously taken tralokinumab **Concomitant medications:** All participants received a stable dose of ICS (≥ 500 µg fluticasone propionate dry powder or equivalent) and a LABA throughout the treatment period.
Participants	**N randomised:** tralokinumab 300 mg Q2W:428; placebo: 428 **N analysed:** tralokinumab 300 mg Q2W: 417; placebo: 420 **N withdrawals, n/N (%):** tralokinumab 300 mg Q2W: 61; placebo 56 **Mean age (SD), years:** tralokinumab 300 mg Q2W: 47.3 (15.6); placebo: 48.0 (15.5) **Gender - male, n (%):** tralokinumab 300 mg Q2W: 144 (34.2); placebo: 127 (30.5)

Pannetieri 2018B *(Continued)*

	BL lung function - mean (SD) pre-BD FEV1, %: tralokinumab 300 mg Q2W: 60.8 (13.5); placebo 61.0 (14.7)
Interventions	**Intervention:** Tralokinumab 300 mg Q2W **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: AAER. Secondary: per cent change from baseline to week-52 in pre-dose/pre-BD FEV1; change from baseline to week-52 in total asthma symptom score (bi-weekly means); change from baseline to week-52 in AQLQ(S)+12 total score; change from baseline to week-52 in ACQ-6 score; AAER associated with an ER/UC visit, or a hospitalisation up to week-52; change from baseline in EQ-5D-5L VAS scores at week-52; change from baseline in total asthma rescue medication use at week-52 (bi-weekly means); change from baseline in home PEF (morning and evening) at week-52; change from baseline in night-time awakenings due to asthma requiring rescue medication use at week-52 (bi-weekly means [percentage]); number of patients with ≥ 1 asthma exacerbation up to week-52; WPAI + CIQ: productivity loss at week-52; WPAI + CIQ: activity impairment at week-52; asthma-related healthcare encounters by type up to week-52; hospitalisations; serum trough concentration of tralokinumab during the study period up to week-72; number of patients positive for anti-drug antibodies **Relevant outcomes reported:** Prespecified outcomes were well reported.
Notes	**Funding for trial; notable author COIs:** AstraZeneca**.** The authors received grants and/or personal fees, or were employees of, AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out in blocks using an Interactive Web or Voice Response System.
Allocation concealment (selection bias)	Low risk	Randomisation was carried out in blocks using an Interactive Web or Voice Response System.
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple (participant, care provider, investigator). Tralokinumab and placebo are visually distinct and so were administered by an unblinded team member not involved in the management of the participants to maintain blinding. The participants and trial site personnel assessing outcomes were unaware of the treatment allocation.
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Triple (participant, care provider, investigator). Tralokinumab and placebo are visually distinct and so were administered by an unblinded team member not involved in the management of the participants to maintain blinding. The participants and trial site personnel assessing outcomes were unaware of the treatment allocation.
Incomplete outcome data (attrition bias)	Low risk	Low and even rates of attrition across arms

Pannetieri 2018B *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Prespecified outcomes (per trial registry) were well reported.
Other bias	Low risk	None identified

Piper 2013

Study characteristics	
Methods	**Study ID and dates performed:** NCT00873860 (June 2009 to August 2010) **Study design:** A phase 2a, randomised, double-blind, placebo-controlled study **Duration of study: 26 weeks:** (2-week run-in, 12-week dosing and 12-week follow-up period) **Study setting, location, number of centres:** 57 study sites in Bulgaria, Germany, Poland, Romania and United Kingdom **Key inclusion criteria:** Adults (aged 18 to 65 years); BMI 18 to 40 kg/m^2; physician-diagnosed moderate-to-severe, persistent asthma requiring treatment with appropriate asthma controller medication; FEV1 reversibility post-bronchodilator of ≥ 12 per cent and ≥ 200 mL or have shown such values in a previous test within the last year, or have a positive airway hyper-responsiveness test result in the last year; pre-bronchodilator FEV 1 ≥ 40 % predicted at visits 1 and 3; uncontrolled asthma consistent with Expert Panel Report-3 in the 2 to 4 weeks preceding screening, a history of ≥ 1 of the following: daytime asthma symptoms ≥ 2 days/week, night-time awakening ≥ 1 night/week, salbutamol use ≥ 2 days/week; ACQ score ≥ 1.5 at visits 1 and 3; ≥ 1 occurrence of asthma exacerbation in the past year that required an unscheduled medical encounter; males, unless surgically sterile, must practice 2 effective methods of birth control (condom with spermicide); otherwise healthy by medical history and physical examination for that age group; chest x-ray or CT scan within the previous 12 months with no findings suggestive of acute or chronic respiratory pathology other than asthma **Key exclusion criteria:** Acute illness other than asthma at the start of the study; history of an active infection within 4 weeks prior to screening, or evidence of clinically significant active infection, including ongoing chronic infection; use of immunosuppressive medication (except oral prednisone up to 10 mg/day and inhaled and topical corticosteroids) within 30 days before randomisation; receipt of immunoglobulin or blood products within 30 days before randomisation or receipt of a vaccine within 4 weeks of screening; history of any immunodeficiency disorder; use of any biologicals including omalizumab within 6 months of the study **Concomitant medications:** See eligibility criteria above
Participants	**N randomised:** TLK 150 mg, 47; TLK 300 mg, 51; 600 mg, 48; placebo, 48 **N completed:** TLK 150 mg, 47; TLK 300 mg, 48; 600 mg, 47; placebo, 44 **N withdrawals, n/N (%):** TLK 150 mg, 0; TLK 300 mg, 3; 600 mg, 1; placebo, 3 **Median age (SD), years:** TLK 150 mg, 43.4 (1.1); TLK 300 mg, 48.7 (11.0); 600 mg, 49.8 (10.4); placebo, 47.2 (9.8) **Gender - male, n (%):** TLK 150 mg, 28 (59.6%); TLK 300 mg, 15 (29.4%); 600 mg, 20(41.7%); placebo, 15 (31.3%) **BL lung function - mean (SD) pre-BD FEV1, L:** TLK 150 mg, 1.94 (0.48); TLK 300 mg, 2.20 (0.67); 600 mg, 1.90 (0.59); placebo, 1.96 (0.66)
Interventions	**Intervention:** Tralokinumab (150, 300 or 600 mg) SC Q2W

Piper 2013 *(Continued)*

	Comparator: Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: change from baseline in the mean ACQ score at day 92. Secondary: Time to first observed asthma control; change from baseline in FEV1 (recorded at study sites) on days 1, 15, 29, 43, 57, 71, 85, 92, 127 and 169; change from baseline in PEF (recorded at home) on days 1 to 169; number of puffs of rescue beta2 agonist per week; AQLQ scores; changes from baseline in AQLQ scores on days 29, 57, 92, 127 and 169; Patient Global Impression of Change; percentage of participants with mean ACQ score ≤ 0.75 or ACQ score > 0.75 but < 1.5; serum concentrations of tralokinumab; number and proportion of participants with anti-drug antibodies to CAT-354 at any visit; annualised rate of and time to first, moderate-to-severe asthma exacerbation; proportion of patients with ≥1 moderate-to-severe asthma exacerbation; safety **Relevant outcomes reported:** All prespecified outcomes were reported.
Notes	**Funding for trial; notable author COIs:** The study was sponsored by MedImmune LLC.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Subjects were randomised according to a computer-generated randomisation list into one of three cohorts.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, care providers and investigators were blinded to treatment allocation.
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Participants were blinded and were outcome assessors for subjective outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Rates of attrition were low and balanced across groups.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes of interest to this review were well reported; limited data were presented for HRQoL and exacerbation rates.
Other bias	Low risk	None identified

Rabe 2018

Study characteristics	
Methods	**Study ID and dates performed:** NCT02528214 (December 2015 to September 2017) **Study design:** A phase 3, randomised, double-blind, placebo-controlled trial **Duration of study:** 24 weeks (24 weeks intervention period, 12 weeks evaluation) **Study setting, location, number of centres:** 80 study locations in the USA, Argentina, Belgium, Brazil, Canada, Chile, Colombia, Hungary, Israel, Italy, Mexico, Netherlands, Poland, Romania, Russian Federation, Spain and Ukraine **Key inclusion criteria:** Adults and adolescents aged ≥ 12 years; physician diagnosis of asthma for ≥ 12 months (GINA 2014 guidelines) and: 1) severe asthma and a well-documented, regular prescribed treatment of maintenance corticosteroids in the 6 months prior to visit 1 and using a stable OCS dose (i.e. no change of OCS dose) for 4 weeks prior to visit 1; 2) taking 5 to 35 mg/day of prednisone/prednisolone, or the equivalent, at visit 1 and at the randomisation visit; 3) participants must agree to switch to study-required prednisone/prednisolone as their OCS and use it per protocol for the duration of the study; existing treatment with high-dose ICS (> 500 µg total daily dose of fluticasone propionate or equivalent) in combination with a second controller (i.e. LABA or LTRA) for ≥ 3 months with a stable dose of ICS for ≥ 1 month prior to visit 1 (participants requiring a third controller for their asthma are eligible for this study if used for ≥ 3 months with a stable dose ≥ 1 month prior to visit 1); FEV1 < 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents, at visit 1; evidence of asthma as documented by either: reversibility of ≥ 12% and 200 mL in FEV1 after the administration of 200 to 400 µg (2 to 4 inhalations of albuterol/salbutamol or levalbuterol/levosalbutamol, or of a nebulised solution of albuterol/salbutamol or levalbuterol/levosalbutamol, if considered as a standard office practice) before randomisation or documented in the 12 months prior to visit 1 OR airway hyper-responsiveness (methacholine PC20 of < 8 mg/mL) documented in the 12 months prior to visit 1 **Key exclusion criteria:** Aged < 12 years of age; weight < 30.0 kg; COPD or other lung diseases (e.g. idiopathic pulmonary fibrosis, Churg-Strauss Syndrome, allergic bronchopulmonary aspergillosis, cystic fibrosis) which may impair lung function; clinical evidence or imaging (e.g. chest X-ray, computed tomography, magnetic resonance imaging) within 12 months of visit 1 with clinically significant findings of lung disease(s) other than asthma, as per local standard of care; deterioration of asthma that results in emergency treatment or hospitalisation within 4 weeks of screening; ≥ 12 puffs or more of rescue medication on any 1 day in the week prior to visit 1; upper or lower respiratory tract infection within the 4 weeks prior to screening; current smoker or cessation of smoking within 6 months prior to visit 1; previous smoker with a smoking history > 10 pack-years; comorbid disease that might interfere with the evaluation of the investigational medicinal product **Concomitant medications:** See inclusion/exclusion criteria (above)
Participants	**N randomised, n:** DUP: 103; PBO: 107 **N analysed, n:** DUP: 103; PBO: 107 **N withdrawals, n/N (%):** DUP: 2; PBO: 1 **Median age (SD), years:** DUP: 51.9 (12.5); PBO: 50.7 (12.8) **Gender - male, n (%):** DUP: 41 (40); PBO: 42 (39) **BL lung function - mean (SD) pre-BD FEV1, L:** DUP: 1.53 (0.53); PBO: 1.63 (0.61)
Interventions	**Intervention:** Dupilumab 300 mg Q2W **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: percentage reduction from baseline in OCS dose at week-24 while maintaining asthma control; median percentage reduction from baseline in OCS dose at week-24 while maintaining asthma control. Secondary: percentage of participants achieving ≥ 50% reduction in OCS dose at week-24 while maintaining asthma control; percentage of participants achiev-

Rabe 2018 *(Continued)*

	ing a reduction in OCS dose to < 5 mg/day at week-24 while maintaining asthma control; percentage of participants who no longer required OCS dose at week-24 while maintaining asthma control; absolute reduction from baseline in oral corticosteroids dose at week-24 while maintaining asthma control; annualised rate of severe exacerbations during 24-week treatment period; change from baseline to week-24 in pre-BD FEV1; ACQ-5 scores at weeks 2, 4, 8, 16 & 20; change from baseline in EQ-5D-5L scores at weeks 12 and 24; change from baseline in HADS total score at weeks 12 and 24; change from baseline in SNOT-22 global score at weeks 12 and 24 **Relevant outcomes reported:** All prespecified outcomes were reported.
Notes	**Funding for trial; notable author COIs:** Sponsored by Sanofi and Regeneron Pharmaceuticals. All authors were employees of, or received honoraria/grant support from the Sanofi and/or Regeneron Pharmaceuticals.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation and assignment were performed by Interactive Voice/Web Response System (IVRS/IWRS).
Allocation concealment (selection bias)	Low risk	Randomisation and assignment were performed by Interactive Voice/Web Response System (IVRS/IWRS).
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple (participant, care provider, investigator) (clinicaltrials.gov/ct2/show/study/NCT02528214
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Participants were blinded and were outcome assessors for subjective outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low and balanced between arms.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were well reported.
Other bias	Low risk	None

Russell 2018

Study characteristics

Russell 2018 *(Continued)*

Methods	**Study ID and dates performed:** NCT02449473 (MESOS; September 2015 to June 2017) **Study design:** A phase 2, randomised, double-blind, placebo-controlled trial **Duration of study:** 30 weeks (4-week run-in; 12-week treatment period; 14-week follow-up period) **Study setting, location, number of centres:** 15 sites in Canada, Denmark and the UK **Key inclusion criteria:** Aged 18 to 75 years; documented history of physician-diagnosed asthma for ≥ 12 months requiring treatment with ICS (≥ 250 µg/day of fluticasone or equivalent) at a stable dose with or without other asthma controller medications; exacerbation free for ≥ 6 weeks before enrolment; < 3 asthma exacerbations requiring OCS treatment in the preceding 12 months; post-BD FEV1 reversibility of ≥ 12% and ≥ 200 mL; evidence of uncontrolled asthma during the run-in period (ACQ-5 score ≥1.5) **Key exclusion criteria:** Clinically significant comorbidities; receiving regular systemic corticosteroids or biologics; current smokers or past smokers of ≥ 10 pack-years **Concomitant medications:** See eligibility criteria above
Participants	**N randomised:** TLK, 39; placebo, 40 **N completed:** TLK, 36; placebo, 40 **N withdrawals, n/N (%):** TLK, 3; placebo, 0 **Median age (SD), years:** TLK, 47.1 (14.2); placebo, 50.1 (14.2) **Gender - male, n (%):** TLK, 16 (41); placebo, 20 (50) **BL lung function - mean (SD) pre-BD FEV1, L:** TLK, 2.46 (0.79); placebo, 2.37 (0.62)
Interventions	**Intervention:** Tralokinumab 300 mg SC Q2W **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: Change from baseline to week-12 in the number of airway submucosal eosinophils per mm^2 of the lamina propria (by bronchial biopsy). Secondary: Change from baseline to week-12 in eosinophil count and eosinophil cationic protein. Exploratory: FENO concentration; total blood IgE; ACQ-6 score; FEV1; FVC **Relevant outcomes reported:** Prespecified outcomes were reported.
Notes	**Funding for trial; notable author COIs:** Sponsored by AstraZeneca. The majority of authors were either employees of or received honoraria/grant support from AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided (NCT record only)
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided (NCT record only)
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.

Russell 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple (participant, care provider, investigator) (clinicaltrials.gov/ct2/show/NCT02449473)
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Triple (participant, care provider, investigator); participants were outcome assessors for subjective outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Results not publicly available
Selective reporting (reporting bias)	Unclear risk	Results not publicly available
Other bias	Low risk	None identified

Scheerens 2014

Study characteristics	
Methods	**Study ID and dates performed:** NCT00781443 (December 2008 to November 2009) **Study design:** A phase 2, randomised, double-blind, parallel-group, placebo-controlled study **Duration of study:** 31 weeks (3-week screening period; 12-week treatment period; 16-week follow-up period) **Study setting, location, number of centres:** Not reported **Key inclusion criteria:** Diagnosis of allergic asthma; diagnosis of asthma ≥ 6 months; currently treated with only intermittent short-acting inhaled β-adrenergic agonists; body weight between 40 to 120 kg; normal chest X-ray within 2 years of screening **Key exclusion criteria:** Require daily controller medication for asthma; history of hypersensitivity to the study drug or to drugs with similar chemical structures or to any ingredients, including excipients of the study medication or drugs related to LBK; documented medical history of anaphylaxis; immunotherapy currently or within the past 3 months prior to screening; lung disease other than mild allergic asthma; pregnant or lactating; significant concurrent medical illness other than asthma; clinically significant abnormality on ECG at the screening visit; smoked in the previous 6 months or have a history of smoking more than 10 pack-years; history of helminthic infection **Concomitant medications:** See eligibility criteria
Participants	**N randomised:** LBK: 13; placebo: 16 **N completed:** LBK: 12; placebo: 16 **N withdrawals, n/N (%):** LBK: 1; placebo: 0 **Median age (SD), years:** LBK: 36 (11); placebo: 32 (11) **Gender - male, n (%):** LBK: 6/13 (46.1%); placebo: 9/16 (56.3%)

Scheerens 2014 *(Continued)*

	BL lung function - mean (SD) pre-BD FEV1, %: LBK: 84.3% (13.6); placebo: 82.4% (8.9)
Interventions	**Intervention:** LBK 5 mg/kg SC at weeks 0, 4, 8 and 12 **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: Late asthmatic response (day 92). Secondary: Early asthmatic response (day 92); safety **Relevant outcomes reported:** Primary: Late asthmatic response (day 92). Secondary: Early asthmatic response (day 92); airway hyper-responsiveness; safety
Notes	**Funding for trial; notable author COIs:** The study was sponsored by Genentech, Inc. The authors were employees of, or received research funding or honoraria from Genentech.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used an interactive voice response system. Randomisation was stratified by study site.
Allocation concealment (selection bias)	Low risk	Used an interactive voice response system and randomisation was stratified by study site.
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Subjects, investigating physicians, study site personnel, and the study sponsor and its agents were blinded to treatment assignment. The study sponsor was unblinded to treatment assignment until after verification of the data collected through week-13 were verified. Subjects, investigating physicians, and study site personnel were unblinded at the end of the week-28 follow-up visit.
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	All personnel involved were blinded to treatment assignment until at earliest week-13 (after the second allergen challenge data collection was completed). Subjects, investigating physicians, and study site personnel were unblinded at the end of the week-28 follow-up visit.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low and balanced across treatment arms.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes (per trial registry) were well reported.
Other bias	Low risk	None identified

Singh 2010

Study characteristics	
Methods	**Study ID and dates performed:** NCT00974675 (September 2006 to August 2007) **Study design:** A phase 1, randomised double-blind, placebo-controlled study **Duration of study:** 25 weeks (28-day run-in; 147-day treatment period) **Study setting, location, number of centres:** Two UK sites (Medicines Evaluation Unit and the Chiltern Clinical Research Unit) **Key inclusion criteria:** Aged 18 to 60 years with a physician diagnosis of asthma; female participants were either postmenopausal (no menstrual period for a minimum of 1 year) or surgically sterilised; FEV1 ≥ 80% of predicted normal and be well controlled on ICS and SABA only with no change in the dose of ICS for 3 months prior to the study; participants were also required to not have smoked in the previous year and have a smoking history of ≤ 10 pack years. **Key exclusion criteria:** An asthma exacerbation requiring hospitalisation within 3 years of the study; a history of any active disease other than eczema, seasonal allergy which was expected to start before the last dose of study drug; poorly controlled asthma defined as SABA > 6 times/day on any one day or > 3 times/day on six or more days within the 2 weeks prior to the study; previous treatment with any other asthma medications within 6 months of the study, treatment for atopic symptoms except eczema within the previous 4 weeks; any acute illness in the prior 2 weeks; a lower respiratory tract infection within 4 weeks; previous treatment with a monoclonal antibody or related protein and participation in another study within 3 months (or 5 half-lives of the investigational product); participants had to have a medical history negative for alcohol or substance abuse and no clinically significant ECG or clinical chemistry, haematology or urinalysis result. **Concomitant medications:** ICS and SABA only
Participants	**N randomised:** TLK 1 mg/kg, 8; TLK 5 mg/kg, 8; TLK 10 mg/kg, 3; placebo, 4 **N completed:** TLK 1 mg/kg, 6; TLK 5 mg/kg, 7; TLK 10 mg/kg, 2; placebo, 2 **N withdrawals, n/N (%):** TLK 1 mg/kg, 2; TLK 5 mg/kg, 1; TLK 10 mg/kg, 1; placebo, 2 **Median age (SD), years:** TLK 1 mg/kg, 39.4 (9.1); TLK 5 mg/kg, 34.6 (7.6); TLK 10 mg/kg, 43.3 (14.5); placebo, 40.0 (13.0) **Gender - male, n (%):** TLK 1 mg/kg, 8 (100); TLK 5 mg/kg, 8 (100); TLK 10 mg/kg, 2 (66.6); placebo, 4 (100) **BL lung function - mean (SD) pre-BD FEV1, L:** TLK 1 mg/kg, 3.83 (0.54); TLK 5 mg/kg, 4.17(0.54); TLK 10 mg/kg, 3.01 (1.35); placebo, 3.64 (0.68)
Interventions	**Intervention:** Tralokinumab 1, 5 or 10 mg/kg Q4W **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: Pharmacokinetic parameters. Secondary: Proportion of patients experiencing any treatment-emergent adverse event or treatment-emergent serious adverse event **Relevant outcomes reported:** All prespecified outcomes were reported.
Notes	**Funding for trial; notable author COIs:** Funded by MedImmune. Authors NAM, RF and LR are employees of MedImmune, LLC.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Singh 2010 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information provided
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Insufficient information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	The study was terminated early and only three patients were randomised to tralokinumab or placebo in the highest dose group (this was a phase I study).
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (per trial registry) were well reported.
Other bias	Low risk	None identified

Tripp 2017

Study characteristics	
Methods	**Study ID and dates performed:** NCT00986037 (October 2009 to July 2010) **Study design:** A phase 1, randomised, double-blind placebo-controlled, 3-part clinical trial **Duration of study:** 16 weeks **Study setting, location, number of centres:** Single centre, USA **Key inclusion criteria:** Diagnosis of well-controlled, mild-to-moderate asthma by GINA guidelines for ≥ 6 months; a condition of good health (other than mild to moderate asthma) based upon the results of medical history, physical examination, vital signs laboratory profile and ECG; BMI 18 to 34 mg/kg^2, inclusive **Key exclusion criteria:** Asthma exacerbation within 8 weeks of study day 1; clinically significant allergic reaction to any drug, biologic, food, or vaccine; history of allergic reaction or significant sensitivity to constituents of study drug; receipt of any investigational product within 30 days or 5 half-lives (whichever is longer) prior to study drug administration; participant is a smoker or has a history of

Tripp 2017 *(Continued)*

	smoking within the 6-month period preceding study drug administration; current enrolment in another clinical study **Concomitant medications:** Not reported
Participants	**N randomised:** 27 (RPC4046, 20; placebo, 7; excluding healthy volunteers) **N completed:** 26 **N withdrawals, n/N (%):** 1 (6%) **Median age (SD), years:** Part 2 RPC4046: 33 (12); Part 2 placebo: 23 (2); Part 3 RP4046**:** 29 (8); Part 3 placebo: 28 (8.3) **Gender - male, n (%):** Part 2 RPC4046: 9(75); Part 2 placebo: 3 (100); Part 3 RPC4046: 7 (87.5); Part 3 placebo: 4 (100) **BL lung function - mean (SD) pre-BD FEV1, %:** Not reported
Interventions	**Intervention:** IL-13 monoclonal antibody, IV RPC4046 **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Safety and tolerability **Relevant outcomes reported:** Pharmacokinetics; immunogenicity
Notes	**Funding for trial; notable author COIs:** AbbVie

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple masking (participant, care provider and investigator)
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Triple masking (participant, care provider and investigator). Participants were outcome assessors for subjective outcomes.
Incomplete outcome data (attrition bias)	Low risk	All randomised patients were included in the analyses.

Tripp 2017 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Prespecified outcomes (per clintrials.gov registry entry) were well reported.
Other bias	Low risk	None identified

Wenzel 2007a

Study characteristics	
Methods	**Study ID and dates performed:** NCT00535028 (January-May 2005) **Study design:** A phase 2, single-centre, double-blind, randomised, parallel-group study **Duration of study:** 28-day treatment period **Study setting, location, number of centres:** Single centre in the UK **Key inclusion criteria:** Patients with atopic asthma (aged >18 years); baseline FEV1 of ≥ 70% of predicted; needed regular or as required use of β-agonists; showed a late phase response (≥ 15% drop in FEV1 between 4 to 10 h) to allergen challenge at screening; on a stable regimen of medications for asthma for ≥ 1 month; PC20 < 8 mg/mL **Key exclusion criteria:** No systemic immunosuppressive therapy within 1 month of screening; any medical condition that would preclude allergen challenge; had a greater than 10 pack-year smoking history, or had smoked in the 3 months before screening; received any corticosteroid medications (systemic or inhaled) in the month before screening **Concomitant medications:** Participants were to continue their non-steroidal concomitant treatments without change during the study. No participants used leukotriene receptor antagonists while on study.
Participants	**N randomised:** Pitrakinra: 12; placebo: 12 **N completed:** Pitrakinra: 12; placebo: 12 **N withdrawals, n/N (%):** Pitrakinra: 0; placebo: 0 **Median age (SD), years:** Pitrakinra: 31 (10); placebo: 30 (9) **Gender - male, n (%):** Pitrakinra: 5/12 (41.7); placebo: 7/12 (58.3) **BL lung function - mean (SD) pre-BD FEV1, %:** Pitrakinra: 102 (13); placebo: 100 (20)
Interventions	**Intervention:** Pitrakinra 25 mg SC once daily for 28 days **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: Max percentage fall in FEV1 during the late phase asthmatic response (4-10 hours after allergen challenge) on day 28. Secondary: The effects of pitrakinra on cutaneous antigen response, antigen induced airway hyperactivity and sputum eosinophilia; safety **Relevant outcomes reported:** All prespecified outcomes were reported.
Notes	**Funding for trial; notable author COIs:** The study was sponsored by Aerovance, Inc. Authors were employees of Aerovance or Quintiles, or had received honoraria from Aerovance.
Risk of bias	

Wenzel 2007a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation list was generated with SAS version 8.2 by the Guy's Drug Research Unit.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quadruple masking (participant, care provider, investigator, outcomes assessor). See www.clinicaltrials.gov
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Quadruple masking (participant, care provider, investigator, outcomes assessor). See www.clinicaltrials.gov
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study and were included in the analyses.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes per clinicaltrials.gov were well reported.
Other bias	Low risk	None identified

Wenzel 2007b

Study characteristics	
Methods	**Study ID and dates performed:** NCT00535431 (December 2005 to October 2006) **Study design:** A phase 2, single-centre, double-blind, randomised, parallel-group study **Duration of study:** 28-day treatment period **Study setting, location, number of centres:** Single centre in the UK **Key inclusion criteria:** Patients with atopic asthma (aged > 18 years); baseline FEV1 of ≥ 70% of predicted; needed regular or as required use of β-agonists; showed a late phase response (≥ 15% drop in FEV1 between 4 to 10 h) to allergen challenge at screening; on a stable regimen of medications for asthma for ≥ 1 month; PC20 to adenosine monophosphate of > 3.125 mg/mL **Key exclusion criteria:** No systemic immunosuppressive therapy within 1 month of screening; any medical condition that would preclude allergen challenge; had a greater than 10 pack-year smoking

Wenzel 2007b *(Continued)*

	history, or had smoked in the 3 months before screening; received any corticosteroid medications (systemic or inhaled) in the month before screening **Concomitant medications:** Participants were to continue their non-steroidal concomitant treatments without change during the study. No participants used leukotriene receptor antagonists while on study.
Participants	**N randomised:** Pitrakinra: 16; placebo: 16 **N completed:** Pitrakinra: 15; placebo: 14 **N withdrawals, n/N (%):** Pitrakinra: 1; placebo: 2 **Median age (SD), years:** Pitrakinra: 25 (5); placebo: 29 (8) **Gender - male, n (%):** Pitrakinra: 12/15 (80.0); placebo: 7/15 (46.7) **BL lung function - mean (SD) pre-BD FEV1, %:** Pitrakinra: 99 (15); placebo: 96 (18)
Interventions	**Intervention:** Pitrakinra 60 mg nebulised twice daily for 28 days **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: Max percentage fall in FEV1 during the late phase asthmatic response (4-10 hours after allergen challenge) on day 28. Secondary: the effects of pitrakinra on antigen induced airway hyperactivity to adenosine monophosphate and blood levels of circulating IgE; pharmacokinetics; safety **Relevant outcomes reported:** All prespecified outcomes were reported.
Notes	**Funding for trial; notable author COIs:** The study was sponsored by Aerovance, Inc. Authors were employees of Aerovance or Quintiles, or had received honoraria from Aerovance.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation list was generated with SAS version 8.2 by the Guy's Drug Research Unit.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quadruple masking (participant, care provider, investigator, outcomes assessor). See www.clinicaltrials.gov
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias)	Low risk	Quadruple masking (participant, care provider, investigator, outcomes assessor). See www.clinicaltrials.gov

Wenzel 2007b *(Continued)*

Objective outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low and balanced between groups.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes per clinicaltrials.gov were well reported.
Other bias	Low risk	None identified

Wenzel 2010

Study characteristics	
Methods	**Study ID and dates performed:** NCT00801853 (March 2009 to February 2010) **Study design:** A phase IIb, double-blind, randomised, placebo-controlled, parallel-group, repeated-dose study **Duration of study:** 16 weeks (4-week run-in; 12-week treatment period) **Study setting, location, number of centres:** 71 centres in the USA, Hungary, Poland and UK **Key inclusion criteria:** Aged ≥ 18 years of age with a documented clinical history of asthma, has been treated for asthma and, in the opinion of the Investigator, is not fully controlled on current asthma therapy; moderate-to severe persistent asthma (GINA definition); maintained on moderate-to-high doses of ICS and LABA in the form of combination therapy or as individual agents (equivalent to fluticasone ≥ 250 µg twice daily and salmeterol ≥ 50 µg twice daily for ≥ 4 weeks before screening; ≥ 1 asthma exacerbation in the past 2 years (defined as physician prescribed oral corticosteroids or asthma requiring treatment increase approximately 4 times the baseline dose of ICS or hospitalisation due to asthma); pre-bronchodilator FEV1 ≥ 50% but ≤ 95% of predicted value at screening and visit 2; ≥ 12% reversibility (and a ≥ 200 mL difference) from pre-bronchodilator FEV1 within 15 to 30 minutes of receiving up to 4 puffs of a short-acting beta-agonist at screening or has ≥ 10% reversibility from pre-bronchodilator FEV1 plus a documented reversibility of ≥ 12% within the previous 12 months (documented methacholine or histamine PC20 < 8 mg/mL is also acceptable evidence or reversible airways disease); scores ≤ 20 on ACT Test at screening; adequate methods of contraception if female of childbearing potential; non-smoker for ≥ 6 months before screening and < 10 pack/year history of smoking **Key exclusion criteria:** A current diagnosis of a respiratory order other than asthma; has received oral corticosteroid treatment within 8 weeks of randomisation or patient has been intubated for ventilation in the past 5 years; has used any leukotriene antagonist within 1 week before screening or anti-IgE medications within 4 weeks of screening; pregnant or breastfeeding **Concomitant medications:** See eligibility criteria above
Participants	**N randomised:** Pitrakinra 1 mg, 132; Pitrakinra 3 mg, 137; Pitrakinra 10 mg, 128; placebo, 137 **N completed:** Not reported **N withdrawals, n/N (%):** Not reported **Median age (SD), years:** Not reported **Gender - male, n (%):** Not reported **BL lung function - mean (SD) pre-BD FEV1, %:** Not reported
Interventions	**Intervention:** Pitrakinra 1/3/10 mg

Wenzel 2010 *(Continued)*

	Comparator: Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: incidence of asthma exacerbations. Secondary: time to exacerbation; spirometry; symptom scores; FENO and serum IgE (prespecified subgroup analyses included those with high and low blood eosinophil counts) **Relevant outcomes reported:** Non-significance of endpoints (listed above) was reported. Exacerbation and spirometry endpoints reported in patients with blood eosinophilia ≥ 350 cells/mm^3 (abstract only)
Notes	**Funding for trial; notable author COIs:** The study was sponsored by Aerovance, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided (abstract only)
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided (abstract only)
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided (abstract only)
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Insufficient information provided (abstract only)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information provided (abstract only)
Selective reporting (reporting bias)	Unclear risk	Insufficient information provided (abstract only)
Other bias	Unclear risk	Insufficient information provided (abstract only)

Wenzel 2013

Study characteristics	
Methods	**Study ID and dates performed:** NCT01312961 (March 2011 to October 2012)

Wenzel 2013 *(Continued)*

	Study design: A phase 2, randomised, double-blind, placebo-controlled, parallel-group study **Duration of study:** 22 weeks (2-week screening period; 12-week treatment period; 4-week follow-up) **Study setting, location, number of centres:** 50 centres in the USA **Key inclusion criteria:** Aged 18 to 65 years old; had persistent, moderate-to-severe asthma; an elevated blood eosinophil count (≥ 300 cells per µL) or an elevated sputum eosinophil level (≥ 3%) at screening; symptoms that were not well controlled with medium-dose to high-dose ICS plus LABAs (fluticasone [≥ 250 µg] and salmeterol [50 µg] twice daily or the equivalent); a diagnosis of asthma for at least 12 months was substantiated by the reversibility of the FEV during screening or earlier or by a positive methacholine challenge within 12 months before screening; FEV1 that was 50% or more of the predicted value during screening and at randomisation; ACQ-5 score of 1.5 to 3.0 at screening; ≥ 1 asthma exacerbation within 2 years before screening (defined as treatment with ≥ 1 systemic glucocorticoid burst, in-patient hospitalisation, or an emergency department visit for worsening asthma) **Key exclusion criteria:** COPD or other lung disease; use of beta-adrenergic blockers; current smoker or cessation of smoking within the 6 months prior to screening; previous smoking with a smoking history > 10 cigarette pack/years; pregnancy or breastfeeding, or intention to become pregnant during study **Concomitant medications:** See eligibility criteria above
Participants	**N randomised:** Dupilumab: 52; placebo: 52 **N completed:** Dupilumab: 45; placebo: 35 (Note: 52 participants in each group were included in the analyses) **N withdrawals, n/N (%):** Dupilumab: 7; placebo: 17 **Median age (SD), years:** Dupilumab: 37.8 (13.2); placebo: 41.6 (13.1) **Gender - male, n (%):** Dupilumab: 26/52 (50); placebo: 26/52 (50) **BL lung function - mean (SD) pre-BD FEV1, %:** Dupilumab: 72.0 (12.6); placebo: 72.0 (12.7)
Interventions	**Intervention:** Dupilumab 300 mg SC once-weekly **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: Percentage of participants with asthma exacerbation to week-12. Secondary: Time to first asthma exacerbation; percentage of participants with composite asthma events (a 30% or greater reduction from baseline in morning PEF on 2 consecutive days together with 6 or more additional reliever puffs of albuterol or levalbuterol in a 24-hour period [compared to baseline] on 2 consecutive days); change from baseline in FEV1 to week-12; change from baseline in PEF to week-12; change from baseline to week-12 in ACQ-5 score; change from baseline in SNOT-22 score to week-12; change from baseline in morning and evening asthma symptom scores to week-12; change from baseline in number of nocturnal awakenings per day to week-12; change from baseline in number of albuterol or levalbuterol inhalations per day to week-12 **Relevant outcomes reported:** All prespecified outcomes were reported.
Notes	**Funding for trial; notable author COIs:** Supported by Sanofi and Regeneron Pharmaceuticals. Authors were employees of, or had received honoraria from Sanofi or Regeneron.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The Study Biostatistician will provide the randomisation scheme to the centralized treatment allocation system. This centralised treatment allocation system will generate the patient randomisation list according to which it will allocate the treatments to the patients".

Wenzel 2013 *(Continued)*

Allocation concealment (selection bias)	Low risk	Patients were randomly assigned in a 1:1 ratio by means of a "centralised system".
Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple masking: Participant, care provider and investigators. (clinicaltrials.gov/ct2/show/NCT01312961)
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Triple masking: Participant, care provider and investigators; data were collected by the investigators (clinicaltrials.gov/ct2/show/NCT01312961).
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was high (33% withdrew from placebo arm and 13% from dupilumab arm; large difference between the two arms).
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (per trial registry) were well reported.
Other bias	Unclear risk	Baseline eotaxin 3 seems to be quite different in each arm with dupilumab arm having seemingly much lower level – this is reflected by figure 3. Unsure how significant this is as all other biomarkers have similar baseline characteristics and the measurement outcome is change of levels rather than absolute values.

Wenzel 2016

Study characteristics	
Methods	**Study ID and dates performed:** NCT01854047 (November 2014 to April 2015) **Study design:** A randomised, double-blind, placebo-controlled, dose-ranging study **Duration of study:** 21-day screening period; 24-week treatment period; 14-week follow-up period **Study setting, location, number of centres:** 174 study sites in the USA, Argentina, Australia, Chile, France, Italy, Japan, Republic of Korea, Mexico, New Zealand, Poland, Russian Federation, South Africa, Spain, Turkey, Ukraine **Key inclusion criteria:** Adults aged ≥ 18 years with an asthma diagnosis for ≥ 12 months (GINA 2009 criteria); existing treatment with medium-to-high-dose ICS plus a LABA (fluticasone propionate ≥ 250 µg, or equivalent ICS, twice daily) with a stable dose of ICS plus a long-acting β2 agonist for ≥ 1 month before screening; a pre-bronchodilator FEV1 of 40 to 80% predicted at screening and at baseline; ACQ-5 score of 1.5 or higher at screening and at baseline; reversibility of ≥ 12% and 200 mL in FEV1 after 200 to 400 µg of salbutamol at screening; patients were also required for study inclusion to have had any of the following within 1 year before screening: at least one systemic (oral or parenteral) corticosteroid

Wenzel 2016 *(Continued)*

	burst therapy, or a hospital admission or an emergency or urgent medical care visit that required treatment with systemic steroids for worsening asthma. **Key exclusion criteria:** a diagnosis of COPD or other diseases that impair pulmonary function tests; use of β-adrenergic receptor blockers for any reason; use of systemic corticosteroids within 28 days of, or during, the screening period; current smokers or smokers who had stopped within 6 months before screening or had a previous history of more than 10 pack-years **Concomitant medications:** See eligibility criteria above
Participants	**N randomised:** Dupilumab 200 mg Q4W: 154; 300 mg Q4W: 157; 200 mg Q2W: 150; 300 mg Q4W: 157; placebo: 158 **N completed:** Dupilumab 200 mg Q4W: 135; 300 mg Q4W: 142; 200 mg Q2W: 137; 300 mg Q4W: 149; placebo: 146 **N withdrawals, n/N (%):** Dupilumab 200 mg Q4W: 15; 300 mg Q4W: 15; 200 mg Q2W: 11; 300 mg Q4W: 7; placebo: 12 **Median age (SD), years:** Dupilumab 200 mg Q4W: 47.9 (13.1); 300 mg Q4W: 47.9 (13.1); 200 mg Q2W: 51.0 (13.4); 300 mg Q4W: 47.5 (12.4); placebo: 49.0 (12.7) **Gender - male, n (%):** Dupilumab 200 mg Q4W: 67 (43.5); 300 mg Q4W: 57 (36.3); 200 mg Q2W: 54 (36.0); 300 mg Q4W: 54 (34.4); placebo: 54 (34.2) **BL lung function - mean (SD) pre-BD FEV1, %:** Dupilumab 200 mg Q4W: 60.3 (11.2); 300 mg Q4W: 60·7 (10·4); 200 mg Q2W: 61·2 (11·0); 300 mg Q4W: 60·8 (10·4); placebo: 61.0 (10.7)
Interventions	**Intervention:** Dupilumab 200 mg Q2W; dupilumab 300 mg Q4W **Comparator:** Placebo
Outcomes	**Relevant prespecified outcomes:** Primary: change from baseline at week-12 in FEV1 in patients with baseline blood eosinophil counts of ≥ 300 eosinophils per µL. Secondary: prespecified at week-12 and week-24 for both the overall population and for the subgroup with eosinophil counts of ≥ 300 eosinophils per µL and included: percentage change from baseline in FEV1; annualised severe asthma exacerbation rate (defined as deterioration of asthma that required use of systemic corticosteroids for ≥ 3 days, or hospital admission or emergency department visit because of asthma treated with systemic corticosteroids) during treatment and overall study periods (which included follow-up); time to severe exacerbation events during treatment and overall study periods; change from baseline at week-12 and week-24 in morning and evening asthma symptom scores; ACQ-5 score, AQLQ score; number of inhalations per day of salbutamol or levosalbutamol for symptom relief; changes from baseline in FENO concentrations at weeks 12 and 24 **Relevant outcomes reported:** All prespecified outcomes were reported.
Notes	**Funding for trial; notable author COIs:** Supported by Sanofi and Regeneron Pharmaceuticals. Authors were employees of, or had received honoraria, grant support or trial funding from Sanofi or Regeneron.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised randomisation scheme provided by an interactive voice response system or interactive web response system. Randomisation stratified by central laboratory blood eosinophil counts at screening and by country
Allocation concealment (selection bias)	Low risk	Centralised randomisation scheme provided by an interactive voice response system or interactive web response system

Wenzel 2016 *(Continued)*

Blinding of participants and personnel (performance bias; objective outcomes)) All outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of performance bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple masking: Participant, care provider (site personnel) and investigator. (clinicaltrials.gov/ct2/show/NCT01854047)
Blinding of outcome assessment (detection bias; objective outcomes) Objective outcomes	Low risk	Knowledge of intervention would be unlikely to result in risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Triple masking: Participant, care provider (site personnel) and investigator - data were collected by the investigators and participants were outcome assessors for subjective outcomes (clinicaltrials.gov/ct2/show/NCT01854047).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were low and balanced across treatment arms.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (per trial registry) were well reported.
Other bias	Low risk	None identified

Abbreviations: AAER: annualised asthma exacerbation rate; ACQ(-5)(-6)(-7): Asthma Control Questionnaire; AE: adverse event; AER: annual exacerbation rate; am: ante meridiem; ATS: American Thoracic Society; AQLQ(S): asthma quality of life questionnaire (standardised); BD: bronchodilator; BDP: beclomethasone dipropionate; BL: baseline; BMI: body mass index; bpm: beats per minute; COI: conflict of interest; COPD: chronic obstructive pulmonary disease; CT: computed tomography; DPI: dry powder inhaler; DUP: dupilumab; ECG: electrocardiogram; ED: emergency department; EQ-5D-5L: European Quality of Life 5 Dimensions 5 levels; ERS: European Respiratory Society; ER: emergency room; FENO: exhaled nitric oxide; FEV1: forced expiratory volume in 1 second; FP: fluticasone propionate; FVC: forced vital capacity; GINA: Global Initiative for Asthma; HADS: hospital anxiety and depression score; Hg: mercury; HIV: human immunodeficiency virus; ICS: inhaled corticosteroids; Ig: immunoglobulin; IL: interleukin; IL-13: interleukin-13; IL-4R: interleukin-4 receptor; ITT: intention-to-treat; IV: intravenous; L: litre; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; LBK: lebrikizumab; LOCF: last-observation-carried-forward; LTRA: leukotriene receptor antagonist; MCP-4: monocyte chemoattractant protein-4; MRI: magnetic resonance imaging; NO: nitric oxide; OCS: oral corticosteroids; PBO: placebo; PC20: provocative concentration causing a 20% drop; PEF: peak expiratory flow; PEFR: peak expiratory flow rate; PIF: peak inspiratory flow; pm: post meridiem; PNV: predicted normal value; Q1/2/4W: every 1/2/4 week; QoL: quality of life; QW: every week; SABA: short-acting beta agonist; SAE: serious adverse event; SC: subcutaneous; SD: standard deviation; SE: standard error; SNOT-22: 22-item Sinonasal Outcome Test; Th1: T helper 1; TLK: tralokinumab; VAS: visual analogue scale; WPAI + CIQ: work productivity and activity impairment plus classroom impairment questions.

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

Study	Reason for exclusion
Bachert 2016	Wrong population (chronic sinusitis with nasal polyps; only 58% of patients had asthma)
Bachert 2019	Wrong population (patients with chronic rhinosinusitis with nasal polyps (with and without asthma).
Banfield 2008	Not randomised

Study	Reason for exclusion
Djukanovic 2004	Wrong intervention (omalizumab)
NCT00339872	No control arm
NCT00638989	No control arm
NCT00785668	No control arm
NCT01592396	No control arm
NCT01875003	Wrong population (majority of participant aged < 16 years)
NCT02085473	No control arm
NCT02099656	Reported histological data from the CLAVIER study, an RCT of lebrikizumab versus placebo, which was terminated early
NCT02134028	No control arm
NCT02546869	No control arm; non-randomised
NCT02902809	No control arm
Nsouli 2018	No control arm
Oh 2009	Wrong population (healthy volunteers); wrong study design (open-label)
Parsey 2004	Wrong study design (sequential)
Weinstein 2017	Wrong population (respiratory morbidity - allergic rhinitis)

Abbreviations: RCT: Randomised controlled trial

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

Euctr 2015-001572-22

Methods	An exploratory, randomised, double-blind, placebo-controlled study of the effects of dupilumab on airway inflammation
Participants	Adults with persistent asthma (target enrolment n = 42)
Interventions	Intervention: Dupilumab 300 mg SC Q2W Comparator: Placebo
Outcomes	Primary: Change from baseline in eosinophils cells count in the bronchial submucosa at week-12
Notes	Study completed in January 2018 but no data have been reported

NCT00024544

Methods	A phase I/II, randomised, double-blind, placebo-controlled, parallel-group pilot study of SB 240683 (pascolizumab)
Participants	Adult patients (aged 18-70 years) with symptomatic steroid-naive asthma (target enrolment n = 120)
Interventions	Intervention: SB 240683 (pascolizumab) Comparator: Placebo
Outcomes	Not reported
Notes	Study completed in February 2003 but no data have been reported

NCT01987492

Methods	A phase II, randomised, double-blind, placebo-controlled, multicentre trial to assess the oral corticosteroid-sparing effect of lebrikizumab
Participants	Patients (aged 12 to 75 years) with severe, corticosteroid-dependent asthma
Interventions	Intervention: Lebrikizumab SC Q4W (dose not stated) Comparator: Placebo
Outcomes	Primary: Relative change from baseline in daily OCS dose at week-44
Notes	Study completed in December 2016 but no data have been reported

NCT02948959

Methods	A randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of dupilumab
Participants	Children 6 to < 12 years of age with uncontrolled persistent asthma
Interventions	Intervention: Dupilumab Q2W (dose not specified) Comparator: Placebo
Outcomes	Primary: Annualised rate of severe exacerbations during the placebo-controlled treatment period
Notes	Study completed in August 2020 but no data have been reported

NCT03112577

Methods	A randomised, placebo-controlled, parallel-panel study to assess the effects of REGN3500, dupilumab, and combination of REGN3500 plus dupilumab on markers of inflammation after bronchial allergen challenge
Participants	Adult patients (aged 18-60 years) with mild allergic asthma

NCT03112577 *(Continued)*

Interventions	Interventions: REGN3500 (IV); dupilumab (SC); REGN3500 plus dupilumab (doses not specified) Comparator: Placebo
Outcomes	Difference in bronchial allergen challenge-induced changes in sputum inflammatory markers in individuals treated with REGN3500, dupilumab and the combination of REGN3500 plus dupilumab or placebo (screening to week-4)
Notes	Study completed in December 2019 but no data have been reported

NCT03387852

Methods	A randomised, double-blind, placebo-controlled, parallel-group, 12-week proof-of-concept study to assess the efficacy, safety, and tolerability of SAR440340 and the co-administration of SAR440340 and dupilumab
Participants	Adults (aged 18-70 years) with moderate-to-severe asthma who are not well controlled on ICS plus LABA therapy
Interventions	Interventions: SAR440340/REGN3500 monotherapy; dupilumab monotherapy; SAR440340/REGN3500 and dupilumab co-administration Comparator: Placebo
Outcomes	Primary outcome: Loss of asthma control events from baseline to week-12
Notes	Study completed in August 2019 but no data have been reported

Abbreviations: ICS: Inhaled corticosteroids; IV: intravenous; LABA: long-acting beta-agonist; OCS: oral corticosteroid; QW(2/4): every 2/4 weeks; SC: subcutaneous.

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

NCT03782532

Study name	Efficacy and safety study of dupilumab in patients with persistent asthma
Methods	A randomised, double-blind, placebo-controlled, parallel-group phase 3 study
Participants	Adults and adolescent patients (≥ 12 years of age); physician diagnosis of asthma for ≥ 12 months (GINA 2017); pre-bronchodilator FEV1 ≤ 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents at the screening visit and the randomisation visit, prior to randomisation; ACQ-5 score ≥ 1.5 at screening and randomisation visits; patients requiring maintenance OCS with a stable dose ≤ 10 mg/day prednisone or equivalent will be allowed; OCS should be used for at least 3 months with a stable dose ≥ 1 month prior to the screening visit.
Interventions	Intervention: Dupilumab (dose not stated) Comparator: Placebo
Outcomes	Primary: Change in FEV1 (baseline to week-36). Secondary: Annualised rate of severe exacerbation events during 24-week placebo-controlled period; change from baseline in pre-bronchodilator FEV1 to week-12; annualised rate of loss of asthma control and time to first event during 24-week placebo-controlled period; annualised rate of severe exacerbations and time to first event during 24-week placebo-controlled period; change from baseline in ACQ-5 and ACQ-7 scores to week-24; morning and evening asthma symptom score to week-24; nocturnal awakenings, puffs on

NCT03782532 *(Continued)*	rescue medication to week-24; change from baseline in AQLQ to week-24; change from baseline in EQ-5D-5L score to week-24; safety
Starting date	January 2019 (estimated completion September 2022)
Contact information	Study director, Clinical Sciences & Operations, Sanofi
Notes	None

Abbreviations: ACQ(-5)(-7): Asthma Control Questionnaire (-5)(-7); AQLQ: Asthma Quality of Life Questionnaire; EQ-5D-5L: EuroQoL-5 dimension-5 level; FEV1: forced expiratory volume in one second; GINA: Global Initiative for Asthma; OCS: Oral corticosteroid.

