Appendix 1 Search criteria

Electronic search; electronic search was conducted monthly from 25th November 2015 till 25th January 2016. A second search was conducted on the 21st June 2017 to include articles published between 1st December 2015 and 30th June 2017.

Data base	Frequency of search
CENTRAL (Cochrane library)	Monthly
MEDLINE (Ovid)	Monthly
Embase (Ovid)	Monthly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED(EBSCO)	Monthly

The MEDLINE strategy and RCT filter (**Lefebvre 2011**) are adapted to identify trials in electronic databases.

#1 MeSH DESCRIPTOR severe asthma Explode All

#2 severe asthma

#3 brittle asthma

#4 uncontrolled asthma

#5 refractory asthma

#6 difficult to treat asthma

#7 poorly controlled asthma

#8 steroid dependent asthma

#9 irreversible asthma

#10 #2 or #3 or #4 or #5 or #6 or #7 or #8 AND #10

Filter to identify randomised controlled trials (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. 10 not 9

Appendix 2 Characteristics of included studies

Study reference	Ayres (Omalizumab) 2004
Study tittle	Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma
Study duration	52 weeks
Trial registration:	Not documented
Study Population	Participants: omalizumab group, n = 206; best standard care (BSC) alone group, n=106 Eligibility criteria: patients' age 12–75 years, with persistent (>2 years) moderate-to-severe allergic asthma (according to the NHLBI guidelines), whose disease was poorly controlled. Poor control was defined as ≥1 emergency room visit/hospitalization and ≥1 additional course of oral corticosteroids because of asthma in the last year
Setting	49 centres in five European countries; France, n = 10; Germany, n = 9; Spain, n= 7; Switzerland, n =3; United Kingdom, n =20
Interventions	BSC with or without subcutaneous omalizumab for 12 months
Adherence reported yes/no	No
Primary outcomes	The annualised number of asthma deterioration-related incidents (ADRIs)
Secondary outcomes	Annualized number of clinically significant asthma exacerbations, morning FEV1, use of rescue salbutamol, and Wasserfallen asthma symptom score

Study reference	Bardelas (Omalizumab) 2012
Study tittle	A 26-Week, Randomized, Double-Blind, Placebo-Controlled, Multicentre Study to Evaluate the Effect of Omalizumab on Asthma Control in Patients with Persistent Allergic Asthma
Study duration	2-week screening period. 24 weeks
Trial registration:	NCT00267202
Study Population	Participants: omalizumab group, n= 136; control group, n= 135 Eligibility criteria: patients' age ≥12 years; inadequately controlled persistent allergic asthma (ACT total score of ≤19); treated with Step 4 or higher asthma maintenance therapy(ICS + LABA/leukotriene receptor antagonist/theophylline/zileuton) according to the 2007 NHLBI guidelines; total serum IgE 30 to 700 IU/mL. One or more of the following with four weeks of screening phase: symptoms > 2 days/week; night-time awakenings ≥ 1 time/week; use of SABA > 2 days/week; FEV1 ≤ 80% predicted; background inhaled steroid dose: at least 250 mcg fluticasone twice daily or 320 mcg budesonide twice daily
Setting	United States
Interventions	Omalizumab administered subcutaneously based on body weight and serum IgE; 150 or 300 mg every four weeks or 225, 300 or 375 mg every two weeks versus placebo with same inactive ingredients as study drug for 24 weeks
Adherence reported yes/no	No
Primary outcomes	The change from baseline to week 24 in ACT total score
Secondary outcomes	The change from baseline to week 24 for the following outcomes; the Investigator's Global Evaluation of Treatment Effectiveness (IGETE). Work productivity and activity impairment questionnaire–asthma (WPAI-A), electronic diaries, FEV1, use of rescue corticosteroids, safety assessment

Study reference	Beeh (Tiotropium) 2014
Study tittle	Tiotropium Respimat® in asthma: a double-blind, randomised, dose-ranging study in adult patients with moderate asthma
Study duration	4-week run-in period. 16 weeks of treatment phase and 3 weeks follow up period
Trial registration:	NCT01233284
Study Population	Participants: crossover trial, 149 patients randomised Eligibility criteria: Male or female patients aged 18–75 years, with at least a 3-month history of asthma at the time of enrolment and an initial diagnosis of asthma made before the age of 40 years. Asthma maintenance treatment; stable medium-dose ICS (400–800 μg budesonide or equivalent), alone or in a fixed-dose combination with a LABA or short-acting β2-agonist, for at least 4 weeks prior to Visit 1. A diagnosis of asthma confirmed at Visit 1 was required with bronchodilator reversibility (15–30 minutes after 400 μg salbutamol) of ≥12% and ≥200 mL; ACQ-7 mean score of ≥1.5 at Visits 1 and 2, to have a pre-bronchodilator FEV1 of ≥60% and ≤90% of predicted normal FEV1 at Visit 1, and to demonstrate absolute FEV1 variability within 30% between Visits 1 and 2
Setting	19 sites in three European countries; Germany, Austria and Ukraine
Interventions	tiotropium 5 μg, 2.5 μg or 1.25 μg or placebo, all delivered via the Respimat® Soft Mist™ inhaler for 16 weeks
Adherence reported yes/no	No
Primary outcomes	Peak FEV1 measured within the first 3 hours after dosing, after every 4-week treatment period
Secondary outcomes	Trough FEV1; peak FVC within the first 3 hours after dosing (FVC)(0-3h); trough FVC; FEV1 area under the curve (AUC) within the first 3 hours after dosing {FEV1 AUC(0-3h)}; FVC AUC(0-3h); pre-dose PEF morning and PEF evening ACQ-7 at the end of every 4-week treatment period

Study reference	Berry (Eternacept) 2006
Study tittle	Evidence of a Role of Tumor Necrosis Factor α in Refractory Asthma
Study duration	24 weeks
Trial registration:	NCT00276029
Study Population	Participants: Crossover trial, 30 patients were randomised Eligibility criteria stated as: Patients with refractory asthma, as per ATS criteria with the exception that the daily dose of ICS required to meet the definition was modified to >2000 μg of beclomethasone or its equivalent to reflect European practice
Setting	Leicester, United Kingdom
Interventions	Placebo (1 ml of 0.9% saline) or etanercept (25 mg made into a 1-ml solution with the addition of the manufacturer's diluent) was administered subcutaneously twice weekly
Adherence reported yes/no	Yes
Primary outcomes	The difference in the change in the PC20 from 0 to 10 weeks between the placebo and etanercept treatment phases and the difference in the change in the asthma quality-of-life score from 0 to 10 weeks between the treatment phases
Secondary outcomes	The net change in post-bronchodilator FEV1, FEF25–75, and FVC; symptom scores; exhaled nitric oxide concentrations; computed alveolar nitric oxide concentrations; differential inflammatory cell counts in sputum; and mediator concentrations in sputum supernatant

Study reference	Bel Mepolizumab 2014
Study tittle	Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma
Study duration	3-8-week run-in period. 32 weeks
Trial registration:	NCT01691508
Study Population	Participants: mepolizumab group, n=69; placebo group, n=66 Eligibility criteria: at least a 6-month history of maintenance treatment with systemic glucocorticoids (5 to 35 mg per day of prednisone or its equivalent) before entering the study; high-dose inhaled glucocorticoids and an additional controller; blood eosinophil level of either ≥ 300 cells/μL during the 12-month period before screening or ≥150 cells/μL during the optimization phase
Setting	Amsterdam, Australia and United Kingdom
Interventions	Mepolizumab 100mg or placebo was administered subcutaneously once every 4 weeks until week 20
Adherence reported yes/no	No
Primary outcomes	Percentage reduction in the daily oral glucocorticoid dose during weeks 20 to 24 as compared with the dose determined during the optimization phase
Secondary outcomes	Proportions of patients who had a reduction of 50% or more in the oral glucocorticoid dose, who had a reduction in the oral glucocorticoid dose to a value of ≤5.0 mg per day, and who had a total cessation in oral glucocorticoid use; the median percentage reduction in the oral glucocorticoid dose; annualised rates of asthma exacerbations; the mean change from baseline in the FEV1 before and after bronchodilation; ACQ-5 score; SGRQ score; safety; immunogenicity

Study reference	Bjermer (Reslizumab) 2016
Study tittle	Reslizumab for Inadequately Controlled Asthma with Elevated Blood Eosinophil Levels: A Randomized Phase 3 Study
Study duration	20 weeks
Trial registration:	NCT01270464
Study Population	Participants: reslizumab 0.3mg/kg group, n=104; reslizumab 3.0mg/kg group, n= 106; placebo group, n=104 Eligibility criteria stated as: patients of the age 12-75 years with moderate-severe asthma, inadequately controlled (ACQ-7 score ≥1.5), airway reversibility (≥12% to SABA), were receiving treatment with at least a medium-dose ICS (fluticasone propionate ≥440 μg/day or equivalent) and had at least one blood eosinophil count of ≥400 cells/μL during the screening period
Setting	68 locations across 13 countries
Interventions	IV infusion of reslizumab 0.3 mg/kg, reslizumab 3.0 mg/kg, or placebo once every 4 weeks (total of 4 doses)
Adherence reported yes/no	Yes
Primary outcomes	Improvement in prebronchodilator FEV1 compared with placebo over 16 weeks
Secondary outcomes	FVC, ACQ-5, Asthma Symptom Utility Index (ASUI19), AQLQ, rescue inhaler use, and blood eosinophil levels over 16 weeks

Study reference	Bleecker (Benralizumab) 2016
Study tittle	Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial
Study duration	48 weeks
Trial registration:	NCT01928771
Study Population	Participants: benralizumab 30 mg 4 weekly group, n=399; benralizumab 30 mg 8 weekly group, n=398; or placebo group, n=407 Eligibility criteria: ≥ 2 exacerbations in the previous 12 months; ACQ-6 score ≥ 1.5 at enrolment FEV1 < 80% (if 12-17 years old, < 90%); maintenance treatment with high-dose (≥ 500 μg/d FP or equivalent) ICS/LABA for ≥ 12 months for adults > 18 years, or at least medium-dose (≥ 250 μg/d FP or equivalent) ICS/LABA for children (12-17 years)
Setting	374 sites in Australia, Brazil, Bulgaria, Czech Republic, France, Italy, Mexico, Peru, Poland, Russia, South Africa, South Korea, Spain, Turkey, the UK, the USA, and Vietnam
Interventions	SC benralizumab 30 mg/mL every 4 weeks or every 8 weeks versus placebo
Adherence reported yes/no	Yes
Primary outcomes	Annual asthma exacerbation rate at week 48 weeks
Secondary outcomes	Prebronchodilator FEV1 and total asthma symptom score (a composite of daytime and night-time symptoms scored 0–6 overall) at week 48

Study reference	Brightling (Tralokinumab) 2015
Study tittle	Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial
Study duration	5-week screening and run-in period. 52 weeks
Trial registration:	NCT01402986
Study Population	Participants: tralokinumab 2 weekly group, n=150 or 4 weekly group, n=151 or placebo group, n=151 Eligibility criteria: patients of the age 18–75 years with severe uncontrolled asthma, consistent with the ERS/ATS definition, who were receiving high dose ICS (total daily dose >500 μg fluticasone dry powder inhaler or equivalent via metered dose inhaler) plus a LABA at least 30 days before visit 1 (run-in day –35), and who had at least two, but no more than six, exacerbations in the previous 12 months.
Setting	98 sites in North America, South America, Europe, and Asia
Interventions	Placebo or tralokinumab administered subcutaneously either every 2 weeks to week 50, or every 2 weeks for 12 weeks followed by every 4 weeks to week 48
Adherence reported yes/no	Yes
Primary outcomes	Annual asthma exacerbation rate at week 52 weeks
Secondary outcomes	Change in FEV1, FVC, IC, and PEF, EQ-5D; at week 52

Study reference	Brinke (IM triamcinolone) 2004
Study tittle	"Refractory" Eosinophilic Airway Inflammation in Severe Asthma Effect of Parenteral Corticosteroids
Study duration	2 weeks
Trial registration:	Not specified
Study Population	Participants: triamcinolone group, n= 22, placebo group, n=11 Eligibility criteria: patients of the age 21–73 years; clinically stable for at least 4 weeks; percentage sputum eosinophils above the upper limit of normal (2%); beclomethasone dose of 1,600–6,400 g/day or equivalent and LABA for more than 1 year and had had at least one (median, 4; range, 1–7) course of oral corticosteroids during the past year or 5 mg or more of oral prednisone daily.
Setting	Amsterdam and Netherlands
Interventions	One single intramuscular injection of 3 ml (40 mg/ml) long-acting triamcinolone acetonide (Kenacort-A40; Bristol-Myers Squibb, Woerden, The Netherlands) or matched placebo (3 ml NaCl 0.9%) was given.
Adherence reported yes/no	No
Primary outcomes	Not specified
Secondary outcomes	Sputum and peripheral blood eosinophil /neutrophil counts, FEV1, exhaled nitric oxide

Study reference	Brusselle (Azithromycin) 2013
Study tittle	Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial
Study duration	2-week run-in period. 26 weeks
Trial registration:	NCT00760838
Study Population	Participants: azithromycin group, n=55; placebo group, n=54 Eligibility criteria: patients of the age 18–75 years, with a diagnosis of persistent asthma, a history consistent with Global Initiative for Asthma step 4 or 5 clinical features, received high doses of inhaled corticosteroids (≥1000 mg fluticasone or equivalent) plus inhaled long-acting β2 agonists for at least 6 months prior to screening and had had at least two independent severe asthma exacerbations requiring systemic corticosteroids and/or LRTI requiring antibiotics within the previous 12 months.
Setting	Belgium
Interventions	Capsules with 250 mg azithromycin (prepared from capsules of Zitromax) or placebo. After randomisation, the patients took one capsule per day for 5 days and then one capsule three times a week.
Adherence reported yes/no	Yes
Primary outcomes	The rate of severe asthma exacerbations and/or LRTI requiring antibiotics during the 26-week treatment phase
Secondary outcomes	Pre- and post-bronchodilation FEV1 morning and evening peak expiratory flow (PEF), AQLQ score and (ACQ score). All secondary outcomes were ascertained at visits 2, 3, 4, 5 and 6 (at randomisation and weeks 4, 10, 18 and 26 of the treatment period), except for the questionnaires which were completed by the patient at visits 2, 4 and 6 only.

Study reference	Busse (Omalizumab) 2001
Study tittle	Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma
Study duration	4-6-week run-in period. 28 weeks
Trial registration:	Not specified
Study Population	Participants: Omalizumab group, n= 268; Placebo group, n=257 Eligibility criteria: patients of the age 12–75 years; Male or female symptomatic allergic asthmatics despite treatment with ICS; duration of asthma, ≥1 year; positive immediate responses on skin prick testing to at least 1 common allergen, including Dermatophagoides farinae, Dermatophagoides pteronyssinus, cockroach (whole body), dog, or cat; total serum IgE ≥30 IU/mL to ≤700 IU/mL; FEV1 reversibility of ≥12% within 30 minutes after administration of albuterol (90-180 μg); baseline FEV1 ≥40% and ≤80% of predicted; and treatment with 420 to 840 μg/day of beclomethasone dipropionate or its equivalent ICS for ≥3 months prior to randomization
Setting	United States and United Kingdom
Interventions	Placebo or omalizumab administered subcutaneously every 2 or 4 weeks, depending on baseline IgE level and body weight.
Adherence reported yes/no	No
Primary outcomes	Number of exacerbation episodes experienced by a patient during the steroid reduction period (4 months) and during the stable steroid phase (3 months)
Secondary outcomes	Number of patients experiencing at least 1 exacerbation; daily asthma symptoms; rescue medication use; pulmonary function; and global evaluation of treatment effectiveness(time frame at week 16 and week 28)

Study reference	Busse (Brodalumab) 2013
Study tittle	Randomized, Double-Blind, Placebo-controlled Study of Brodalumab, a Human Anti–IL-17 Receptor Monoclonal Antibody, in Moderate to Severe Asthma
Study duration	4-week run-in period. 12 weeks
Trial registration:	NCT01199289
Study Population	Participants: Brodalumab Q2W 140 mg group, n=74; 210 mg group, n= 76; 280 mg group, n =76; placebo group, n = 76 Eligibility criteria: patients of the age 18–65 years with inadequately controlled (ACQ≥1.5, ≥50% to ≤ 80% predicted FEV1, and ≥12% reversibility over baseline FEV1 with SABA inhalation) physician diagnosed moderate to severe asthma on stable ICS (>200 and <1,000 mg/d of fluticasone powder or equivalent for >3 month before screening, and had to be on a stable dose for >30 days) with or without additional LABAs
Setting	47 sites in 10 countries; Austria, Belgium, Canada, Finland, Hungary, Netherlands, Poland, Russia, South Korea, and the United States
Interventions	Brodalumab (140, 210, 280 mg) or placebo subcutaneously at day 1 and weeks 1, 2, 4, 6, 8, and 10
Adherence reported yes/no	No
Primary outcomes	The total change in ACQ-7 score from baseline to Week 12
Secondary outcomes	Changes from baseline to week 12 in pre- and post-bronchodilator FEV1, morning PEF, rescue SABA use, daily asthma symptom score, and symptom-free days

