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[Intervention Review]

Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

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ABSTRACT

Background

Chronic obstructive pulmonary disease (COPD) is associated with cough, sputum production or dyspnoea and a reduction in lung function, quality of life and life expectancy. Apart from smoking cessation, there are no other treatments that slow lung function decline. Roflumilast and cilomilast are oral phosphodiesterase 4 (PDE₄) inhibitors proposed to reduce the airway inflammation and bronchoconstriction seen in COPD. This is an update of a Cochrane review first published in 2011 and updated in 2013.

Objectives

To evaluate the efficacy and safety of oral PDE₄ inhibitors in the management of stable COPD.

Search methods

We identified randomised controlled trials (RCTs) from the Cochrane Airways Trials Register (date of last search October 2016). We found other trials from web-based clinical trials registers.

Selection criteria

We included RCTs if they compared oral PDE₄ inhibitors with placebo in people with COPD. We allowed co-administration of standard COPD therapy.

Data collection and analysis

One review author extracted data and a second review author checked the data. We reported pooled data in Review Manager as mean differences (MD), standardised mean differences (SMD) or odds ratios (OR). We converted the odds ratios into absolute treatment effects in a 'Summary of findings' table.

Main results

Thirty-four separate RCTs studying roflumilast (20 trials with 17,627 participants) or cilomilast (14 trials with 6457 participants) met the inclusion criteria, with a duration of between six weeks and one year. These included people across international study centres with moderate to very severe COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades II-IV), with a mean age of 64 years.

We considered that the methodological quality of the 34 published and unpublished trials was acceptable overall. Treatment with a PDE₄ inhibitor was associated with a significant improvement in forced expiratory volume in one second (FEV₁) over the trial period compared with placebo (MD 51.53 mL, 95% confidence interval (CI) 43.17 to 59.90, 27 trials with 20,585 participants, moderate-quality evidence due to moderate levels of heterogeneity and risk of reporting bias). There were small improvements in quality of life (St George's Respiratory Questionnaire (SGRQ), MD -1.06 units, 95% CI -1.68 to -0.43, 11 trials with 7645 participants, moderate-quality evidence due to

Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease (Review)

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moderate levels of heterogeneity and risk of reporting bias) and COPD-related symptoms, but no significant change in exercise tolerance. Treatment with a PDE₄ inhibitor was associated with a reduced likelihood of COPD exacerbation (OR 0.78, 95% CI 0.73 to 0.83; 23 trials with 19,948 participants, high-quality evidence). For every 100 people treated with PDE₄ inhibitors, five more remained exacerbation-free during the study period compared with placebo (number needed to treat for an additional beneficial outcome (NNTB) 20, 95% CI 16 to 26). More participants in the treatment groups experienced non-serious adverse events compared with controls, particularly a range of gastrointestinal symptoms such as diarrhoea, nausea, vomiting or dyspepsia. For every 100 people treated with PDE₄ inhibitors, seven more suffered from diarrhoea during the study period compared with placebo (number needed to treat for an additional harmful outcome (NNTH) 15, 95% CI 13 to 17). Roflumilast in particular was associated with weight loss during the trial period and an increase in insomnia and depressive mood symptoms. There was no significant effect of treatment on non-fatal serious adverse events (OR 0.99, 95% CI 0.91 to 1.07) or mortality (OR 0.97, 95% CI 0.76 to 1.23), although mortality was a rare event during the trials. Participants treated with PDE₄ inhibitors were more likely to withdraw from the trials because of adverse effects; on average 14% in the treatment groups withdrew compared with 8% in the control groups.

Authors' conclusions

In people with COPD, PDE₄ inhibitors offered benefit over placebo in improving lung function and reducing the likelihood of exacerbations; however, they had little impact on quality of life or symptoms. Gastrointestinal adverse effects and weight loss were common, and safety data submitted to the US Food and Drug Administration (FDA) have raised concerns over psychiatric adverse events with roflumilast. The findings of this review give cautious support to the use of PDE₄ inhibitors in COPD. They may be best used as add-on therapy in a subgroup of people with persistent symptoms or exacerbations despite optimal COPD management. This is in accordance with the GOLD 2017 guidelines. Longer-term trials are needed to determine whether or not PDE₄ inhibitors modify FEV₁ decline, hospitalisation or mortality in COPD.

PLAIN LANGUAGE SUMMARY

In people with chronic obstructive pulmonary disease (COPD), what are the benefits and risks of phosphodiesterase 4 inhibitors?

Background of the review

Chronic obstructive pulmonary disease (COPD) is a progressive lung condition caused by damage from harmful chemicals that are breathed in and is predominantly seen in people who smoke tobacco. These chemicals set up a cascade of inflammatory reactions, which damage structures in the lung but also increase mucus production in the airways. These processes lead to intermittent symptoms of breathlessness and decreased capacity to perform day-to-day tasks. In addition, people with COPD are at greater risk of developing exacerbations ('flare ups'), which become more frequent and severe over time. People vary in terms of how they are affected by COPD. This is in part related to the severity of the disease but also to differences in response to medicines, an individual's fitness and coexistent conditions. The only way to prevent further lung damage in most people is to stop smoking.

Medicines prescribed to manage COPD generally aim to improve symptoms, reduce exacerbations or both. In the early stages, bronchodilator medicines are helpful because these relax the small muscles in the airway allowing more air to move freely in and out of the lungs. Some long-acting agents may reduce exacerbations. Steroid-containing inhalers may be added specifically to target inflammation in the lungs and thus modestly reduce the number of exacerbations.

Phosphodiesterase 4 (PDE₄) inhibitors are a relatively new class of medicines that have been marketed to improve COPD. They have both bronchodilator and anti-inflammatory effects. Moreover, the two currently available medicines, roflumilast and cilomilast, are taken as a tablet. Our review collated and analysed existing trials to define the benefits and risks of PDE₄ inhibitors in COPD.

What did we look at?

We found 34 completed trials involving 24,084 adults, with results reported up to October 2016. These consisted mainly of trials in people with moderate to very severe disease who discontinued other regular COPD medications. However, there were seven trials that allowed continuation of usual COPD medicines. The trials ranged from 6 to 52 weeks' duration and the average age of participants was 64 years. The trials were all sponsored by the manufacturers of PDE₄ inhibitors.

What did we find out?

Compared with placebo, these medicines provide a small improvement in lung function measurements and reduce the likelihood of an exacerbation of COPD. Based on these results, we would expect that out of 100 people who took PDE₄ inhibitors every day for a year, 28 would experience at least one exacerbation which is five fewer than for others who did not receive these medicines.

However, people reported that these medicines only provided a small effect on levels of breathlessness and quality of life. Furthermore, around 5% to 10% of people in trials who received roflumilast or cilomilast reported side effects such as diarrhoea, nausea and vomiting. We would expect that out of 100 people who took PDE₄ inhibitors every day for a year, 11 would experience diarrhoea, which is seven more than for others who did not receive these medicines. There was also a two- to three-fold increase in the risk of sleep or mood disturbance

for the roflumilast 500 µg dose, although overall the total number of reported incidents was still small. There was no effect on rates of hospitalisation and deaths. The effects were the same regardless of the severity of COPD, or whether other medicines for COPD were being taken.

Quality of the evidence

The studies were generally well designed, as people did not know if they were receiving this new treatment or a placebo medicine. Overall we rated the evidence as being of moderate to high quality.

It is of concern that results seen in trials published in journals by pharmaceutical companies showed a greater benefit of these medicines than those which were unpublished. Therefore, this relies on unpublished trial data being made accessible and up to date. The psychiatric adverse effects data remain unpublished. Longer-term trials are necessary to get a more accurate estimate of the benefits and safety of these medicines over time, including whether they slow COPD disease progression.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Phosphodiesterase 4 inhibitors compared to placebo for chronic obstructive pulmonary disease

Phosphodiesterase 4 inhibitors compared to placebo for chronic obstructive pulmonary disease

Patient or population: people with stable chronic obstructive pulmonary disease
Settings: community-based, randomised, parallel, double-blind, placebo-controlled trials
Intervention: phosphodiesterase 4 inhibitors
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) ¹	Comments
	Assumed risk	Corresponding risk				
	Placebo	Phosphodiesterase IV inhibitors				
Change in FEV₁ lung function (mL) Follow-up: mean 28.0 weeks	The mean change in FEV ₁ lung function in the control groups was a fall of 20.67 mL	The mean change in FEV ₁ lung function in the intervention groups was 49.27 mL better (44.11 to 54.44 higher)		20,585 (27 studies)	⊕⊕⊕⊖ moderate ^{2,3}	
Change in quality of life St George's Respiratory Questionnaire Follow-up: mean 24.2 weeks	The mean change in quality of life in the control groups was an improvement of 2.21 SGRQ units	The mean change in quality of life in the intervention groups was 1.06 units better (0.43 to 1.68)		7645 (11 studies)	⊕⊕⊕⊖ moderate ^{2,3}	Lower scores on SGRQ represent improved quality of life. This result does not reach the minimum clinically important difference for this scale.
COPD exacerbations No. of participants with exacerbations Follow-up: 12 to 52 weeks	33 per 100	28 per 100 (26 to 29)	OR 0.78 (0.73 to 0.83)	19,948 (23 studies)	⊕⊕⊕⊕ high	See Figure 1
Adverse events No. of participants experiencing any adverse event Follow-up: 6 to 52 weeks	64 per 100	69 per 100 (70 to 73)	OR 1.29 (1.22 to 1.37)	20,988 (27 studies)	⊕⊕⊕⊖ moderate ⁴	This outcome includes participants who reported COPD exacerbations as an adverse event
Gastrointestinal side effects No. of participants experiencing diarrhoea	4 per 100	11 per 100 (10 to 12)	OR 3.13 (2.76 to 3.54)	20,181 (25 studies)	⊕⊕⊕⊕ high	Diarrhoea was the most commonly reported gastrointestinal side effect. See Figure 2

Follow-up: 6 to 52 weeks						Weight loss was more common, and may be a result of diarrhoea
Psychiatric adverse events (roflumilast 500 µg) No. of participants Follow-up: 12 to 52 weeks	35 per 1000	71 per 1000 (60 to 83)	OR 2.13 (1.79 to 2.54)	11,168 (14 studies)	⊕⊕⊕⊖ moderate ⁵	Pooled data from FDA website, not individual trial reports
Mortality (all-cause) No. of participants Follow-up: 6 to 52 weeks	1 per 100	1 per 100 (1 to 2)	OR 0.97 (0.76 to 1.23)	19,344 (23 studies)	⊕⊕⊕⊖ moderate ⁶	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **COPD:** chronic obstructive pulmonary disease; **FDA:** Food and Drug Administration (USA); **FEV₁:** forced expiratory volume in one second; **OR:** odds ratio; **SGRQ:** St George's Respiratory Questionnaire

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹There was a greater proportion of participant withdrawals in the treatment (24%) compared with the control group (19%), but not sufficient to warrant downgrading the quality of evidence.

²There was moderate heterogeneity between the studies ($I^2 = 30\%$ to 50%).

³There was a statistically significant difference between published and unpublished studies.

⁴There was high level of heterogeneity between study results ($I^2 > 50\%$).

⁵Based on data from the combined [COPD safety pool](#). Individual study data not obtained.

⁶There were very few events, leading to wide confidence intervals.

Figure 1. In the control group 33 people out of 100 had an exacerbation of COPD over 6-52 weeks, compared to 28 (95% CI 27 to 29) out of 100 for the active treatment group.

Figure 2. In the control group 4 people out of 100 had diarrhoea over 6-52 weeks, compared to 11 (95% CI 10 to 12) out of 100 for the active treatment group.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of global morbidity and mortality, resulting in a growing social and economic burden (GOLD 2017). In 2002, it was estimated to be the fifth leading cause of death, responsible for approximately 4.8% of total deaths worldwide and it is projected to rise to fourth position by the year 2030 (Mathers 2005).

This diagnosis of COPD by the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2017) says that it is a "common, preventable and treatable disease, characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by exposure to noxious particles or gases." COPD may be punctuated by periods of acute worsening of respiratory symptoms, called exacerbations. Besides exposures, host factors predispose individuals to develop COPD. Co-morbidities contribute to the overall severity and mortality in individual people. (GOLD 2017). Diagnosis is based on a history of exposure to risk factors for this disease and symptoms of cough, sputum production or dyspnoea (shortness of breath). Spirometry is required for diagnosis, with airflow obstruction being confirmed by a post-bronchodilator forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) of 0.7 or lower (Celli 2004). Life expectancy is reduced in people diagnosed with COPD and, although prognosis is variable, age and FEV₁ are the strongest predictors of mortality.

The predominant risk factor for COPD is tobacco smoking, with other environmental pollutants also known to contribute. Cigarette smoke leads to the activation of macrophages and CD8 T lymphocytes that release inflammatory mediators and cytokines. The process also involves neutrophil attraction and cell apoptosis (Barnes 2000). To date, smoking cessation is the only intervention known to slow the decline in lung function associated with COPD (GOLD 2017).

Pharmacotherapy is commonly used to treat people with COPD, with effects on symptoms, quality of life, or frequency and severity of exacerbations (Celli 2004; GOLD 2017). Mainstays of treatment include short- and long-acting inhaled beta-2 agonists and anticholinergics, corticosteroids and methylxanthines. New approaches to treatment are needed, as no individual agent slows the decline in lung function or survival. In the TORCH study (Calverley 2007) a combination of salmeterol 50 µg and fluticasone 500 µg twice daily reduced the risk of death by 17% compared with placebo over the three-year trial period; however, this did not reach the pre-defined level of statistical significance for the study.

An exacerbation of COPD is an acute and sustained increase in symptoms that result in additional therapy (GOLD 2017). The risk of exacerbation significantly increases in more severe COPD. Exacerbations have a negative impact on quality of life and lead to more rapid COPD progression, as well as higher health care utilisation and associated costs. Common triggers are respiratory viral infections, bacterial infections or air pollution (Wedzicha 2007; White 2003), which may lead to an increase in airway inflammation, production of mucus, acute deterioration in lung function, hyperinflation from gas trapping, or a combination of these symptoms (Van Geffen 2015). These processes contribute to

the symptoms of increased dyspnoea and cough, as well as to changes in the character or volume of sputum.

Description of the intervention

The intervention is an oral medicine that is a selective inhibitor of the isoenzyme phosphodiesterase 4 (PDE₄). This isoenzyme has a role in airway inflammation and bronchoconstriction, both of which are pathological features of COPD (Boswell-Smith 2006). Two medicines in this class that have been studied are roflumilast and cilomilast.

How the intervention might work

Cyclic adenosine monophosphate (cAMP) is a secondary messenger that suppresses the activity of inflammatory cells and mediates the process of smooth muscle relaxation in the airways. Phosphodiesterases, in turn, hydrolyse and turn off the biological activity of cAMP (Boswell-Smith 2006). Therefore, inhibitors of phosphodiesterase action should theoretically provide improvements in the extent of airway narrowing and damage from inflammation.

Non-selective phosphodiesterase (PDE) inhibitors such as theophylline, a methylxanthine, have been used in the management of people with COPD for years. These are recommended by current international guidelines as part of adjunctive therapy to long-acting bronchodilators (GOLD 2017). Limitations to their use include a narrow therapeutic margin, and the frequency of adverse effects, which may occur even when the plasma level is within the therapeutic range (Boswell-Smith 2006). Common adverse effects associated with theophylline include headache, nausea, vomiting, diarrhoea, restlessness, nervousness, insomnia and gastrointestinal effects (Barnes 2003). Less common, but more serious, are the increased risks of cardiac arrhythmias and seizures (Barnes 2003). Some of the adverse effects associated with theophylline have been attributed to its non-selective PDE inhibition and concurrent adenosine receptor antagonism (Barnes 2005).

The isoenzyme PDE₄ is the predominant isoenzyme involved with metabolising cAMP in immune and inflammatory immune cells, such as neutrophils, macrophages, T cells and endothelial cells in COPD, in airway smooth muscle and pulmonary nerves (Agusti 2005; Boswell-Smith 2006; Torphy 1998; Vignola 2004). Inhibition of PDE₄ leads to elevation of cAMP in inflammatory and immunomodulatory cells, resulting in suppression of inflammatory cell function, relaxation of airways smooth muscle and modulation of pulmonary nerves (Boswell-Smith 2006; Essayan 2001; Torphy 1999). Thus, PDE₄ is an attractive target for inhibition in COPD. Furthermore, the central nervous system (CNS) and cardiovascular adverse effects experienced in patients treated with the non-selective PDE inhibitor, theophylline, are a result of adenosine receptor antagonism. This feature is not present with PDE₄ specific inhibitors (Vignola 2004).

Why it is important to do this review

The development of selective PDE₄ inhibitors offers new hope for therapy offering both anti-inflammatory and bronchodilatory effects in COPD, with fewer of the adverse effects encountered with non-selective inhibitors. Additionally, PDE₄ inhibitors may be easier to use because there is less pharmacokinetic variability and lower

potential for drug interactions compared with theophylline ([Barnes 2005](#)). Several PDE₄ inhibitors have been developed, with some progressing to phase III clinical trials. These include the second-generation PDE₄ inhibitors roflumilast (Nycomed, formerly Altana) and cilomilast (GlaxoSmithKline).

The 2017 GOLD guidelines ([GOLD 2017](#)) state that roflumilast may be considered in patients on triple inhaled therapy who still have exacerbations, an FEV₁ of less than 50% predicted and chronic bronchitis, especially if they have had a hospitalisation in the last year.

This review focuses on the effect of PDE₄ inhibitors in the management of people with stable COPD, using clinically important outcomes. Collating this evidence into a systematic review allows an assessment as to whether or not the theoretical benefits of PDE₄ inhibitors translate into useful clinical effects, and may suggest the potential place of PDE₄ inhibitors within the increasing pharmacopoeia of COPD treatments.

OBJECTIVES

To evaluate the efficacy and safety of oral PDE₄ inhibitors in the management of stable COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) that compared orally administered PDE₄ inhibitors with placebo. We included any chronic treatment trials, but excluded single-dose trials, as well as trials in acute exacerbations of COPD. We also excluded cross-over trials.

Types of participants

Adults (over 18 years of age) with COPD, as defined by the American Thoracic Society, European Respiratory Society or GOLD, with airflow obstruction evident by spirometry with post-bronchodilator FEV₁/FVC of 0.7 or less ([GOLD 2017](#)). We considered trials that included participants with both COPD and asthma only if data from participants with COPD could be extracted separately from the study report, or through correspondence with the study authors. We excluded ex-vivo experiments and trials with participants requiring mechanical ventilation on presentation.

Types of interventions

We included trials if they compared outcomes for participants who received an orally administered PDE₄ inhibitor with those of control participants who received placebo.

In this latest update of the review, although not mentioned in the initial protocol, we have excluded cross-over design studies as a way to minimise non-random sources of bias between studies.

Types of outcome measures

Primary outcomes

- Changes in lung function from baseline including forced expiratory volume in one second (FEV₁), forced vital capacity (FVC) or peak expiratory flow rate (PEF)
- Quality of life (e.g. total score on St George's Respiratory Questionnaire (SGRQ))

Secondary outcomes

- Incidence of COPD exacerbations
- Symptoms (breathlessness on Borg and other scales and Shortness of Breath Questionnaire; composite measures (summary symptom score))
- Exercise tolerance (six-minute walk test)
- Adverse effects (number of participants experiencing one or more adverse event, e.g. gastrointestinal, central nervous system (CNS) and cardiovascular adverse events, change in weight, withdrawal rates)
- Serious adverse events and mortality

Search methods for identification of studies

Electronic searches

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

- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org);
- weekly searches of MEDLINE Ovid SP 1946 to date;
- weekly searches of Embase Ovid SP 1974 to date;
- Monthly searches of PsycINFO Ovid SP;
- Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature);
- Monthly searches of AMED EBSCO (Allied and Complementary Medicine);
- handsearches of the proceedings of major respiratory conferences.

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

We conducted the most recent search in October 2016, with no restriction on language of publication. The original strategy for this review, which was more sensitive but less specific, is in [Appendix 3](#).