DATA AND ANALYSES

Comparison 1. Anti-interleukin-13 or -4 agents with placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Exacerbation requiring hospitalisation or ED visit	2	2039	Rate Ratio (IV, Fixed, 95% CI)	0.68 [0.47, 0.98]
1.1.1 Tralokinumab 300 mg SC Q2W	2	1435	Rate Ratio (IV, Fixed, 95% CI)	0.63 [0.41, 0.99]
1.1.2 Tralokinumab 300 mg SC Q4W	1	604	Rate Ratio (IV, Fixed, 95% CI)	0.78 [0.41, 1.49]
1.2 Health-related quality of life (adjusted mean diff versus placebo)	7	4960	Mean Difference (IV, Fixed, 95% CI)	0.18 [0.12, 0.24]
1.2.1 Lebrikizumab 125 mg SC Q4W	1	209	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.29, 0.17]
1.2.2 Dupilumab 200 mg SC Q2W	2	1111	Mean Difference (IV, Fixed, 95% CI)	0.29 [0.16, 0.42]
1.2.3 Dupilumab 200 mg SC Q4W	1	159	Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.13, 0.59]
1.2.4 Dupilumab 300 mg SC Q2W	2	1127	Mean Difference (IV, Fixed, 95% CI)	0.27 [0.14, 0.40]
1.2.5 Dupilumab 300 mg SC Q4W	1	164	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.06, 0.66]
1.2.6 Tralokinumab 300 mg SC Q2W	3	1262	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.00, 0.23]
1.2.7 Tralokinumab 300 mg SC Q4W	2	634	Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.02, 0.30]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.8 AMG317 75 mg SC Q1W	1	98	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.60, 0.36]
1.2.9 AMG317 150 mg SC Q1W	1	98	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.44, 0.58]
1.2.10 AMG317 300 mg SC Q1W	1	98	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.44, 0.64]
1.3 Serious adverse events	22	7739	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.09]
1.3.1 Soluble IL-4R 500 ug nebulised	1	12	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3.2 Soluble IL-4R 1500 ug nebulised	1	13	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3.3 Tralokinumab 1 mg/kg IV Q4W	2	12	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3.4 Tralokinumab 5 mg/kg IV Q4W	2	14	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.02, 23.07]
1.3.5 Tralokinumab 10 mg/kg IV Q4W	2	10	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.03, 53.51]
1.3.6 Tralokinumab 150 mg SC Q2W	1	62	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.05, 7.39]
1.3.7 Tralokinumab 300 mg SC Q2W	6	1955	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.05]
1.3.8 Tralokinumab 300 mg SC Q4W	2	831	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.58, 1.40]
1.3.9 Tralokinumab 600 mg SC Q2W	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.02, 5.42]
1.3.10 Lebrikizumab 37.5 mg SC Q4W	1	155	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 1.76]
1.3.11 Lebrikizumab 125 mg SC Q4W	3	428	Odds Ratio (M-H, Fixed, 95% CI)	1.47 [0.43, 5.05]
1.3.12 Lebrikizumab 250 mg SC Q4W	3	445	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.28, 1.86]
1.3.13 Lebrikizumab 500 mg SC Q4W	1	70	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.04, 27.64]
1.3.14 AMG317 75 mg SC Q1W	1	97	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.06, 7.91]
1.3.15 AMG317 150 mg SC Q1W	1	98	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3.16 AMG317 300 mg SC Q1W	1	96	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3.17 GSK679586 2.5 mg/kg IV Q4W	1	8	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.18 GSK679586 10 mg/kg IV Q4W	2	206	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [0.52, 5.24]
1.3.19 GSK679586 20 mg/kg IV Q4W	1	12	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.04, 38.30]
1.3.20 RPC4046 0.3 mg/kg IV Q1W	1	6	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3.21 RPC4046 3 mg/kg IV Q1W	1	6	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3.22 Dupilumab 300 mg SC Q1W	1	104	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.03, 3.18]
1.3.23 Dupilumab 200 mg SC Q2W	2	1131	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.60, 1.54]
1.3.24 Dupilumab 200 mg SC Q4W	1	189	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.15, 3.98]
1.3.25 Dupilumab 300 mg SC Q2W	3	1359	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.76, 1.77]
1.3.26 Dupilumab 300 mg SC Q4W	1	197	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.39, 5.06]
1.3.27 IMA-638 IV 0.2 mg/kg (D1/8/28/56/84)	1	21	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3.28 IMA-638 IV 0.6 mg/kg (D1/8/28/56/84)	1	22	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.04, 28.30]
1.3.29 IMA-638 IV 2 mg/kg (D1/8/28/56/84)	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.05, 9.70]
1.3.30 IMA-638 IV 200 mg SC (D1/8/28/42/56/70/84)	1	67	Odds Ratio (M-H, Fixed, 95% CI)	2.59 [0.12, 56.20]
1.3.31 IMA-638 IV 75 mg SC (D1/8/28/42/56/70/84)	1	27	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.4 Exacerbation requiring OCS (rate ratio)	1	452	Rate Ratio (IV, Fixed, 95% CI)	0.98 [0.72, 1.32]
1.4.1 Tralokinumab 300 mg SC Q2W	1	225	Rate Ratio (IV, Fixed, 95% CI)	0.94 [0.62, 1.42]
1.4.2 Tralokinumab 300 mg SC Q4W	1	227	Rate Ratio (IV, Fixed, 95% CI)	1.02 [0.65, 1.59]
1.5 Exacerbation requiring OCS (dichotomous)	2	453	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.49, 1.78]
1.5.1 AMG317 75 mg SC	1	98	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.33, 3.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5.2 AMG317 150 mg SC	1	98	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.12, 1.83]
1.5.3 AMG317 300 mg SC	1	98	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.14, 2.69]
1.5.4 IMA638 75 mg SC	1	68	Odds Ratio (M-H, Fixed, 95% CI)	6.38 [0.34, 120.65]
1.5.5 IMA638 200 mg SC	1	26	Odds Ratio (M-H, Fixed, 95% CI)	19.29 [0.65, 573.83]
1.5.6 IMA638 0.2 mg/kg IV	1	21	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5.7 IMA638 0.6 mg/kg IV	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 2.48]
1.5.8 IMA638 2 mg/kg IV	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 6.37]
1.6 Change from baseline in pre-bronchodilator FEV1	13	4829	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.08, 0.12]
1.6.1 Tralokinumab 150 mg SC Q2W	1	58	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.17, 0.35]
1.6.2 Tralokinumab 300 mg SC Q2W	3	331	Mean Difference (IV, Fixed, 95% CI)	0.13 [0.03, 0.22]
1.6.3 Tralokinumab 300 mg SC Q4W	1	185	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.06, 0.14]
1.6.4 Tralokinumab 600 mg SC Q2W	1	58	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.07, 0.47]
1.6.5 AMG317 75 mg SC Q1W	1	98	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.18, 0.10]
1.6.6 AMG317 150 mg SC Q1W	1	98	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.15, 0.21]
1.6.7 AMG317 300 mg SC Q1W	1	98	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.03, 0.25]
1.6.8 Lebrikizumab 125 mg SC Q4W	2	279	Mean Difference (IV, Fixed, 95% CI)	0.08 [0.01, 0.16]
1.6.9 Lebrikizumab 250 mg SC Q4W	2	288	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.03, 0.19]
1.6.10 Lebrikizumab 500 mg SC Q4W	1	70	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.11, 0.22]
1.6.11 GSK679586 10 mg/kg IV Q4W	1	198	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.19, -0.01]
1.6.12 Dupilumab 300 mg SC Q1W	1	104	Mean Difference (IV, Fixed, 95% CI)	0.27 [0.11, 0.43]
1.6.13 Dupilumab 200 mg SC Q2W	2	1114	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.09, 0.20]
1.6.14 Dupilumab 300 mg SC Q2W	3	1329	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.10, 0.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6.15 Dupilumab 200 mg SC Q4W	1	157	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.04, 0.24]
1.6.16 Dupilumab 300 mg SC Q4W	1	164	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.01, 0.27]
1.6.17 IMA-638 0.2 mg/kg IV	1	21	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.20, 0.40]
1.6.18 IMA-638 0.6 mg/kg IV	1	22	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.28, 0.28]
1.6.19 IMA-638 2 mg/kg IV	1	22	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.31, 0.31]
1.6.20 IMA-638 75 mg SC	1	49	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.11, 0.31]
1.6.21 IMA-638 200 mg SC	1	86	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.13, 0.13]
1.7 Change from baseline in ACQ score	14	6251	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.24, -0.14]
1.7.1 Tralokinumab 150 mg SC Q2W	1	61	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.72, 0.48]
1.7.2 Tralokinumab 300 mg SC Q2W	5	1484	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.21, -0.03]
1.7.3 Tralokinumab 300 mg SC Q4W	2	685	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.27, 0.02]
1.7.4 Tralokinumab 600 mg SC Q2W	1	63	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.82, 0.32]
1.7.5 AMG317 75 mg SC Q1W	1	98	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.33, 0.45]
1.7.6 AMG317 150 mg SC Q1W	1	97	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.51, 0.33]
1.7.7 AMG317 300 mg SC Q1W	1	98	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.57, 0.15]
1.7.8 Lebrikizumab 125 mg SC Q4W	1	70	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.68, 0.28]
1.7.9 Lebrikizumab 250 mg SC Q4W	2	288	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.30, 0.17]
1.7.10 Lebrikizumab 500 mg SC Q4W	1	70	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.86, 0.06]
1.7.11 GSK679586 10 mg/kg IV Q4W	1	198	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.31, 0.15]
1.7.12 Dupilumab 300 mg SC Q1W	1	104	Mean Difference (IV, Fixed, 95% CI)	-0.73 [-1.15, -0.31]
1.7.13 Dupilumab 200 mg SC Q2W	2	1114	Mean Difference (IV, Fixed, 95% CI)	-0.38 [-0.51, -0.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.14 Dupilumab 300 mg SC Q2W	3	1341	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.39, -0.15]
1.7.15 Dupilumab 200 mg SC Q4W	1	158	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.53, 0.17]
1.7.16 Dupilumab 300 mg SC Q4W	1	163	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.54, 0.14]
1.7.17 IMA-638 0.2 mg/kg IV	1	21	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-1.12, 0.92]
1.7.18 IMA-638 0.6 mg/kg IV	1	22	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.75, 0.95]
1.7.19 IMA-638 2 mg/kg IV	1	22	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.25, 0.45]
1.7.20 IMA-638 75 mg SC	1	8	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.65, 1.85]
1.7.21 IMA-638 200 mg SC	1	86	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.23, 0.63]
1.8 Adverse events	18	7419	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [1.04, 1.30]
1.8.1 Tralokinumab 150 mg SC Q2W	1	62	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.44, 5.01]
1.8.2 Tralokinumab 300 mg SC Q2W	5	1816	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [1.11, 1.69]
1.8.3 Tralokinumab 600 mg SC Q2W	1	64	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [0.57, 5.78]
1.8.4 Tralokinumab 300 mg SC Q4W	2	831	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.95, 1.81]
1.8.5 Tralokinumab 1 mg/kg IV	1	9	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.8.6 Tralokinumab 5 mg/kg IV	1	9	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.8.7 Tralokinumab 10 mg/kg IV	1	4	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.8.8 AMG317 75 mg SC Q1W	1	97	Odds Ratio (M-H, Fixed, 95% CI)	2.16 [0.73, 6.37]
1.8.9 AMG317 150 mg SC Q1W	1	98	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.53, 4.26]
1.8.10 AMG317 300 mg SC Q1W	1	96	Odds Ratio (M-H, Fixed, 95% CI)	2.07 [0.66, 6.46]
1.8.11 Lebrikizumab 37.5 mg SC Q4W	1	155	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.52, 2.67]
1.8.12 Lebrikizumab 125 mg SC Q4W	3	428	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.70, 1.64]
1.8.13 Lebrikizumab 250 mg SC Q4W	3	445	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.58, 1.44]

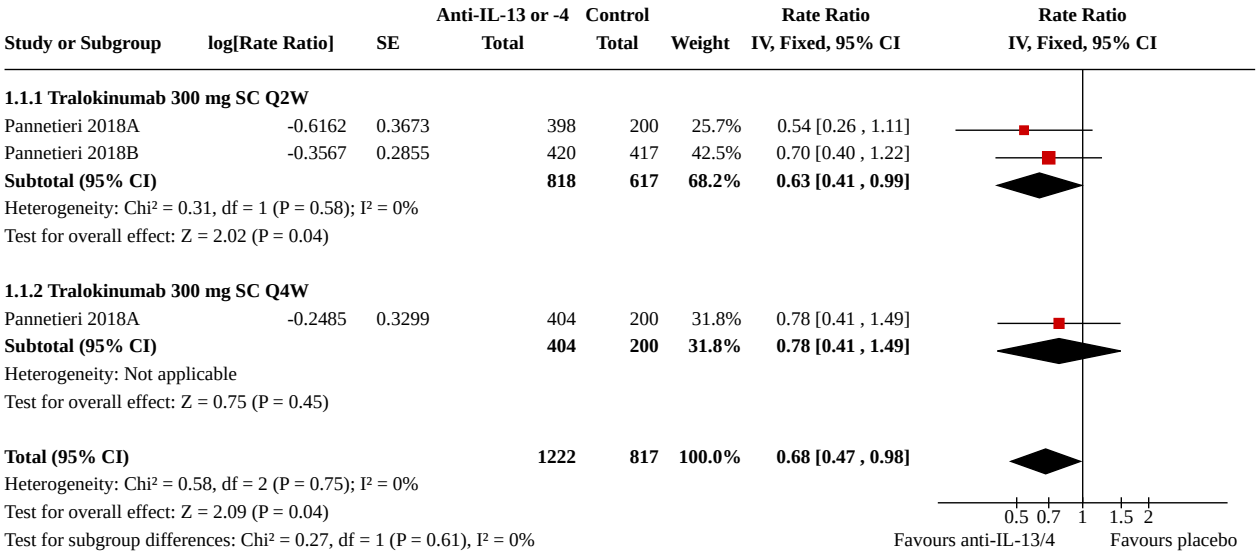
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8.14 Lebrikizumab 500 mg SC Q4W	1	70	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.47, 4.80]
1.8.15 GSK679586 10 mg/kg IV Q4W	1	198	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.65, 1.97]
1.8.16 Dupilumab 300 mg SC Q1W	1	104	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.49, 3.24]
1.8.17 Dupilumab 200 mg SC Q2W	2	1131	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.70, 1.33]
1.8.18 Dupilumab 300 mg SC Q2W	3	1358	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.67, 1.18]
1.8.19 Dupilumab 200 mg SC Q4W	1	190	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.45, 2.28]
1.8.20 Dupilumab 300 mg SC Q4W	1	197	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [0.70, 3.67]
1.8.21 VR492 0.5 mg	1	11	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.06, 7.35]
1.8.22 VR492 10 mg	1	11	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.93]
1.8.23 VR492 20 mg	1	23	Odds Ratio (M-H, Fixed, 95% CI)	1.83 [0.28, 12.07]
1.8.24 RPC4046 0.3 mg/kg IV Q1W	1	6	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.8.25 RPC4046 3 mg/kg IV Q1W	1	6	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.03, 29.81]
1.9 Change from baseline in FENO, ppb	11	3577	Mean Difference (IV, Fixed, 95% CI)	-14.68 [-16.56, -12.80]
1.9.1 Lebrikizumab 125 mg SC Q4W	2	279	Mean Difference (IV, Fixed, 95% CI)	-21.25 [-29.12, -13.37]
1.9.2 Lebrikizumab 250 mg SC Q4W	2	288	Mean Difference (IV, Fixed, 95% CI)	-11.70 [-17.34, -6.05]
1.9.3 Lebrikizumab 500 mg SC Q4W	1	70	Mean Difference (IV, Fixed, 95% CI)	-14.10 [-32.86, 4.66]
1.9.4 Tralokinumab 300 mg Q2W	1	76	Mean Difference (IV, Fixed, 95% CI)	-11.67 [-20.32, -3.02]
1.9.5 Dupilumab 200 mg SC Q2W	2	1088	Mean Difference (IV, Fixed, 95% CI)	-14.21 [-17.27, -11.16]
1.9.6 Dupilumab 300 mg SC Q2W	3	1317	Mean Difference (IV, Fixed, 95% CI)	-12.52 [-16.61, -8.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9.7 Dupilumab 200 mg SC Q4W	1	132	Mean Difference (IV, Fixed, 95% CI)	-16.39 [-40.06, 7.28]
1.9.8 Dupilumab 300 mg SC Q4W	1	145	Mean Difference (IV, Fixed, 95% CI)	-27.53 [-51.21, -3.85]
1.9.9 Soluble IL-4R 500 ug nebulised	1	12	Mean Difference (IV, Fixed, 95% CI)	-15.50 [-57.42, 26.42]
1.9.10 Soluble IL-4R 1500 ug nebulised	1	13	Mean Difference (IV, Fixed, 95% CI)	-26.40 [-67.03, 14.23]
1.9.11 GSK679586 2.5 mg/kg IV Q4W	2	8	Mean Difference (IV, Fixed, 95% CI)	-28.00 [-52.29, -3.71]
1.9.12 GSK679586 10 mg/kg IV Q4W	2	8	Mean Difference (IV, Fixed, 95% CI)	-40.00 [-55.96, -24.04]
1.9.13 GSK679586 20 mg/kg IV Q4W	2	96	Mean Difference (IV, Fixed, 95% CI)	-24.14 [-32.12, -16.15]
1.9.14 VR492 0.5 mg	1	11	Mean Difference (IV, Fixed, 95% CI)	-3.80 [-15.80, 8.20]
1.9.15 VR492 10 mg	1	11	Mean Difference (IV, Fixed, 95% CI)	-17.50 [-29.50, -5.50]
1.9.16 VR492 20 mg	1	23	Mean Difference (IV, Fixed, 95% CI)	-11.60 [-20.50, -2.70]
1.10 Change from baseline in blood eosinophils, cells x 10*9/L	6	2598	Mean Difference (IV, Fixed, 95% CI)	0.06 [0.04, 0.09]
1.10.1 Tralokinumab 300 mg Q2W	1	76	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.02, 0.18]
1.10.2 Lebrikizumab 250 mg SC Q4W	1	218	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.06, 0.16]
1.10.3 Dupilumab 300 mg SC Q1W	1	87	Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.02, 0.36]
1.10.4 Dupilumab 200 mg SC Q2W	1	944	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.03, 0.06]
1.10.5 Dupilumab 300 mg SC Q2W	1	953	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.01, 0.09]
1.10.6 IMA-638 0.2 mg/kg IV	1	21	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.10, 0.30]
1.10.7 IMA-638 0.6 mg/kg IV	1	22	Mean Difference (IV, Fixed, 95% CI)	0.20 [0.00, 0.40]
1.10.8 IMA-638 2 mg/kg IV	1	22	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.09, 0.29]
1.10.9 IMA-638 75 mg SC	1	8	Mean Difference (IV, Fixed, 95% CI)	0.20 [-1.13, 1.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10.10 IMA-638 200 mg SC	1	49	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.10, 0.30]
1.10.11 GSK679586 10 mg/kg IV	1	198	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.00, 0.16]
1.11 Change from baseline in periostin, ng/mL	2	2106	Mean Difference (IV, Fixed, 95% CI)	-9.04 [-10.92, -7.17]
1.11.1 Lebrikizumab 125 mg SC Q4W	1	209	Mean Difference (IV, Fixed, 95% CI)	-4.20 [-6.84, -1.56]
1.11.2 Dupilumab 200 mg SC Q2W	1	944	Mean Difference (IV, Fixed, 95% CI)	-14.06 [-17.70, -10.42]
1.11.3 Dupilumab 300 mg SC Q2W	1	953	Mean Difference (IV, Fixed, 95% CI)	-13.85 [-17.73, -9.97]
1.12 Percentage reduction from baseline in OCS use	2	350	Mean Difference (IV, Fixed, 95% CI)	-15.58 [-23.30, -7.85]
1.12.1 Tralokinumab 300 mg SC Q2W	1	140	Mean Difference (IV, Fixed, 95% CI)	-7.77 [-17.60, 2.06]
1.12.2 Dupilumab 300 mg SC Q2W	1	210	Mean Difference (IV, Fixed, 95% CI)	-28.20 [-40.70, -15.70]
1.13 Exacerbation requiring hospitalisation/ED/OCS (rate ratio)	7	6998	Rate Ratio (IV, Fixed, 95% CI)	0.71 [0.65, 0.77]
1.13.1 Tralokinumab 300 mg SC Q2W	3	1575	Rate Ratio (IV, Fixed, 95% CI)	0.94 [0.80, 1.11]
1.13.2 Tralokinumab 300 mg SC Q4W	1	604	Rate Ratio (IV, Fixed, 95% CI)	0.90 [0.66, 1.22]
1.13.3 Lebrikizumab 37.5 mg SC Q4W	2	1074	Rate Ratio (IV, Fixed, 95% CI)	0.68 [0.53, 0.87]
1.13.4 Lebrikizumab 125 mg SC Q4W	2	1074	Rate Ratio (IV, Fixed, 95% CI)	0.74 [0.59, 0.93]
1.13.5 Dupilumab 200mg SC Q2W	2	1135	Rate Ratio (IV, Fixed, 95% CI)	0.51 [0.40, 0.64]
1.13.6 Dupilumab 200 mg SC Q4W	1	195	Rate Ratio (IV, Fixed, 95% CI)	0.46 [0.18, 1.16]
1.13.7 Dupilumab 300mg SC Q2W	2	1144	Rate Ratio (IV, Fixed, 95% CI)	0.52 [0.42, 0.65]
1.13.8 Dupilumab 300 mg SC Q4W	1	197	Rate Ratio (IV, Fixed, 95% CI)	0.67 [0.29, 1.55]

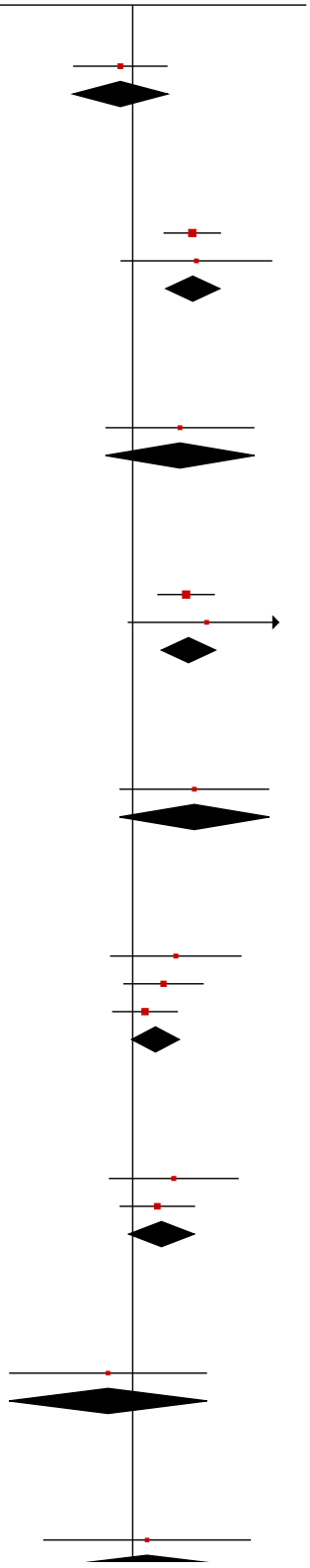
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.14 Exacerbation requiring hospitalisation/ED/OCS (relative risk)	1	210	Risk Ratio (IV, Fixed, 95% CI)	0.41 [0.26, 0.63]
1.14.1 Dupilumab 300mg SC Q2W	1	210	Risk Ratio (IV, Fixed, 95% CI)	0.41 [0.26, 0.63]

Analysis 1.1. Comparison 1: Anti-interleukin-13 or -4 agents with placebo, Outcome 1: Exacerbation requiring hospitalisation or ED visit



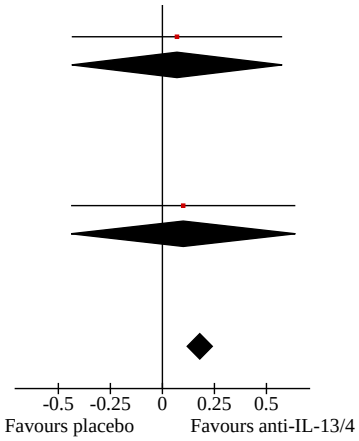
Analysis 1.2. Comparison 1: Anti-interleukin-13 or -4 agents with placebo, Outcome 2: Health-related quality of life (adjusted mean diff versus placebo)

Study or Subgroup	MD	SE	Anti-IL-13 or -4 Total	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Lebrikizumab 125 mg SC Q4W						
Korenblat 2018	-0.06	0.1173	104	105	6.8%	-0.06 [-0.29 , 0.17]
Subtotal (95% CI)			**104**	**105**	**6.8%**	**-0.06 [-0.29 , 0.17]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
1.2.2 Dupilumab 200 mg SC Q2W						
Castro 2018	0.29	0.0714	631	317	18.5%	0.29 [0.15 , 0.43]
Wenzel 2016	0.31	0.1884	132	31	2.7%	0.31 [-0.06 , 0.68]
Subtotal (95% CI)			**763**	**348**	**21.1%**	**0.29 [0.16 , 0.42]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 4.38 (P < 0.0001)						
1.2.3 Dupilumab 200 mg SC Q4W						
Wenzel 2016	0.23	0.185	127	32	2.7%	0.23 [-0.13 , 0.59]
Subtotal (95% CI)			**127**	**32**	**2.7%**	**0.23 [-0.13 , 0.59]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.21)						
1.2.4 Dupilumab 300 mg SC Q2W						
Castro 2018	0.26	0.0714	633	321	18.5%	0.26 [0.12 , 0.40]
Wenzel 2016	0.36	0.196	141	32	2.4%	0.36 [-0.02 , 0.74]
Subtotal (95% CI)			**774**	**353**	**20.9%**	**0.27 [0.14 , 0.40]**
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 4.05 (P < 0.0001)						
1.2.5 Dupilumab 300 mg SC Q4W						
Wenzel 2016	0.3	0.186	132	32	2.7%	0.30 [-0.06 , 0.66]
Subtotal (95% CI)			**132**	**32**	**2.7%**	**0.30 [-0.06 , 0.66]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.61 (P = 0.11)						
1.2.6 Tralokinumab 300 mg SC Q2W						
Brightling 2015	0.21	0.1633	109	53	3.5%	0.21 [-0.11 , 0.53]
Pannetieri 2018A	0.15	0.0998	304	157	9.4%	0.15 [-0.05 , 0.35]
Pannetieri 2018B	0.06	0.0816	321	318	14.1%	0.06 [-0.10 , 0.22]
Subtotal (95% CI)			**734**	**528**	**27.1%**	**0.11 [-0.00 , 0.23]**
Heterogeneity: Chi² = 0.91, df = 2 (P = 0.63); I² = 0%						
Test for overall effect: Z = 1.88 (P = 0.06)						
1.2.7 Tralokinumab 300 mg SC Q4W						
Brightling 2015	0.2	0.1612	101	54	3.6%	0.20 [-0.12 , 0.52]
Pannetieri 2018A	0.12	0.0937	321	158	10.7%	0.12 [-0.06 , 0.30]
Subtotal (95% CI)			**422**	**212**	**14.3%**	**0.14 [-0.02 , 0.30]**
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.73 (P = 0.08)						
1.2.8 AMG317 75 mg SC Q1W						
Corren 2010	-0.12	0.2457	73	25	1.6%	-0.12 [-0.60 , 0.36]
Subtotal (95% CI)			**73**	**25**	**1.6%**	**-0.12 [-0.60 , 0.36]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.63)						
1.2.9 AMG317 150 mg SC Q1W						
Corren 2010	0.07	0.2579	73	25	1.4%	0.07 [-0.44 , 0.58]
Subtotal (95% CI)			**73**	**25**	**1.4%**	**0.07 [-0.44 , 0.58]**



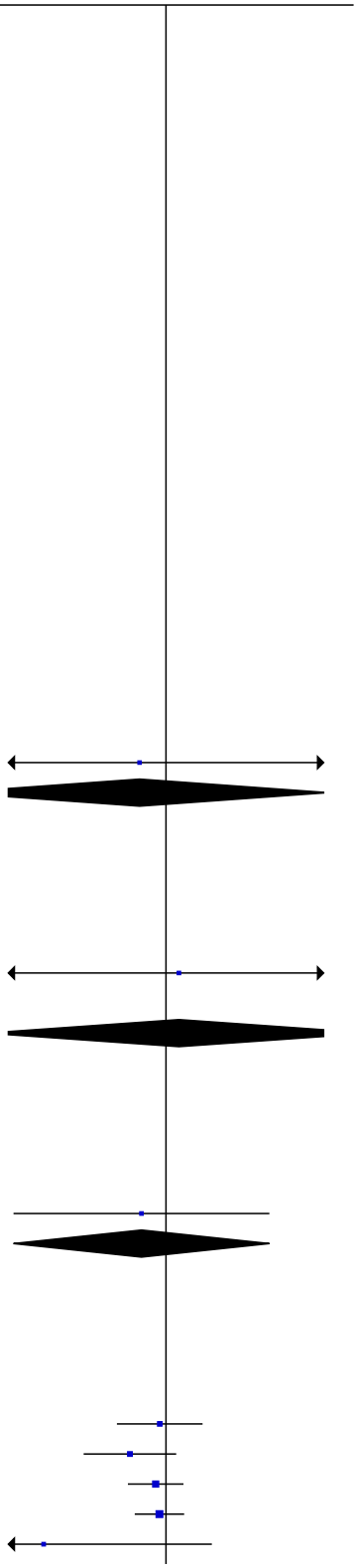
Analysis 1.2. (Continued)

1.2.9 AMG317 150 mg SC Q1W						
Corren 2010	0.07	0.2579	73	25	1.4%	0.07 [-0.44 , 0.58]
Subtotal (95% CI)			**73**	**25**	**1.4%**	**0.07 [-0.44 , 0.58]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
1.2.10 AMG317 300 mg SC Q1W						
Corren 2010	0.1	0.2749	74	24	1.2%	0.10 [-0.44 , 0.64]
Subtotal (95% CI)			**74**	**24**	**1.2%**	**0.10 [-0.44 , 0.64]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.36 (P = 0.72)						
Total (95% CI)			**3276**	**1684**	**100.0%**	**0.18 [0.12 , 0.24]**
Heterogeneity: Chi² = 14.09, df = 14 (P = 0.44); I² = 1%						
Test for overall effect: Z = 5.85 (P < 0.00001)						
Test for subgroup differences: Chi² = 12.76, df = 9 (P = 0.17), I² = 29.5%						

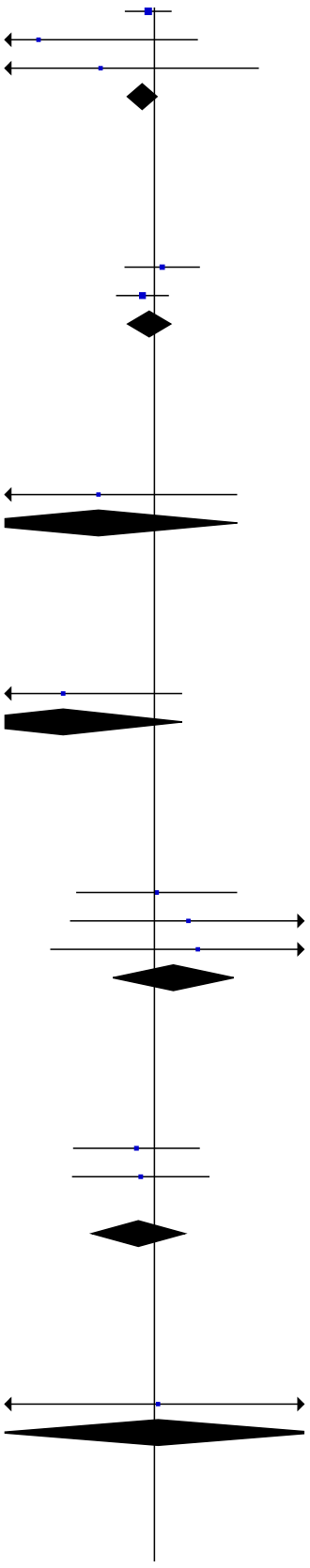


Analysis 1.3. Comparison 1: Anti-interleukin-13 or -4 agents with placebo, Outcome 3: Serious adverse events

Study or Subgroup	Anti-IL-13 or -4 Events	Anti-IL-13 or -4 Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Soluble IL-4R 500 ug nebulised						
Borish 1999	0	8	0	4		Not estimable
Subtotal (95% CI)		**8**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.3.2 Soluble IL-4R 1500 ug nebulised						
Borish 1999	0	9	0	4		Not estimable
Subtotal (95% CI)		**9**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.3.3 Tralokinumab 1 mg/kg IV Q4W						
NCT00640016	0	2	0	1		Not estimable
Singh 2010	0	8	0	1		Not estimable
Subtotal (95% CI)		**10**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.3.4 Tralokinumab 5 mg/kg IV Q4W						
NCT00640016	0	4	0	1		Not estimable
Singh 2010	1	8	0	1	0.3%	0.60 [0.02 , 23.07]
Subtotal (95% CI)		**12**		**2**	**0.3%**	**0.60 [0.02 , 23.07]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.78)						
1.3.5 Tralokinumab 10 mg/kg IV Q4W						
NCT00640016	1	4	0	1	0.2%	1.29 [0.03 , 53.51]
Singh 2010	0	3	0	2		Not estimable
Subtotal (95% CI)		**7**		**3**	**0.2%**	**1.29 [0.03 , 53.51]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.89)						
1.3.6 Tralokinumab 150 mg SC Q2W						
Piper 2013	2	47	1	15	0.6%	0.62 [0.05 , 7.39]
Subtotal (95% CI)		**47**		**15**	**0.6%**	**0.62 [0.05 , 7.39]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.71)						
1.3.7 Tralokinumab 300 mg SC Q2W						
Brightling 2015	18	150	10	75	4.6%	0.89 [0.39 , 2.03]
Busse 2015	9	70	16	70	5.5%	0.50 [0.20 , 1.22]
Pannetieri 2018A	40	398	24	200	11.4%	0.82 [0.48 , 1.40]
Pannetieri 2018B	35	425	39	422	14.2%	0.88 [0.55 , 1.42]
Piper 2013	0	51	1	15	0.9%	0.09 [0.00 , 2.43]



Analysis 1.3. (Continued)

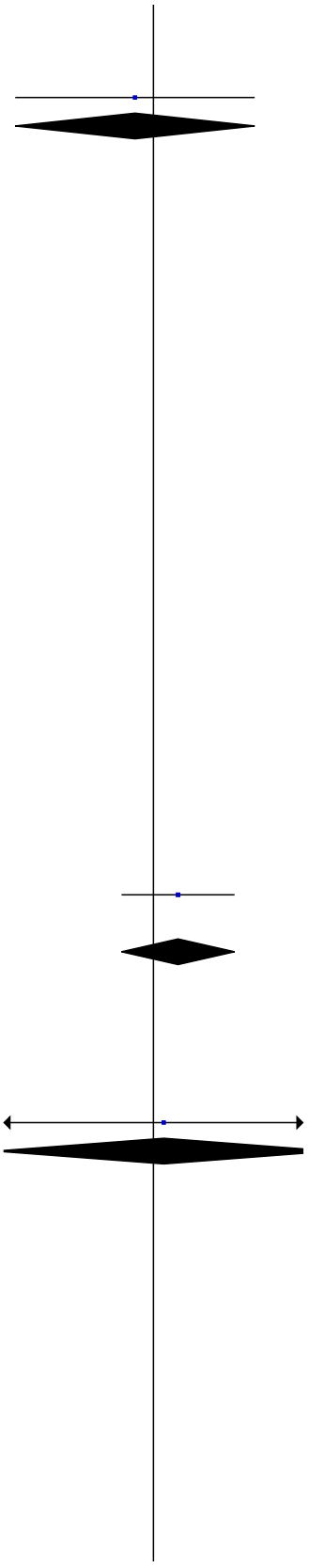


Pannetieri 2018B	55	423	59	422	14.2%	0.80 [0.55 , 1.42]
Piper 2013	0	51	1	15	0.9%	0.09 [0.00 , 2.43]
Russell 2018	0	39	1	40	0.6%	0.33 [0.01 , 8.43]
Subtotal (95% CI)		**1133**		**822**	**37.2%**	**0.78 [0.58 , 1.05]**
Total events:	102		91			
Heterogeneity: Chi² = 3.24, df = 5 (P = 0.66); I² = 0%						
Test for overall effect: Z = 1.62 (P = 0.11)						
1.3.8 Tralokinumab 300 mg SC Q4W						
Brightling 2015	25	151	11	76	4.8%	1.17 [0.54 , 2.53]
Pannetieri 2018A	39	404	24	200	11.5%	0.78 [0.46 , 1.34]
Subtotal (95% CI)		**555**		**276**	**16.3%**	**0.90 [0.58 , 1.40]**
Total events:	64		35			
Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.63)						
1.3.9 Tralokinumab 600 mg SC Q2W						
Piper 2013	1	48	1	16	0.6%	0.32 [0.02 , 5.42]
Subtotal (95% CI)		**48**		**16**	**0.6%**	**0.32 [0.02 , 5.42]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
1.3.10 Lebrikizumab 37.5 mg SC Q4W						
Hanania 2015a	1	117	2	38	1.2%	0.16 [0.01 , 1.76]
Subtotal (95% CI)		**117**		**38**	**1.2%**	**0.16 [0.01 , 1.76]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
1.3.11 Lebrikizumab 125 mg SC Q4W						
Hanania 2015a	6	112	2	39	1.1%	1.05 [0.20 , 5.42]
Korenblat 2018	2	104	1	103	0.4%	2.00 [0.18 , 22.40]
Noonan 2013	3	53	0	17	0.3%	2.43 [0.12 , 49.34]
Subtotal (95% CI)		**269**		**159**	**1.8%**	**1.47 [0.43 , 5.05]**
Total events:	11		3			
Heterogeneity: Chi² = 0.33, df = 2 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
1.3.12 Lebrikizumab 250 mg SC Q4W						
Corren 2011	4	106	6	112	2.2%	0.69 [0.19 , 2.53]
Hanania 2015a	7	118	3	39	1.7%	0.76 [0.19 , 3.08]
Noonan 2013	0	53	0	17		Not estimable
Subtotal (95% CI)		**277**		**168**	**3.9%**	**0.72 [0.28 , 1.86]**
Total events:	11		9			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.3.13 Lebrikizumab 500 mg SC Q4W						
Noonan 2013	1	52	0	18	0.3%	1.08 [0.04 , 27.64]
Subtotal (95% CI)		**52**		**18**	**0.3%**	**1.08 [0.04 , 27.64]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						

Analysis 1.3. (Continued)

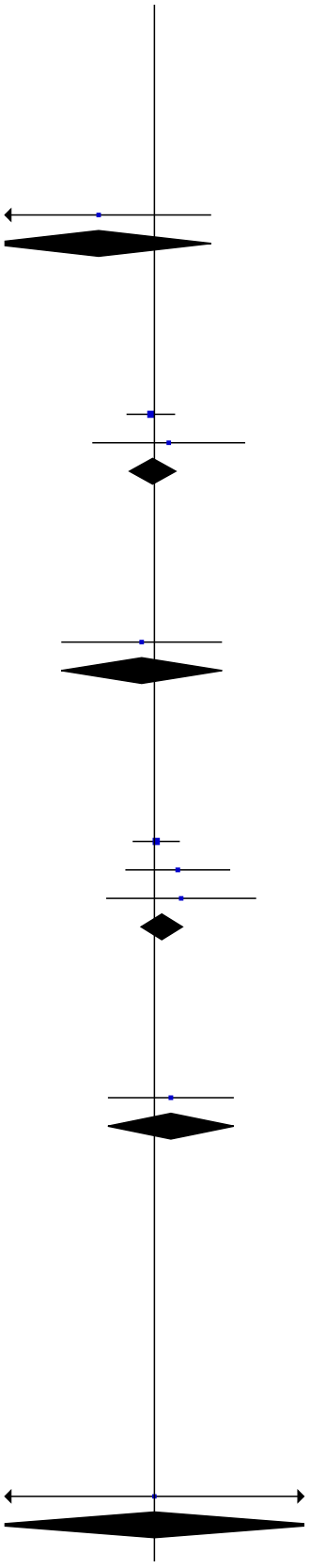
Test for overall effect: Z = 0.05 (P = 0.96)

1.3.14 AMG317 75 mg SC Q1W							
Corren 2010	2	72	1	25	0.6%	0.69 [0.06 , 7.91]	
Subtotal (95% CI)		**72**		**25**	**0.6%**	**0.69 [0.06 , 7.91]**	
Total events:	2		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.30 (P = 0.76)							
1.3.15 AMG317 150 mg SC Q1W							
Corren 2010	0	73	0	25		Not estimable	
Subtotal (95% CI)		**73**		**25**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.3.16 AMG317 300 mg SC Q1W							
Corren 2010	0	72	0	24		Not estimable	
Subtotal (95% CI)		**72**		**24**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.3.17 GSK679586 2.5 mg/kg IV Q4W							
Hodsman 2013	0	6	0	2		Not estimable	
Subtotal (95% CI)		**6**		**2**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.3.18 GSK679586 10 mg/kg IV Q4W							
De Boever 2014	8	99	5	99	1.8%	1.65 [0.52 , 5.24]	
Hodsman 2013	0	6	0	2		Not estimable	
Subtotal (95% CI)		**105**		**101**	**1.8%**	**1.65 [0.52 , 5.24]**	
Total events:	8		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.85 (P = 0.39)							
1.3.19 GSK679586 20 mg/kg IV Q4W							
Hodsman 2013	1	9	0	3	0.2%	1.24 [0.04 , 38.30]	
Subtotal (95% CI)		**9**		**3**	**0.2%**	**1.24 [0.04 , 38.30]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.12 (P = 0.90)							
1.3.20 RPC4046 0.3 mg/kg IV Q1W							
Tripp 2017	0	4	0	2		Not estimable	
Subtotal (95% CI)		**4**		**2**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.3.21 RPC4046 3 mg/kg IV Q1W							
Tripp 2017	0	4	0	2		Not estimable	
Subtotal (95% CI)		**4**		**2**		**Not estimable**	



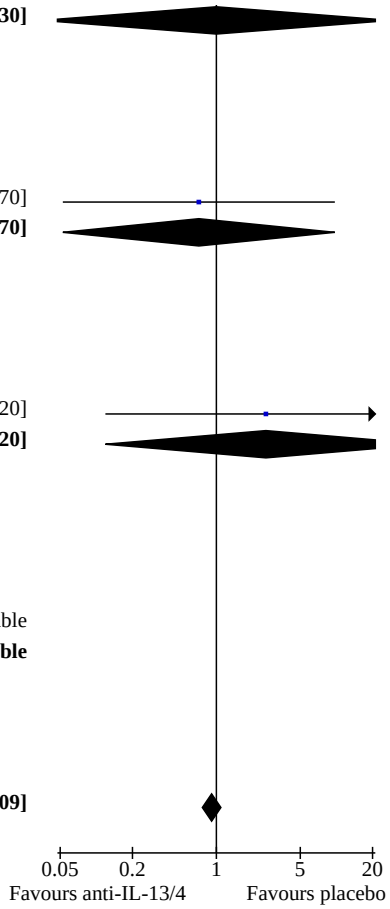
Analysis 1.3. (Continued)

Tripp 2017	0	4	0	2		Not estimable
Subtotal (95% CI)		**4**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.3.22 Dupilumab 300 mg SC Q1W						
Wenzel 2013	1	52	3	52	1.2%	0.32 [0.03 , 3.18]
Subtotal (95% CI)		**52**		**52**	**1.2%**	**0.32 [0.03 , 3.18]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
1.3.23 Dupilumab 200 mg SC Q2W						
Castro 2018	49	631	26	313	12.7%	0.93 [0.57 , 1.53]
Wenzel 2016	10	148	2	39	1.2%	1.34 [0.28 , 6.39]
Subtotal (95% CI)		**779**		**352**	**13.8%**	**0.96 [0.60 , 1.54]**
Total events:	59		28			
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.15 (P = 0.88)						
1.3.24 Dupilumab 200 mg SC Q4W						
Wenzel 2016	6	150	2	39	1.2%	0.77 [0.15 , 3.98]
Subtotal (95% CI)		**150**		**39**	**1.2%**	**0.77 [0.15 , 3.98]**
Total events:	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
1.3.25 Dupilumab 300 mg SC Q2W						
Castro 2018	55	632	27	321	12.9%	1.04 [0.64 , 1.68]
Rabe 2018	9	103	6	107	2.1%	1.61 [0.55 , 4.70]
Wenzel 2016	13	156	2	40	1.2%	1.73 [0.37 , 7.99]
Subtotal (95% CI)		**891**		**468**	**16.2%**	**1.16 [0.76 , 1.77]**
Total events:	77		35			
Heterogeneity: Chi² = 0.83, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.48)						
1.3.26 Dupilumab 300 mg SC Q4W						
Wenzel 2016	16	157	3	40	1.7%	1.40 [0.39 , 5.06]
Subtotal (95% CI)		**157**		**40**	**1.7%**	**1.40 [0.39 , 5.06]**
Total events:	16		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
1.3.27 IMA-638 IV 0.2 mg/kg (D1/8/28/56/84)						
NCT00425061	0	16	0	5		Not estimable
Subtotal (95% CI)		**16**		**5**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.3.28 IMA-638 IV 0.6 mg/kg (D1/8/28/56/84)						
NCT00425061	1	17	0	5	0.3%	1.00 [0.04 , 28.30]
Subtotal (95% CI)		**17**		**5**	**0.3%**	**1.00 [0.04 , 28.30]**
Total events:	1		0			



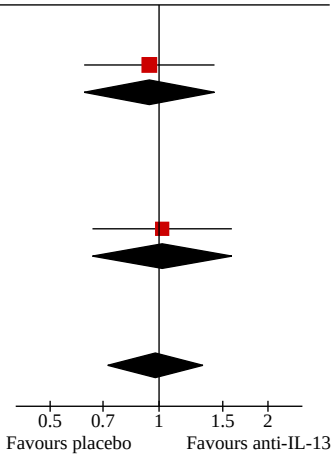
Analysis 1.3. (Continued)

Subtotal (95% CI)		**17**		**5**	**0.3%**	**1.00 [0.04 , 28.30]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
1.3.29 IMA-638 IV 2 mg/kg (D1/8/28/56/84)							
NCT00425061	2	16	1	6	0.5%	0.71 [0.05 , 9.70]	
Subtotal (95% CI)		**16**		**6**	**0.5%**	**0.71 [0.05 , 9.70]**	
Total events:	2		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.25 (P = 0.80)							
1.3.30 IMA-638 IV 200 mg SC (D1/8/28/42/56/70/84)							
NCT00425061	2	45	0	22	0.2%	2.59 [0.12 , 56.20]	
Subtotal (95% CI)		**45**		**22**	**0.2%**	**2.59 [0.12 , 56.20]**	
Total events:	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.60 (P = 0.55)							
1.3.31 IMA-638 IV 75 mg SC (D1/8/28/42/56/70/84)							
NCT00425061	0	4	0	23		Not estimable	
Subtotal (95% CI)		**4**		**23**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**5016**		**2723**	**100.0%**	**0.91 [0.76 , 1.09]**	
Total events:	370		220				
Heterogeneity: Chi² = 13.85, df = 32 (P = 1.00); I² = 0%							
Test for overall effect: Z = 1.01 (P = 0.31)							
Test for subgroup differences: Chi² = 8.79, df = 20 (P = 0.99), I² = 0%							



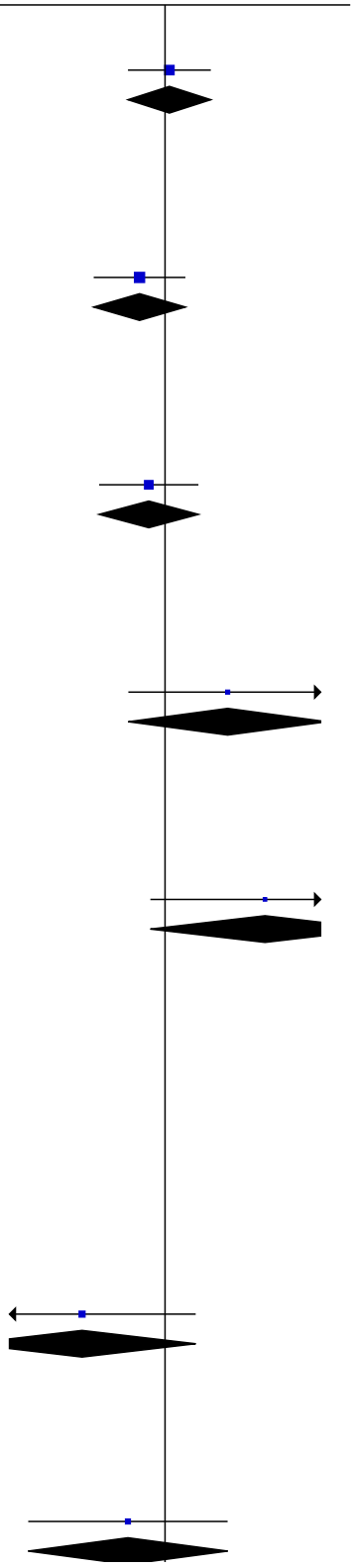
Analysis 1.4. Comparison 1: Anti-interleukin-13 or -4 agents with placebo, Outcome 4: Exacerbation requiring OCS (rate ratio)

Study or Subgroup	log[Rate Ratio]	SE	Anti-IL-13 or -4 Total	Control Total	Weight	Rate Ratio IV, Fixed, 95% CI	Rate Ratio IV, Fixed, 95% CI
1.4.1 Tralokinumab 300 mg SC Q2W							
Brightling 2015	-0.0619	0.2116	150	75	53.4%	0.94 [0.62 , 1.42]	
Subtotal (95% CI)			**150**	**75**	**53.4%**	**0.94 [0.62 , 1.42]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.29 (P = 0.77)							
1.4.2 Tralokinumab 300 mg SC Q4W							
Brightling 2015	0.0198	0.2263	151	76	46.6%	1.02 [0.65 , 1.59]	
Subtotal (95% CI)			**151**	**76**	**46.6%**	**1.02 [0.65 , 1.59]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.09 (P = 0.93)							
Total (95% CI)			**301**	**151**	**100.0%**	**0.98 [0.72 , 1.32]**	
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%							
Test for overall effect: Z = 0.15 (P = 0.88)							
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%							



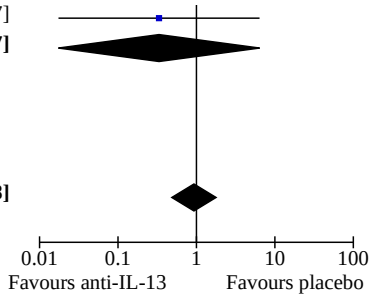
Analysis 1.5. Comparison 1: Anti-interleukin-13 or -4 agents with placebo, Outcome 5: Exacerbation requiring OCS (dichotomous)