Study reference	Busse (Daclizumab) 2008
Study tittle	Daclizumab Improves Asthma Control in Patients with Moderate to Severe Persistent Asthma A Randomized, Controlled Trial
Study duration	2-5 weeks run-in period. 20 weeks of treatment period and 16 weeks of follow up
Trial registration:	NCT00028288
Study Population	Participants: Daclizumab group, n=88; placebo group, n= 27 Eligibility criteria: non-smoking adults with asthma; 18–70 years old; asthma history of 6 months or longer; FEV1 of 50–80% of predicted; reversibility of at least 12% with inhaled short-acting β2- agonist; at least 1,200 mg daily inhaled triamcinolone acetate acetonide (or equivalent ICS) for 3 months or more before enrolment
Setting	24 centres in the United States
Interventions	Daclizumab (intravenous loading dose, 2 mg/kg, then 1 mg/kg) or placebo every 2 weeks, added to stable-dose triamcinolone acetate acetonide through week 12
Adherence reported yes/no	No
Primary outcomes	Percent change in FEV1 from randomization to day 84
Secondary outcomes	Asthma exacerbations, time to asthma exacerbation, morning/evening PEF, rescue medication use, daytime/ night-time asthma symptoms, and asthma-free days from randomization to day 84

Study reference	Busse (AMG 853) 2013
Study tittle	Safety and efficacy of the prostaglandin D2 receptor antagonist AMG 853 in asthmatic patients
Study duration	4-weeks run-in period. 12 weeks
Trial registration:	Not documented
Study Population	Participants: 200 mg of AMG 853 n=80 ; 100 mg of AMG 853 n= 79; 25 mg of AMG 853, n= 79; 5 mg of AMG 853, n=80; placebo group, n= 79 Eligibility criteria: patients of the age 18 to 65 years; moderate-to-severe asthma, with ongoing asthma symptoms {ACQ scores of ≥1.5 at screening and baseline, or FEV1 of ≥50% and ≤80% at screening, and at least 12% reversibility over baseline FEV1 with SABA; ≤8 puffs or nebulized equivalent (≤2 treatments with 2.5 mg of albuterol)} and were receiving stable inhaled corticosteroids (ICSs; ≥200 and ≤1000 mg/day fluticasone or equivalent) for 30 or more days, with consecutive use for at least the prior 3 months before screening
Setting	73 centres in the United States, Canada, and Europe
Interventions	Oral placebo; 5, 25, or 100 mg of AMG 853 twice daily ; or 200 mg of AMG 853 once daily
Adherence reported yes/no	No
Primary outcomes	The change in ACQ symptom scores from baseline to week 12
Secondary outcomes	The change from baseline to week 12 in prebronchodilator and postbronchodilator FEV1 (percentage change), morning and evening PEFR, frequency of rescue SABA use, daily asthma symptoms, AQLQ scores, and the proportion of symptom-free days over the treatment period. The incidence of asthma exacerbations was evaluated as an exploratory end point. Other exploratory end points included fraction of exhaled nitric oxide (FENO) and induced sputum eosinophil numbers (sub study). Blood eosinophil numbers and serum IgE levels

Study reference	Cahill (Imatinib) 2017
Study tittle	KIT Inhibition by Imatinib in Patients with Severe Refractory Asthma
Study duration	4-week run-in period. 24weeks
Trial registration:	NCT01097694
Study Population	Participants: Imatinib group, n=32 ; placebo group n= 30 Eligibility criteria: patients of the age 18–55 years, diagnosed with asthma for at least 1 year; refractory asthmatics, defined as reporting that their asthma has not been completely controlled in the past 3 months despite continuous treatment with high dose ICS (fluticasone ≥ 1000 mg or equivalent) and LABA, with or without continuous OCS; uncontrolled asthma(ACQ ≥ 1.5) during the run-in period; FEV1 > 55% predicted; methacholine PC20 < 4 mg/ml; > 80% compliance with peak flow recording and diary completion during the screening period
Setting	7 centres in the United States
Interventions	Imatinib or placebo once daily for 24 weeks. Imatinib treatment was initiated at an oral dose of 200 mg per day for 2 weeks, after which the dose was increased to 400 mg per day
Adherence reported yes/no	Yes
Primary outcomes	The change in airway hyperresponsiveness, assessed as PC20, from baseline to 3 and 6 months of therapy in the imatinib group as compared with the corresponding changes in the control group
Secondary outcomes	Airway physiological outcomes, computed tomography bronchial wall thickness and patient reported outcomes: (from baseline to 3 and 6 months): FEV1, morning and evening PEF, maximum FEV1 post-bronchodilator (FEV1 after 4-8 puffs albuterol), Adenosine Monophosphate (AMP), PC20, use of as needed rescue medication, ACQ scores, AQLQ, score, symptom free days, asthma exacerbations

Study reference	Castro (Bronchial thermoplasty) 2010
Study tittle	Effectiveness and Safety of Bronchial Thermoplasty in the Treatment of Severe Asthma A Multicentre, Randomized, Double-Blind, Sham-Controlled Clinical Trial
Study duration	52 weeks
Trial registration:	NCT00231114
Study Population	Participants: Bronchial thermoplasty (BT) group, n=190; sham group, n= 98 Eligibility criteria: adults (18–65 years of age) diagnosed with asthma who required regular maintenance medications of ICS (1,000 mg/d beclomethasone or equivalent) and LABA >100 mg/d salmeterol or equivalent) for at least 4 weeks before entry; baseline AQLQ score ≤6.25; prebronchodilator FEV1 >60% of predicted, airway hyperresponsiveness (methacholine PC20 ,8 mg/ml), at least 2 days of asthma symptoms during the 4-week baseline period, and being a non-smoker for at least 1 year with less than 10 pack-years smoking history.
Setting	30 investigational sites in six countries; United States, United Kingdom, Canada, Brazil, Netherlands, Australia
Interventions	BT or the sham group. The bronchoscopy procedures were performed 3 weeks apart
Adherence reported yes/no	No
Primary outcomes	The difference between study groups in the AQLQ score change from baseline to the average of the 6-, 9-, and 12-month scores (integrated AQLQ)
Secondary outcomes	ACQ scores, percentage of symptom-free days, symptom scores, morning PEF, rescue medication use, and FEV1, the numbers of severe asthma exacerbations, the percentage of subjects experiencing severe exacerbations, respiratory-related unscheduled physician office visits, emergency department (ED) visits, hospitalizations, and days missed from work/school or other activities due to asthma

Study reference	Castro (Benralizumab) 2014
Study tittle	Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study
Study duration	52 weeks
Trial registration:	NCT01238861
Study Population	Participants: 324 eosinophilic patients: benralizumab 2 mg dose, n=81; 20 mg dose, n=81;100 mg dose, n=82; placebo group, n=80: 285 non-eosinophilic patients : 100 mg benralizumab n=142; placebo group, n=143 Eligibility criteria: 2–6 exacerbations in the previous 12 months, ACQ-6 score ≥ 1.5 at least twice during screening, morning pre-bronchodilator FEV1 40%–90% maintenance treatment with medium- to high-dose ICS in combination with LABA for ≥ 12 months
Setting	33 sites in the United States, Canada, Bulgaria, Brazil, Peru, Mexico, Poland, Russia, Argentina, and Colombia
Interventions	6 arms: benralizumab 2 mg or benralizumab 20 mg or benralizumab 100 mg or placebo delivered by 2 SC injections every 4 weeks for the first 3 doses (weeks 1, 4, and 8), then every 8 weeks (weeks 16, 24, 32, and 40)
Adherence reported yes/no	No
Primary outcomes	Asthma annual exacerbation rate in eosinophilic individuals, calculated as the total number of reported exacerbations in each group up to week 52 divided by the total duration of person-year follow-up in each group
Secondary outcomes	The change from baseline in FEV1, mean ACQ-6 score, overall symptom score, and mean AQLQ score at week 52. Exploratory endpoints included change in FeNO, and blood eosinophil counts

Study reference	Castro (Reslizumab) 2015
Study tittle	Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials
Study duration	48 weeks
Trial registration:	NCT01287039 (study 1) and NCT01285323 (study 2)
Study Population	Participants: Study 1; reslizumab group, n=245; placebo group, n=244 Study 2: reslizumab group n= 232; placebo group, n=232 Eligibility criteria: patients with moderate-severe asthma, ACQ-7 score ≥ 1.5; maintenance treatment with medium-dose ICS (i.e. ≥ 440 μg/d FP or equivalent daily); ± additional controller or maintenance OCS and at least 1 exacerbation in the past 12 months); blood eosinophils ≥ 400 cells/μL during 2-4 week screening period
Setting	128 clinical research centres in study 1 and 104 centres in study 2 from Asia, Australia, North America, South America, South Africa, and Europe
Interventions	IV infusion of reslizumab 3 mg/kg or matching placebo every 4 weeks (13 doses with last dose in week 48)
Adherence reported yes/no	No
Primary outcomes	The frequency of clinical asthma exacerbations per patient during the 52-week treatment period
Secondary outcomes	The change from baseline in FEV1, ACQ-7 score,21,25 ASUI score, rescue use of short-acting β-agonist, and blood eosinophil count to each scheduled visit; AQLQ total score were assessed at weeks 16, 32, and 52

Study reference	Castro (Reslizumab) 2011
Study tittle	Reslizumab for Poorly Controlled, Eosinophilic Asthma A Randomized, Placebo-controlled Study
Study duration	15 weeks
Trial registration:	Not documented
Study Population	Participants: reslizumab group, n= 53; placebo group, n=53 Eligibility criteria: patients of the age 18–75 years with a diagnosis of asthma confirmed by airway hyperreactivity (a ≥20% reduction in FEV1 after administration of methacholine up to 16 mg/ml) or by airway reversibility (a >12% improvement in FEV1 after administration of a beta-agonist); treated with high-dose ICS (>440 mg of fluticasone twice per day) in combination with at least one other agent (including SABA, leukotriene antagonists, and cromolyn sodium); that was poorly controlled as indicated by an ACQ score of ≥1.5 and associated with induced sputum eosinophils of ≥3%
Setting	25 sites in the United States and Canada
Interventions	to infusions of reslizumab (3.0 mg/kg) or placebo (0.9% saline) at a 1:1 ratio at baseline and at Weeks 4, 8, and 12
Adherence reported yes/no	No
Primary outcomes	The difference between the reslizumab and placebo groups in the change from baseline to end of therapy (Week 15 or early withdrawal) in the ACQ score
Secondary outcomes	Spirometry, blood and induced sputum eosinophil counts, and the percentage of patients with clinical asthma exacerbations

Study reference	Chanez (Omalizumab) 2010
Study tittle	Omalizumab-induced decrease of Fc3RI expression in patients with severe allergic asthma
Study duration	16 weeks
Trial registration:	NCT00454051
Study Population	Participants: omalizumab group, n= 20; control group: n=11 Eligibility criteria: adults aged ≥ 18 years; participants with severe persistent allergic asthma with the following characteristics: FEV1 < 80% of predicted; frequent daily symptoms (≥ four days/week on average) or nocturnal awakening (≥ one/week on average); multiple severe asthma exacerbations: either ≥ two severe asthma exacerbations requiring an unscheduled medical intervention with systemic corticosteroid in the past year, or hospitalisation (including emergency room treatment) for an asthma exacerbation in the past year, despite a high-dose ICS > 1000 mg beclomethasone dipropionate or equivalent and LABA; an allergy to a perennial allergen demonstrated with convincing criteria {i.e. positive prick skin test or in vitro reactivity to a perennial aeroallergen (RAST)}; total serum IgE level ≥ 30 to ≤ 700 IU/mL and suitable serum total IgE level; weight according to Xolair dosing tablets
Setting	France
Interventions	Omalizumab injected subcutaneously every two weeks or every four weeks for 16 weeks (dose and dosing interval determined on the basis of participant body weight and pre-treatment serum IgE level) versus placebo
Adherence reported yes/no	No
Primary outcomes	The change (%) from baseline in FcεRI (high-affinity IgE receptor) expression on blood basophils and dendritic cells after 16 weeks of treatment with omalizumab as compared with placebo (time frame: baseline and week 16); change (%) from baseline in mean fluorescence intensity of FcεRI after 16 weeks of treatment with omalizumab as compared with placebo (time frame: baseline and week 16)
Secondary outcomes	The change (%) from baseline in percent of basophils and dendritic cells expressing FcεRI after 4, 8, 12 and 16 weeks of treatment (time frame: baseline, weeks 4, 8, 12 and 16); change (%) from baseline in mean fluorescence intensity of FcεRI after 4, 8, 12 and 16 weeks of treatment (time frame: baseline, weeks 4, 8, 12 and 16); change from baseline in the number of days with asthma symptoms per week (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of puffs of rescue medication per week (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of nights with awakenings per week (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of days with impairment in daily activities per week (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of days with absence from school or work due to asthma symptoms (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16));

	change from baseline in the number of days with hospitalisations (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of unscheduled clinic visits (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in morning daily peak expiratory flow (PEF) (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); physician's overall assessment of treatment effectiveness (time frame: after 16 weeks of treatment)

Study reference	Corren (AMG 317) 2010
Study tittle	A Randomized, Controlled, Phase 2 Study of AMG 317, an IL-4Ra Antagonist, in Patients with Asthma
Study duration	16 weeks
Trial registration:	NCT 00436670
Study Population	Participants: AMG 317 75 mg group, n =73; AMG 317 150 mg group, n = 73; AMG 317 300 mg group, n =72 ; placebo group, n=74 Eligibility criteria: patients of the age 18-65 years, with moderate to severe asthma, and receiving stable doses of inhaled corticosteroids (ICS) (>200 to <1,000 mg/d fluticasone or equivalent; ACQ score ≥1.5, FEV1% predicted of ≥50% to ≤80% at screening, and greater than or equal to 12% reversibility over baseline FEV1 with β2-agonist inhalation
Setting	United States
Interventions	AMG 317 (75 mg, 150 mg, or 300 mg) or placebo subcutaneously once weekly for 12 weeks
Adherence reported yes/no	No
Primary outcomes	The change in ACQ symptom score from baseline to Week 12.
Secondary outcomes	Changes in pre and post-bronchodilator FEV1, morning and evening PEFR, diurnal and interday variation of PEFR, rescue b-agonist use, and Asthma AQLQ score. Asthma exacerbations were also evaluated, and two definitions were used: (1) need for systemic steroids, or (2) need for systemic steroids or doubling of ICS dose

Study reference	Corren (Lebrikizumab) 2011
Study tittle	Lebrikizumab Treatment in Adults with Asthma
Study duration	2-week run in period. 32 weeks
Trial registration:	NCT00930163
Study Population	Participants: lebrikizumab group, n=106; placebo group, n=112 Eligibility criteria: patients had asthma diagnosed by a physician { at least a 12% increase in the FEV1 after inhalation of a SABA, and prebronchodilator FEV1 between 40% and 80% (inclusive)}; the use for at least 6 months of inhaled glucocorticoids (≥200 and ≤1000 μg of inhaled fluticasone propionate daily, administered by means of a dry powder inhaler, or a nominal equivalent); evidence of uncontrolled asthma (ACQ-5 ≥1.5) on the day of randomization
Setting	United States
Interventions	Lebrikizumab 250 mg or placebo was given subcutaneously once a month for a total of 6 months
Adherence reported yes/no	Yes
Primary outcomes	The relative change in prebronchodilator FEV1 from baseline to week 12.
Secondary outcomes	Rates of protocol- defined exacerbations and severe exacerbations through week 24, morning prebronchodilator peak exploratory flow, change in ACQ5 score from baseline to week 12, asthma symptom score as assessed by means of the ACDD, and use of rescue medication

Study reference	Corren (Reslizumab) 2016
Study tittle	Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma Effects Across a Broad Range of Eosinophil Counts
Study duration	3-week screening period. 28 weeks
Trial registration:	NCT01508936
Study Population	Participants: reslizumab group, n=398; placebo group, n=98 Eligibility criteria: patients with moderate-severe asthma, inadequately controlled (ACQ-7 ≥ 1.5); maintenance treatment with medium-dose ICS
Setting	66 sites across the United States
Interventions	Reslizumab 3.0 mg/kg was given intravenously or placebo once every 4 weeks (total of 4 doses)
Adherence reported yes/no	No
Primary outcomes	The change in FEV1 from baseline to week 16
Secondary outcomes	ACQ-7 score14; rescue (SABA) use within the previous 3 days (assessed using 3-day recall at scheduled visits); FVC; and blood eosinophils (standard complete blood count) from baseline to week 16

Study reference	Cox (Bronchial thermoplasty) 2007
Study tittle	Asthma Control during the Year after Bronchial Thermoplasty
Study duration	52 weeks
Trial registration:	NCT00214526
Study Population	Participants: Bronchial thermoplasty (BT) group, n=56, control group n=56 Eligibility criteria: patients aged 18–65 years of age; moderate or severe persistent asthma, defined according to the GINA guidelines, requiring daily therapy with ICS equivalent to a dose of 200 μg or more of beclomethasone and LABA, at a dose of 100 μg or more of salmeterol (Serevent, GlaxoSmithKline) or the equivalent, to maintain reasonable asthma control; airflow obstruction, assessed as a prebronchodilator FEV1 of 60 to 85% of the predicted value, and airway hyperresponsiveness, defined by a provocative concentration of methacholine required to lower the FEV1 by 20% (PC20) of less than 8 mg/mL, as well as stable asthma during the 6 weeks before enrolment
Setting	11 centres in four countries; Canada, Brazil, UK and Denmark
Interventions	The BT group underwent three bronchoscopy procedures performed with the use of the Altair system (Asthmatx) at intervals of approximately 3 weeks. Control subjects had three treatment visits at intervals of 3 weeks for clinical review and spirometric assessment and received a systemic corticosteroid similar to that administered to subjects in the BT group
Adherence reported yes/no	No
Primary outcomes	The difference between the two groups in the change in the rate of mild exacerbations between baseline and later time point
Secondary outcomes	ACQ, PEF, AQLQ