Searching other resources

We reviewed the reference lists of all primary trials and review articles for additional references. We contacted investigators in this area and pharmaceutical companies manufacturing PDE₄ inhibitors to ascertain if they could provide any potentially relevant trial data. We also searched the [US Food & Drug Administration](#)

(FDA) website and US National Institutes of Health (NIH) clinical trials registry, [ClinicalTrials.gov](https://clinicaltrials.gov) (last accessed 31 May 2017).

Data collection and analysis

Selection of studies

Two review authors (JC, PP) independently screened the search results to select citations to retrieve in full text. The same two review authors then screened the full-text articles to identify studies for inclusion.

Data extraction and management

One review author (JC) extracted data from the eligible studies and a second review author (BL or PP) checked the data. We entered data into Review Manager 5 (RevMan 5) [RevMan 2014](#). In some cases, we estimated information regarding outcomes from graphs. Where standard errors (SE) were reported, we converted them to standard deviations (SD).

We extracted the following data.

- Methods: trial design, duration of follow-up
- Participants: age, gender, smoking status, study setting, inclusion and exclusion criteria
- Intervention: drug name, dose, duration of treatment, control and/or standard therapy
- Outcome measures

We categorised references according to the trial name (by drug name and number, or by author and year). We obtained data on additional outcomes from other references to the same trial, and more detailed descriptions of study populations from information submitted by the drug manufacturer to the FDA website.

Where there were data from more than one report of the same trial, we considered the data from the primary published reference with the most complete data on the primary outcome(s) to take priority. For primary outcomes, we used intention-to-treat analysis in preference to per-protocol analysis. On the other hand, the trial data on the company website for [Cilomilast 076](#) provided more complete details of adverse events than [Gamble 2003](#), and we used this preferentially.

Our initial plan had been to perform meta-analysis on the change from baseline in post-bronchodilator FEV₁. Only pre-bronchodilator values were reported for the majority of cilomilast trials, with pre- and post-bronchodilator values available for most trials of roflumilast, with the exception of [Roflumilast DAL-MD-01](#), [Roflumilast FK1 101](#), [Roflumilast FK1 103](#), [Roflumilast FLUI-2011-77](#) and [Roflumilast IN-108](#) for which only post-bronchodilator measures were available and only predose measurements available for [Roflumilast ROF-MD-07\(RE2SPOND\)](#).

In order to increase the number of trials in the meta-analysis, we decided to use the change in the pre-bronchodilator FEV₁ for all trials, except for the five just mentioned, where it was not available. Between them, these three trials contributed only 3.4% to the mean difference (MD), with the mean change seen from baseline in FEV₁ similar to other trials.

Lung function is reported in millilitres (mL). Exercise tolerance is reported in metres (m).

The outcome 'total adverse events' included the participants in each group experiencing one or more adverse events, including an acute exacerbation of COPD. Similarly, serious adverse events included conditions requiring hospital-level treatment and encompassed more serious COPD exacerbations.

Assessment of risk of bias in included studies

We assessed trials using the 'Risk of bias' methods outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)) as low, unclear or high.

Measures of treatment effect

Where appropriate, we combined data from trials using [RevMan 2014](#). We expressed results for continuous variables using a fixed-effect MD, or standardised mean difference (SMD), with 95% confidence intervals (CI). We expressed results for pooled outcomes with dichotomous variables using a fixed-effect odds ratio (OR) with 95% CI. We considered a P value of less than 0.05 statistically significant. We combined rate ratios on a natural logarithm scale and weighted them by the inverse of the variance of the log rate ratio.

Unit of analysis issues

The unit of analysis was the participant, with the exception of analysis of exacerbation rates

Dealing with missing data

We contacted the respective pharmaceutical companies for missing trial data. In particular, Nycomed and Forest Laboratories provided us with some study details and results extracted from published articles and abstracts that were not identified in our initial search.

Assessment of heterogeneity

We used Chi² and I² statistics, along with P values ([Higgins 2003](#)) to measure heterogeneity among the trials in each analysis. Where we identified substantial heterogeneity we planned to report it and explore possible causes by prespecified subgroup analysis.

Assessment of reporting biases

We compared available published outcomes with prescribed methods and, where available, original study protocols.

Data synthesis

We presented the findings of our primary outcomes in a 'Summary of findings' table generated using [GRADEpro GDT 2015](#) software and based on the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Schünemann 2011](#)).

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses a priori.

- Severity of airflow obstruction at baseline (FEV₁ % predicted GOLD Grade II 50% to 80%, Grade III 30% to 50%, Grade IV less than 30%) ([GOLD 2017](#))
- Drug (e.g. roflumilast, cilomilast)
- Dose (e.g. roflumilast 250 µg or 500 µg)
- Duration of therapy (12 weeks or less; 24 to 26 weeks; 52 weeks)

- Concomitant therapy (inhaled or oral corticosteroids, inhaled long-acting beta-2 agonists, or anticholinergics, or both)

Sensitivity analysis

We planned the following sensitivity analyses a priori.

- Fixed-effect versus random-effects models for studies with unexplained heterogeneity
- Methodological quality

We did not anticipate the large number of unpublished trials at the protocol stage. Consequently, we undertook a sensitivity analysis of the effect sizes of the primary outcomes seen in published and unpublished trials.

RESULTS**Description of studies****Results of the search**

See [Figure 3](#) for study flow diagram ([Moher 2009](#)).

Figure 3. Study flow diagram

For the initial search in October 2006, we identified 477 abstracts of potentially relevant trials, which was narrowed to 71 abstracts using a less sensitive search of the Cochrane Airways Specialised Register. We searched again in 2008 and located 79 abstracts; in 2010 finding 17 abstracts; and in 2013, locating 20 abstracts. For the present update, the search found 55 abstracts (48 excluding

duplicates). In total 648 records were identified from database screening. Many abstracts were reports of earlier trials. We decided whether or not to seek the full text based on a review of the abstract text, title and MeSH headings of all identified citations, with the numbers of full papers sought outlined in [Table 1](#).

For this update we sought full papers for 28 abstracts. For each update, two review authors (JC and PP) assessed the full-text versions of the trials to determine whether or not they met the inclusion criteria. We resolved any differences by discussion. We then assessed trials that met the inclusion criteria for methodological quality.

In addition, in the course of earlier updates we found 15 completed trials for roflumilast and one for cilomilast in participants with COPD in a search of the online clinical trials registry of the US National Institutes of Health (NIH). After attempting to correlate each unique NIH study number with trials already identified in the above searches of the Airways registry, there were seven studies of roflumilast on the NIH clinical trials registry that had not been published elsewhere in any form. For the 2016 update, no new completed trials were located on the NIH websites that had not already been published.

For cilomilast, we identified one trial ([Compton 2001](#)) from the literature search and obtained the full text. Further, we found a summary of the study design, along with a report of results, for 12 individual phase II or III trials on the GlaxoSmithKline (GSK) website.

We identified another two trials, both through the literature search and from the GSK website ([Cilomilast 039](#); [Cilomilast 076](#)). [Gamble 2003](#) is the primary published reference for the latter study.

During the 2016 update we identified 5 new studies of roflumilast but none of cilomilast. All the roflumilast studies used a study dose of 500 µg ([RO-2455-301-RD \(ACROSS\)](#); [RO-2455-404-RD \(REACT\)](#); [Roflumilast DAL-MD-01](#); [Roflumilast FLUI-2011-77](#); [Roflumilast ROF-MD-07\(RE2SPOND\)](#)).

Included studies

Thirty-four separate RCTs studying roflumilast (20 trials with 17,627 participants) or cilomilast (14 trials with 6457 participants) met the inclusion criteria. Twenty-one of these 34 studies have been published in full in a peer-reviewed journal. Further details may be found in the [Characteristics of included studies](#) table.

Those for roflumilast included the following.

- An early-dose selection study comparing participants given roflumilast 250 µg and 500 µg ([Roflumilast M2-107](#)) for 24 weeks. Subsequent studies all used 500 µg of roflumilast in the intervention group and this is the dose that appears in the analyses except where otherwise stipulated.
- The first published one-year study of PDE₄ inhibitor treatment in COPD ([Roflumilast M2-112](#)). This was the only trial included in this review that allowed concomitant corticosteroid use during the treatment period. Since then, the results of a replicate study have been published ([Roflumilast M2-111](#)).
- This was followed by two, year-long studies ([Roflumilast M2-124](#); [Roflumilast M2-125](#)) investigating the effect in a specific subgroup - severe to very severe COPD associated with chronic bronchitis in participants at risk of exacerbations.
- Two studies ([Roflumilast M2-127](#); [Roflumilast M2-128](#)) that evaluated the add-on use of roflumilast with long-acting bronchodilator agents, the first with salmeterol and the second with tiotropium. Both studies ran for 24 weeks. A further two [RO-2455-404-RD \(REACT\)](#) and [Roflumilast ROF-](#)

[MD-07\(RE2SPOND\)](#) added roflumilast or placebo to a fixed-dose inhaled corticosteroid-long-acting beta-2 agonist combination.

- [Roflumilast M2-118](#) was a 12-week study that focused on airway physiology during rest and exercise in participants with moderate to severe disease. In addition, [Roflumilast M2-119](#) investigated pulmonary function and safety in a group of participants recruited in centres across the Asia-Pacific regions. [Roflumilast DAL-MD-01](#) was mainly interested in effect on sputum and other biomarkers, and [Roflumilast FLUI-2011-77](#), airway architecture by imaging techniques.
- More recent large RCTs were [RO-2455-301-RD \(ACROSS\)](#), a 24 week trial across three centres in mainland China, Hong Kong and Singapore, and [RO-2455-404-RD \(REACT\)](#) and [Roflumilast ROF-MD-07\(RE2SPOND\)](#) year-long multi-centre trials.

There were two trials reported only as conference posters: [Roflumilast FK1 101](#) and [Roflumilast FK1 103](#). The first compared roflumilast 500 µg, roflumilast 250 µg and placebo for 26 weeks; the second compared roflumilast 500 µg once daily for 24 weeks with roflumilast 500 µg once daily for 12 weeks, then placebo once daily for the following 12 weeks.

Unpublished results were identified for two further studies: [Roflumilast IN-108](#) compared the safety and efficacy of roflumilast 250 µg and 500 µg in participants recruited from five centres across India; however, no inclusion criteria were stated, concomitant medications were poorly described and only 15 participants in the placebo group completed the protocol; [Roflumilast JP-706](#) was a 24-week study sponsored by a different collaborator that, in addition to treatment effects, monitored pharmacokinetic levels of roflumilast and its metabolite roflumilast-N-oxide.

All of these were designed as randomised, double-blind, placebo-controlled studies and, apart from [Roflumilast JP-706](#), all studies prior to 2013 were included in combined safety figures for roflumilast that have been made available through publications on the FDA website (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022522Orig1s000MedR.pdf). This also includes participants in two other 24-week studies ([Roflumilast M2-110](#); [Roflumilast M2-121](#)), which have results that have not been published (roflumilast 500 µg: 5970, roflumilast 250 µg: 1002 and placebo: 5682).

For cilomilast, data were mainly from phase III clinical trials with one phase II/III trial. These included unpublished studies. All used a 15 mg dose twice daily except for [Compton 2001](#).

The trials fell into four groups:

- [Compton 2001](#) was a parallel, six-week, dose-ranging study comparing placebo with 5 mg, 10 mg and 15 mg doses of cilomilast, with FEV₁ as the primary outcome.
- Pivotal efficacy studies ([Cilomilast 039](#); [Cilomilast 042](#); [Cilomilast 091](#); [Cilomilast 156](#)), all of which were 24 weeks in duration. The studies [Cilomilast 039](#) and [Cilomilast 156](#) were conducted in North America, while [Cilomilast 042](#) and [Cilomilast 091](#) were conducted in the European Union. Here the primary study outcomes were change in FEV₁, lung function and SGRQ quality-of-life score.
- Supporting studies ([Cilomilast 076](#); [Cilomilast 110](#); [Cilomilast 111](#); [Cilomilast 168](#)), all of which lasted for less than 24 weeks,

with an average trial duration of 10.8 weeks, where neither FEV₁ lung function nor SGRQ were the primary outcomes.

- Other studies were [Cilomilast 121](#) (phase II/III 24 weeks), [Cilomilast 157](#) (52 weeks) and [Cilomilast 103657](#) (24 weeks), which followed the pivotal efficacy studies and were smaller in sample size. [Cilomilast 180](#) (18 weeks) had a primary lung function endpoint, functional residual capacity, and [Cilomilast 181](#) (13 weeks) assessed the number of inflammatory cells in a bronchial biopsy.

Almost all studies used inclusion criteria of spirometry and a history of smoking. Only four of the 29 studies mandated a history of exacerbation in the previous year ([Cilomilast 103657](#); [Cilomilast 121](#); [Roflumilast M2-124](#); [Roflumilast M2-125](#)).

The mean age of participants in the trials ranged from 60 to 70 years with the proportion of male participants between 49% and 96%. Mean FEV₁ (% predicted) in the trials that reported it ranged from 33% to 51%. The majority of trials included participants at all stages of COPD, however limitation to those with severe and very severe COPD occurred in [Roflumilast M2-124](#); [Roflumilast M2-125](#); [RO-2455-301-RD \(ACROSS\)](#); [RO-2455-404-RD \(REACT\)](#); [Roflumilast](#)

[DAL-MD-01](#); [Roflumilast M2-111](#); [Roflumilast M2-112](#); [Roflumilast ROF-MD-07\(RE2SPOND\)](#).

Excluded studies

We excluded 75 records after studying the full text. We provided reasons for the exclusion of 26 studies, which can be found in [Characteristics of excluded studies](#). For some of these the reason was that data were unusable (e.g. [Borker 2003](#); [Knobil 2003](#)).

Risk of bias in included studies

We considered that the methodological quality of the 34 published and unpublished trials was acceptable overall.

Allocation

In the roflumilast trials, there were adequate descriptions of allocation concealment and method of blinding in nine out of 20 trials. Information about allocation concealment and blinding was only provided for one of the 14 cilomilast trials, while further details for the remaining trials were unclear. The risk of bias for each parameter in the 34 studies is shown in [Figure 4](#).

Figure 4. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Allocation concealment (selection bias)	Randomised?	Method of randomisation described?	Blinding?	Method of blinding described?	Description of withdrawals and drop-outs?	Baseline profile: anticholinergic use	Baseline profile: β_2 agonist use	Baseline profile: corticosteroid use
Cilomilast 039	?	+	?	+	?	+	+	+	+
Cilomilast 042	?	+	?	+	?	+	?	?	?
Cilomilast 076	?	+	?	+	?	+	?	?	?
Cilomilast 091	?	+	?	+	?	+	?	?	?
Cilomilast 103657	?	+	?	+	?	+	?	?	?
Cilomilast 110	?	+	?	+	?	+	?	?	?
Cilomilast 111	?	+	?	+	?	+	?	?	?
Cilomilast 121	?	+	?	+	?	+	?	?	?
Cilomilast 156	?	+	?	+	?	+	?	?	?
Cilomilast 157	?	+	?	+	?	+	?	?	?
Cilomilast 168	?	+	?	+	?	+	?	?	?
Cilomilast 180	?	+	?	+	?	+	?	?	?
Cilomilast 181	?	+	?	+	?	+	?	?	?
Compton 2001	?	+	?	+	?	+	?	+	+
COPD safety pool	?	+	?	?	?	?	?	?	?
RO-2455-301-RD (ACROSS)	+	+	+	+	+	?	+	?	+
RO-2455-404-RD (REACT)	+	+	+	+	+	?	?	?	?
Roflumilast DAL-MD-01	?	?	?	+	+	+	?	?	?
Roflumilast FK1 101	?	+	?	+	?	-	?	?	?
Roflumilast FK1 103	?	+	?	+	?	-	?	?	?
Roflumilast FLUI-2011-77	?	+	?	+	?	?	?	?	?
Roflumilast IN-108	?	+	?	+	?	+	?	?	?
Roflumilast JP-706	?	+	?	+	?	-	+	?	?

Figure 4. (Continued)

	?	+	?	+	?	-	+	?	?
Roflumilast JP-706	?	+	?	+	?	-	+	?	?
Roflumilast M2-107	+	+	+	+	+	+	?	?	?
Roflumilast M2-110	?	+	?	+	?	?	?	?	?
Roflumilast M2-111	+	+	+	+	+	+	+	+	+
Roflumilast M2-111+M2-112	+	+	+	+	+	+	+	+	+
Roflumilast M2-112	+	+	+	+	+	+	+	+	+
Roflumilast M2-118	?	+	?	+	?	+	?	?	?
Roflumilast M2-119	?	+	+	+	?	+	?	?	?
Roflumilast M2-121	?	+	?	+	?	?	?	?	?
Roflumilast M2-124	+	+	+	+	+	+	?	?	-
Roflumilast M2-124+M2-125	+	+	+	+	+	+	+	+	-
Roflumilast M2-125	+	+	+	+	+	+	+	+	-
Roflumilast M2-127	+	+	+	+	+	+	?	?	?
Roflumilast M2-128	+	+	+	+	+	+	?	?	?
Roflumilast ROF-MD-07(RE2SPOND)	?	+	?	+	?	?	?	?	?

Blinding

All studies included in this review were double-blind, RCTs.

Incomplete outcome data

The percentage of participant withdrawals varied among the 34 trials that reported this outcome. Withdrawals were significantly higher in the PDE₄ inhibitor-treated groups compared with control groups. The mean withdrawal rate for roflumilast studies, because of adverse events, was 13% in the treatment group (range 3% to 37%) and 8% in the control group (range 3% to 27%). In the cilomilast studies a mean of 25% of the participants withdrew due to adverse events in the treatment group (range 13% to 34%) and 21% (range 9% to 40%) in the control group.

Since the participants who withdraw tended to have poorer outcome measures than those remaining, the higher withdrawal rates for the PDE₄ inhibitor-treated groups may have inflated the apparent benefits of treatment.

Selective reporting

There were 23 published and 11 unpublished trials. We performed analyses of differences in treatment effect between published and unpublished treatment groups for primary outcomes and this is reported in the subgroup and sensitivity analysis below.

Other potential sources of bias

In some trials there were minor differences in baseline characteristics such as age, gender, FEV₁ and smoking history.

Effects of interventions

See: [Summary of findings for the main comparison Phosphodiesterase 4 inhibitors compared to placebo for chronic obstructive pulmonary disease](#)

Change in lung function from baseline

Based on the 27 trials that reported this outcome, there was a statistically significant improvement in FEV₁ from baseline in the PDE₄ inhibitor-treated participants compared with controls (MD 51.53 mL, 95% CI 43.17 to 59.90, 20,585 participants), over the study period ([Analysis 1.1](#)).

The effect on FEV₁ was seen for roflumilast 500 µg (MD 56.45 mL, 95% CI 48.01 to 64.89), roflumilast 250 µg (MD 56.88 mL, 95% CI 24.38 to 89.38) and for cilomilast 15 mg twice daily (MD 41.03 mL, 95% CI 23.93 to 58.13). A moderate level of heterogeneity existed for this outcome (Chi² = 56, df = 29, P = 0.002; I² = 48%), which is only partially explained by investigating differences between roflumilast and cilomilast. This is discussed further in the sensitivity analysis below. Analysis of a dose effect was possible in three trials: [Roflumilast FK1 101](#); [Roflumilast M2-107](#) and [Roflumilast IN-108](#). Roflumilast 500 µg was associated with a greater change in FEV₁

than roflumilast 250 µg, but this was not statistically significant (MD 22.61, 95% CI -5.95 to 51.16).

With respect to PDE₄ inhibitor use with concomitant therapies (Analysis 1.5), the largest increases in FEV₁ were seen in the two trials where participants were taking regular, long-acting bronchodilators: in one, salmeterol (Roflumilast M2-127) and in the other, tiotropium (Roflumilast M2-128) (overall MD 60.52 mL, 95% CI 40.57 to 80.46). The next largest improvements were seen in trials where all concomitant medications (including long-acting bronchodilators if previously received) were continued (RO-2455-301-RD (ACROSS); RO-2455-404-RD (REACT); Roflumilast ROF-MD-07(RE2SPOND)) (MD 56.58 mL, 95% CI 46.91 to 66.25).

Similar improvements were seen in trials where all medications apart from short-acting beta 2 agonists were stopped (MD 44.78 mL, 95% CI 37.67 to 51.90) and in the three trials (Roflumilast M2-111; Roflumilast M2-112; Roflumilast M2-118) where both treatment and control groups continued on an inhaled corticosteroid (MD 42.26 mL, 95% CI 25.46 to 59.05).