Study or Subgroup	Anti-IL-13 or -4 Events	Anti-IL-13 or -4 Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 AMG317 75 mg SC						
Corren 2010	13	73	4	25	26.1%	1.14 [0.33 , 3.88]
Subtotal (95% CI)		**73**		**25**	**26.1%**	**1.14 [0.33 , 3.88]**
Total events:	13		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.84)						
1.5.2 AMG317 150 mg SC						
Corren 2010	6	73	4	25	29.1%	0.47 [0.12 , 1.83]
Subtotal (95% CI)		**73**		**25**	**29.1%**	**0.47 [0.12 , 1.83]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.09 (P = 0.28)						
1.5.3 AMG317 300 mg SC						
Corren 2010	6	74	3	24	22.2%	0.62 [0.14 , 2.69]
Subtotal (95% CI)		**74**		**24**	**22.2%**	**0.62 [0.14 , 2.69]**
Total events:	6		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
1.5.4 IMA638 75 mg SC						
NCT00425061	5	45	0	23	3.1%	6.38 [0.34 , 120.65]
Subtotal (95% CI)		**45**		**23**	**3.1%**	**6.38 [0.34 , 120.65]**
Total events:	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.22)						
1.5.5 IMA638 200 mg SC						
NCT00425061	1	4	0	22	0.7%	19.29 [0.65 , 573.83]
Subtotal (95% CI)		**4**		**22**	**0.7%**	**19.29 [0.65 , 573.83]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.71 (P = 0.09)						
1.5.6 IMA638 0.2 mg/kg IV						
NCT00425061	0	16	0	5		Not estimable
Subtotal (95% CI)		**16**		**5**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.7 IMA638 0.6 mg/kg IV						
NCT00425061	0	17	1	5	11.6%	0.09 [0.00 , 2.48]
Subtotal (95% CI)		**17**		**5**	**11.6%**	**0.09 [0.00 , 2.48]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						
1.5.8 IMA638 2 mg/kg IV						
NCT00425061	1	16	1	6	7.3%	0.33 [0.02 , 6.37]
Subtotal (95% CI)		**16**		**6**	**7.3%**	**0.33 [0.02 , 6.37]**



Analysis 1.5. (Continued)

NCT00425061	1	16	1	6	7.3%	0.33 [0.02 , 6.37]
Subtotal (95% CI)		**16**		**6**	**7.3%**	**0.33 [0.02 , 6.37]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
Total (95% CI)		**318**		**135**	**100.0%**	**0.93 [0.49 , 1.78]**
Total events:	32		13			
Heterogeneity: Chi² = 8.48, df = 6 (P = 0.20); I² = 29%						
Test for overall effect: Z = 0.22 (P = 0.82)						
Test for subgroup differences: Chi² = 8.35, df = 6 (P = 0.21), I² = 28.1%						



Analysis 1.6. Comparison 1: Anti-interleukin-13 or -4 agents with placebo, Outcome 6: Change from baseline in pre-bronchodilator FEV1

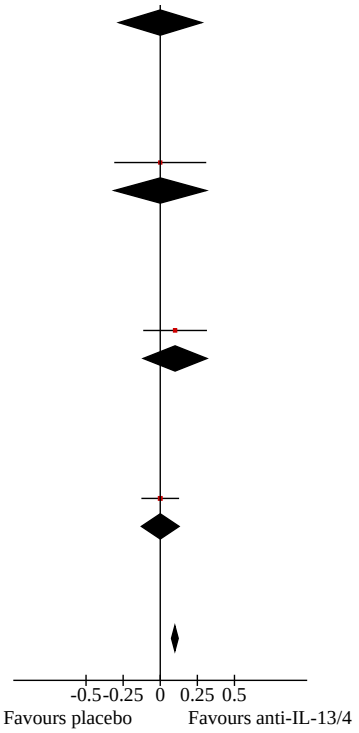
Study or Subgroup	MD	SE	Anti-IL-13 or -4 Total	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 Tralokinumab 150 mg SC Q2W						
Piper 2013	0.09	0.1306	44	14	0.8%	0.09 [-0.17 , 0.35]
Subtotal (95% CI)			**44**	**14**	**0.8%**	**0.09 [-0.17 , 0.35]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.6.2 Tralokinumab 300 mg SC Q2W						
Brightling 2015	0.13	0.0544	130	62	4.5%	0.13 [0.02 , 0.24]
Piper 2013	0.15	0.1323	49	14	0.8%	0.15 [-0.11 , 0.41]
Russell 2018	0.05	0.1695	36	40	0.5%	0.05 [-0.28 , 0.38]
Subtotal (95% CI)			**215**	**116**	**5.7%**	**0.13 [0.03 , 0.22]**
Heterogeneity: Chi² = 0.24, df = 2 (P = 0.89); I² = 0%						
Test for overall effect: Z = 2.62 (P = 0.009)						
1.6.3 Tralokinumab 300 mg SC Q4W						
Brightling 2015	0.04	0.0497	122	63	5.4%	0.04 [-0.06 , 0.14]
Subtotal (95% CI)			**122**	**63**	**5.4%**	**0.04 [-0.06 , 0.14]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						
1.6.4 Tralokinumab 600 mg SC Q2W						
Piper 2013	0.2	0.1378	44	14	0.7%	0.20 [-0.07 , 0.47]
Subtotal (95% CI)			**44**	**14**	**0.7%**	**0.20 [-0.07 , 0.47]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
1.6.5 AMG317 75 mg SC Q1W						
Corren 2010	-0.04	0.0702	73	25	2.7%	-0.04 [-0.18 , 0.10]
Subtotal (95% CI)			**73**	**25**	**2.7%**	**-0.04 [-0.18 , 0.10]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
1.6.6 AMG317 150 mg SC Q1W						
Corren 2010	0.03	0.0943	73	25	1.5%	0.03 [-0.15 , 0.21]
Subtotal (95% CI)			**73**	**25**	**1.5%**	**0.03 [-0.15 , 0.21]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
1.6.7 AMG317 300 mg SC Q1W						
Corren 2010	0.11	0.0714	74	24	2.6%	0.11 [-0.03 , 0.25]
Subtotal (95% CI)			**74**	**24**	**2.6%**	**0.11 [-0.03 , 0.25]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.54 (P = 0.12)						
1.6.8 Lebrikizumab 125 mg SC Q4W						
Korenblat 2018	0.083	0.0439	104	105	6.9%	0.08 [-0.00 , 0.17]
Noonan 2013	0.0875	0.0838	53	17	1.9%	0.09 [-0.08 , 0.25]
Subtotal (95% CI)			**157**	**122**	**8.8%**	**0.08 [0.01 , 0.16]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 2.16 (P = 0.03)						
1.6.9 Lebrikizumab 250 mg SC Q4W						
Corren 2011	0.11	0.0459	106	112	6.3%	0.11 [0.02 , 0.20]
Noonan 2013	0.1104	0.0821	53	17	2.0%	0.11 [-0.05 , 0.27]
Subtotal (95% CI)			**159**	**129**	**8.3%**	**0.11 [0.03 , 0.19]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						

Analysis 1.6. (Continued)

Subtotal (95% CI)			**159**	**129**	**8.3%**	**0.11 [0.03 , 0.19]**	
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%							
Test for overall effect: Z = 2.75 (P = 0.006)							
1.6.10 Lebrikizumab 500 mg SC Q4W							
Noonan 2013	0.0552	0.0837	52	18	1.9%	0.06 [-0.11 , 0.22]	
Subtotal (95% CI)			**52**	**18**	**1.9%**	**0.06 [-0.11 , 0.22]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.66 (P = 0.51)							
1.6.11 GSK679586 10 mg/kg IV Q4W							
De Boever 2014	-0.1	0.0459	99	99	6.3%	-0.10 [-0.19 , -0.01]	
Subtotal (95% CI)			**99**	**99**	**6.3%**	**-0.10 [-0.19 , -0.01]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.18 (P = 0.03)							
1.6.12 Dupilumab 300 mg SC Q1W							
Wenzel 2013	0.27	0.0816	52	52	2.0%	0.27 [0.11 , 0.43]	
Subtotal (95% CI)			**52**	**52**	**2.0%**	**0.27 [0.11 , 0.43]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.31 (P = 0.0009)							
1.6.13 Dupilumab 200 mg SC Q2W							
Castro 2018	0.14	0.0306	631	317	14.2%	0.14 [0.08 , 0.20]	
Wenzel 2016	0.16	0.0737	135	31	2.4%	0.16 [0.02 , 0.30]	
Subtotal (95% CI)			**766**	**348**	**16.6%**	**0.14 [0.09 , 0.20]**	
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%							
Test for overall effect: Z = 5.06 (P < 0.00001)							
1.6.14 Dupilumab 300 mg SC Q2W							
Castro 2018	0.13	0.0255	633	321	20.4%	0.13 [0.08 , 0.18]	
Rabe 2018	0.22	0.0663	97	104	3.0%	0.22 [0.09 , 0.35]	
Wenzel 2016	0.16	0.0743	143	31	2.4%	0.16 [0.01 , 0.31]	
Subtotal (95% CI)			**873**	**456**	**25.8%**	**0.14 [0.10 , 0.19]**	
Heterogeneity: Chi² = 1.66, df = 2 (P = 0.44); I² = 0%							
Test for overall effect: Z = 6.32 (P < 0.00001)							
1.6.15 Dupilumab 200 mg SC Q4W							
Wenzel 2016	0.1	0.0729	126	31	2.5%	0.10 [-0.04 , 0.24]	
Subtotal (95% CI)			**126**	**31**	**2.5%**	**0.10 [-0.04 , 0.24]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.37 (P = 0.17)							
1.6.16 Dupilumab 300 mg SC Q4W							
Wenzel 2016	0.13	0.0725	132	32	2.5%	0.13 [-0.01 , 0.27]	
Subtotal (95% CI)			**132**	**32**	**2.5%**	**0.13 [-0.01 , 0.27]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.79 (P = 0.07)							
1.6.17 IMA-638 0.2 mg/kg IV							
NCT00425061	0.1	0.1537	16	5	0.6%	0.10 [-0.20 , 0.40]	
Subtotal (95% CI)			**16**	**5**	**0.6%**	**0.10 [-0.20 , 0.40]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.65 (P = 0.52)							
1.6.18 IMA-638 0.6 mg/kg IV							
NCT00425061	0	0.1427	17	5	0.7%	0.00 [-0.28 , 0.28]	
Subtotal (95% CI)			**17**	**5**	**0.7%**	**0.00 [-0.28 , 0.28]**	
Heterogeneity: Not applicable							

Analysis 1.6. (Continued)

Subtotal (95% CI)			**17**	**5**	**0.7%**	**0.00 [-0.28 , 0.28]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
1.6.19 IMA-638 2 mg/kg IV							
NCT00425061	0	0.1581	16	6	0.5%	0.00 [-0.31 , 0.31]	
Subtotal (95% CI)			**16**	**6**	**0.5%**	**0.00 [-0.31 , 0.31]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
1.6.20 IMA-638 75 mg SC							
NCT00425061	0.1	0.1095	4	45	1.1%	0.10 [-0.11 , 0.31]	
Subtotal (95% CI)			**4**	**45**	**1.1%**	**0.10 [-0.11 , 0.31]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.91 (P = 0.36)							
1.6.21 IMA-638 200 mg SC							
NCT00425061	0	0.0648	45	41	3.2%	0.00 [-0.13 , 0.13]	
Subtotal (95% CI)			**45**	**41**	**3.2%**	**0.00 [-0.13 , 0.13]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
Total (95% CI)			**3159**	**1670**	**100.0%**	**0.10 [0.08 , 0.12]**	
Heterogeneity: Chi² = 42.03, df = 27 (P = 0.03); I² = 36%							
Test for overall effect: Z = 8.55 (P < 0.00001)							
Test for subgroup differences: Chi² = 40.06, df = 20 (P = 0.005), I² = 50.1%							

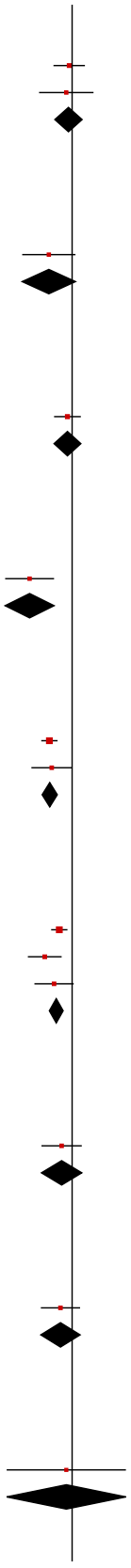


Analysis 1.7. Comparison 1: Anti-interleukin-13 or -4 agents with placebo, Outcome 7: Change from baseline in ACQ score

Study or Subgroup	MD	SE	Anti-IL-13 or -4 Total	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.7.1 Tralokinumab 150 mg SC Q2W						
Piper 2013	-0.12	0.3056	46	15	0.7%	-0.12 [-0.72 , 0.48]
Subtotal (95% CI)			**46**	**15**	**0.7%**	**-0.12 [-0.72 , 0.48]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.69)						
1.7.2 Tralokinumab 300 mg SC Q2W						
Brightling 2015	-0.19	0.1458	115	64	3.0%	-0.19 [-0.48 , 0.10]
Pannetieri 2018A	-0.16	0.0812	324	164	9.8%	-0.16 [-0.32 , -0.00]
Pannetieri 2018B	-0.08	0.0663	341	334	14.7%	-0.08 [-0.21 , 0.05]
Piper 2013	-0.09	0.2727	51	15	0.9%	-0.09 [-0.62 , 0.44]
Russell 2018	-0.08	0.199	36	40	1.6%	-0.08 [-0.47 , 0.31]
Subtotal (95% CI)			**867**	**617**	**30.0%**	**-0.12 [-0.21 , -0.03]**
Heterogeneity: $Chi^2 = 0.89$, df = 4 (P = 0.93); $I^2 = 0\%$						
Test for overall effect: Z = 2.53 (P = 0.01)						
1.7.3 Tralokinumab 300 mg SC Q4W						
Brightling 2015	-0.13	0.1455	112	64	3.1%	-0.13 [-0.42 , 0.16]
Pannetieri 2018A	-0.12	0.0877	344	165	8.4%	-0.12 [-0.29 , 0.05]
Subtotal (95% CI)			**456**	**229**	**11.4%**	**-0.12 [-0.27 , 0.02]**
Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.95); $I^2 = 0\%$						
Test for overall effect: Z = 1.63 (P = 0.10)						
1.7.4 Tralokinumab 600 mg SC Q2W						
Piper 2013	-0.25	0.292	47	16	0.8%	-0.25 [-0.82 , 0.32]
Subtotal (95% CI)			**47**	**16**	**0.8%**	**-0.25 [-0.82 , 0.32]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
1.7.5 AMG317 75 mg SC Q1W						
Corren 2010	0.06	0.1996	73	25	1.6%	0.06 [-0.33 , 0.45]
Subtotal (95% CI)			**73**	**25**	**1.6%**	**0.06 [-0.33 , 0.45]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
1.7.6 AMG317 150 mg SC Q1W						
Corren 2010	-0.09	0.214	73	24	1.4%	-0.09 [-0.51 , 0.33]
Subtotal (95% CI)			**73**	**24**	**1.4%**	**-0.09 [-0.51 , 0.33]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.67)						
1.7.7 AMG317 300 mg SC Q1W						
Corren 2010	-0.21	0.1819	74	24	2.0%	-0.21 [-0.57 , 0.15]
Subtotal (95% CI)			**74**	**24**	**2.0%**	**-0.21 [-0.57 , 0.15]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
1.7.8 Lebrikizumab 125 mg SC Q4W						
Noonan 2013	-0.2	0.2444	53	17	1.1%	-0.20 [-0.68 , 0.28]
Subtotal (95% CI)			**53**	**17**	**1.1%**	**-0.20 [-0.68 , 0.28]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
1.7.9 Lebrikizumab 250 mg SC Q4W						

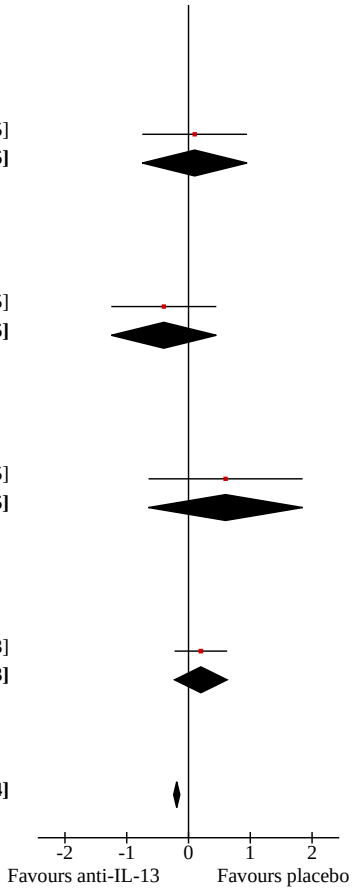
Analysis 1.7. (Continued)

1.7.9 Lebrikizumab 250 mg SC Q4W							
Corren 2011	-0.05	0.1378	106	112	3.4%	-0.05 [-0.32 , 0.22]	
Noonan 2013	-0.1	0.2385	53	17	1.1%	-0.10 [-0.57 , 0.37]	
Subtotal (95% CI)			**159**	**129**	**4.5%**	**-0.06 [-0.30 , 0.17]**	
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%							
Test for overall effect: Z = 0.52 (P = 0.60)							
1.7.10 Lebrikizumab 500 mg SC Q4W							
Noonan 2013	-0.4	0.2333	52	18	1.2%	-0.40 [-0.86 , 0.06]	
Subtotal (95% CI)			**52**	**18**	**1.2%**	**-0.40 [-0.86 , 0.06]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.71 (P = 0.09)							
1.7.11 GSK679586 10 mg/kg IV Q4W							
De Boever 2014	-0.08	0.1173	99	99	4.7%	-0.08 [-0.31 , 0.15]	
Subtotal (95% CI)			**99**	**99**	**4.7%**	**-0.08 [-0.31 , 0.15]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.68 (P = 0.50)							
1.7.12 Dupilumab 300 mg SC Q1W							
Wenzel 2013	-0.73	0.2143	52	52	1.4%	-0.73 [-1.15 , -0.31]	
Subtotal (95% CI)			**52**	**52**	**1.4%**	**-0.73 [-1.15 , -0.31]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.41 (P = 0.0007)							
1.7.13 Dupilumab 200 mg SC Q2W							
Castro 2018	-0.39	0.0714	631	317	12.7%	-0.39 [-0.53 , -0.25]	
Wenzel 2016	-0.35	0.1783	134	32	2.0%	-0.35 [-0.70 , -0.00]	
Subtotal (95% CI)			**765**	**349**	**14.7%**	**-0.38 [-0.51 , -0.25]**	
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%							
Test for overall effect: Z = 5.80 (P < 0.00001)							
1.7.14 Dupilumab 300 mg SC Q2W							
Castro 2018	-0.22	0.0714	633	321	12.7%	-0.22 [-0.36 , -0.08]	
Rabe 2018	-0.47	0.148	103	107	2.9%	-0.47 [-0.76 , -0.18]	
Wenzel 2016	-0.31	0.1721	145	32	2.2%	-0.31 [-0.65 , 0.03]	
Subtotal (95% CI)			**881**	**460**	**17.8%**	**-0.27 [-0.39 , -0.15]**	
Heterogeneity: Chi² = 2.37, df = 2 (P = 0.31); I² = 16%							
Test for overall effect: Z = 4.52 (P < 0.00001)							
1.7.15 Dupilumab 200 mg SC Q4W							
Wenzel 2016	-0.18	0.1766	126	32	2.1%	-0.18 [-0.53 , 0.17]	
Subtotal (95% CI)			**126**	**32**	**2.1%**	**-0.18 [-0.53 , 0.17]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.02 (P = 0.31)							
1.7.16 Dupilumab 300 mg SC Q4W							
Wenzel 2016	-0.2	0.172	132	31	2.2%	-0.20 [-0.54 , 0.14]	
Subtotal (95% CI)			**132**	**31**	**2.2%**	**-0.20 [-0.54 , 0.14]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.16 (P = 0.24)							
1.7.17 IMA-638 0.2 mg/kg IV							
NCT00425061	-0.1	0.5225	16	5	0.2%	-0.10 [-1.12 , 0.92]	
Subtotal (95% CI)			**16**	**5**	**0.2%**	**-0.10 [-1.12 , 0.92]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.19 (P = 0.85)							



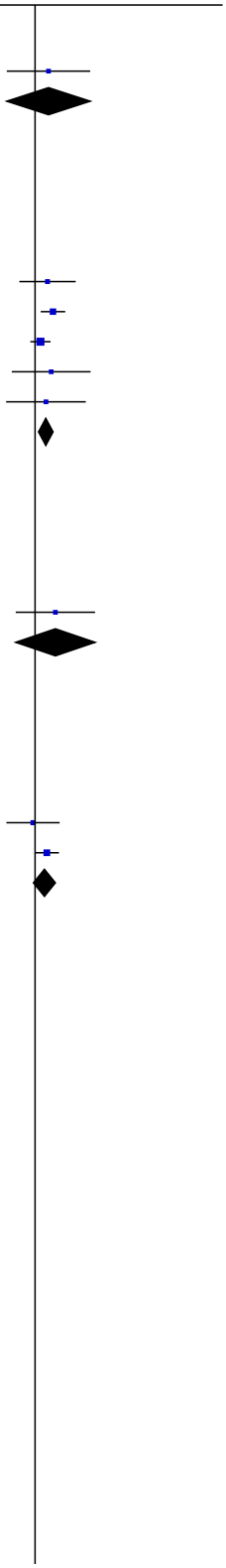
Analysis 1.7. (Continued)

Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						
1.7.18 IMA-638 0.6 mg/kg IV						
NCT00425061	0.1	0.4325	17	5	0.3%	0.10 [-0.75 , 0.95]
Subtotal (95% CI)			**17**	**5**	**0.3%**	**0.10 [-0.75 , 0.95]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.23 (P = 0.82)						
1.7.19 IMA-638 2 mg/kg IV						
NCT00425061	-0.4	0.4336	16	6	0.3%	-0.40 [-1.25 , 0.45]
Subtotal (95% CI)			**16**	**6**	**0.3%**	**-0.40 [-1.25 , 0.45]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
1.7.20 IMA-638 75 mg SC						
NCT00425061	0.6	0.6364	4	4	0.2%	0.60 [-0.65 , 1.85]
Subtotal (95% CI)			**4**	**4**	**0.2%**	**0.60 [-0.65 , 1.85]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.35)						
1.7.21 IMA-638 200 mg SC						
NCT00425061	0.2	0.217	45	41	1.4%	0.20 [-0.23 , 0.63]
Subtotal (95% CI)			**45**	**41**	**1.4%**	**0.20 [-0.23 , 0.63]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
Total (95% CI)			**4053**	**2198**	**100.0%**	**-0.19 [-0.24 , -0.14]**
Heterogeneity: Chi² = 33.63, df = 29 (P = 0.25); I² = 14%						
Test for overall effect: Z = 7.51 (P < 0.00001)						
Test for subgroup differences: Chi² = 30.29, df = 20 (P = 0.07), I² = 34.0%						



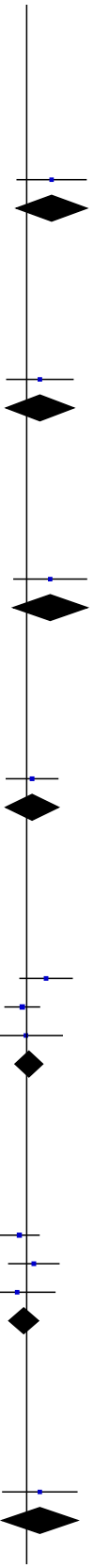
Analysis 1.8. Comparison 1: Anti-interleukin-13 or -4 agents with placebo, Outcome 8: Adverse events

Study or Subgroup	Anti-IL-13 Events	Anti-IL-13 Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.8.1 Tralokinumab 150 mg SC Q2W						
Piper 2013	20	47	5	15	0.8%	1.48 [0.44 , 5.01]
Subtotal (95% CI)		**47**		**15**	**0.8%**	**1.48 [0.44 , 5.01]**
Total events:	20		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.8.2 Tralokinumab 300 mg SC Q2W						
Brightling 2015	134	150	64	75	1.6%	1.44 [0.63 , 3.28]
Pannetieri 2018A	287	398	121	200	8.0%	1.69 [1.18 , 2.42]
Pannetieri 2018B	306	425	290	422	14.5%	1.17 [0.87 , 1.57]
Piper 2013	25	51	6	16	0.8%	1.60 [0.51 , 5.07]
Russell 2018	33	39	32	40	0.9%	1.38 [0.43 , 4.41]
Subtotal (95% CI)		**1063**		**753**	**25.9%**	**1.37 [1.11 , 1.69]**
Total events:	785		513			
Heterogeneity: Chi^2 = 2.48, df = 4 (P = 0.65); I^2 = 0%						
Test for overall effect: Z = 2.90 (P = 0.004)						
1.8.3 Tralokinumab 600 mg SC Q2W						
Piper 2013	25	48	6	16	0.8%	1.81 [0.57 , 5.78]
Subtotal (95% CI)		**48**		**16**	**0.8%**	**1.81 [0.57 , 5.78]**
Total events:	25		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
1.8.4 Tralokinumab 300 mg SC Q4W						
Brightling 2015	128	151	65	76	2.3%	0.94 [0.43 , 2.05]
Pannetieri 2018A	278	404	122	200	9.1%	1.41 [0.99 , 2.01]
Subtotal (95% CI)		**555**		**276**	**11.4%**	**1.31 [0.95 , 1.81]**
Total events:	406		187			
Heterogeneity: Chi^2 = 0.86, df = 1 (P = 0.35); I^2 = 0%						
Test for overall effect: Z = 1.67 (P = 0.09)						
1.8.5 Tralokinumab 1 mg/kg IV						
Singh 2010	8	8	1	1		Not estimable
Subtotal (95% CI)		**8**		**1**		**Not estimable**
Total events:	8		1			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.8.6 Tralokinumab 5 mg/kg IV						
Singh 2010	8	8	1	1		Not estimable
Subtotal (95% CI)		**8**		**1**		**Not estimable**
Total events:	8		1			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.8.7 Tralokinumab 10 mg/kg IV						
Singh 2010	3	3	1	1		Not estimable
Subtotal (95% CI)		**3**		**1**		**Not estimable**
Total events:	3		1			



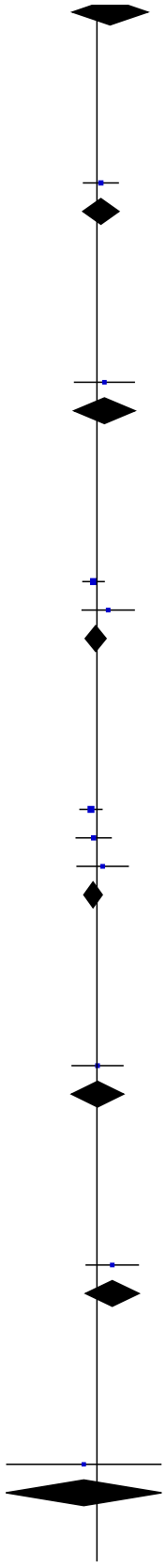
Analysis 1.8. (Continued)

Subtotal (95% CI)		**3**		**1**			**Not estimable**
Total events:	3		1				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.8.8 AMG317 75 mg SC Q1W							
Corren 2010	61	72	18	25	0.7%	2.16 [0.73 , 6.37]	
Subtotal (95% CI)		**72**		**25**	**0.7%**	**2.16 [0.73 , 6.37]**	
Total events:	61		18				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.39 (P = 0.16)							
1.8.9 AMG317 150 mg SC Q1W							
Corren 2010	58	73	18	25	1.0%	1.50 [0.53 , 4.26]	
Subtotal (95% CI)		**73**		**25**	**1.0%**	**1.50 [0.53 , 4.26]**	
Total events:	58		18				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.77 (P = 0.44)							
1.8.10 AMG317 300 mg SC Q1W							
Corren 2010	62	72	18	24	0.7%	2.07 [0.66 , 6.46]	
Subtotal (95% CI)		**72**		**24**	**0.7%**	**2.07 [0.66 , 6.46]**	
Total events:	62		18				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.25 (P = 0.21)							
1.8.11 Lebrikizumab 37.5 mg SC Q4W							
Hanania 2015a	87	117	27	38	1.9%	1.18 [0.52 , 2.67]	
Subtotal (95% CI)		**117**		**38**	**1.9%**	**1.18 [0.52 , 2.67]**	
Total events:	87		27				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.40 (P = 0.69)							
1.8.12 Lebrikizumab 125 mg SC Q4W							
Hanania 2015a	90	112	27	39	1.4%	1.82 [0.80 , 4.15]	
Korenblat 2018	42	104	45	103	4.8%	0.87 [0.50 , 1.52]	
Noonan 2013	34	53	11	17	1.1%	0.98 [0.31 , 3.06]	
Subtotal (95% CI)		**269**		**159**	**7.3%**	**1.07 [0.70 , 1.64]**	
Total events:	166		83				
Heterogeneity: Chi^2 = 2.13, df = 2 (P = 0.34); I^2 = 6%							
Test for overall effect: Z = 0.31 (P = 0.75)							
1.8.13 Lebrikizumab 250 mg SC Q4W							
Corren 2011	79	106	88	112	3.9%	0.80 [0.43 , 1.50]	
Hanania 2015a	87	118	27	39	1.9%	1.25 [0.56 , 2.76]	
Noonan 2013	34	53	12	17	1.2%	0.75 [0.23 , 2.44]	
Subtotal (95% CI)		**277**		**168**	**6.9%**	**0.91 [0.58 , 1.44]**	
Total events:	200		127				
Heterogeneity: Chi^2 = 0.88, df = 2 (P = 0.64); I^2 = 0%							
Test for overall effect: Z = 0.40 (P = 0.69)							
1.8.14 Lebrikizumab 500 mg SC Q4W							
Noonan 2013	39	52	12	18	0.8%	1.50 [0.47 , 4.80]	
Subtotal (95% CI)		**52**		**18**	**0.8%**	**1.50 [0.47 , 4.80]**	
Total events:	39		12				



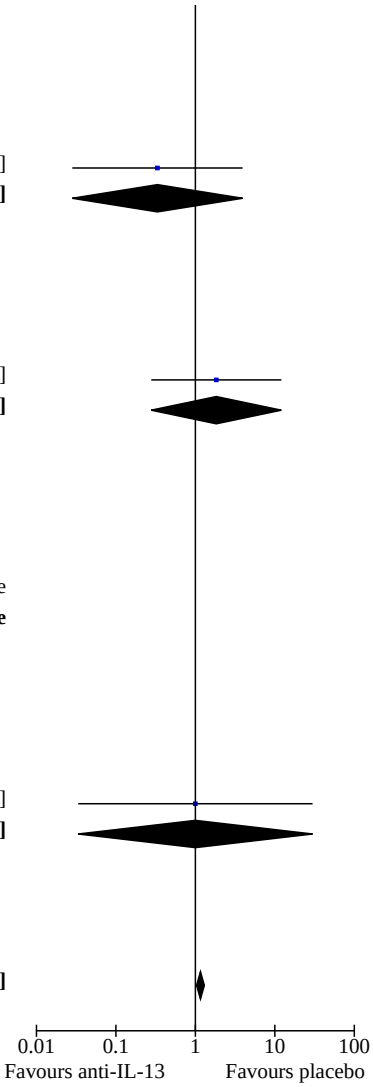
Analysis 1.8. (Continued)

Subtotal (95% CI)		**52**		**18**	**0.8%**	**1.50 [0.47 , 4.80]**	
Total events:	39		12				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.68 (P = 0.49)							
1.8.15 GSK679586 10 mg/kg IV Q4W							
De Boever 2014	52	99	49	99	4.1%	1.13 [0.65 , 1.97]	
Subtotal (95% CI)		**99**		**99**	**4.1%**	**1.13 [0.65 , 1.97]**	
Total events:	52		49				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.43 (P = 0.67)							
1.8.16 Dupilumab 300 mg SC Q1W							
Wenzel 2013	42	52	40	52	1.4%	1.26 [0.49 , 3.24]	
Subtotal (95% CI)		**52**		**52**	**1.4%**	**1.26 [0.49 , 3.24]**	
Total events:	42		40				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.48 (P = 0.63)							
1.8.17 Dupilumab 200 mg SC Q2W							
Castro 2018	508	631	257	313	11.9%	0.90 [0.63 , 1.28]	
Wenzel 2016	119	148	29	39	1.6%	1.41 [0.62 , 3.23]	
Subtotal (95% CI)		**779**		**352**	**13.5%**	**0.96 [0.70 , 1.33]**	
Total events:	627		286				
Heterogeneity: Chi^2 = 0.98, df = 1 (P = 0.32); I^2 = 0%							
Test for overall effect: Z = 0.24 (P = 0.81)							
1.8.18 Dupilumab 300 mg SC Q2W							
Castro 2018	515	632	270	321	11.8%	0.83 [0.58 , 1.19]	
Rabe 2018	64	103	69	107	4.6%	0.90 [0.52 , 1.58]	
Wenzel 2016	121	156	29	39	1.9%	1.19 [0.53 , 2.68]	
Subtotal (95% CI)		**891**		**467**	**18.2%**	**0.89 [0.67 , 1.18]**	
Total events:	700		368				
Heterogeneity: Chi^2 = 0.64, df = 2 (P = 0.73); I^2 = 0%							
Test for overall effect: Z = 0.83 (P = 0.40)							
1.8.19 Dupilumab 200 mg SC Q4W							
Wenzel 2016	113	150	30	40	2.1%	1.02 [0.45 , 2.28]	
Subtotal (95% CI)		**150**		**40**	**2.1%**	**1.02 [0.45 , 2.28]**	
Total events:	113		30				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.04 (P = 0.97)							
1.8.20 Dupilumab 300 mg SC Q4W							
Wenzel 2016	130	157	30	40	1.5%	1.60 [0.70 , 3.67]	
Subtotal (95% CI)		**157**		**40**	**1.5%**	**1.60 [0.70 , 3.67]**	
Total events:	130		30				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.12 (P = 0.26)							
1.8.21 VR492 0.5 mg							
Burgess 2018	3	6	3	5	0.3%	0.67 [0.06 , 7.35]	
Subtotal (95% CI)		**6**		**5**	**0.3%**	**0.67 [0.06 , 7.35]**	
Total events:	3		3				
Heterogeneity: Not applicable							



Analysis 1.8. (Continued)

Total events:	3		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.33 (P = 0.74)							
1.8.22 VR492 10 mg							
Burgess 2018	2	6	3	5	0.4%	0.33 [0.03 , 3.93]	
Subtotal (95% CI)		**6**		**5**	**0.4%**	**0.33 [0.03 , 3.93]**	
Total events:	2		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.87 (P = 0.38)							
1.8.23 VR492 20 mg							
Burgess 2018	11	17	3	6	0.3%	1.83 [0.28 , 12.07]	
Subtotal (95% CI)		**17**		**6**	**0.3%**	**1.83 [0.28 , 12.07]**	
Total events:	11		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.63 (P = 0.53)							
1.8.24 RPC4046 0.3 mg/kg IV Q1W							
Tripp 2017	4	4	2	2		Not estimable	
Subtotal (95% CI)		**4**		**2**		**Not estimable**	
Total events:	4		2				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.8.25 RPC4046 3 mg/kg IV Q1W							
Tripp 2017	2	4	1	2	0.1%	1.00 [0.03 , 29.81]	
Subtotal (95% CI)		**4**		**2**	**0.1%**	**1.00 [0.03 , 29.81]**	
Total events:	2		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
Total (95% CI)		**4829**		**2590**	**100.0%**	**1.16 [1.04 , 1.30]**	
Total events:	3614		1832				
Heterogeneity: Chi² = 22.33, df = 32 (P = 0.90); I² = 0%							
Test for overall effect: Z = 2.57 (P = 0.01)							
Test for subgroup differences: Chi² = 14.43, df = 20 (P = 0.81), I² = 0%							

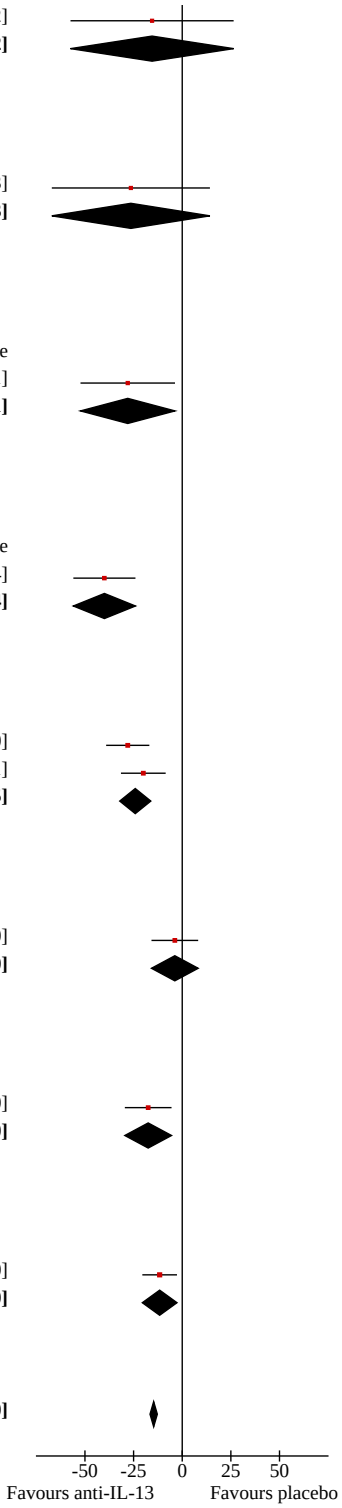


Analysis 1.9. Comparison 1: Anti-interleukin-13 or -4 agents with placebo, Outcome 9: Change from baseline in FENO, ppb

Study or Subgroup	MD	SE	Anti-IL-13 or -4 Total	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 Lebrikizumab 125 mg SC Q4W						
Korenblat 2018	-21	4.2426	104	105	5.1%	-21.00 [-29.32 , -12.68]
Noonan 2013	-23.4	12.5721	53	17	0.6%	-23.40 [-48.04 , 1.24]
Subtotal (95% CI)			**157**	**122**	**5.7%**	**-21.25 [-29.12 , -13.37]**
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 5.29 (P < 0.00001)						
1.9.2 Lebrikizumab 250 mg SC Q4W						
Corren 2011	-10.6	3.0103	106	112	10.1%	-10.60 [-16.50 , -4.70]
Noonan 2013	-23.5	9.882	53	17	0.9%	-23.50 [-42.87 , -4.13]
Subtotal (95% CI)			**159**	**129**	**11.1%**	**-11.70 [-17.34 , -6.05]**
Heterogeneity: Chi² = 1.56, df = 1 (P = 0.21); I² = 36%						
Test for overall effect: Z = 4.06 (P < 0.0001)						
1.9.3 Lebrikizumab 500 mg SC Q4W						
Noonan 2013	-14.1	9.5733	52	18	1.0%	-14.10 [-32.86 , 4.66]
Subtotal (95% CI)			**52**	**18**	**1.0%**	**-14.10 [-32.86 , 4.66]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						
1.9.4 Tralokinumab 300 mg Q2W						
Russell 2018	-11.67	4.4121	36	40	4.7%	-11.67 [-20.32 , -3.02]
Subtotal (95% CI)			**36**	**40**	**4.7%**	**-11.67 [-20.32 , -3.02]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.64 (P = 0.008)						
1.9.5 Dupilumab 200 mg SC Q2W						
Castro 2018	-13.9	1.5708	631	313	37.2%	-13.90 [-16.98 , -10.82]
Wenzel 2016	-32.77	12.1033	114	30	0.6%	-32.77 [-56.49 , -9.05]
Subtotal (95% CI)			**745**	**343**	**37.9%**	**-14.21 [-17.27 , -11.16]**
Heterogeneity: Chi² = 2.39, df = 1 (P = 0.12); I² = 58%						
Test for overall effect: Z = 9.12 (P < 0.00001)						
1.9.6 Dupilumab 300 mg SC Q2W						
Castro 2018	-10.7	2.2845	632	321	17.6%	-10.70 [-15.18 , -6.22]
Rabe 2018	-17.6	5.6569	103	107	2.9%	-17.60 [-28.69 , -6.51]
Wenzel 2016	-40.31	12.1034	124	30	0.6%	-40.31 [-64.03 , -16.59]
Subtotal (95% CI)			**859**	**458**	**21.1%**	**-12.52 [-16.61 , -8.43]**
Heterogeneity: Chi² = 6.71, df = 2 (P = 0.03); I² = 70%						
Test for overall effect: Z = 6.00 (P < 0.00001)						
1.9.7 Dupilumab 200 mg SC Q4W						
Wenzel 2016	-16.39	12.0782	102	30	0.6%	-16.39 [-40.06 , 7.28]
Subtotal (95% CI)			**102**	**30**	**0.6%**	**-16.39 [-40.06 , 7.28]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.36 (P = 0.17)						
1.9.8 Dupilumab 300 mg SC Q4W						
Wenzel 2016	-27.53	12.0794	115	30	0.6%	-27.53 [-51.21 , -3.85]
Subtotal (95% CI)			**115**	**30**	**0.6%**	**-27.53 [-51.21 , -3.85]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.28 (P = 0.02)						
1.9.9 Soluble IL-4R 500 ug nebulised						
Borish 1999	-15.5	21.3892	8	4	0.2%	-15.50 [-57.42 , 26.42]
Subtotal (95% CI)			**8**	**4**	**0.2%**	**-15.50 [-57.42 , 26.42]**

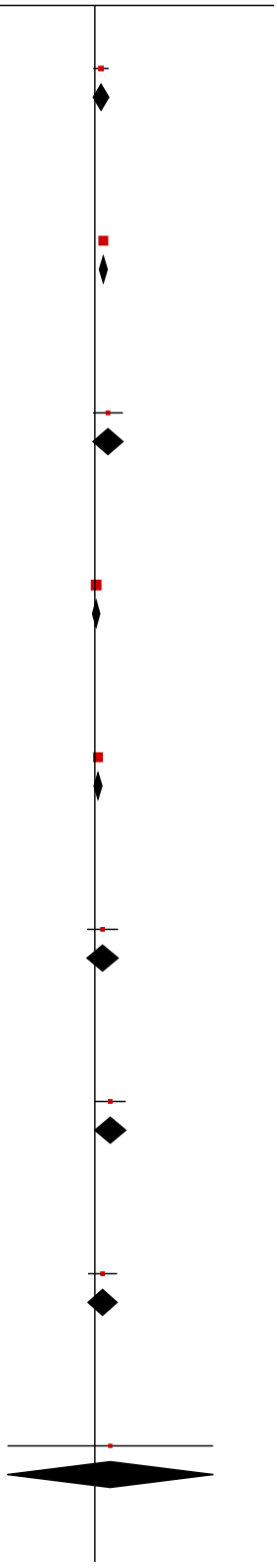
Analysis 1.9. (Continued)

Borish 1999	-15.5	21.3892	8	4	0.2%	-15.50 [-57.42 , 26.42]	
Subtotal (95% CI)			**8**	**4**	**0.2%**	**-15.50 [-57.42 , 26.42]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.72 (P = 0.47)							
1.9.10 Soluble IL-4R 1500 ug nebulised							
Borish 1999	-26.4	20.7308	9	4	0.2%	-26.40 [-67.03 , 14.23]	
Subtotal (95% CI)			**9**	**4**	**0.2%**	**-26.40 [-67.03 , 14.23]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.27 (P = 0.20)							
1.9.11 GSK679586 2.5 mg/kg IV Q4W							
De Boever 2014	0	0	0	0		Not estimable	
Hodsman 2013	-28	12.3911	6	2	0.6%	-28.00 [-52.29 , -3.71]	
Subtotal (95% CI)			**6**	**2**	**0.6%**	**-28.00 [-52.29 , -3.71]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.26 (P = 0.02)							
1.9.12 GSK679586 10 mg/kg IV Q4W							
De Boever 2014	0	0	0	0		Not estimable	
Hodsman 2013	-40	8.143	6	2	1.4%	-40.00 [-55.96 , -24.04]	
Subtotal (95% CI)			**6**	**2**	**1.4%**	**-40.00 [-55.96 , -24.04]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 4.91 (P < 0.00001)							
1.9.13 GSK679586 20 mg/kg IV Q4W							
De Boever 2014	-28	5.6639	40	44	2.9%	-28.00 [-39.10 , -16.90]	
Hodsman 2013	-20	5.8621	9	3	2.7%	-20.00 [-31.49 , -8.51]	
Subtotal (95% CI)			**49**	**47**	**5.5%**	**-24.14 [-32.12 , -16.15]**	
Heterogeneity: Chi² = 0.96, df = 1 (P = 0.33); I² = 0%							
Test for overall effect: Z = 5.93 (P < 0.00001)							
1.9.14 VR492 0.5 mg							
Burgess 2018	-3.8	6.1226	6	5	2.5%	-3.80 [-15.80 , 8.20]	
Subtotal (95% CI)			**6**	**5**	**2.5%**	**-3.80 [-15.80 , 8.20]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.62 (P = 0.53)							
1.9.15 VR492 10 mg							
Burgess 2018	-17.5	6.1226	6	5	2.5%	-17.50 [-29.50 , -5.50]	
Subtotal (95% CI)			**6**	**5**	**2.5%**	**-17.50 [-29.50 , -5.50]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.86 (P = 0.004)							
1.9.16 VR492 20 mg							
Burgess 2018	-11.6	4.5409	17	6	4.5%	-11.60 [-20.50 , -2.70]	
Subtotal (95% CI)			**17**	**6**	**4.5%**	**-11.60 [-20.50 , -2.70]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.55 (P = 0.01)							
Total (95% CI)			**2332**	**1245**	**100.0%**	**-14.68 [-16.56 , -12.80]**	
Heterogeneity: Chi² = 38.55, df = 21 (P = 0.01); I² = 46%							
Test for overall effect: Z = 15.32 (P < 0.00001)							
Test for subgroup differences: Chi² = 26.89, df = 15 (P = 0.03), I² = 44.2%							



Analysis 1.10. Comparison 1: Anti-interleukin-13 or -4 agents with placebo, Outcome 10: Change from baseline in blood eosinophils, cells x 10*9/L

Study or Subgroup	MD	SE	Anti-IL-13 or -4 Total	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.10.1 Tralokinumab 300 mg Q2W						
Russell 2018	0.08	0.0509	36	40	6.1%	0.08 [-0.02 , 0.18]
Subtotal (95% CI)			**36**	**40**	**6.1%**	**0.08 [-0.02 , 0.18]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.57 (P = 0.12)						
1.10.2 Lebrikizumab 250 mg SC Q4W						
Corren 2011	0.11	0.0255	106	112	24.3%	0.11 [0.06 , 0.16]
Subtotal (95% CI)			**106**	**112**	**24.3%**	**0.11 [0.06 , 0.16]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.31 (P < 0.0001)						
1.10.3 Dupilumab 300 mg SC Q1W						
Wenzel 2013	0.17	0.0985	44	43	1.6%	0.17 [-0.02 , 0.36]
Subtotal (95% CI)			**44**	**43**	**1.6%**	**0.17 [-0.02 , 0.36]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.73 (P = 0.08)						
1.10.4 Dupilumab 200 mg SC Q2W						
Castro 2018	0.017	0.0237	631	313	28.2%	0.02 [-0.03 , 0.06]
Subtotal (95% CI)			**631**	**313**	**28.2%**	**0.02 [-0.03 , 0.06]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
1.10.5 Dupilumab 300 mg SC Q2W						
Castro 2018	0.041	0.0256	632	321	24.2%	0.04 [-0.01 , 0.09]
Subtotal (95% CI)			**632**	**321**	**24.2%**	**0.04 [-0.01 , 0.09]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.60 (P = 0.11)						
1.10.6 IMA-638 0.2 mg/kg IV						
NCT00425061	0.1	0.1025	16	5	1.5%	0.10 [-0.10 , 0.30]
Subtotal (95% CI)			**16**	**5**	**1.5%**	**0.10 [-0.10 , 0.30]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
1.10.7 IMA-638 0.6 mg/kg IV						
NCT00425061	0.2	0.1018	17	5	1.5%	0.20 [0.00 , 0.40]
Subtotal (95% CI)			**17**	**5**	**1.5%**	**0.20 [0.00 , 0.40]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.96 (P = 0.05)						
1.10.8 IMA-638 2 mg/kg IV						
NCT00425061	0.1	0.0957	16	6	1.7%	0.10 [-0.09 , 0.29]
Subtotal (95% CI)			**16**	**6**	**1.7%**	**0.10 [-0.09 , 0.29]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
1.10.9 IMA-638 75 mg SC						
NCT00425061	0.2	0.6788	4	4	0.0%	0.20 [-1.13 , 1.53]
Subtotal (95% CI)			**4**	**4**	**0.0%**	**0.20 [-1.13 , 1.53]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						



Analysis 1.10. (Continued)

Test for overall effect: Z = 0.29 (P = 0.77)

1.10.10 IMA-638 200 mg SC

NCT00425061	0.1	0.1045	45	4	1.4%	0.10 [-0.10 , 0.30]
Subtotal (95% CI)			**45**	**4**	**1.4%**	**0.10 [-0.10 , 0.30]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)

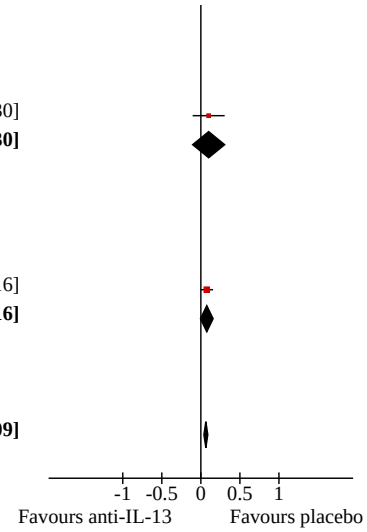
1.10.11 GSK679586 10 mg/kg IV

De Boever 2014	0.076	0.0412	99	99	9.3%	0.08 [-0.00 , 0.16]
Subtotal (95% CI)			**99**	**99**	**9.3%**	**0.08 [-0.00 , 0.16]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.84 (P = 0.07)

Total (95% CI)			**1646**	**952**	**100.0%**	**0.06 [0.04 , 0.09]**

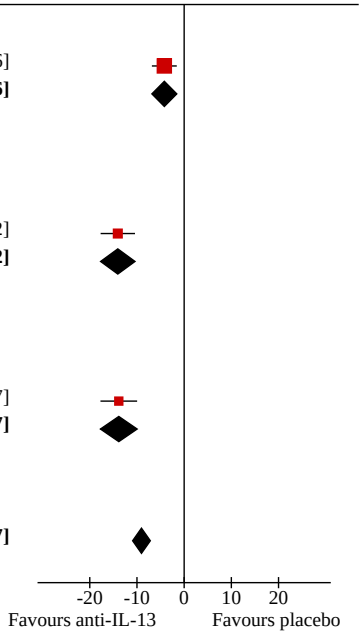
Heterogeneity: Chi² = 11.54, df = 10 (P = 0.32); I² = 13%
Test for overall effect: Z = 5.09 (P < 0.00001)
Test for subgroup differences: Chi² = 11.54, df = 10 (P = 0.32), I² = 13.4%