Study reference	Coyle (Bosentan) 2013
Study tittle	The Effect of the Endothelin-1 Receptor Antagonist, Bosentan, on Patients with Poorly Controlled Asthma: A 17-week, Double-Blind, Placebo-Controlled Crossover Pilot Study
Study duration	7-10-day run-in period. 16weeks
Trial registration:	Not documented
Study Population	Participants: Bosentan group, n= 4 ; placebo group n= 3 Eligibility criteria: patients aged 21–70 years with a history of asthma, previously maintained on anti-inflammatory and long acting bronchodilator therapy (excluding tiotropium bromide), with a baseline FEV1% predicted of 40–70% and a minimum of 12% reversibility of FEV1 (after administration of albuterol) documented within the prior 2 years; poorly controlled asthma defined as symptoms including wheezing, chest tightness, or shortness of breath occurring at least three times a week or requiring use of "rescue" SABA at least three times a week
Setting	United States
Interventions	Bosentan 62.5 mg twice daily for 4 weeks (Tracleer®, Actelion Pharmaceuticals, California, USA) followed by the therapeutic dose of bosentan 125 mg twice daily for an additional 4 weeks or identical shape and size placebo (crossover pilot study)
Adherence reported yes/no	No
Primary outcomes	The change in mean daily asthma symptom score between baseline and during the last week of bosentan 125 mg
Secondary outcomes	The change in ACT, change in FEV1 after therapy, albuterol use during the last week of therapy, and acute bronchodilator effect of bosentan as assessed by measuring change in FEV1 after bosentan 125 mg

Study reference	DeBoever (GSK679586) 2014
Study tittle	Efficacy and safety of an anti–IL-13 mAb in patients with severe asthma: A randomized trial
Study duration	4-week run-in period. 24weeks
Trial registration:	NCT00843193
Study Population	Participants: GSK679586 group, n=599; placebo group, n=599 Eligibility criteria: patients of the age 18 to 75 years with severe asthma, symptomatic (ACQ-7 score 1.5) while receiving ≥500μg/day fluticasone propionate or equivalent (FPE) and had a prebronchodilator FEV1 of 35% to 80% of predicted normal value with ≥12% reversibility on β-2-agonist inhalation; LABAs or OCSs (≤25 mg/d prednisolone or equivalent) were allowed
Setting	34 sites across 8 countries including United Kingdome and United States
Interventions	10 mg/kg GSK679586 intravenously or normal saline at day 1, week 4, and week 8
Adherence reported yes/no	No
Primary outcomes	The change from baseline in ACQ-7 score over 12 weeks
Secondary outcomes	The changes from baseline in free and total serum IL-13 levels, serum total IgE levels, and blood eosinophil counts were evaluated over the same time period as exploratory end points

Study reference	Dente (Prednisolone) 2010
Study tittle	Effects of oral prednisone on sputum eosinophils and cytokines in patients with severe refractory asthma
Study duration	2 weeks
Trial registration:	Not documented
Study Population	Participants: prednisone group, n=39; placebo group, n=20 Eligibility criteria: compliance with functional measurements and treatment, acceptable sputum samples, and no contraindications for the use of systemic corticosteroids; symptomatic asthma and a history of airway obstruction reversibility (a 12% increase in FEV1 of baseline value after 400 g of salbutamol); treated with 1,600 to 3,200 g/day of inhaled beclomethasone propionate or equivalent associated with LABA in the year preceding the study, ±additional controller therapy (oral leukotriene receptor antagonists, inhaled anticholinergics, oral theophylline, and regular low-dose oral corticosteroids)
Setting	Italy
Interventions	Oral prednisone (0.5 mg/kg daily) or placebo for 2 weeks, in addition to current regular treatment
Adherence reported yes/no	Yes
Primary outcomes	Outcomes: FEV1, PEFR, sputum eosinophil, sputum IL-5 and IL-8 level at 2weeks
Secondary outcomes	Not specified

Study reference	Erin (Infiliximab) 2006
Study tittle	The Effects of a Monoclonal Antibody Directed against Tumor Necrosis Factor- in Asthma
Study duration	2–4-week run-in period. 12 weeks
Trial registration:	Not documented
Study Population	Participants: infliximab group, n=18; placebo group, n=20 Eligibility criteria: a mean total daily symptom score of at least 4 in the last 7 d of the run-in period (baseline period: Days 7 to 1), or at least 10% but less than 40% diurnal variation in peak PEF measured on at least 2 of 7 days in the same period
Setting	United Kingdom
Interventions	Infliximab (5 mg/kg) or placebo at Weeks 0 (Day 1), 2 (Day 15), and 6 (Day 43)
Adherence reported yes/no	No
Primary outcomes	The change from baseline (Days 7 to 1) to Week 8 (Days 50 to 56) in mean morning PEF, obtained from the patient diary data in the per protocol population
Secondary outcomes	The change from baseline (Days 7 to 1) to Week 8 (Days 50 to 56) in FEV1, asthma symptom scores, use of rescue SABA

Study reference	Fernandes (Prednisolone) 2014
Study tittle	Bronchodilator response as a hallmark of uncontrolled asthma: a randomised clinical trial
Study duration	10±5-day run-in period. 15± 5 days
Trial registration:	NCT00597064
Study Population	Participants: prednisolone group, n= 36; placebo group, n=35 Eligibility criteria: patients over 15 years old; non-smokers or ex-smokers (less than 5 packs/year); treated with ICS therapy (400 mcg Budesonide) plus LABA (12 mcg Formoterol) twice daily for at least 3 months (step 4 of GINA), exhibiting positive bronchodilator response (≥12% increase in post-bronchodilator FEV1 value compared to pre bronchodilator FEV1 value, and an increase in the absolute value of FEV1 of greater than 200 mL at the screening visit (V0), and controlled asthma by ACQ5 definition
Setting	Brazil
Interventions	Prednisone 40 mg daily or placebo for 2 weeks
Adherence reported yes/no	No
Primary outcomes	
Secondary outcomes	Outcomes assessed: the change in FEV1, PEFR, sputum eosinophils and neutrophil counts at the final evaluation visit

Study reference	FitzGerald (Benralizumab) 2016
Study tittle	Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials
Study duration	56 weeks (final follow-up at 60 weeks).
Trial registration:	NCT01287039 (study 1) and NCT01285323 (study 2)
Study Population	Participants: 1306 participants enrolled. Allocation: eosinophil ≥ 300 cells per μL benralizumab 30 mg every four weeks, n=241; eosinophil ≥ 300 cells per μL benralizumab 30 mg Q8W, n=239; eosinophil ≥ 300 cells per μL placebo group, n= 248; eosinophil < 300 cells per μL benralizumab 30 mg every four weeks, n=116; eosinophil < 300 cells per μL benralizumab 30 mg Q8W, n=125; eosinophil < 300 cells per μL; placebo group, n=122 Eligibility criteria: patients with moderate-severe asthma; ≥ 2 exacerbations in the previous 12 months; ACQ-6 score ≥ 1.5 at enrolment; FEV1 < 80%; maintenance treatment with medium- (≥ 250 μg/day FP or equivalent) to high-dose (≥ 500 μg/day FP or equivalent) ICS/LABA for ≥ 12 months; high-dose ICS/LABA for ≥ 3 months
Setting	303 clinical research centres in the United States, Canada, Germany, Sweden, Poland, Romania, Ukraine, Argentina, Chile, Japan, and the Philippines
Interventions	Placebo or benralizumab 30 mg administered subcutaneously every 4 weeks for 56 weeks or every 4 weeks for 3 doses then 8 weeks thereafter for 56 weeks
Adherence reported yes/no	Yes
Primary outcomes	The frequency of clinical asthma exacerbations per patient during the 52-week treatment period, with events adjudicated by an independent review committee
Secondary outcomes	The pre-bronchodilator FEV1 and total asthma symptom score for patients receiving high-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per μL, time to first asthma exacerbation; annual rate of asthma exacerbations associated with an emergency department visit, urgent care visit, or admission to hospital; post-bronchodilator FEV1; ACQ-6 score; and AQLQ score.

Study reference	Flood-Page (Mepolizumab) 2007
Study tittle	A Study to Evaluate Safety and Efficacy of Mepolizumab in Patients with Moderate Persistent Asthma
Study duration	4-week run-in period. 12 weeks treatment period and 8 weeks follow up period
Trial registration:	Not documented
Study Population	Participants: mepolizumab 750mg group n=116 ; mepolizumab 250mg group, n=120 ; placebo group, n=126 Eligibility criteria: non-smoking patients, aged 18–55 years, with asthma managed with ICS (maximum dose of beclomethasone dipropionate [BDP] or equivalent, 1,000 mg/d); FEV1% predicted of at least 50% and not >80% with documented b2-agonist reversibility of at least 12% after administration of 180 mg of albuterol (salbutamol);daily symptom score of at least 4 (maximum score, 12) during the 7 days preceding the baseline assessment
Setting	55 centres in five countries; France, Germany, the Netherlands, the United Kingdom, and the United States
Interventions	Mepolizumab (750 mg), mepolizumab (250 mg), or placebo
Adherence reported yes/no	No
Primary outcomes	The change from baseline in domiciliary morning PEF recorded at weeks 12 and 20
Secondary outcomes	The changes from baseline of FEV1, asthma summary symptom scores (the total of the daytime asthma, night-time asthma, and morning asthma scores), use of rescue medication such as albuterol (salbutamol), quality of life scores, asthma exacerbation rates, and eosinophil counts in blood and sputum

Study reference	Gao J-M (Montelukast) 2013
Study tittle	Montelukast improves air trapping, not airway remodelling, in patients with moderate-to-severe asthma: a pilot study
Study duration	2-week run-in period. 24 weeks
Trial registration:	NCT00699062
Study Population	Participants: salmeterol/fluticasone(SFC) plus Montelukast (SFC+M) group, n=19; salmeterol/fluticasone group, n=19 Eligibility criteria: patients of the age 16–65 years; FEV1 60%–80% predicted or less than 60% predicted
Setting	Beijing, China
Interventions	Salmeterol/fluticasone (SFC) alone or SFC plus Montelukast (SFC+M)
Adherence reported yes/no	No
Primary outcomes	The difference in the variables of small airways between the SFC group and SFC+M group after 24 weeks of treatment
Secondary outcomes	FEV1, FEV1% predicted FEV1/FVC), air trapping expressed by RV/TLC at 24 weeks with SFC alone or SFC+M

Study reference	Garcia (Omalizumab) 2013
Study tittle	A Proof-of-Concept, Randomized, Controlled Trial of Omalizumab in Patients with Severe, Difficult-to-Control, Nonatopic Asthma
Study duration	2-week screening period. 16 weeks
Trial registration:	NCT01007149
Study Population	Participants: omalizumab group, n= 20; placebo group, n=21 Eligibility criteria: patients aged 18 to 70 years with severe, persistent, nonatopic asthma that was uncontrolled according to the GINA guidelines despite daily high-dose ICS treatment (1,000 mg beclomethasone dipropionate or equivalent per day) plus a LABA with or without maintenance oral corticosteroid; at least two exacerbations requiring systemic corticosteroids, at least one hospitalization or ED visit in the year prior to randomization, or both; total serum IgE levels range: 30 to 700 IU/mL
Setting	10 centres in France
Interventions	Omalizumab or placebo subcutaneously every 2 weeks
Adherence reported yes/no	No
Primary outcomes	The change from baseline in FcƐRI expression on basophils and pDC2s at 16 weeks.
Secondary outcomes	Lung function, asthma control questionnaire scores, physician and patient global evaluation of treatment effectiveness (GETE), asthma exacerbation rates, and fraction of exhaled nitric oxide at 16 weeks

Study reference	Gevaert (Omalizumab) 2013
Study tittle	Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma
Study duration	2-week screening period. 16 weeks
Trial registration:	Not specified
Study Population	Participants: Omalizumab group, n=16; placebo group, n=8 Eligibility criteria: patients aged ≥ 18 years with CRSwNP (according to the European Position: Paper on Rhinosinusitis and Nasal Polyps guidelines) and comorbid asthma (based on GINA guidelines and diagnosed by a respiratory physician) for more than 2 years
Setting	Belgium
Interventions	Placebo or subcutaneous treatment with 2 weekly/8 injections in total or every month/4 injections in total) of omalizumab
Adherence reported yes/no	No
Primary outcomes	The reduction in total nasal endoscopic polyp score after 16 weeks
Secondary outcomes	The change in the following: sinus computed tomography scan, nasal and asthma symptoms, validated questionnaires (SF-36, RSOM-31 and AQLQ) and serum/nasal secretion biomarkers

Study reference	Girodet (Gallopamil) 2015
Study tittle	Calcium Channel Blocker Reduces Airway Remodelling in Severe Asthma A Proof-of-Concept Study
Study duration	3-month run-in period. 52 weeks
Trial registration:	NCT 00896428
Study Population	Participants: placebo group, n=15; Gallopamil group, n=16 Eligibility criteria: patients of the age ≥18 years with a clinical diagnosis of severe asthma according to ATS criteria, including characteristic symptoms (i.e., wheezing and breathlessness) and bronchial hyperresponsiveness confirmed either by a significant improvement by greater than 15% in the FEV1 10 minutes after the inhalation of 200 mg of salbutamol, or a provocative concentration of methacholine required to lower the FEV1 by 20% of less than 4 mg/ml
Setting	France
Interventions	100 mg of oral gallopamil hydrochloride twice daily or a matching placebo
Adherence reported yes/no	No
Primary outcomes	The bronchial smooth muscle (BSM) area assessed as the percentage of BSM surface on the whole bronchial sections surface at month 12
Secondary outcomes	Bronchial wall thickness, normalized BSM thickness, frequency of asthma exacerbations, ACQ, SABA use, AQLQ, FEV1, fractional exhaled nitric oxide (FENO), lung hyperinflation (VI950) or air trapping (VE850, difference or ratio between inspiratory and expiratory mean lung density), epithelial area, subepithelial membrane thickness, and lamina propria thickness at month 12

Study reference	Gotfried (Clarithromycin) 2004
Study tittle	Effects of Six-Week Clarithromycin Therapy in Corticosteroid-Dependent Asthma: A Randomized, Double-Blind, Placebo-Controlled Pilot Study
Study duration	4-week of observation period. 14 weeks
Trial registration:	Not documented
Study Population	Participants: clarithromycin group, n=15; placebo group, n=6 Eligibility criteria: patients of the age 18 to 75 years with an established diagnosis of asthma and who had been receiving ~5 mg/d of prednisone for the preceding 6 months; stable asthma with a ~20% change in prednisone or bronchodilator dosage in the previous 4 weeks
Setting	USA
Interventions	Oral clarithromycin 500-mg tablets twice daily or identical placebo
Adherence reported yes/no	No
Primary outcomes	Outcomes: FVC, FEV1, FEV/FVC ratio, PEF, quality of life and asthma symptoms at the end of four weeks treatment
Secondary outcomes	

Study reference	Haldar (Mepolizumab) 2009
Study tittle	Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma
Study duration	2-week run-in period. 50 weeks
Trial registration:	ISRCTN75169762
Study Population	Participants: mepolizumab 750 mg group, n=29; placebo group, n= 32 Eligibility criteria: ≥ 3% sputum eosinophils on at least 1 occasion in previous 2 years despite high-dose corticosteroid treatment; ≥ 2 exacerbations in previous 12 months; maintenance treatment with high-dose ICS
Setting	Single centre trial conducted at Institute for Lung Health, Leicester, UK
Interventions	Intravenous mepolizumab (750 mg) versus matched placebo (150 mL of 0.9% saline) at monthly intervals for 1 year
Adherence reported yes/no	No
Primary outcomes	The number of severe exacerbations per participant during the 50-week treatment phase
Secondary outcomes	Changes in eosinophil values in blood and sputum samples, FeNO, FEV1 (percent of the predicted value) after bronchodilator use, PC20, AQLQ score, symptom scores, computed assessment of airway-wall geometry, and bronchoscopic assessment of eosinophilic airway inflammation

Study reference	Hanania (Omalizumab) 2011
Study tittle	Omalizumab in Severe Allergic Asthma Inadequately Controlled with Standard Therapy
Study duration	2-4-week run-in period. 48 weeks
Trial registration:	NCT00314575
Study Population	Participants: omalizumab group: n=427; placebo group, n=423 (421 completed). Eligibility criteria: patients of the age 12 to 75 years with a history of severe allergic asthma for at least one year before screening; physician diagnosis of asthma on the basis of criteria specified by the NAEPP guidelines; uncontrolled asthma despite treatment with high-dose ICS and LABAs with or without other controllers (including OCS); baseline pre-bronchodilator FEV1 of 40% to 80% of predicted values; serum IgE level of 30 to 700 IU/mL and body weight of 30 to 150 kg; objective evidence of allergy to a relevant perennial aeroallergen, defined as a positive skin test result or in vitro response (radio-allergosorbent test) to dog, cat, cockroach, Dermatophagoides farinae (dust mite) or D. pteronyssinus documented in the 12 months before screening
Setting	193 sites in the United States and four sites in Canada
Interventions	Minimum dose of 0.008 mg/kg of body weight per IgE (IU/mL) every two weeks or 0.016 mg/kg per IgE (IU/mL) every four weeks versus placebo
Adherence reported yes/no	Yes
Primary outcomes	The rate of protocol-defined asthma exacerbations during the 48-week treatment period
Secondary outcomes	Change from baseline to week 48 in total asthma symptom severity score(TASS) ; change from baseline to week 48 in mean puffs per day of albuterol; and change from baseline to week 48 in overall asthma-specific health-related quality of life, as measured by the standardized version of the AQLQ score