Treatment with a PDE₄ inhibitor was associated with a statistically greater change in FVC from baseline than placebo (MD 87.28 mL, 95% CI 74.87 to 99.70) with minimal heterogeneity among the 16 trials (Analysis 1.9). Change in PEF was measured in only five of the 34 trials, but was significantly higher with treatment than in controls (MD 6.54 L/min, 95% CI 3.95 to 9.13) (Analysis 1.10).

Quality of life

Note that with the SGRQ, a decrease in the total score represents an improvement in the quality of life. We noted a small but statistically significant decrease in total score on the SGRQ from baseline in participants treated with PDE₄ inhibitors compared with those in the control groups (MD -1.06, 95% CI -1.68 to -0.43, $P = 0.0009$) (Analysis 1.11). There was heterogeneity in this observation ($\chi^2 = 21$, $df = 11$, $P = 0.03$, $I^2 = 47\%$).

It was notable that in the two trials with a duration of one year that reported total SGRQ, there was no significant change in quality of life seen with treatment compared with control (MD 0.26, 95% CI -1.18 to 1.69). We did not include outcome data for Roflumilast M2-111 as data were provided in the form of a 'repeated measures analysis' and pooled data did not equal the sum of numbers in each of the individual studies.

Exacerbations

Use of PDE₄ inhibitors was associated with a statistically significant reduction in the numbers of participants experiencing one or more COPD exacerbations. This is a relative reduction of more than 20% (OR 0.78, 95% CI 0.73 to 0.83) (Analysis 1.16), from a representative risk of 33 per 100 on placebo to 28 per hundred on PDE₄ inhibitors over 12 to 52 weeks (Figure 1 and Summary of findings for the main comparison). There was little heterogeneity among trials ($\chi^2 = 23$, $df = 22$, $P = 0.38$, $I^2 = 6\%$). Similar efficacy was seen for both roflumilast and cilomilast and where use of concomitant long-acting bronchodilators was permitted (Analysis 1.17).

In terms of exacerbation rate and the number of exacerbations experienced on average per participant per year (Analysis 1.18), we observed a small significant benefit with treatment, representing a 12% reduction in the rate ratio (rate ratio 0.88, 95% CI 0.83 to 0.93).

The Roflumilast FK1 101 trial reported that the probability of experiencing an exacerbation was reduced by 8% with 250 µg of roflumilast and 48% with 500 µg, although the absolute value was not reported, nor whether this was statistically significant.

Symptoms and exercise tolerance

Overall, the mean difference in change from baseline with PDE₄ inhibitor treatment compared with controls on COPD-related symptoms was small, regardless of the scale used to measure it. The only statistically significant effect was seen in one trial of cilomilast, for breathlessness scored using a Borg scale (MD -0.19, 95% CI -0.33 to -0.05) (Analysis 1.19). This is a small absolute difference so is of doubtful clinical relevance.

Exercise tolerance using the six-minute walk test was measured in four cilomilast trials. There was no significant difference in walk test distance between treatment and controls (MD 2.09 m, 95% CI -7.39 to 11.57) (Analysis 1.22).

Adverse events

The likelihood of a participant experiencing an adverse event was higher with PDE₄ inhibitor treatment than with placebo (OR 1.29, 95% CI 1.22 to 1.37) (Analysis 1.23). This effect was seen for both roflumilast and cilomilast.

We noted a range of adverse effects that occurred more frequently in PDE₄ inhibitor-treated participants. Diarrhoea was more common in PDE₄ inhibitor-treated groups than in controls (OR 3.13, 95% CI 2.76 to 3.54) (Analysis 1.25 and Figure 2), as was nausea (OR 3.78, 95% CI 3.23 to 4.43) (Analysis 1.26), headache (OR 1.69, 95% CI 1.47 to 1.95) (Analysis 1.27), vomiting (OR 4.01, 95% CI 2.80 to 5.74) (Analysis 1.28), dyspepsia (OR 3.17, 95% CI 2.33 to 4.30) (Analysis 1.29) and abdominal pain (OR 2.04, (95% CI 1.63 to 2.55) (Analysis 1.30). More than 10% of participants in the treatment group experienced gastrointestinal-related side effects, with the most frequently reported symptom being diarrhoea Figure 2 (number needed to treat for an additional harmful outcome (NNTH): 15, 95% CI 13 to 17). Weight loss was more likely in the treatment groups in the 10 roflumilast trials (OR 3.76, 95% CI 3.11 to 4.54) (Analysis 1.31), but was not reported in the cilomilast trials. There were no significant differences in the incidence of either influenza-like symptoms (Analysis 1.32) or upper respiratory tract infections (Analysis 1.33) between treatment and control groups.

The higher dose of roflumilast (500 µg) was associated with more adverse effects than the 250 µg dose; however, this was based on only four trials and confidence intervals were wide (OR 1.21, 95% CI 1.01 to 1.46) (Analysis 1.24). In the trial of Compton 2001 that studied the effects of varying doses of cilomilast, adverse effects were seen in 52% of the placebo group, 48% of the cilomilast 5 mg group, 47% of the 10 mg group and 61% of the 15 mg group, with rates of serious adverse events similar across the groups.

An increase in withdrawals attributed to adverse effects was recorded for both roflumilast and cilomilast treatment groups (OR 1.90, 95% CI 1.74 to 2.09) (Analysis 1.34). There was, however, no significant effect of treatment on non-fatal serious adverse events (OR 0.99, 95% CI 0.91 to 1.07) (Analysis 1.35) or mortality (OR 0.97, 95% CI 0.76 to 1.23) (Analysis 1.36), although mortality was a relatively rare event during the trials.

We recorded the number of psychiatric adverse events from pooled data from all parallel-design, double-blind studies investigating roflumilast collated and presented to the FDA. This included data from the 15 fully published trials, but excluded [Roflumilast JP-706](#), which was conducted by a different study collaborator. These results reported symptoms of depression separately from depressed mood, depressive symptoms or major depression. There was a higher risk in the roflumilast 500 µg treatment group, compared with placebo, of experiencing a psychiatric-related adverse event (OR 2.13, 95% CI 1.79 to 2.54) ([Analysis 1.37](#)). This was reported in three people out of 100 in the placebo group, compared to seven (95% CI 6 to 8) out of 100 for the PDE₄ inhibitor-treated group (NNTH 28, 95% CI 21 to 39). Based on outcomes reported in more recent roflumilast trials the numbers of participants experiencing insomnia or sleep disorders (OR 1.48, 95% CI 0.81 to 2.70) ([Analysis 1.38](#)), symptoms of anxiety (OR 1.81, 95% CI 1.26 to 2.62) ([Analysis 1.39](#)) or depression (OR 1.59, 95% CI 1.11 to 2.27) ([Analysis 1.40](#)) were higher in the roflumilast group compared with the placebo. There was no statistically significant difference in the rate of psychiatric adverse events in the roflumilast 250 µg treatment group compared with placebo as in each of the analyses, the 95% confidence intervals crossed the midline.

In the roflumilast COPD safety database (n = 12,054 participants), there were three reports of completed suicides and two suicide attempts in roflumilast-treated participants compared to none in participants treated with placebo.

Subgroup and sensitivity analyses

A moderate but significant level of heterogeneity existed for the change in FEV₁ outcome when all trials were pooled ($I^2 = 48\%$). Using a random-effects model made no difference to the levels of statistical significance or degree of heterogeneity for the change in FEV₁ ([Analysis 1.7](#)). There were too many 'Risk of bias' domains judged to be at 'unclear' risk of bias to do subgroup analysis according to study quality. Of note, some effect sizes were greater in the published trials; for example, the treatment effect on FEV₁ was MD 55.75 mL (95% CI 49.44 to 62.06) in the 19 published trials, and MD 34.82 (95% CI 25.44 to 44.19) in the eight unpublished trials ([Analysis 1.6](#)), which was a statistically significant difference (test for subgroup differences: $\text{Chi}^2 = 13.18$, $\text{df} = 1$ ($P = 0.0003$)). This is illustrated in the funnel plot with more unpublished studies showing a smaller treatment effect ([Figure 5](#)).

Figure 5. Funnel plot of comparison: 1 PDE₄ inhibitor versus placebo, outcome: 1.6 FEV₁ (published versus unpublished).

By visual analysis of the forest plot and sequential elimination, the six-week [Compton 2001](#) cilomilast trial was identified as a major

contributor towards the heterogeneity of pooled FEV₁ results. When it was removed, the overall I^2 statistic decreased from 48% to

31% and in the cilomilast subgroup from 62% to 0%. It is notable that this study had the shortest treatment duration of six weeks and showed the largest improvement in FEV₁ lung function from baseline in the treatment group across all studies.

To see whether the size of the treatment effect varied with COPD severity, we conducted subgroup analyses of trials where the mean per cent predicted FEV₁ at baseline was available ([Analysis 1.2](#)). The effects seen in both old GOLD grades I or II (FEV₁ 50% or more) predicted and old GOLD grades III or IV (FEV₁ less than 50%) were both statistically significant, and of similar magnitude, test for subgroup differences: $\text{Chi}^2 = 0.03$, $\text{df} = 1$ ($P = 0.86$).

Similarly, there was a difference in the effect size of the total SGRQ score between published and unpublished trials (MD -1.98, 95% CI -3.07 to -0.89 versus MD -0.43, 95% CI -1.26 to 0.40, test for subgroup differences: $\text{Chi}^2 = 4.94$, $\text{df} = 1$ ($P = 0.03$)) ([Analysis 1.12](#)). Subgroup analysis showed COPD severity had no bearing on the size of the change in quality-of-life score test for subgroup differences: $\text{Chi}^2 = 0.02$, $\text{df} = 1$ ($P = 0.89$) ([Analysis 1.14](#)).

For both primary outcomes, that is, FEV₁ and SGRQ score, the size of the treatment effect, that is, the mean difference between PDE₄ and placebo groups, was significantly greater in short studies of 6 to 12 weeks, compared with 24- and 52-week studies ([Analysis 1.4](#); [Analysis 1.13](#)).

DISCUSSION

Summary of main results

This systematic review evaluated randomised controlled trials (RCTs) that assessed the efficacy and safety of oral phosphodiesterase 4 (PDE₄) inhibitors in people with chronic obstructive pulmonary disease (COPD). The first major finding, based on data from 34 trials, was that both roflumilast and cilomilast led to significantly greater improvements in lung function from baseline, as measured by forced expiratory volume in one second (FEV₁), forced vital capacity (FVC) or peak expiratory flow rate (PEF), than placebo. Furthermore, the improvement in lung function was seen regardless of the severity of the disease. This improvement in FEV₁ lung function occurred whether or not treatment was given in addition to other COPD treatments, such as long-acting beta-2 agonists or anticholinergics, compared to treatment alone or with inhaled corticosteroids (ICS).

The mean change in FEV₁ was, however, below what is usually considered a minimum clinically important difference (100 mL, [Donohue 2005](#)), but comparable to those seen with other COPD treatments in recent large RCTs. For example, the mean improvement in FEV₁ of 49 mL with treatment seen in moderate to severe COPD in this review is of similar magnitude to that seen with fluticasone (47 mL), salmeterol (42 mL), and fluticasone and salmeterol combined (92 mL) in the [TORCH 2007](#) study in people with severe COPD.

A second major finding, based on data from 23 trials, was that participants were more likely to be exacerbation-free while being treated with PDE₄ inhibitors compared with controls. Overall, participants were 22% less likely to have an exacerbation, translating to a number needed to treat for an additional beneficial outcome (NNTB) of around 20 (95% CI 16 to 26), for one person to be

exacerbation-free in the study period [Figure 1](#). While the likelihood of an individual experiencing an exacerbation was lowered with PDE₄ inhibitor treatment, the decrease in the overall rate of exacerbations was less marked, with a relative reduction of 13%.

Taken together, these two major findings suggest that PDE₄ inhibitors in people with COPD are acting independently of other treatments, particularly bronchodilators. This is an encouraging finding that could be consistent with a broad anti-inflammatory effect ([Fabbri 2009](#)). On the other hand, short-duration studies showed more favourable results than the longer studies, but the reasons for this are unclear. Significant heterogeneity was noted among the trials, suggesting that unmeasured differences between the trials may be having an impact.

A third major finding of the review was that, despite significant improvements in lung function and a reduction in exacerbations in participants treated with PDE₄ inhibitors, there was only a small improvement in quality of life as assessed by the St George's Respiratory Questionnaire (SGRQ) total score. Quality of life had been chosen as a primary outcome because of concerns as to whether or not the adverse effects of PDE₄ inhibitors might outweigh any beneficial COPD-related effects. The average change in SGRQ total score was 1.06 units (over a duration of between six and 12 months), and was of similar magnitude among trials of participants with milder or more severe COPD. Although this improvement was statistically significant, a change of greater than four units is usually regarded as the minimum clinically important difference ([Jones 2005](#)). While symptom scores were marginally better in the treatment groups, there was no change seen in exercise tolerance, suggesting that improvements in respiratory symptoms may not necessarily translate into enhancement of physical functioning. There were, though, fewer trials assessable for these outcomes, raising the possibility of type 1 or type 2 errors.

This review found that adverse effects were greater in the roflumilast and cilomilast-treated participants than in those receiving placebo, particularly gastrointestinal-related effects such as diarrhoea, nausea, vomiting and dyspepsia. More recently, there has been greater awareness of the risk of psychiatric adverse events associated with roflumilast treatment, in particular the increased likelihood of experiencing sleep disturbances, anxiety and depressed mood. Participants in the treatment groups were also more likely to withdraw from the trials because of adverse effects; on average 14% in the treatment groups withdrew compared with 8% in the control groups. Similarly, there is a slight excess in the total number of participants in the treatment groups experiencing any adverse effect, compared with controls ([Analysis 1.23](#)). As this analysis included symptoms as well as exacerbations, which were reduced in the treatment groups, this analysis will tend to under-estimate the excess of non COPD-related adverse effects occurring with PDE₄ inhibitor treatment.

It was notable that treatment with roflumilast was associated with a significant chance of weight loss. Whether this was due to anorexia from gastrointestinal adverse effects, or another effect, is not yet clear. Also not clear is whether cilomilast has the same effect, as it has not been studied. Weight loss may be a beneficial effect in people with COPD who are obese. In contrast, low body mass in the later stages of COPD is associated with a worse prognosis and is notoriously difficult to reverse ([GOLD 2017](#)). This adverse effect warrants further investigation. Reassuringly, there was no

increase in serious adverse effects or mortality, although trials were of relatively short duration, and analyses were underpowered to report on the latter outcome.

While a lower dose (250 µg) of roflumilast produced similar improvements in FEV₁ ([Analysis 1.8](#)) and was associated with slightly fewer adverse effects ([Analysis 1.24](#)) than the larger dose, this was associated with a smaller reduction in rate of exacerbations than the 500 µg dose, in the one trial that reported this ([Roflumilast FK1 101](#)). Moreover, data on the lower dose were only available in a limited number of studies and it has not been studied as add-on therapy to other bronchodilators.

Overall completeness and applicability of evidence

We have reviewed all known published and unpublished trials identified from standard Cochrane searches, as well as from the trials register for the NIH and from pharmaceutical websites.

We have not been able to verify the pooled endpoint data for psychiatric- (treatment possibly harmful) and cardiovascular-related adverse events (treatment possibly beneficial) as they were obtained from reports on the US Food and Drug Administration (FDA) website and from [White 2013](#), respectively.

To ensure our Cochrane systematic review accurately reflects all known outcomes of roflumilast therapy, for the previous update we approached the manufacturer of roflumilast for study-level data on each of the cardiovascular outcomes (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) as well as the composite outcome, major adverse cardiovascular events (MACE). This would have allowed us to perform comparisons both within (i.e. between roflumilast and placebo groups) and among the studies. Unfortunately, our request for individual trial data was refused with the following reasons being cited:

- it is inappropriate from a statistical perspective to look into individual trials with too small a sample size for this kind of relatively rare endpoint;
- it was part of the retrospective analyses to evaluate the whole data set with a sufficiently broad database and not to go into subcuts per study that would comprise studies with numbers in each treatment arm that were too low for conclusive interpretation;
- in none of the studies was the blinded adjudication of the events implemented as a prospective analysis, which would have required a data release in terms of transparency in each individual study (which is the reason why it was not mentioned in the original publications of the individual trials).

In response to the statement by representatives of Takeda Pharmaceuticals Limited, we have urged that these issues be reconsidered for future studies and that study data be made more widely available. Finally, caution must be used when interpreting associations between COPD exacerbations and MACE, because although the treatment groups were matched at baseline, it cannot be assumed that these groups are equivalent when looking only at the group of participants who experienced exacerbations. These concerns could not be assessed in this review as further study data were not provided.

Quality of the evidence

For the key outcomes of changes in lung function and quality of life, there were greater beneficial effects of PDE₄ inhibitors reported in the published studies than in the unpublished studies, raising concerns about publication bias. There was a moderate level of heterogeneity identified in both of the primary outcomes for this review, which is not fully explained by subgroup or sensitivity analyses according to study duration or concomitant medication use. This suggests unknown factors that may impact on the effect size, and has led us to downgrade the quality of the evidence and certainty of our findings ([Summary of findings for the main comparison](#)). In contrast, the blinded design of the studies comparing roflumilast or cilomilast with placebo protected against detection bias in our view. The quality of evidence for a reduction in exacerbation was therefore higher for this comparison. On balance, we believe the true beneficial effect of PDE₄ inhibitors is likely to be no greater than we have reported, and probably less; equally the harms may have been understated (partly due to higher withdrawal rates in active treatment arms). On the other hand, as subgroup analyses for COPD severity are based on the mean predicted lung function for the study group and not individual participants, we cannot rule out that there is a benefit for individuals of a specific COPD phenotype.

Potential biases in the review process

Potential biases in the review process were minimised by double-checking of data extraction and input. The authors have no conflicts of interest to declare and have not been involved in prescribing these medicines as neither roflumilast nor cilomilast are available on the New Zealand pharmaceutical schedule.

Agreements and disagreements with other studies or reviews

There have been several other meta analyses conducted, such as [Oba 2013](#); [Yan 2014](#) and [Luo 2016](#). Each of these had fewer studies than the present review, but had findings and conclusions that were similar.

In a post hoc pooled analysis (n =5595) of four trials in this review ([Rennard 2014](#)), roflumilast significantly improved transition dyspnoea index (TDI) focal scores of breathlessness versus placebo at week 52 (treatment difference, 0.327; P < 0.0001). Roflumilast was associated with significantly greater TDI responders and significantly fewer TDI deteriorators (≥ 1-unit increase or decrease from baseline, respectively) versus placebo at week 52 (P < 0.01, both). Rates of MACE in COPD participants treated with PDE₄ inhibitors have been meta-analysed and reported in a paper published by [White 2013](#). This found that the risk of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, when combined into a composite outcome (MACE), was reduced in the roflumilast group compared with placebo (hazard ratio 0.65, 95% CI 0.45 to 0.93; P = 0.019). On the other hand, hazard ratios for treatment effects for each of these types of event individually were statistically different. Cardiovascular events were higher in participants with baseline cardiovascular risk factors than in those without baseline cardiovascular risk (defined as the presence of hypertension, diabetes mellitus, hyperlipidaemia and/or a history of heart disease). In addition, it was found that the difference between treatment and placebo was only statistically significant in the group of participants without baseline risk factors.

Event rates in a subgroup of trials that were one year in duration found no significant difference between treatment and placebo groups in the proportion of participants who reported a MACE, even when divided into those who did, or did not experience a COPD exacerbation. Similarly, between participants with and without MACE events, the proportions of participants experiencing exacerbations was similar (43.2% and 42.1%, respectively).

AUTHORS' CONCLUSIONS

Implications for practice

Phosphodiesterase 4 inhibitors (PDE₄) are oral medicines that may be taken in combination with other standard chronic obstructive pulmonary disease (COPD) treatments. Most evidence exists for roflumilast at a dose of 500 µg daily and cilomilast at 15 mg twice daily.