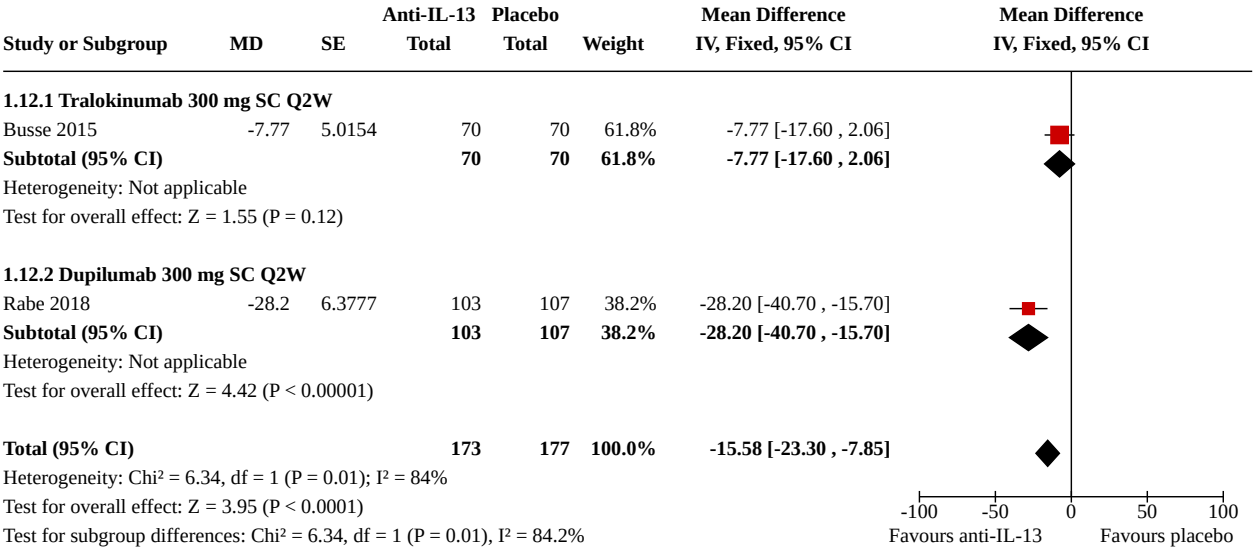
Analysis 1.11. Comparison 1: Anti-interleukin-13 or -4 agents with placebo, Outcome 11: Change from baseline in periostin, ng/mL

Study or Subgroup	MD	SE	Anti-IL-13 or -4 Total	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.11.1 Lebrikizumab 125 mg SC Q4W						
Korenblat 2018	-4.2	1.3454	105	104	50.4%	-4.20 [-6.84 , -1.56]
Subtotal (95% CI)			**105**	**104**	**50.4%**	**-4.20 [-6.84 , -1.56]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.12 (P = 0.002)						
1.11.2 Dupilumab 200 mg SC Q2W						
Castro 2018	-14.06	1.8578	631	313	26.4%	-14.06 [-17.70 , -10.42]
Subtotal (95% CI)			**631**	**313**	**26.4%**	**-14.06 [-17.70 , -10.42]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.57 (P < 0.00001)						
1.11.3 Dupilumab 300 mg SC Q2W						
Castro 2018	-13.85	1.982	632	321	23.2%	-13.85 [-17.73 , -9.97]
Subtotal (95% CI)			**632**	**321**	**23.2%**	**-13.85 [-17.73 , -9.97]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.99 (P < 0.00001)						
Total (95% CI)			**1368**	**738**	**100.0%**	**-9.04 [-10.92 , -7.17]**

Heterogeneity: Chi² = 26.13, df = 2 (P < 0.00001); I² = 92%
Test for overall effect: Z = 9.47 (P < 0.00001)
Test for subgroup differences: Chi² = 26.13, df = 2 (P < 0.00001), I² = 92.3%

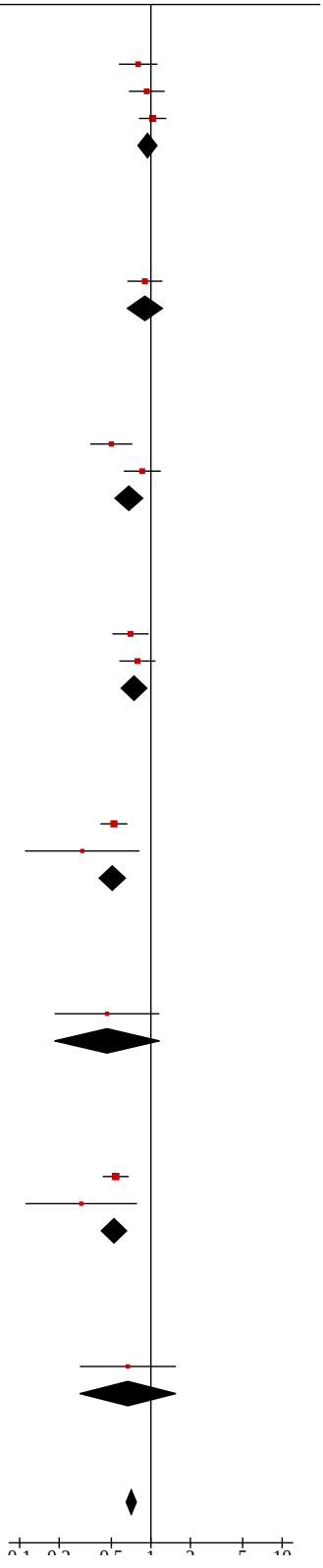


Analysis 1.12. Comparison 1: Anti-interleukin-13 or -4 agents with placebo, Outcome 12: Percentage reduction from baseline in OCS use



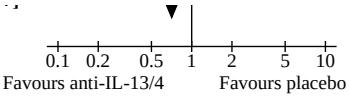
Analysis 1.13. Comparison 1: Anti-interleukin-13 or -4 agents with placebo, Outcome 13: Exacerbation requiring hospitalisation/ED/OCS (rate ratio)

Study or Subgroup	log[Rate Ratio]	SE	Anti-IL-13 or -4 Total	Control Total	Weight	Rate Ratio IV, Fixed, 95% CI
1.13.1 Tralokinumab 300 mg SC Q2W						
Busse 2015	-0.2231	0.1729	70	70	6.9%	0.80 [0.57 , 1.12]
Pannetieri 2018A	-0.0726	0.16	398	200	8.1%	0.93 [0.68 , 1.27]
Pannetieri 2018B	0.0296	0.1226	420	417	13.8%	1.03 [0.81 , 1.31]
Subtotal (95% CI)			**888**	**687**	**28.9%**	**0.94 [0.80 , 1.11]**
Heterogeneity: Chi² = 1.43, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.48)						
1.13.2 Tralokinumab 300 mg SC Q4W						
Pannetieri 2018A	-0.1054	0.157	404	200	8.4%	0.90 [0.66 , 1.22]
Subtotal (95% CI)			**404**	**200**	**8.4%**	**0.90 [0.66 , 1.22]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
1.13.3 Lebrikizumab 37.5 mg SC Q4W						
Hanania 2016a	-0.6931	0.1881	360	181	5.9%	0.50 [0.35 , 0.72]
Hanania 2016b	-0.1508	0.1653	356	177	7.6%	0.86 [0.62 , 1.19]
Subtotal (95% CI)			**716**	**358**	**13.5%**	**0.68 [0.53 , 0.87]**
Heterogeneity: Chi² = 4.69, df = 1 (P = 0.03); I² = 79%						
Test for overall effect: Z = 3.12 (P = 0.002)						
1.13.4 Lebrikizumab 125 mg SC Q4W						
Hanania 2016a	-0.3567	0.1622	359	181	7.9%	0.70 [0.51 , 0.96]
Hanania 2016b	-0.2357	0.1615	357	177	8.0%	0.79 [0.58 , 1.08]
Subtotal (95% CI)			**716**	**358**	**15.9%**	**0.74 [0.59 , 0.93]**
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 2.59 (P = 0.010)						
1.13.5 Dupilumab 200mg SC Q2W						
Castro 2018	-0.6482	0.1205	631	317	14.3%	0.52 [0.41 , 0.66]
Wenzel 2016	-1.204	0.5121	148	39	0.8%	0.30 [0.11 , 0.82]
Subtotal (95% CI)			**779**	**356**	**15.1%**	**0.51 [0.40 , 0.64]**
Heterogeneity: Chi² = 1.12, df = 1 (P = 0.29); I² = 10%						
Test for overall effect: Z = 5.77 (P < 0.00001)						
1.13.6 Dupilumab 200 mg SC Q4W						
Wenzel 2016	-0.77	0.4686	156	39	0.9%	0.46 [0.18 , 1.16]
Subtotal (95% CI)			**156**	**39**	**0.9%**	**0.46 [0.18 , 1.16]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.64 (P = 0.10)						
1.13.7 Dupilumab 300mg SC Q2W						
Castro 2018	-0.6162	0.1162	633	321	15.4%	0.54 [0.43 , 0.68]
Wenzel 2016	-1.2208	0.4985	150	40	0.8%	0.29 [0.11 , 0.78]
Subtotal (95% CI)			**783**	**361**	**16.2%**	**0.52 [0.42 , 0.65]**
Heterogeneity: Chi² = 1.40, df = 1 (P = 0.24); I² = 28%						
Test for overall effect: Z = 5.72 (P < 0.00001)						
1.13.8 Dupilumab 300 mg SC Q4W						
Wenzel 2016	-0.4035	0.4298	157	40	1.1%	0.67 [0.29 , 1.55]
Subtotal (95% CI)			**157**	**40**	**1.1%**	**0.67 [0.29 , 1.55]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.35)						
Total (95% CI)			**4599**	**2399**	**100.0%**	**0.71 [0.65 , 0.77]**
Heterogeneity: Chi² = 38.85, df = 13 (P = 0.0002); I² = 67%						
Test for overall effect: Z = 7.55 (P < 0.00001)						



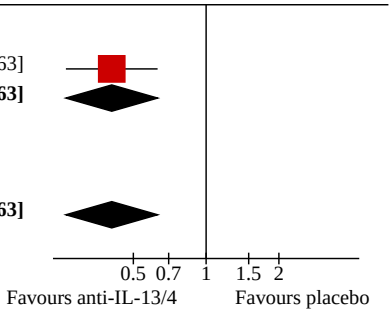
Analysis 1.13. (Continued)

Heterogeneity: Chi² = 38.85, df = 13 (P = 0.0002); I² = 67%
Test for overall effect: Z = 7.55 (P < 0.00001)
Test for subgroup differences: Chi² = 29.94, df = 7 (P < 0.0001), I² = 76.6%



Analysis 1.14. Comparison 1: Anti-interleukin-13 or -4 agents with placebo, Outcome 14: Exacerbation requiring hospitalisation/ED/OCS (relative risk)

Study or Subgroup	log[RR]	SE	Anti-IL-13 or -4 Total	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
1.14.1 Dupilumab 300mg SC Q2W						
Rabe 2018	-0.8989	0.2228	103	107	100.0%	0.41 [0.26 , 0.63]
Subtotal (95% CI)			**103**	**107**	**100.0%**	**0.41 [0.26 , 0.63]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.03 (P < 0.0001)						
Total (95% CI)			**103**	**107**	**100.0%**	**0.41 [0.26 , 0.63]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.03 (P < 0.0001)						
Test for subgroup differences: Not applicable						



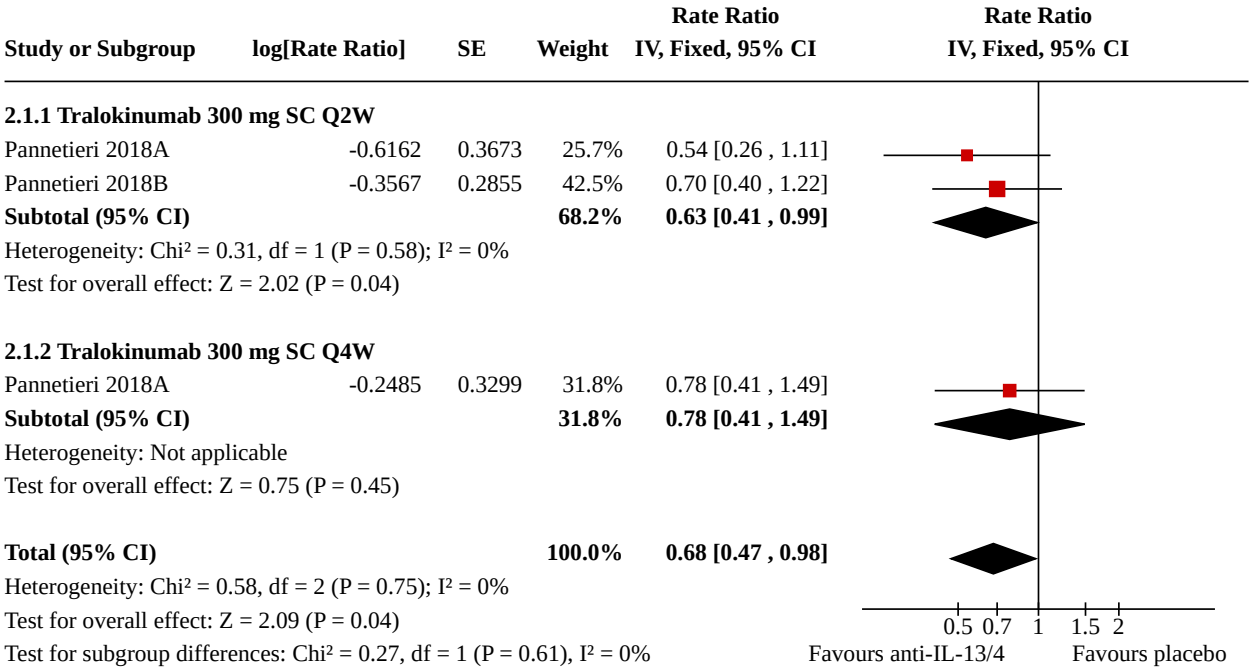
Comparison 2. Subanalysis: agents directly targeting IL-13

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Exacerbation requiring hospitalisation or ED visit	2		Rate Ratio (IV, Fixed, 95% CI)	0.68 [0.47, 0.98]
2.1.1 Tralokinumab 300 mg SC Q2W	2		Rate Ratio (IV, Fixed, 95% CI)	0.63 [0.41, 0.99]
2.1.2 Tralokinumab 300 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.78 [0.41, 1.49]
2.2 Health-related quality of life (adjusted mean diff versus placebo)	4		Mean Difference (IV, Fixed, 95% CI)	0.10 [0.01, 0.18]
2.2.1 Lebrikizumab 125 mg SC Q4W	1		Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.29, 0.17]
2.2.2 Tralokinumab 300 mg SC Q2W	3		Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.00, 0.23]
2.2.3 Tralokinumab 300 mg SC Q4W	2		Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.02, 0.30]
2.3 Serious adverse events	16	4443	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.67, 1.05]
2.3.1 Tralokinumab 1 mg/kg IV Q4W	2	12	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

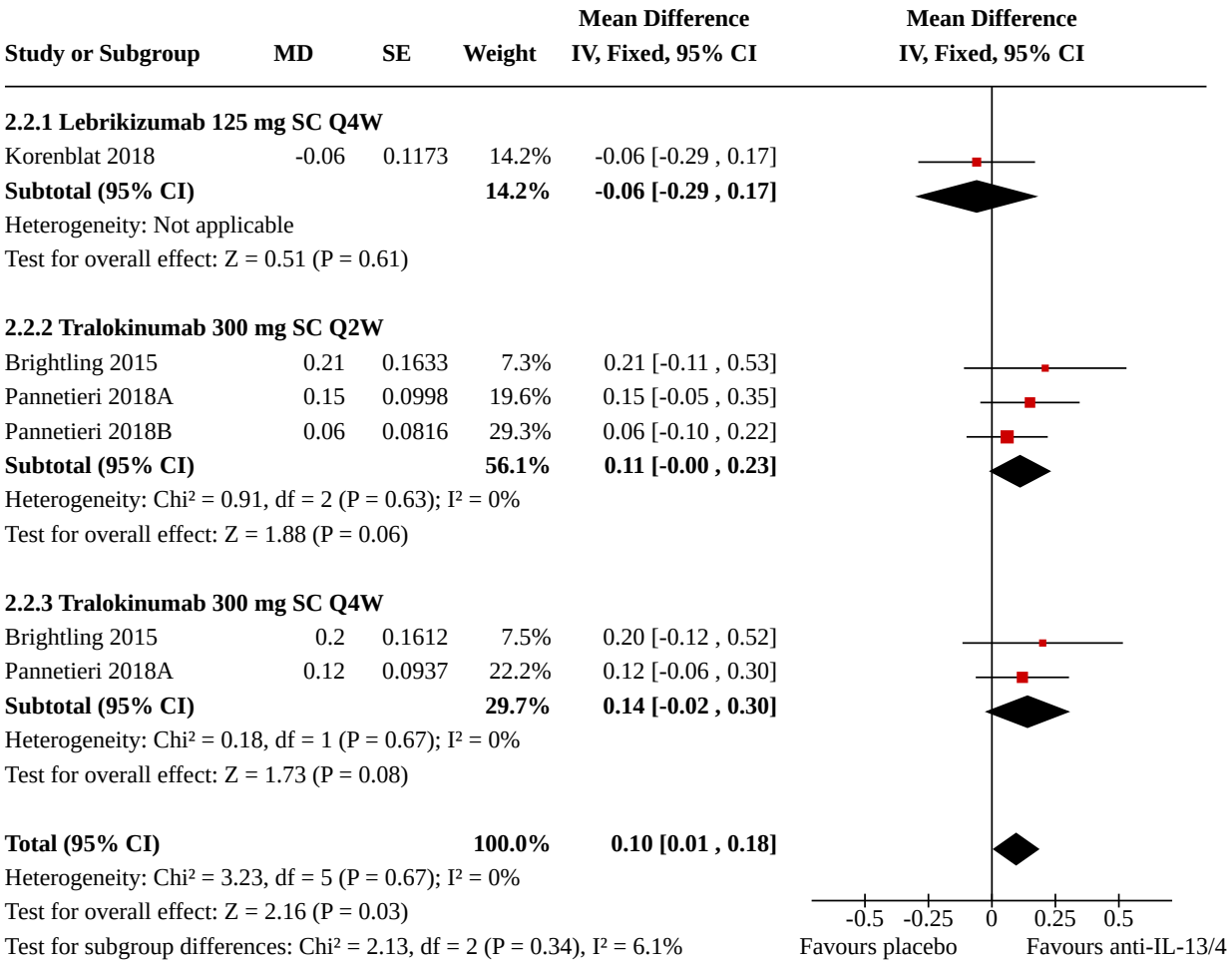
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3.2 Tralokinumab 5 mg/kg IV Q4W	2	14	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.02, 23.07]
2.3.3 Tralokinumab 10 mg/kg IV Q4W	2	10	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.03, 53.51]
2.3.4 Tralokinumab 150 mg SC Q2W	1	62	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.05, 7.39]
2.3.5 Tralokinumab 300 mg SC Q2W	6	1955	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.05]
2.3.6 Tralokinumab 300 mg SC Q4W	2	831	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.58, 1.40]
2.3.7 Tralokinumab 600 mg SC Q2W	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.02, 5.42]
2.3.8 Lebrikizumab 37.5 mg SC Q4W	1	155	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 1.76]
2.3.9 Lebrikizumab 125 mg SC Q4W	3	428	Odds Ratio (M-H, Fixed, 95% CI)	1.47 [0.43, 5.05]
2.3.10 Lebrikizumab 250 mg SC Q4W	3	445	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.28, 1.86]
2.3.11 Lebrikizumab 500 mg SC Q4W	1	70	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.04, 27.64]
2.3.12 GSK679586 2.5 mg/kg IV Q4W	1	8	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3.13 GSK679586 10 mg/kg IV Q4W	2	206	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [0.52, 5.24]
2.3.14 GSK679586 20 mg/kg IV Q4W	1	12	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.04, 38.30]
2.3.15 RPC4046 0.3 mg/kg IV Q1W	1	6	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3.16 RPC4046 3 mg/kg IV Q1W	1	6	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3.17 IMA-638 IV 0.2 mg/kg (D1/8/28/56/84)	1	21	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3.18 IMA-638 IV 0.6 mg/kg (D1/8/28/56/84)	1	22	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.04, 28.30]
2.3.19 IMA-638 IV 2 mg/kg (D1/8/28/56/84)	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.05, 9.70]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3.20 IMA-638 IV 200 mg SC (D1/8/28/42/56/70/84)	1	67	Odds Ratio (M-H, Fixed, 95% CI)	2.59 [0.12, 56.20]
2.3.21 IMA-638 IV 75 mg SC (D1/8/28/42/56/70/84)	1	27	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2.4 Exacerbation requiring hospitalisation/ED/OCS (rate ratio)	5		Rate Ratio (IV, Fixed, 95% CI)	0.83 [0.74, 0.92]
2.4.1 Tralokinumab 300 mg SC Q2W	3		Rate Ratio (IV, Fixed, 95% CI)	0.94 [0.80, 1.11]
2.4.2 Tralokinumab 300 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.90 [0.66, 1.22]
2.4.3 Lebrikizumab 37.5 mg SC Q4W	2		Rate Ratio (IV, Fixed, 95% CI)	0.68 [0.53, 0.87]
2.4.4 Lebrikizumab 125 mg SC Q4W	2		Rate Ratio (IV, Fixed, 95% CI)	0.74 [0.59, 0.93]

Analysis 2.1. Comparison 2: Subanalysis: agents directly targeting IL-13, Outcome 1: Exacerbation requiring hospitalisation or ED visit

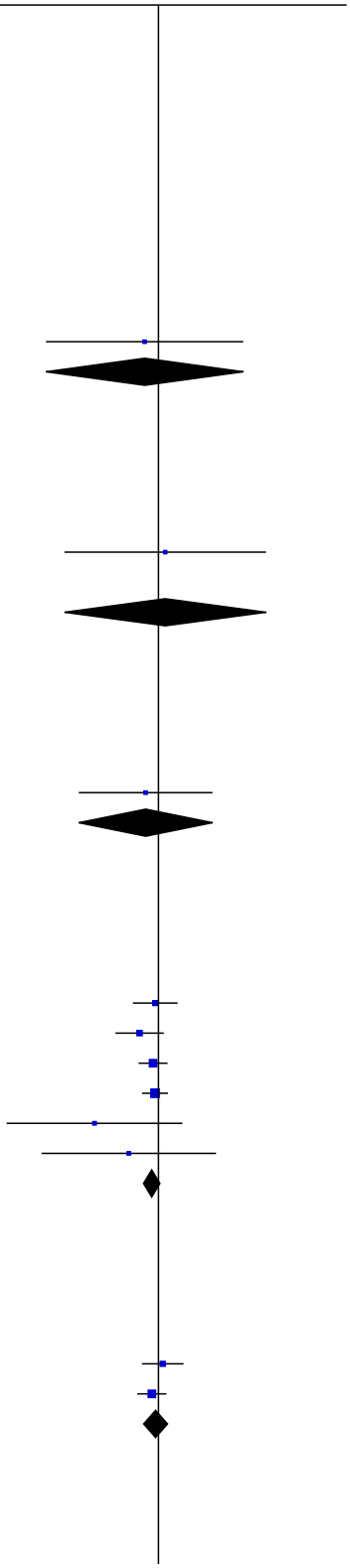


Analysis 2.2. Comparison 2: Subanalysis: agents directly targeting IL-13, Outcome 2: Health-related quality of life (adjusted mean diff versus placebo)



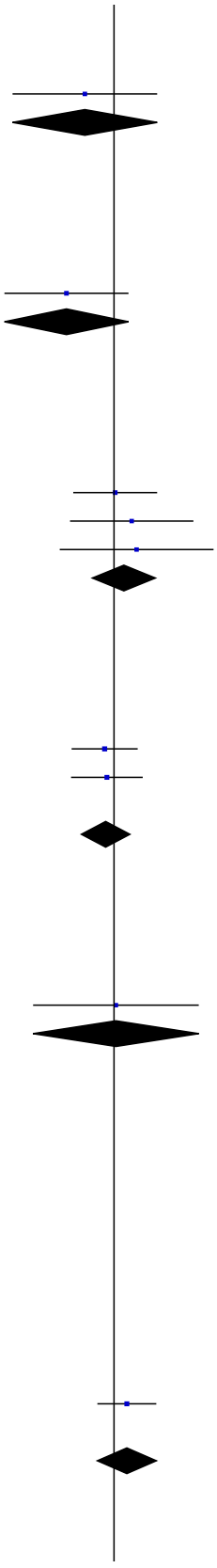
Analysis 2.3. Comparison 2: Subanalysis: agents directly targeting IL-13, Outcome 3: Serious adverse events

Study or Subgroup	Anti-IL-13 or -4 Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.3.1 Tralokinumab 1 mg/kg IV Q4W						
NCT00640016	0	2	0	1		Not estimable
Singh 2010	0	8	0	1		Not estimable
Subtotal (95% CI)		**10**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.3.2 Tralokinumab 5 mg/kg IV Q4W						
NCT00640016	0	4	0	1		Not estimable
Singh 2010	1	8	0	1	0.4%	0.60 [0.02 , 23.07]
Subtotal (95% CI)		**12**		**2**	**0.4%**	**0.60 [0.02 , 23.07]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.78)						
2.3.3 Tralokinumab 10 mg/kg IV Q4W						
NCT00640016	1	4	0	1	0.3%	1.29 [0.03 , 53.51]
Singh 2010	0	3	0	2		Not estimable
Subtotal (95% CI)		**7**		**3**	**0.3%**	**1.29 [0.03 , 53.51]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.89)						
2.3.4 Tralokinumab 150 mg SC Q2W						
Piper 2013	2	47	1	15	0.9%	0.62 [0.05 , 7.39]
Subtotal (95% CI)		**47**		**15**	**0.9%**	**0.62 [0.05 , 7.39]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.71)						
2.3.5 Tralokinumab 300 mg SC Q2W						
Brightling 2015	18	150	10	75	7.1%	0.89 [0.39 , 2.03]
Busse 2015	9	70	16	70	8.4%	0.50 [0.20 , 1.22]
Pannetieri 2018A	40	398	24	200	17.4%	0.82 [0.48 , 1.40]
Pannetieri 2018B	35	425	39	422	21.7%	0.88 [0.55 , 1.42]
Piper 2013	0	51	1	15	1.4%	0.09 [0.00 , 2.43]
Russell 2018	0	39	1	40	0.9%	0.33 [0.01 , 8.43]
Subtotal (95% CI)		**1133**		**822**	**56.9%**	**0.78 [0.58 , 1.05]**
Total events:	102		91			
Heterogeneity: $Chi^2 = 3.24$, df = 5 (P = 0.66); $I^2 = 0\%$						
Test for overall effect: Z = 1.62 (P = 0.11)						
2.3.6 Tralokinumab 300 mg SC Q4W						
Brightling 2015	25	151	11	76	7.4%	1.17 [0.54 , 2.53]
Pannetieri 2018A	39	404	24	200	17.6%	0.78 [0.46 , 1.34]
Subtotal (95% CI)		**555**		**276**	**24.9%**	**0.90 [0.58 , 1.40]**
Total events:	64		35			
Heterogeneity: $Chi^2 = 0.71$, df = 1 (P = 0.40); $I^2 = 0\%$						
Test for overall effect: Z = 0.47 (P = 0.63)						



Analysis 2.3. (Continued)

Test for overall effect: Z = 0.47 (P = 0.63)



2.3.7 Tralokinumab 600 mg SC Q2W						
Piper 2013	1	48	1	16	0.9%	0.32 [0.02 , 5.42]
Subtotal (95% CI)		**48**		**16**	**0.9%**	**0.32 [0.02 , 5.42]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
2.3.8 Lebrikizumab 37.5 mg SC Q4W						
Hanania 2015a	1	117	2	38	1.8%	0.16 [0.01 , 1.76]
Subtotal (95% CI)		**117**		**38**	**1.8%**	**0.16 [0.01 , 1.76]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
2.3.9 Lebrikizumab 125 mg SC Q4W						
Hanania 2015a	6	112	2	39	1.7%	1.05 [0.20 , 5.42]
Korenblat 2018	2	104	1	103	0.6%	2.00 [0.18 , 22.40]
Noonan 2013	3	53	0	17	0.4%	2.43 [0.12 , 49.34]
Subtotal (95% CI)		**269**		**159**	**2.7%**	**1.47 [0.43 , 5.05]**
Total events:	11		3			
Heterogeneity: $Chi^2 = 0.33$, df = 2 (P = 0.85); $I^2 = 0\%$						
Test for overall effect: Z = 0.61 (P = 0.54)						
2.3.10 Lebrikizumab 250 mg SC Q4W						
Corren 2011	4	106	6	112	3.4%	0.69 [0.19 , 2.53]
Hanania 2015a	7	118	3	39	2.6%	0.76 [0.19 , 3.08]
Noonan 2013	0	53	0	17		Not estimable
Subtotal (95% CI)		**277**		**168**	**6.0%**	**0.72 [0.28 , 1.86]**
Total events:	11		9			
Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0\%$						
Test for overall effect: Z = 0.68 (P = 0.50)						
2.3.11 Lebrikizumab 500 mg SC Q4W						
Noonan 2013	1	52	0	18	0.4%	1.08 [0.04 , 27.64]
Subtotal (95% CI)		**52**		**18**	**0.4%**	**1.08 [0.04 , 27.64]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
2.3.12 GSK679586 2.5 mg/kg IV Q4W						
Hodsman 2013	0	6	0	2		Not estimable
Subtotal (95% CI)		**6**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.3.13 GSK679586 10 mg/kg IV Q4W						
De Boever 2014	8	99	5	99	2.8%	1.65 [0.52 , 5.24]
Hodsman 2013	0	6	0	2		Not estimable
Subtotal (95% CI)		**105**		**101**	**2.8%**	**1.65 [0.52 , 5.24]**
Total events:	8		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.39)						

Analysis 2.3. (Continued)

Heterogeneity: Not applicable
Test for overall effect: Z = 0.85 (P = 0.39)

2.3.14 GSK679586 20 mg/kg IV Q4W

Hodsman 2013	1	9	0	3	0.4%	1.24 [0.04 , 38.30]	
Subtotal (95% CI)		**9**		**3**	**0.4%**	**1.24 [0.04 , 38.30]**	
Total events:	1		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.90)

2.3.15 RPC4046 0.3 mg/kg IV Q1W

Tripp 2017	0	4	0	2		Not estimable	
Subtotal (95% CI)		**4**		**2**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable

2.3.16 RPC4046 3 mg/kg IV Q1W

Tripp 2017	0	4	0	2		Not estimable	
Subtotal (95% CI)		**4**		**2**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable

2.3.17 IMA-638 IV 0.2 mg/kg (D1/8/28/56/84)

NCT00425061	0	16	0	5		Not estimable	
Subtotal (95% CI)		**16**		**5**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable

2.3.18 IMA-638 IV 0.6 mg/kg (D1/8/28/56/84)

NCT00425061	1	17	0	5	0.4%	1.00 [0.04 , 28.30]	
Subtotal (95% CI)		**17**		**5**	**0.4%**	**1.00 [0.04 , 28.30]**	
Total events:	1		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

2.3.19 IMA-638 IV 2 mg/kg (D1/8/28/56/84)

NCT00425061	2	16	1	6	0.8%	0.71 [0.05 , 9.70]	
Subtotal (95% CI)		**16**		**6**	**0.8%**	**0.71 [0.05 , 9.70]**	
Total events:	2		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)

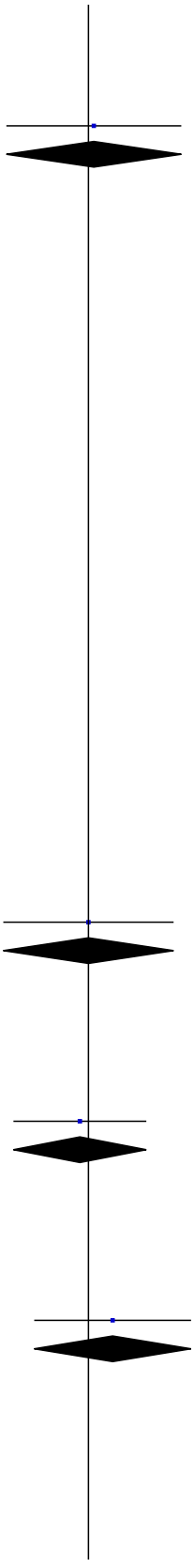
2.3.20 IMA-638 IV 200 mg SC (D1/8/28/42/56/70/84)

NCT00425061	2	45	0	22	0.4%	2.59 [0.12 , 56.20]	
Subtotal (95% CI)		**45**		**22**	**0.4%**	**2.59 [0.12 , 56.20]**	
Total events:	2		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)

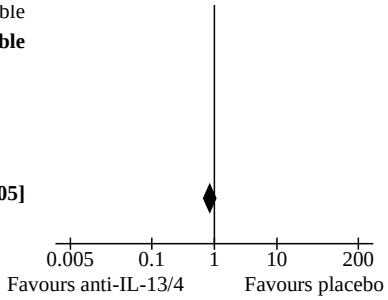
2.3.21 IMA-638 IV 75 mg SC (D1/8/28/42/56/70/84)

NCT00425061	0	4	0	23		Not estimable	
Subtotal (95% CI)		**4**		**23**		**Not estimable**	



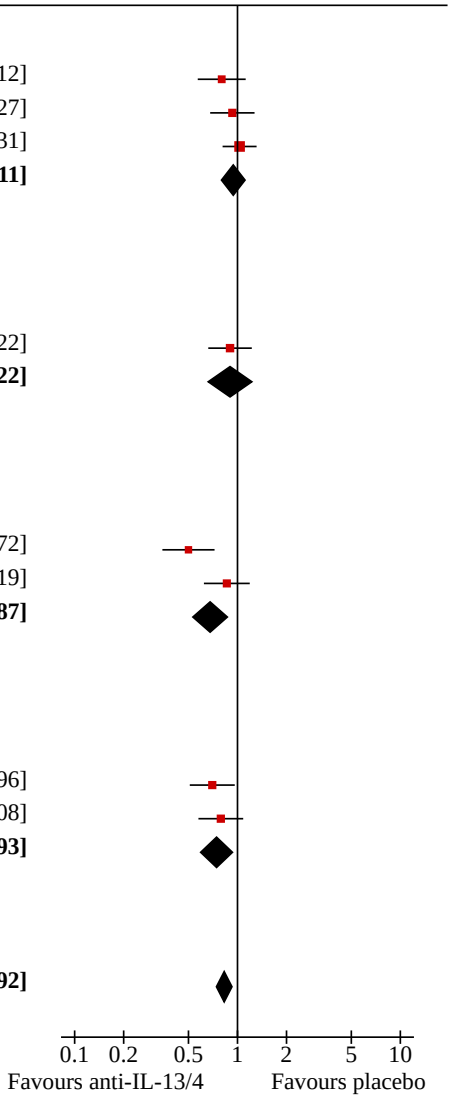
Analysis 2.3. (Continued)

NCT00425061	0	4	0	23		Not estimable
Subtotal (95% CI)		**4**		**23**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2753**		**1690**	**100.0%**	**0.84 [0.67 , 1.05]**
Total events:	209		148			
Heterogeneity: Chi² = 9.74, df = 23 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.50 (P = 0.13)						
Test for subgroup differences: Chi² = 5.60, df = 14 (P = 0.98), I² = 0%						



Analysis 2.4. Comparison 2: Subanalysis: agents directly targeting IL-13, Outcome 4: Exacerbation requiring hospitalisation/ED/OCS (rate ratio)

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI
2.4.1 Tralokinumab 300 mg SC Q2W				
Busse 2015	-0.2231	0.1729	10.4%	0.80 [0.57 , 1.12]
Pannetieri 2018A	-0.0726	0.16	12.2%	0.93 [0.68 , 1.27]
Pannetieri 2018B	0.0296	0.1226	20.7%	1.03 [0.81 , 1.31]
Subtotal (95% CI)			**43.3%**	**0.94 [0.80 , 1.11]**
Heterogeneity: Chi² = 1.43, df = 2 (P = 0.49); I² = 0%				
Test for overall effect: Z = 0.71 (P = 0.48)				
2.4.2 Tralokinumab 300 mg SC Q4W				
Pannetieri 2018A	-0.1054	0.157	12.6%	0.90 [0.66 , 1.22]
Subtotal (95% CI)			**12.6%**	**0.90 [0.66 , 1.22]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.67 (P = 0.50)				
2.4.3 Lebrikizumab 37.5 mg SC Q4W				
Hanania 2016a	-0.6931	0.1881	8.8%	0.50 [0.35 , 0.72]
Hanania 2016b	-0.1508	0.1653	11.4%	0.86 [0.62 , 1.19]
Subtotal (95% CI)			**20.2%**	**0.68 [0.53 , 0.87]**
Heterogeneity: Chi² = 4.69, df = 1 (P = 0.03); I² = 79%				
Test for overall effect: Z = 3.12 (P = 0.002)				
2.4.4 Lebrikizumab 125 mg SC Q4W				
Hanania 2016a	-0.3567	0.1622	11.8%	0.70 [0.51 , 0.96]
Hanania 2016b	-0.2357	0.1615	12.0%	0.79 [0.58 , 1.08]
Subtotal (95% CI)			**23.8%**	**0.74 [0.59 , 0.93]**
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%				
Test for overall effect: Z = 2.59 (P = 0.010)				
Total (95% CI)			**100.0%**	**0.83 [0.74 , 0.92]**
Heterogeneity: Chi² = 12.42, df = 7 (P = 0.09); I² = 44%				
Test for overall effect: Z = 3.37 (P = 0.0008)				
Test for subgroup differences: Chi² = 6.02, df = 3 (P = 0.11), I² = 50.2%				

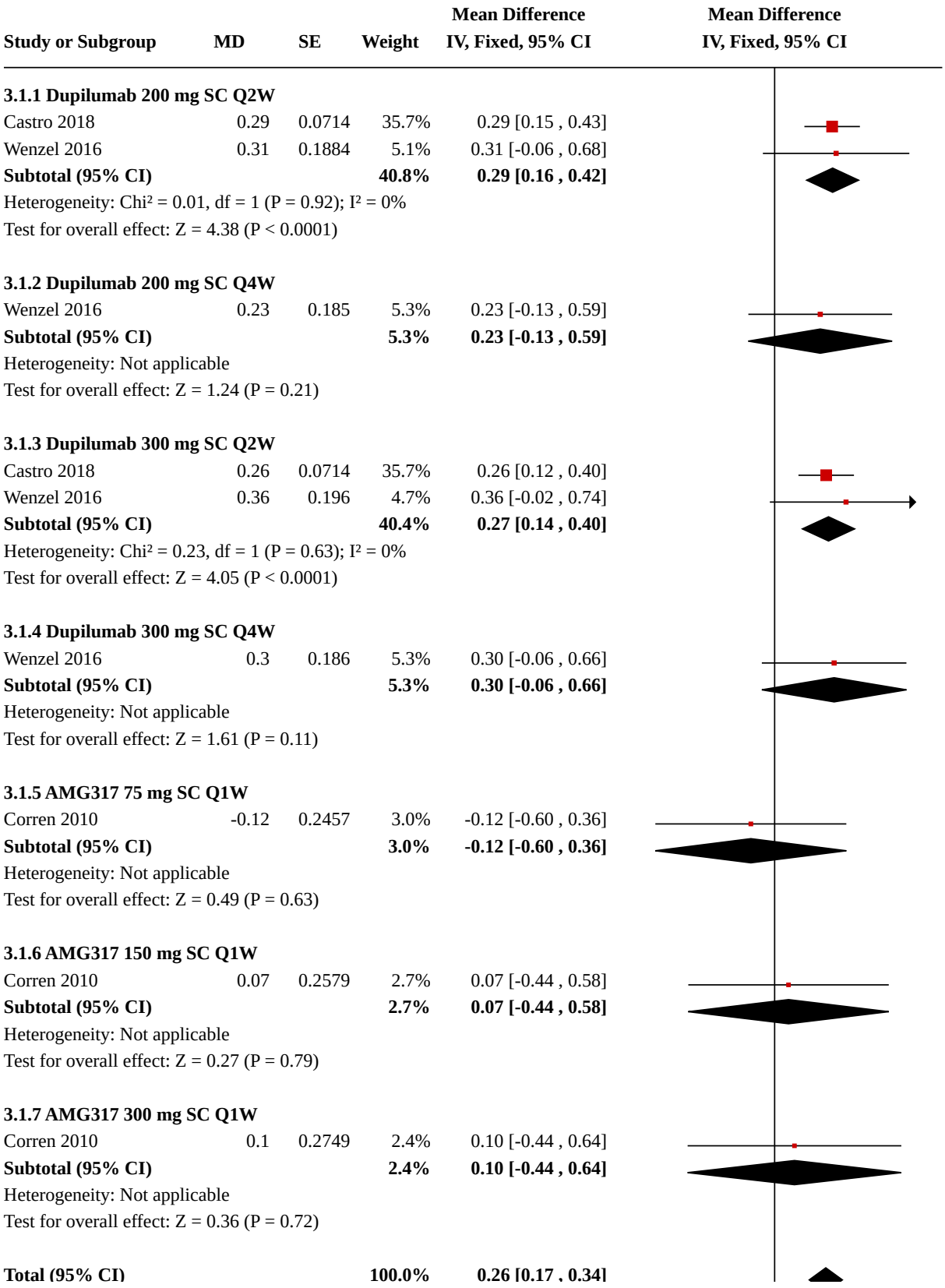


Comparison 3. Subanalysis: agents directly targeting IL-4R

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Health-related quality of life (adjusted mean diff versus placebo)	3		Mean Difference (IV, Fixed, 95% CI)	0.26 [0.17, 0.34]
3.1.1 Dupilumab 200 mg SC Q2W	2		Mean Difference (IV, Fixed, 95% CI)	0.29 [0.16, 0.42]
3.1.2 Dupilumab 200 mg SC Q4W	1		Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.13, 0.59]
3.1.3 Dupilumab 300 mg SC Q2W	2		Mean Difference (IV, Fixed, 95% CI)	0.27 [0.14, 0.40]
3.1.4 Dupilumab 300 mg SC Q4W	1		Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.06, 0.66]
3.1.5 AMG317 75 mg SC Q1W	1		Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.60, 0.36]
3.1.6 AMG317 150 mg SC Q1W	1		Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.44, 0.58]
3.1.7 AMG317 300 mg SC Q1W	1		Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.44, 0.64]
3.2 Serious adverse events	6	3296	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.78, 1.40]
3.2.1 Soluble IL-4R 500 ug nebulised	1	12	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2.2 Soluble IL-4R 1500 ug nebulised	1	13	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2.3 AMG317 75 mg SC Q1W	1	97	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.06, 7.91]
3.2.4 AMG317 150 mg SC Q1W	1	98	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2.5 AMG317 300 mg SC Q1W	1	96	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2.6 Dupilumab 300 mg SC Q1W	1	104	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.03, 3.18]
3.2.7 Dupilumab 200 mg SC Q2W	2	1131	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.60, 1.54]
3.2.8 Dupilumab 200 mg SC Q4W	1	189	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.15, 3.98]
3.2.9 Dupilumab 300 mg SC Q2W	3	1359	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.76, 1.77]
3.2.10 Dupilumab 300 mg SC Q4W	1	197	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.39, 5.06]
3.3 Exacerbation requiring hospitalisation/ED/OCS (rate ratio)	2		Rate Ratio (IV, Fixed, 95% CI)	0.52 [0.44, 0.61]

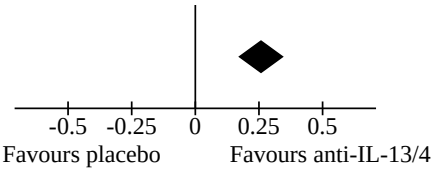
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.1 Dupilumab 200mg SC Q2W	2		Rate Ratio (IV, Fixed, 95% CI)	0.51 [0.40, 0.64]
3.3.2 Dupilumab 200 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.46 [0.18, 1.16]
3.3.3 Dupilumab 300mg SC Q2W	2		Rate Ratio (IV, Fixed, 95% CI)	0.52 [0.42, 0.65]
3.3.4 Dupilumab 300 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.67 [0.29, 1.55]

Analysis 3.1. Comparison 3: Subanalysis: agents directly targeting IL-4R, Outcome 1: Health-related quality of life (adjusted mean diff versus placebo)



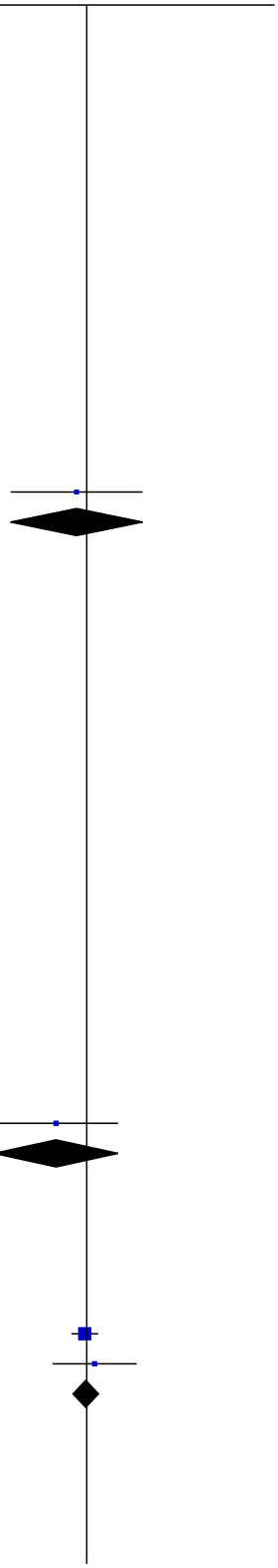
Analysis 3.1. (Continued)

Total (95% CI)	**100.0%**	**0.26 [0.17 , 0.34]**	
Heterogeneity: Chi² = 3.85, df = 8 (P = 0.87); I² = 0%			
Test for overall effect: Z = 6.05 (P < 0.00001)			
Test for subgroup differences: Chi² = 3.61, df = 6 (P = 0.73), I² = 0%			



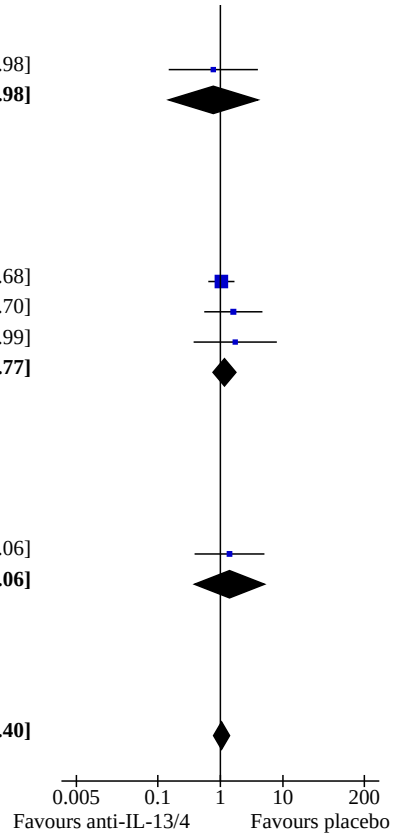
Analysis 3.2. Comparison 3: Subanalysis: agents directly targeting IL-4R, Outcome 2: Serious adverse events

Study or Subgroup	Anti-IL-13 or -4 Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.2.1 Soluble IL-4R 500 ug nebulised						
Borish 1999	0	8	0	4		Not estimable
Subtotal (95% CI)		**8**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.2.2 Soluble IL-4R 1500 ug nebulised						
Borish 1999	0	9	0	4		Not estimable
Subtotal (95% CI)		**9**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.2.3 AMG317 75 mg SC Q1W						
Corren 2010	2	72	1	25	1.6%	0.69 [0.06 , 7.91]
Subtotal (95% CI)		**72**		**25**	**1.6%**	**0.69 [0.06 , 7.91]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
3.2.4 AMG317 150 mg SC Q1W						
Corren 2010	0	73	0	25		Not estimable
Subtotal (95% CI)		**73**		**25**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.2.5 AMG317 300 mg SC Q1W						
Corren 2010	0	72	0	24		Not estimable
Subtotal (95% CI)		**72**		**24**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.2.6 Dupilumab 300 mg SC Q1W						
Wenzel 2013	1	52	3	52	3.4%	0.32 [0.03 , 3.18]
Subtotal (95% CI)		**52**		**52**	**3.4%**	**0.32 [0.03 , 3.18]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
3.2.7 Dupilumab 200 mg SC Q2W						
Castro 2018	49	631	26	313	36.5%	0.93 [0.57 , 1.53]
Wenzel 2016	10	148	2	39	3.4%	1.34 [0.28 , 6.39]
Subtotal (95% CI)		**779**		**352**	**39.9%**	**0.96 [0.60 , 1.54]**
Total events:	59		28			
Heterogeneity: $Chi^2 = 0.19$, df = 1 (P = 0.66); $I^2 = 0\%$						
Test for overall effect: Z = 0.15 (P = 0.88)						
3.2.8 Dupilumab 200 mg SC Q4W						

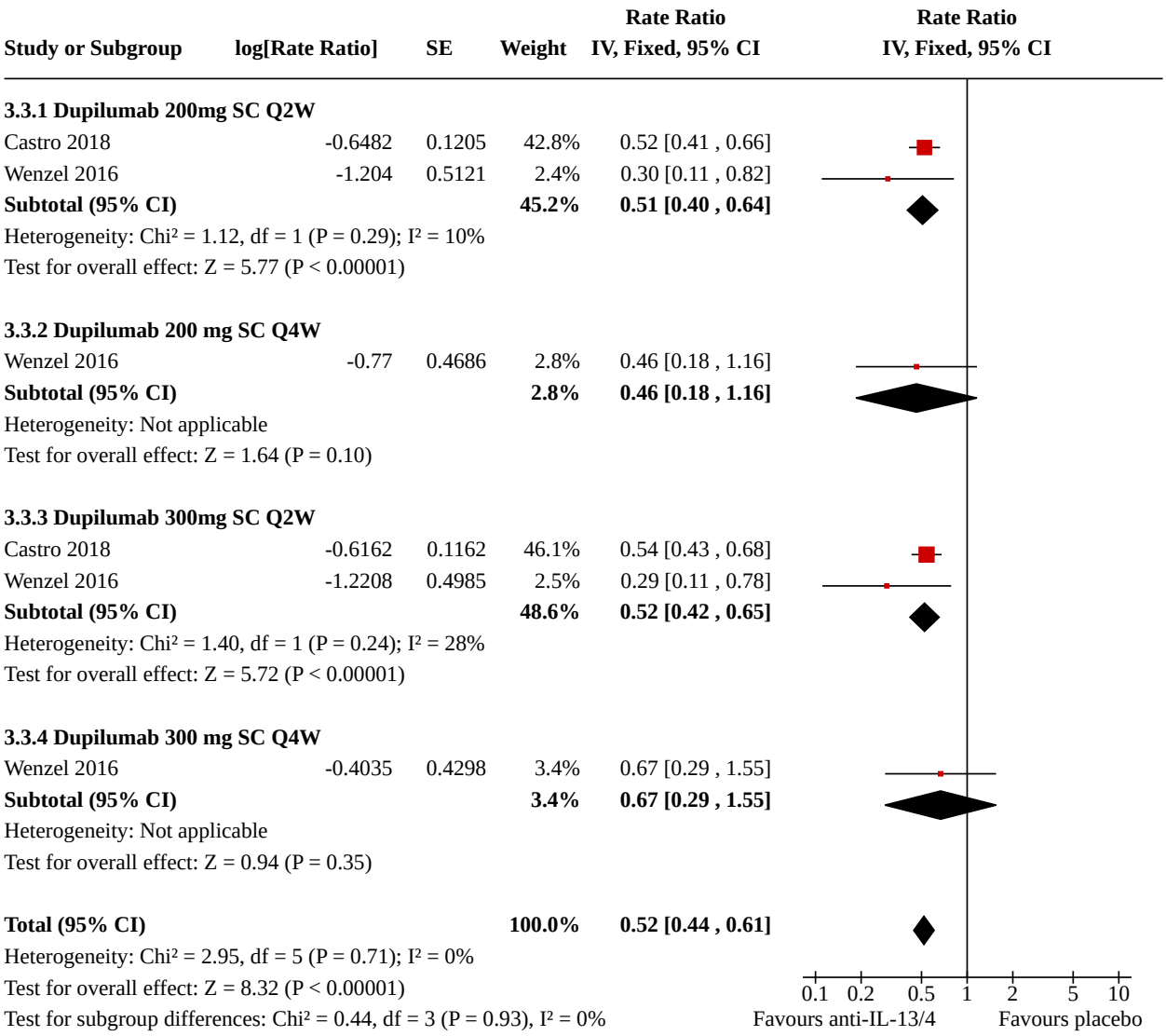


Analysis 3.2. (Continued)

