Buhl 2015 [19]	**Inclusion criteria**: Diagnosis of chronic obstructive pulmonary disease; 40 years of age or older; Relatively stable airway obstruction with post FEV1< 80% predicted normal and post FEV1/FVC <70%; 40 years of age or older; Smoking history of more than 10 pack years. **Exclusion criteria**: Significant disease other than COPD; History of asthma; Regular use of daytime oxygen therapy for more than one hour per day **Allowed co-medications**: ICS as required, salbutamol/albuterol inhaler as rescue medication. Temporary increases in the dose or addition of oral steroids or theophylline were allowed.
Celli 2014 [20]	**Inclusion criteria**: Diagnosis of COPD, 10 pack-year or greater history of cigarette smoking, Post-bronchodilator FEV1/FVC ratio of <0.7, Predicted FEV1 of 70% of normal or less, mMRC dyspnea score of 2 or greater. 40 years of age or older. **Exclusion criteria**: Current diagnosis of asthma or other known respiratory disorder, any clinically significant uncontrolled disease, an abnormal and significant ECG or 24-h Holter finding. **Allowed co-medications:** Salbutamol rescue medication, and regular use of ICS at a stable dose (≤1000 mcg/day of fluticasone propionate or equivalent)
Decramer 2014 a &b [21]	**Inclusion criteria**: History of COPD as defined by ATS–ERS; current or former cigarette smoker with a smoking history of 10 pack-years or more; a post-salbutamol FEV1/FVC ratio < 0·70 and a post-salbutamol FEV1 of 70% of predicted normal values or less and a score of 2 or higher on the mMRC Dyspnoea score. **Exclusion criteria**: Hospital admission for COPD or pneumonia within the 12 weeks before study visit. Present diagnosis of asthma or other known respiratory disorder. **Allowed co-medications:** Salbutamol rescue medication, and regular use of ICS at a stable dose (≤1000 mcg/day of fluticasone propionate or equivalent)
D'Urzo 2014 [22]	**Inclusion criteria**: Current or former cigarette smokers with a cigarette smoking history of at least 10 pack-years; a diagnosis of stable moderate to severe COPD and stable airway obstruction as defined by the GOLD guidelines with a post-bronchodilator FEV1 = 30 % and < 80% of predicted normal and a post-bronchodilator FEV1/FVC <70%;40 years of age or older. **Exclusion criteria**: Recent hospitalization for an acute COPD exacerbation within three months prior to Visit 1; Any respiratory tract infection (including the upper respiratory tract) or COPD exacerbation in the six weeks before Visit 1; clinically significant respiratory conditions other than COPD; Clinical history of asthma; Chronic use of oxygen therapy ≥ 15 hours/day; clinically significant cardiovascular conditions. **Allowed co-medications**: albuterol/salbutamol as rescue medication. theophylline, ICS, oral or parenteral corticosteroids (≤10 mg/day or 20 mg every other day of prednisone)
Maleki-Yazdi 2014 [23]	**Inclusion criteria**: A pre and post-albuterol/salbutamol FEV1/FVC ratio of <0.70 and a pre and post-albuterol/salbutamol FEV1 of <=70% of predicted; COPD diagnosis defined by ATS/ERS guidelines; 40 years of age or older; a history of cigarette smoking of $\geq$ 10 pack-years. **Exclusion criteria**: a current diagnosis of asthma; Clinically significant