Phosphodiesterase 4 inhibitors join an increasing list of treatments for COPD that improve short-term lung function and reduce exacerbations, but have not been shown to increase life expectancy. Trials to date have been one year or less in duration. In contrast to long-acting bronchodilators, PDE₄ inhibitors have minimal benefits on symptoms on a day-to-day basis, or quality of life, and are often associated with adverse effects, especially of the gastrointestinal system, and headaches. Roflumilast is associated with significant weight loss and more psychiatric symptoms than placebo treatment. Thus, the findings of this review support the use of PDE₄ inhibitors: however, their use may best be limited to add-on therapy in a subgroup of people with persistent symptoms or exacerbations despite optimal COPD management, providing they are well-tolerated.

Implications for research

This review has highlighted several possible areas for further study:

- longer-duration studies to look at the effect of PDE₄ inhibitors on forced expiratory volume in one second (FEV₁) decline and mortality;
- subgroup analysis in participants with/without chronic bronchitis and with/without history of exacerbations;
- effect of PDE₄ inhibitors in participants with frequent exacerbations;
- effect of PDE₄ inhibitors on healthcare utilisation, including hospitalisation (incidence and bed days);
- a direct comparison of PDE₄ inhibitors and inhaled corticosteroids (ICS), when used as add-on therapies to either tiotropium or long-acting beta-2 agonists, or both;

- a direct comparison of either tiotropium or long-acting beta-2 agonists, or both, as add-on therapies to PDE₄ inhibitors (+/- ICS);
- effect of roflumilast on quality of life;
- better characterisation of the weight loss seen with PDE₄ inhibitors in COPD;
- better description of the nature of the effect on the exacerbations that do occur;
- use of PDE₄ inhibitors in acute exacerbations;
- cost-effectiveness of PDE₄ inhibitors;
- ascertaining more exercise-tolerance data for roflumilast;
- determining if there is any benefit on cardiovascular outcomes with PDE₄ inhibitors in COPD;
- using the effects of PDE₄ inhibitors to better understand the pathophysiology of COPD.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Cilomilast 039

Methods	Parallel-group study
	Randomisation: randomised, double-blind, placebo-controlled trial

Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease (Review)

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Cilomilast 039 (Continued)

Trial duration: 24 weeks

Intention-to-treat analysis: stated

Participants	<p>Setting: 102 centres in Canada, Mexico and the USA</p> <p>Participants: 647 (15 mg cilomilast: 431, placebo: 216)</p> <p>Baseline characteristics: mean age: 65 years, 62% male, mean FEV₁% predicted of 49.7%, mean smoking history of 59.9 pack-years for cilomilast and 56.1 pack-years for placebo, or current smokers (44% and 47%, respectively)</p> <p>Inclusion criteria: FEV₁/FVC ≤ 0.7, FEV₁ 30% -70% with smoking history > 10 pack-years or current smokers</p> <p>Exclusion criteria: active tuberculosis, lung cancer and bronchiectasis</p> <p>Total number of participant withdrawals: 137 (32%) and 52 (24%) from treatment and control groups, respectively</p>
Interventions	<p>Run-in: 4 weeks, single-blind. Placebo tablets to assess suitability</p> <p>Cilomilast 15 mg twice daily</p> <p>Placebo twice daily</p> <p>Concomitant medication</p> <ul style="list-style-type: none"> • Short-acting anticholinergic: "The only other permitted medications for the treatment of airways disease were stable doses of Ipratropium, via a metered-dose inhaler, and mucolytic agents." • Short-acting β₂ agonist: "...the short-acting β₂-agonist Albuterol, which was administered via a metered-dose inhaler, was supplied for the relief of acute respiratory symptoms." • Corticosteroid: none • Long-acting β₂ bronchodilator: none
Outcomes	<p>Primary outcomes: lung function; change in FEV₁, SGRQ averaged over 24 weeks</p> <p>Secondary outcomes: incidence rate of COPD exacerbations, adverse events, FVC at the trough, 6-MWT, post-exercise dyspnoea</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	"Eligible subjects were randomised in a 2:1 ratio to receive oral cilomilast, 15 mg bid, or placebo for 24 weeks."
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated

Cilomilast 039 (Continued)

Description of withdrawals and drop-outs?	Low risk	"The primary reasons for the withdrawal of subjects from the study prior to randomisation were the failure to meet inclusion/exclusion criteria (15.4%) and the presence of adverse effects, including COPD exacerbations (8.5%). More subjects receiving cilomilast than placebo withdrew from the double-blind phase of study (31.8% (n = 137) versus 24.1% (n = 52)."
Baseline profile: anti-cholinergic use	Low risk	54% in cilomilast; 58% placebo used ipratropium
Baseline profile: β 2 agonist use	Low risk	99% in cilomilast; 100% placebo used albuterol. 9% in cilomilast; 12% placebo used salmeterol
Baseline profile: corticosteroid use	Low risk	7% in cilomilast; 8% placebo used triamcinolone. 6% in cilomilast; 7% placebo used beclomethasone

Cilomilast 042

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: stated
Participants	Setting: 98 centres in Australia and New Zealand, Germany, Spain, South Africa and the UK Participants: 700 (15 mg cilomilast: 474, placebo: 226) Baseline characteristics: mean age: 64.6 years, 80% male, mean FEV ₁ % predicted of 49% with 5.1% reversibility, DLCO was 71% predicted, also with higher rates of chronic bronchitis 80.1%. 45% active smokers Inclusion criteria: aged 40-80 years, FEV ₁ /FVC $\leq$ 0.7, FEV ₁ 30%-70% with smoking history > 10 pack-years Exclusion criteria: active tuberculosis, lung cancer and bronchiectasis Total number of participant withdrawals: 122 (26%) and 51 (23%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks, single-blind with placebo Cilomilast 15 mg twice daily Placebo twice daily Concomitant medication <ul style="list-style-type: none"> • Short-acting anticholinergic: 2% in cilomilast; 3% placebo used salbutamol. 3% in cilomilast; 1% placebo used ipratropium • Short-acting β2 agonist: "Albuterol MDI was used as rescue medication" • Corticosteroid: none • Long-acting β2 bronchodilator: none
Outcomes	Primary outcomes: lung function; change in FEV ₁ , SGRQ averaged over 24 weeks Secondary outcomes: incidence rate of COPD exacerbations, summary symptom score, FVC at the trough, 6-MWT, post-exercise dyspnoea

Cilomilast 042 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Participants were randomised in a 2:1 ratio to receive oral cilomilast, 15 mg twice daily, or placebo for 24 weeks
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 51 (23%) placebo, 122 (26%) cilomilast, primarily due to adverse events, of which most were not from COPD exacerbations
Baseline profile: anti-cholinergic use	Unclear risk	No information available
Baseline profile: β_2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 076

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Analysis was done per-protocol population
Participants	Setting: not stated Participants: 59 (15 mg cilomilast: 29, placebo: 30) Baseline characteristics: mean age: 61-62 years, 81% male, 53% active smokers, mean 46 pack-years, 53%-58% FEV ₁ predicted Inclusion criteria: aged 40-80 years, fixed airflow obstruction, smoking history > 10 pack-years Exclusion criteria: not stated Total number of participant withdrawals: 4 (14%) and 2 (7%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks, single-blind with placebo

Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease (Review)

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Cilomilast 076 (Continued)

Cilomilast 15 mg twice daily

Placebo twice daily

Concomitant medication

- Short-acting anticholinergic: "14 of 59 used ipratropium bromide at a constant dosage (eight in the placebo group, six in the cilomilast group)."
- Short-acting β_2 agonist: "All patients were given albuterol for use as required"
- Corticosteroid: none
- Long-acting β_2 bronchodilator: none

Used alongside short-acting β_2 agonists (available to all) and anticholinergic drugs (offered to 24%)

Outcomes

Primary outcomes: change in neutrophil percentage in induced sputum

Secondary outcomes: FEV₁, numbers of subepithelial CD8+ cells, CD 68+ cells, epithelial and subepithelial neutrophils

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Randomised to a ratio of 1:1
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	"One patient was lost to follow-up 3 days after randomisation and another withdrawn for non-compliance 32 days after randomisation. Four patients were withdrawn after adverse events."
Baseline profile: anti-cholinergic use	Unclear risk	No information available
Baseline profile: β_2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 091

Methods

Parallel-group study

Randomisation: randomised, double-blind, placebo-controlled trial

Cilomilast 091 (Continued)

Trial duration: 24 weeks

Intention-to-treat analysis: stated

Participants	<p>Setting: 110 centres in Belgium, Finland, France, Italy, the Netherlands, Norway, Portugal, Spain and the UK</p> <p>Participants: 711 (15 mg cilomilast: 469, placebo: 242)</p> <p>Baseline characteristics: mean age: 64.6 years, 86% male, mean FEV₁ % predicted of 53% with 5.0% reversibility. 38% active smokers</p> <p>Inclusion criteria: FEV₁/FVC ≤ 0.7 with smoking history > 10 pack-years</p> <p>Exclusion criteria: active tuberculosis, lung cancer and bronchiectasis</p> <p>Total number of participant withdrawals: 121 (26%) and 63 (26%) from treatment and control groups, respectively</p>	
Interventions	<p>Run-in: 4 weeks, single-blind with placebo</p> <p>Cilomilast 15 mg twice daily</p> <p>Placebo twice daily</p> <p>Concomitant medication</p> <ul style="list-style-type: none">• Short-acting anticholinergic: 0.9% in cilomilast; 4% placebo used salbutamol. 1% in cilomilast; 3% placebo used ipratropium• Short-acting β₂ agonist: "Albuterol MDI was used as rescue medication"• Corticosteroid: none• Long-acting β₂ bronchodilator: none	
Outcomes	<p>Primary outcomes: lung function; change in FEV₁, SGRQ averaged over 24 weeks</p> <p>Secondary outcomes: incidence rate of COPD exacerbations, summary symptom score, FVC at the trough, 6-MWT, post-exercise dyspnoea</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	"Eligible patients were randomised to receive either SB 207499 or matching placebo in a ratio of 2:1 for 24 weeks."
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated

Cilomilast 091 (Continued)

Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 63 (26%) placebo, 121 (26%) cilomilast, primarily due to adverse events, of which most were not from COPD exacerbations
Baseline profile: anticholinergic use	Unclear risk	No information available
Baseline profile: β 2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 103657

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: stated
Participants	Setting: 103 centres in the USA Participants: 613 (15 mg cilomilast: 296, placebo: 317) Baseline characteristics: mean age: 63.2 years: placebo and 63.1 years; cilomilast. 47% male: placebo and 46% male: cilomilast. Mean FEV ₁ % predicted not available Inclusion criteria: aged $\geq$ 40 years of age. FEV ₁ /FVC $\leq$ 0.7 with smoking history $>$ 10 pack-years. $\leq$ 70%, post-albuterol reversibility $\leq$ 15% or $\leq$ 200 mL (or both), post-albuterol FEV ₁ $\leq$ 70% of predicted normal and at least 1 COPD exacerbation within the 12 months prior to screening Exclusion criteria: not stated Total number of participant withdrawals: 105 (35%) and 76 (24%) from treatment and control groups, respectively
Interventions	Run-in: not stated Cilomilast 15 mg twice daily Placebo twice daily Concomitant medication <ul style="list-style-type: none"> • Short-acting anticholinergic: no information available • Short-acting β2 agonist: no information available • Corticosteroid: no information available • Long-acting β2 bronchodilator: no information available
Outcomes	Primary outcomes: change from baseline to endpoint in trough pre-bronchodilator FEV ₁ . Change in total score of SGRQ averaged over 24 weeks Secondary outcomes: changes from baseline in clinic trough FVC, time to first level 2 or level 3 COPD exacerbation

Cilomilast 103657 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Randomised. No other information given
Randomised?	Low risk	Participants were randomised to receive either 15 mg of cilomilast or matching placebo twice daily
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 76 (24%) placebo, 105 (35%) cilomilast
Baseline profile: anti-cholinergic use	Unclear risk	No information available
Baseline profile: β_2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 110

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Analysis was done per-protocol population
Participants	Setting: 10 centres in the USA Participants: 65 (15 mg cilomilast: 31, placebo: 34) Baseline characteristics: mean age: 64.4 years: placebo and 66.1 years: cilomilast. 67% male: placebo and 84% male: cilomilast. Mean FEV ₁ % predicted not available Inclusion criteria: aged 40-80 years. FEV ₁ /FVC $\leq$ 0.7 with smoking history $>$ 10 pack-years. Post-salbutamol reversibility $\leq$ 15% or 200 mL and a post-salbutamol FEV ₁ at least 1.0 L and between 30% and 70% of predicted Exclusion criteria: not stated Total number of participant withdrawals: 1 (3%) and 1 (3%) from treatment and control groups, respectively

Cilomilast 110 (Continued)

Interventions	Run-in: not stated Cilomilast 15 mg twice daily Placebo twice daily Concomitant medication <ul style="list-style-type: none"> • Short-acting anticholinergic: no information available • Short-acting β_2 agonist: no information available • Corticosteroid: no information available • Long-acting β_2 bronchodilator: no information available
Outcomes	Primary outcomes: change from baseline at endpoint in neutrophils as a percentage of total cells in induced sputum Secondary outcomes: FVC at the trough, sputum macrophages, eosinophils and lymphocytes as a percentage of total cells in induced sputum. Total cell counts in induced sputum

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	All participants were randomised to receive either cilomilast 15 mg or matching placebo
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 1 (3%) placebo, 1 (3%) cilomilast
Baseline profile: anti-cholinergic use	Unclear risk	No information available
Baseline profile: β_2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 111

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial
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Cilomilast 111 (Continued)

Trial duration: 12 weeks

Intention-to-treat analysis: stated

Participants	<p>Setting: 32 centres in the USA, Canada and Australia</p> <p>Participants: 156 (15 mg cilomilast: 79, placebo: 77)</p> <p>Baseline characteristics: mean age: 64.2 years: placebo and 65 years; cilomilast. 66% male: placebo and 65% male: cilomilast. Mean FEV₁ % predicted not available</p> <p>Inclusion criteria: aged 40-80 years. FEV₁/FVC ≤ 0.7 with smoking history > 10 pack-years. Post-salbutamol reversibility ≤ 15% or 200 mL and a post-salbutamol FEV₁ at least 1.0 L and between 30% and 70% of predicted. Baseline RV (from plethysmography) ≥ 120% of predicted RV</p> <p>Exclusion criteria: not stated</p> <p>Total number of participant withdrawals: 15 (19%) and 14 (18%) from treatment and control groups, respectively</p>
Interventions	<p>Run-in: not stated</p> <p>Cilomilast 15 mg twice daily</p> <p>Placebo twice daily</p> <p>Concomitant medication</p> <ul style="list-style-type: none"> • Short-acting anticholinergic: no information available • Short-acting β₂ agonist: no information available • Corticosteroid: no information available • Long-acting β₂ bronchodilator: no information available
Outcomes	<p>Primary outcomes: change from baseline to endpoint in volume of trapped gas (D)</p> <p>Secondary outcomes: lung volume measurements, including SVC and RV, 6-MWT and exertional dyspnoea</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Participants were randomised to receive either 15 mg of cilomilast or matching placebo
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 14 (18%) placebo, 15 (19%) cilomilast

Cilomilast 111 (Continued)

Baseline profile: anti-cholingeric use	Unclear risk	No information available
Baseline profile: β 2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 121

Methods	<p>Parallel-group study</p> <p>Randomisation: randomised, double-blind, placebo-controlled trial</p> <p>Trial duration: 24 weeks</p> <p>Intention-to-treat analysis: stated</p>
Participants	<p>Setting: 22 centres in China</p> <p>Participants: 1018 (15 mg cilomilast: 678, placebo: 340)</p> <p>Baseline characteristics: mean age: 63.9 years: placebo and 64.6 years; cilomilast. 91% male: placebo and 93% male: cilomilast. Mean FEV₁ % predicted not available</p> <p>Inclusion criteria: aged 40-75 years. FEV₁/FVC $\leq$ 0.7 with smoking history > 10 pack-years. Documented history of COPD exacerbations each year for 3 years prior to screening. At least 1 exacerbation in the last year that required oral corticosteroids or antibiotics. Post-salbutamol reversibility $\leq$ 15% or 200 mL and a post-salbutamol FEV₁ at least 1.0 L and between 25% and 70% of predicted. % predicted FRC of $\geq$ 120% from plethysmography</p> <p>Exclusion criteria: not stated</p> <p>Total number of participant withdrawals: 124 (18%) and 35 (10%) from treatment and control groups, respectively</p>
Interventions	<p>Run-in: not stated</p> <p>Cilomilast 15 mg twice daily</p> <p>Placebo twice daily</p> <p>Concomitant medication</p> <ul style="list-style-type: none"> • Short-acting anticholingeric: no information available • Short-acting β2 agonist: no information available • Corticosteroid: no information available • Long-acting β2 bronchodilator: no information available
Outcomes	<p>Primary outcomes: change from baseline to endpoint in trough pre-bronchodilator FEV₁</p> <p>Secondary outcomes: time to first level 2 or level 3 COPD exacerbation. Level 2 is defined as acute worsening of COPD that requires additional treatment or hospital outpatient visit. Level 3 is hospital admission for treatment. Change from baseline to endpoint RV and FRC. Change from baseline total score of SGRQ</p>
Notes	

Cilomilast 121 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Participants were randomised to a 2:1 ratio for cilomilast 15 mg to placebo
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 35 (10%) placebo, 124 (18%) cilomilast
Baseline profile: anti-cholinergic use	Unclear risk	No information available
Baseline profile: β_2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 156

Methods	<p>Parallel-group study</p> <p>Randomisation: randomised, double-blind, placebo-controlled trial</p> <p>Trial duration: 24 weeks</p> <p>Intention-to-treat analysis: stated</p>
Participants	<p>Setting: 132 centres in USA and Canada</p> <p>Participants: 825 (15 mg cilomilast: 418, placebo: 407)</p> <p>Baseline characteristics: mean age: 64.4 years: placebo and 64.5 years; cilomilast. 62% male: placebo and 56% male: cilomilast > 50% predicted FEV₁ for both groups</p> <p>Inclusion criteria: aged 40-80 years. FEV₁/FVC $\leq$ 0.7 with smoking history > 10 pack-years. Post-salbutamol reversibility $\leq$ 15% or 200 mL and a post-salbutamol FEV₁ at least 1.0 L and between 30% and 70% of predicted</p> <p>Exclusion criteria: not stated</p> <p>Total number of participant withdrawals: 143 (34%) and 96 (24%) from treatment and control groups, respectively</p>
Interventions	<p>Run-in: not stated</p> <p>Cilomilast 15 mg twice daily</p>

Cilomilast 156 (Continued)

Placebo twice daily

Concomitant medication

- Short-acting anticholinergic: 8.1% in cilomilast; 8.6% placebo used salbutamol. 1.7% in cilomilast; 2% placebo used ipratropium bromide
- Short-acting β 2 agonist: "Albuterol MDI was used as rescue medication"
- Corticosteroid: none
- Long-acting β 2 bronchodilator: none

Outcomes

Primary outcomes: change from baseline to endpoint in trough pre-bronchodilator FEV₁. Change in total score of SGRQ averaged over 24 weeks

Secondary outcomes: post-exercise breathlessness, clinic trough FVC, time to first level 2 or level 3 COPD exacerbation

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Participants were randomised to receive either 15 mg of cilomilast or matching placebo twice daily
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 96 (24%) placebo, 143 (34%) cilomilast
Baseline profile: anti-cholinergic use	Unclear risk	No information available
Baseline profile: β 2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 157

Methods

Parallel-group study

Randomisation: randomised, double-blind, placebo-controlled trial

Trial duration: 52 weeks

Cilomilast 157 (Continued)