3.2.8 Dupilumab 200 mg SC Q4W						
Wenzel 2016	6	150	2	39	3.5%	0.77 [0.15 , 3.98]
Subtotal (95% CI)		**150**		**39**	**3.5%**	**0.77 [0.15 , 3.98]**
Total events:	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
3.2.9 Dupilumab 300 mg SC Q2W						
Castro 2018	55	632	27	321	37.3%	1.04 [0.64 , 1.68]
Rabe 2018	9	103	6	107	6.1%	1.61 [0.55 , 4.70]
Wenzel 2016	13	156	2	40	3.3%	1.73 [0.37 , 7.99]
Subtotal (95% CI)		**891**		**468**	**46.7%**	**1.16 [0.76 , 1.77]**
Total events:	77		35			
Heterogeneity: Chi² = 0.83, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.48)						
3.2.10 Dupilumab 300 mg SC Q4W						
Wenzel 2016	16	157	3	40	4.9%	1.40 [0.39 , 5.06]
Subtotal (95% CI)		**157**		**40**	**4.9%**	**1.40 [0.39 , 5.06]**
Total events:	16		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
Total (95% CI)		**2263**		**1033**	**100.0%**	**1.05 [0.78 , 1.40]**
Total events:	161		72			
Heterogeneity: Chi² = 2.82, df = 8 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Test for subgroup differences: Chi² = 1.82, df = 5 (P = 0.87), I² = 0%						



Analysis 3.3. Comparison 3: Subanalysis: agents directly targeting IL-4R, Outcome 3: Exacerbation requiring hospitalisation/ED/OCS (rate ratio)



Comparison 4. Subanalysis: study duration <= 6 months

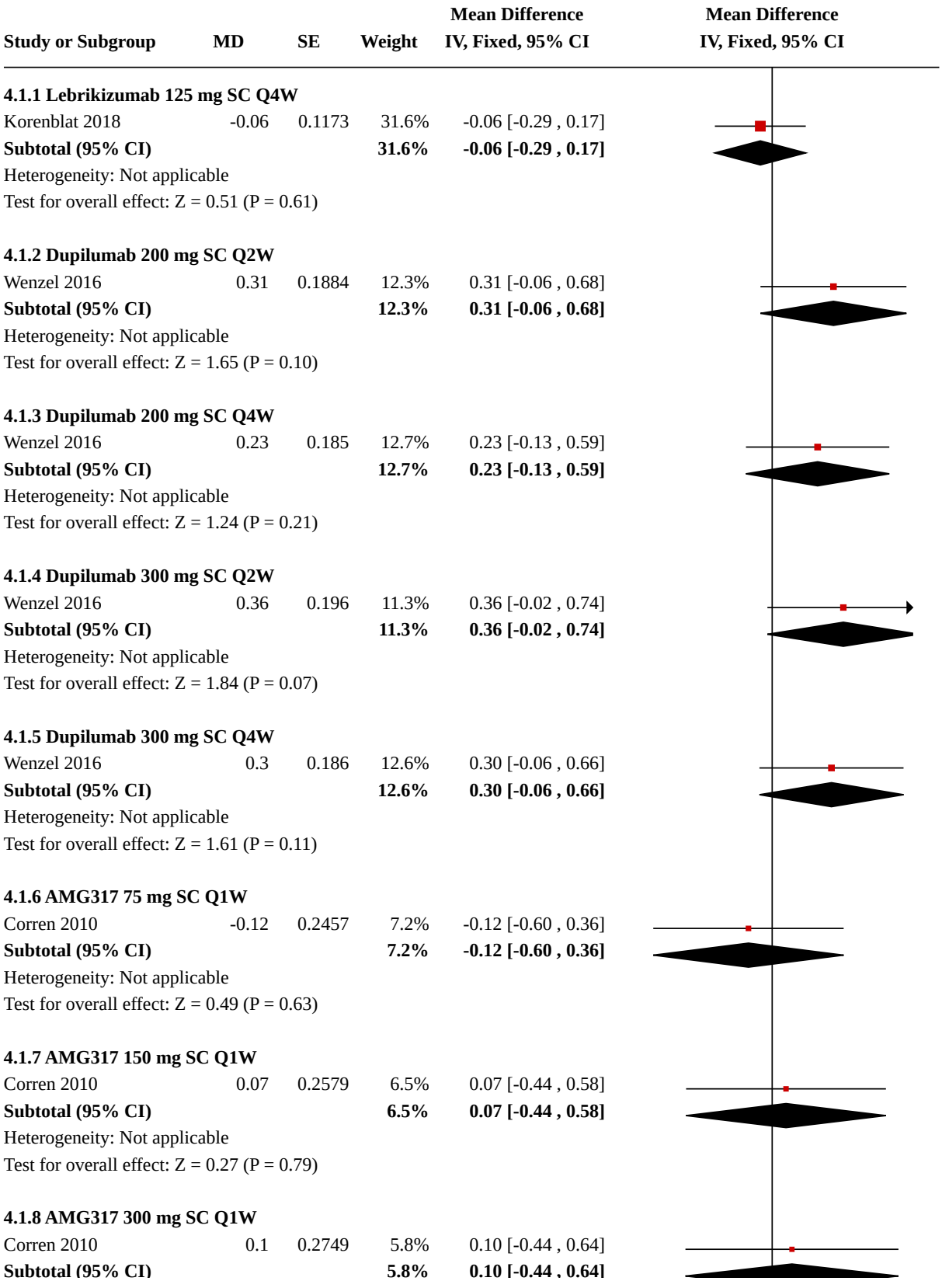
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Health-related quality of life (adjusted mean diff versus placebo)	3		Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.00, 0.26]
4.1.1 Lebrikizumab 125 mg SC Q4W	1		Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.29, 0.17]
4.1.2 Dupilumab 200 mg SC Q2W	1		Mean Difference (IV, Fixed, 95% CI)	0.31 [-0.06, 0.68]
4.1.3 Dupilumab 200 mg SC Q4W	1		Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.13, 0.59]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.4 Dupilumab 300 mg SC Q2W	1		Mean Difference (IV, Fixed, 95% CI)	0.36 [-0.02, 0.74]
4.1.5 Dupilumab 300 mg SC Q4W	1		Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.06, 0.66]
4.1.6 AMG317 75 mg SC Q1W	1		Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.60, 0.36]
4.1.7 AMG317 150 mg SC Q1W	1		Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.44, 0.58]
4.1.8 AMG317 300 mg SC Q1W	1		Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.44, 0.64]
4.2 Serious adverse events	16	2738	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.73, 1.63]
4.2.1 Soluble IL-4R 500 ug nebulised	1	12	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2.2 Soluble IL-4R 1500 ug nebulised	1	13	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2.3 Tralokinumab 1 mg/kg IV Q4W	2	12	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2.4 Tralokinumab 5 mg/kg IV Q4W	2	14	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.02, 23.07]
4.2.5 Tralokinumab 10 mg/kg IV Q4W	2	10	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.03, 53.51]
4.2.6 Tralokinumab 150 mg SC Q2W	1	62	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.05, 7.39]
4.2.7 Tralokinumab 300 mg SC Q2W	2	145	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.02, 1.89]
4.2.8 Tralokinumab 600 mg SC Q2W	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.02, 5.42]
4.2.9 Lebrikizumab 125 mg SC Q4W	2	277	Odds Ratio (M-H, Fixed, 95% CI)	2.18 [0.33, 14.31]
4.2.10 Lebrikizumab 250 mg SC Q4W	2	288	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.19, 2.53]
4.2.11 Lebrikizumab 500 mg SC Q4W	1	70	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.04, 27.64]
4.2.12 AMG317 75 mg SC Q1W	1	97	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.06, 7.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2.13 AMG317 150 mg SC Q1W	1	98	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2.14 AMG317 300 mg SC Q1W	1	96	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2.15 GSK679586 2.5 mg/kg IV Q4W	1	8	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2.16 GSK679586 10 mg/kg IV Q4W	2	206	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [0.52, 5.24]
4.2.17 GSK679586 20 mg/kg IV Q4W	1	12	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.04, 38.30]
4.2.18 RPC4046 0.3 mg/kg IV Q1W	1	6	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2.19 RPC4046 3 mg/kg IV Q1W	1	6	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2.20 Dupilumab 300 mg SC Q1W	1	104	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.03, 3.18]
4.2.21 Dupilumab 200 mg SC Q2W	1	187	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.28, 6.39]
4.2.22 Dupilumab 200 mg SC Q4W	1	189	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.15, 3.98]
4.2.23 Dupilumab 300 mg SC Q2W	2	406	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [0.69, 3.97]
4.2.24 Dupilumab 300 mg SC Q4W	1	197	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.39, 5.06]
4.2.25 IMA-638 IV 0.2 mg/kg (D1/8/28/56/84)	1	21	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2.26 IMA-638 IV 0.6 mg/kg (D1/8/28/56/84)	1	22	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.04, 28.30]
4.2.27 IMA-638 IV 2 mg/kg (D1/8/28/56/84)	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.05, 9.70]
4.2.28 IMA-638 IV 200 mg SC (D1/8/28/42/56/70/84)	1	67	Odds Ratio (M-H, Fixed, 95% CI)	2.59 [0.12, 56.20]
4.2.29 IMA-638 IV 75 mg SC (D1/8/28/42/56/70/84)	1	27	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3 Exacerbation requiring hospitalisation/ED/OCS (rate ratio)	1		Rate Ratio (IV, Fixed, 95% CI)	0.43 [0.27, 0.68]
4.3.1 Dupilumab 200mg SC Q2W	1		Rate Ratio (IV, Fixed, 95% CI)	0.30 [0.11, 0.82]

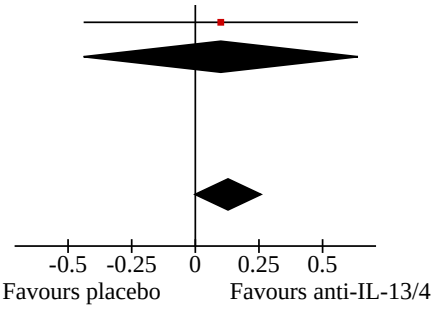
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3.2 Dupilumab 200 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.46 [0.18, 1.16]
4.3.3 Dupilumab 300mg SC Q2W	1		Rate Ratio (IV, Fixed, 95% CI)	0.29 [0.11, 0.78]
4.3.4 Dupilumab 300 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.67 [0.29, 1.55]

Analysis 4.1. Comparison 4: Subanalysis: study duration <= 6 months, Outcome 1: Health-related quality of life (adjusted mean diff versus placebo)



Analysis 4.1. (Continued)

Corren 2010	0.1	0.2749	5.8%	0.10 [-0.44 , 0.64]
Subtotal (95% CI)			**5.8%**	**0.10 [-0.44 , 0.64]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.36 (P = 0.72)				
Total (95% CI)			**100.0%**	**0.13 [-0.00 , 0.26]**
Heterogeneity: Chi² = 7.14, df = 7 (P = 0.41); I² = 2%				
Test for overall effect: Z = 1.95 (P = 0.05)				
Test for subgroup differences: Chi² = 7.14, df = 7 (P = 0.41), I² = 2.0%				

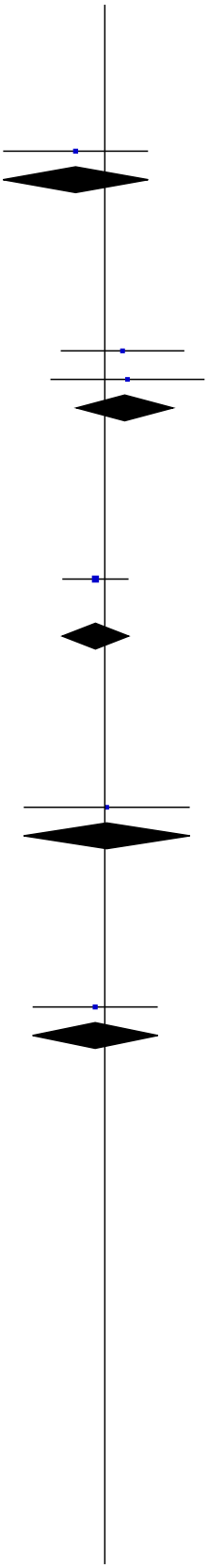


Analysis 4.2. Comparison 4: Subanalysis: study duration <= 6 months, Outcome 2: Serious adverse events

Study or Subgroup	Anti-IL-13 or -4 Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.2.1 Soluble IL-4R 500 ug nebulised						
Borish 1999	0	8	0	4		Not estimable
Subtotal (95% CI)		**8**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.2.2 Soluble IL-4R 1500 ug nebulised						
Borish 1999	0	9	0	4		Not estimable
Subtotal (95% CI)		**9**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.2.3 Tralokinumab 1 mg/kg IV Q4W						
NCT00640016	0	2	0	1		Not estimable
Singh 2010	0	8	0	1		Not estimable
Subtotal (95% CI)		**10**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.2.4 Tralokinumab 5 mg/kg IV Q4W						
NCT00640016	0	4	0	1		Not estimable
Singh 2010	1	8	0	1	1.5%	0.60 [0.02 , 23.07]
Subtotal (95% CI)		**12**		**2**	**1.5%**	**0.60 [0.02 , 23.07]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.78)						
4.2.5 Tralokinumab 10 mg/kg IV Q4W						
NCT00640016	1	4	0	1	1.1%	1.29 [0.03 , 53.51]
Singh 2010	0	3	0	2		Not estimable
Subtotal (95% CI)		**7**		**3**	**1.1%**	**1.29 [0.03 , 53.51]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.89)						
4.2.6 Tralokinumab 150 mg SC Q2W						
Piper 2013	2	47	1	15	3.1%	0.62 [0.05 , 7.39]
Subtotal (95% CI)		**47**		**15**	**3.1%**	**0.62 [0.05 , 7.39]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.71)						
4.2.7 Tralokinumab 300 mg SC Q2W						
Piper 2013	0	51	1	15	4.9%	0.09 [0.00 , 2.43]
Russell 2018	0	39	1	40	3.1%	0.33 [0.01 , 8.43]
Subtotal (95% CI)		**90**		**55**	**8.0%**	**0.19 [0.02 , 1.89]**
Total events:	0		2			
Heterogeneity: Chi² = 0.30, df = 1 (P = 0.59); I² = 0%						

Analysis 4.2. (Continued)

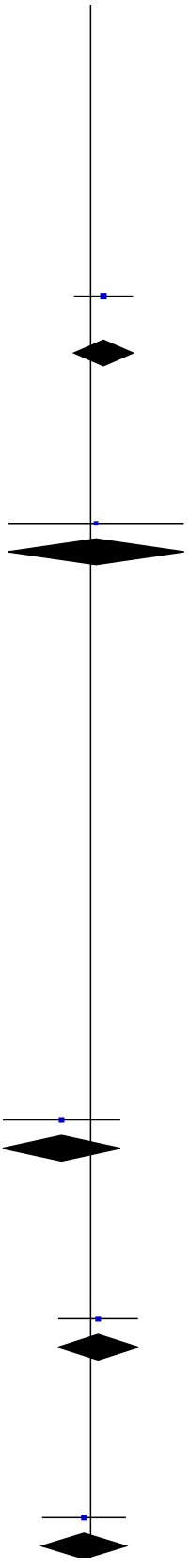
Total events:	0		2			
Heterogeneity: Chi² = 0.30, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 1.42 (P = 0.16)						
4.2.8 Tralokinumab 600 mg SC Q2W						
Piper 2013	1	48	1	16	3.2%	0.32 [0.02 , 5.42]
Subtotal (95% CI)		**48**		**16**	**3.2%**	**0.32 [0.02 , 5.42]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
4.2.9 Lebrikizumab 125 mg SC Q4W						
Korenblat 2018	2	104	1	103	2.1%	2.00 [0.18 , 22.40]
Noonan 2013	3	53	0	17	1.5%	2.43 [0.12 , 49.34]
Subtotal (95% CI)		**157**		**120**	**3.6%**	**2.18 [0.33 , 14.31]**
Total events:	5		1			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 0.81 (P = 0.42)						
4.2.10 Lebrikizumab 250 mg SC Q4W						
Corren 2011	4	106	6	112	12.0%	0.69 [0.19 , 2.53]
Noonan 2013	0	53	0	17		Not estimable
Subtotal (95% CI)		**159**		**129**	**12.0%**	**0.69 [0.19 , 2.53]**
Total events:	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
4.2.11 Lebrikizumab 500 mg SC Q4W						
Noonan 2013	1	52	0	18	1.5%	1.08 [0.04 , 27.64]
Subtotal (95% CI)		**52**		**18**	**1.5%**	**1.08 [0.04 , 27.64]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
4.2.12 AMG317 75 mg SC Q1W						
Corren 2010	2	72	1	25	3.1%	0.69 [0.06 , 7.91]
Subtotal (95% CI)		**72**		**25**	**3.1%**	**0.69 [0.06 , 7.91]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
4.2.13 AMG317 150 mg SC Q1W						
Corren 2010	0	73	0	25		Not estimable
Subtotal (95% CI)		**73**		**25**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.2.14 AMG317 300 mg SC Q1W						
Corren 2010	0	72	0	24		Not estimable
Subtotal (95% CI)		**72**		**24**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Analysis 4.2. (Continued)

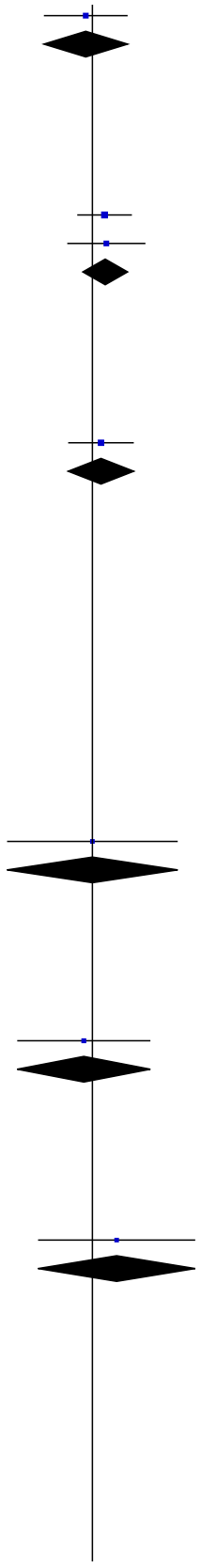
Test for overall effect: Not applicable

4.2.15 GSK679586 2.5 mg/kg IV Q4W						
Hodsman 2013	0	6	0	2		Not estimable
Subtotal (95% CI)		**6**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.2.16 GSK679586 10 mg/kg IV Q4W						
De Boever 2014	8	99	5	99	9.9%	1.65 [0.52 , 5.24]
Hodsman 2013	0	6	0	2		Not estimable
Subtotal (95% CI)		**105**		**101**	**9.9%**	**1.65 [0.52 , 5.24]**
Total events:	8		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.39)						
4.2.17 GSK679586 20 mg/kg IV Q4W						
Hodsman 2013	1	9	0	3	1.3%	1.24 [0.04 , 38.30]
Subtotal (95% CI)		**9**		**3**	**1.3%**	**1.24 [0.04 , 38.30]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.90)						
4.2.18 RPC4046 0.3 mg/kg IV Q1W						
Tripp 2017	0	4	0	2		Not estimable
Subtotal (95% CI)		**4**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.2.19 RPC4046 3 mg/kg IV Q1W						
Tripp 2017	0	4	0	2		Not estimable
Subtotal (95% CI)		**4**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.2.20 Dupilumab 300 mg SC Q1W						
Wenzel 2013	1	52	3	52	6.3%	0.32 [0.03 , 3.18]
Subtotal (95% CI)		**52**		**52**	**6.3%**	**0.32 [0.03 , 3.18]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
4.2.21 Dupilumab 200 mg SC Q2W						
Wenzel 2016	10	148	2	39	6.3%	1.34 [0.28 , 6.39]
Subtotal (95% CI)		**148**		**39**	**6.3%**	**1.34 [0.28 , 6.39]**
Total events:	10		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
4.2.22 Dupilumab 200 mg SC Q4W						
Wenzel 2016	6	150	2	39	6.5%	0.77 [0.15 , 3.98]
Subtotal (95% CI)		**150**		**39**	**6.5%**	**0.77 [0.15 , 3.98]**



Analysis 4.2. (Continued)

Wenzel 2016	6	150	2	39	6.5%	0.77 [0.15 , 3.98]
Subtotal (95% CI)		**150**		**39**	**6.5%**	**0.77 [0.15 , 3.98]**
Total events:	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
4.2.23 Dupilumab 300 mg SC Q2W						
Rabe 2018	9	103	6	107	11.5%	1.61 [0.55 , 4.70]
Wenzel 2016	13	156	2	40	6.3%	1.73 [0.37 , 7.99]
Subtotal (95% CI)		**259**		**147**	**17.8%**	**1.65 [0.69 , 3.97]**
Total events:	22		8			
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.94); I^2 = 0%						
Test for overall effect: Z = 1.12 (P = 0.26)						
4.2.24 Dupilumab 300 mg SC Q4W						
Wenzel 2016	16	157	3	40	9.2%	1.40 [0.39 , 5.06]
Subtotal (95% CI)		**157**		**40**	**9.2%**	**1.40 [0.39 , 5.06]**
Total events:	16		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
4.2.25 IMA-638 IV 0.2 mg/kg (D1/8/28/56/84)						
NCT00425061	0	16	0	5		Not estimable
Subtotal (95% CI)		**16**		**5**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.2.26 IMA-638 IV 0.6 mg/kg (D1/8/28/56/84)						
NCT00425061	1	17	0	5	1.5%	1.00 [0.04 , 28.30]
Subtotal (95% CI)		**17**		**5**	**1.5%**	**1.00 [0.04 , 28.30]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
4.2.27 IMA-638 IV 2 mg/kg (D1/8/28/56/84)						
NCT00425061	2	16	1	6	2.7%	0.71 [0.05 , 9.70]
Subtotal (95% CI)		**16**		**6**	**2.7%**	**0.71 [0.05 , 9.70]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
4.2.28 IMA-638 IV 200 mg SC (D1/8/28/42/56/70/84)						
NCT00425061	2	45	0	22	1.4%	2.59 [0.12 , 56.20]
Subtotal (95% CI)		**45**		**22**	**1.4%**	**2.59 [0.12 , 56.20]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
4.2.29 IMA-638 IV 75 mg SC (D1/8/28/42/56/70/84)						
NCT00425061	0	4	0	23		Not estimable
Subtotal (95% CI)		**4**		**23**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

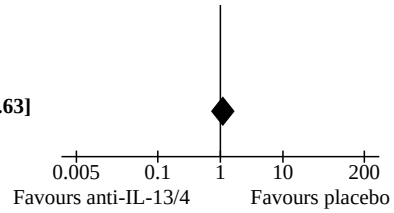


Analysis 4.2. (Continued)

Heterogeneity: Not applicable
Test for overall effect: Not applicable

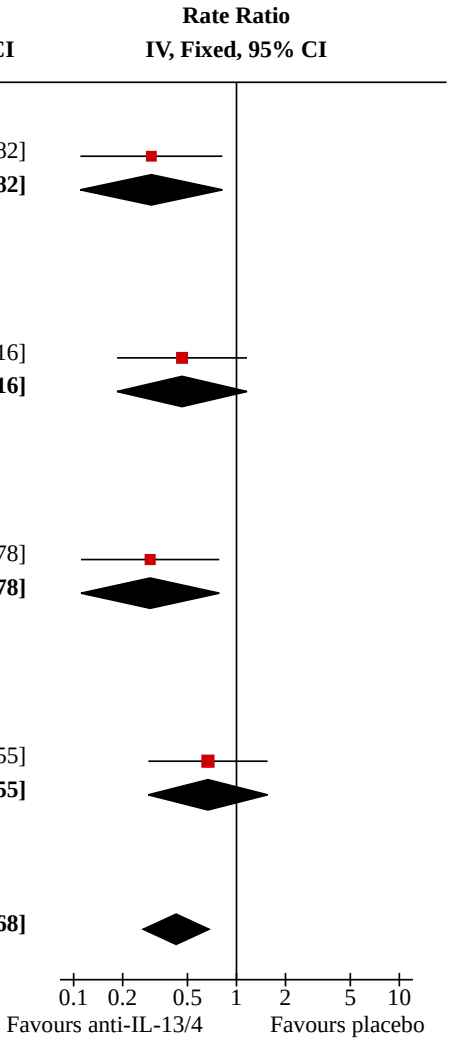
Total (95% CI)	**1808**	**930**	**100.0%**	**1.09 [0.73 , 1.63]**	
Total events:	86	36			

Heterogeneity: Chi² = 8.10, df = 21 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Chi² = 7.63, df = 18 (P = 0.98), I² = 0%



Analysis 4.3. Comparison 4: Subanalysis: study duration <= 6 months, Outcome 3: Exacerbation requiring hospitalisation/ED/OCS (rate ratio)

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI
4.3.1 Dupilumab 200mg SC Q2W				
Wenzel 2016	-1.204	0.5121	21.4%	0.30 [0.11 , 0.82]
Subtotal (95% CI)			**21.4%**	**0.30 [0.11 , 0.82]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.35 (P = 0.02)				
4.3.2 Dupilumab 200 mg SC Q4W				
Wenzel 2016	-0.77	0.4686	25.6%	0.46 [0.18 , 1.16]
Subtotal (95% CI)			**25.6%**	**0.46 [0.18 , 1.16]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.64 (P = 0.10)				
4.3.3 Dupilumab 300mg SC Q2W				
Wenzel 2016	-1.2208	0.4985	22.6%	0.29 [0.11 , 0.78]
Subtotal (95% CI)			**22.6%**	**0.29 [0.11 , 0.78]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.45 (P = 0.01)				
4.3.4 Dupilumab 300 mg SC Q4W				
Wenzel 2016	-0.4035	0.4298	30.4%	0.67 [0.29 , 1.55]
Subtotal (95% CI)			**30.4%**	**0.67 [0.29 , 1.55]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.94 (P = 0.35)				
Total (95% CI)			**100.0%**	**0.43 [0.27 , 0.68]**
Heterogeneity: Chi² = 2.14, df = 3 (P = 0.54); I² = 0%				
Test for overall effect: Z = 3.60 (P = 0.0003)				
Test for subgroup differences: Chi² = 2.14, df = 3 (P = 0.54), I² = 0%				

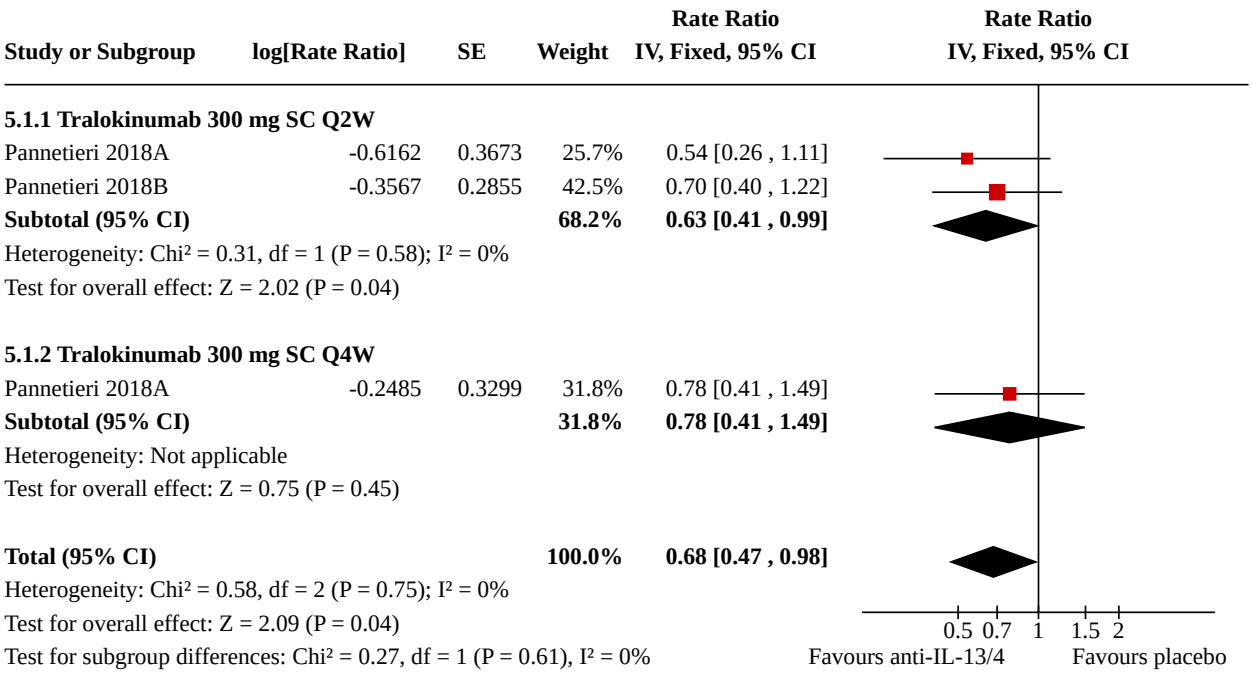


Comparison 5. Subanalysis: study duration > 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Exacerbation requiring hospitalisation or ED visit	2		Rate Ratio (IV, Fixed, 95% CI)	0.68 [0.47, 0.98]
5.1.1 Tralokinumab 300 mg SC Q2W	2		Rate Ratio (IV, Fixed, 95% CI)	0.63 [0.41, 0.99]
5.1.2 Tralokinumab 300 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.78 [0.41, 1.49]
5.2 Health-related quality of life (adjusted mean diff versus placebo)	4		Mean Difference (IV, Fixed, 95% CI)	0.19 [0.13, 0.26]
5.2.1 Dupilumab 200 mg SC Q2W	1		Mean Difference (IV, Fixed, 95% CI)	0.29 [0.15, 0.43]
5.2.2 Dupilumab 300 mg SC Q2W	1		Mean Difference (IV, Fixed, 95% CI)	0.26 [0.12, 0.40]
5.2.3 Tralokinumab 300 mg SC Q2W	3		Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.00, 0.23]
5.2.4 Tralokinumab 300 mg SC Q4W	2		Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.02, 0.30]
5.3 Serious adverse events	6	5001	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.72, 1.06]
5.3.1 Tralokinumab 300 mg SC Q2W	4	1810	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.59, 1.09]
5.3.2 Tralokinumab 300 mg SC Q4W	2	831	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.58, 1.40]
5.3.3 Lebrikizumab 37.5 mg SC Q4W	1	155	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 1.76]
5.3.4 Lebrikizumab 125 mg SC Q4W	1	151	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.20, 5.42]
5.3.5 Lebrikizumab 250 mg SC Q4W	1	157	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.19, 3.08]
5.3.6 Dupilumab 200 mg SC Q2W	1	944	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.57, 1.53]
5.3.7 Dupilumab 200 mg SC Q4W	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3.8 Dupilumab 300 mg SC Q2W	1	953	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.64, 1.68]
5.4 Exacerbation requiring hospitalisation/ED/OCS (rate ratio)	6		Rate Ratio (IV, Fixed, 95% CI)	0.72 [0.66, 0.79]

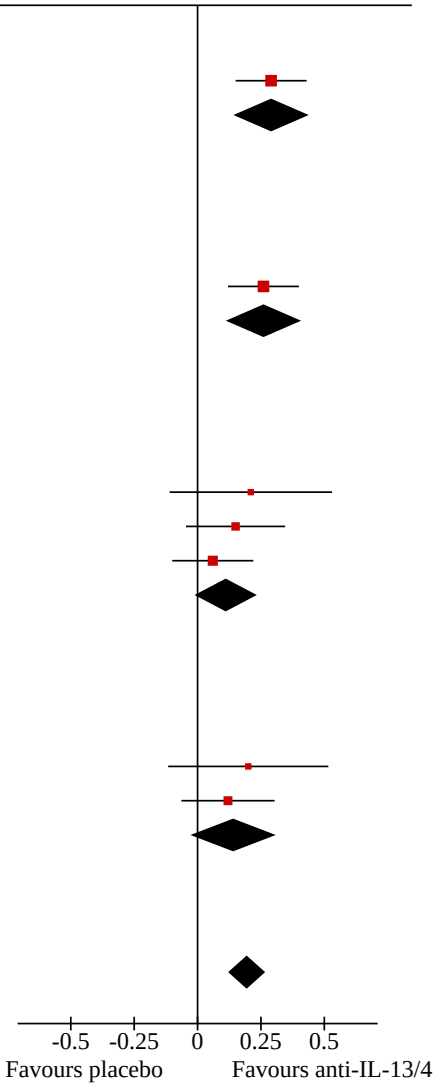
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.4.1 Tralokinumab 300 mg SC Q2W	3		Rate Ratio (IV, Fixed, 95% CI)	0.94 [0.80, 1.11]
5.4.2 Tralokinumab 300 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.90 [0.66, 1.22]
5.4.3 Lebrikizumab 37.5 mg SC Q4W	2		Rate Ratio (IV, Fixed, 95% CI)	0.68 [0.53, 0.87]
5.4.4 Lebrikizumab 125 mg SC Q4W	2		Rate Ratio (IV, Fixed, 95% CI)	0.74 [0.59, 0.93]
5.4.5 Dupilumab 200mg SC Q2W	1		Rate Ratio (IV, Fixed, 95% CI)	0.52 [0.41, 0.66]
5.4.6 Dupilumab 300mg SC Q2W	1		Rate Ratio (IV, Fixed, 95% CI)	0.54 [0.43, 0.68]

Analysis 5.1. Comparison 5: Subanalysis: study duration > 6 months, Outcome 1: Exacerbation requiring hospitalisation or ED visit



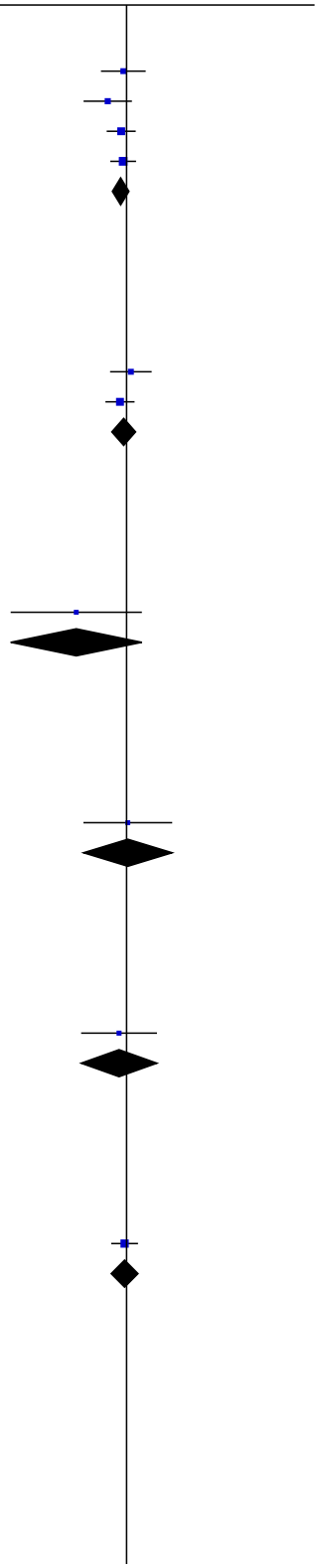
Analysis 5.2. Comparison 5: Subanalysis: study duration > 6 months, Outcome 2: Health-related quality of life (adjusted mean diff versus placebo)

Study or Subgroup	MD	SE	Weight	Mean Difference IV, Fixed, 95% CI
5.2.1 Dupilumab 200 mg SC Q2W				
Castro 2018	0.29	0.0714	23.6%	0.29 [0.15 , 0.43]
Subtotal (95% CI)			**23.6%**	**0.29 [0.15 , 0.43]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 4.06 (P < 0.0001)				
5.2.2 Dupilumab 300 mg SC Q2W				
Castro 2018	0.26	0.0714	23.6%	0.26 [0.12 , 0.40]
Subtotal (95% CI)			**23.6%**	**0.26 [0.12 , 0.40]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 3.64 (P = 0.0003)				
5.2.3 Tralokinumab 300 mg SC Q2W				
Brightling 2015	0.21	0.1633	4.5%	0.21 [-0.11 , 0.53]
Pannetieri 2018A	0.15	0.0998	12.1%	0.15 [-0.05 , 0.35]
Pannetieri 2018B	0.06	0.0816	18.0%	0.06 [-0.10 , 0.22]
Subtotal (95% CI)			**34.6%**	**0.11 [-0.00 , 0.23]**
Heterogeneity: Chi² = 0.91, df = 2 (P = 0.63); I² = 0%				
Test for overall effect: Z = 1.88 (P = 0.06)				
5.2.4 Tralokinumab 300 mg SC Q4W				
Brightling 2015	0.2	0.1612	4.6%	0.20 [-0.12 , 0.52]
Pannetieri 2018A	0.12	0.0937	13.7%	0.12 [-0.06 , 0.30]
Subtotal (95% CI)			**18.3%**	**0.14 [-0.02 , 0.30]**
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%				
Test for overall effect: Z = 1.73 (P = 0.08)				
Total (95% CI)			**100.0%**	**0.19 [0.13 , 0.26]**
Heterogeneity: Chi² = 6.19, df = 6 (P = 0.40); I² = 3%				
Test for overall effect: Z = 5.59 (P < 0.00001)				
Test for subgroup differences: Chi² = 5.09, df = 3 (P = 0.17), I² = 41.1%				



Analysis 5.3. Comparison 5: Subanalysis: study duration > 6 months, Outcome 3: Serious adverse events

Study or Subgroup	Anti-IL -13 or -4 Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
5.3.1 Tralokinumab 300 mg SC Q2W						
Brightling 2015	18	150	10	75	5.7%	0.89 [0.39 , 2.03]
Busse 2015	9	70	16	70	6.8%	0.50 [0.20 , 1.22]
Pannetieri 2018A	40	398	24	200	13.9%	0.82 [0.48 , 1.40]
Pannetieri 2018B	35	425	39	422	17.4%	0.88 [0.55 , 1.42]
Subtotal (95% CI)		**1043**		**767**	**43.8%**	**0.80 [0.59 , 1.09]**
Total events:	102		89			
Heterogeneity: Chi² = 1.30, df = 3 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.40 (P = 0.16)						
5.3.2 Tralokinumab 300 mg SC Q4W						
Brightling 2015	25	151	11	76	5.9%	1.17 [0.54 , 2.53]
Pannetieri 2018A	39	404	24	200	14.1%	0.78 [0.46 , 1.34]
Subtotal (95% CI)		**555**		**276**	**20.0%**	**0.90 [0.58 , 1.40]**
Total events:	64		35			
Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.63)						
5.3.3 Lebrikizumab 37.5 mg SC Q4W						
Hanania 2015a	1	117	2	38	1.5%	0.16 [0.01 , 1.76]
Subtotal (95% CI)		**117**		**38**	**1.5%**	**0.16 [0.01 , 1.76]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
5.3.4 Lebrikizumab 125 mg SC Q4W						
Hanania 2015a	6	112	2	39	1.4%	1.05 [0.20 , 5.42]
Subtotal (95% CI)		**112**		**39**	**1.4%**	**1.05 [0.20 , 5.42]**
Total events:	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
5.3.5 Lebrikizumab 250 mg SC Q4W						
Hanania 2015a	7	118	3	39	2.1%	0.76 [0.19 , 3.08]
Subtotal (95% CI)		**118**		**39**	**2.1%**	**0.76 [0.19 , 3.08]**
Total events:	7		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
5.3.6 Dupilumab 200 mg SC Q2W						
Castro 2018	49	631	26	313	15.5%	0.93 [0.57 , 1.53]
Subtotal (95% CI)		**631**		**313**	**15.5%**	**0.93 [0.57 , 1.53]**
Total events:	49		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
5.3.7 Dupilumab 200 mg SC Q4W						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Analysis 5.3. (Continued)

Heterogeneity: Not applicable
Test for overall effect: Not applicable

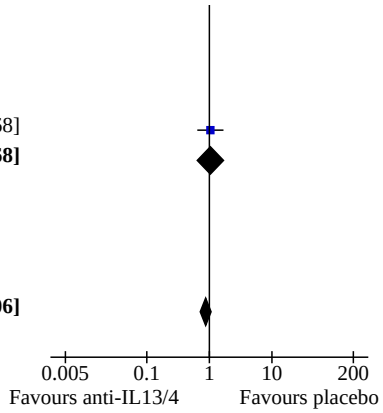
5.3.8 Dupilumab 300 mg SC Q2W

Castro 2018	55	632	27	321	15.8%	1.04 [0.64 , 1.68]
Subtotal (95% CI)		**632**		**321**	**15.8%**	**1.04 [0.64 , 1.68]**
Total events:	55		27			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)

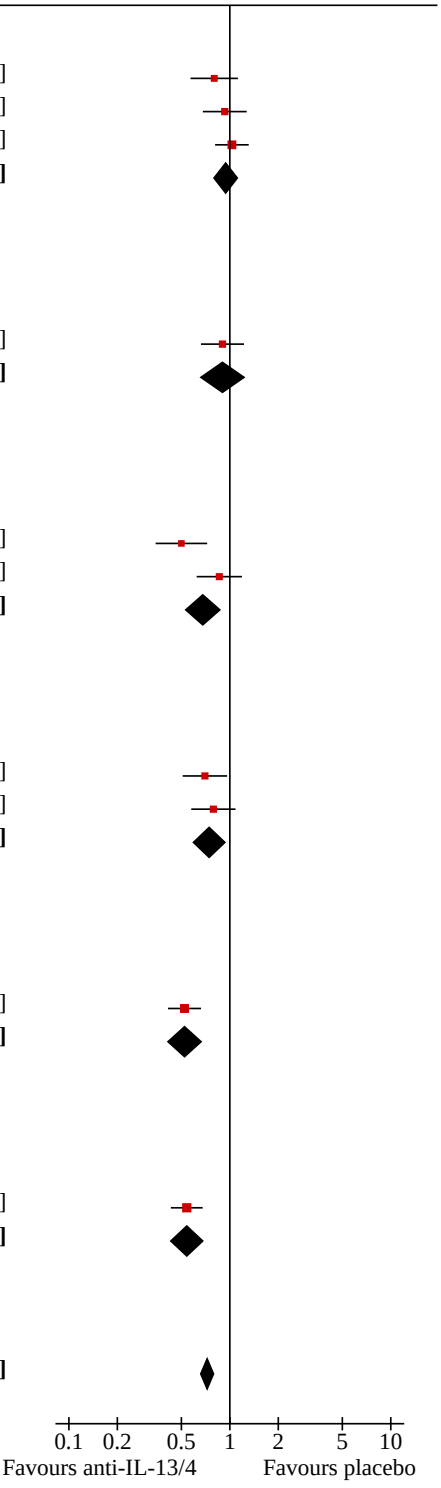
Total (95% CI)		**3208**		**1793**	**100.0%**	**0.87 [0.72 , 1.06]**
Total events:	284		184			

Heterogeneity: Chi² = 4.87, df = 10 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.35 (P = 0.18)
Test for subgroup differences: Chi² = 2.89, df = 6 (P = 0.82), I² = 0%



Analysis 5.4. Comparison 5: Subanalysis: study duration > 6 months, Outcome 4: Exacerbation requiring hospitalisation/ED/OCS (rate ratio)

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI
5.4.1 Tralokinumab 300 mg SC Q2W				
Busse 2015	-0.2231	0.1729	7.2%	0.80 [0.57 , 1.12]
Pannetieri 2018A	-0.0726	0.16	8.4%	0.93 [0.68 , 1.27]
Pannetieri 2018B	0.0296	0.1226	14.3%	1.03 [0.81 , 1.31]
Subtotal (95% CI)			**30.0%**	**0.94 [0.80 , 1.11]**
Heterogeneity: Chi² = 1.43, df = 2 (P = 0.49); I² = 0%				
Test for overall effect: Z = 0.71 (P = 0.48)				
5.4.2 Tralokinumab 300 mg SC Q4W				
Pannetieri 2018A	-0.1054	0.157	8.7%	0.90 [0.66 , 1.22]
Subtotal (95% CI)			**8.7%**	**0.90 [0.66 , 1.22]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.67 (P = 0.50)				
5.4.3 Lebrikizumab 37.5 mg SC Q4W				
Hanania 2016a	-0.6931	0.1881	6.1%	0.50 [0.35 , 0.72]
Hanania 2016b	-0.1508	0.1653	7.9%	0.86 [0.62 , 1.19]
Subtotal (95% CI)			**14.0%**	**0.68 [0.53 , 0.87]**
Heterogeneity: Chi² = 4.69, df = 1 (P = 0.03); I² = 79%				
Test for overall effect: Z = 3.12 (P = 0.002)				
5.4.4 Lebrikizumab 125 mg SC Q4W				
Hanania 2016a	-0.3567	0.1622	8.2%	0.70 [0.51 , 0.96]
Hanania 2016b	-0.2357	0.1615	8.3%	0.79 [0.58 , 1.08]
Subtotal (95% CI)			**16.5%**	**0.74 [0.59 , 0.93]**
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%				
Test for overall effect: Z = 2.59 (P = 0.010)				
5.4.5 Dupilumab 200mg SC Q2W				
Castro 2018	-0.6482	0.1205	14.9%	0.52 [0.41 , 0.66]
Subtotal (95% CI)			**14.9%**	**0.52 [0.41 , 0.66]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 5.38 (P < 0.00001)				
5.4.6 Dupilumab 300mg SC Q2W				
Castro 2018	-0.6162	0.1162	16.0%	0.54 [0.43 , 0.68]
Subtotal (95% CI)			**16.0%**	**0.54 [0.43 , 0.68]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 5.30 (P < 0.00001)				
Total (95% CI)			**100.0%**	**0.72 [0.66 , 0.79]**
Heterogeneity: Chi² = 31.92, df = 9 (P = 0.0002); I² = 72%				
Test for overall effect: Z = 6.99 (P < 0.00001)				
Test for subgroup differences: Chi² = 25.52, df = 5 (P = 0.0001), I² = 80.4%				

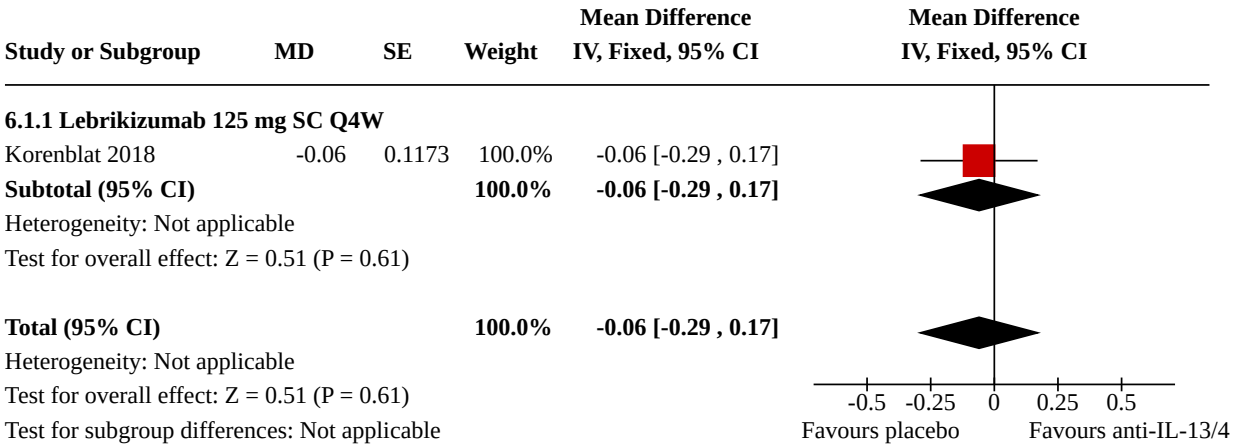


Comparison 6. Subanalysis: asthma severity mild-to-moderate

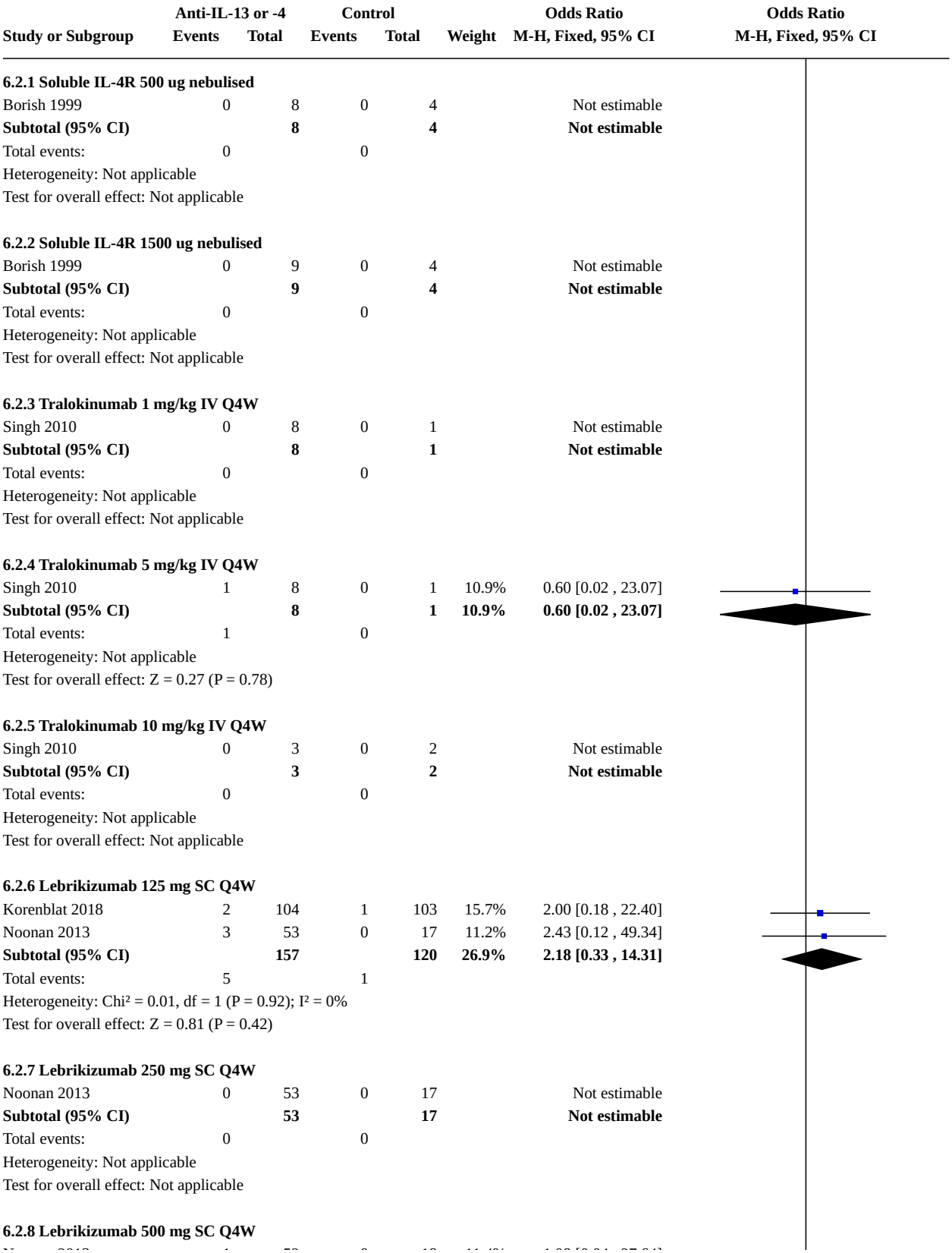
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Health-related quality of life (adjusted mean diff versus placebo)	1		Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.29, 0.17]
6.1.1 Lebrikizumab 125 mg SC Q4W	1		Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.29, 0.17]
6.2 Serious adverse events	7	664	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.49, 4.01]
6.2.1 Soluble IL-4R 500 ug nebulised	1	12	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2.2 Soluble IL-4R 1500 ug nebulised	1	13	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2.3 Tralokinumab 1 mg/kg IV Q4W	1	9	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2.4 Tralokinumab 5 mg/kg IV Q4W	1	9	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.02, 23.07]
6.2.5 Tralokinumab 10 mg/kg IV Q4W	1	5	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2.6 Lebrikizumab 125 mg SC Q4W	2	277	Odds Ratio (M-H, Fixed, 95% CI)	2.18 [0.33, 14.31]
6.2.7 Lebrikizumab 250 mg SC Q4W	1	70	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2.8 Lebrikizumab 500 mg SC Q4W	1	70	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.04, 27.64]
6.2.9 GSK679586 2.5 mg/kg IV Q4W	1	8	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2.10 GSK679586 10 mg/kg IV Q4W	1	8	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2.11 GSK679586 20 mg/kg IV Q4W	1	12	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.04, 38.30]
6.2.12 RPC4046 0.3 mg/kg IV Q1W	1	6	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2.13 RPC4046 3 mg/kg IV Q1W	1	6	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2.14 IMA-638 IV 0.2 mg/kg (D1/8/28/56/84)	1	21	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2.15 IMA-638 IV 0.6 mg/kg (D1/8/28/56/84)	1	22	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.04, 28.30]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2.16 IMA-638 IV 2 mg/kg (D1/8/28/56/84)	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.05, 9.70]
6.2.17 IMA-638 IV 200 mg SC (D1/8/28/42/56/70/84)	1	67	Odds Ratio (M-H, Fixed, 95% CI)	2.59 [0.12, 56.20]
6.2.18 IMA-638 IV 75 mg SC (D1/8/28/42/56/70/84)	1	27	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 6.1. Comparison 6: Subanalysis: asthma severity mild-to-moderate, Outcome 1: Health-related quality of life (adjusted mean diff versus placebo)