Study reference	Hanania (Lebrikizumab) 2016
Study tittle	Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials
Study duration	2-week screening period, 52-weeks
Trial registration:	LAVOLTA; INCT01867125, and LAVOLTA II; NCT01868061
Study Population	Participants: 1081 patients were treated in LAVOLTA I and 1067 patients in LAVOLTA II Eligibility criteria: patients of the age 18–75 years with uncontrolled asthma, pre-bronchodilator FEV1 40–80% predicted, bronchodilator response of at least 12%, and on stable background therapy with ICS (500–2000 μg per day fluticasone propionate or equivalent) for at least 6 months and at least one additional controller medication
Setting	United States, Canada, South Africa, Italy Czech Republic and Japan.
Interventions	Lebrikizumab 37.5 mg or 125 mg, or placebo subcutaneously, once every 4 weeks
Adherence reported yes/no	Yes
Primary outcomes	The rate of asthma exacerbations during the 52-week placebo-controlled period in biomarker-high patients (periostin ≥50 ng/mL or blood eosinophils ≥300 cells per μL, and including patients high in both)
Secondary outcomes	The absolute change in pre-bronchodilator FEV1 from baseline at week 52; time to first asthma exacerbation during the 52-week placebo-controlled period; rate of urgent asthma related health-care use during the 52-week placebo controlled period; absolute change in AQLQ from baseline at week 52; absolute change in asthma rescue medication use from baseline at week 52; and absolute change in asthma control, as measured by the ACQ-5, from baseline at week 52

Study reference	Hanania (Lebrikizumab) 2015
Study tittle	Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies
Study duration	No run-in period. 52 weeks
Trial registration:	LUTE study; NCT01545440 VERSE study; NCT01545453
Study Population	Participants: Lebrikizumab 37.5 mg group, n=117; Lebrikizumab 125 mg group, n=112; Lebrikizumab 250 mg group, n=118; placebo group, n=116 Eligibility criteria: a diagnosis of asthma ≥12 months; acute bronchodilator response (≥12% relative improvement) and pre-bronchodilator FEV1 40–80% of predicted; uncontrolled asthma (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
Setting	United States
Interventions	Lebrikizumab 37.5, 125, 250 mg, or placebo subcutaneously every four weeks
Adherence reported yes/no	No
Primary outcomes	The rate of asthma exacerbations during the placebo-controlled period
Secondary outcomes	The change in prebronchodilator FEV1 from baseline, time to first asthma exacerbation during the placebo-controlled period, change from baseline in the AQLQ score, change in asthma rescue medication use from baseline, rate of urgent asthma-related healthcare use (i.e., hospitalisations, emergency department visits and acute care visits) during the placebo-controlled period

Study reference	Hedman (Methotrexate) 1996
Study tittle	Controlled trial of Methotrexate in patients with severe chronic asthma
Study duration	2-week run-in period. 24 weeks
Trial registration:	Not documented
Study Population	Participants: 13 patients enrolled, crossover trial Eligibility criteria: severe chronic asthma with continuous oral steroids treatment of at least 2.5mg/day for a year; Inhaled budesonide dose of ≥1.6mg; patient age <65years of age
Setting	Finland and Sweden
Interventions	15mg Methotrexate or identical placebo
Adherence reported yes/no	No
Primary outcomes	PEFR, FEV1
Secondary outcomes	

Study reference	Hodgson (Ciclesonide) 2015
Study tittle	A randomised controlled trial of small particle inhaled steroids in refractory eosinophilic asthma (SPIRA)
Study duration	12 weeks
Trial registration:	NCT01171365
Study Population	Participants: ciclesonide group n=15; placebo group n=15 Eligibility criteria: patients meeting the ATS criteria for refractory asthma with evidence of ongoing eosinophilic inflammation (sputum differential cell count ≥3% or blood eosinophils ≥0.4×109/mL)
Setting	United Kingdom
Interventions	Ciclesonide 320 mg twice daily or placebo for 8 weeks in addition to their usual maintenance medication
Adherence reported yes/no	Yes
Primary outcomes	The change in sputum differential eosinophil count between randomisation and week 8
Secondary outcomes	ACQ score, AQLQ score, pre-bronchodilator FEV1, bronchial NO and alveolar NO at week 8.

Study reference	Holgate (Omalizumab) 2004
Study tittle	Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma
Study duration	6–10-week run-in period. 32 weeks
Trial registration:	Not documented
Study Population	Participants: Omalizumab , n=126; placebo, n=120 Eligibility criteria: patients aged 12–75 years; required 1000 mg/day fluticasone for symptom control (all patients were switched to inhaled fluticasone during the run-in period); demonstrated positive skin prick test to aeroallergen/s, and had serum total IgE 30–700 IU/mL
Setting	Canada and European countries
Interventions	Omalizumab administered subcutaneously [minimum 0.016mg/kg/IgE (IU/mL) per 4 weeks; or matching placebo at intervals of 2 or 4 weeks
Adherence reported yes/no	No
Primary outcomes	The percentage reduction from baseline in fluticasone dose after 32 weeks' treatment
Secondary outcomes	Absolute reduction in fluticasone dose compared to baseline, asthma exacerbation episodes, use of rescue medication, asthma symptom score, peak expiratory flow (PEF) and post-bronchodilator spirometry, QoL.

Study reference	Holgate (Etanercept) 2011
Study tittle	Efficacy and safety of etanercept in moderate-to-severe asthma: a randomised, controlled trial
Study duration	12 weeks
Trial registration:	NCT00141791
Study Population	Participants: etanercept group, n=68; placebo group, n=64 Eligibility criteria: patients of the age 18–70 years, with moderate to severe persistent asthma{defined by the National Heart, Lung and Blood Institute (NHLBI)} for at least 1 year; demonstrated reversibility of at least 9% and (FEV1) 50% to 80% predicted after a SABA or 12 h after a LABA at screening or baseline; have a mean ACQ-5 score of ≥2; treated with high-dose ICS (≥1,000 μg/day beclomethasone–chlorofluorocarbons, 500 mg/day beclomethasone–hydrofluoroalkane, 500 mg/day fluticasone or 1,000 mg/day budesonide, or equivalent); and be receiving stable doses of their current medications for asthma >4 weeks prior to randomisation
Setting	United States
Interventions	Subcutaneous injection of either 25 mg ETN or placebo twice weekly
Adherence reported yes/no	No
Primary outcomes	Change in FEV1% predicted from baseline to week 12 (before bronchodilator administration)
Secondary outcomes	The change in PEFR, ACQ, asthma exacerbations at week from baseline to week 12

Study reference	Humbert (Omalizumab) 2005
Study tittle	Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE
Study duration	7-day screening period; 8-week run-in period. 28 weeks
Trial registration:	Not documented
Study Population	Participants: Omalizumab group, n=209; placebo group, n=210 Eligibility criteria: positive skin prick test to ≥1 aeroallergen; serum IgE: 30 to 700 IU/mL; severe persistent asthma requiring > 1000 BDP or equivalent and LABA treatment; FEV1 40% to 80%; FEV1 reversibility ≥ 12% post SABA; ≥ two exacerbations requiring OCS in previous 12 months or one severe exacerbation resulting in hospitalisation
Setting	France, New Zealand , Scotland, Canada, France, Germany, Spain, Italy, United Kingdom
Interventions	Subcutaneous omalizumab (0.016 mg/kg per IU/mL) (plus usual care or placebo
Adherence reported yes/no	Yes
Primary outcomes	The rate of clinically significant asthma exacerbations during the 28-week double-blind treatment phase
Secondary outcomes	The change in asthma symptoms, morning PEF, rescue medication use and FEV1, Asthma-related QoL from baseline to week 28

Study reference	Humbert (Masitinib) 2009
Study tittle	Masitinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics
Study duration	16 weeks
Trial registration:	NCT00842270
Study Population	Participants: masitinib 3 mg/kg/day (n = 12); masitinib 4.5 mg/kg/day (n = 11); masitinib 6 mg/kg/day (n = 10); all masitinib groups, (n = 33): placebo group, (n = 11) Eligibility criteria: Patients of the age 18–75 years with a diagnosis of asthma for≥3 years and severe uncontrolled disease for ≥1 year; stable disease with no exacerbation episode for at least one month before inclusion; postbronchodilator reversibility in FEV1 of ≥12%; to have experienced asthma symptoms more than once in 3 days for ≥3 months before screening despite continuous treatment with high-dose ICS (beclomethasone ≥1000mg or equivalent), LABA and daily oral corticosteroids (10–50 mg of equivalent prednisolone, with stable dosage for at least 3 months) and (iii) patients had to be non-smokers for at least 1 year with a prior tobacco consumption of <10 pack-years
Setting	France
Interventions	One of four masitinib groups for a 16-week treatment period: masitinib at 3, 4.5 or 6 mg/ kg/day or placebo control
Adherence reported yes/no	No
Primary outcomes	The decrease in oral corticosteroid therapy (weaning extent) at week 16
Secondary outcomes	Asthma control/ improvement and asthma exacerbation rate at week 16

Study reference	Juergens (Eucalyptol) 2003
Study tittle	Anti-inflammatory activity of1.8 -cineol (eucalyptol) in bronchial asthma: a double-blind placebo-controlled trial
Study duration	2 months run-in. 12 weeks
Trial registration:	Not documented
Study Population	Participants: 1.8 -cineol group, n=16; placebo group, n=16 Eligibility criteria: a reversibility of at least 15% in FEV1 10 min after inhalation of 200 mg fenoterol, and an airway resistance (RAW) below 0.6 kPa(l/s); Lung function criteria and values conformed to ATS guidelines
Setting	Germany
Interventions	1.8 -cineol 200 mg here times per day (at 8 a.m., 2 p.m., and 8 p.m.) or placebo capsules
Adherence reported yes/no	No
Primary outcomes	The change from the baseline to week 12 of oral steroid dosage
Secondary outcomes	The duration of dose reduction tolerated and stable lung function as determined by body plethysmography, stable clinical condition as measured by outpatient PEFR, symptom scores and bronchodilators use, and overall assessment of efficacy by the patient and the study physician.

Study reference	Kaler (Pioglitazone) 2017
Study tittle	A Randomized, Placebo-controlled, Double-blinded, Crossover Trial 2 of Pioglitazone for Severe Asthma
Study duration	4-week run-in period. 44 weeks
Trial registration:	Not documented
Study Population	Participants: pioglitazone group, n=14; placebo group, n=12 Eligibility criteria: severe asthmatics, between 18 and 75 years of age, who were persistently symptomatic and required use of a rescue β2-agonist inhaler > 2x per week despite treatment with high-dose inhaled corticosteroids (e.g., equivalent to > 1,000mg daily of fluticasone propionate inhalation powder) or oral corticosteroids; documented history of reversible airflow obstruction, as defined by a positive response to an inhaled bronchodilator or a positive methacholine bronchial provocation challenge, as well as a left ventricular ejection fraction of > 50% by echocardiography
Setting	United States
Interventions	Pioglitazone 30mg daily or matching placebo (crossover trial)
Adherence reported yes/no	No
Primary outcomes	The between group change in AQLQ from baseline to 16 weeks
Secondary outcomes	The change in ACQ score, daily asthma symptom score, rescue inhaler utilization (# puffs/day), asthma symptom-free days, nights with asthma symptoms, asthma exacerbations (mild and severe), pre- and post-bronchodilator FEV1, blood inflammatory cell counts (eosinophils, neutrophils, lymphocytes, monocytes and basophils), serum IgE levels, and FeNO from baseline to week 16

Study reference	Kanzow (Methotrexate) 1995
Study tittle	Short term effect of Methotrexate in severe steroid-dependent asthma
Study duration	3-week run-in period. 16 weeks of treatment period and 8 weeks of run-out period
Trial registration:	Not documented
Study Population	Participants: methotrexate group, n=12, Placebo group, n=9 Eligibility criteria: age>30 years; diagnosis of asthma as per ATS criteria; continuous use of oral prednisolone or its equivalent for >1 year at a minimum dose of 15mg/day with at least one documented corticosteroid toxicity; high-dose ICS (beclomethasone/budesonide at least 800µg/day
Setting	Germany
Interventions	15mg methotrexate or identical placebo
Adherence reported yes/no	No
Primary outcomes	Reduction in prednisolone dose, PEFR, FEV1, symptom score, Nocturnal awakenings
Secondary outcomes	

Study reference	Kenyon (L-Arginine) 2011
Study tittle	L-Arginine Supplementation and Metabolism in Asthma
Study duration	3 months
Trial registration:	NCT00280683
Study Population	Participants: L-arginine group, n=10; placebo group, n=10 Eligibility criteria: moderate to severe persistent asthma, were at least 18 years of age, not pregnant; patients did not have an acute exacerbation at the time of enrolment and were on the same asthma medications for at least one month
Setting	United States
Interventions	0.01 g/kg/day of L-arginine in divided doses for three months. Placebo tablets that match the L-arginine intervention tablets were given for three months
Adherence reported yes/no	No
Primary outcomes	Number of asthma exacerbations in three months
Secondary outcomes	L-arginine serum concentration [Time Frame: 90 days]

Study reference	Kerstjens (Tiotropium) 2011
Study tittle	Tiotropium improves lung function in patients with severe uncontrolled asthma: A randomized controlled trial
Study duration	2-week run-in period. 24 weeks
Trial registration:	NCT00365560
Study Population	Participants: 107 patients randomised Eligibility criteria: patients of the age 18 to 75 years with at least a 5-year history of asthma and a current diagnosis of severe persistent asthma; They were persistent airflow obstruction and symptomatic with ACQ-5 score of ≥1.5; postbronchodilator FEV1 of ≤80% of predicted value and ≤70% of FVC 30 minutes after inhalation of 4x100µg of salbutamol at screening) despite therapy with a high-dose ICS (≥800 mg of budesonide or equivalent, see this article's Online Repository) and a LABA; non-smokers or not have smoked for a year and have a smoking history of <10 pack-years
Setting	Germany, Denmark and Netherlands
Interventions	Random sequence for 8 weeks in a crossover design (5 or 10 mg of tiotropium or matching placebo administered as 2 actuations once daily through the Respimat inhaler
Adherence reported yes/no	No
Primary outcomes	The FEV1 response (within 3 hours post dosing) determined at the end of the 8-week treatment period
Secondary outcomes	The trough FEV1 and peak and trough FVC at the end of each 8–week treatment period, the area under the curve (AUC) of the first 3 hours of FEV1 (FEV1 AUC0-3h) and FVC (FVC AUC0-3h) and weekly means of pre dose morning and evening PEF and FEV1, asthma symptoms (5-point rating scale), use of rescue medication in the last 5 weeks of treatment, asthma symptom-free days, and AQLQ

Study reference	Kerstjens (Tiotropium) 2015
Study tittle	Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials
Study duration	4-week run-in period. 24 weeks
Trial registration:	NCT01172808 and NCT01172821
Study Population	Participants: tiotropium 5 μg group, n=519; tiotropium 2·5 μg group, n=520; salmeterol group, n=541; or placebo group, n=523 Eligibility criteria: male or female, aged between 18 and 75 years, and had been diagnosed with asthma before age 40 years and at least 3 months before enrolment; diagnosis of asthma confirmed at screening on the basis of bronchodilator reversibility, with an FEV1 increase of ≥12% and ≥200 mL 5–30 min after 400 μg salbutamol; symptomatic (mean ACQ-7 score of ≥1·5) at screening and before randomisation, had to have a pre-bronchodilator FEV1 60–90% of predicted at screening, and had to show FEV1 variability at randomisation within plus or minus 30% of the screening value. stable treatment with medium-dose inhaled corticosteroids of 400–800 μg budesonide or equivalent (alone or in fixed combination with a LABA or short-acting β2 agonist) for at least 4 weeks before screening. Patients were to have never smoked or been ex-smokers for more than 1 year, with a total of ≤10 pack-years
Setting	233 sites in 14 countries (Latvia, Poland, Romania, Russia, Brazil, China, Colombia, Germany, Guatemala, India, Japan, Mexico, Peru, and the USA)
Interventions	Once daily tiotropium 5 μg or 2·5 μg, twice-daily salmeterol 50 μg, or placebo.
Adherence reported yes/no	No
Primary outcomes	The peak FEV1 response, measured within the first 3 h after evening dosing, and trough FEV1 response, measured at the end of the dosing interval (24 h after drug administration), 10 min before the next dose, both determined at the end of the 24-week treatment period. The improvement in ACQ-7 score of ≥0·5 or more at the end of week 24
Secondary outcomes	All determined at the end of the 24-week treatment period, included peak FVC, trough FVC, mean weekly pre-dose morning PEF response, and mean weekly pre-dose evening PEF response, AQLQ, and times to first severe asthma exacerbation and first asthma exacerbation (both during the 24-week treatment period)

Study reference	Kishiyama (IVIG) 1999
Study tittle	A Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial of High-Dose Intravenous Immunoglobulin for Oral Corticosteroid-Dependent Asthma
Study duration	2-month observation/run-in period. 7 months
Trial registration:	Not documented
Study Population	Participants: IVIG (2 gm/kg) group, n=16; IVIG (1 gm/kg) group, n=9; placebo group, n=15 Eligibility criteria: patients of the age 6 to 66 years with a previously diagnosis of asthma, defined by the ATS criteria; unable to decrease their steroid dosage to <0.1 mg/kg/day prednisone (or the equivalent) during the prior 3 months of optimizing therapy or failed to maintain peak flows of > 80% of predicted values on their current dose of prednisone
Setting	United States
Interventions	2 g IVIG/kg/month, 1 g IVIG/kg/month, or 2 g IV albumin (placebo)/kg/month.
Adherence reported yes/no	No
Primary outcomes	The mean daily prednisone-equivalent dose requirements, determined during the observation month preceding initiation of treatment and compared to the month preceding the seventh infusion
Secondary outcomes	FEV1, frequency of emergency room visits or hospitalizations, and number of days absent from school or work