Intention-to-treat analysis: stated

Participants	<p>Setting: 137 centres from 18 countries</p> <p>Participants: 907 (15 mg cilomilast: 455, placebo: 452)</p> <p>Baseline characteristics: mean age: 63.3 years: placebo and 64.6 years; cilomilast. 73% male: placebo and 78% male: cilomilast. 42% current smokers</p> <p>Inclusion criteria: aged 40-80 years. FEV₁/FVC ≤ 0.7 with smoking history > 10 pack-years. Poor re- versibility of airway obstruction, defined by ≤ 10% of predicted normal or ≤ 200 mL (or both) increase in FEV₁ after administration of salbutamol 400 µg via MDI at screening; post-salbutamol FEV₁ of between 30%-70% predicted normal at screening</p> <p>Exclusion criteria: not stated</p> <p>Total number of participant withdrawals: 167 (37%) and 121 (27%) from treatment and control groups, respectively</p>	
Interventions	<p>Run-in: not stated</p> <p>Cilomilast 15 mg twice daily</p> <p>Placebo twice daily</p> <p>Concomitant medication</p> <ul style="list-style-type: none">• Short-acting anticholinergic: no information available• Short-acting β2 agonist: no information available• Corticosteroid: no information available• Long-acting β2 bronchodilator: no information available	
Outcomes	<p>Primary outcomes: mean change from baseline in trough pre-bronchodilator FEV₁ averaged over 52 weeks. Incidence rate of level 2 (moderate) and level 3 (severe) COPD exacerbations during the treat- ment period</p> <p>Secondary outcomes: time to first level 2 or level 3 COPD exacerbation. Quality of life determined by SGRQ</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Participants were randomised to receive either 15 mg of cilomilast or match- ing placebo twice daily
Method of randomisation described?	Unclear risk	A randomisation criteria was used. No other information available
Blinding?	Low risk	Double-blinded
Method of blinding de- scribed?	Unclear risk	Not stated

Cilomilast 157 (Continued)

Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 121 (27%) placebo, 167 (37%) cilomilast
Baseline profile: anticholinergic use	Unclear risk	No information available
Baseline profile: β_2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 168

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Intention-to-treat analysis: not stated
Participants	Setting: 42 centres in the USA Participants: 306 (15 mg cilomilast: 203, placebo: 103) Baseline characteristics: mean age: 64.3 years: placebo and 65.0 years; cilomilast. 64% male: placebo and 70% male: cilomilast Inclusion criteria: pre-albuterol $FEV_1/FVC \leq 0.7$. Post-albuterol FEV_1 between 30% and 70% of predicted Exclusion criteria: not stated Total number of participant withdrawals: 61 (30%) and 14 (14%) from treatment and control groups, respectively
Interventions	Run-in: not stated Cilomilast 15 mg twice daily Placebo twice daily Concomitant medication <ul style="list-style-type: none"> • Short-acting anticholinergic: no information available • Short-acting β_2 agonist: no information available • Corticosteroid: no information available • Long-acting β_2 bronchodilator: no information available
Outcomes	Primary outcomes: no primary efficacy or safety analyses were defined. Descriptive statistics of change from baseline in minimum and maximum heart rate via 24-h Holter monitoring reported Secondary outcomes: no secondary efficacy or safety analyses were defined
Notes	
Risk of bias	

Cilomilast 168 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Participants were randomised at 2:1 ratio of cilomilast to placebo
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 14 (14%) placebo, 61 (30%) cilomilast
Baseline profile: anti-cholinergic use	Unclear risk	No other information available
Baseline profile: β_2 agonist use	Unclear risk	No other information available
Baseline profile: corticosteroid use	Unclear risk	No other information available

Cilomilast 180

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 18 weeks Intention-to-treat analysis: stated
Participants	Setting: 34 centres in the USA, Canada and South America 2) Participants: 199 (15 mg cilomilast: 97, placebo: 102) Baseline characteristics: mean age: 64.7 years: placebo and 63.7 years; cilomilast. 76% male: placebo and 69% male: cilomilast Inclusion criteria: age at least 40 years. $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years. Baseline $FEV_1 < 70\%$ predicted normal. Moderate to severe chronic dyspnoea defined by baseline Dyspnoea Index focal score ≤ 7 , evidence of hyperinflation defined by RFRC at least 140% of predicted. Exercise limitation, defined as peak symptom limited $VO_2 < 75\%$ Exclusion criteria: not stated Total number of participant withdrawals: 24 (25%) and 13 (13%) from treatment and control groups, respectively
Interventions	Run-in: not stated Cilomilast 15 mg twice daily

Cilomilast 180 (Continued)

Placebo twice daily

Concomitant medication

- Short-acting anticholinergic: no information available
- Short-acting β_2 agonist: no information available
- Corticosteroid: no information available
- Long-acting β_2 bronchodilator: no information available

Outcomes	<p>Primary outcomes: change from baseline at endpoint in RFRC</p> <p>Secondary outcomes: change from baseline at endpoint in IC during exercise, exertional dyspnoea as measured by the modified Borg scale</p>
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	Participants were randomised to receive either 15 mg of cilomilast or matching placebo twice daily
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Total number of participants withdrawn 13 (13%) placebo, 24 (25%) cilomilast
Baseline profile: anti-cholinergic use	Unclear risk	No information available
Baseline profile: β_2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Cilomilast 181

Methods	<p>Parallel-group study</p> <p>Randomisation: randomised, double-blind, placebo-controlled trial</p> <p>Trial duration: 13 weeks</p> <p>Analysis was done per-protocol population</p>
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Cilomilast 181 (Continued)

Participants	<p>Setting: 27 centres in Australia, Canada, Finland, Ireland, Lithuania, Norway, Romania, Slovakia, Slovenia, South Africa, Sweden and the UK</p> <p>Participants: 127 (15 mg cilomilast: 65, placebo: 62)</p> <p>Baseline characteristics: mean age: 63.4 years: placebo and 61.4 years; cilomilast. 76% male: placebo and 72% male: cilomilast</p> <p>Inclusion criteria: aged 40-80 years. FEV₁/FVC ≤ 0.7 with smoking history > 10 pack-years. Post-bronchodilator FEV₁ between 40% and 80% predicted normal. Poor reversibility of ≤ 10% or 200 mL increase in FEV₁</p> <p>Exclusion criteria: not stated</p> <p>Total number of participant withdrawals: 8 (12%) and 6 (10%) from treatment and control groups, respectively</p>
Interventions	<p>Run-in: not stated</p> <p>Cilomilast 15 mg twice daily</p> <p>Placebo twice daily</p> <p>Concomitant medication</p> <ul style="list-style-type: none">• Short-acting anticholinergic: no information available• Short-acting β2 agonist: no information available• Corticosteroid: no information available• Long-acting β2 bronchodilator: no information available
Outcomes	<p>Primary outcome: change from baseline at endpoint in CD68+ (macrophages) and CD8+ (cytotoxic T-lymphocytes) per unit area of tissue</p> <p>Secondary outcome: change from baseline in numbers of sub-epithelial cells per unit area in biopsy for neutrophil elastase positive (ne+) cells, CD4+, IL-8 mRNA positive cells, TNF-alpha mRNA positive cells</p>
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment (selection bias)	Unclear risk Randomised. No other information available
Randomised?	Low risk Participants were randomised to receive either 15 mg of cilomilast or matching placebo twice daily
Method of randomisation described?	Unclear risk Not stated
Blinding?	Low risk Double-blinding
Method of blinding described?	Unclear risk Not stated
Description of withdrawals and drop-outs?	Low risk Total number of participants withdrawn 6 (10%) placebo, 8 (12%) cilomilast

Cilomilast 181 (Continued)

Baseline profile: anti-cholingeric use	Unclear risk	No other information available
Baseline profile: β 2 agonist use	Unclear risk	No other information available
Baseline profile: corticosteroid use	Unclear risk	No other information available

Compton 2001

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 6 weeks Intention-to-treat analysis: stated
Participants	Setting: 60 centres in Austria, France, Germany, the Netherlands and the UK Participants: 424 (5 mg cilomilast: 109, 10 mg cilomilast: 102, 15 mg cilomilast: 107, placebo: 106) Baseline characteristics: mean age: 62-63 years, 75%-78% male, mean FEV ₁ % predicted of 46.8%, mean smoking history of 36-43 (SD 22.4) pack-years Inclusion criteria: FEV ₁ /FVC $\leq$ 0.7 with smoking history > 10 pack-years Exclusion criteria: asthma, poorly controlled COPD needing hospital visit 6 weeks before study, recent COPD exacerbations or recent corticosteroid use Total number of participant withdrawals: 18 (17%) and 17 (16%) from treatment and control groups, respectively
Interventions	Run-in: 2 weeks, single-blind. Placebo tablets to assess compliance Cilomilast 5 mg, 10 mg, 15 mg twice daily Placebo twice daily Concomitant medication <ul style="list-style-type: none"> Short-acting anticholingeric: 382 (90%) participants were given concomitant treatment for COPD during the study; 267 (70%) salbutamol and 115 (30%) ipratropium bromide Short-acting β2 agonist: salbutamol used in 70% Corticosteroid: none Long-acting β2 bronchodilator: none
Outcomes	Primary outcomes: lung function: change in FEV ₁ , SGRQ Secondary outcomes: peak expiratory flow and FVC, the first dose effect of active treatment on FEV ₁
Notes	Post-bronchodilator results not given so pre-bronchodilator values used in analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
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Compton 2001 (Continued)

Allocation concealment (selection bias)	Unclear risk	Described as randomised. No other information available
Randomised?	Low risk	"Eligible patients were randomly assigned to receive a 5, 10, or 15 mg tablet of cilomilast twice daily (morning and evening) or matching placebo for 6 weeks."
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	"14 patients (13%) taking cilomilast 15 mg had adverse events leading to patient withdrawal, as did 12 each in the 5 and 10 mg groups (11 and 12%, respectively) and eight (8%) in the placebo group."
Baseline profile: anti-cholinergic use	Unclear risk	Information not available
Baseline profile: β_2 agonist use	Low risk	102 (24%) participants had been taking long-acting β_2 -agonists; e.g. salmeterol, formoterol
Baseline profile: corticosteroid use	Low risk	331 (78%) individuals had taken other medications for their COPD, the most common being inhaled steroids. 229 (54%) took beclomethasone, budesonide or fluticasone

COPD safety pool

Methods	14 double-blind and placebo-controlled studies (Roflumilast FK1 101 ; Roflumilast FK1 103 ; Roflumilast IN-108 ; Roflumilast M2-107 ; Roflumilast M2-110 ; Roflumilast M2-111 ; Roflumilast M2-112 ; Roflumilast M2-118 ; Roflumilast M2-119 ; Roflumilast M2-121 ; Roflumilast M2-124 ; Roflumilast M2-125 ; Roflumilast M2-127 ; Roflumilast M2-128)	
Participants	See individual studies	
Interventions	Roflumilast 500 μ g once daily Roflumilast 250 μ g once daily Placebo once daily	
Outcomes		
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	See individual studies
Randomised?	Low risk	Randomised

COPD safety pool (Continued)

Method of randomisation described?	Unclear risk	See individual studies
Blinding?	Unclear risk	Double-blind
Method of blinding described?	Unclear risk	See individual studies
Description of withdrawals and drop-outs?	Unclear risk	See individuals studies
Baseline profile: anti-cholinergic use	Unclear risk	See individuals studies
Baseline profile: β 2 agonist use	Unclear risk	See individuals studies
Baseline profile: corticosteroid use	Unclear risk	See individuals studies

RO-2455-301-RD (ACROSS)

Methods	<p>Parallel-group study</p> <p>Randomisation: randomised, double-blind, placebo-controlled trial</p> <p>Trial duration: 24 weeks</p> <p>Intention-to-treat analysis: stated</p>
Participants	<p>Setting: 43 centres in mainland China, Hong Kong and Singapore</p> <p>Participants: 626 (500 μg roflumilast: 313, placebo: 313)</p> <p>Baseline characteristics: mean age: 64 years, 91% male, mean FEV₁% predicted of 36%, mean smoking history of 37.2 pack-years for roflumilast and 37.5 pack-years for placebo) or current smokers (24% and 29%, respectively)</p> <p>Inclusion criteria: Chinese, Malay or Indian ethnicity, age 40-80 years with severe-very severe COPD FEV₁/FVC $\leq$ 0.7, and post-bronchodilator FEV₁ $\leq$ 50%. Current smokers or ex-smokers with smoking history > 10 pack-years or current smokers. 12-month history of COPD and $\geq$ 14 puffs of rescue medication during the week prior to randomisation</p> <p>Exclusion criteria: primary bronchiectasis, cystic fibrosis, bronchiolitis, lung resection, lung cancer, interstitial lung disease, or active TB, lower respiratory tract infection, diagnosis of asthma at < 40 years of age, or α₁-antitrypsin deficiency</p> <p>Total number of participant withdrawals: 67 (21.4%) and 50 (16%) from treatment and control groups, respectively</p>
Interventions	<p>Run-in: 4 weeks, single-blind. Placebo tablets to assess suitability</p> <p>Roflumilast 500 μg once daily</p> <p>Placebo once daily</p> <p>Concomitant medication</p>

RO-2455-301-RD (ACROSS) (Continued)

Participants were allowed to continue taking fixed combinations of ICS plus LABA or LAMA monotherapy (e.g. tiotropium) if taken at a stable dose for at least 6 months prior to the run-in period. SAMAs (e.g., ipratropium) were allowed at a constant daily dose as concomitant medication if taken on a regular basis for at least 4 weeks prior to study inclusion. All other COPD treatments were not allowed

Outcomes	<p>Primary outcomes: lung function; change in pre-bronchodilator FEV₁</p> <p>Secondary outcomes: change in post-bronchodilator FEV₁, FVC, incidence rate of COPD exacerbations, time to first COPD exacerbation, transition dyspnoea index, proportional of participants experiencing a COPD exacerbation, adverse events, changes in body weight, laboratory values, vital signs and physical examination findings</p>
Notes	<p>NCT number: NCT01313494</p> <p>Funded by Takeda</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling.
Randomised?	Low risk	The investigators used an automated, interactive voice-response system to randomly assign participants.
Method of randomisation described?	Low risk	The sponsor generated a list of participant numbers using a pseudorandom number generator
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	Tablets were identical in appearance.
Description of withdrawals and drop-outs?	Unclear risk	Total number of participants that discontinued 50 (16%) placebo, 67 (21.4%) roflumilast
Baseline profile: anti-cholinergic use	Low risk	LAMA: 17.9% for placebo; 20.4% for roflumilast SAMA: 18.2% for placebo; 17.3% for roflumilast
Baseline profile: β 2 agonist use	Unclear risk	No information available. SABA allowed
Baseline profile: corticosteroid use	Low risk	ICS/LABA: 55.9% for placebo; 59.7% for roflumilast

RO-2455-404-RD (REACT)

Methods	<p>Parallel-group study</p> <p>Randomisation: randomised, double-blind, placebo-controlled trial</p> <p>Trial duration: 52 weeks</p> <p>Intention-to-treat analysis: stated</p>
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RO-2455-404-RD (REACT) (Continued)

Participants	<p>Setting: 203 centres in 21 countries (see online appendix)</p> <p>Participants: 1945 (500 µg roflumilast: 969; placebo: 966)</p> <p>Baseline characteristics: mean age: 65 years, 75% male, mean FEV₁% predicted of 35%, mean smoking history of 48 pack-years for roflumilast and 48 pack-years for placebo) or current smokers (42% and 45%, respectively)</p> <p>Inclusion criteria: ≥ 40 years with a smoking history of at least 20 pack-years and a diagnosis of chronic obstructive pulmonary disease with severe airflow limitation (confirmed by a post-bronchodilator FEV₁/FVC ratio < 0.70 and a post-bronchodilator FEV₁ of ≤ 50% predicted), symptoms of chronic bronchitis, and a history of at least two exacerbations in the previous year</p> <p>Participants must have been taking an ICS–LABA combination for 12 months before the study and a constant dose of an ICS–LABA fixed combination for at least 3 months before enrolment, with placebo tablet compliance of 80%–125% during the 4-week baseline observation period and with a total cough and sputum score of ≥ 14 (in which the score was a sum of daily scores on 4-point scales for cough and sputum) recorded in a daily diary during the week preceding the randomisation visit</p> <p>Exclusion criteria: chronic obstructive pulmonary disease exacerbation that was ongoing during the baseline period, or had a diagnosis of asthma or other major lung disease</p> <p>Total number of participant withdrawals: 269 (28%) and 192 (20%) from treatment and control groups, respectively</p>
Interventions	<p>Run-in: 4 weeks, single-blind. Placebo tablets to assess suitability</p> <p>Roflumilast 500 µg once daily</p> <p>Placebo once daily</p> <p>Concomitant medication</p> <p>All participants used a fixed-dose ICS–LABA combination during the baseline and treatment period. If a participant had an exacerbation that needed additional treatment during the study, the investigator could give them up to 40 mg prednisolone, administered systemically, per day for 7–14 days. In the case of purulent sputum or suspected bacterial infection, additional antibiotic therapy was allowed</p> <p>The use of the following treatments was not allowed: oral and parenteral glucocorticosteroids (except to treat acute exacerbations), LABA or ICS mono therapy, SAMA, and any short-acting β₂ agonists (with the exception of salbutamol) or oral β₂ agonists</p> <p>Participants already taking inhaled tiotropium bromide (a LAMA) were allowed to continue this treatment</p>
Outcomes	<p>Primary outcomes: rate of moderate-to-severe chronic obstructive pulmonary disease exacerbations per patient per year. This was assessed in several ways: rate of exacerbations; % with exacerbation; time to first, second or third exacerbation; NNTB to avoid 1 moderate to severe exacerbation</p> <p>Secondary outcomes: change in post-bronchodilator FEV₁, rate of severe chronic obstructive pulmonary disease exacerbations per patient per year, laboratory values, vital signs, physical examination findings, changes in bodyweight and body-mass index, and reported adverse events, including mortality</p>
Notes	<p>NCT number: NCT01329029</p> <p>Sponsored by Takeda</p>
Risk of bias	
Bias	Authors' judgement Support for judgement

RO-2455-404-RD (REACT) (Continued)

Allocation concealment (selection bias)	Low risk	All parties involved in the study were masked to treatment assignment
Randomised?	Low risk	Randomised
Method of randomisation described?	Low risk	Enrolled participants were randomly assigned in a 1:1 ratio, with a block size of 4, by a computerised central randomisation system, the Interactive Voice Response System–Interactive Web Response System (PPD Global Limited, Cambridge, UK)
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	Roflumilast and placebo were supplied as identical yellow triangular tablets in wallet cards containing 40 tablets
Description of withdrawals and drop-outs?	Unclear risk	269 participants (28%) discontinued from study in the roflumilast group and 192 (20%) discontinued from the placebo group
Baseline profile: anti-cholinergic use	Unclear risk	LAMA: 69% for placebo; 70% for roflumilast
Baseline profile: β_2 agonist use	Unclear risk	No group differences stated; however 1900 (98%) of 1935 participants were using a combination of ICS–LABA according to the protocol
Baseline profile: corticosteroid use	Unclear risk	As above

Roflumilast DAL-MD-01

Methods	<p>Parallel-group study</p> <p>Randomisation: randomised, double-blind, placebo-controlled trial</p> <p>Trial duration: 12 weeks</p> <p>Intention-to-treat analysis: stated</p>
Participants	<p>Setting: single centre in USA</p> <p>Participants: 27 (500 µg roflumilast: 11, placebo: 16)</p> <p>Baseline characteristics: mean age: 62 years, 64% male, mean FEV₁% predicted of 45%, mean smoking history of 44 pack-years for roflumilast and 47 pack-years for placebo) or current smokers (63% and 55%, respectively)</p> <p>Inclusion criteria: > 40 years old with a diagnosis of moderate-to-severe COPD as defined by Global Initiative for Chronic Obstructive Lung Disease criteria, current or former cigarette smokers with more than 10 pack-years of total consumption, chronic bronchitis defined by chronic cough and sputum production lasting at least 3 months for 2 consecutive years</p> <p>Exclusion criteria: asthma as defined by the American Thoracic Society/European Respiratory Society guidelines, clinically significant bronchiectasis, known sensitivity to roflumilast, the use of other methylxanthines (specifically theophylline) within 1 month of screening, changes to maintenance COPD therapy within 1 month of screening</p>

Roflumilast DAL-MD-01 (Continued)

Total number of participant withdrawals: 1 (9%) and 1 (6%) from treatment and control groups, respectively