	comorbidity; Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1; home oxygen greater than 12 hours a day. As-needed oxygen use (i.e., ≥ 12 hours per day) was allowed. **Allowed co-medications**: Albuterol/salbutamol rescue medication, and regular use of ICS at a stable dose (≤1000 mcg/day of fluticasone propionate or equivalent).
Singh 2014 [24]	**Inclusion criteria**: Smoking history of at least 10 pack-years; a diagnosis of stable moderate to severe COPD and stable airway obstruction as defined by the GOLD guidelines with a post-bronchodilator FEV1 > 30 % and < 80% of predicted normal and a post-bronchodilator FEV1/FVC <70%; 40 years of age or older. **Exclusion criteria**: Use of long-term oxygen therapy (≥ 15 hours/day).History or current diagnosis of asthma; Any respiratory tract infection (including the upper respiratory tract) or COPD exacerbation in the 6 weeks before screening visit; History of interstitial lung or massive pulmonary thromboembolic disease. **Allowed co-medications**: salbutamol as rescue medication. ICS, oral sustained-release methylxanthines, oxygen therapy (<15 hours/day) and oral or parenteral corticosteroids equivalent to ≤10 mg/day of prednisone or 20 mg every other day.
ZuWallack 2014 [26]	**Inclusion criteria**: Diagnosis of chronic obstructive pulmonary disease; relatively stable airway obstruction with a post-bronchodilator FEV1 > 30 % and < 80% of predicted normal and a post-bronchodilator FEV1/FVC <70% at Visit 1; 40 years of age or older; a smoking history of more than 10 pack years. **Exclusion criteria**: A significant disease other than COPD in the opinion of the investigator; history of asthma, cystic fibrosis or bronchiectasis; regular use of daytime oxygen therapy for more than one hour per day. **Allowed co-medications**: albuterol as rescue medicine was allowed. ICS, cromolyn sodium/nedocromil sodium, antihistamines, antileukotrienes, methylxanthines, long-term oral steroids, mucolytics, and theophylline were NOT allowed.
Donohue 2013 [29]	**Inclusion criteria**: 40 years of age or older with a clinically established history of COPD ; smoking history of 10 pack-years; a post-salbutamol FEV1/ FVC ratio of <0.70 and a post-salbutamol FEV1 of 70% of predicted normal values ; a score of 2 on the mMRC Dyspnea Scale. **Exclusion criteria**: current diagnosis of asthma or other known respiratory disorders, any clinically significant uncontrolled disease as determined by the study investigators, an abnormal and clinically significant ECG or 24-h Holter ECG (if conducted), or significantly abnormal clinical laboratory finding. **Allowed co-medications**: inhaled salbutamol (albuterol) as rescue medication. ICS were allowed at a stable dose of 1000 mcg/day of fluticasone propionate or equivalent from 30 days prior to screening.
Donohue 2014 [31]	**Inclusion criteria**: 40 years of age or older with a diagnosis of COPD and 10 pack-years smoking history; Post-salbutamol FEV1/ FVC ratio of <0.70, a post-salbutamol FEV1 of >35% and < 80% of predicted normal values. **Exclusion criteria**: Current diagnosis of asthma, alfa1-antitrypsin deficiency, any clinically significant uncontrolled disease, a significant ECG or clinical laboratory finding, or a lower respiratory tract infection or recent COPD exacerbation were excluded.

	Allowed co-medications: Inhaled salbutamol (albuterol) as rescue medication. Concurrent use of ICS at a stable dose. Concurrent use of systemic corticosteroids, long-acting bronchodilators, including theophyllines, was NOT allowed.
DB2114417 2012 [32]	**Inclusion criteria**: 40 years of age or older with a current COPD diagnosis with a post albuterol FEV1/FVC <0.7, 35%-70% FEV1 predicted, >120% forced residual capacity and 2 or more on the mMRC scale. **Exclusion criteria**: Current diagnosis of asthma or other known respiratory disorder, any clinically significant uncontrolled disease. **Allowed co-medications**: albuterol/salbutamol for "as-needed" use. Short-acting anticholinergics were permitted during the run-in and washout periods. Concurrent use of ICS at a stable dose (≤1000 mcg/day of fluticasone propionate or equivalent).
DB2114418 2012 [33]	**Inclusion criteria**: 40 years of age or older with a current COPD diagnosis with a post albuterol FEV1/FVC <0.7, 35%-70% FEV1 predicted, >120% forced residual capacity and 2 or more on the mMRC scale. **Exclusion criteria**: Current diagnosis of asthma or other known respiratory disorder, any clinically significant uncontrolled disease. **Allowed co-medications**: albuterol/salbutamol for "as-needed" use. Short-acting anticholinergics were permitted during the run-in and washout periods. Concurrent use of ICS at a stable dose (≤1000 mcg/day of fluticasone propionate or equivalent).
Vincken 2014 [25]	**Inclusion criteria**: 40 years of age or older with a current COPD diagnosis with a post albuterol FEV1/FVC <0.7, 30%-80% FEV1 predicted; current or ex-smokers with a smoking history of at least 10 pack-years. **Exclusion criteria**: Respiratory tract infection within 6 weeks prior to screening; COPD exacerbation 6 weeks prior to screening; current diagnosis of asthma or other known respiratory disorder, any clinically significant uncontrolled disease. **Allowed co-medications:** Inhaled salbutamol (albuterol) as rescue medication and stable dose of ICS.
Bateman 2013 [27]	**Inclusion criteria**: 40 years of age or older; Smoking history of at least 10 pack years; Diagnosis of COPD (GOLD Guidelines, 2008); Post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal value and post-bronchodilator FEV1/FVC <70%. **Exclusion criteria**: a respiratory tract infection within 4 weeks prior to Visit 1. Current diagnosis of asthma or other known respiratory disorder, any clinically significant uncontrolled disease. **Allowed co-medications**: Inhaled salbutamol (albuterol) as rescue medication and fixed dose of ICS.
Dahl 2013 [28]	**Inclusion criteria:** 40 years of age or older; Smoking history of at least 10 pack years; Diagnosis of COPD (GOLD Guidelines, 2008); Post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal value and post-bronchodilator FEV1/FVC <70%. **Exclusion criteria**: a respiratory tract infection within 4 weeks prior to Visit 1; concomitant pulmonary disease, asthma, alpha-1 antitrypsin deficiency or lung; certain cardiovascular co-morbid conditions. **Allowed co-medications:** Inhaled salbutamol (albuterol) as rescue medication