Study reference	Lanier (Omalizumab) 2003
Study tittle	Omalizumab is the effective in the long-term control of severe allergic asthma
Study duration	24 weeks
Trial registration:	Extension phase of Busse 2001
Study Population	Participants: omalizumab group, n= 245; placebo group, n=215 Eligibility criteria: male or female allergic asthmatics aged 12 to 75 years who were symptomatic despite treatment with ICSs; duration of asthma ≥1 year; positive immediate responses on skin prick testing to at least 1 common allergen, including Dermatophagoides farinae, Dermatophagoides pteronyssinus, cockroach (whole body), dog, or cat; total serum IgE ≥30 IU/mL to ≤700 IU/mL; FEV1 reversibility of ≥12% within 30 minutes after administration of albuterol (90-180 μg); baseline FEV1 ≥40% and ≤80% of predicted; and treatment with 420 to 840 μg/day of beclomethasone dipropionate (BDP) or its equivalent ICS for ≥3 months prior to randomization
Setting	United States and United Kingdom
Interventions	placebo or omalizumab subcutaneously every 2 or 4 weeks, depending on baseline IgE level and body weight
Adherence reported yes/no	No
Primary outcomes	The number of patients experiencing at least 1 asthma exacerbation
Secondary outcomes	FEV1

Study reference	Laviollette (Benralizumab) 2013
Study tittle	Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia
Study duration	14-day screening period. 84 days
Trial registration:	NCT00659659
Study Population	Participants: Cohort 1; benralizumab,1 mg/kg group, n= 8; placebo group, n = 5. Cohort 2: benralizumab, 100 mg group, n= ; benralizumab 200 mg group, n =5; placebo group, n =5 Eligibility criteria: patients of the age 18 to 65 years; documented diagnosis of asthma supported by at least 1 of the following criteria: (1) 12% or greater increase in FEV1 after inhalation of 400 mg of albuterol during screening, (2) history of ≥12% FEV1 reversibility within 1 year of randomization, or (3) history of 20% reduction in FEV1 in response to a provocative methacholine challenge (PC20) of less than 8 mg/mL within 1 year of randomization; sputum eosinophil counts of ≥2.5%, postbronchodilator FEV1 of ≥65%, prebronchodilator FEV1/FVC ratio of less than age-adjusted norms, and an asthma therapeutic regimen that was unchanged for 4 weeks before randomization and maintained from screening to the first follow-up airway mucosal/submucosal biopsy
Setting	3 United States and 4 Canadian medical centres.
Interventions	Intravenous infusion of 1 mg/kg benralizumab or placebo (2:1) on day 0 (cohort 1) or 100 or 200 mg of benralizumab or placebo (1:1:1) delivered in 4 subcutaneous injections on days 0, 28, and 56 (cohort 2).
Adherence reported yes/no	No
Primary outcomes	Safety and the effect of benralizumab on eosinophil counts in airway mucosal/submucosal biopsy specimens 28 days after completion of dosing
Secondary outcomes	Evaluate the pharmacokinetics (PK) of MEDI-563 in adults with atopic asthma and evaluate the immunogenicity (IM) of MEDI-563 in adults with atopic asthma. [Time Frame: Day 84 or 140]

Study reference	Li (Omalizumab) 2014
Study tittle	Omalizumab Improves Quality of Life and Asthma Control in Chinese Patients with Moderate to Severe Asthma: A Randomized Phase III Study
Study duration	6-week screening period. 24 weeks.
Trial registration:	NCT01202903
Study Population	Participants: omalizumab group, n=310; placebo group, n=299 Eligibility criteria: patients of the age 18-75 years, with confirmed diagnosis of moderate-to-severe persistent allergic asthma {inadequately controlled symptoms despite medium-to high-dose ICS+LABA (GINA step 4) therapy; positive reaction to at least 1 perennial aeroallergen and reported ≥ 2 or ≥3 exacerbation events in previous 12 or 24 months, respectively; FEV1 of 40%-80% of predicted normal with post-bronchodilator reversibility of ≥12% within 30 minutes and compliance with completion of PEF electronic diary (eDiary) during the run-in period
Setting	
Interventions	Add-on omalizumab or add-on placebo by subcutaneous injections for 24 weeks
Adherence reported yes/no	No
Primary outcomes	The mean change from baseline in morning PEF (am PEF, L/min) measured using a PEF meter after 24 weeks of treatment
Secondary outcomes	FEV1 % predicted at weeks 16 and 24 weeks and ACQ, AQLQ, Global Evaluation of Treatment Effectiveness (GETE) responder analysis, scores at Weeks 16 and 24. The rate and seasonal effect of protocol-defined asthma exacerbations were assessed as exploratory outcomes

Study reference	Lock (Ciclosporin) 1996
Study tittle	Double-blind, Placebo-controlled Study of Cyclosporin A as a Corticosteroid-sparing Agent In Corticosteroid-dependent Asthma
Study duration	4-week run-in period. 52 weeks
Trial registration:	Not documented
Study Population	Participants: cyclosporin group, n=19; placebo group, n=20 Eligibility criteria: corticosteroid-dependent asthmatic patients; documented variability of at least 20% in their FEV1 or PEFR, either spontaneously or following treatment with a bronchodilator (nebulized salbutamol 5mg)
Setting	United Kingdom
Interventions	Cyclosporin at a starting dose of 5mg/kg/d (ideal body weight) or identical placebo presented as capsules, for a period of 36 weeks
Adherence reported yes/no	No
Primary outcomes	Reduction in prednisolone dosage at 36 weeks
Secondary outcomes	FEV1/FVC, response to bronchodilator, diurnal variability of PEFR, or day/night symptom scores

Study reference	Lomia (Carbamazepine) 2006
Study tittle	Bronchial asthma as neurogenic paroxysmal inflammatory disease: A randomized trial with carbamazepine
Study duration	4-week run-in period. 13 weeks
Trial registration:	Not documented
Study Population	Participants: carbamazepine group, n= 37; placebo group, n=37 Eligibility criteria: asthma diagnosis for at least for 1 year, poorly controlled asthma due to various reasons, absence of long-term remissions of asthma (lasting more than 1 month), and if pulmonary function testing demonstrated at least 12% acute response in FEV1 to beta-agonist inhalation
Setting	Georgia
Interventions	100 mg capsules of carbamazepine) or placebo for 13 weeks
Adherence reported yes/no	No
Primary outcomes	Efficacy of carbamazepine was evaluated by disappearance of any asthmatic syndrome, and normalization of PEF, FEV1
Secondary outcomes	The daytime scores of asthma, number of night-time awakening per week due to asthma symptoms and also by discontinuation of any other anti-asthmatic therapy except carbamazepine

Study reference	Marin (Nedocromil sodium) 1996
Study tittle	Effects of nedocromil sodium in steroid resistant asthma: A randomized controlled trial
Study duration	2-week observation period. 2 years
Trial registration:	Not documented
Study Population	Participants: Nedocromil sodium group, n=13, placebo group, n=13 Eligibility criteria: non-smoking adults (>18 years of age) with moderate or severe asthma; inadequately controlled by means of inhaled or orally administered corticoids; basal FEV1 <70% of the predicted
Setting	Spain
Interventions	Nedocromil sodium or placebo by means of a manual nebulizer for 3 months
Adherence reported yes/no	Yes
Primary outcomes	Morning PEF (L/min) and the daily use of inhaled salbutamol
Secondary outcomes	FEV~ value, variability of the PEF, value of the questionnaire for quality of life, intake of prednisolone, and number of asthma attacks that occurred during the treatment period. The changes found in FEV 1 between the groups during each visit and the mean morning PEF values, together with the use of salbutamol during the week before each visit in the treatment and washout periods, were compared with their baseline values b

Study reference	Morjaria (Etanercept) 2008
Study tittle	The role of a soluble TNFα receptor fusion protein (etanercept) in corticosteroid refractory asthma: a double blind, randomised, placebo-controlled trial
Study duration	2-week run-in period. 16 weeks
Trial registration:	Not documented
Study Population	Participants: etanercept group, n=13; placebo group, n=13 Eligibility criteria: severe refractory asthma as per GINA guidelines {current treatment with oral prednisolone (2–30 mg/day) and/or high dose ICS (>2000 μg/day beclomethasone equivalent) and LABA}; variable airflow obstruction and/or BHR confirmed by an increase in FEV1 by at least 12% after inhalation of 400 μg of salbutamol delivered by a metered dose inhaler and spacer, the concentration of methacholine required to cause a 20% (PC20) reduction in FEV1 of <8 mg/ml
Setting	United Kingdom
Interventions	50 mg of etanercept or matched placebo by subcutaneous injections once a week for 12 weeks
Adherence reported yes/no	Yes
Primary outcomes	The differences in change of the mean AQLQ score from baseline (visit 0) and the end of treatment (week 12) and change in mean ACQ scores from baseline and the last two treatment visits (week 12 and week 14)
Secondary outcomes	The differences from baseline to visit 12 for BHR, and to the last two treatment visits for predicted FEV1, FEV1/FVC, morning, evening and average daily PEF, and diurnal variation in PEF (calculated by the difference in the evening and morning PEF values)

Study reference	Nair (SCH 527123) 2012
Study tittle	Safety and efficacy of a CXCR2 antagonist in patients with severe asthma and sputum neutrophils: a randomized, placebo-controlled clinical trial
Study duration	2-week run-in period. 4 weeks
Trial registration:	Not documented
Study Population	Participants: SCH527123 group, n=22; placebo group, n=12 Eligibility criteria: patients of the age 18 and 70 years with severe asthma, meeting the National Heart Lung Blood Institute Severe Asthma Programme criteria; asthma diagnosis: ≥12% and 200 mL improvement in FEV1 after inhaling salbutamol or by a methacholine PC20 of < 8 mg/mL within the past 5 years; treatment with inhaled beclomethasone or equivalent in a dose of > 1000µg daily; sputum neutrophil differentials of > 40% at the screening visit, a total cell count of < 10 million cells/g of sputum selected from saliva and had negative standard cultures for bacteria: non-smokers for at least a year, had < 20 pack-years of smoking, were stable for the past 4 weeks and had been on stable treatment under the care of a specialist for at least 3 months
Setting	8 academic centres in Canada, Germany, Greece, France, Italy and the United Kingdom
Interventions	SCH527123 30 mg ingested once daily or a matching placebo for 4 weeks
Adherence reported yes/no	No
Primary outcomes	Safety as defined by the proportion of subjects in each treatment group who maintain a peripheral neutrophil count 1500/lL during the 4-week treatment period
Secondary outcomes	The change in ACQ score, minor and major exacerbations, PEF and sputum neutrophil activation markers in the 4-week treatment period

Study reference	Nair (Mepolizumab) 2009
Study tittle	Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia
Study duration	6-week run-in period. 26 weeks
Trial registration:	NCT00292877
Study Population	Participants: mepolizumab group, n=9; placebo group, n=11 Eligibility criteria: patients of the age 18-70 years, who have been found to require a minimum dose of prednisone treatment (in addition to high-dose inhaled steroid treatment) to prevent frequent exacerbations associated with induced sputum eosinophilia; on the same doses of corticosteroids for a least one-month
Setting	Hamilton, Ontario, Canada
Interventions	Mepolizumab 750mg or an identical placebo (normal saline diluent) was given intravenously over a 30-minute period at weeks 2, 6, 10, 14, and 18
Adherence reported yes/no	No
Primary outcomes	The proportion of patients with exacerbations in each study group and the mean reduction in the dose of prednisone as a percentage of the maximum possible reduction
Secondary outcomes	The reduction in the number of eosinophils in sputum and blood in phase 1; the time to an exacerbation, a reduction in the number of sputum and blood eosinophils, and changes in FEV1 and symptom scores in phase 2; and a reduction in the number of sputum and blood eosinophils and changes in FEV1 and symptoms in phase 3

Study reference	Nair (Benralizumab) 2017
Study tittle	Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma
Study duration	8-week run-in period. 28 weeks
Trial registration:	NCT02075255
Study Population	Participants: benralizumab, 4-weekly group, n=72; benralizumab 8-weekly group, n =73; placebo group, n=75 Eligibility criteria: female and male aged from 18 to 75 years; physician-diagnosed asthma requiring treatment with medium- to high-dose ICS (total daily dose equivalent to >250 μg fluticasone dry powder formulation) and LABA for ≥12 months prior to enrolment; documented treatment with high-dose inhaled glucocorticoid total daily dose equivalent to >500 μg fluticasone dry powder formulation) and LABA for ≥ 6 months prior to enrolment; peripheral blood eosinophil count of ≥150 cells/μl; chronic oral glucocorticoid therapy for ≥6 continuous months directly preceding enrolment(patients must have been receiving doses equivalent to 7.5–40 mg/d of prednisolone/prednisone at visit 1 and must have been on a stable dose for ≥2 weeks before randomization); evidence of asthma as documented by: (Airway reversibility (FEV1 ≥12% and 200 mL) demonstrated at visit 1, visit 2, or visit 3 (week –10, –8, or –6) using the Maximum Post-bronchodilator Procedure, or documented reversibility in the previous 24 months prior to enrolment, or Airway hyper-responsiveness (provocative concentration of methacholine causing a 20% drop in FEV1 methacholine concentration ≤8 mg/ml) documented in the previous 12 months prior to planned date of randomization, or Airflow variability in clinic FEV1 ≥20% between two consecutive clinic visits documented in the 12 months prior to the planned date of randomization (FEV1 recorded during an exacerbation were considered for this criterion); At least one documented asthma exacerbation in the 12 months prior to the date informed consent was obtained.
Setting	Argentina, Bulgaria, Canada, Chile, France, Germany, South Korea, Poland, Spain, Turkey, Ukraine, United States.
Interventions	Subcutaneous injections of benralizumab at a dose of 30 mg every 4 weeks, benralizumab at a dose of 30 mg administeredevery 4 weeks for the first three doses and then every 8 weeks (with placebo administered at the 4-week interim visits; hereafter referred to as the group that received benralizumab every 8 weeks),or placebo administered every 4 weeks
Adherence reported yes/no	Yes
Primary outcomes	The percentage reduction in the oral glucocorticoid dose from baseline (randomization at week 0) to the final dose at the end of the maintenance phase (week 28) while asthma control was maintained
Secondary outcomes	The percentages of patients who had a reduction in the average daily oral glucocorticoid dose of 25% or more, of 50% or more, or of 100% (discontinuation of oral glucocorticoid therapy) from baseline to end of the maintenance phase and

	the percentage of patients with an average final oral glucocorticoid dose of 5.0 mg or less per day while asthma control was maintained; the annual asthma exacerbation rate, the time to the first asthma exacerbation, the percentage of patients with at least one asthma exacerbation (including exacerbations associated with emergency department visits or hospitalization), the pre-bronchodilator FEV1, ACQ-6 score, and the AQLQ score

Study reference	Nizankowska (Ciclosporin) 1995
Study tittle	Treatment of steroid-dependent bronchial asthma with cyclosporin
Study duration	12-week baseline period. 42 weeks
Trial registration:	Not documented
Study Population	Participants: Cyclosporin group, n=34; placebo group, n=17 Eligibility criteria: non-smoking adults aged 25–57 years; severe chronic asthma; required long-term oral steroid treatment at a minimum dose of 5–35 mg daily, in addition to standard therapy consisting of theophylline, inhaled beclomethasone and β-mimetics; Airflow variability of ≥15% increase in FEV1 or in PEF following 200 µg fenoterol inhalation
Setting	Poland
Interventions	Cyclosporin or placebo for 12 weeks
Adherence reported yes/no	No
Primary outcomes	Outcomes: asthma symptoms score, (daily peak expiratory flow PEF and bi-weekly FVC, FEV1 and maximal mid- expiratory flow (MEF50), biochemical profile and blood cyclosporin
Secondary outcomes	Not specified

Study reference	Ogirala (IM triamcinolone) 1995
Study tittle	Single, High-dose Intramuscular Triamcinolone Acetonide versus Weekly Oral Methotrexate in Life-threatening Asthma: A Double-blind Study
Study duration	2-month 28 weeks 5 months
Trial registration:	Not documented
Study Population	Participants: 360-mg dose of triamcinolone 360mg dose, n=6; Placebo triamcinolone group, n=7; control group, n = 6 Eligibility criteria: patients of either sex between the ages of 21 and 70 years, with a diagnosis of asthma as per ATS criteria; on chronic steroid therapy (at least 5 mg of prednisone or its equivalent daily) during the year prior to entry into the study; a history of life-threatening asthma attacks (requiring mechanical ventilation or treatment in the intensive care unit) at least once in the preceding 4 years
Setting	United states
Interventions	Group 1: a single 360-mg dose of triamcinolone acetonide intramuscularly, followed by placebo methotrexate tablets taken orally each week for 6 months Group 2: placebo (normal saline) triamcinolone injection at entry, followed by oral methotrexate at a dose of 7.5mg the first week, followed by 15 mg every week for 6 months Group3: control group, receiving a placebo triamcinolone injection on the first day, followed by placebo-methotrexate tablets each week for the ensuing 6 months
Adherence reported yes/no	No
Primary outcomes	Outcomes: FEV1, PEFR, PC20
Secondary outcomes	