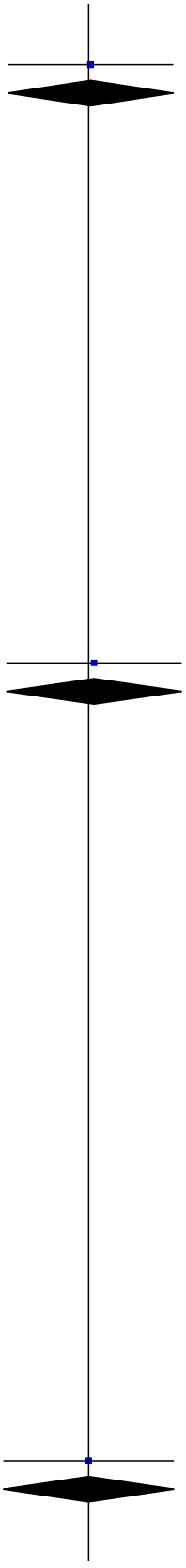
Analysis 6.2. Comparison 6: Subanalysis: asthma severity mild-to-moderate, Outcome 2: Serious adverse events



Study or Subgroup	Anti-IL-13 or -4 Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
6.2.1 Soluble IL-4R 500 ug nebulised						
Borish 1999	0	8	0	4		Not estimable
Subtotal (95% CI)		**8**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.2.2 Soluble IL-4R 1500 ug nebulised						
Borish 1999	0	9	0	4		Not estimable
Subtotal (95% CI)		**9**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.2.3 Tralokinumab 1 mg/kg IV Q4W						
Singh 2010	0	8	0	1		Not estimable
Subtotal (95% CI)		**8**		**1**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.2.4 Tralokinumab 5 mg/kg IV Q4W						
Singh 2010	1	8	0	1	10.9%	0.60 [0.02 , 23.07]
Subtotal (95% CI)		**8**		**1**	**10.9%**	**0.60 [0.02 , 23.07]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.78)						
6.2.5 Tralokinumab 10 mg/kg IV Q4W						
Singh 2010	0	3	0	2		Not estimable
Subtotal (95% CI)		**3**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.2.6 Lebrikizumab 125 mg SC Q4W						
Korenblat 2018	2	104	1	103	15.7%	2.00 [0.18 , 22.40]
Noonan 2013	3	53	0	17	11.2%	2.43 [0.12 , 49.34]
Subtotal (95% CI)		**157**		**120**	**26.9%**	**2.18 [0.33 , 14.31]**
Total events:	5		1			
Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.92); $I^2 = 0\%$						
Test for overall effect: Z = 0.81 (P = 0.42)						
6.2.7 Lebrikizumab 250 mg SC Q4W						
Noonan 2013	0	53	0	17		Not estimable
Subtotal (95% CI)		**53**		**17**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.2.8 Lebrikizumab 500 mg SC Q4W						

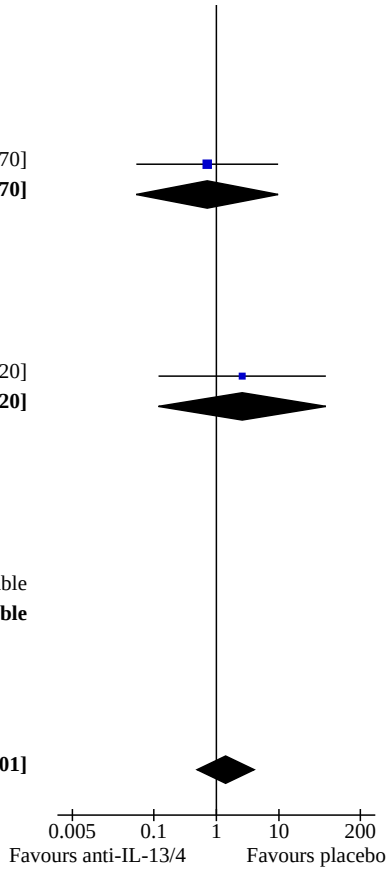
Analysis 6.2. (Continued)

6.2.8 Lebrikizumab 500 mg SC Q4W						
Noonan 2013	1	52	0	18	11.4%	1.08 [0.04 , 27.64]
Subtotal (95% CI)		**52**		**18**	**11.4%**	**1.08 [0.04 , 27.64]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
6.2.9 GSK679586 2.5 mg/kg IV Q4W						
Hodsman 2013	0	6	0	2		Not estimable
Subtotal (95% CI)		**6**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.2.10 GSK679586 10 mg/kg IV Q4W						
Hodsman 2013	0	6	0	2		Not estimable
Subtotal (95% CI)		**6**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.2.11 GSK679586 20 mg/kg IV Q4W						
Hodsman 2013	1	9	0	3	9.7%	1.24 [0.04 , 38.30]
Subtotal (95% CI)		**9**		**3**	**9.7%**	**1.24 [0.04 , 38.30]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.90)						
6.2.12 RPC4046 0.3 mg/kg IV Q1W						
Tripp 2017	0	4	0	2		Not estimable
Subtotal (95% CI)		**4**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.2.13 RPC4046 3 mg/kg IV Q1W						
Tripp 2017	0	4	0	2		Not estimable
Subtotal (95% CI)		**4**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.2.14 IMA-638 IV 0.2 mg/kg (D1/8/28/56/84)						
NCT00425061	0	16	0	5		Not estimable
Subtotal (95% CI)		**16**		**5**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.2.15 IMA-638 IV 0.6 mg/kg (D1/8/28/56/84)						
NCT00425061	1	17	0	5	10.9%	1.00 [0.04 , 28.30]
Subtotal (95% CI)		**17**		**5**	**10.9%**	**1.00 [0.04 , 28.30]**
Total events:	1		0			
Heterogeneity: Not applicable						



Analysis 6.2. (Continued)

Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
6.2.16 IMA-638 IV 2 mg/kg (D1/8/28/56/84)						
NCT00425061	2	16	1	6	20.3%	0.71 [0.05 , 9.70]
Subtotal (95% CI)		**16**		**6**	**20.3%**	**0.71 [0.05 , 9.70]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
6.2.17 IMA-638 IV 200 mg SC (D1/8/28/42/56/70/84)						
NCT00425061	2	45	0	22	10.0%	2.59 [0.12 , 56.20]
Subtotal (95% CI)		**45**		**22**	**10.0%**	**2.59 [0.12 , 56.20]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
6.2.18 IMA-638 IV 75 mg SC (D1/8/28/42/56/70/84)						
NCT00425061	0	4	0	23		Not estimable
Subtotal (95% CI)		**4**		**23**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**425**		**239**	**100.0%**	**1.41 [0.49 , 4.01]**
Total events:	13		2			
Heterogeneity: $Chi^2 = 0.90$, df = 7 (P = 1.00); $I^2 = 0\%$						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: $Chi^2 = 0.89$, df = 6 (P = 0.99), $I^2 = 0\%$						



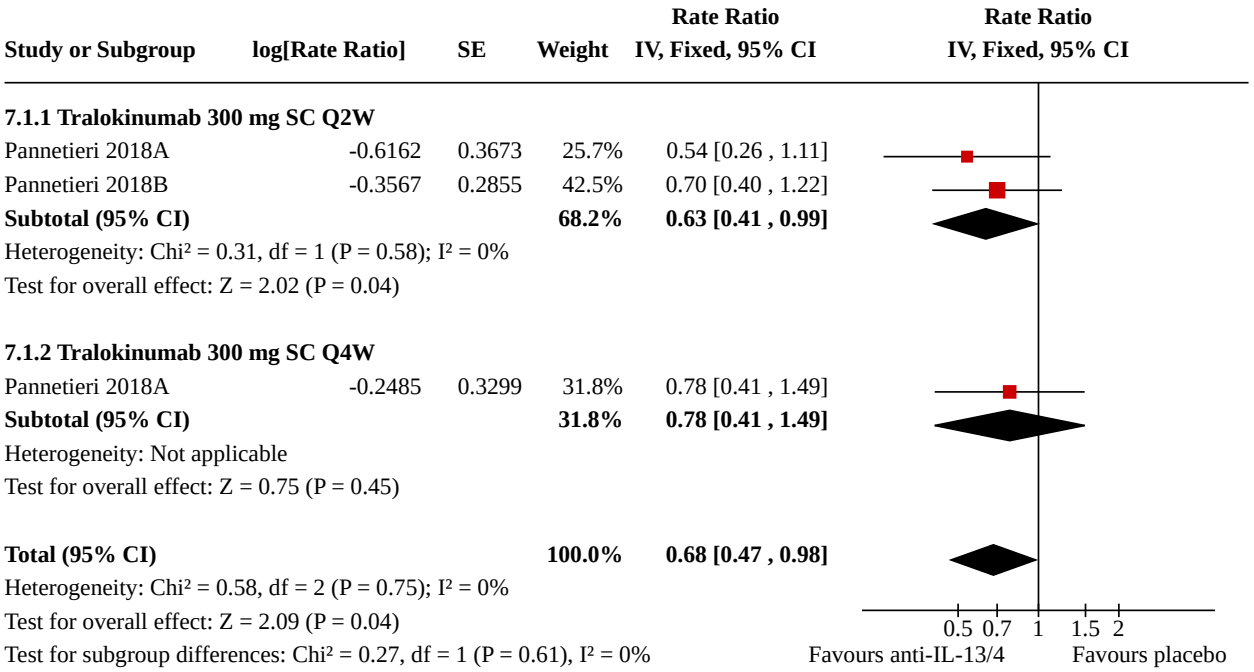
Comparison 7. Subanalysis: asthma severity severe

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Exacerbation requiring hospitalisation or ED visit	2		Rate Ratio (IV, Fixed, 95% CI)	0.68 [0.47, 0.98]
7.1.1 Tralokinumab 300 mg SC Q2W	2		Rate Ratio (IV, Fixed, 95% CI)	0.63 [0.41, 0.99]
7.1.2 Tralokinumab 300 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.78 [0.41, 1.49]
7.2 Health-related quality of life (adjusted mean diff versus placebo)	5		Mean Difference (IV, Fixed, 95% CI)	0.21 [0.14, 0.27]
7.2.1 Dupilumab 200 mg SC Q2W	2		Mean Difference (IV, Fixed, 95% CI)	0.29 [0.16, 0.42]
7.2.2 Dupilumab 200 mg SC Q4W	1		Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.13, 0.59]

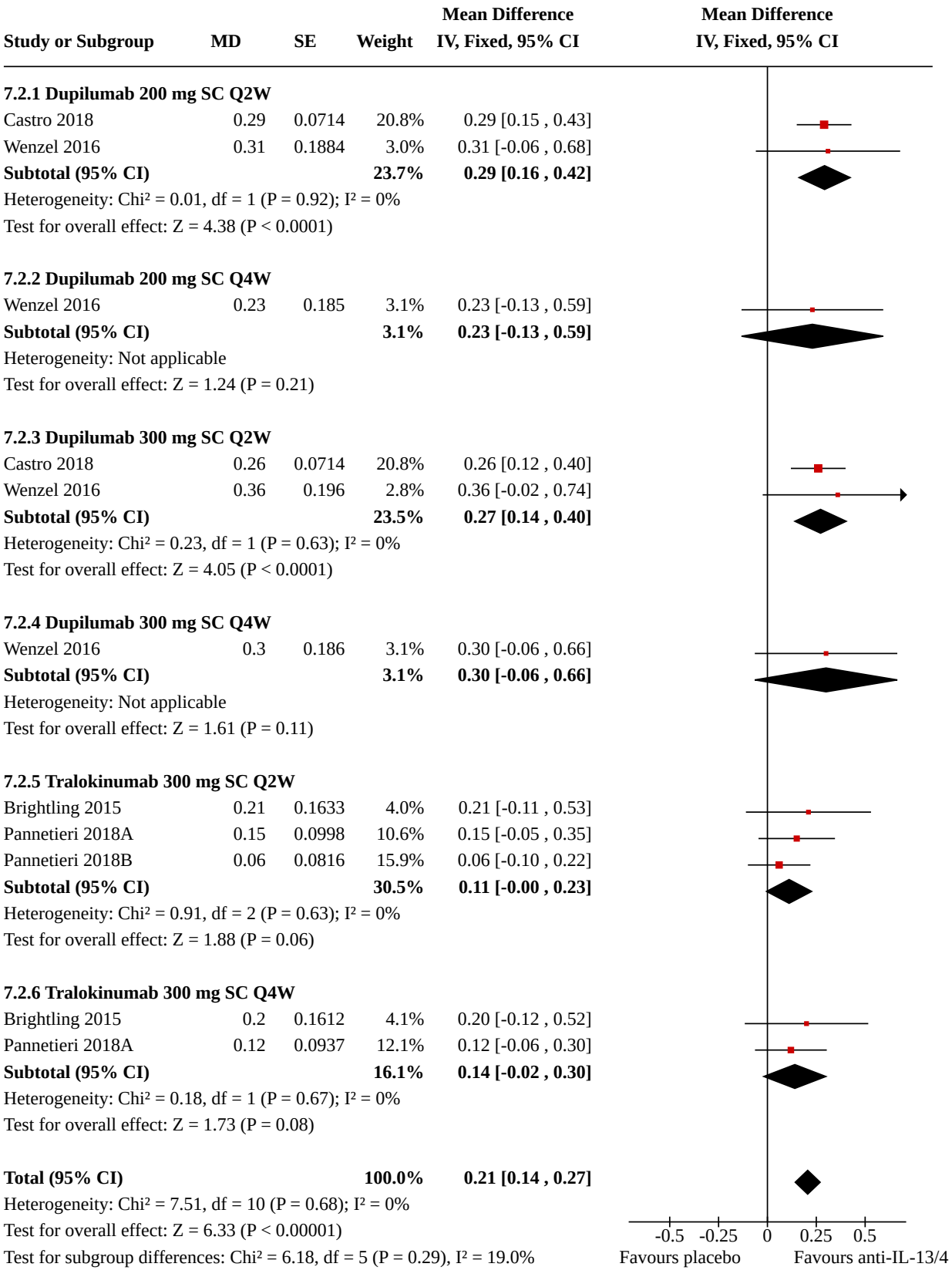
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2.3 Dupilumab 300 mg SC Q2W	2		Mean Difference (IV, Fixed, 95% CI)	0.27 [0.14, 0.40]
7.2.4 Dupilumab 300 mg SC Q4W	1		Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.06, 0.66]
7.2.5 Tralokinumab 300 mg SC Q2W	3		Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.00, 0.23]
7.2.6 Tralokinumab 300 mg SC Q4W	2		Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.02, 0.30]
7.3 Serious adverse events	10	5946	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.13]
7.3.1 Tralokinumab 1 mg/kg IV Q4W	1	3	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
7.3.2 Tralokinumab 5 mg/kg IV Q4W	1	5	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
7.3.3 Tralokinumab 10 mg/kg IV Q4W	1	5	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.03, 53.51]
7.3.4 Tralokinumab 300 mg SC Q2W	4	1810	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.59, 1.09]
7.3.5 Tralokinumab 300 mg SC Q4W	2	831	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.58, 1.40]
7.3.6 Lebrikizumab 250 mg SC Q4W	1	218	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.19, 2.53]
7.3.7 GSK679586 10 mg/kg IV Q4W	1	198	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [0.52, 5.24]
7.3.8 Dupilumab 200 mg SC Q2W	2	1131	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.60, 1.54]
7.3.9 Dupilumab 200 mg SC Q4W	1	189	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.15, 3.98]
7.3.10 Dupilumab 300 mg SC Q2W	3	1359	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.76, 1.77]
7.3.11 Dupilumab 300 mg SC Q4W	1	197	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.39, 5.06]
7.4 Exacerbation requiring hospitalisation/ED/OCS (rate ratio)	7		Rate Ratio (IV, Fixed, 95% CI)	0.71 [0.65, 0.77]
7.4.1 Tralokinumab 300 mg SC Q2W	3		Rate Ratio (IV, Fixed, 95% CI)	0.94 [0.80, 1.11]
7.4.2 Tralokinumab 300 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.90 [0.66, 1.22]
7.4.3 Lebrikizumab 37.5 mg SC Q4W	2		Rate Ratio (IV, Fixed, 95% CI)	0.68 [0.53, 0.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.4.4 Lebrikizumab 125 mg SC Q4W	2		Rate Ratio (IV, Fixed, 95% CI)	0.74 [0.59, 0.93]
7.4.5 Dupilumab 200mg SC Q2W	2		Rate Ratio (IV, Fixed, 95% CI)	0.51 [0.40, 0.64]
7.4.6 Dupilumab 200 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.46 [0.18, 1.16]
7.4.7 Dupilumab 300mg SC Q2W	2		Rate Ratio (IV, Fixed, 95% CI)	0.52 [0.42, 0.65]
7.4.8 Dupilumab 300 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.67 [0.29, 1.55]

Analysis 7.1. Comparison 7: Subanalysis: asthma severity severe, Outcome 1: Exacerbation requiring hospitalisation or ED visit



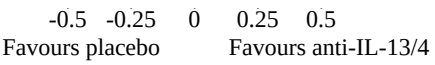
Analysis 7.2. Comparison 7: Subanalysis: asthma severity severe, Outcome 2: Health-related quality of life (adjusted mean diff versus placebo)



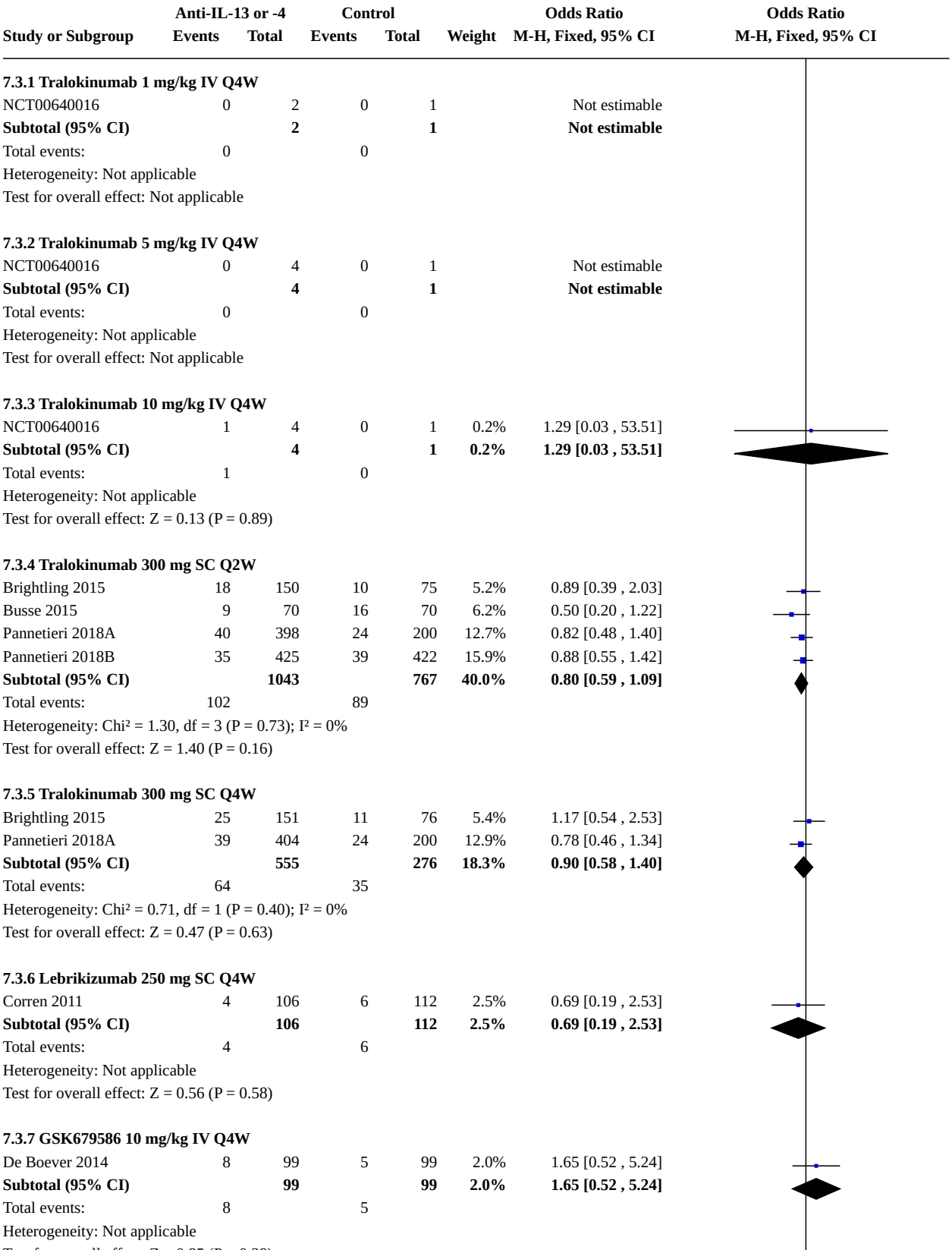
Analysis 7.2. (Continued)

Test for overall effect: Z = 6.33 (P < 0.00001)

Test for subgroup differences: Chi² = 6.18, df = 5 (P = 0.29), I² = 19.0%

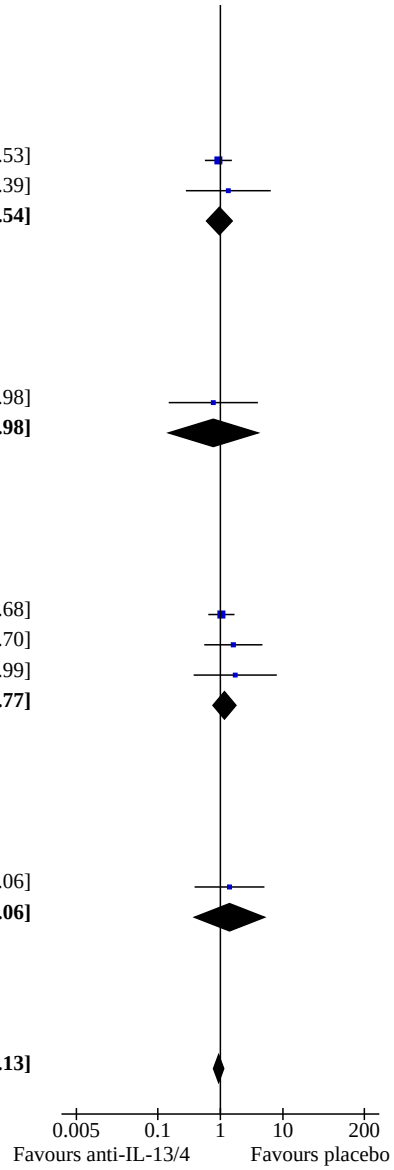


Analysis 7.3. Comparison 7: Subanalysis: asthma severity severe, Outcome 3: Serious adverse events

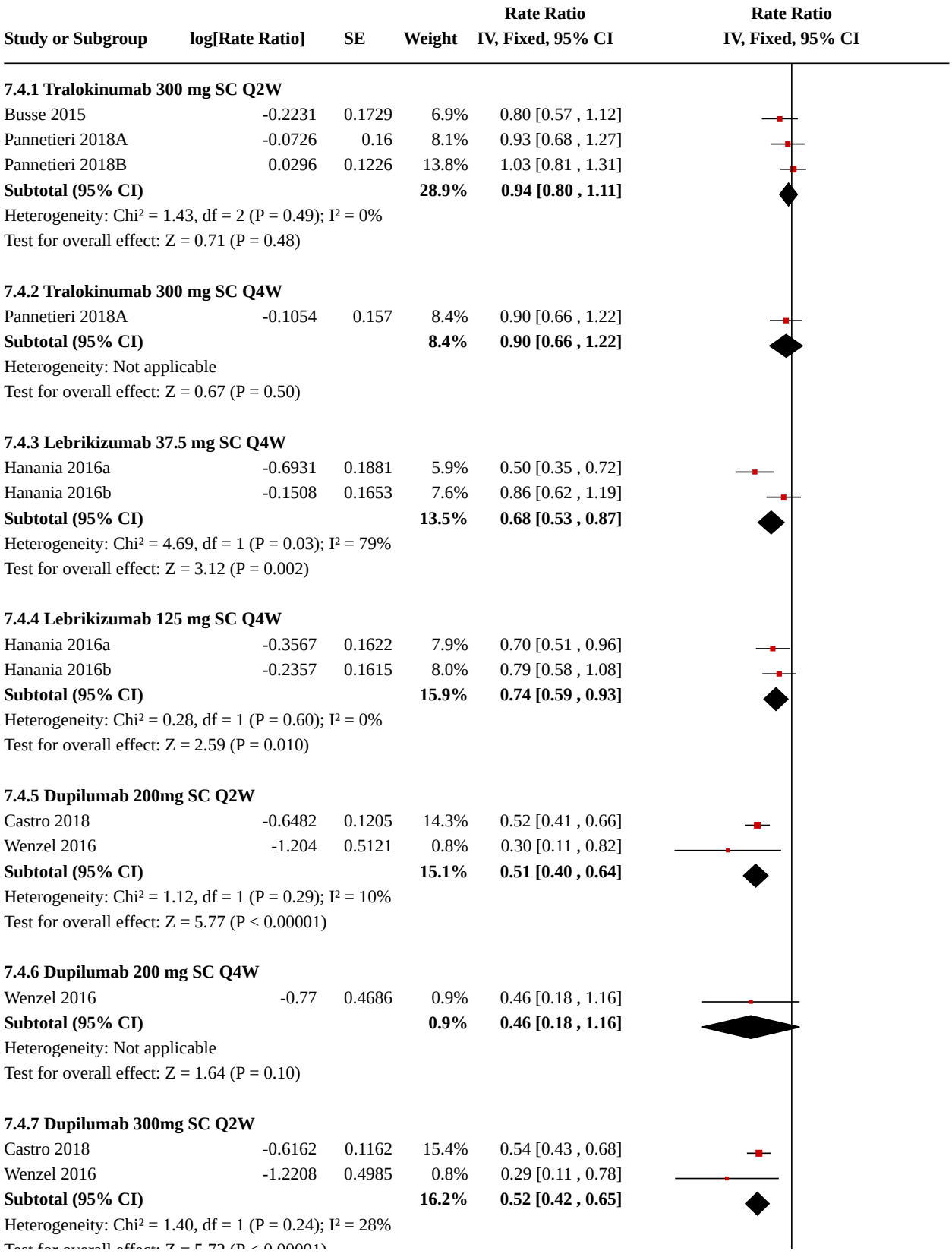


Analysis 7.3. (Continued)

Total events:	8		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.39)						
7.3.8 Dupilumab 200 mg SC Q2W						
Castro 2018	49	631	26	313	14.2%	0.93 [0.57 , 1.53]
Wenzel 2016	10	148	2	39	1.3%	1.34 [0.28 , 6.39]
Subtotal (95% CI)		**779**		**352**	**15.5%**	**0.96 [0.60 , 1.54]**
Total events:	59		28			
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.15 (P = 0.88)						
7.3.9 Dupilumab 200 mg SC Q4W						
Wenzel 2016	6	150	2	39	1.4%	0.77 [0.15 , 3.98]
Subtotal (95% CI)		**150**		**39**	**1.4%**	**0.77 [0.15 , 3.98]**
Total events:	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
7.3.10 Dupilumab 300 mg SC Q2W						
Castro 2018	55	632	27	321	14.5%	1.04 [0.64 , 1.68]
Rabe 2018	9	103	6	107	2.4%	1.61 [0.55 , 4.70]
Wenzel 2016	13	156	2	40	1.3%	1.73 [0.37 , 7.99]
Subtotal (95% CI)		**891**		**468**	**18.2%**	**1.16 [0.76 , 1.77]**
Total events:	77		35			
Heterogeneity: Chi² = 0.83, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.48)						
7.3.11 Dupilumab 300 mg SC Q4W						
Wenzel 2016	16	157	3	40	1.9%	1.40 [0.39 , 5.06]
Subtotal (95% CI)		**157**		**40**	**1.9%**	**1.40 [0.39 , 5.06]**
Total events:	16		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
Total (95% CI)		**3790**		**2156**	**100.0%**	**0.94 [0.78 , 1.13]**
Total events:	337		203			
Heterogeneity: Chi² = 6.56, df = 15 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Chi² = 3.62, df = 8 (P = 0.89), I² = 0%						



Analysis 7.4. Comparison 7: Subanalysis: asthma severity severe, Outcome 4: Exacerbation requiring hospitalisation/ED/OCS (rate ratio)



Analysis 7.4. (Continued)

Heterogeneity: Chi² = 1.40, df = 1 (P = 0.24); I² = 28%
Test for overall effect: Z = 5.72 (P < 0.00001)

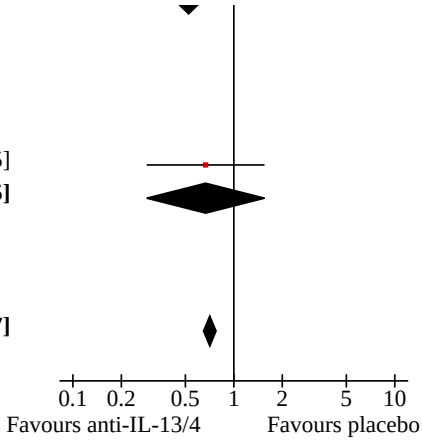
7.4.8 Dupilumab 300 mg SC Q4W

Wenzel 2016	-0.4035	0.4298	1.1%	0.67 [0.29 , 1.55]
Subtotal (95% CI)			**1.1%**	**0.67 [0.29 , 1.55]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)

Total (95% CI)			**100.0%**	**0.71 [0.65 , 0.77]**

Heterogeneity: Chi² = 38.85, df = 13 (P = 0.0002); I² = 67%
Test for overall effect: Z = 7.55 (P < 0.00001)
Test for subgroup differences: Chi² = 29.94, df = 7 (P < 0.0001), I² = 76.6%

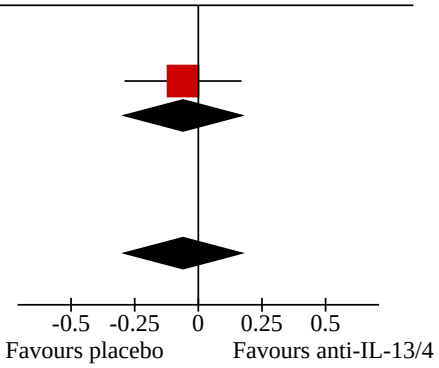


Comparison 8. Subanalysis: no concomitant ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Health-related quality of life (adjusted mean diff versus placebo)	1		Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.29, 0.17]
8.1.1 Lebrikizumab 125 mg SC Q4W	1		Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.29, 0.17]
8.2 Serious adverse events	4	470	Odds Ratio (M-H, Fixed, 95% CI)	1.73 [0.40, 7.48]
8.2.1 Soluble IL-4R 500 ug nebulised	1	12	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
8.2.2 Soluble IL-4R 1500 ug nebulised	1	13	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
8.2.3 Lebrikizumab 125 mg SC Q4W	2	277	Odds Ratio (M-H, Fixed, 95% CI)	2.18 [0.33, 14.31]
8.2.4 Lebrikizumab 250 mg SC Q4W	1	70	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
8.2.5 Lebrikizumab 500 mg SC Q4W	1	70	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.04, 27.64]
8.2.6 GSK679586 2.5 mg/kg IV Q4W	1	8	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
8.2.7 GSK679586 10 mg/kg IV Q4W	1	8	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
8.2.8 GSK679586 20 mg/kg IV Q4W	1	12	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.04, 38.30]

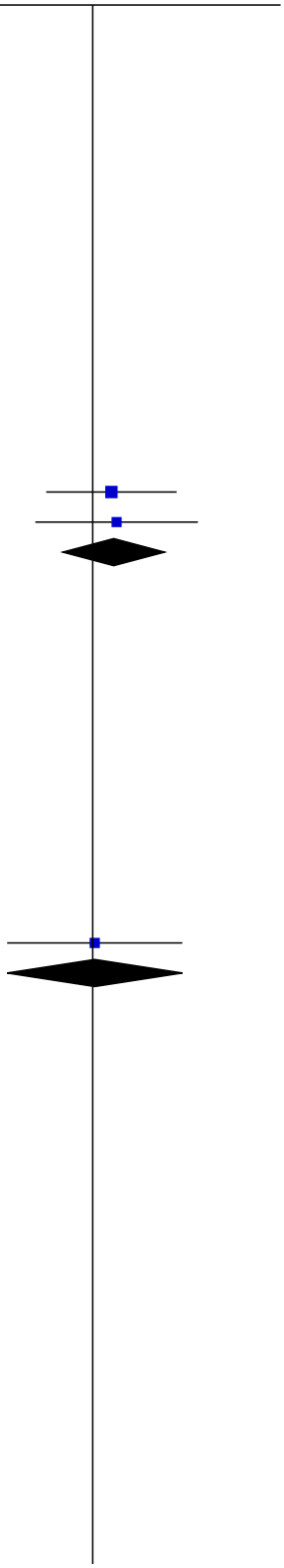
Analysis 8.1. Comparison 8: Subanalysis: no concomitant ICS, Outcome 1: Health-related quality of life (adjusted mean diff versus placebo)

Study or Subgroup	MD	SE	Weight	Mean Difference IV, Fixed, 95% CI
8.1.1 Lebrikizumab 125 mg SC Q4W				
Korenblat 2018	-0.06	0.1173	100.0%	-0.06 [-0.29 , 0.17]
Subtotal (95% CI)			**100.0%**	**-0.06 [-0.29 , 0.17]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.51 (P = 0.61)				
Total (95% CI)			**100.0%**	**-0.06 [-0.29 , 0.17]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.51 (P = 0.61)				
Test for subgroup differences: Not applicable				



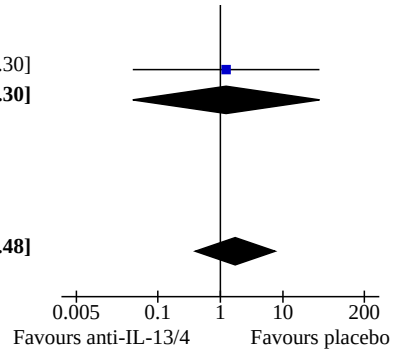
Analysis 8.2. Comparison 8: Subanalysis: no concomitant ICS, Outcome 2: Serious adverse events

Study or Subgroup	Anti-IL-13 or -4 Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
8.2.1 Soluble IL-4R 500 ug nebulised						
Borish 1999	0	8	0	4		Not estimable
Subtotal (95% CI)		**8**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.2.2 Soluble IL-4R 1500 ug nebulised						
Borish 1999	0	9	0	4		Not estimable
Subtotal (95% CI)		**9**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.2.3 Lebrikizumab 125 mg SC Q4W						
Korenblat 2018	2	104	1	103	32.7%	2.00 [0.18 , 22.40]
Noonan 2013	3	53	0	17	23.3%	2.43 [0.12 , 49.34]
Subtotal (95% CI)		**157**		**120**	**56.1%**	**2.18 [0.33 , 14.31]**
Total events:	5		1			
Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.92); $I^2 = 0\%$						
Test for overall effect: Z = 0.81 (P = 0.42)						
8.2.4 Lebrikizumab 250 mg SC Q4W						
Noonan 2013	0	53	0	17		Not estimable
Subtotal (95% CI)		**53**		**17**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.2.5 Lebrikizumab 500 mg SC Q4W						
Noonan 2013	1	52	0	18	23.8%	1.08 [0.04 , 27.64]
Subtotal (95% CI)		**52**		**18**	**23.8%**	**1.08 [0.04 , 27.64]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
8.2.6 GSK679586 2.5 mg/kg IV Q4W						
Hodsman 2013	0	6	0	2		Not estimable
Subtotal (95% CI)		**6**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.2.7 GSK679586 10 mg/kg IV Q4W						
Hodsman 2013	0	6	0	2		Not estimable
Subtotal (95% CI)		**6**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.2.8 GSK679586 20 mg/kg IV Q4W						



Analysis 8.2. (Continued)

8.2.8 GSK679586 20 mg/kg IV Q4W						
Hodsman 2013	1	9	0	3	20.2%	1.24 [0.04 , 38.30]
Subtotal (95% CI)		**9**		**3**	**20.2%**	**1.24 [0.04 , 38.30]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.90)						
Total (95% CI)		**300**		**170**	**100.0%**	**1.73 [0.40 , 7.48]**
Total events:	7		1			
Heterogeneity: Chi² = 0.18, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.47)						
Test for subgroup differences: Chi² = 0.18, df = 2 (P = 0.92), I² = 0%						



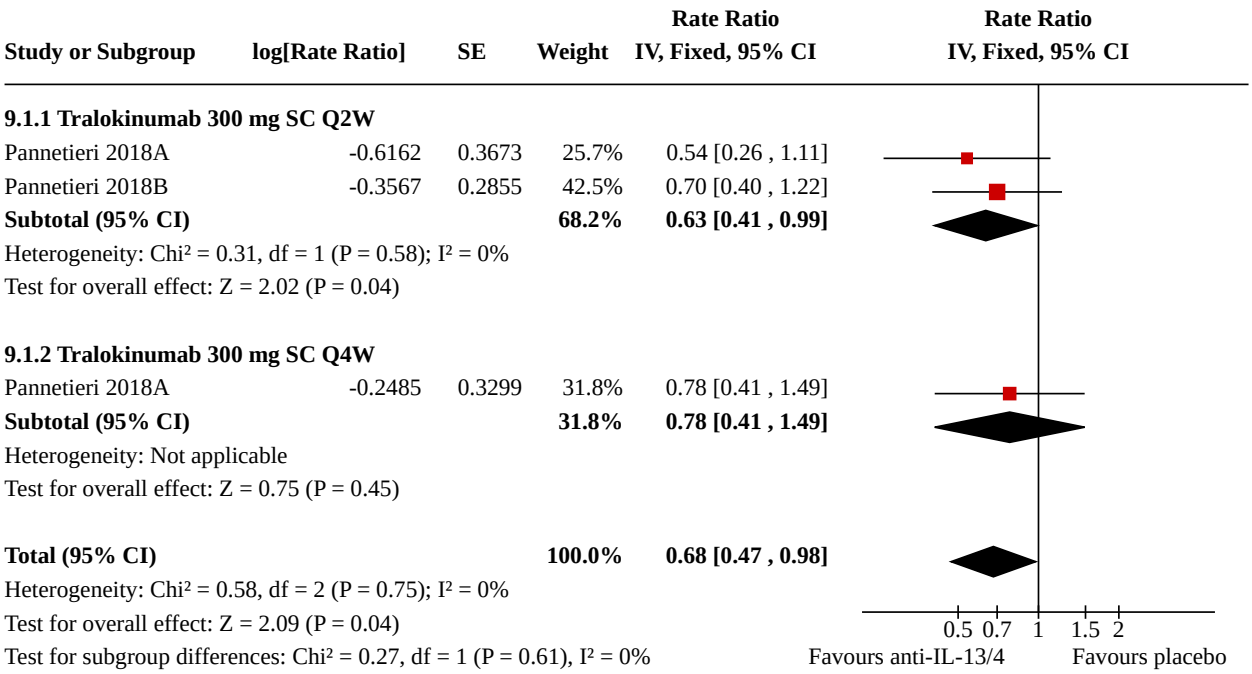
Comparison 9. Subanalysis: concomitant ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Exacerbation requiring hospitalisation or ED visit	2		Rate Ratio (IV, Fixed, 95% CI)	0.68 [0.47, 0.98]
9.1.1 Tralokinumab 300 mg SC Q2W	2		Rate Ratio (IV, Fixed, 95% CI)	0.63 [0.41, 0.99]
9.1.2 Tralokinumab 300 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.78 [0.41, 1.49]
9.2 Health-related quality of life (adjusted mean diff versus placebo)	6		Mean Difference (IV, Fixed, 95% CI)	0.20 [0.13, 0.26]
9.2.1 Dupilumab 200 mg SC Q2W	2		Mean Difference (IV, Fixed, 95% CI)	0.29 [0.16, 0.42]
9.2.2 Dupilumab 200 mg SC Q4W	1		Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.13, 0.59]
9.2.3 Dupilumab 300 mg SC Q2W	2		Mean Difference (IV, Fixed, 95% CI)	0.27 [0.14, 0.40]
9.2.4 Dupilumab 300 mg SC Q4W	1		Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.06, 0.66]
9.2.5 Tralokinumab 300 mg SC Q2W	3		Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.00, 0.23]
9.2.6 Tralokinumab 300 mg SC Q4W	2		Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.02, 0.30]
9.2.7 AMG317 75 mg SC Q1W	1		Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.60, 0.36]
9.2.8 AMG317 150 mg SC Q1W	1		Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.44, 0.58]

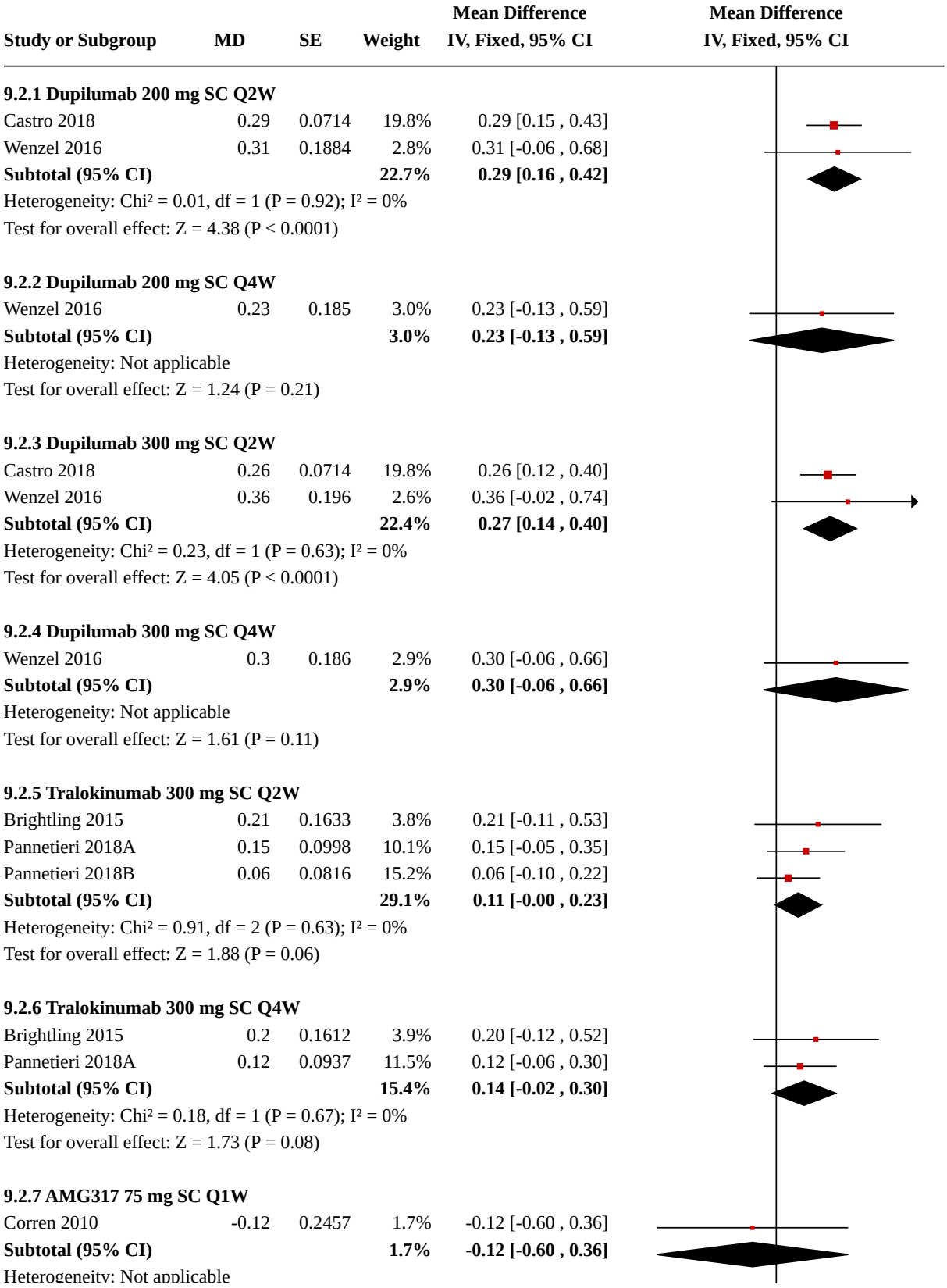
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2.9 AMG317 300 mg SC Q1W	1		Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.44, 0.64]
9.3 Serious adverse events	18	7269	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.76, 1.08]
9.3.1 Tralokinumab 1 mg/kg IV Q4W	2	12	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9.3.2 Tralokinumab 5 mg/kg IV Q4W	2	14	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.02, 23.07]
9.3.3 Tralokinumab 10 mg/kg IV Q4W	2	10	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.03, 53.51]
9.3.4 Tralokinumab 150 mg SC Q2W	1	62	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.05, 7.39]
9.3.5 Tralokinumab 300 mg SC Q2W	6	1955	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.05]
9.3.6 Tralokinumab 300 mg SC Q4W	2	831	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.58, 1.40]
9.3.7 Tralokinumab 600 mg SC Q2W	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.02, 5.42]
9.3.8 Lebrikizumab 37.5 mg SC Q4W	1	155	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 1.76]
9.3.9 Lebrikizumab 125 mg SC Q4W	1	151	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.20, 5.42]
9.3.10 Lebrikizumab 250 mg SC Q4W	2	375	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.28, 1.86]
9.3.11 AMG317 75 mg SC Q1W	1	97	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.06, 7.91]
9.3.12 AMG317 150 mg SC Q1W	1	98	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9.3.13 AMG317 300 mg SC Q1W	1	96	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9.3.14 GSK679586 10 mg/kg IV Q4W	1	198	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [0.52, 5.24]
9.3.15 RPC4046 0.3 mg/kg IV Q1W	1	6	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9.3.16 RPC4046 3 mg/kg IV Q1W	1	6	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9.3.17 Dupilumab 300 mg SC Q1W	1	104	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.03, 3.18]
9.3.18 Dupilumab 200 mg SC Q2W	2	1131	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.60, 1.54]
9.3.19 Dupilumab 200 mg SC Q4W	1	189	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.15, 3.98]
9.3.20 Dupilumab 300 mg SC Q2W	3	1359	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.76, 1.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3.21 Dupilumab 300 mg SC Q4W	1	197	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.39, 5.06]
9.3.22 IMA-638 IV 0.2 mg/kg (D1/8/28/56/84)	1	21	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9.3.23 IMA-638 IV 0.6 mg/kg (D1/8/28/56/84)	1	22	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.04, 28.30]
9.3.24 IMA-638 IV 2 mg/kg (D1/8/28/56/84)	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.05, 9.70]
9.3.25 IMA-638 IV 200 mg SC (D1/8/28/42/56/70/84)	1	67	Odds Ratio (M-H, Fixed, 95% CI)	2.59 [0.12, 56.20]
9.3.26 IMA-638 IV 75 mg SC (D1/8/28/42/56/70/84)	1	27	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9.4 Exacerbation requiring hospitalisation/ED/OCS (rate ratio)	7		Rate Ratio (IV, Fixed, 95% CI)	0.71 [0.65, 0.77]
9.4.1 Tralokinumab 300 mg SC Q2W	3		Rate Ratio (IV, Fixed, 95% CI)	0.94 [0.80, 1.11]
9.4.2 Tralokinumab 300 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.90 [0.66, 1.22]
9.4.3 Lebrikizumab 37.5 mg SC Q4W	2		Rate Ratio (IV, Fixed, 95% CI)	0.68 [0.53, 0.87]
9.4.4 Lebrikizumab 125 mg SC Q4W	2		Rate Ratio (IV, Fixed, 95% CI)	0.74 [0.59, 0.93]
9.4.5 Dupilumab 200mg SC Q2W	2		Rate Ratio (IV, Fixed, 95% CI)	0.51 [0.40, 0.64]
9.4.6 Dupilumab 200 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.46 [0.18, 1.16]
9.4.7 Dupilumab 300mg SC Q2W	2		Rate Ratio (IV, Fixed, 95% CI)	0.52 [0.42, 0.65]
9.4.8 Dupilumab 300 mg SC Q4W	1		Rate Ratio (IV, Fixed, 95% CI)	0.67 [0.29, 1.55]