	and ICS.
Wedzicha 2013 [30]	**Inclusion criteria**: 40 years of age or older; severe to very severe COPD (Stage III or IV GOLD Guidelines 2008).Current or ex-smokers with a smoking history of at least 10 pack years; a post-bronchodilator FEV1 <50% of the predicted normal value, and post-bronchodilator FEV1/FVC <0.70 at Visit 2. A documented history of at least 1 COPD exacerbation in the previous 12 months that required treatment with systemic glucocorticosteroids and/or antibiotics. **Exclusion criteria**: Patients requiring long term oxygen therapy (> 15 h a day) on a daily basis; a COPD exacerbation that required treatment with antibiotics, systemic steroids or hospitalization in the 6 weeks prior to visit 1. Current diagnosis of asthma or other known respiratory disorder; a clinically significant abnormality on the screening or baseline ECG. **Allowed co-medications**: Inhaled salbutamol (albuterol) as rescue medication and fixed dose of ICS.
Novartis A1301 2012 [35]	**Inclusion criteria**: 40 years of age or older; smoking history of at least 10 pack years. Diagnosis of COPD (GOLD Guidelines, 2008). Post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal value and post-bronchodilator FEV1/FVC <70%. **Exclusion criteria**: Current diagnosis of asthma or other known respiratory disorder, any clinically significant uncontrolled disease. **Allowed co-medications:** Not described.
Mahler 2012a&b [34]	**Inclusion criteria**: patients aged ≥ 40 years with COPD (GOLD 2007 criteria), with a smoking history ≥10 pack-years and postbronchodilator FEV1 ≤ 65% and ≥ 30% of predicted normal, and post-bronchodilator FEV1/FVC <70% at screening. **Exclusion criteria**: Current diagnosis of asthma or other known respiratory disorder, certain cardiovascular disease; a respiratory tract infection or COPD exacerbation within the previous 6 weeks. **Allowed co-medications**: Inhaled salbutamol (albuterol) as rescue medication and fixed dose of ICS.
Tashkin 2009 [36]	**Inclusion criteria**: patients aged ≥40 years with a clinical history of COPD. a postbronchodilator FEV1 < 70% and >30% predicted normal or >0.75 L and a FEV1/FVC ratio of <0.70 at screening and run-in. Daytime and/or nighttime symptoms of COPD, including dyspnea, must have been present on ≥4 of the 7 days before the baseline visit. **Exclusion criteria**: Current diagnosis of asthma or other known respiratory disorder, any clinically significant disease that may have interfered with study treatment as assessed by the investigator. Smoking cessation within the previous 3 months, ventilator support for respiratory failure within the previous year, the use of oxygen (≥2 L/min or for >2 hours/day). **Allowed co-medications:** Inhaled salbutamol (albuterol) as rescue medication and a fixed dose of ICS. Ipratropium bromide, leukotriene antagonists, and theophylline were NOT allowed.
Vogelmeier 2008 [37]	**Inclusion criteria**: stable COPD aged ≥40 years with a smoking history of ≥10 pack-years, FEV1 < 70% of patient's predicted normal value (and ≤1.00 L), and FEV1/FVC < 70%. Patients were to be symptomatic on at least 4 of 7 days prior to randomization (symptom score >0 on diary card).

	Exclusion criteria: a concomitant pulmonary disease; a respiratory tract infection within a month prior to screening; a clinically significant condition such as ischemic heart disease that might compromise patient safety or compliance. **Allowed co-medications**: On demand salbutamol and a fixed dose of ICS.
Aaron 2007 [38]	**Inclusion criteria**: Age older than 35 years; a history of 10 pack-years or more of cigarette smoking; moderate or severe COPD with an FEV1/FVC ratio < 0.70 and a postbronchodilator FEV1 < 65% of the predicted value; at least 1 exacerbation of COPD that required treatment with systemic steroids or antibiotics within the 12 months before randomization; a recent COPD exacerbation requiring antibiotics or steroids were required to wait until treatment with these agents had been discontinued for 28 days before entering the study. **Exclusion criteria**: Physician-diagnosed asthma before 40 years of age; bronchiectasis; lung transplant; lung volume reduction surgery; chronic congestive heart failure with known persistent severe left ventricular dysfunction. **Allowed co-medications**: Inhaled albuterol as rescue medication, antileukotrienes, and methylxanthines. ICS, long-acting beta 2-agonists, and anticholinergics were NOT allowed.

Table S4 Characteristics of included studies. Abbreviations: ATS–ERS= American Thoracic Society-European Respiratory Society; ECG= electrocardiogram; FEV1= forced expiratory volume in one second; FVC= forced vital capacity; GOLD= Global Initiative for Chronic Obstructive Lung Disease; ICS= inhaled corticosteroids; mMRC= Modified Medical Research Council.