Study reference	Oh (MEDI528) 2013
Study tittle	A randomized, controlled trial to evaluate the effect of an anti-interleukin-9 monoclonal antibody in adults with uncontrolled asthma
Study duration	4-week screening period, a 13-week steroid stable treatment period, an 11-week steroid reduction treatment period, and a 22-week follow-up period
Trial registration:	NCT00968669
Study Population	Participants: MEDI-528 30mg group, n=80; MEDI-528 100mg group, n=80, or MEDI-528 300 mg group, n=80; placebo group, n=80 Eligibility criteria: patients of the age 18–65 years with BMI of 18–35 kg/m2 and a clinical diagnosis of asthma, confirmed by pre-bronchodilator FEV1 of ≥ 40% predicted and post-bronchodilator FEV1 reversibility ≥ 12% and ≥ 200 mL; poor asthma symptom control (ACQ-6 score of ≥ 1.5; daytime symptoms on ≥ 2 days/week, night-time awakening ≥ 1 night/week, rescue medication use on ≥ 2 days/week); ≥ 1 asthma exacerbation in the past year; medium to high-dose ICS or were eligible to take them based on Expert Panel Report 3 guidelines, and were started on medium to high-dose ICS at the start of the run-in phase of the study
Setting	53 sites in North America, Central America, South America, and Asia
Interventions	Placebo or one of three doses of MEDI-528 (30, 100, or 300 mg) subcutaneously every 2 weeks for 24 weeks (13 doses)
Adherence reported yes/no	No
Primary outcomes	The change from baseline in mean ACQ-6 score at week 13 among individual MEDI-528 treatment groups and placebo
Secondary outcomes	The change from baseline in mean ACQ-6 score at week 25, asthma exacerbation rates (week 25), pre-bronchodilator FEV1 (weeks 13 and 25), AQLQ scores; weeks 12 and 25), and the safety of MEDI-528 throughout the study period

Study reference	Ohta (Omalizumab) 2009
Study tittle	Efficacy and safety of omalizumab in an Asian population with moderate-to-severe persistent asthma
Study duration	2-week pre-treatment period, 16-week treatment period and 12-week follow up
Trial registration:	Not documented
Study Population	Participants: omalizumab group, n=158; placebo group, n=169 Eligibility criteria: patients (aged 20–75 years) with moderate-to-severe asthma according to the GINA guidelines; treated with beclomethasone dipropionate chlorofluorocarbon (CFC)-containing metered-dose inhaler at 800 mg/day (or equivalent), and one or more of the following additional controller medications recommended as step 3 and step 4 treatments LABA (sustained-release theophylline, leukotriene receptor antagonist (LTRA), oral corticosteroid); positive skin test or in vitro reactivity to a perennial aeroallergen; serum total IgE of 30–700 IU/mL; insufficient asthma control, (asthma symptoms interfere with night-time sleep one day/week or asthma symptoms restrict daily activities or rescue medication/SABA needed one day/week or PEF diurnal variation 20% on one day/week or FEV1 or mean PEF value in the range of 40–80% of the predicted normal value
Setting	Japan
Interventions	Omalizumab subcutaneous injection every two or four weeks according to the patient's pre-treatment bodyweight and baseline IgE levels, using a dosing table to provide a dose of at least 0.016 mg/kg per IU/mL of IgE or placebo
Adherence reported yes/no	No
Primary outcomes	The change from baseline in morning PEF (L/min), as recorded on diary cards at 16 weeks
Secondary outcomes	The change from baseline in FEV1, asthma symptom score, daily activity score, sleep score and rescue medication use, clinically significant asthma exacerbations at week 16

Study reference	Ortega (Mepolizumab) 2014
Study tittle	Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma
Study duration	1-6 weeks run-in period, 32-week treatment intervention and 8-week follow-up
Trial registration:	NCT01691521
Study Population	Participants: mepolizumab 75 mg group, n=191; mepolizumab 100 mg group, n=194; placebo group, n= 191 Eligibility criteria: Blood eosinophils ≥ 150 cells/μL at screening or ≥ 300 cells/μL in previous 12 months; ≥ 2 exacerbations in previous 12 months; FEV1 < 80%; maintenance treatment with high-dose ICS for ≥ 12 months; plus additional controller for ≥ 3 months; ± maintenance OCS
Setting	Baltimore, Middlesex, Ghent, Vancouver, Parma, Marseille and Paris
Interventions	Mepolizumab in a 75 mg intravenous dose versus mepolizumab in a 100 mg subcutaneous dose versus placebo every 4 weeks for 32 weeks
Adherence reported yes/no	No
Primary outcomes	Number of annualized frequency of clinically significant exacerbations
Secondary outcomes	Number of clinically significant exacerbations requiring hospitalisation (including intubation and admittance to an intensive care unit) or ED visits per year Mean change from baseline in clinic pre-bronchodilator FEV1 at week 32 Mean change from baseline in the SGRQ total score at week 32

Study reference	Park (Benralizumab) 2016
Study tittle	A Phase 2a Study of Benralizumab for Patients with Eosinophilic Asthma in South Korea and Japan
Study duration	52 weeks
Trial registration:	NCT01238861
Study Population	Participants: benralizumab 2 mg group, n=26; benralizumab 20 mg group, n=25; benralizumab 100 mg group, n=26; placebo group, n=26 Eligibility criteria: moderate/severe (based on ICS dose (medium/high); post-bronchodilator FEV1 reversibility ≥ 12% and ≥ 200 mL, or a positive response to methacholine challenge (PC20 ≤ 8 mg/mL); 2-6 exacerbations in the previous 12 months; ACQ-6 score ≥ 1.5 at least twice during screening; morning pre-bronchodilator FEV1 40%-90%; maintenance treatment with medium- to high-dose ICS in combination with LABA for ≥ 12 months
Setting	32 sites in South Korea and Japan
Interventions	Subcutaneous doses given at weeks 1, 4, 8, 16, 24, 32, 40. Benralizumab 2 mg, 20 mg or 100 mg subcutaneously
Adherence reported yes/no	No
Primary outcomes	Asthma exacerbation rate at week 52
Secondary outcomes	FEV1, PEFR, ACQ-6, FeNO, Exploratory endpoints included blood eosinophil counts.

Study reference	Pavord (Bronchial thermoplasty) 2007
Study tittle	Safety and Efficacy of Bronchial Thermoplasty in Symptomatic, Severe Asthma
Study duration	2-week run-in period. 52 weeks
Trial registration:	NCT 00214539
Study Population	Participants: Bronchial thermoplasty group, n= 15; control group, n= 17 Eligibility criteria: patients with asthma aged 18 to 65 years; requirement of high-dose ICS (≥750 mg fluticasone propionate per day or equivalent) and LABA (at least 100 mg salmeterol per day or equivalent), with or without oral prednisone (<30 mg/d), leukotriene modifiers, or theophylline; prebronchodilator FEV1 > 50% of predicted; demonstrable airway hyperresponsiveness by challenge with methacholine or reversible bronchoconstriction during prior 12 months as demonstrated by an increase in FEV1 of at least 12% 30 minutes after four puffs of a SABA; uncontrolled symptoms despite taking maintenance medication (demonstrated by the use of rescue medication on at least 8 of the 14 days before enrolment, or daytime symptoms on at least 10 of the 14 days before enrolment); and abstinence from smoking for ≥1 year and past smoking history of <10 pack-years
Setting	8 investigational sites in three countries; Canada, United Kingdom and Brazil
Interventions	Bronchial thermoplasty in addition to ICS/LABA or ICS plus LABA. Bronchial thermoplasty group patients underwent three procedures at least 3 weeks apart
Adherence reported yes/no	Yes
Primary outcomes	The safety of BT was assessed by monitoring adverse events and PEF between weeks 6 to 22
Secondary outcomes	The change in OCS and ICS, use of rescue medication, morning and evening PEF, FEV1, PC20 (provocative concentration causing a 20% fall in FEV1), asthma symptom score, symptom-free days, or AQLQ and ACQ scores PEF between weeks 6 to 22

Study reference	Pavord (Mepolizumab) 2012
Study tittle	Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial
Study duration	52-week
Trial registration:	NCT01000506
Study Population	Participants: mepolizumab 750 mg group, n=156; mepolizumab 250 mg group, n=152; mepolizumab 75 mg group, n=154; placebo group, n=159 Eligibility criteria: ≥ 3% sputum eosinophils or blood eosinophil ≥ 300 cells/μL; ≥ 2 exacerbations in previous 12 months; maintenance treatment with high-dose ICS (i.e. ≥ 880 μg/d FP or equivalent daily); + additional controller; ± maintenance OCS ;patients were aged 12–74 years and had a clinical diagnosis of asthma supported by one or more other characteristics: variability in diurnal PEF of more than 20% for at least 3 days during the 2-week run-in period; improvement in FEV1 of more than 12% and 200 mL after 200 μg inhaled salbutamol at visit one or two, or in the 12 months before study entry; a variability in FEV1 of greater than 20% between two consecutive clinic visits in 12 months; or a provocative concentration of inhaled methacholine needed to reduce FEV1 by 20% (PC20) of 8 mg/mL or less documented in the 12 months before study entry
Setting	81 centres in 13 countries; Argentina, Australia, Canada, Chile, France, Germany, South Korea, Poland, Romania, Russia, Ukraine, the United Kingdom and the United States
Interventions	13 total intravenous infusions of mepolizumab (750 mg), mepolizumab (250 mg), mepolizumab (75 mg) or placebo given every 4 weeks
Adherence reported yes/no	No
Primary outcomes	The rate of clinically significant asthma exacerbations. Exacerbation events occurring in the 52 weeks between completion of the first treatment visit and 4 weeks after the final treatment visit were included in the analysis
Secondary outcomes	The rate of exacerbations requiring admission, visits to the emergency department, blood and sputum eosinophil counts, mean change from baseline in clinic pre-bronchodilator FEV1, ACQ, AQLQ over the 52-week treatment period, time to first clinically significant exacerbation requiring oral or systemic corticosteroids, hospitalisation, and/or ED visits, frequency of exacerbations requiring hospitalisation (including intubation and admittance to an ICU) or ED visits

Study reference	Piper (Tralokinumab) 2013
Study tittle	A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma
Study duration	2-week run-in period. 24 weeks
Trial registration:	NCT01402986
Study Population	Participants: tralokinumab 150mg group, n=47; tralokinumab 300mggrop, n=51; tralokinumab 600mg group, n=48; placebo group, n=48 Eligibility criteria: patients age, 18–65 years; BMI of 18–40 kg/m2 physician-diagnosed, moderate-to-severe uncontrolled asthma; reversible airflow obstruction (post-bronchodilator FEV1 reversibility ≥12% and ≥200 mL either documented within the previous year or at screening); pre-bronchodilator FEV1 of 40% predicted value; ACQ-6 score of ≥1.5 at screening and randomisation, and one or more asthma exacerbations that required medical intervention in the past year
Setting	United Kingdom and United states
Interventions	Tralokinumab 150, 300 or 600 mg or placebo. Treatment was administered every 2 weeks by subcutaneous injection
Adherence reported yes/no	Yes
Primary outcomes	The change from baseline to week 13 in mean ACQ-6 score
Secondary outcomes	Time to asthma control, change from baseline in FEV1 and peak PEF (at study visit and at home), time to first asthma exacerbation, asthma exacerbation rate, requirement for concomitant asthma rescue medications, daily asthma symptoms scores, AQLQ, pre-bronchodilator FEV1, FVC and PEF. Patient-reported outcomes (PROs) included a four-item

Study reference	Robinson (Montelukast) 2001
Study tittle	Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial
Study duration	4 weeks
Trial registration:	Not documented
Study Population	Participants: 100 patients randomised, cross over trial Eligibility criteria: Any patient with a physician diagnosis of asthma in whom the recruiting consultant physician felt a trial of Montelukast was indicated for continued asthma symptoms despite other anti-asthma
Setting	United Kingdom
Interventions	Montelukast sodium or matched placebo capsules for four weeks
Adherence reported yes/no	No
Primary outcomes	Outcomes: PEF; FEV1

Study reference	Rubin (Omalizumab) 2012
Study tittle	Effect of Omalizumab as Add-On Therapy on Asthma-Related Quality of Life in Severe Allergic Asthma: A Brazilian Study (QUALITX)
Study duration	20 weeks
Trial registration:	
Study Population	Participants: Omalizumab group, n=78; control group, n=38 Eligibility criteria: patients of the age 12 and 75 years; severe persistent asthma as per GINA guidelines; uncontrolled despite treatment with, at least, ICS (500 μg/day of fluticasone equivalent) and LABA; 20 and 150 kg body weight; serum total IgE levels between 30 and 700 IU/mL; positive skin prick test (diameter of wheal 3 mm) for at least one perennial aeroallergen
Setting	Brazil
Interventions	Omalizumab+ LABA + ICS or the control group (LABA + ICS). Omalizumab 150–375 mg was administered subcutaneously every 2 or 4 weeks
Adherence reported yes/no	No
Primary outcomes	The mean change from baseline in overall AQLQ score in omalizumab-treated patients compared with the control group mean change at week 12 and at week 20
Secondary outcomes	Rescue medication use, incidence of asthma exacerbations, perception of treatment efficacy among patients, mean change from baseline in AQLQ score, and >1.5-point increase in overall AQLQ score percentage of patients with a >1.5-point increase from baseline in the overall AQLQ; FEV1, FVC, Global Evaluation of Treatment Effectiveness

Study reference	Salmun (IVIG) 1999
Study tittle	Effect of intravenous immunoglobulin on steroid consumption in patients with severe asthma: A double-blind , placebo controlled randomized trial
Study duration	3 months
Trial registration:	Not documented
Study Population	Participants: Immune Globulin Intravenous 5% group, n=16, placebo group, n=12 Eligibility criteria: Age 5 to 35 years with a clinical diagnosis of asthma per ATS criteria; steroid dependent asthma (patients who required oral steroid on a daily or alternate day basis for at least 6 months before study entry or patients who required at least 30 days of oral steroids per year despite chronic use of inhaled steroids)
Setting	Massachusetts, Turkey, Austria
Interventions	Iveegam Immune Globulin Intravenous 5%, and 5% albumin was the placebo
Adherence reported yes/no	No
Primary outcomes	Comparison of dosage of oral steroids consumed at baseline (first 3 months of the study) and a during the treatment phase (the last 3months of the study).
Secondary outcomes	Comparison of dosage other medication use, parameters of clinical symptomatology, and pulmonary function tests at baseline(first 3 months of the study) and a during the treatment phase (the last 3months of the study)

Study reference	Sano (Sodium cromoglycate) 2006
Study tittle	Effects of nebulized sodium cromoglycate on adult patients with severe refractory asthma
Study duration	2-week observation period. 10 weeks
Trial registration:	Not documented
Study Population	Participants: sodium cromoglycate group, n =114, placebo group, n =114 Eligibility criteria: Patients of the age ≥20; severe persistent asthma; Step 4 therapy according to the Classification for Asthma Severity in the Asthma Prevention and Management Guidelines 20001 in Japan; ICS regiment : 4800 mg/day of inhaled beclomethasone dipropionate (BDP-CFC), 4400 mg/day of inhaled fluticasone propionate (FP-DPI), or 4400 mg/day of inhaled budesonide (BUD-DPI); mean morning PEF during the observation period <80% of normal predicted value, or diurnal variation in PEF during the observation period >20% were evaluated at least 2 days/each week; asthmatic symptoms (wheezing, dyspnoea, or slight asthmatic attack) were reported at least 2 times/week
Setting	30 medical centres in Japan
Interventions	Sodium cromoglycate or isotonic saline was used as placebo
Adherence reported yes/no	No
Primary outcomes	The percentage change from baseline at the end of the treatment in morning PEF at 2, 4, 6, 8 and 10 weeks
Secondary outcomes	The change in FVC, FEV1,PEF, asthmatic symptom score, QOL at baseline, 4, 8 and 10 weeks

Study reference	Bosquet (Omalizumab) 2011
Study tittle	Persistency of response to Omalizumab therapy in severe allergic (IgE-mediated) asthma
Study duration	8-week run-in period. 32 weeks
Trial registration:	Not documented
Study Population	Participants: Omalizumab group, n=272, Optimised asthma therapy (OAT) group, n=128 Eligibility criteria: patients of the aged 12-75 years, with severe allergic asthma; ≥2 severe asthma exacerbations (requiring treatment with systemic corticosteroid s) while receiving ≥800µg beclomethasone dipropionate or equivalent plus LABA during the 3 years prior to screening, with ≥1 severe exacerbation within the previous year; body weight of 20-150kg and baseline serum IgE level of 30-700IU/ml: positive skin prick or radio-allergosobernt test to at least one perennial allergen; ≥12% reversibility in FEV1 within taking 2-4x100µg salbutamol; FEV1 between 40% and 80% of predicted
Setting	106 centres in 14 countries; Belgium, Canada, Denmark, Germany, Hungary, Israel, Italy, Norway, Poland, Spain, Sweden, turkey, United Kingdom and Switzerland
Interventions	Optimised asthma therapy (OAT) or optimised asthma therapy and omalizumab
Adherence reported yes/no	No
Primary outcomes	The persistency rate of response in patients receiving omalizumab at weeks 16 and 32
Secondary outcomes	Persistency rates of non-response in patients receiving omalizumab at weeks 16 and 32; persistency rates of response/nonresponse in patients receiving OAT alone; patients' GETE at weeks 16 and 32; change from baseline in FEV1 and %-predicted at weeks 16 and 32; clinically significant asthma exacerbations over the 32-week treatment period; severe exacerbations over the 32-week treatment period ; hospitalizations and total emergency room visits because of asthma exacerbation over the 32-week treatment period; change from baseline ACQ overall score which was assessed at weeks 16 and 32; change from baseline at week 32 in the number of night in the previous 2 weeks with an awakening requiring rescue medication