Analysis 9.1. Comparison 9: Subanalysis: concomitant ICS, Outcome 1: Exacerbation requiring hospitalisation or ED visit

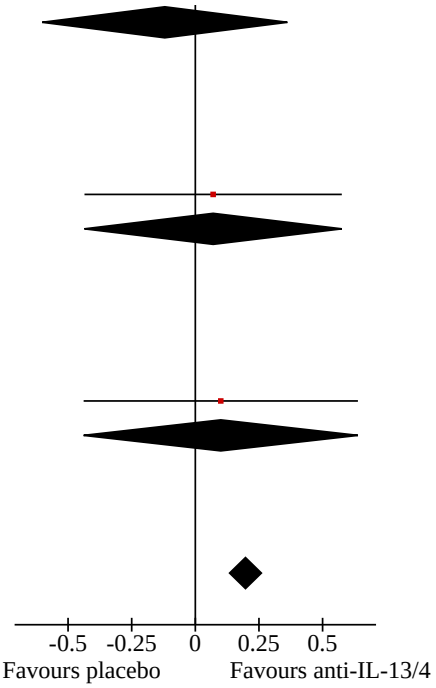


Analysis 9.2. Comparison 9: Subanalysis: concomitant ICS, Outcome 2: Health-related quality of life (adjusted mean diff versus placebo)

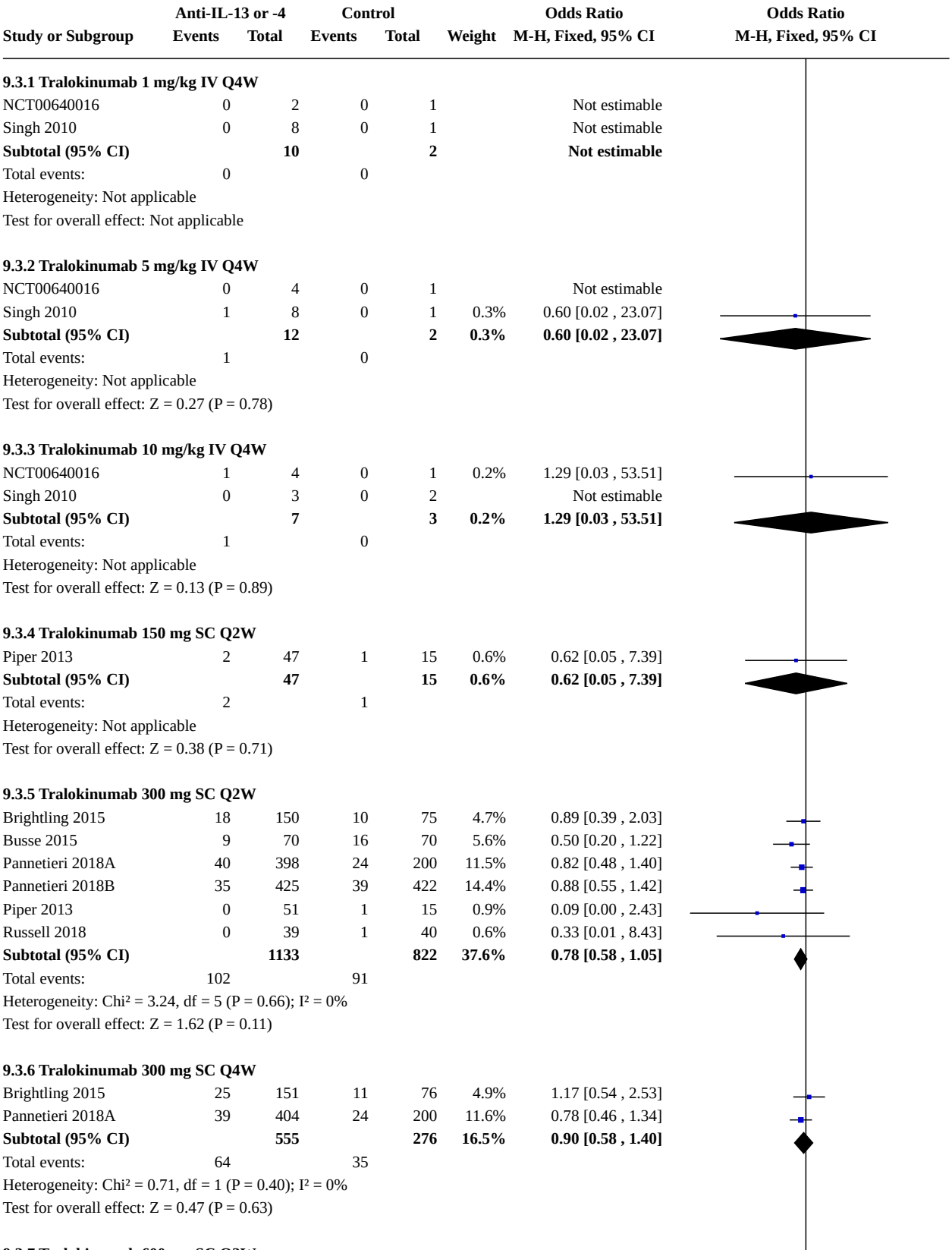


Analysis 9.2. (Continued)

Subtotal (95% CI)			**1.7%**	**-0.12 [-0.60 , 0.36]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.49 (P = 0.63)				
9.2.8 AMG317 150 mg SC Q1W				
Corren 2010	0.07	0.2579	1.5%	0.07 [-0.44 , 0.58]
Subtotal (95% CI)			**1.5%**	**0.07 [-0.44 , 0.58]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.27 (P = 0.79)				
9.2.9 AMG317 300 mg SC Q1W				
Corren 2010	0.1	0.2749	1.3%	0.10 [-0.44 , 0.64]
Subtotal (95% CI)			**1.3%**	**0.10 [-0.44 , 0.64]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.36 (P = 0.72)				
Total (95% CI)			**100.0%**	**0.20 [0.13 , 0.26]**
Heterogeneity: Chi² = 9.62, df = 13 (P = 0.72); I² = 0%				
Test for overall effect: Z = 6.20 (P < 0.00001)				
Test for subgroup differences: Chi² = 8.28, df = 8 (P = 0.41), I² = 3.4%				

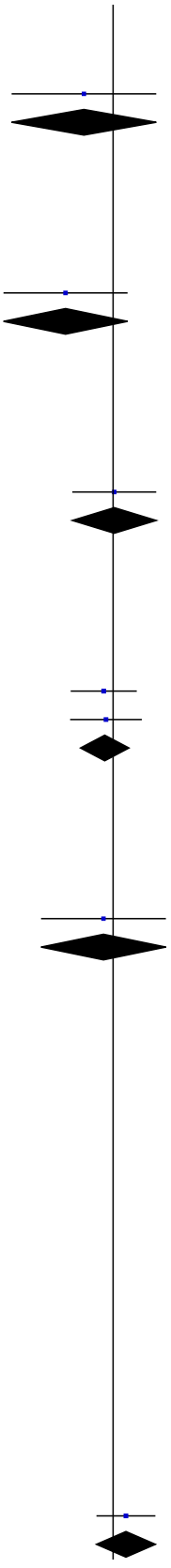


Analysis 9.3. Comparison 9: Subanalysis: concomitant ICS, Outcome 3: Serious adverse events



Analysis 9.3. (Continued)

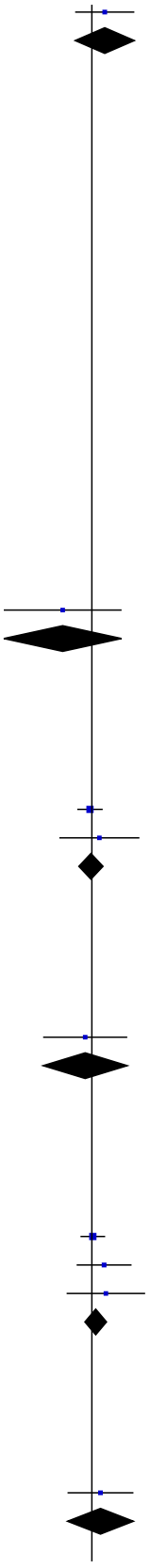
Test for overall effect: Z = 0.47 (P = 0.63)



9.3.7 Tralokinumab 600 mg SC Q2W						
Piper 2013	1	48	1	16	0.6%	0.32 [0.02 , 5.42]
Subtotal (95% CI)		**48**		**16**	**0.6%**	**0.32 [0.02 , 5.42]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
9.3.8 Lebrikizumab 37.5 mg SC Q4W						
Hanania 2015a	1	117	2	38	1.2%	0.16 [0.01 , 1.76]
Subtotal (95% CI)		**117**		**38**	**1.2%**	**0.16 [0.01 , 1.76]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
9.3.9 Lebrikizumab 125 mg SC Q4W						
Hanania 2015a	6	112	2	39	1.1%	1.05 [0.20 , 5.42]
Subtotal (95% CI)		**112**		**39**	**1.1%**	**1.05 [0.20 , 5.42]**
Total events:	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
9.3.10 Lebrikizumab 250 mg SC Q4W						
Corren 2011	4	106	6	112	2.2%	0.69 [0.19 , 2.53]
Hanania 2015a	7	118	3	39	1.7%	0.76 [0.19 , 3.08]
Subtotal (95% CI)		**224**		**151**	**3.9%**	**0.72 [0.28 , 1.86]**
Total events:	11		9			
Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0\%$						
Test for overall effect: Z = 0.68 (P = 0.50)						
9.3.11 AMG317 75 mg SC Q1W						
Corren 2010	2	72	1	25	0.6%	0.69 [0.06 , 7.91]
Subtotal (95% CI)		**72**		**25**	**0.6%**	**0.69 [0.06 , 7.91]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
9.3.12 AMG317 150 mg SC Q1W						
Corren 2010	0	73	0	25		Not estimable
Subtotal (95% CI)		**73**		**25**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.3.13 AMG317 300 mg SC Q1W						
Corren 2010	0	72	0	24		Not estimable
Subtotal (95% CI)		**72**		**24**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.3.14 GSK679586 10 mg/kg IV Q4W						
De Boever 2014	8	99	5	99	1.8%	1.65 [0.52 , 5.24]
Subtotal (95% CI)		**99**		**99**	**1.8%**	**1.65 [0.52 , 5.24]**

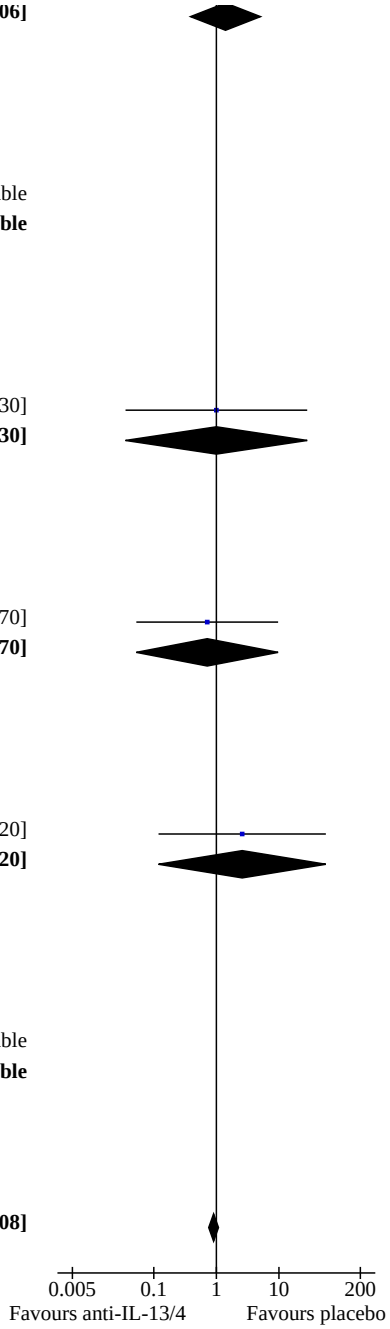
Analysis 9.3. (Continued)

De Boever 2014	8	99	5	99	1.8%	1.65 [0.52 , 5.24]	
Subtotal (95% CI)		**99**		**99**	**1.8%**	**1.65 [0.52 , 5.24]**	
Total events:	8		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.85 (P = 0.39)							
9.3.15 RPC4046 0.3 mg/kg IV Q1W							
Tripp 2017	0	4	0	2		Not estimable	
Subtotal (95% CI)		**4**		**2**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
9.3.16 RPC4046 3 mg/kg IV Q1W							
Tripp 2017	0	4	0	2		Not estimable	
Subtotal (95% CI)		**4**		**2**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
9.3.17 Dupilumab 300 mg SC Q1W							
Wenzel 2013	1	52	3	52	1.2%	0.32 [0.03 , 3.18]	
Subtotal (95% CI)		**52**		**52**	**1.2%**	**0.32 [0.03 , 3.18]**	
Total events:	1		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.97 (P = 0.33)							
9.3.18 Dupilumab 200 mg SC Q2W							
Castro 2018	49	631	26	313	12.8%	0.93 [0.57 , 1.53]	
Wenzel 2016	10	148	2	39	1.2%	1.34 [0.28 , 6.39]	
Subtotal (95% CI)		**779**		**352**	**14.0%**	**0.96 [0.60 , 1.54]**	
Total events:	59		28				
Heterogeneity: $Chi^2 = 0.19$, df = 1 (P = 0.66); $I^2 = 0\%$							
Test for overall effect: Z = 0.15 (P = 0.88)							
9.3.19 Dupilumab 200 mg SC Q4W							
Wenzel 2016	6	150	2	39	1.2%	0.77 [0.15 , 3.98]	
Subtotal (95% CI)		**150**		**39**	**1.2%**	**0.77 [0.15 , 3.98]**	
Total events:	6		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.31 (P = 0.76)							
9.3.20 Dupilumab 300 mg SC Q2W							
Castro 2018	55	632	27	321	13.1%	1.04 [0.64 , 1.68]	
Rabe 2018	9	103	6	107	2.1%	1.61 [0.55 , 4.70]	
Wenzel 2016	13	156	2	40	1.2%	1.73 [0.37 , 7.99]	
Subtotal (95% CI)		**891**		**468**	**16.4%**	**1.16 [0.76 , 1.77]**	
Total events:	77		35				
Heterogeneity: $Chi^2 = 0.83$, df = 2 (P = 0.66); $I^2 = 0\%$							
Test for overall effect: Z = 0.70 (P = 0.48)							
9.3.21 Dupilumab 300 mg SC Q4W							
Wenzel 2016	16	157	3	40	1.7%	1.40 [0.39 , 5.06]	
Subtotal (95% CI)		**157**		**40**	**1.7%**	**1.40 [0.39 , 5.06]**	
Total events:	16		3				

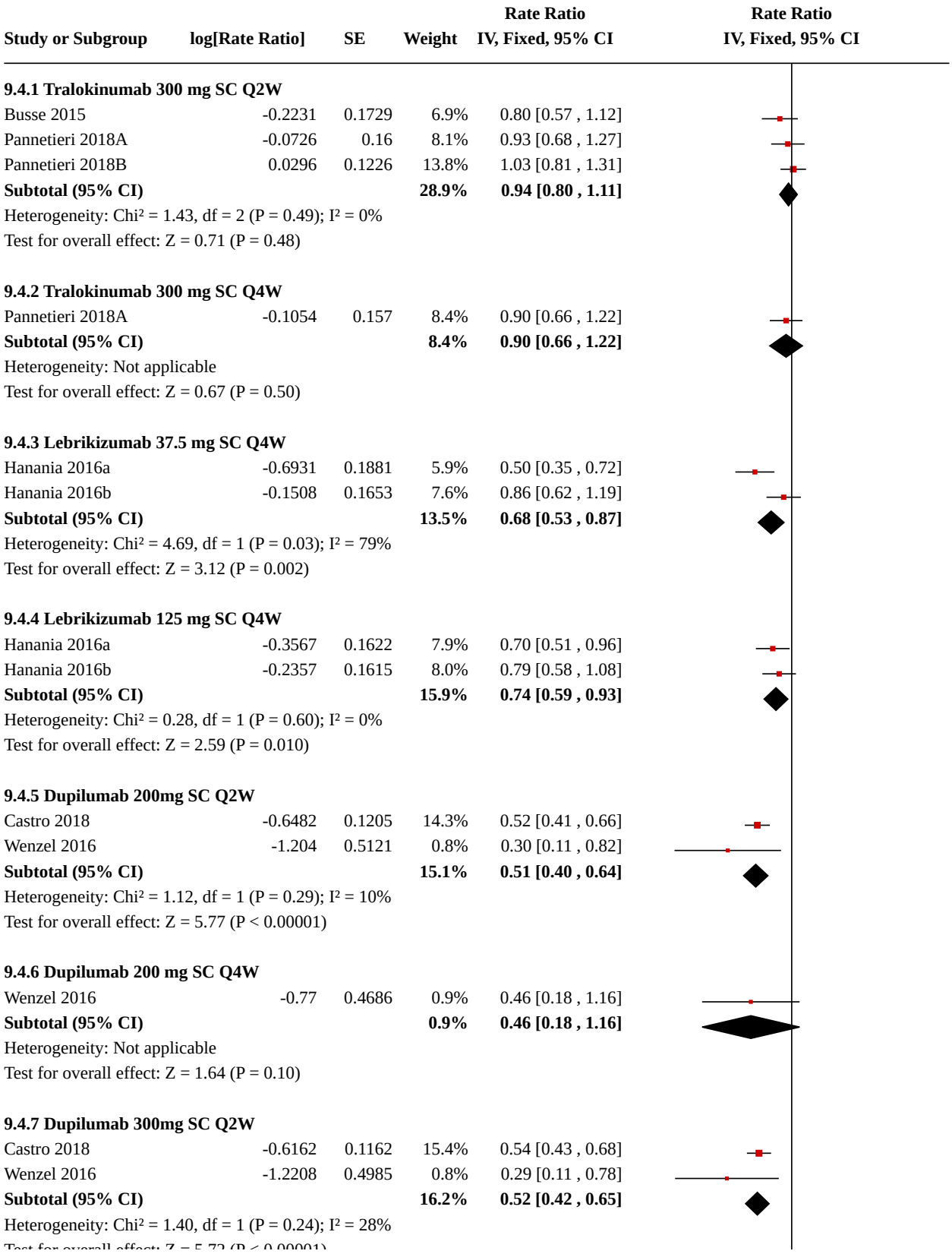


Analysis 9.3. (Continued)

Subtotal (95% CI)		**157**		**40**	**1.7%**	**1.40 [0.39 , 5.06]**
Total events:	16		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
9.3.22 IMA-638 IV 0.2 mg/kg (D1/8/28/56/84)						
NCT00425061	0	16	0	5		Not estimable
Subtotal (95% CI)		**16**		**5**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.3.23 IMA-638 IV 0.6 mg/kg (D1/8/28/56/84)						
NCT00425061	1	17	0	5	0.3%	1.00 [0.04 , 28.30]
Subtotal (95% CI)		**17**		**5**	**0.3%**	**1.00 [0.04 , 28.30]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
9.3.24 IMA-638 IV 2 mg/kg (D1/8/28/56/84)						
NCT00425061	2	16	1	6	0.5%	0.71 [0.05 , 9.70]
Subtotal (95% CI)		**16**		**6**	**0.5%**	**0.71 [0.05 , 9.70]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
9.3.25 IMA-638 IV 200 mg SC (D1/8/28/42/56/70/84)						
NCT00425061	2	45	0	22	0.3%	2.59 [0.12 , 56.20]
Subtotal (95% CI)		**45**		**22**	**0.3%**	**2.59 [0.12 , 56.20]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
9.3.26 IMA-638 IV 75 mg SC (D1/8/28/42/56/70/84)						
NCT00425061	0	4	0	23		Not estimable
Subtotal (95% CI)		**4**		**23**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**4716**		**2553**	**100.0%**	**0.90 [0.76 , 1.08]**
Total events:	363		219			
Heterogeneity: Chi² = 12.98, df = 28 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.12 (P = 0.26)						
Test for subgroup differences: Chi² = 8.18, df = 18 (P = 0.98), I² = 0%						



Analysis 9.4. Comparison 9: Subanalysis: concomitant ICS, Outcome 4: Exacerbation requiring hospitalisation/ED/OCS (rate ratio)



Analysis 9.4. (Continued)

Heterogeneity: Chi² = 1.40, df = 1 (P = 0.24); I² = 28%
Test for overall effect: Z = 5.72 (P < 0.00001)

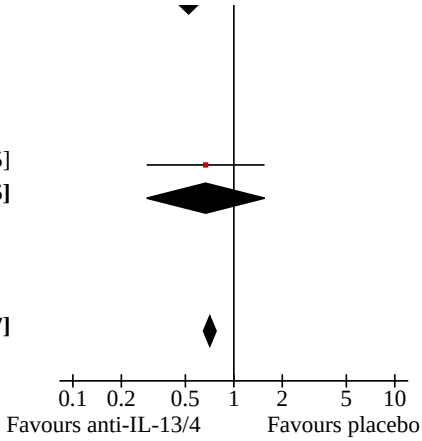
9.4.8 Dupilumab 300 mg SC Q4W

Wenzel 2016	-0.4035	0.4298	1.1%	0.67 [0.29 , 1.55]
Subtotal (95% CI)			**1.1%**	**0.67 [0.29 , 1.55]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)

Total (95% CI)			**100.0%**	**0.71 [0.65 , 0.77]**

Heterogeneity: Chi² = 38.85, df = 13 (P = 0.0002); I² = 67%
Test for overall effect: Z = 7.55 (P < 0.00001)
Test for subgroup differences: Chi² = 29.94, df = 7 (P < 0.0001), I² = 76.6%



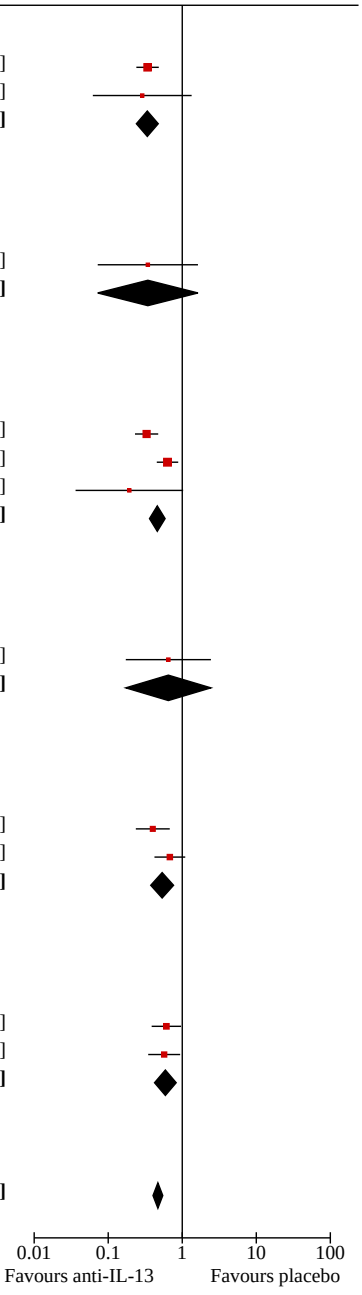
Comparison 10. Subanalysis by blood eosinophil count: exacerbations requiring hospitalisation/ED/OCS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Blood eosinophils high (> 300 cells/uL)	5	2052	Rate Ratio (IV, Fixed, 95% CI)	0.47 [0.40, 0.55]
10.1.1 Dupilumab 200 mg Q2W	2	494	Rate Ratio (IV, Fixed, 95% CI)	0.34 [0.24, 0.47]
10.1.2 Dupilumab 200 mg Q4W	1	77	Rate Ratio (IV, Fixed, 95% CI)	0.34 [0.07, 1.63]
10.1.3 Dupilumab 300 mg Q2W	3	589	Rate Ratio (IV, Fixed, 95% CI)	0.46 [0.36, 0.59]
10.1.4 Dupilumab 300 mg Q4W	1	83	Rate Ratio (IV, Fixed, 95% CI)	0.65 [0.17, 2.44]
10.1.5 Lebrikizumab 37.5 mg Q4W	2	398	Rate Ratio (IV, Fixed, 95% CI)	0.54 [0.38, 0.76]
10.1.6 Lebrikizumab 125 mg Q4W	2	411	Rate Ratio (IV, Fixed, 95% CI)	0.59 [0.42, 0.83]
10.2 Blood eosinophils low (< 300 cells/uL)	4	1881	Rate Ratio (IV, Fixed, 95% CI)	0.75 [0.65, 0.87]
10.2.1 Dupilumab 200 mg Q2W	1	107	Rate Ratio (IV, Fixed, 95% CI)	0.32 [0.09, 1.21]
10.2.2 Dupilumab 200 mg Q4W	1	114	Rate Ratio (IV, Fixed, 95% CI)	0.57 [0.19, 1.75]
10.2.3 Dupilumab 300 mg Q2W	2	237	Rate Ratio (IV, Fixed, 95% CI)	0.69 [0.56, 0.86]
10.2.4 Dupilumab 300 mg Q4W	1	114	Rate Ratio (IV, Fixed, 95% CI)	0.63 [0.21, 1.85]
10.2.5 Lebrikizumab 37.5 mg Q4W	2	645	Rate Ratio (IV, Fixed, 95% CI)	0.79 [0.58, 1.08]
10.2.6 Lebrikizumab 125 mg Q4W	2	664	Rate Ratio (IV, Fixed, 95% CI)	0.92 [0.68, 1.23]
10.3 Blood eosinophils low (> 150 < 300 cells/uL)	1	527	Rate Ratio (IV, Fixed, 95% CI)	0.60 [0.43, 0.83]

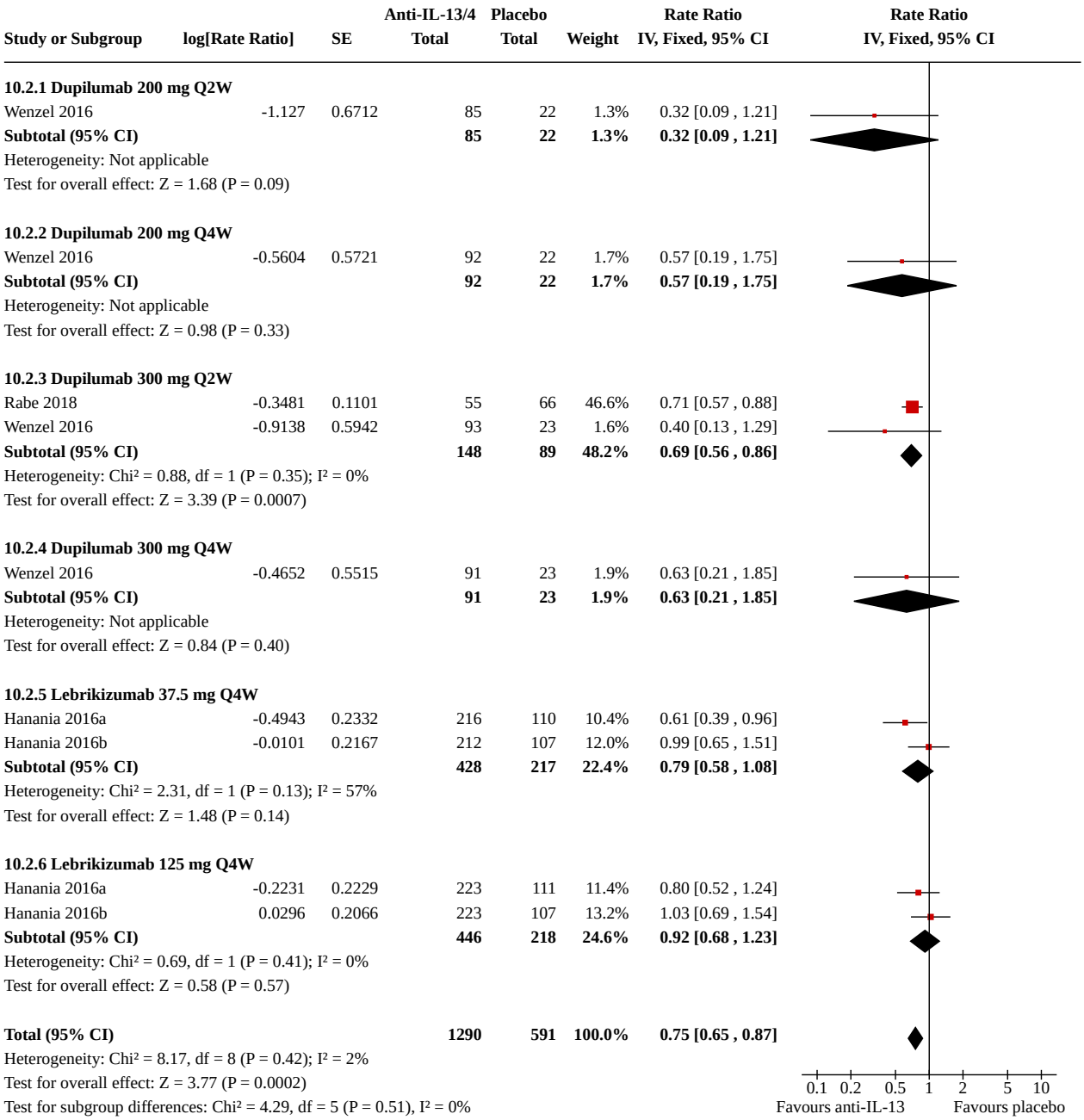
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3.1 Dupilumab 200 mg Q2W	1	257	Rate Ratio (IV, Fixed, 95% CI)	0.64 [0.41, 1.00]
10.3.2 Dupilumab 300 mg Q2W	1	270	Rate Ratio (IV, Fixed, 95% CI)	0.56 [0.35, 0.90]
10.4 Blood eosinophils low (< 150 cells/uL)	1	542	Rate Ratio (IV, Fixed, 95% CI)	1.05 [0.76, 1.43]
10.4.1 Dupilumab 200 mg Q2W	1	278	Rate Ratio (IV, Fixed, 95% CI)	0.93 [0.58, 1.49]
10.4.2 Dupilumab 300 mg Q2W	1	264	Rate Ratio (IV, Fixed, 95% CI)	1.15 [0.75, 1.76]

Analysis 10.1. Comparison 10: Subanalysis by blood eosinophil count: exacerbations requiring hospitalisation/ED/OCS, Outcome 1: Blood eosinophils high (> 300 cells/uL)

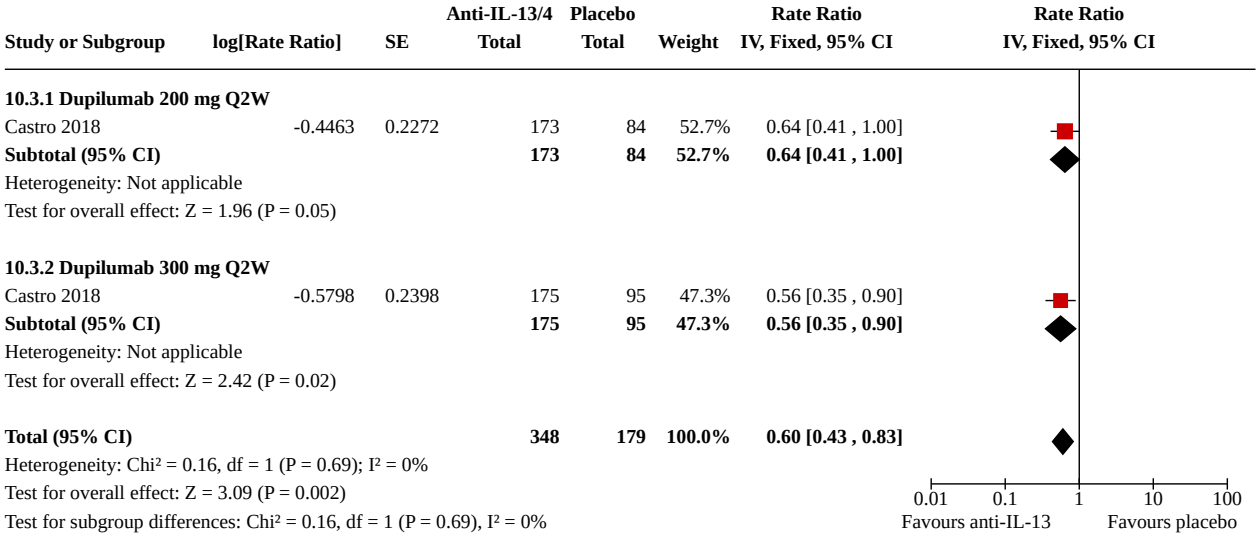
Study or Subgroup	log[Rate Ratio]	SE	Anti-IL-13/4 Total	Placebo Total	Weight	Rate Ratio IV, Fixed, 95% CI
10.1.1 Dupilumab 200 mg Q2W						
Castro 2018	-1.0788	0.1777	264	148	19.0%	0.34 [0.24 , 0.48]
Wenzel 2016	-1.2448	0.7838	65	17	1.0%	0.29 [0.06 , 1.34]
Subtotal (95% CI)			**329**	**165**	**19.9%**	**0.34 [0.24 , 0.47]**
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 6.27 (P < 0.00001)						
10.1.2 Dupilumab 200 mg Q4W						
Wenzel 2016	-1.07	0.7952	60	17	0.9%	0.34 [0.07 , 1.63]
Subtotal (95% CI)			**60**	**17**	**0.9%**	**0.34 [0.07 , 1.63]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.35 (P = 0.18)						
10.1.3 Dupilumab 300 mg Q2W						
Castro 2018	-1.1087	0.1842	277	142	17.6%	0.33 [0.23 , 0.47]
Rabe 2018	-0.4589	0.1699	48	41	20.7%	0.63 [0.45 , 0.88]
Wenzel 2016	-1.6451	0.8535	64	17	0.8%	0.19 [0.04 , 1.03]
Subtotal (95% CI)			**389**	**200**	**39.2%**	**0.46 [0.36 , 0.59]**
Heterogeneity: Chi² = 7.78, df = 2 (P = 0.02); I² = 74%						
Test for overall effect: Z = 6.28 (P < 0.00001)						
10.1.4 Dupilumab 300 mg Q4W						
Wenzel 2016	-0.4323	0.6753	66	17	1.3%	0.65 [0.17 , 2.44]
Subtotal (95% CI)			**66**	**17**	**1.3%**	**0.65 [0.17 , 2.44]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
10.1.5 Lebrikizumab 37.5 mg Q4W						
Hanania 2016a	-0.9163	0.2692	114	70	8.3%	0.40 [0.24 , 0.68]
Hanania 2016b	-0.3857	0.2442	144	70	10.0%	0.68 [0.42 , 1.10]
Subtotal (95% CI)			**258**	**140**	**18.3%**	**0.54 [0.38 , 0.76]**
Heterogeneity: Chi² = 2.13, df = 1 (P = 0.14); I² = 53%						
Test for overall effect: Z = 3.46 (P = 0.0005)						
10.1.6 Lebrikizumab 125 mg Q4W						
Hanania 2016a	-0.4943	0.2332	136	71	11.0%	0.61 [0.39 , 0.96]
Hanania 2016b	-0.5621	0.2534	134	70	9.3%	0.57 [0.35 , 0.94]
Subtotal (95% CI)			**270**	**141**	**20.3%**	**0.59 [0.42 , 0.83]**
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 3.06 (P = 0.002)						
Total (95% CI)			**1372**	**680**	**100.0%**	**0.47 [0.40 , 0.55]**
Heterogeneity: Chi² = 16.38, df = 10 (P = 0.09); I² = 39%						
Test for overall effect: Z = 9.80 (P < 0.00001)						
Test for subgroup differences: Chi² = 6.39, df = 5 (P = 0.27), I² = 21.7%						



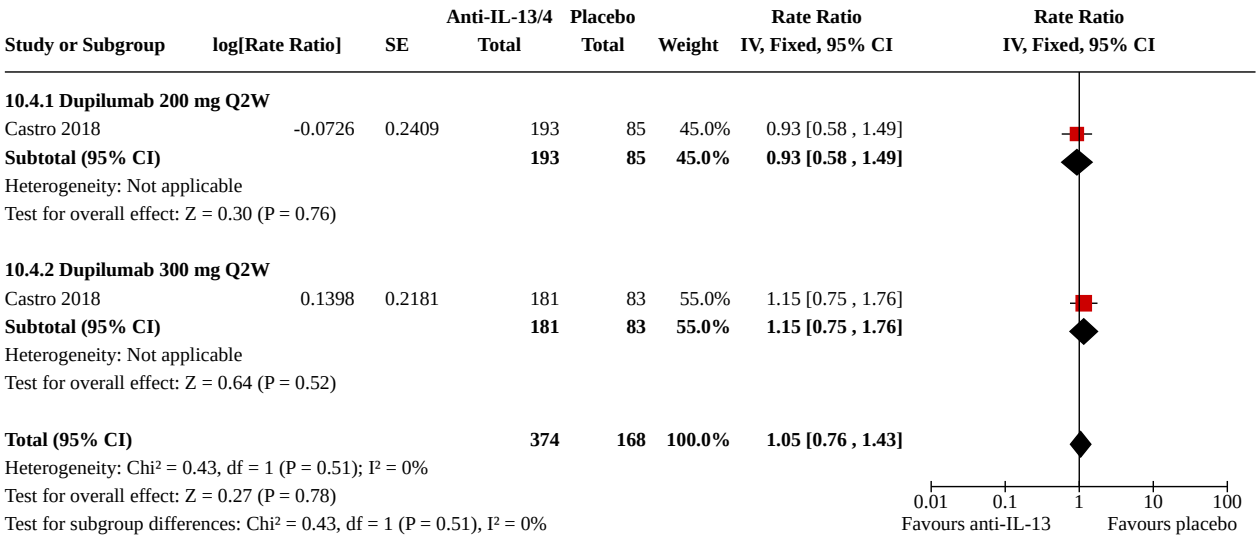
Analysis 10.2. Comparison 10: Subanalysis by blood eosinophil count: exacerbations requiring hospitalisation/ED/OCS, Outcome 2: Blood eosinophils low (< 300 cells/uL)



Analysis 10.3. Comparison 10: Subanalysis by blood eosinophil count: exacerbations requiring hospitalisation/ED/OCS, Outcome 3: Blood eosinophils low (> 150 < 300 cells/uL)



Analysis 10.4. Comparison 10: Subanalysis by blood eosinophil count: exacerbations requiring hospitalisation/ED/OCS, Outcome 4: Blood eosinophils low (< 150 cells/uL)

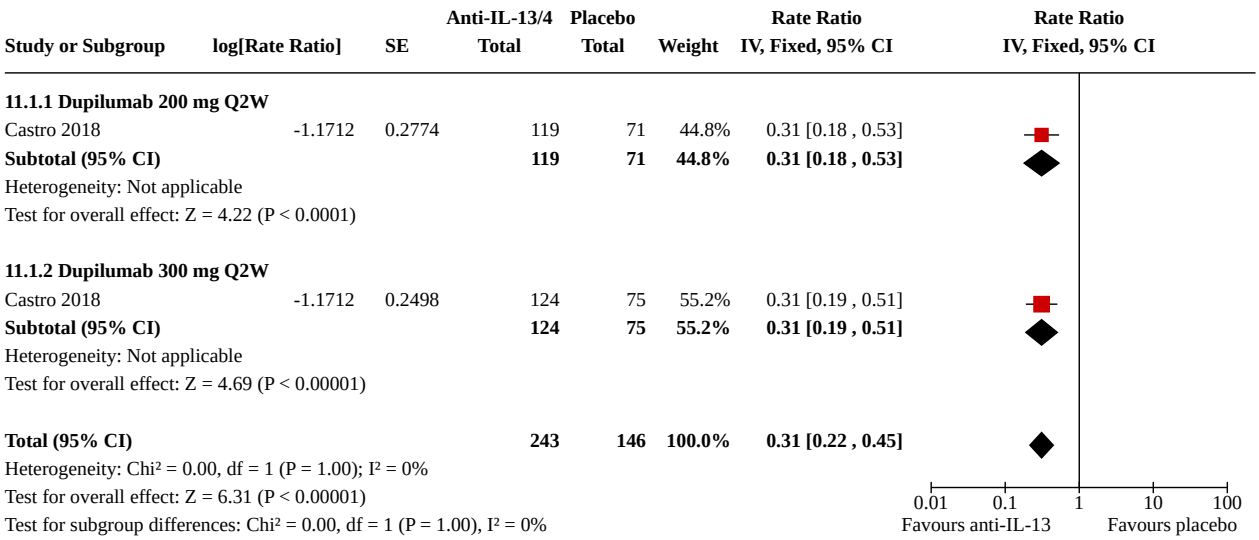


Comparison 11. Subanalysis by FENO: exacerbations requiring hospitalisation/ED/OCS

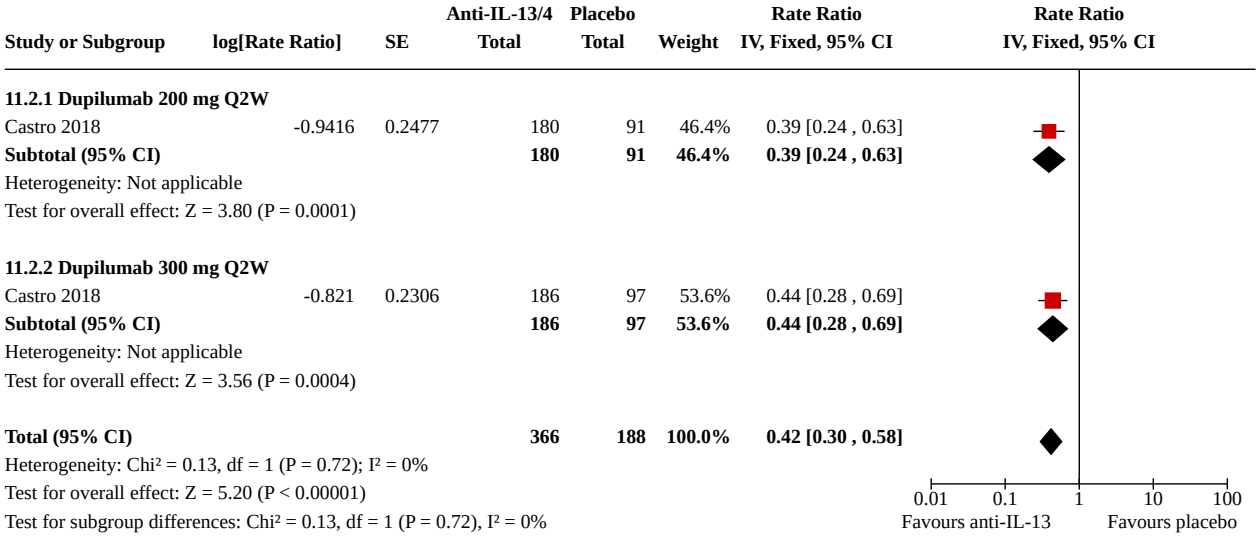
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 FENO high (≥ 50 ppb)	1	389	Rate Ratio (IV, Fixed, 95% CI)	0.31 [0.22, 0.45]
11.1.1 Dupilumab 200 mg Q2W	1	190	Rate Ratio (IV, Fixed, 95% CI)	0.31 [0.18, 0.53]
11.1.2 Dupilumab 300 mg Q2W	1	199	Rate Ratio (IV, Fixed, 95% CI)	0.31 [0.19, 0.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2 FENO medium (≥ 25 to < 50 ppb)	1	554	Rate Ratio (IV, Fixed, 95% CI)	0.42 [0.30, 0.58]
11.2.1 Dupilumab 200 mg Q2W	1	271	Rate Ratio (IV, Fixed, 95% CI)	0.39 [0.24, 0.63]
11.2.2 Dupilumab 300 mg Q2W	1	283	Rate Ratio (IV, Fixed, 95% CI)	0.44 [0.28, 0.69]
11.3 FENO low (< 25 ppb)	1	935	Rate Ratio (IV, Fixed, 95% CI)	0.77 [0.61, 0.97]
11.3.1 Dupilumab 200 mg Q2W	1	474	Rate Ratio (IV, Fixed, 95% CI)	0.75 [0.54, 1.04]
11.3.2 Dupilumab 300 mg Q2W	1	461	Rate Ratio (IV, Fixed, 95% CI)	0.79 [0.57, 1.09]

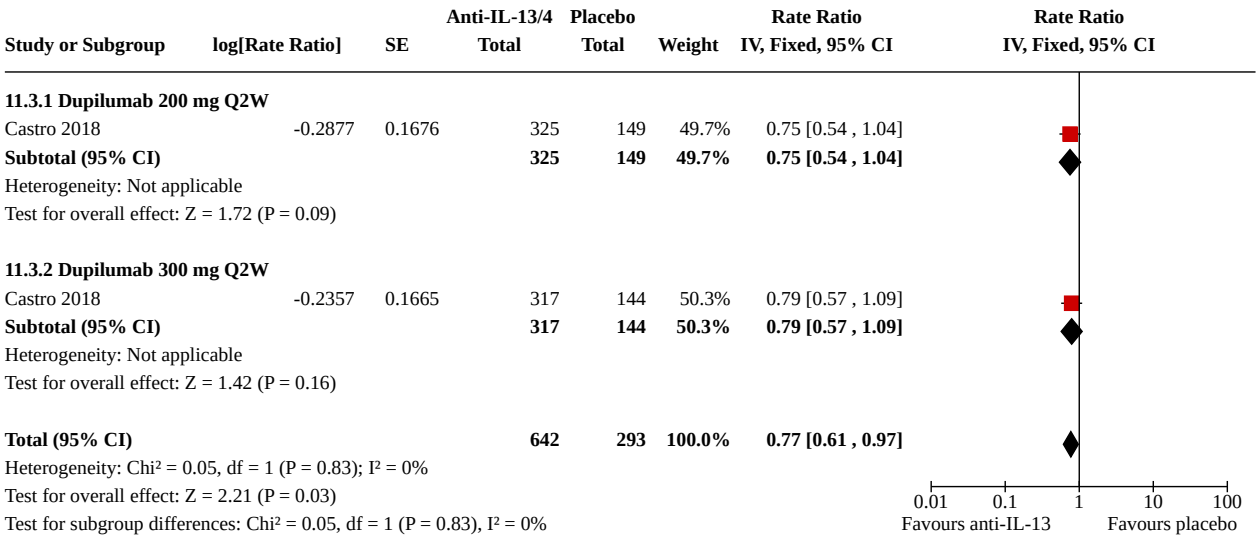
Analysis 11.1. Comparison 11: Subanalysis by FENO: exacerbations requiring hospitalisation/ED/OCS, Outcome 1: FENO high (≥ 50 ppb)



Analysis 11.2. Comparison 11: Subanalysis by FENO: exacerbations requiring hospitalisation/ED/OCS, Outcome 2: FENO medium (≥ 25 to < 50 ppb)



Analysis 11.3. Comparison 11: Subanalysis by FENO: exacerbations requiring hospitalisation/ED/OCS, Outcome 3: FENO low (< 25 ppb)



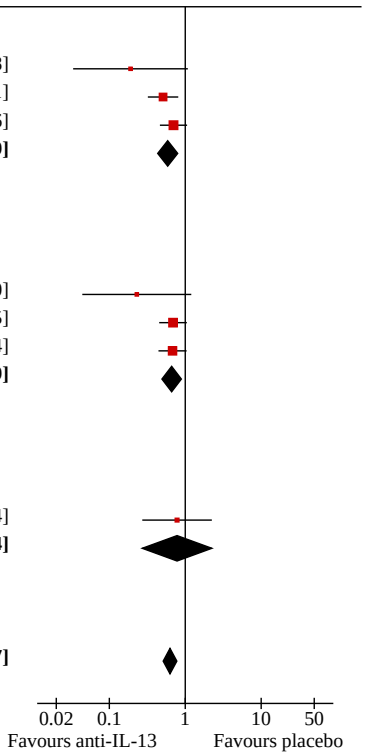
Comparison 12. Subanalysis by periostin level: exacerbations requiring hospitalisation/ED/OCS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Periostin high (≥ 50 ng/mL)	3	1499	Rate Ratio (IV, Fixed, 95% CI)	0.63 [0.51, 0.77]
12.1.1 Lebrikizumab 37.5 mg	3	717	Rate Ratio (IV, Fixed, 95% CI)	0.59 [0.43, 0.79]
12.1.2 Lebrikizumab 125 mg	3	715	Rate Ratio (IV, Fixed, 95% CI)	0.66 [0.49, 0.89]

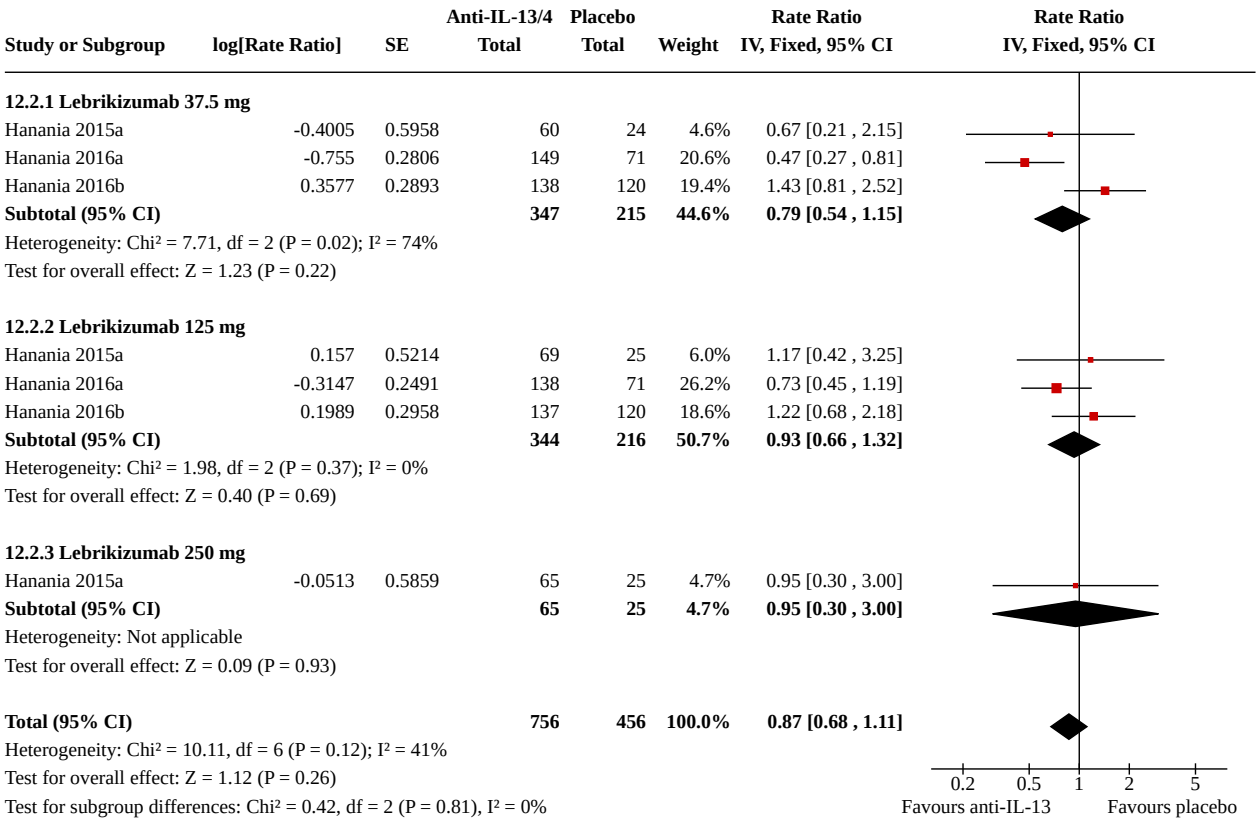
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1.3 Lebrikizumab 250 mg	1	67	Rate Ratio (IV, Fixed, 95% CI)	0.78 [0.27, 2.24]
12.2 Periostin low (< 50 ng/mL)	3	1212	Rate Ratio (IV, Fixed, 95% CI)	0.87 [0.68, 1.11]
12.2.1 Lebrikizumab 37.5 mg	3	562	Rate Ratio (IV, Fixed, 95% CI)	0.79 [0.54, 1.15]
12.2.2 Lebrikizumab 125 mg	3	560	Rate Ratio (IV, Fixed, 95% CI)	0.93 [0.66, 1.32]
12.2.3 Lebrikizumab 250 mg	1	90	Rate Ratio (IV, Fixed, 95% CI)	0.95 [0.30, 3.00]