Interventions	<p>Run-in: no run in</p> <p>Roflumilast 500 µg once daily</p> <p>Placebo once daily</p> <p>Concomitant medication</p> <p>Allowed, except for theophylline. For roflumilast and placebo groups respectively: LAMA was used by 8 (50%) and 6 (55%); ICS or LABA/ICS was used by 10 (63%) 6 (55%)</p>
Outcomes	<p>Primary outcomes: change in induced sputum AcPGP at 12 weeks post-randomisation in an intention-to-treat analysis</p> <p>Secondary outcomes: changes in plasma AcPGP, sputum neutrophil counts, additional sputum biomarkers, 6MWT, the Breathlessness Cough and Sputum Scale, SGRQ scores, and changes in post-bronchodilator FEV₁ at the 12-week visit</p>
Notes	NCT number: NCT01572948

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Unclear risk	Randomised
Method of randomisation described?	Unclear risk	Sealed envelope. Block randomisation schema using a block size of four and an allocation ratio of 1:1. Block randomization was stratified by current smoking status and ICS use
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	Identical white tablets containing a 30-day supply of either roflumilast, 500 mg or placebo
Description of withdrawals and drop-outs?	Low risk	No withdrawals described
Baseline profile: anti-cholinergic use	Unclear risk	Not stated
Baseline profile: β ₂ agonist use	Unclear risk	Not stated
Baseline profile: corticosteroid use	Unclear risk	Not stated

Roflumilast FK1 101

Methods	<p>Parallel-group study</p> <p>Randomisation: randomised, double-blind, placebo-controlled trial</p>
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Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease (Review)

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Roflumilast FK1 101 (Continued)

Trial duration: 26 weeks

Intention-to-treat analysis: stated

Participants	<p>Setting: not stated</p> <p>Participants: 516 (roflumilast 250 µg: 175, roflumilast 500 µg: 169, placebo: 172)</p> <p>Baseline characteristics: median age: 61-62 years. 72% male. Mean 38 to 63 pack-years. 53% current smokers</p> <p>Inclusion criteria: aged 40-75 years. $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years. Reversibility < 12% or 200 mL post-bronchodilator FEV_1 35%-75% predicted</p> <p>Exclusion criteria: not stated</p> <p>Participant withdrawals: not stated</p>
Interventions	<p>Run-in: 2 weeks with placebo</p> <p>Roflumilast 500 µg once daily</p> <p>Roflumilast 250 µg once daily</p> <p>Placebo once daily</p> <p>Concomitant medication</p> <ul style="list-style-type: none"> • Short-acting anticholinergic: allowed at a constant daily dose for those treated before with anticholinergics on a constant dosage • Short-acting β_2 agonist: salbutamol was allowed as rescue medication • Corticosteroid: none • Long-acting β_2 bronchodilator: none
Outcomes	<p>Primary outcomes: post-bronchodilator FEV_1 and FEF between 25%-75% of vital capacity</p> <p>Secondary outcomes: number of moderate or severe COPD exacerbations which required treatment with oral steroids</p>
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment (selection bias)	Unclear risk Randomised. No other information available
Randomised?	Low risk Participants randomised in either roflumilast 250 µg, roflumilast 500 µg or placebo groups
Method of randomisation described?	Unclear risk Not stated
Blinding?	Low risk Double-blinded
Method of blinding described?	Unclear risk Not stated

Roflumilast FK1 101 (Continued)

Description of withdrawals and drop-outs?	High risk	Not stated
Baseline profile: anti-cholinergic use	Unclear risk	No information available
Baseline profile: β_2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Roflumilast FK1 103

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: stated
Participants	Setting: not stated Participants: 518 (roflumilast 500 μ g: 200, placebo: 186) Baseline characteristics: mean age: 60 years. 75% male. 62% current smokers. Average of 35 pack-years Inclusion criteria: aged 40-75 years. $FEV_1/FVC \leq 0.7$. Post-bronchodilator FEV_1 35%-75% of predicted. FEV_1 reversibility $\leq 12\%$ and ≤ 200 mL. Pre-bronchodilator $FEV_1/FVC \leq 70\%$ Exclusion criteria: not stated Participant withdrawals not stated
Interventions	Run-in: 2 weeks with placebo Roflumilast 500 μ g once daily for 24 weeks Roflumilast 500 μ g once daily for 12 weeks. Placebo once daily for following 12 weeks Concomitant medication <ul style="list-style-type: none"> • Short-acting anticholinergic: all medications were withdrawn except constant dose short-acting anticholinergics • Short-acting β_2 agonist: as rescue medication • Corticosteroid: none • Long-acting β_2 bronchodilator: none Used alongside short-acting β_2 agonists (available to all)
Outcomes	Primary outcomes: results for 12/24 week post-bronchodilator FEV_1
Notes	
Risk of bias	

Roflumilast FK1 103 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	No information available
Randomised?	Low risk	"After randomisation, patients received placebo or roflumilast 500 µg once daily for 24 weeks or roflumilast 500 µg for 12 weeks followed by placebo for 12 weeks"
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	High risk	Not stated
Baseline profile: anti-cholinergic use	Unclear risk	No further information available
Baseline profile: β2 agonist use	Unclear risk	No further information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Roflumilast FLUI-2011-77

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 6 months Intention-to-treat analysis: stated Responder analysis for the most part
Participants	Setting: 2 centres Participants: 41 (500 µg roflumilast: 30, placebo: 11) Baseline characteristics: not stated Inclusion criteria: not stated Exclusion criteria: not stated Total number of participant withdrawals: not stated
Interventions	Run-in: not stated Concomitant medication: not stated

Roflumilast FLUI-2011-77 (Continued)

Outcomes **Primary outcomes:** postbronchodilation: spirometry, body plethysmography, 6MWT, Patient reported outcomes

Secondary outcomes: not stated

Notes NCT number: NCT01480661

Funded by Takeda

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Low risk	Randomised
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Unclear risk	Not stated
Baseline profile: anti-cholinergic use	Unclear risk	Not stated
Baseline profile: β 2 agonist use	Unclear risk	Not stated
Baseline profile: corticosteroid use	Unclear risk	Not stated

Roflumilast IN-108

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Intention-to-treat analysis: not stated
Participants	Setting: 5 centres in India Participants: 118 recruited (roflumilast 500 μ g: 47; roflumilast 200 μ g: 46, placebo: 25) Baseline characteristics: mean age: 60 years. 98% male. 41% current smokers. Post-bronchodilator FEV ₁ of 57%-61%. Average of 25 pack-years Inclusion criteria: not stated Exclusion criteria: not stated

Roflumilast IN-108 (Continued)

Participant withdrawals: roflumilast 500 µg: 13 (28%); roflumilast 200 µg: 7 (15%) and 10 (40%) from control group

Interventions	Roflumilast 250 µg once daily Roflumilast 500 µg once daily Placebo once daily Concomitant medication <ul style="list-style-type: none">• Short-acting anticholinergic: not stated• Short-acting β2 agonist: not stated• Corticosteroid: none• Long-acting β2 bronchodilator: not stated
Outcomes	To study the safety and tolerability of roflumilast 250 µg versus roflumilast 500 µg versus placebo To investigate the effect of roflumilast 250 µg versus roflumilast 500 µg versus placebo on pulmonary function, efficacy rating and exacerbation rate To evaluate plasma levels of roflumilast and its major metabolite roflumilast N-oxide Note: only the third objective is discussed here
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment (selection bias)	Unclear risk Not stated
Randomised?	Low risk Randomised
Method of randomisation described?	Unclear risk Not stated
Blinding?	Low risk Double-blind
Method of blinding described?	Unclear risk Not stated
Description of withdrawals and drop-outs?	Low risk Data as above
Baseline profile: anti-cholinergic use	Unclear risk No information available
Baseline profile: β2 agonist use	Unclear risk No information available
Baseline profile: corticosteroid use	Unclear risk No information available

Roflumilast JP-706

Methods	Parallel-group study
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Roflumilast JP-706 (Continued)

Randomisation: randomised, double-blind, placebo-controlled trial

Trial duration: 24 weeks

Intention-to-treat analysis: not stated

Participants	<p>Setting: Japan</p> <p>Participants: 600 (roflumilast 250 µg: 205, roflumilast 500 µg: 204, placebo: 191)</p> <p>Baseline characteristics: mean age: 70 years. 96% male. Post-bronchodilator FEV₁ not stated. Average of 56 pack-years. 37% current smokers</p> <p>Inclusion criteria: not stated</p> <p>Exclusion criteria: not stated</p> <p>Total number of participant withdrawals: not stated</p>
Interventions	<p>Run-in: single-blind 4 weeks with placebo</p> <p>Roflumilast 500 µg once daily</p> <p>Roflumilast 250 µg once daily</p> <p>Placebo once daily</p> <p>Concomitant medication</p> <ul style="list-style-type: none"> • Short-acting anticholinergic: used at a constant daily dose • Short-acting β₂ agonist: not stated • Corticosteroid: not stated • Long-acting β₂ bronchodilator: not stated
Outcomes	<p>To investigate the efficacy and safety after 24-week treatment of APTA-2217 (roflumilast) at doses of 500 µg and 250 µg in people with COPD using placebo as a control</p> <p>To investigate the pharmacokinetics of roflumilast and roflumilast N-oxide after repeated administration of APTA-2217 at doses of 500 µg and 250 µg</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Low risk	Randomised
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blind
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	High risk	Not described

Roflumilast JP-706 (Continued)

Baseline profile: anti-cholinergic use	Low risk	Constant dose of short anticholinergics used in 35% (roflumilast 500 µg), 33% (roflumilast 200 µg) and 33% (placebo), respectively
Baseline profile: β2 agonist use	Unclear risk	Not described
Baseline profile: corticosteroid use	Unclear risk	Not described

Roflumilast M2-107

Methods	<p>Parallel-group study</p> <p>Randomisation: randomised, double-blind, placebo-controlled trial</p> <p>Trial duration: 24 weeks</p> <p>Intention-to-treat analysis: stated</p>
Participants	<p>Setting: 159 centres in Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, South Africa, Spain and the UK</p> <p>Participants: 1411 (roflumilast 250 µg: 576, roflumilast 500 µg: 555, placebo: 280)</p> <p>Baseline characteristics: median age: 64 years. 74% male. Post-bronchodilator FEV₁ is 51% for both groups. Average of 42 pack-years. 45% current smokers</p> <p>Inclusion criteria: aged ≥ 40 with history of COPD > 12 months. FEV₁ < 50% predicted, FEV₁/FVC ≤ 0.7 with smoking history > 10 pack-years. Reversibility < 12% or 200 mL. Mean post-bronchodilator FEV₁ 30%-80% predicted</p> <p>Exclusion criteria: asthma, lung cancer or bronchiectasis, long-term oxygen treatment, recent exacerbation that required a course of systemic corticosteroids, emergency room treatment or hospital admission within 4 weeks before the run-in period</p> <p>Total number of participant withdrawals: 124 (22%) and 32 (11%) from treatment and control groups, respectively</p>
Interventions	<p>Run-in: 4 weeks with placebo</p> <p>Roflumilast 500 µg once daily</p> <p>Roflumilast 250 µg once daily</p> <p>Placebo once daily</p> <p>Concomitant medication</p> <ul style="list-style-type: none"> • Short-acting anticholinergic: used at a constant daily dose • Short-acting β2 agonist: salbutamol as rescue medication • Corticosteroid: none • Long-acting β2 bronchodilator: none
Outcomes	<p>Primary outcomes: post-bronchodilator FEV₁ and SGRQ total score</p> <p>Secondary outcomes: change from baseline in pre-bronchodilator FEV₁, post-bronchodilator FVC, post-bronchodilator FEV in 6 seconds and FVC, FEF rate between 25%-75% of vital capacity and number of moderate or severe COPD exacerbations</p>

Roflumilast M2-107 (Continued)

Notes There is inconsistency in the quoting of statistical errors. Within the text and Table 2, data are quoted as "least squares means and SD", however in Figures 2 and 3, SE bars are shown. It is more likely that the results represent SE and not SD

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	"No person involved in data analysis had knowledge of the randomisation sequence"
Randomised?	Low risk	"Treatment was assigned by the investigators with sequential study numbers according to a block randomisation list in ratios of 2:2:1 (Roflumilast 250 µg, Roflumilast 500 µg, Placebo)."
Method of randomisation described?	Low risk	"The randomisation sequence was generated by ALTANA Pharma AG in a blinded manner"
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	"Medication boxes were labelled with the study protocol number, randomisation number, and visit code; coding prevented the investigator and people at the study centre from knowing which medication was given."
Description of withdrawals and drop-outs?	Low risk	100 participants discontinued from study from the roflumilast 250 µg group, 124 from the roflumilast 500 µg group and 32 from the placebo group
Baseline profile: anti-cholinergic use	Unclear risk	No information available
Baseline profile: β2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Roflumilast M2-110

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 24 weeks Intention-to-treat analysis: not stated
Participants	Setting: 36 centres in Argentina, Canada, Columbia, Mexico, Peru and the USA Participants: estimated enrolment of 1000 participants Baseline characteristics: not stated Inclusion criteria: <ul style="list-style-type: none"> Clinical diagnosis of COPD Currently stable COPD with no change in COPD treatment in the prior 4 weeks Exclusion criteria:

Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease (Review)

Roflumilast M2-110 (Continued)

- Clinical diagnosis of asthma
- Poorly controlled COPD
- Regular need for daily oxygen therapy

Total number of participant withdrawals: not stated

Interventions	Roflumilast 500 µg daily versus placebo
Outcomes	Primary outcomes: pulmonary function Secondary outcomes: exacerbation rate, quality of life, symptoms, use of rescue medication, safety and tolerability
Notes	ClinicalTrials.gov Identifier: nCT00062582

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Low risk	Randomised
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blind
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Unclear risk	Not stated
Baseline profile: anti-cholinergic use	Unclear risk	Not stated
Baseline profile: β2 agonist use	Unclear risk	Not stated
Baseline profile: corticosteroid use	Unclear risk	Not stated

Roflumilast M2-111

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 52 weeks Intention-to-treat analysis: stated
Participants	Setting: M2-111 was conducted in 188 centres in 6 countries, and M2-112 in 159 centres in 14 countries Participants: data combined with M2-112 showing 2686 (roflumilast 500 µg: 1327, placebo: 1359), suggesting total n for this study was 1173.

Roflumilast M2-111 (Continued)

Baseline characteristics: severe COPD according to GOLD criteria grades III and IV. Mean age: 64-65 years. 72% male

Inclusion criteria: aged ≥ 40 years. Post-bronchodilator FEV₁ < 50% predicted. Reversibility < 15%. Mean post-bronchodilator FEV₁ 42%. FEV₁/FVC ≤ 0.7 with smoking history > 10 pack-years. 40% current smokers, 60% ex-smokers; average 46-48 pack-years

Exclusion criteria: history of asthma, lung cancer or bronchiectasis, need for long-term oxygen therapy, known α_1 antitrypsin deficiency or clinically significant cardiopulmonary co-morbidity

Total number of participant withdrawals: data combined with M2-112 showing 433 (33%) and 348 (26%) from treatment and control groups, respectively

Interventions	<p>Run-in: 4 weeks with placebo</p> <p>Roflumilast 500 µg once daily</p> <p>Placebo once daily</p> <p>Concomitant medication</p> <ul style="list-style-type: none"> • Short-acting anticholinergic: 891 patients on short-acting anticholinergics • Short-acting β_2 agonist: salbutamol as rescue medication • Corticosteroid: 943 patients continued corticosteroid use • Long-acting β_2 bronchodilator: none <p>Used alongside corticosteroids, anticholinergics and rescue short-acting β_2 agonists 54% overall (available to all)</p>
Outcomes	<p>Primary outcomes: change from baseline to endpoint in post-bronchodilator FEV₁ and the number of moderate or severe exacerbations per patient per year</p> <p>Secondary outcomes: change from baseline in SGRQ total score, change from baseline in prebronchial FEV₁, post-bronchodilator FEV in 6 seconds and FVC, FEF rate between 25%-75% of vital capacity and number of moderate or severe COPD exacerbations requiring systemic corticosteroid treatment per patient per year</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	"Each study participant who qualified was assigned a number in sequential order. Code labelling prevented the investigator and the patient from knowing which drug was administered."
Randomised?	Low risk	"randomised (1:1)"
Method of randomisation described?	Low risk	"The randomisation list was generated using a multiplicative congruential pseudorandom number generator (program RANDOM, based on Fishman and Moore)."
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	"There was a stratification of patients according to smoking status (current smokers/ex-smokers) and treatment with inhaled corticosteroids (yes/no)."

Roflumilast M2-111 (Continued)

Description of withdrawals and drop-outs?	Low risk	Data combined with M2-112
Baseline profile: anti-cholinergic use	Low risk	Data combined with M2-112 showing 1604 (60%) participants used anticholinergics
Baseline profile: β_2 agonist use	Low risk	1463 (55%) participants on short-acting β_2 -agonists
Baseline profile: corticosteroid use	Low risk	1622 (61%) on concomitant ICS

Roflumilast M2-111+M2-112

Methods	As described in separate studies above and below	
Participants		
Interventions		
Outcomes		
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	See individual trials
Randomised?	Low risk	See individual trials
Method of randomisation described?	Low risk	See individual trials
Blinding?	Low risk	See individual trials
Method of blinding described?	Low risk	See individual trials
Description of withdrawals and drop-outs?	Low risk	See individual trials
Baseline profile: anti-cholinergic use	Low risk	See individual trials
Baseline profile: β_2 agonist use	Low risk	See individual trials
Baseline profile: corticosteroid use	Low risk	See individual trials

Roflumilast M2-112

Methods	<p>Parallel-group study</p> <p>Randomisation: randomised, double-blind, placebo-controlled trial</p> <p>Trial duration: 52 weeks</p> <p>Intention-to-treat analysis: stated</p>
Participants	<p>Setting: 159 centres in 14 countries</p> <p>Participants: 1513 (roflumilast 500 µg: 760, placebo: 753)</p> <p>Baseline characteristics: severe COPD according to GOLD criteria grades III and IV. Mean age: 65 years. 75% male</p> <p>Inclusion criteria: aged ≥ 40 years. Post-bronchodilator FEV₁ < 50% predicted. Reversibility < 15%. Mean post-bronchodilator FEV₁ 41%. FEV₁/FVC ≤ 0.7 with smoking history > 10 pack-years. 37% current smokers, 63% ex-smokers; average 44 pack-years</p> <p>Exclusion criteria: history of asthma, lung cancer or bronchiectasis, need for long-term oxygen therapy, known α₁antitrypsin deficiency or clinically significant cardiopulmonary co-morbidity</p> <p>Total number of participant withdrawals: 217 (29%) and 163 (22%) from treatment and control groups, respectively</p>
Interventions	<p>Run-in: 4 weeks with placebo</p> <p>Roflumilast 500 µg once daily</p> <p>Placebo once daily</p> <p>Concomitant medication</p> <ul style="list-style-type: none"> • Short-acting anticholinergic: 891 participants on short-acting anticholinergics • Short-acting β₂ agonist: salbutamol as rescue medication • Corticosteroid: 943 participants continued corticosteroid use • Long-acting β₂ bronchodilator: none <p>Used alongside corticosteroids, anticholinergics and rescue short-acting β₂ agonists 54% overall (available to all)</p>
Outcomes	<p>Primary outcomes: change from baseline to endpoint in post-bronchodilator FEV₁ and the number of moderate or severe exacerbations per patient per year</p> <p>Secondary outcomes: change from baseline in SGRQ total score, change from baseline in prebronchial FEV₁, post-bronchodilator FEV in 6 seconds and FVC, FEF rate between 25%-75% of vital capacity and number of moderate or severe COPD exacerbations requiring systemic corticosteroid treatment per patient per year</p>
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment (selection bias)	<p>Low risk</p> <p>"Each study participant who qualified was assigned a number in sequential order. Code labelling prevented the investigator and the patient from knowing which drug was administered."</p>

Roflumilast M2-112 (Continued)

Randomised?	Low risk	"randomised (1:1)"
Method of randomisation described?	Low risk	"The randomisation list was generated using a multiplicative congruential pseudorandom number generator (program RANDOM, based on Fishman and Moore)."
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	"There was a stratification of patients according to smoking status (current smokers/ex-smokers) and treatment with inhaled corticosteroids (yes/no)."
Description of withdrawals and drop-outs?	Low risk	<p>"Over 70% of patients completed the study. The reasons for withdrawal were similar between groups except for adverse events, which occurred more frequently with roflumilast."</p> <p>"Withdrawal due to COPD exacerbations was reported in 3.5 and 3.2% of patients in roflumilast and placebo groups, respectively."</p>
Baseline profile: anti-cholinergic use	Low risk	739 participants used anticholinergics
Baseline profile: β_2 agonist use	Low risk	820 participants on short-acting β_2 -agonists
Baseline profile: corticosteroid use	Low risk	727 participants on beclomethasone dipropionate 2000 μg or less