Study reference	Simpson (Clarithromycin) 2008
Study tittle	Clarithromycin Targets Neutrophilic Airway Inflammation in Refractory Asthma
Study duration	12-week run-in period. 8 weeks treatment period
Trial registration:	No. 12605000318684
Study Population	Participants: Clarithromycin group, n=23; placebo group, n=23 Eligibility criteria: Non-smoking adults with symptomatic refractory asthma according to GINA guidelines, with demonstrated airway hyperresponsiveness to hypertonic saline
Setting	Australia
Interventions	Oral clarithromycin 500 mg twice daily (Klacid; Abbot Australasia, Botany NSW, Australia) or placebo duration pf treatment
Adherence reported yes/no	No
Primary outcomes	IL-8 levels in sputum supernatant after 8 weeks of treatment
Secondary outcomes	The sputum neutrophil numbers, neutrophil elastase and matrix metalloproteinase (MMP)-9 levels, FEV1% predicted, dose–response slope to hypertonic saline, symptom severity, asthma control score, and asthma quality-of-life questionnaire score

Study reference	Smith (Isoflavane) 2015
Study tittle	Effect of a Soy Isoflavone Supplement on Lung Function and Clinical Outcomes in Patients with Poorly Controlled Asthma A Randomized Clinical Trial
Study duration	6 months
Trial registration:	NCT01052116
Study Population	Participants: Isoflavane group, n=193; placebo group, n=193 Eligibility criteria: age ≥12; physician diagnosed asthma; pre-bronchodilator FEV1 ≥50% predicted; at least 12% increase in FEV1 15-30 minutes after inhaling 2-4 puffs of albuterol or positive methacholine challenge (20% fall in FEV1 at less than 8 mg/mL); prescribed daily controller asthma medication; non-smokers for ≥6months or longer with <10 pack-years smoking history; poor asthma control (at least one of the following: ACQ score of ≥1.5; use of beta-agonist for asthma symptoms two or more times per week; nocturnal awakening with asthma symptoms more than once per week); two or more episodes of asthma symptoms in the past 12 months with each requiring at least one of the following: emergency department visit, unscheduled physician visit, prednisone course, hospitalization
Setting	United States
Interventions	Soy isoflavone supplement or a matching placebo twice daily for 6 months
Adherence reported yes/no	No
Primary outcomes	The mean changes in prebronchodilator FEV1 over 24 weeks
Secondary outcomes	ACT score, the Asthma Symptoms Utility Index , AQLQ, PEF, symptom-free days (defined as days with no asthma episodes reported on diary card); and rates of episodes of poor asthma control

Study reference	Soler (Omalizumab) 2001
Study tittle	The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics
Study duration	4–6-week run-in period
Trial registration:	Not documented
Study Population	Participants: Omalizumab group, n=274; placebo group, n= 272 Eligibility criteria: age, 12-75years; diagnosis of asthma of at ≥1 yr. duration who met the standard criteria of ATS and the following additional criteria: a positive skin-prick test to at least one of the allergens Dermatophagoides farinae, D. pteronyssinus, dog or cat; serum total IgE level ≥30 and ≤700 International Units (IU)/mL and body weight ≤150 kg to allow optimal dosing of omalizumab; baseline forced expiratory volume in one second (FEV1) off bronchodilators ≥40% and ≤80% of predicted increasing by ≥12% within 30 min of taking inhaled salbutamol; a mean total daily symptom score of ≥3.0 (maximum 9) during the 14 days prior to randomization; treatment with inhaled corticosteroids in doses equivalent to 500–1,200 mg of beclomethasone dipropionate (BDP) per day for ≥3 months prior to randomization and use of b2-adrenoceptor agonists on an as-needed or regular basis; stable asthma, with no significant change in regular medication and no acute exacerbation requiring additional corticosteroid treatment for≥1 month prior to the screening visit
Setting	United States, Germany, United Kingdom and South Africa
Interventions	Omalizumab or placebo subcutaneously for 7 months every 4 weeks
Adherence reported yes/no	No
Primary outcomes	The number of asthma exacerbations experienced per patient during the stable-steroid phase(first 16 weeks of the study) and the steroid-reduction phase(the last 12 weeks of the study)
Secondary outcomes	The number of patients experiencing at least one asthma exacerbation during both the stable-steroid and the steroid-reduction phases, per cent reduction in the BDP dose at the end of the steroid-reduction phase as a continuous variable and by category, salbutamol rescue use, asthma symptom scores, morning PEF and FEV1 % predicted

Study reference	Tamaoki (Th2 inhibitor IL5/IL4) 2000
Study tittle	Effect of suplatast tosilate, a Th2 cytokine inhibitor, on steroid dependent asthma: a double-blind randomised study
Study duration	2-week run-in. 8-week treatment period
Trial registration:	Not documented
Study Population	Participants: suplatast tosilate group, n= 43; placebo group, n= 42 Eligibility criteria: age ≥21 years, who had been taking 1500 g or more inhaled beclomethasone daily for at least 6 weeks before the study; asthma diagnosis as per the ATS guidelines; FEV1 predicted of at least 60% and a documented FEV1 reversibility of at least 15% of compared with baseline 15 min after inhalation of the 2-agonist procaterol (20 g)
Setting	Japan
Interventions	Suplatast tosilate (100 mg per capsule three capsules daily) or placebo (identical in taste and appearance to suplatast tosilate)
Adherence reported yes/no	Yes
Primary outcomes	Outcomes: PEFR, FEV1 and asthma symptoms scores at 4 and 8 weeks

Study reference	Vignola (Omalizumab) 2004
Study tittle	Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR
Study duration	4-week run-in. 28 weeks
Trial registration:	Not documented
Study Population	Participants: Omalizumab group, n =209; placebo group, n =196 Eligibility criteria: age 12–75 years; history of allergic asthma for at least 1 year with ≥ 12% increase in FEV1 after 400μg salbutamol; IgE level from ≥30 to ≤1300 IU/ml and a positive skin-prick test to at least one indoor allergen: moderate-to-severe persistent allergic rhinitis symptoms for ≥2 years was also necessary for inclusion: treated with ≥400 μg/day of ICS and had a history of ≥ 2 unscheduled medical visits for their asthma during the past year or ≥3 in the past 2 years: AQLQ score of >64/192; RQLQ>56/168 Rhinitis Quality of Life Questionnaire
Setting	United Kingdom, France, Canada, France and Italy
Interventions	Placebo or omalizumab administered every 2 or 4 weeks
Adherence reported yes/no	No
Primary outcomes	The incidence of asthma exacerbations during the 28-week treatment period and the proportion of patients with improvement in both asthma and rhinitis QoL scores
Secondary outcomes	Rescue-medication use, separate AQLQ and RQLQ evaluations, Wasserfallen asthma and rhinitis clinical symptom scores, patient and investigator global evaluations of treatment effectiveness, pulmonary function tests [FEV1, forced vital capacity (FVC), morning peak expiratory flow (PEF)] and ICS use

Study reference	Virchow (Zafirlukast) 2000
Study tittle	Zafirlukast Improves Asthma Control in Patients Receiving High-Dose Inhaled Corticosteroids
Study duration	2-week pre-randomisation phase. 6 weeks
Trial registration:	Not documented
Study Population	Participants: Zafirlukast group, n=180; placebo group, n=188 Eligibility criteria: age 17 to 71 years; asthma diagnosis according to GINA criteria and NHLBI guidelines; patient were required to have not smoked during the preceding 6 months; FEV1% predicted of 50% to 75%, a reversibility PEFR or FEV1 of ≥15% after inhalation of ≤400 mg albuterol, and current therapy with inhaled corticosteroids (beclomethasone ≥1,200 mg/day or equivalent)
Setting	United Kingdom
Interventions	Zafirlukast 80 mg twice daily, placebo for 6 weeks
Adherence reported yes/no	No
Primary outcomes	The change in mean morning PEFR from baseline to week 6
Secondary outcomes	The change in mean evening PEFR, FEV1 daytime symptom score, SABA use from baseline to week 6 risk of an exacerbation of asthma

Study reference	Wang (Cordyceps sinensis) 2016
Study tittle	Herbal Medicine Cordyceps sinensis Improves Health-Related Quality of Life in Moderate-to-Severe Asthma
Study duration	3 months
Trial registration:	ChiCTR-IPC-16008730
Study Population	Participants: cordyceps group, n=60; control group, n=60 Eligibility criteria: age ≥ 18 years; moderate or severe asthma with evidence of fixed airflow obstruction following a trial of maximum bronchodilator therapy and a trial of oral corticosteroids of at least 3-week duration
Setting	China
Interventions	Cordyceps sinensis (1.2 g, 3 times per day, Corbrin capsule, Hangzhou Huadong Pharmaceutical Co. Ltd.) in addition to ICS/LABA or placebo
Adherence reported yes/no	No
Primary outcomes	AQLQ 1 day before, 1 day after, and 3 months after the intervention period
Secondary outcomes	FEV1, PEFR, and FEV1/FVC, and serum IgG, IgE, MMP9, IFN-γ,IL-4, and ICAM-1 levels were evaluated before and after the treatment period

Study reference	Wenzel (Nebulized dehydroepi-androsterone-3-sulfate) 2010
Study tittle	Nebulised Nebulized dehydroepi-androsterone-3-sulfate
Study duration	5-week run-in period. 6weeks
Trial registration:	ANZCTR: 012607000192482
Study Population	Participants: Nebulised Nebulized dehydroepi-androsterone-3-sulfate group, n=140; placebo group, n=140 Eligibility criteria: Patients 18-70 years of age, with ≥1-year history of asthma and FEV1% predicted of ≥60 at screening , ≥3 month of therapy with ≥500µg of fluticasone equivalent +LABA , rescue ß-agonist use within the past month , non-smoking for ≥1 year, and a total pack-year smoking history of <10years
Setting	20 sites in Australia and 14 site in India
Interventions	70mg GenaFlow(Nebulised Nebulized dehydroepi-androsterone-3-sulfate) once daily or placebo
Adherence reported yes/no	No
Primary outcomes	Median change from baseline ACQ at 6 weeks
Secondary outcomes	Proportions of patients who achieved a minimally important difference of -0.5 in ACQ and the average change in ACQ

Study reference	Wenzel (Golimumab) 2009
Study tittle	A Randomized, Double-blind, Placebo-controlled Study of Tumor Necrosis Factor-a Blockade in Severe Persistent Asthma
Study duration	2-week run-in period. 52 weeks
Trial registration:	NCT00207740
Study Population	Participants: golimumab 200mg group, n=78; golimumab100mg group, n=76; golimumab 50mg group, n=77;placebo group, n=78 Eligibility criteria: age ≥18 years; diagnosed with asthma for ≥3 years; uncontrolled severe asthma for ≥1 years: symptomatic despite (asthma symptoms on more than one-third of days for 3 or more months before screening) despite continuous treatment with high-dose ICS (fluticasone >1000 mg or equivalent) and LABA, with or without continuous oral corticosteroids (OCS); two or more asthma exacerbations within the previous year; 1 or more years without smoking and a smoking history of less than 10 pack-years and a history of at least one of the following within 5 years of screening: postbronchodilator reversibility in FEV1 of ≥12%, or PEFR diurnal variation of ≥30% or BHR
Setting	United Kingdom, France, Poland, Hungary, France, The Netherlands, Hungary and Italy
Interventions	Subcutaneous injections of placebo, 50 mg golimumab (75 mg loading dose at baseline), 100 mg golimumab (150 mg at baseline), or 200 mg golimumab (300 mg at baseline) were given every 4 weeks for 52 weeks
Adherence reported yes/no	No
Primary outcomes	The change in prebronchodilator percent predicted FEV1 and number of severe asthma exacerbations from baseline through week 24
Secondary outcomes	The change from baseline through week 24 in the AQLQ score, rescue medication use, and domiciliary morning PEFR

Study reference	Wenzel (Dupilumab) 2013
Study tittle	Dupilumab in Persistent Asthma with Elevated Eosinophil Levels
Study duration	2-week screening period. 20 weeks
Trial registration:	NCT01312961
Study Population	Participants: Dupilumab group, n=52; Placebo group, n=52 Eligibility criteria: age 18 to 65 years old; persistent, moderate-to-severe asthma; elevated blood eosinophil count (≥300 cells per microliter) or an elevated sputum eosinophil level (≥3%) at screening; asthma 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)
Setting	United States
Interventions	Once weekly subcutaneous injections of dupilumab (300 mg) or placebo for 12 weeks
Adherence reported yes/no	No
Primary outcomes	The occurrence of an asthma exacerbation, during the 12-week intervention period
Secondary outcomes	The time to an asthma exacerbation and the change from baseline at each visit and at week 12 in FEV1, morning and evening PEF, ACQ5 score, morning and evening asthma symptom scores nocturnal awakenings, and the number of albuterol or levalbuterol inhalations per day

Appendix 3 Risk of bias

Risk of bias in included studies

Allocation

Forty-eight studies (55·2%) were assessed as having a low risk of selection bias for the random sequence domain because the authors used computer-generated random sequencing. The remaining 39 (44·8%) studies were categorised as having an unclear risk of bias because, despite being described as 'randomised', no further information was provided. Twenty-eight (32·2%) studies were assessed as having a low risk for the allocation concealment domain, and 59 (67·8%) studies were evaluated as having an unclear risk of bias in the allocation domain because no information was provided that described how allocation concealment was maintained throughout the study.

Blinding

Thirty-seven studies (42·5%) were judged as having a low risk of performance bias, and 46 (52·9%) studies were evaluated as having an unclear risk of performance bias. Four studies (4·6%) were assessed as having a high risk of performance bias. Of these, 2 studies [6, 76] were open-label design; one study [29] both investigators and participants were not blinded, and in the other study [90] the study investigators were blinded, but no information was provided regarding blinding of study participants.

Four (4·6%) studies were assessed as having a high risk of detection bias. Two of these studies, [6, 76] were open-label design, and in the other 2 studies [29, 90], the outcome assessors were not blinded. Twenty-five (28·7%) studies were assessed to have a low risk of detection bias, while the remaining 58 (66·7%) studies were judged as having unclear detection bias because they did not provide information regarding blinding of outcome assessors.

Incomplete outcome data

Most studies were assessed as having a low risk of attrition bias with only 3 (3·4%) studies evaluated as having an unclear risk, and two (2·3%) studies were assessed as high risk. Gotfried et al. reported clinical outcomes for the clarithromycin group and omitted data in the control group, the rationale was that valid comparisons could not be conducted because of unequal population distribution between the two groups. Kishiyama et al. enrolled 54 participants, only 30 participants completed the study, but details about patients who did not complete the study were not reported. Of the three studies assessed as unclear risk; Pavord et al. did not provide information on the two out of 17 who did not complete the study; Salmun et al. omitted information on the patients who were screened and patients who withdrew from the study, while Wenzel et al. did not provide reasons why patients withdrew from the study.

Selective reporting

Eighty-five (97·7%) studies were judged as having a low risk of selection bias. Two (2·3%) studies had a high risk of selection bias; one study [39] pre-specified PEF and spirometry as their secondary outcomes but the results were not reported while the other study [41], there was selective reporting of outcomes in the clarithromycin group and the control group outcomes were not published.

Table 1 Risk of bias summary for all included trials. The table is composed of the consensus opinion of the review authors' judgements about each methodological quality item.