Analysis 12.1. Comparison 12: Subanalysis by periostin level: exacerbations requiring hospitalisation/ED/OCS, Outcome 1: Periostin high (≥ 50 ng/mL)

Study or Subgroup	log[Rate Ratio]	SE	Anti-IL-13/4 Total	Placebo Total	Weight	Rate Ratio IV, Fixed, 95% CI
12.1.1 Lebrikizumab 37.5 mg						
Hanania 2015a	-1.6607	0.8874	57	14	1.4%	0.19 [0.03 , 1.08]
Hanania 2016a	-0.6733	0.2353	211	110	20.1%	0.51 [0.32 , 0.81]
Hanania 2016b	-0.3567	0.2103	218	107	25.2%	0.70 [0.46 , 1.06]
Subtotal (95% CI)			**486**	**231**	**46.7%**	**0.59 [0.43 , 0.79]**
Heterogeneity: Chi² = 2.67, df = 2 (P = 0.26); I² = 25%						
Test for overall effect: Z = 3.45 (P = 0.0006)						
12.1.2 Lebrikizumab 125 mg						
Hanania 2015a	-1.4697	0.8432	43	14	1.6%	0.23 [0.04 , 1.20]
Hanania 2016a	-0.3711	0.2138	221	110	24.4%	0.69 [0.45 , 1.05]
Hanania 2016b	-0.3857	0.2176	220	107	23.5%	0.68 [0.44 , 1.04]
Subtotal (95% CI)			**484**	**231**	**49.4%**	**0.66 [0.49 , 0.89]**
Heterogeneity: Chi² = 1.62, df = 2 (P = 0.44); I² = 0%						
Test for overall effect: Z = 2.75 (P = 0.006)						
12.1.3 Lebrikizumab 250 mg						
Hanania 2015a	-0.2485	0.5381	53	14	3.8%	0.78 [0.27 , 2.24]
Subtotal (95% CI)			**53**	**14**	**3.8%**	**0.78 [0.27 , 2.24]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
Total (95% CI)			**1023**	**476**	**100.0%**	**0.63 [0.51 , 0.77]**
Heterogeneity: Chi² = 4.77, df = 6 (P = 0.57); I² = 0%						
Test for overall effect: Z = 4.38 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.47, df = 2 (P = 0.79), I² = 0%						



Analysis 12.2. Comparison 12: Subanalysis by periostin level: exacerbations requiring hospitalisation/ED/OCS, Outcome 2: Periostin low (< 50 ng/mL)



Comparison 13. Sensitvity analysis - random-effects

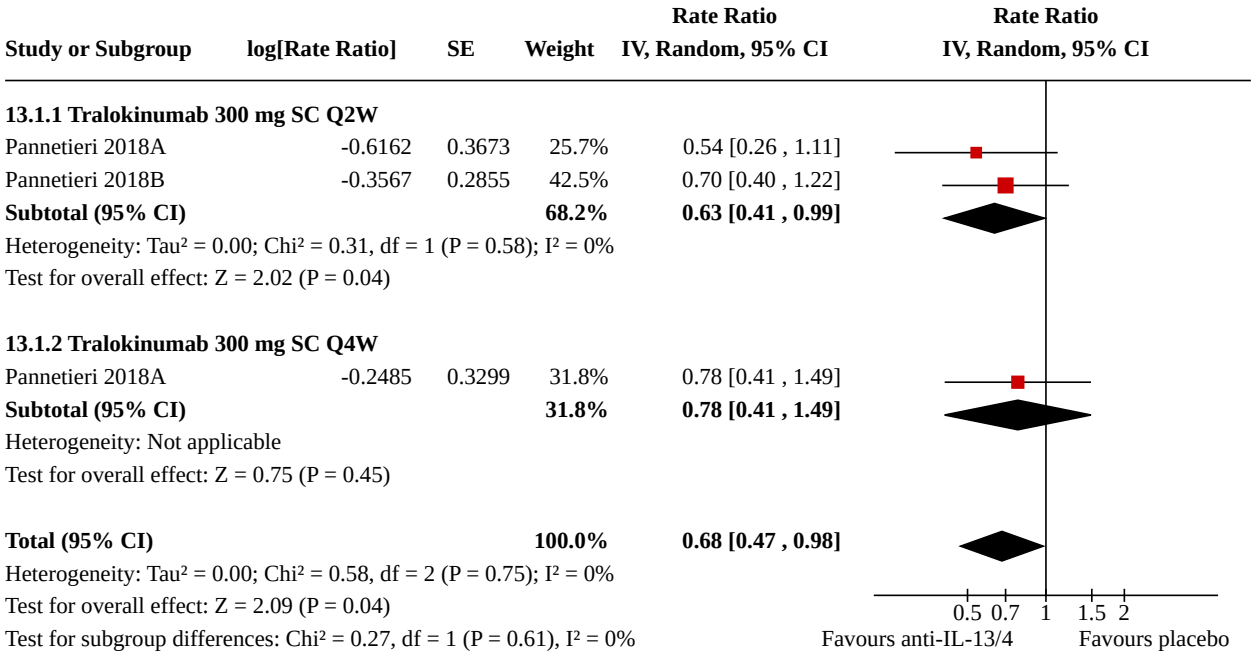
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Exacerbation requiring hospitalisation or ED visit	2		Rate Ratio (IV, Random, 95% CI)	0.68 [0.47, 0.98]
13.1.1 Tralokinumab 300 mg SC Q2W	2		Rate Ratio (IV, Random, 95% CI)	0.63 [0.41, 0.99]
13.1.2 Tralokinumab 300 mg SC Q4W	1		Rate Ratio (IV, Random, 95% CI)	0.78 [0.41, 1.49]
13.2 Health-related quality of life (adjusted mean diff versus placebo)	7		Mean Difference (IV, Random, 95% CI)	0.18 [0.12, 0.24]
13.2.1 Lebrikizumab 125 mg SC Q4W	1		Mean Difference (IV, Random, 95% CI)	-0.06 [-0.29, 0.17]
13.2.2 Dupilumab 200 mg SC Q2W	2		Mean Difference (IV, Random, 95% CI)	0.29 [0.16, 0.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2.3 Dupilumab 200 mg SC Q4W	1		Mean Difference (IV, Random, 95% CI)	0.23 [-0.13, 0.59]
13.2.4 Dupilumab 300 mg SC Q2W	2		Mean Difference (IV, Random, 95% CI)	0.27 [0.14, 0.40]
13.2.5 Dupilumab 300 mg SC Q4W	1		Mean Difference (IV, Random, 95% CI)	0.30 [-0.06, 0.66]
13.2.6 Tralokinumab 300 mg SC Q2W	3		Mean Difference (IV, Random, 95% CI)	0.11 [-0.00, 0.23]
13.2.7 Tralokinumab 300 mg SC Q4W	2		Mean Difference (IV, Random, 95% CI)	0.14 [-0.02, 0.30]
13.2.8 AMG317 75 mg SC Q1W	1		Mean Difference (IV, Random, 95% CI)	-0.12 [-0.60, 0.36]
13.2.9 AMG317 150 mg SC Q1W	1		Mean Difference (IV, Random, 95% CI)	0.07 [-0.44, 0.58]
13.2.10 AMG317 300 mg SC Q1W	1		Mean Difference (IV, Random, 95% CI)	0.10 [-0.44, 0.64]
13.3 Serious adverse events	22	7739	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.76, 1.09]
13.3.1 Soluble IL-4R 500 ug nebulised	1	12	Odds Ratio (M-H, Random, 95% CI)	Not estimable
13.3.2 Soluble IL-4R 1500 ug nebulised	1	13	Odds Ratio (M-H, Random, 95% CI)	Not estimable
13.3.3 Tralokinumab 1 mg/kg IV Q4W	2	12	Odds Ratio (M-H, Random, 95% CI)	Not estimable
13.3.4 Tralokinumab 5 mg/kg IV Q4W	2	14	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.02, 23.07]
13.3.5 Tralokinumab 10 mg/kg IV Q4W	2	10	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.03, 53.51]
13.3.6 Tralokinumab 150 mg SC Q2W	1	62	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.05, 7.39]
13.3.7 Tralokinumab 300 mg SC Q2W	6	1955	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.58, 1.06]
13.3.8 Tralokinumab 300 mg SC Q4W	2	831	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.58, 1.39]
13.3.9 Tralokinumab 600 mg SC Q2W	1	64	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.02, 5.42]

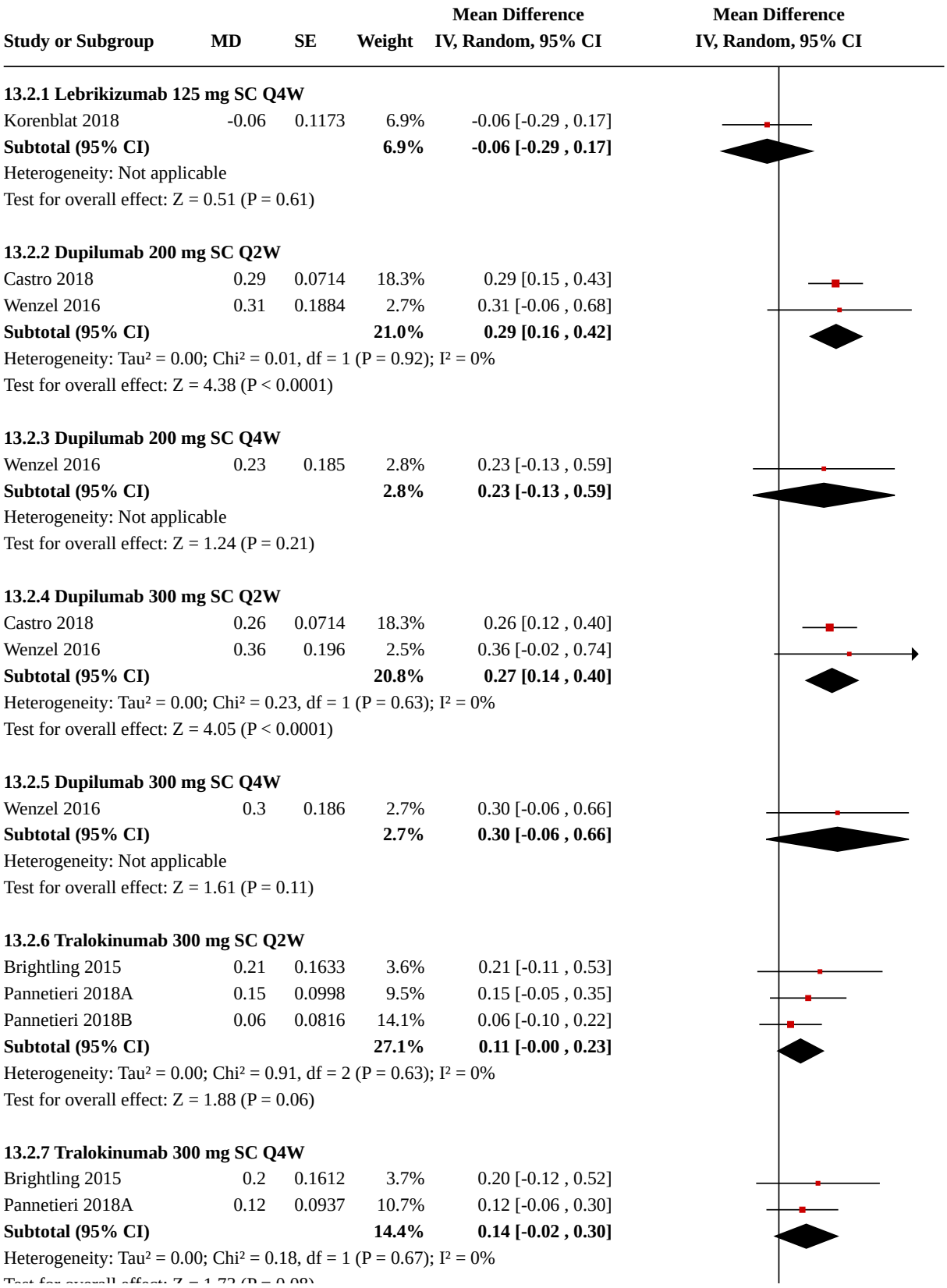
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.3.10 Lebrikizumab 37.5 mg SC Q4W	1	155	Odds Ratio (M-H, Random, 95% CI)	0.16 [0.01, 1.76]
13.3.11 Lebrikizumab 125 mg SC Q4W	3	428	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.41, 4.94]
13.3.12 Lebrikizumab 250 mg SC Q4W	3	445	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.28, 1.87]
13.3.13 Lebrikizumab 500 mg SC Q4W	1	70	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.04, 27.64]
13.3.14 AMG317 75 mg SC Q1W	1	97	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.06, 7.91]
13.3.15 AMG317 150 mg SC Q1W	1	98	Odds Ratio (M-H, Random, 95% CI)	Not estimable
13.3.16 AMG317 300 mg SC Q1W	1	96	Odds Ratio (M-H, Random, 95% CI)	Not estimable
13.3.17 GSK679586 2.5 mg/kg IV Q4W	1	8	Odds Ratio (M-H, Random, 95% CI)	Not estimable
13.3.18 GSK679586 10 mg/kg IV Q4W	2	206	Odds Ratio (M-H, Random, 95% CI)	1.65 [0.52, 5.24]
13.3.19 GSK679586 20 mg/kg IV Q4W	1	12	Odds Ratio (M-H, Random, 95% CI)	1.24 [0.04, 38.30]
13.3.20 RPC4046 0.3 mg/kg IV Q1W	1	6	Odds Ratio (M-H, Random, 95% CI)	Not estimable
13.3.21 RPC4046 3 mg/kg IV Q1W	1	6	Odds Ratio (M-H, Random, 95% CI)	Not estimable
13.3.22 Dupilumab 300 mg SC Q1W	1	104	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.03, 3.18]
13.3.23 Dupilumab 200 mg SC Q2W	2	1131	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.60, 1.54]
13.3.24 Dupilumab 200 mg SC Q4W	1	189	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.15, 3.98]
13.3.25 Dupilumab 300 mg SC Q2W	3	1359	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.76, 1.76]
13.3.26 Dupilumab 300 mg SC Q4W	1	197	Odds Ratio (M-H, Random, 95% CI)	1.40 [0.39, 5.06]
13.3.27 IMA-638 IV 0.2 mg/kg (D1/8/28/56/84)	1	21	Odds Ratio (M-H, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.3.28 IMA-638 IV 0.6 mg/kg (D1/8/28/56/84)	1	22	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.04, 28.30]
13.3.29 IMA-638 IV 2 mg/kg (D1/8/28/56/84)	1	22	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.05, 9.70]
13.3.30 IMA-638 IV 200 mg SC (D1/8/28/42/56/70/84)	1	67	Odds Ratio (M-H, Random, 95% CI)	2.59 [0.12, 56.20]
13.3.31 IMA-638 IV 75 mg SC (D1/8/28/42/56/70/84)	1	27	Odds Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 13.1. Comparison 13: Sensitvity analysis - random-effects, Outcome 1: Exacerbation requiring hospitalisation or ED visit



Analysis 13.2. Comparison 13: Sensitvity analysis - random-effects, Outcome 2: Health-related quality of life (adjusted mean diff versus placebo)



Analysis 13.2. (Continued)

Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.73 (P = 0.08)

13.2.8 AMG317 75 mg SC Q1W

Corren 2010	-0.12	0.2457	1.6%	-0.12 [-0.60 , 0.36]
Subtotal (95% CI)			**1.6%**	**-0.12 [-0.60 , 0.36]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.63)

13.2.9 AMG317 150 mg SC Q1W

Corren 2010	0.07	0.2579	1.4%	0.07 [-0.44 , 0.58]
Subtotal (95% CI)			**1.4%**	**0.07 [-0.44 , 0.58]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)

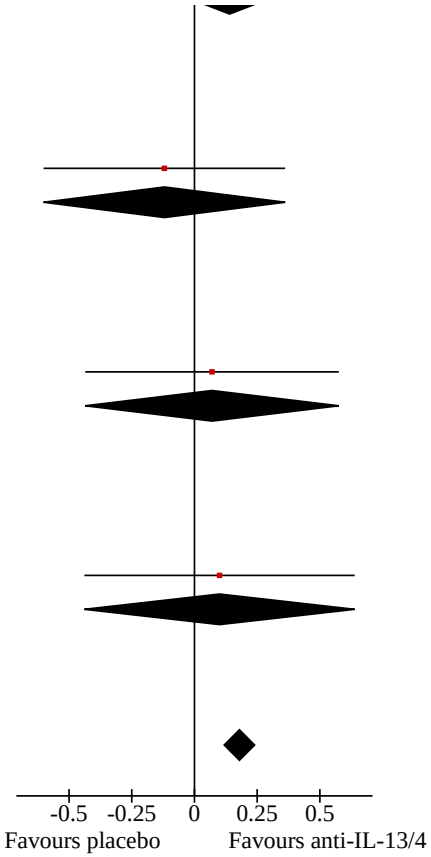
13.2.10 AMG317 300 mg SC Q1W

Corren 2010	0.1	0.2749	1.3%	0.10 [-0.44 , 0.64]
Subtotal (95% CI)			**1.3%**	**0.10 [-0.44 , 0.64]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

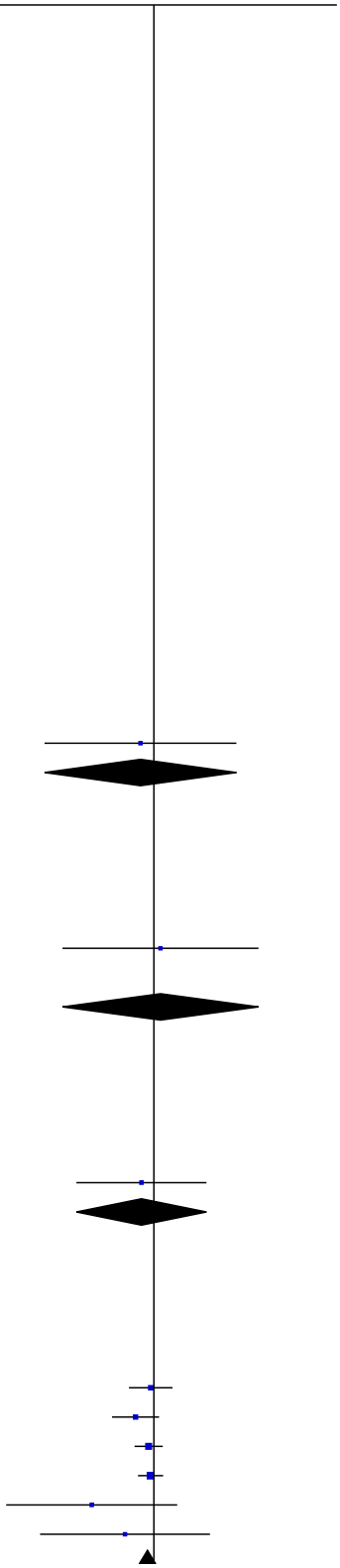
Total (95% CI)			**100.0%**	**0.18 [0.12 , 0.24]**

Heterogeneity: Tau² = 0.00; Chi² = 14.09, df = 14 (P = 0.44); I² = 1%
Test for overall effect: Z = 5.81 (P < 0.00001)
Test for subgroup differences: Chi² = 12.76, df = 9 (P = 0.17), I² = 29.5%



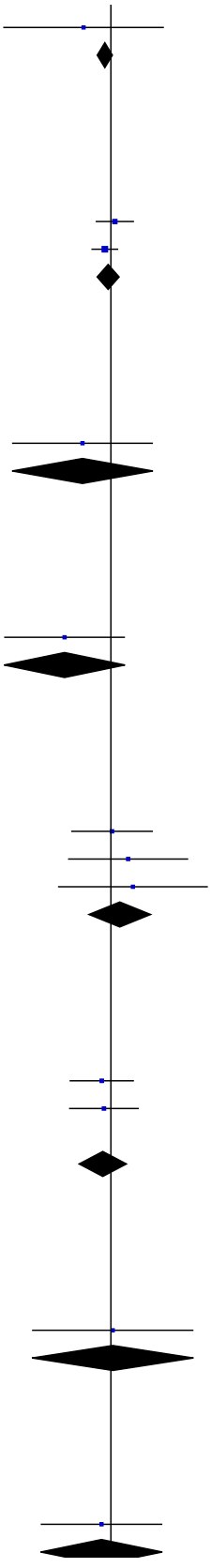
Analysis 13.3. Comparison 13: Sensitvity analysis - random-effects, Outcome 3: Serious adverse events

Study or Subgroup	Anti-IL-13 or -4 Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
13.3.1 Soluble IL-4R 500 ug nebulised						
Borish 1999	0	8	0	4		Not estimable
Subtotal (95% CI)		**8**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
13.3.2 Soluble IL-4R 1500 ug nebulised						
Borish 1999	0	9	0	4		Not estimable
Subtotal (95% CI)		**9**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
13.3.3 Tralokinumab 1 mg/kg IV Q4W						
NCT00640016	0	2	0	1		Not estimable
Singh 2010	0	8	0	1		Not estimable
Subtotal (95% CI)		**10**		**2**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
13.3.4 Tralokinumab 5 mg/kg IV Q4W						
NCT00640016	0	4	0	1		Not estimable
Singh 2010	1	8	0	1	0.2%	0.60 [0.02 , 23.07]
Subtotal (95% CI)		**12**		**2**	**0.2%**	**0.60 [0.02 , 23.07]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.78)						
13.3.5 Tralokinumab 10 mg/kg IV Q4W						
NCT00640016	1	4	0	1	0.2%	1.29 [0.03 , 53.51]
Singh 2010	0	3	0	2		Not estimable
Subtotal (95% CI)		**7**		**3**	**0.2%**	**1.29 [0.03 , 53.51]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.89)						
13.3.6 Tralokinumab 150 mg SC Q2W						
Piper 2013	2	47	1	15	0.5%	0.62 [0.05 , 7.39]
Subtotal (95% CI)		**47**		**15**	**0.5%**	**0.62 [0.05 , 7.39]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.71)						
13.3.7 Tralokinumab 300 mg SC Q2W						
Brightling 2015	18	150	10	75	4.7%	0.89 [0.39 , 2.03]
Busse 2015	9	70	16	70	4.0%	0.50 [0.20 , 1.22]
Pannetieri 2018A	40	398	24	200	11.2%	0.82 [0.48 , 1.40]
Pannetieri 2018B	35	425	39	422	14.2%	0.88 [0.55 , 1.42]
Piper 2013	0	51	1	15	0.3%	0.09 [0.00 , 2.43]
Russell 2018	0	39	1	40	0.3%	0.33 [0.01 , 8.43]
Subtotal (95% CI)		**1133**		**822**	**34.7%**	**0.78 [0.58 , 1.06]**



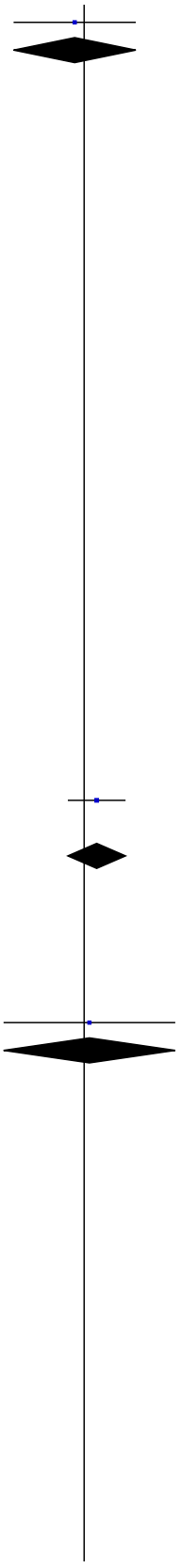
Analysis 13.3. (Continued)

Russell 2018	0	39	1	40	0.3%	0.33 [0.01 , 8.43]
Subtotal (95% CI)		**1133**		**822**	**34.7%**	**0.78 [0.58 , 1.06]**
Total events:	102		91			
Heterogeneity: Tau² = 0.00; Chi² = 3.24, df = 5 (P = 0.66); I² = 0%						
Test for overall effect: Z = 1.57 (P = 0.12)						
13.3.8 Tralokinumab 300 mg SC Q4W						
Brightling 2015	25	151	11	76	5.5%	1.17 [0.54 , 2.53]
Pannetieri 2018A	39	404	24	200	11.1%	0.78 [0.46 , 1.34]
Subtotal (95% CI)		**555**		**276**	**16.6%**	**0.89 [0.58 , 1.39]**
Total events:	64		35			
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.62)						
13.3.9 Tralokinumab 600 mg SC Q2W						
Piper 2013	1	48	1	16	0.4%	0.32 [0.02 , 5.42]
Subtotal (95% CI)		**48**		**16**	**0.4%**	**0.32 [0.02 , 5.42]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
13.3.10 Lebrikizumab 37.5 mg SC Q4W						
Hanania 2015a	1	117	2	38	0.5%	0.16 [0.01 , 1.76]
Subtotal (95% CI)		**117**		**38**	**0.5%**	**0.16 [0.01 , 1.76]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
13.3.11 Lebrikizumab 125 mg SC Q4W						
Hanania 2015a	6	112	2	39	1.2%	1.05 [0.20 , 5.42]
Korenblat 2018	2	104	1	103	0.6%	2.00 [0.18 , 22.40]
Noonan 2013	3	53	0	17	0.4%	2.43 [0.12 , 49.34]
Subtotal (95% CI)		**269**		**159**	**2.1%**	**1.43 [0.41 , 4.94]**
Total events:	11		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.57 (P = 0.57)						
13.3.12 Lebrikizumab 250 mg SC Q4W						
Corren 2011	4	106	6	112	1.9%	0.69 [0.19 , 2.53]
Hanania 2015a	7	118	3	39	1.6%	0.76 [0.19 , 3.08]
Noonan 2013	0	53	0	17		Not estimable
Subtotal (95% CI)		**277**		**168**	**3.6%**	**0.72 [0.28 , 1.87]**
Total events:	11		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
13.3.13 Lebrikizumab 500 mg SC Q4W						
Noonan 2013	1	52	0	18	0.3%	1.08 [0.04 , 27.64]
Subtotal (95% CI)		**52**		**18**	**0.3%**	**1.08 [0.04 , 27.64]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
13.3.14 AMG317 75 mg SC Q1W						
Corren 2010	2	72	1	25	0.5%	0.69 [0.06 , 7.91]
Subtotal (95% CI)		**72**		**25**	**0.5%**	**0.69 [0.06 , 7.91]**



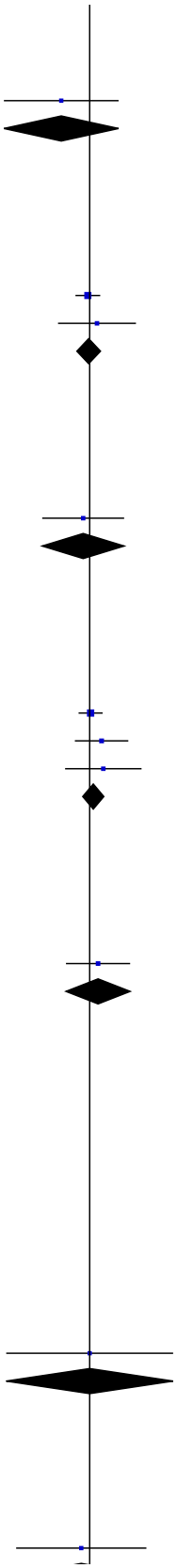
Analysis 13.3. (Continued)

Corren 2010	2	72	1	25	0.5%	0.69 [0.06 , 7.91]	
Subtotal (95% CI)		**72**		**25**	**0.5%**	**0.69 [0.06 , 7.91]**	
Total events:	2		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.30 (P = 0.76)							
13.3.15 AMG317 150 mg SC Q1W							
Corren 2010	0	73	0	25		Not estimable	
Subtotal (95% CI)		**73**		**25**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
13.3.16 AMG317 300 mg SC Q1W							
Corren 2010	0	72	0	24		Not estimable	
Subtotal (95% CI)		**72**		**24**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
13.3.17 GSK679586 2.5 mg/kg IV Q4W							
Hodsman 2013	0	6	0	2		Not estimable	
Subtotal (95% CI)		**6**		**2**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
13.3.18 GSK679586 10 mg/kg IV Q4W							
De Boever 2014	8	99	5	99	2.4%	1.65 [0.52 , 5.24]	
Hodsman 2013	0	6	0	2		Not estimable	
Subtotal (95% CI)		**105**		**101**	**2.4%**	**1.65 [0.52 , 5.24]**	
Total events:	8		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.85 (P = 0.39)							
13.3.19 GSK679586 20 mg/kg IV Q4W							
Hodsman 2013	1	9	0	3	0.3%	1.24 [0.04 , 38.30]	
Subtotal (95% CI)		**9**		**3**	**0.3%**	**1.24 [0.04 , 38.30]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.12 (P = 0.90)							
13.3.20 RPC4046 0.3 mg/kg IV Q1W							
Tripp 2017	0	4	0	2		Not estimable	
Subtotal (95% CI)		**4**		**2**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
13.3.21 RPC4046 3 mg/kg IV Q1W							
Tripp 2017	0	4	0	2		Not estimable	
Subtotal (95% CI)		**4**		**2**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



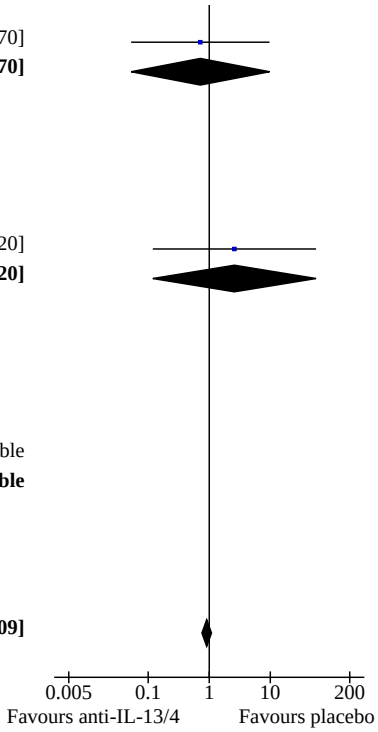
Analysis 13.3. (Continued)

Test for overall effect: Not applicable						
13.3.22 Dupilumab 300 mg SC Q1W						
Wenzel 2013	1	52	3	52	0.6%	0.32 [0.03 , 3.18]
Subtotal (95% CI)		**52**		**52**	**0.6%**	**0.32 [0.03 , 3.18]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
13.3.23 Dupilumab 200 mg SC Q2W						
Castro 2018	49	631	26	313	13.1%	0.93 [0.57 , 1.53]
Wenzel 2016	10	148	2	39	1.3%	1.34 [0.28 , 6.39]
Subtotal (95% CI)		**779**		**352**	**14.5%**	**0.96 [0.60 , 1.54]**
Total events:	59		28			
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.16 (P = 0.87)						
13.3.24 Dupilumab 200 mg SC Q4W						
Wenzel 2016	6	150	2	39	1.2%	0.77 [0.15 , 3.98]
Subtotal (95% CI)		**150**		**39**	**1.2%**	**0.77 [0.15 , 3.98]**
Total events:	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
13.3.25 Dupilumab 300 mg SC Q2W						
Castro 2018	55	632	27	321	13.9%	1.04 [0.64 , 1.68]
Rabe 2018	9	103	6	107	2.8%	1.61 [0.55 , 4.70]
Wenzel 2016	13	156	2	40	1.4%	1.73 [0.37 , 7.99]
Subtotal (95% CI)		**891**		**468**	**18.1%**	**1.16 [0.76 , 1.76]**
Total events:	77		35			
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
13.3.26 Dupilumab 300 mg SC Q4W						
Wenzel 2016	16	157	3	40	2.0%	1.40 [0.39 , 5.06]
Subtotal (95% CI)		**157**		**40**	**2.0%**	**1.40 [0.39 , 5.06]**
Total events:	16		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
13.3.27 IMA-638 IV 0.2 mg/kg (D1/8/28/56/84)						
NCT00425061	0	16	0	5		Not estimable
Subtotal (95% CI)		**16**		**5**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
13.3.28 IMA-638 IV 0.6 mg/kg (D1/8/28/56/84)						
NCT00425061	1	17	0	5	0.3%	1.00 [0.04 , 28.30]
Subtotal (95% CI)		**17**		**5**	**0.3%**	**1.00 [0.04 , 28.30]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
13.3.29 IMA-638 IV 2 mg/kg (D1/8/28/56/84)						
NCT00425061	2	16	1	6	0.5%	0.71 [0.05 , 9.70]



Analysis 13.3. (Continued)

13.3.29 IMA-638 IV 2 mg/kg (D1/8/28/56/84)						
NCT00425061	2	16	1	6	0.5%	0.71 [0.05 , 9.70]
Subtotal (95% CI)		**16**		**6**	**0.5%**	**0.71 [0.05 , 9.70]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
13.3.30 IMA-638 IV 200 mg SC (D1/8/28/42/56/70/84)						
NCT00425061	2	45	0	22	0.3%	2.59 [0.12 , 56.20]
Subtotal (95% CI)		**45**		**22**	**0.3%**	**2.59 [0.12 , 56.20]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
13.3.31 IMA-638 IV 75 mg SC (D1/8/28/42/56/70/84)						
NCT00425061	0	4	0	23		Not estimable
Subtotal (95% CI)		**4**		**23**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**5016**		**2723**	**100.0%**	**0.91 [0.76 , 1.09]**
Total events:	370		220			
Heterogeneity: Tau² = 0.00; Chi² = 13.85, df = 32 (P = 1.00); I² = 0%						
Test for overall effect: Z = 1.04 (P = 0.30)						
Test for subgroup differences: Chi² = 8.55, df = 20 (P = 0.99), I² = 0%						



ADDITIONAL TABLES

Table 1. Summary of included study characteristics

Study	Intervention	Treatment duration (weeks[c])	Asthma severity	ICS use	N randomised	Age range, years	Range % male	BL % pred. FEV1
Borish 1999	IL-4R 500/1500 µg single dose	2	Moderate atopic	Discontinued prior to study drug	25 (17/8)	35 to 38	25 to 63	7 to 87
Borish 2001	IL-4R 0.75/1.5/3.0 mg Q1W	12	Moderate-to-severe	Discontinued prior to study drug	62 (46/16)	36 to 46	25 to 37	75 to76
Brightling 2015 (NCT01402986)	Tralokinumab 300 mg Q2W or Q4W	52	Severe uncontrolled	Maintained through study	452 (376/76)	50 to 51	33 to 36	68 to 69
Burgess 2018 (NCT02473939)	VR492 0.5/10/20 mg as DPI	28	Mild	Maintained through study	45 (29/16)	29 to 30	100	77 to 89
Busse 2015 (NCT02281357)	Tralokinumab 300 mg Q2W	40	Severe	Maintained through study	140 (70/70)	54 to 55	32 to 44	NR
Castro 2018 (NCT02414854)	Dupilumab 200/300 mg SC Q2W	52	Severe uncontrolled	ICS permitted (≥ 500 µg FP or equiv.)	1902 (1264/638)	48	37	58
Corren 2010 (NCT 00436670)	Tralokinumab 75/150/300 mg Q1W	12	Moderate-to-severe	Stable doses of ICS (200 to 1000 µg FP or equiv.)	294 (220/74)	40 to 43	38 to 46	67 to 70
Corren 2011 (NCT00930163)	Lebrikizumab 250 mg SC Q4W	24	Moderate-to-severe uncontrolled	ICS maintained throughout study (≥ 200 and ≤ 1000 µg FP daily or equiv.)	218 (106/112)	44 to 45	33 to 35	64 to 66
De Boever 2014 (NCT00843193)	GSK679586 10 mg/kg IV Q4W	12	Severe refractory	Max recommended ICS doses maintained	198 (99/99)	51	48 to 51	55 to 58
Gauvreau 2011a (NCT00410280)	IMA-638 4 mg/kg (2 doses, 1 week apart)	AC study (2)	Mild, allergic asthma	Not permitted	27 (14/13)	26 to 32	38 to 50	87 to 93

Table 1. Summary of included study characteristics *(Continued)*

Gauvreau 2011b (NCT00725582)	IMA-638 4 mg/kg (2 doses, 1 week apart)	AC study (2)	Mild, allergic asthma	Not permitted	29 (14/15)	33 to 34	50 to 53	87 to 91
Hanania 2011	Lebrikizumab (dose not stated)	24	Uncontrolled by ICS	Maintained throughout study	180 (88/92)	NR	NR	NR
Hanania 2015a (NCT01545440)	Lebrikizumab 37.5/125/250 mg SC Q4W	52[a]	Moderate-to-severe uncontrolled	SOC maintained (500 to 2000 µg/day FPA or equiv.)	463 (347/116)	47 to 50	39 to 57	61 to 63
Hanania 2015b (NCT01545453)	Lebrikizumab 37.5/125/250 mg SC Q4W	52[a]	Moderate-to-severe uncontrolled	SOC maintained (500 to 2000 µg/day FPA or equiv.)	See Hanania 2015a [a]			
Hanania 2016a (NCT01867125)	Lebrikizumab 37.5/125 mg SC Q4W	52	Moderate-to-severe uncontrolled	SOC maintained (500 to 2000 µg/day FPA or equiv.)	1081 (719/362)	51	31 to 36	61
Hanania 2016b (NCT01868061)	Lebrikizumab 37.5/125 mg SC Q4W	52	Moderate-to-severe uncontrolled	SOC maintained (500 to 2000 µg/day FPA or equiv.)	1067 (713/354)	50 to 51	34 to 43	61
Hodsman 2013 [b] (NCT00411814)	GSK679586 2.5/10/20 mg/kg Q4W	12	Mild bronchial	Not permitted	28 (21/7)	25 to 32	100	102 to 105
Korenblat 2018 (NCT02104674)	Lebrikizumab 125 mg SC Q4W	12	Mild-to-moderate	Discontinued 30 days prior to study drug	211 (105/106)	43 to 45	37 to 39	72
NCT00425061	IMA-638 0.2/0.6/2/ mg/kg SC D1/8/28/56/70/84	16	Moderate-to-severe persistent	Medium-to-high dose permitted	159 (98/61)	NR	39 to 45	NR
NCT00640016	Tralokinumab 1/5/10 mg/kg Q4W	12	Uncontrolled refractory	Maintained (≥ 800 µg BDP or equiv.)	14 (11/3)	34 to 41	0 to 75	NR
Noonan 2013 (NCT00971035)	Lebrikizumab 125/250/500 mg SC Q4W	12	Stable, mild-to-moderate	Not permitted	212 (160/52)	38 to 41	32 to 43	72 to 4
Pannetieri 2018A (NCT02161757)	Tralokinumab 300 mg SC Q2W or Q4W	52	Severe uncontrolled	Stable dose (≥ 500 µg FP or equiv.)	1207 (807/400)	49 to 51	30 to 37	60 to 62

Table 1. Summary of included study characteristics *(Continued)*

Pannetieri 2018B (NCT02194699)	Tralokinumab 300 mg SC Q2W	52	Severe uncontrolled	Stable dose (≥ 500 µg FP or equiv.)	856 (428/428)	47 to 48	31 to 34	61
Piper 2013 (NCT00873860)	Tralokinumab 150/300/600 mg SC Q2W	12	Moderate-to-severe uncontrolled	Permitted	194 (146/48)	43 to 50	29 to 60	NR
Rabe 2018 (NCT02528214)	Dupilumab 300 mg SC Q2W	24	Severe asthma	Tapered down	210 (103/107)	51 to 52	39 to 40	NR
Russell 2018 (NCT02449473)	Tralokinumab 300 mg SC Q2W	12	Moderate-to-severe uncontrolled	Stable dose (≥ 250 µg FP daily or equiv.)	79 (39/40)	47 to 50	41 to 50	NR
Scheerens 2014 (NCT00781443)	Lebrikizumab 5 mg/kg SC Q4W	AC study (12)	Mild	Not stated	29 (13/16)	32 to 66	46 to 56	82-84
Singh 2010 [b] (NCT00974675)	Tralokinumab 1/5/10 mg/kg IV Q4W	21	Mild well-controlled	Permitted	23 (19/4)	35 to 43	67 to 100	NR
Tripp 2017 [b] (NCT00986037)	RPC4046 0.3/3 mg/kg IV Q1W	16	Mild-to-moderate controlled	Low-to-medium dose permitted	27 (20/7)	23 to 33	75 to 100	NR
Wenzel 2007a (NCT00535028)	Pitrakinra 25 mg SC once daily for 28 days	AC study (28 days)	Mild-to-moderate	Discontinued 1 month prior to study drug	24 (12/12)	30 to 31	42 to 58	100-102
Wenzel 2007b (NCT00535031)	Pitrakinra 60 mg nebulised twice daily for 28 days	AC study (28 days)	Mild-to-moderate	Discontinued 1 month prior to study drug	32 (16/16)	25 to 29	47 to 80	96 to -99
Wenzel 2010 (NCT00801853)	Pitrakinra 1/3/10 mg	12	Moderate-to-severe uncontrolled	Fluticasone withdrawal from 6 weeks after initiation of blinded treatment	534 (397/137)	NR	NR	NR
Wenzel 2013 (NCT01312961)	Dupilumab 300 mg SC Q1W	12	Moderate-to-severe	Medium-to-high dose discontinued during weeks 6 to 9	104 (52/52)	38 to 42	50	72

Table 1. Summary of included study characteristics *(Continued)*

Wenzel 2016 (NCT01854047)	Dupilumab 200/300 mg SC Q2/4W	24	Uncontrolled persistent asthma	Medium-to-high dose plus LABA	619 (461/158)	48 to 51	34 to 44	60 to 61

[a]This trial was designed to be 52 weeks; however, the trial was terminated early and the median duration of treatment was approximately 24 weeks. Pooled data are reported for the two replicate studies.
[b]Phase 1 safety and PK study
[c]Unless otherwise stated
Abbreviations: AC: allergen challenge; BDP: beclomethasone dipropionate; DPI: dry powder inhaler; FEV1: forced expiratory volume in one second; FP: fluticasone propionate; ICS: inhaled corticosteroids; IL-4R: interleukin-4 receptor; IL-13: interleukin-13; IV: intravenous; LABA: long-acting beta-agonist; NR: not reported; PK: pharmacokinetic; Q1/2/4W: every 1/2/4 weeks; SC: subcutaneous; SOC: standard of care.

Table 2. Sensitivity analysis: random effects versus fixed effects

Outcome	Fixed-effect model	Random-effects model
Exacerbation requiring hospitalisation or ED visit	RR 0.68, 95% CI 0.47 to 0.98 (participants = 2039; studies = 2)	RR 0.68, 95% CI 0.47 to 0.98
HRQoL (AQLQ)	MD 0.18, 95% CI 0.12 to 0.24 (participants = 4960; studies = 7)	MD 0.18, 95% CI 0.12 to 0.24
Serious adverse events	OR 0.91, 95% CI 0.76 to 1.09 (participants = 7739; studies = 22)	OR 0.91, 95% CI 0.76 to 1.09

Abbreviations: AQLQ: asthma quality of life questionnaire; CI: confidence interval; ED: emergency department; HRQoL: health-related quality of life; MD: mean difference; OR: odds ratio; RR: rate ratio.

APPENDICES

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

Electronic searches: core databases

Database	Dates searched	Frequency of search
CENTRAL (via the Cochrane Register of Studies (CRS))	From inception	Monthly
MEDLINE (Ovid)	1946 onwards	Weekly
Embase (Ovid)	1974 onwards	Weekly
PsycINFO (Ovid)	1967 onwards	Monthly
CINAHL (EBSCO)	1937 onwards	Monthly
AMED (EBSCO)	From inception	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards

(Continued)

International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

Asthma search

1. exp Asthma/

2. asthma$.mp.

3. (antiasthma$ or anti-asthma$).mp.

4. Respiratory Sounds/

5. wheez$.mp.

6. Bronchial Spasm/

7. bronchospas$.mp.

8. (bronch$ adj3 spasm$).mp.

9. bronchoconstrict$.mp.

10. exp Bronchoconstriction/

11. (bronch$ adj3 constrict$).mp.

12. Bronchial Hyperreactivity/

13. Respiratory Hypersensitivity/

14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.

15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.

16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomized or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

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

Appendix 2. Search strategy to identify relevant studies from the Cochrane Airways Trials Register

1. AST:MISC1

2. MeSH DESCRIPTOR Asthma Explode All

3. asthma*:ti,ab

4. #1 or #2 or #3

5. Lebrikizumab:TI,AB,KW

6. MILR1444A

7. GSK679586

8. Tralokinumab:TI,AB,KW

9. CAT-354

10. Anrukinzumab:TI,AB,KW

11. IMA-638

12. IMA-026

13. Pascolizumab:ti,ab,kw

14. SB 240683

15. Altrakincept:ti,ab,kw

16. AMG-317

17. Dupilumab:ti,ab,kw

18. REGN668

19. pitrakinra:ti,ab,kw

20. aerovant:ti,ab,kw

21. AER 001

22. IL-13:ti,ab,kw

23.anti-IL-13:ti,ab,kw

24. Interleukin 13:ti,ab,kw

25. anti-Interleukin-13:ti,ab,kw

26. IL-4:ti,ab,kw

27. anti-IL-4:ti,ab,kw

28. Interleukin 4:ti,ab,kw

29. anti-interleukin-4:ti,ab,kw

30. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29

31. #30 AND #4

HISTORY

Protocol first published: Issue 1, 2018

CONTRIBUTIONS OF AUTHORS

Andrew Gallagher: Developed the protocol, screened the search results, extracted the outcome data and interpreted the findings.

Michaela Edwards: Developed the protocol and conducted the risk of bias assessments.

Parameswaran Nair: Developed the protocol and interpreted the findings.

Stewart Drew: Developed the protocol, extracted the outcome data and extracted the study characteristics.

Aashish Vyas: Developed the protocol.

Rashmi Sharma: Developed the protocol and extracted the outcome data.

Paul A Marsden: Developed the protocol, extracted the outcome data, conducted the GRADE assessment and interpreted the findings.

Ran Wang: Developed the protocol, conducted the risk of bias assessments, extracted the study characteristics and interpreted the findings.

David JW Evans: Developed the protocol, screened the study results, extracted the outcome data, inputted the outcome data into RevMan, conducted the analyses and the GRADE assessment, extracted the study characteristics and interpreted the findings.

All review authors read and approved the final review version.

Contributions of editorial team

Chris Cates (Co-ordinating Editor) checked the data entry prior to the full write-up of the review.

Rebecca Fortescue: edited the review; advised on methodology, interpretation and content, approved the review prior to publication.

Wouter van Geffen (Contact Editor): edited the review; advised on methodology, interpretation and content.

Emma Dennett (Managing Editor): co-ordinated the editorial process; advised on interpretation and content; edited the review.

Emma Jackson (Assistant Managing Editor): conducted peer review; and edited the reference and other sections of the review.

Elizabeth Stovold (Information Specialist): designed the search strategy; ran the searches; edited the search methods section.

DECLARATIONS OF INTEREST

Andrew Gallagher: None known.

Michaela Edwards: None known.

Parameswaran Nair: In the past 2 years, has received research grants from Roche, Teva, Sanofi, AZ, Novartis, and BI, and has provided consultation and received honoraria from Roche, Teva, Sanofi, AZ, Novartis, Theravance, Knopp.

Drew Stuart: None known.

Aashish Vyas: None known.

Rashmi Sharma: None known.

Paul A Marsden: Has received lecture fees and conference accommodation and fees from industry and a resarch grant from Merck unrelated to the current review.

Ran Wang: None known.

David JW Evans: Provides freelance medical writing services to medical communications agencies.

SOURCES OF SUPPORT

Internal sources

- Lancaster University, UK

  David Evans was employed by Lancaster University as a Senior Research Associate. As part of his role, David worked on Cochrane systematic reviews.

External sources

- All, Other

The authors declare that no such funding was received for this systematic review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As few studies reported data on the prespecified primary endpoint for efficacy (exacerbations requiring hospitalisation or ED visit) and more studies reported the rate of exacerbations requiring hospitalisation, ED visit, or OCS use, this outcome was explored as an exploratory outcome. For future updates of the review, we would suggest that this outcome is selected for the primary efficacy outcome.

The protocol originally stated that we would use a random-effects model to allow for study heterogeneity, and perform sensitivity analysis with a fixed-effect model. However, the main analyses were conducted using a fixed-effect model, and the sensitivity analyses were conducted using a random-effects model; comparison of the data derived using the two models showed no difference in findings for the primary endpoints.

We did not explore possible small study and publication biases, as planned in the original protocol.

The protocol-specified inclusion and exclusion criteria resulted in several allergen challenge studies being eligible for inclusion in the review. However, these studies tended to evaluate a different clinical question (i.e. what was the effect of one or two doses of anti-interleukin-4/-13 agents on the asthmatic response to allergen triggers) that was not aligned with the primary objective of the review. Data from the allergen challenge studies was not considered in the present review, although, per the protocol, the studies were included and described narratively. We would suggest that the protocol is amended for future updates of this review to exclude allergen challenge studies.

INDEX TERMS

Medical Subject Headings (MeSH)

*Anti-Asthmatic Agents [therapeutic use]; *Asthma [drug therapy]; Disease Progression; Immunoglobulin E; Interleukin-13 [therapeutic use]; Interleukin-4 [therapeutic use]; Interleukin-5 [therapeutic use]; Quality of Life

MeSH check words

Adolescent; Adult; Child; Humans; Middle Aged; Young Adult