Roflumilast M2-118

Methods	<p>Parallel-group study</p> <p>Randomisation: randomised, double-blind, placebo-controlled trial</p> <p>Trial duration: 12 weeks</p> <p>Intention-to-treat analysis: stated</p>
Participants	<p>Setting: 22 centres in 4 countries</p> <p>Participants: 250 (roflumilast 500 μg: 127, placebo: 123)</p> <p>Baseline characteristics: mean age: 60 years. 73% (roflumilast) versus 84% (placebo) male. Post-bronchodilator FEV₁ 55% predicted. Average of 41 pack-years. 53% current smokers</p> <p>Inclusion criteria: participants were clinically stable patients ≥ 40 years with a smoking history of > 10 pack-years and a 12-month history of COPD. Other inclusion criteria included: post-bronchodilator FEV₁ 30%-80% predicted, FEV₁/forced vital capacity (FVC) < 0.7 and set plethysmographic FRC and peak oxygen uptake requirements</p> <p>Exclusion criteria: asthma or a lung disease other than COPD; α_1-antitrypsin deficiency; participation in a pulmonary rehabilitation programme within 2 months; supplemental oxygen therapy; a significant medical comorbidity that may influence exercise tolerance</p> <p>Total number of participant withdrawals: 16 (13%) and 12 (10%) from treatment and control groups, respectively</p>
Interventions	Roflumilast 500 μg once daily

Roflumilast M2-118 (Continued)

Placebo once daily

Concomitant medication

- Short-acting anticholinergic: participants could use ipratropium bromide in regular stable doses as needed
- Short-acting β_2 agonist: participants could use short-acting β_2 -agonists as needed
- Corticosteroid: ICS were permitted throughout the study if taken at a constant dosage for > 3 months prior to the study
- Long-acting β_2 bronchodilator: none

Outcomes	Activity-related dyspnoea (TDI). Spirometry and body plethysmography. Symptom-limited exercise tests
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Low risk	A 1:1 randomisation ratio was used
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blinded
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Low risk	Of the 250 randomised participants, 16 from the roflumilast group and 12 from the placebo group discontinued prematurely
Baseline profile: anti-cholinergic use	Unclear risk	Not stated
Baseline profile: β_2 agonist use	Unclear risk	Not stated
Baseline profile: corticosteroid use	Unclear risk	Not stated

Roflumilast M2-119

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Intention-to-treat analysis: stated
Participants	Setting: 32 centres in 5 countries

Roflumilast M2-119 (Continued)

Participants: 410 (roflumilast 500 µg: 203, placebo: 207)

Baseline characteristics: mean age: 68 years. 93% male. Post-bronchodilator FEV₁ 50.5% predicted. Average of 44 pack-years. 69% current smokers

Inclusion criteria: former or current smokers with at least a 10 pack-year history. Aged ≥ 40 years. Post-bronchodilator FEV₁/FVC ≤ 0.7 and FEV₁ of 30%-80%. Clinically stable COPD within 4 weeks prior to baseline

Exclusion criteria: history of asthma or other relevant lung disease, COPD exacerbation with the 4 weeks prior to baseline, need for long-term oxygen therapy, known α₁antitrypsin deficiency or clinically significant cardiopulmonary co-morbidity

Total number of participant withdrawals: 40 (20%) and 18 (9%) from treatment and control groups, respectively

Interventions	<p>Run-in: 4 weeks with placebo</p> <p>Roflumilast 500 µg once daily</p> <p>Placebo once daily</p> <p>Concomitant medication</p> <ul style="list-style-type: none">• Short-acting anticholinergic: "Short-acting anticholinergics at a constant daily dosage as concomitant medication if already taken on a regular basis at a constant dosage for at least 4 weeks prior to the study."• Short-acting β2 agonist: patients could use short-acting β2 agonists as needed• Corticosteroid: none• Long-acting β2 bronchodilator: none
Outcomes	<p>Primary outcome: mean change in post-bronchodilator FEV₁ from baseline</p> <p>Secondary outcomes: mean change in pre-bronchodilator FEV₁ from baseline, change in other lung function measures, time to COPD exacerbation, proportion of participants experiencing exacerbations, time to study withdrawal and adverse effects</p>
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment (selection bias)	Unclear risk Not stated
Randomised?	Low risk Randomised
Method of randomisation described?	Low risk Computer-generated randomisation list used
Blinding?	Low risk Double-blinded
Method of blinding described?	Unclear risk Not stated
Description of withdrawals and drop-outs?	Low risk Participant numbers at different stages of the study described in figure

Roflumilast M2-119 (Continued)

Baseline profile: anti-cholingeric use	Unclear risk	Not stated
Baseline profile: β 2 agonist use	Unclear risk	Not stated
Baseline profile: corticosteroid use	Unclear risk	Not stated

Roflumilast M2-121

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 12 weeks Intention-to-treat analysis: stated
Participants	Setting: 16 centres in 6 countries Participants: estimated enrolment 550 participants Baseline characteristics: not stated Inclusion criteria: people with a history of COPD for at least 12 months as defined by the GOLD criteria, age ≥ 40 years, FEV ₁ /FVC ratio (post-bronchodilator) $\leq 70\%$, FEV ₁ (post-bronchodilator) $\leq 65\%$ of predicted, FRC (post-bronchodilator) $\leq 120\%$ of predicted Exclusion criteria: COPD exacerbation indicated by a treatment with systemic glucocorticosteroids not stopped at least 4 weeks prior to the baseline visit, non-smoker, current smoker or ex-smoker (smoking cessation at least 1 year ago) with a smoking history of < 10 pack-years, or suffering from any concomitant disease that might interfere with study procedures or evaluation Total number of participant withdrawals: not stated
Interventions	500 μ g roflumilast tablets once daily versus placebo
Outcomes	Primary outcome: lung function parameters indicative of hyperinflation in people with COPD Secondary outcomes: <ul style="list-style-type: none"> Mean change from randomisation to endpoint in additional pre- and post-bronchodilator spirometric and lung volume parameters Measurement of quality of life parameters and dyspnoea
Notes	ClinicalTrials.gov Identifier: NCT00108823

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Low risk	Randomised

Roflumilast M2-121 (Continued)

Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double-blind
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Unclear risk	Not stated
Baseline profile: anti-cholinergic use	Unclear risk	Not stated
Baseline profile: β_2 agonist use	Unclear risk	Not stated
Baseline profile: corticosteroid use	Unclear risk	Not stated

Roflumilast M2-124

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial Trial duration: 52 weeks Intention-to-treat analysis: stated
Participants	Setting: 246 centres in 10 countries Participants: 1513 (roflumilast 500 μ g: 760, placebo: 753) Baseline characteristics: mean age: 64 years. 71% male. Post-bronchodilator FEV ₁ 37.6% predicted. Average of 47 pack-years. 48% current smokers Inclusion criteria: former or current smokers with at least a 20 pack-year history. Aged $\geq$ 40 years. Post-bronchodilator FEV ₁ /FVC $\leq$ 0.7. Chronic cough and sputum production. Post-bronchodilator FEV ₁ < 50% predicted. At least 1 recorded COPD exacerbation requiring systemic glucocorticosteroids or treatment in hospital in previous year Exclusion criteria: available in the online web appendix (pg 11) Total number of participant withdrawals: 264 (34%) and 234 (31%) from treatment and control groups, respectively
Interventions	Run-in: 4 weeks with placebo Roflumilast 500 μ g once daily Placebo once daily Concomitant medication <ul style="list-style-type: none"> Short-acting anticholinergic: 31% of those in the roflumilast group and 32% on placebo Short-acting β_2 agonist: "Patients could use short acting β_2 agonists as needed" Corticosteroid: none

Roflumilast M2-124 (Continued)

- Long-acting β_2 bronchodilator: "Eligible patients were stratified according to their use of long acting β_2 agonists and smoking status." Roflumilast 49%, placebo 51%

Outcomes	<p>Primary outcomes: mean change in pre-bronchodilator FEV₁ from baseline to each post-randomisation visit during the treatment period. Mean rate of COPD exacerbations requiring oral or parenteral glucocorticosteroids or requiring hospitalisation or leading to death, per patient per year</p> <p>Secondary outcomes: mean change in post-bronchodilator FEV₁ from baseline to each post-randomisation visit during the treatment period. Time to mortality due to any reason. Natural log-transformed C Reactive Protein (mg/L), Mean TDI focal score during the treatment period</p>
Notes	Adverse event data are pooled with numbers from study M2-125 that followed an identical study design

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	All individuals involved in the studies were unaware of treatment assignment
Randomised?	Low risk	"Randomly assigned to oral roflumilast 500 μ g once daily or placebo."
Method of randomisation described?	Low risk	"The sponsor generated a randomisation list of patient random numbers using a pseudorandom number generator. The investigator used an automated, interactive voice response system to randomly assign patients."
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	"All individuals involved in the studies were unaware of treatment assignment. Tablets were identical in appearance. The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling."
Description of withdrawals and drop-outs?	Low risk	264 participants discontinued from study in the roflumilast group and 234 discontinued from the placebo group
Baseline profile: anti-cholinergic use	Unclear risk	No other information available
Baseline profile: β_2 agonist use	Unclear risk	No other information available
Baseline profile: corticosteroid use	High risk	Pretreatment of 44% in both roflumilast and placebo groups

Roflumilast M2-124+M2-125

Methods	As described in separate studies above and below
Participants	
Interventions	
Outcomes	
Notes	

Roflumilast M2-124+M2-125 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	See individual studies
Randomised?	Low risk	See individual studies
Method of randomisation described?	Low risk	See individual studies
Blinding?	Low risk	See individual studies
Method of blinding described?	Low risk	See individual studies
Description of withdrawals and drop-outs?	Low risk	See individual studies
Baseline profile: anti-cholinergic use	Low risk	See individual studies
Baseline profile: β_2 agonist use	Low risk	See individual studies
Baseline profile: corticosteroid use	High risk	See individual studies

Roflumilast M2-125

Methods	<p>Parallel-group study</p> <p>Randomisation: randomised, double-blind, placebo-controlled trial</p> <p>Trial duration: 52 weeks</p> <p>Intention-to-treat analysis: stated</p>
Participants	<p>Setting: 221 centres in 8 countries</p> <p>Participants: 1571 (roflumilast 500 μg: 773, placebo: 798)</p> <p>Baseline characteristics: mean age: 64 years. 80% male. Average of 48 pack-years. 35% current smokers</p> <p>Inclusion criteria: former or current smokers with at least a 20 pack-year history. Aged ≥ 40 years. Post-bronchodilator $FEV_1/FVC \leq 0.7$. Chronic cough and sputum production. Post-bronchodilator $FEV_1 < 50\%$ predicted. At least 1 recorded COPD exacerbation requiring systemic glucocorticosteroids or treatment in hospital in previous year</p> <p>Exclusion criteria: available in the online web appendix (pg 11)</p> <p>Total number of participant withdrawals: 246 (32%) and 248 (31%) from treatment and control groups, respectively</p>
Interventions	<p>Run-in: 4 weeks with placebo</p> <p>Roflumilast 500 μg once daily</p>

Roflumilast M2-125 (Continued)

Placebo once daily

Concomitant medication

- Short-acting anticholinergic: 38% of those in the roflumilast group and 41% on placebo
- Short-acting β_2 agonist: "Patients could use short acting β_2 agonists as needed"
- Corticosteroid: none
- Long-acting β_2 bronchodilator: "Eligible patients were stratified according to their use of long acting β_2 agonists and smoking status." Roflumilast 48%, placebo 51%

Outcomes	<p>Primary outcomes: mean change in pre-bronchodilator FEV₁ from baseline to each post-randomisation visit during the treatment period. Mean rate of COPD exacerbations requiring oral or parenteral glucocorticosteroids or requiring hospitalisation or leading to death, per patient per year</p> <p>Secondary outcomes: mean change in post-bronchodilator FEV₁ from baseline to each post-randomisation visit during the treatment period. Time to mortality due to any reason. Natural log-transformed CRP (mg/L), Mean TDI focal score during the treatment period</p>
Notes	Adverse event data are pooled with numbers from study M2-124 that followed an identical study design

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	All individuals involved in the studies were unaware of treatment assignment
Randomised?	Low risk	"Randomly assigned to oral roflumilast 500 µg once daily or placebo."
Method of randomisation described?	Low risk	"The sponsor generated a randomisation list of patient random numbers using a pseudorandom number generator. The investigator used an automated, interactive voice response system to randomly assign patients."
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	"All individuals involved in the studies were unaware of treatment assignment. Tablets were identical in appearance. The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling."
Description of withdrawals and drop-outs?	Low risk	246 patients discontinued from study in the roflumilast group and 248 discontinued from the placebo group
Baseline profile: anti-cholinergic use	Low risk	No other information available
Baseline profile: β_2 agonist use	Low risk	No other information available
Baseline profile: corticosteroid use	High risk	Pretreatment of 40% in both roflumilast and placebo groups

Roflumilast M2-127

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled trial
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Roflumilast M2-127 (Continued)

Trial duration: 24 weeks

Intention-to-treat analysis: stated

Participants	<p>Setting: 135 centres in 10 countries</p> <p>Participants: 1221 (roflumilast 500 µg: 467, placebo: 468)</p> <p>Baseline characteristics: mean age: 65 years. 71% male. Post-bronchodilator FEV₁ 54.7% and 55.3% predicted (roflumilast and placebo). Average of 43 pack-years. 39% current smokers</p> <p>Inclusion criteria: former or current smokers with (≥ 1 year smoking cessation) and at least a 10 pack-year history. Aged ≥ 40 years. Post-bronchodilator FEV₁/FVC ≤ 0.7. Post-bronchodilator FEV₁ 40% to 70% predicted. Partial reversibility to albuterol with increase from baseline FEV₁ of ≤ 12% or 200 mL</p> <p>Exclusion criteria: available in the online web appendix (pg 10)</p> <p>Total number of participant withdrawals: 107 (23%) and 82 (18%) from treatment and control groups, respectively</p>	
Interventions	<p>Run-in: 4 weeks with placebo once a day</p> <p>Roflumilast 500 µg and salmeterol once daily</p> <p>Placebo once daily</p> <p>Concomitant medication</p> <ul style="list-style-type: none">• Short-acting anticholinergic: none• Short-acting β₂ agonist: participants used short-acting β₂ as rescue medication• Corticosteroid: none• Long-acting β₂ bronchodilator: none	
Outcomes	<p>Primary outcomes: change in mean pre-bronchodilator FEV₁ from baseline to each post-randomisation visit</p> <p>Secondary outcomes: post-bronchodilator FEV₁ and FVC, TDI score, SOBQ, rate of COPD exacerbations, and use of rescue medication</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	All individuals involved in the studies were unaware of treatment assignment
Randomised?	Low risk	"Randomly assigned to oral roflumilast 500 µg once daily or placebo."
Method of randomisation described?	Low risk	"The sponsor generated a randomisation list of patient random numbers using a pseudorandom number generator. The investigator used an automated, interactive voice response system to randomly assign patients."
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	"All individuals involved in the studies were unaware of treatment assignment. The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling. Tablets were identical in appearance."

Roflumilast M2-127 (Continued)

Description of withdrawals and drop-outs?	Low risk	107 participants discontinued from study in the roflumilast group and 82 discontinued from the placebo group
Baseline profile: anti-cholinergic use	Unclear risk	No other information available
Baseline profile: β_2 agonist use	Unclear risk	No other information available
Baseline profile: corticosteroid use	Unclear risk	No other information available

Roflumilast M2-128

Methods	<p>Parallel-group study</p> <p>Randomisation: randomised, double-blind, placebo-controlled trial</p> <p>Trial duration: 24 weeks</p> <p>Intention-to-treat analysis: stated</p>
Participants	<p>Setting: 85 centres in 7 countries</p> <p>Participants: 910 (roflumilast 500 μg: 372, placebo: 372)</p> <p>Baseline characteristics: mean age: 64 years. 71% male. Post-bronchodilator FEV₁ 56.0% and 56.2% predicted (roflumilast and placebo). Average of 44 pack-years. 40% current smokers</p> <p>Inclusion criteria: former or current smokers with (≥ 1 year smoking cessation) and at least a 10 pack-year history. Aged ≥ 40 years. Post-bronchodilator FEV₁/FVC ≤ 0.7. Post-bronchodilator FEV₁ 40% to 70% predicted. Partial reversibility to albuterol with increase from baseline FEV₁ of $\leq 12\%$ or 200 mL</p> <p>Exclusion criteria: available in the online web appendix (pg 10)</p> <p>Total number of participant withdrawals: 62 (17%) and 39 (11%) from treatment and control groups, respectively</p>
Interventions	<p>Run-in: 4 weeks with placebo once a day</p> <p>Roflumilast 500 μg and tiotropium once daily</p> <p>Placebo once daily</p> <p>Concomitant medication</p> <ul style="list-style-type: none"> • Short-acting anticholinergic: none • Short-acting β_2 agonist: participants used short-acting β_2 as rescue medication • Corticosteroid: none • Long-acting β_2 bronchodilator: none
Outcomes	<p>Primary outcomes: change in mean pre-bronchodilator FEV₁ from baseline to each post-randomisation visit</p> <p>Secondary outcomes: post-bronchodilator FEV₁ and FVC, TDI score, SOBQ, rate of COPD exacerbations and use of rescue medication</p>
Notes	

Roflumilast M2-128 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	All individuals involved in the studies were unaware of treatment assignment
Randomised?	Low risk	"Randomly assigned to oral roflumilast 500 µg once daily or placebo."
Method of randomisation described?	Low risk	"The sponsor generated a randomisation list of patient random numbers using a pseudorandom number generator. The investigator used an automated, interactive voice response system to randomly assign patients."
Blinding?	Low risk	Double-blinded
Method of blinding described?	Low risk	"All individuals involved in the studies were unaware of treatment assignment. The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling. Tablets were identical in appearance."
Description of withdrawals and drop-outs?	Low risk	62 participants discontinued from study in the roflumilast group and 39 discontinued from the placebo group
Baseline profile: anti-cholingeric use	Unclear risk	No information available
Baseline profile: β2 agonist use	Unclear risk	No information available
Baseline profile: corticosteroid use	Unclear risk	No information available

Roflumilast ROF-MD-07(RE2SPOND)

Methods	<p>Parallel-group study</p> <p>Randomisation: randomised, double-blind, placebo-controlled trial</p> <p>Trial duration: 52 weeks</p> <p>Intention-to-treat analysis: stated</p>
Participants	<p>Setting: 338 locations across Australia, Argentina, Canada, Chile, Columbia, Italy, Malaysia, Peru, Phillippines, Romania, Russia, Serbia, Spain, Taiwan, Ukraine</p> <p>Participants: 2354 (500 µg roflumilast: 1178; placebo: 1176)</p> <p>Baseline characteristics: mean age: 64 years, 68% male, mean FEV₁% predicted of 33%, mean smoking history of 52.2 pack-years for roflumilast and 53.1 pack-years for placebo) or current smokers (39% and 40%, respectively)</p> <p>Inclusion criteria: ≥ 40 years with severe-very severe COPD, chronic bronchitis, ≥ 2 exacerbations and/or hospitalisations in the previous year, and were receiving ICS/LABA with or without LAMA daily for ≥ 3 months</p> <p>Exclusion criteria: participants were excluded if, within the 4 weeks prior to enrolment, they had a moderate or severe COPD exacerbation and/or COPD exacerbation treated with antibiotics or systemic corticosteroids or a lower respiratory tract infection. Other exclusionary criteria included diagnoses of oth-</p>

Roflumilast ROF-MD-07(RE2SPOND) (Continued)

er lung diseases, moderate-to-severe liver impairment (Child-Pugh B or C), HIV or hepatitis infection, current diagnosis of asthma, cancer in the past 5 years, α 1-antitrypsin deficiency, a clinically significant cardiovascular condition, a resting QTc interval > 470 ms, or a body mass index $\geq$ 45 kg/m