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants & personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Selection bias)	Other bias
Ayres (Omalizumab) 2004	?	?	+	+	-	-	-
Bardelas (Omalizumab) 2012	?	?	?	?	-	-	-
Beeh (Tiotropium) 2014	-	-	?	?	-	-	-
Bel (Mepolizumab) 2014	-	-	-	-	-	-	-
Berry (Eternacept) 2006	-	?	?	?	-	-	-
Bjermer (Reslizumab) 2016	?	?	?	?	-	-	-
Bleecker (Benralizumab) 2016	-	-	-	-	-	-	-
Brightling (Tralokinumab) 2015	-	-	-	-	-	-	-
Brinke (IM triamcinolone) 2004	?	?	?	?	-	-	-
Brusselle (Azithromycin) 2013	-	?	?	?	-	-	-
Busse (Omalizumab) 2001	?	?	?	?	-	-	-
Busse (Brodalumab) 2013	-	-	?	?	-	-	-

Busse (Daclizumab) 2008	?	?	?	?	-	-	-
Busse (AMG 853) 2013	?	?	?	?	-	-	-
Cahill (Imatinib) 2017	?	?	?	?	-	-	-
Castro (Bronchial thermoplasty) 2010	-	?	-	-	-	-	-
Castro (Benralizumab) 2014	-	-	-	?	-	-	-
Castro (Reslizumab) 2015	-	-	-	-	-	-	-
Castro (Reslizumab) 2011	-	-	-	-	-	-	-
Chanez (Omalizumab) 2010	?	?	-	?	-	-	-
Corren (AMG 317) 2010	-	?	?	?	-	-	-
Corren (Lebrikizumab) 2011	-	-	-	-	-	-	-
Corren (Reslizumab) 2016	?	?	-	-	-	-	+
Cox (Bronchial thermoplasty) 2007	-	?	+	+	-	-	-
Coyle (Bosentan) 2013	-	-	-	?	-	-	-
DeBoever (GSK679586) 2014	-	-	-	-	-	-	-
Dente (Prednisolone) 2010	?	?	?	?	-	-	-
Erin (Infiliximab) 2006	?	?	-	-	-	-	-
Fernandes (Prednisolone) 2014	-	?	?	?	-	-	-
FitzGerald (Benralizumab) 2016	-	-	-	?	-	-	-
Flood-Page (Mepolizumab) 2007	?	?	-	?	-	-	-
Gao J-M (Montelukast) 2013	?	?	?	?	-	-	-

Garcia (Omalizumab) 2013	-	?	?	?	-	-	-
Gevaert (Omalizumab) 2013	-	?	-	?	-	+	-
Girodet (Gallopamil) 2015	-	-	-	-	-	-	-
Gotfried (Clarithromycin) 2004	?	?	?	?	+	+	-
Haldar (Mepolizumab) 2009	-	?	-	-	-	-	-
Hanania (Omalizumab) 2011	-	-	-	-	-	-	-
Hanania (Lebrikizumab) 2015	-	-	-	-	-	-	-
Hanania (Lebrikizumab) 2016	-	-	-	?	-	-	-
Hedman (Methotrexate) 1996	?	?	?	?	-	-	-
Hodgson (Ciclesonide) 2015,	?	?	?	?	-	-	-
Holgate (Omalizumab) 2004	?	?	?	?	-	-	-
Holgate (Etanercept) 2011	?	?	?	?	-	-	-
Humbert (Omalizumab) 2005	?	?	-	-	-	-	-
Humbert (Masitinib) 2009	?	?	?	?	-	-	-
Juergens (Eucalyptol) 2003	-	-	-	?	-	-	-
Kaler (Pioglitazone) 2017	-	-	-	?	-	-	-
Kanzow (Methotrexate) 1995	?	?	?	?	-	-	-
Kenyon (L-Arginine) 2011	?	?	-	?	-	-	-
Kerstjens (Tiotropium) 2011	-	?	?	?	-	-	-
Kerstjens (Tiotropium) 2015	-	?	-	?	-	-	-

Kishiyama (IVIG) 1999	?	?	?	-	+	-	-
Lanier (Omalizumab) 2003	?	?	?	?	-	-	-
Laviollette (Benralizumab) 2013	-	?	?	?	-	-	-
Li (Omalizumab) 2014	-	?	?	?	-	-	-
Lock (Ciclosporin) 1996	?	?	-	-	-	-	-
Lomia (Carbamazepine) 2006	-	-	-	?	-	-	-
Marin (Nedocromil sodium) 1996	-	?	?	?	-	-	-
Morjaria (Etanercept) 2008	?	?	?	?	-	-	-
Nair (SCH 527123) 2012	?	?	?	?	-	-	-
Nair (Mepolizumab) 2009	-	-	-	-	-	-	-
Nair (Benralizumab) 2017	-	-	?	-	-	-	-
Nizankowska (Ciclosporin) 1995	?	?	-	-	-	-	-
Ogirala (IM triamcinolone) 1995	?	?	?	?	-	-	-
Oh (MEDI528) 2013	-	-	?	?	-	-	-
Ohta (Omalizumab) 2009	?	?	?	?	-	-	-
Ortega (Mepolizumab) 2014	-	-	-	-	-	-	-
Park (Benralizumab) 2016	-	?	?	?	-	-	-
Pavord (Bronchial thermoplasty) 2007	-	?	+	+	?	-	-
Pavord (Mepolizumab) 2012	-	-	-	-	-	-	-
Piper (Tralokinumab) 2013	?	?	?	?	-	-	-

Robinson (Montelukast) 2001	?	-	?	?	-	-	-
Rubin (Omalizumab) 2012	?	?	+	+	-	-	-
Salmun (IVIG) 1999	-	?	-	?	?	-	-
Sano (Sodium cromoglicate) 2006	-	?	-	?	-	-	-
Bosquet (Omalizumab) 2011	-	?	?	?	-	-	-
Simpson (Clarithromycin) 2008	-	?	-	?	-	-	-
Smith (Isoflavane) 2015	-	-	-	-	-	-	-
Soler (Omalizumab) 2001	?	?	?	?	-	-	-
Tamaoki (Th2 inhibitor IL5/IL4) 2000	-	-	?	?	-	-	-
Vignola (Omalizumab) 2004	?	?	?	?	-	-	-
Virchow (Zafirlukast) 2000	?	?	?	?	-	-	-
Wang (Cordyceps sinensis) 2016	?	?	?	?	-	-	-
Wenzel (Nebulized dehydroepi-androsterone-3-sulfate) 2010	?	?	?	?	?	-	-
Wenzel (Golimumab) 2009	-	?	?	-	-	-	-
Wenzel (Dupilumab) 2013	-	-	-	-	-	-	-
'?' = unclear risk of bias (ROB), '-' = low ROB, '+' = high ROB							

Appendix 4 Modelling effects of assessing adherence on FEV1

Determining the effect of adherence variations on FEV1

To estimate the effects of variations in adherence to maintenance therapy on FEV1, it is first necessary to determine the effect of ICS/LABA treatment on FEV1 compared to no treatment. The majority of trials of ICS/LABA treatment compare to ICS or LABA alone, and so do not provide an unbiased estimate of effectiveness. However, Shapiro et al conducted an RCT of fluticasone/salmeterol against placebo. Shapiro et al reported a mean change in FEV1 at week 12 of 0.48 litres with a standard error of 0.05 giving a standard deviation of 0.45 litres. They assessed adherence to fluticasone/salmeterol using paper diary and dose counting to assess adherence during the screening phase and the 12 weeks duration of the study. They reported mean treatment adherence rates that ranged from 91% to 95% across treatment groups which is consistent with pill count adherence rates obtained in Suilaman's study.

However, since this study was performed without the use of an objective measure of adherence, it is likely that actual adherence was sub-optimal, and so these results may be an under-estimate of the true effect of fluticasone/salmeterol on FEV1. To estimate the 'true' mean change in FEV1, we follow the assumption that the actual adherence rate will be similar to Sulaiman's actual adherence rate at baseline ($\mu = 0.65, \sigma = 0.3$) . Assuming the measured mean change in FEV1 is a linear function of the fluticasone/salmeterol adherence rate, then the measured mean change in FEV1 is equal to the "true effect" multiplied by the fluticasone/salmeterol adherence rate, and so hence the 'true' mean change in FEV1 is given by;

$$\mu_{measured} = \mu_{true}\mu_{adherence}$$

$\mu_{true} = \mu_{measured} \div 0.65 = \frac{0.48}{0.65} = 0.74$ litres

Similarly, using the standard formula for the variance of a product, the 'true' standard deviation can be calculated;

$$\sigma^2_{measured} = \sigma^2_{adherence}\sigma^2_{true} + \sigma^2_{adherence}\mu^2_{true} + \sigma^2_{true}\mu^2_{adherence}$$

σ^2_{true} = $\{0.45^2 - (0.3^2 \text{ x } 0.74^2)\} \div \{0.3^2+0.65^2\}$ =0.3

$\sigma = 0.55$ litres

The estimated 'true' mean change in FEV1 adjusted for baseline adherence rate of 0.65±0.3 is 0.74±0.55 litres where $\mu_{ICSLABA}$ = 0.74 and $\sigma_{ICSLABA}$ = 0.55. This estimate was used in our model to determine the effects of adherence variations on FEV1 adjusted for objectively measured adherence.

Scenario 1: Month-to-month variability in the absence of adherence monitoring throughout the trial

A model of the variance introduced into study outcomes due to within-subjects variations in month to month adherence to ICS/LABA was conducted. Sulaiman et al found that there was a large within subjects variability, with a mean absolute change of more than 20% from month 1 to month 3. The change in adherence to fluticasone/salmeterol in the control group was -0.8%± 31.3% from month 1 to month 3. While the change in the mean is negligible, there is a large variability that can affect the significance of the study results.

Assuming that the mean adherence rate does not change from month to month, the standard deviation of the within-subject month to month variation in adherence can be used to estimate the additional adherence introduced by the absence of assessing adherence throughout the study. Using $(\mu_{adh}, \sigma_{adh}) = (0, 0.313)$, the estimated 'true' change in FEV1, $\mu_{ICSLABA}$ = 0.74 and $\sigma_{ICSLABA}$ = 0.55 and the standard formula for the variance

of a product the additional variance in outcomes attributable to adherence variations can be estimated. The estimated month to month variance introduced into FEV1 outcomes is

$$\sigma^2_{additional} = \sigma^2_{adh}\sigma^2_{ICSLABA} + \mu^2_{ICSLABA}\sigma^2_{adh} + \mu^2_{adh}\sigma^2_{ICSLABA}$$
$$= (0.313^2 \times 0.55^2) + (0.74^2 \times 0.313^2) + (0^2 \times 0.55^2) = 0.0832$$

Scenario 2: Regression to the mean

Using the data from Sulaiman 's study data, the difference in adherence between month 3 (M3) and month 1 (M1) for the patients who achieved ≥80% adherence at baseline (59 of 170 patients) was calculated. On average from M1 to M3 adherence decreased significantly (mean change -8.4± 21.17%) giving,

$(\mu_{adh}, \sigma_{adh}) = (-0.084, 0.2117)$

Using the estimated 'true' mean change in FEV1 (0.74±0.55 litres where $\mu_{ICSLABA}$ = 0.74 and $\sigma_{ICSLABA}$ = 0.55) and the mean change adherence rate for the patients who achieved adherence rate of ≥80% the estimated additional variance introduced by assessing adherence only at baseline mean is calculated below;

The estimate of the variance introduced into the FEV1 outcome is

$(0.2117^2 \times 0.55^2) + (0.74^2 \times 0.2117^2) + (0.084^2 \times 0.55^2) = 0.040233278$

The additional variance in FEV1 due to the absence of monitoring adherence to ICS/LABA is 0.0402.

This additional variance was subtracted from the variance in each individual study to calculate the new standard deviations (example below).

Example: In the Bjermer study the mean change in FEV1 from baseline in the Reslizumab group was (0.286±0.553). The estimate of the variance introduced into FEV1 outcome in the absence of adherence monitoring was 0.0402. The FEV1 variance is:

$\{(0.553)^2 - 0.0402\} = 0.265576$

And this gives a new standard deviation of 0.54 (square root of 0.265576).

Scenario 3: Hawthorne Effect

The variance of the difference between two random variables is given by:

$Var(Y - X) = Var(Y) + Var(X) - 2Cov(X, Y)$

Where $Cov(X, Y)$ is the covariance of X and Y.

Where X and Y are independent, this gives $Var(Y - X) = Var(Y) + Var(X)$, however, if X and Y are positively correlated, then the covariance is positive and hence the variance of the change is reduced. The minimum of $Var(Y - X)$ is thus found where Y and X are perfectly positively correlated, and the covariance is at a maximum. The minimum variance introduced by the Hawthorne effect can be estimated. Assuming perfect correlation between Y and X, we have

$Y = aX + c$, where $a = \frac{\sigma_y}{\sigma_x}$ and $c = \mu_y - \mu_x$

Hence

$Cov(X, Y) = Cov(X, aX + c) = aCov(X, X) = aVar(X)$

And so we have

$$Var(Y - X) = Var(Y) + Var(X) - 2aVar(X) = Var(Y) + (1 - 2\frac{\sigma_y}{\sigma_x})Var(X)$$

Using the above formula the minimum variance of the change in adherence can be calculated. Given initial standard deviation, σ_{init}, and post-change standard deviation σ_{post} , the variance of the change in adherence is given by

$\sigma_{adh}^2 = \sigma_{post}^2 + (1 - 2\frac{\sigma_{post}}{\sigma_{init}})\sigma_{init}^2$

Assuming that after the Hawthorne effect, all patients achieve ≥80% adherence, then the maximum subsequent standard deviation is $\sigma_{post} = 10\%$

However, this maximum post-change standard deviation is achieved if precisely half of the patients have adherence of 80%, the remaining half have 100%, which contradicts the assumption that initial and post-change values are perfectly correlated. Excluding such unlikely multimodal distributions, then the largest reasonable standard deviation is when the distribution is uniform between 80% and 100%. This gives $\sigma_{post} \simeq 5 \cdot 8\%$ which in turn gives:

$\sigma_{adh}^2 \simeq 0 \cdot 0493$

Corresponding to $\sigma_{adh} = 22 \cdot 3\%$, where the post-change mean is 90%, corresponding to a mean change, $\mu_{adh} = 25\%$. We thus choose $(\mu_{adh}, \sigma_{adh}) = (0 \cdot 25, 0 \cdot 223)$ as our estimate of the mean and standard deviation of the adherence change.

Using the estimates of effect on FEV1 as before, we get

$\sigma_{additional}^2 = \sigma_{adh}^2\sigma_{ICSLABA}^2 + \mu_{ICSLABA}^2\sigma_{adh}^2 + \mu_{adh}^2\sigma_{ICSLABA}^2 = 0 \cdot 0612$

Appendix 5 Modelling effects of assessing adherence on exacerbations

While inconsistency in both the definition of exacerbations and reporting of exacerbation rates makes it impractical to apply the models described in Appendix 4 to the exacerbation outcomes, we believe that similar reasoning applies to exacerbations, and that statistical power to detect exacerbation reductions in RCTs is likely to be improved by optimizing adherence to maintenance therapy before randomization. Here we offer a brief summary of this argument and our statistical reasoning.

As discussed in the introduction to this article, baseline adherence rates to ICS/LABA are generally poor and highly variable. Thus, it is likely that optimization of adherence to ICS/LABA prior to study enrollment would improve asthma control and reduce the baseline exacerbation rate in enrolled patients. The expected impact of this reduction in the baseline rate on statistical power depends strongly on how we expect the effects of the maintenance therapy and the add-on therapy to combine.

In particular, we may model the effect of add-on therapy as multiplicative, where exacerbations will be reduced by a fixed proportion of the rate achieved with maintenance therapy alone, or additive, where the expected number of exacerbations will be reduced by a fixed amount regardless of the effect of the maintenance therapy. In the multiplicative case, the power to detect a difference in exacerbation rate is expected to increase as function of the baseline rate, and so a reduction in the baseline rate (e.g. due to optimization of adherence) would result in a loss in power. However, in the additive case this is reversed, and the relationship between the baseline rate and study power is approximately the inverse of that in the multiplicative case, as shown below. We would argue that this model is more appropriate than the multiplicative model to describe the effects of add-on biological therapy.

The biologic therapies considered in these studies have been developed with the specific aim of treating patients whose asthma is poorly controlled by ICS therapy, and are designed to target distinct inflammatory pathways not affected by ICS. Hence we can think of asthma exacerbations as being divided into two phenotypes: those preventable with ICS, and those potentially preventable with biologic therapy. If we assume that there is little overlap between these phenotypes, then a reduction in the number of ICS-treatable exacerbations (e.g. due to adherence optimization) should not affect the number of exacerbations potentially prevented by biologic therapy, and so the effects can be considered purely additive. By contrast, treating the effects as multiplicative is equivalent to assuming complete overlap between these phenotypes. This is not only unlikely given current understanding of severe asthma, but would also seem to negate the need for add-on biological treatment. As a result it appears clear that the additive assumption is the more appropriate.

The effect of baseline rate on statistical power in poisson regression

The standard model for comparing the incidence rates between groups is poisson regression.

In this model, the mean exacerbation rate, λ in each arm of the study is modelled by a poisson distribution with mean rate

$$\lambda_i = \exp(\beta_0 + \beta_1 X_i),$$

Where the coefficient β_0 represents the natural logarithm of the baseline rate (i.e. the rate of exacerbations achieved with normal maintenance therapy) and β_1 is the logarithm of the Incidence Rate Ratio. X is an indicator variable equal to 0 for subjects in the placebo group, and 1 for subjects in the treatment group.

A statistical test for a difference in exacerbation rates between these two groups is equivalent to testing for a difference between the means of the two groups.

The difference between the means is given by

$$\delta\lambda = \exp(\beta_0) - \exp(\beta_0 + \beta_1) = (1 - \exp(\beta_1))\ \exp(\beta_0),$$

While the pooled variance across the two groups is approximated by

$$\sigma_p^2 = \frac{1}{2}(\lambda_0 + \lambda_1) = \frac{1}{2}(1 + \exp(\beta_1))\ \exp(\beta_0)\ ,$$

And so we can construct the expected value of the Z-score for this difference:

$$Z \simeq \sqrt{n}\ \frac{\delta\lambda}{\sigma_p} \propto \frac{(1 - \exp(\beta_1))\exp(\beta_0)}{\sqrt{(1 + \exp(\beta_1))\exp(\beta_0)}} = \frac{(1 - \exp(\beta_1))\sqrt{\exp(\beta_0)}}{\sqrt{(1 + \exp(\beta_1))}}$$

In the multiplicative case where the Incidence Rate Ratio is fixed, the coefficient β_1 is a constant, independent of β_0, and so the expected Z-score is proportional to the square root of $\exp(\beta_0)$. As a result, the expected value of the Z-score, and hence the power to detect a difference, is reduced as β_0 decreases.

However, in the additive case, the difference between the mean exacerbation rates, $\delta\lambda$, is a constant, so we can set $\delta\lambda = c$, and the coefficient β_1 is related to β_0 by $\beta_1 = \ln(1 - \frac{c}{\exp(\beta_0)})$

The expected Z-score then becomes

$$Z = \frac{\frac{c}{\exp(\beta_0)}\sqrt{\exp(\beta_0)}}{\sqrt{\left(2 - \frac{c}{\exp(\beta_0)}\right)}} = \frac{c}{\sqrt{2\exp(\beta_0) - c}}$$

and so the expected Z-score and hence the power increases as the baseline rate is decreased.