Total number of participant withdrawals: 337 (29%) and 254 (21%) from treatment and control groups, respectively

Interventions	<p>Run-in: 2 weeks, single-blind. Placebo tablets to assess suitability</p> <p>Roflumilast 500 μg once daily</p> <p>Placebo once daily</p> <p>Concomitant medication</p> <p>ICS/LABA FDC (fluticasone propionate/salmeterol, 250/50 mg (1 inhalation twice a day), or budesonide/formoterol, 160/4.5 mg (2 inhalations twice a day)</p> <p>Participants taking fluticasone propionate/salmeterol, 500/50 mg, at study entry were required to switch to the lower dosage (250/50 mg) before entry. Up to 60% of participants were allowed concomitant LAMA (e.g. tiotropium) if administered for $\geq$ 3 months before screening, with no dose change. Those not on LAMA were allowed a SAMA.</p>
Outcomes	<p>Primary outcomes: rate of moderate or severe COPD exacerbations per patient per year</p> <p>Secondary outcomes: rate of severe exacerbations, rate of moderate or severe antibiotic-treated COPD exacerbations, and mean change from baseline in predose FEV₁ over 52 weeks, frequency of moderate or severe COPD exacerbations, median time to first moderate or severe exacerbation, mean changes from baseline in predose FVC, mean changes from baseline over time in the COPD Assessment Test (CAT), and daily symptoms measured via EXacerbation of Chronic Pulmonary Disease Tool–Patient Reported Outcomes (EXACT-PRO), adverse events, Columbia-Suicide Severity Rating Scale, laboratory parameters and vital signs</p>
Notes	<p>NCT01443845</p> <p>Sponsored by Activas and Astra Zeneca</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not stated
Randomised?	Low risk	Randomised
Method of randomisation described?	Unclear risk	Not stated
Blinding?	Low risk	Double blind
Method of blinding described?	Unclear risk	Not stated
Description of withdrawals and drop-outs?	Unclear risk	337 participants (29%) discontinued from study in the roflumilast group and 254 (22%) discontinued from the placebo group
Baseline profile: anti-cholinergic use	Unclear risk	LAMA: 47% for placebo; 47% for roflumilast

Roflumilast ROF-MD-07(RE2SPOND) (Continued)

Baseline profile: β 2 agonist use	Unclear risk	Combined LABA/ICS Fluticasone propionate/salmeterol FDC 65% for placebo; 65% for roflumilast Budesonide/formoterol FDC 35% for placebo; 35% for roflumilast
Baseline profile: corticosteroid use	Unclear risk	As above

CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; DLCO: diffusing capacity of the lung for carbon monoxide; FDC: fixed dose combination; FEF: forced expiratory flow; FEV₁: forced expiratory volume in one second; FRC: functional residual capacity; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IC: inspiratory capacity; ICS: inhaled corticosteroid; L: litre; LABA: Long-acting beta-2 agonist; LAMA: Long acting muscarinic antagonist; MDI: metered dose inhaler; mL: millilitre; RFRC: resting functional residue capacity; RV: residual volume; SAMA: Short acting muscarinic antagonist; SD: standard deviation; SE: standard error; SGRQ: St George's Respiratory Questionnaire
SOBQ: Shortness of Breath Questionnaire; SVC: slow vital capacity; TDI: transition dyspnoea index; 6MWT: 6-minute walk test

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Borker 2003	Insufficient data. Only RR of QOL improvement provided
Ferguson 2003	Integrated results from four 24-week cilomilast trials
Fischer 2003	Analysis focused on participants with a baseline SGRQ score of $\geq$ the median SGRQ score only
Grootendorst 2001	Endpoint: first dose-bronchodilator effects only
Grootendorst 2002	Treatment Bayer BAY 19-8004; 11 participants only 1 week in duration
Grootendorst 2003	Endpoint: first-dose bronchodilator effects only
Grootendorst 2007	Cross-over design
GSK256066	Phase II trial. No primary outcome measure investigating lung function. Only 1 trial to date
Kelsen 2002	No study ID or group numbers identified
Knobil 2003	No SD or SE given
Lim 2004	Combining results from 2 pivotal European phase III cilomilast trials
Nieman 1999	Study 038. Insufficient data available for changes in lung function and exacerbation rates
Pascoe 2007	Treatment QAK423 (Novartis), discontinued. Only 1 trial available
Reisner 2003	Combined results. Individual studies already included in review
Roflumilast JP708	JP108 is an extension study of APTA-2217-06 study. After the key-open of APTA-2217-06 study, administration to placebo group would be terminated. Not all participants enrolled in JP106 continued onto the JP108 study
Sadigov 2014	No placebo group

Study	Reason for exclusion
Sadigov 2015	Open label. No placebo group
SB207499/040	Open-label study. Men or women with COPD who successfully completed study 042 or 091 where participants received cilomilast 15 mg twice daily or placebo for 24 weeks in study 042 and 26 weeks in study 091 without tolerability problems. Concomitant COPD medication use allowed, given placebo or placebo/Ariflo during study period
SB207499/041	Open-label study. Men or women with COPD who successfully completed study 039 where participants received cilomilast 15 mg twice daily or placebo for 24 weeks without tolerability problems. Concomitant COPD medication use allowed, given placebo or placebo/Ariflo during study period
Song 2005	Abstract only. Unable to contact study author
Spencer 2002	No study ID or group numbers identified
Vestbo 2007	Treatment UK-500,001 (Pfizer). Discontinued
Vestbo 2009	Treatment UK-500,001 (Pfizer). Discontinued
Wang 2005	Although quoted as significant, mean and SD figures not provided
Watz 2013	Inhaled therapy

COPD: chronic obstructive pulmonary disease

RR: risk ratio

QOL: quality of life

SD: standard deviation

SE: standard error

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

[Barnes 2014](#)

Methods	An international, 16-week, randomised, double-blind, placebo-controlled, parallel-group study investigating the effects of roflumilast 500 µg once-daily versus placebo on inflammatory parameters in bronchial biopsy tissue specimens, sputum and blood serum
Participants	150 participants with COPD and chronic bronchitis for at least 12 months will be recruited into the study and randomized in a 1:1 ratio to receive either roflumilast or placebo
Interventions	Roflumilast and placebo
Outcomes	The primary endpoint will be the number of CD8+ cells in bronchial biopsy tissue specimens (sub-mucosa) and the key secondary endpoint will be the number of CD68+ cells assessed by indirect immunohistochemistry
Notes	Completed awaiting results

Mahmud 2013

Methods	Single-blind, randomised, placebo-controlled study was carried out in the Department of Respiratory Medicine at National Institute of Diseases of the Chest and Hospital (NIDCH), Dhaka, Bangladesh
Participants	130 participants were recruited initially and randomly distributed into Group-A where they got conventional therapy (inhaled salmeterol + fluticasone and tiotropium) and roflumilast (0.5 mg once daily) and Group- B where participants got placebo with conventional therapy. Study duration was 3 months
Interventions	As above
Outcomes	The primary outcome variable was change in mean FEV ₁ and secondary outcome variable was change in mean CAT score from baseline
Notes	No data provided. Study authors contacted

CAT: COPD Assessment Test

COPD: chronic obstructive pulmonary disease

Characteristics of ongoing studies [ordered by study ID]

NCT02451540 2015

Trial name or title	Evaluation of the effect of roflumilast in hyperinflated COPD patients using functional respiratory imaging
Methods	Parallel RCT
Participants	40 people who are stable on LABA/LAMA therapy and who are prone to dynamics hyperinflation
Interventions	Roflumilast and placebo
Outcomes	Radiological (CT) changes in airway measures Changes in spirometry and body plethysmography
Starting date	September 2015
Contact information	University Hospital of Antwerp
Notes	Other Study ID Numbers: FLUI-2014-134, EudraCT Estimated study completion date: January 2017

NCT02671942 2016

Trial name or title	A multicenter randomized double-blind clinical study evaluated the safety, pharmacokinetic and pharmacodynamic characteristics of roflumilast in COPD patients
Methods	Parallel RCT
Participants	People with COPD in China
Interventions	Roflumilast and placebo

Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease (Review)

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NCT02671942 2016 (Continued)

Outcomes	Area under the plasma concentration after versus drug dose
	Percentage of participants with adverse events of interest
	Change in pre-bronchodilator FEV ₁ during the down titration period
Starting date	March 2016
Contact information	Contact: Zheng Jinping
Notes	Estimated enrolment: 120
	Estimated study completion date: August 2017

COPD: chronic obstructive pulmonary disease

FEV₁: forced expiratory volume in first second

RCT: randomised controlled trial

DATA AND ANALYSES
Comparison 1. PDE₄ inhibitor versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV₁ (by drug)	27	20585	Mean Difference (IV, Random, 95% CI)	51.53 [43.17, 59.90]
1.1 Roflumilast 500 µg	17	14230	Mean Difference (IV, Random, 95% CI)	56.45 [48.01, 64.89]
1.2 Roflumilast 250 µg	3	1033	Mean Difference (IV, Random, 95% CI)	56.88 [24.38, 89.38]
1.3 Cilomilast 15 mg	10	5322	Mean Difference (IV, Random, 95% CI)	41.03 [23.93, 58.13]
2 FEV₁ (by mean COPD severity)	21	16659	Mean Difference (IV, Fixed, 95% CI)	52.77 [46.73, 58.82]
2.1 GOLD grade I + II (FEV ₁ ≥ 50% predicted)	9	4647	Mean Difference (IV, Fixed, 95% CI)	51.79 [38.99, 64.59]
2.2 GOLD grade III + IV (FEV ₁ < 50% predicted)	12	12012	Mean Difference (IV, Fixed, 95% CI)	53.06 [46.19, 59.92]
3 FEV₁ (Roflumilast 500 µg by mean COPD severity)	15	13742	Mean Difference (IV, Fixed, 95% CI)	55.51 [48.88, 62.14]
3.1 GOLD grade I + II (FEV ₁ ≥ 50% predicted)	6	3187	Mean Difference (IV, Fixed, 95% CI)	69.86 [53.34, 86.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 GOLD grade III + IV (FEV ₁ < 50% predicted)	9	10555	Mean Difference (IV, Fixed, 95% CI)	52.75 [45.52, 59.99]
4 FEV ₁ (by study duration)	27	19785	Mean Difference (IV, Fixed, 95% CI)	49.08 [43.85, 54.32]
4.1 Duration ≤ 12 weeks	7	1037	Mean Difference (IV, Fixed, 95% CI)	102.21 [71.26, 133.16]
4.2 Duration 24 to 26 weeks	13	8086	Mean Difference (IV, Fixed, 95% CI)	46.14 [38.44, 53.84]
4.3 Duration 52 weeks	7	10662	Mean Difference (IV, Fixed, 95% CI)	48.77 [41.44, 56.10]
5 FEV ₁ (additional medication)	27	19565	Mean Difference (IV, Fixed, 95% CI)	49.08 [43.84, 54.31]
5.1 Long-acting bronchodilator	2	1645	Mean Difference (IV, Fixed, 95% CI)	60.52 [40.57, 80.46]
5.2 Corticosteroids	3	2904	Mean Difference (IV, Fixed, 95% CI)	42.26 [25.46, 59.05]
5.3 PDE ₄ i treatment only	19	10169	Mean Difference (IV, Fixed, 95% CI)	44.78 [37.67, 51.90]
5.4 Various concomitant treatments	3	4847	Mean Difference (IV, Fixed, 95% CI)	56.58 [46.91, 66.25]
6 FEV ₁ (published versus unpublished)	27	19785	Mean Difference (IV, Fixed, 95% CI)	49.23 [43.99, 54.46]
6.1 Published	19	15244	Mean Difference (IV, Fixed, 95% CI)	55.75 [49.44, 62.06]
6.2 Unpublished	8	4541	Mean Difference (IV, Fixed, 95% CI)	34.82 [25.44, 44.19]
7 FEV ₁ (random-effects model)	27	19785	Mean Difference (IV, Random, 95% CI)	51.47 [42.68, 60.26]
8 FEV ₁ (roflumilast 500 µg versus 250 µg)	3	1560	Mean Difference (IV, Fixed, 95% CI)	22.61 [-5.95, 51.16]
9 FVC	16	21954	Mean Difference (IV, Fixed, 95% CI)	87.28 [74.87, 99.70]
10 PEF	5	4245	Mean Difference (IV, Fixed, 95% CI)	6.54 [3.95, 9.13]
10.1 Roflumilast 500 µg	4	3685	Mean Difference (IV, Fixed, 95% CI)	5.46 [2.74, 8.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Roflumilast 250 µg	1	347	Mean Difference (IV, Fixed, 95% CI)	7.0 [-4.05, 18.05]
10.3 Cilomilast 15 mg	1	213	Mean Difference (IV, Fixed, 95% CI)	34.0 [20.14, 47.86]
11 SGRQ total score	11	7645	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-1.68, -0.43]
11.1 Roflumilast 500 µg	3	2235	Mean Difference (IV, Fixed, 95% CI)	-0.79 [-2.16, 0.58]
11.2 Roflumilast 250 µg	1	716	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-3.56, 0.36]
11.3 Cilomilast 15 mg	8	4694	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-1.81, -0.31]
12 SGRQ total score (by published versus unpublished)	11	7069	Mean Difference (IV, Fixed, 95% CI)	1.00 [-1.65, -0.34]
12.1 Published	5	3079	Mean Difference (IV, Fixed, 95% CI)	-1.98 [-3.07, -0.89]
12.2 Unpublished	6	3990	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-1.26, 0.40]
13 SGRQ total score (by duration)	11	7069	Mean Difference (IV, Fixed, 95% CI)	-0.99 [-1.65, -0.33]
13.1 Duration < 12 weeks	2	240	Mean Difference (IV, Fixed, 95% CI)	-4.19 [-7.60, -0.78]
13.2 Duration 24 to 26 weeks	7	4600	Mean Difference (IV, Fixed, 95% CI)	-1.18 [-1.94, -0.42]
13.3 Duration 52 weeks	2	2229	Mean Difference (IV, Fixed, 95% CI)	0.26 [-1.18, 1.69]
14 SGRQ total score (by mean COPD severity)	8	4851	Mean Difference (IV, Fixed, 95% CI)	-1.56 [-2.39, -0.74]
14.1 GOLD grade I and II	3	2042	Mean Difference (IV, Fixed, 95% CI)	-1.62 [-2.80, -0.44]
14.2 GOLD grade III and IV	5	2809	Mean Difference (IV, Fixed, 95% CI)	-1.51 [-2.67, -0.34]
15 SGRQ symptom score	2	1048	Mean Difference (IV, Fixed, 95% CI)	-1.53 [-4.11, 1.06]
15.1 Roflumilast	1	835	Mean Difference (IV, Fixed, 95% CI)	1.00 [-3.78, 1.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.2 Cilomilast	1	213	Mean Difference (IV, Fixed, 95% CI)	-4.80 [-11.73, 2.13]
16 Number of participants with one or more exacerbations (by drug)	23	19948	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.73, 0.83]
16.1 Roflumilast 500 µg	13	14420	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.73, 0.86]
16.2 Cilomilast	10	5528	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.67, 0.85]
17 Number of participants on roflumilast with one or more exacerbations (additional medication)	13	14420	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.73, 0.86]
17.1 Long-acting bronchodilators	2	1676	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.54, 0.88]
17.2 Corticosteroids	1	2686	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.70, 0.95]
17.3 Treatment only	7	5145	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.67, 0.93]
17.4 Various concomitant treatments	3	4913	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.72, 0.91]
18 Exacerbation rate (inverse variance)	9		Rate Ratio (Fixed, 95% CI)	0.88 [0.83, 0.93]
18.1 Roflumilast	8		Rate Ratio (Fixed, 95% CI)	0.87 [0.82, 0.92]
18.2 Cilomilast	1		Rate Ratio (Fixed, 95% CI)	0.95 [0.78, 1.17]
19 Borg Scale	6	2860	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.33, -0.05]
19.1 Cilomilast	6	2860	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.33, -0.05]
20 Summary symptom score	5	6186	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.07, 0.03]
20.1 Roflumilast	2	4287	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.08, 0.04]
20.2 Cilomilast	3	1899	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.13, 0.06]
21 Shortness of breath questionnaire	2	1633	Mean Difference (IV, Fixed, 95% CI)	-1.09 [-2.47, 0.28]
22 6-minute walk test	5	1975	Mean Difference (IV, Fixed, 95% CI)	2.09 [-7.39, 11.57]
22.1 Roflumilast	1	27	Mean Difference (IV, Fixed, 95% CI)	55.0 [-111.29, 221.29]
22.2 Cilomilast	4	1948	Mean Difference (IV, Fixed, 95% CI)	1.92 [-7.58, 11.41]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23 Number of participants experiencing an adverse effect	27	20988	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [1.22, 1.37]
23.1 Roflumilast 500 µg	13	14446	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [1.24, 1.42]
23.2 Cilomilast 15 mg	14	6542	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [1.08, 1.36]
24 Number of participants experiencing an adverse event (Roflumilast 500 µg versus 250 µg)	4	1977	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [1.01, 1.46]
25 Diarrhoea	25	20181	Odds Ratio (M-H, Fixed, 95% CI)	3.13 [2.76, 3.54]
25.1 Roflumilast	11	13639	Odds Ratio (M-H, Fixed, 95% CI)	3.72 [3.15, 4.38]
25.2 Cilomilast	14	6542	Odds Ratio (M-H, Fixed, 95% CI)	2.47 [2.05, 2.98]
26 Nausea	24	20627	Odds Ratio (M-H, Fixed, 95% CI)	3.78 [3.23, 4.43]
26.1 Roflumilast 500 µg	10	13229	Odds Ratio (M-H, Fixed, 95% CI)	3.21 [2.57, 4.03]
26.2 Roflumilast 250 µg	1	856	Odds Ratio (M-H, Fixed, 95% CI)	3.97 [0.91, 17.39]
26.3 Cilomilast 15 mg	14	6542	Odds Ratio (M-H, Fixed, 95% CI)	4.37 [3.49, 5.47]
27 Headache	21	18977	Odds Ratio (M-H, Fixed, 95% CI)	1.69 [1.47, 1.95]
27.1 Roflumilast 500 µg	10	13327	Odds Ratio (M-H, Fixed, 95% CI)	2.15 [1.76, 2.63]
27.2 Roflumilast 250 µg	1	347	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.24, 3.99]
27.3 Cilomilast 15 mg	11	5303	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [1.08, 1.62]
28 Vomiting	11	5828	Odds Ratio (M-H, Fixed, 95% CI)	4.01 [2.80, 5.74]
28.1 Roflumilast	1	835	Odds Ratio (M-H, Fixed, 95% CI)	1.52 [0.06, 37.37]
28.2 Cilomilast	10	4993	Odds Ratio (M-H, Fixed, 95% CI)	4.06 [2.83, 5.82]
29 Dyspepsia	13	6247	Odds Ratio (M-H, Fixed, 95% CI)	3.17 [2.33, 4.30]
29.1 Roflumilast	1	626	Odds Ratio (M-H, Fixed, 95% CI)	7.07 [0.36, 137.40]
29.2 Cilomilast	12	5621	Odds Ratio (M-H, Fixed, 95% CI)	3.13 [2.30, 4.27]
30 Abdominal pain	13	8165	Odds Ratio (M-H, Fixed, 95% CI)	2.04 [1.63, 2.55]
30.1 Roflumilast	2	2561	Odds Ratio (M-H, Fixed, 95% CI)	2.76 [1.35, 5.62]
30.2 Cilomilast	11	5604	Odds Ratio (M-H, Fixed, 95% CI)	1.97 [1.55, 2.49]
31 Weight loss	9	12178	Odds Ratio (M-H, Fixed, 95% CI)	3.76 [3.11, 4.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.1 Roflumilast	9	12178	Odds Ratio (M-H, Fixed, 95% CI)	3.76 [3.11, 4.54]
32 Influenza-like symptoms	9	11460	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.87, 1.36]
32.1 Roflumilast 500 µg	7	10147	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.87, 1.41]
32.2 Roflumilast 250 µg	1	347	Odds Ratio (M-H, Fixed, 95% CI)	1.98 [0.18, 22.00]
32.3 Cilomilast 15 mg	2	966	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.44, 1.75]
33 Upper respiratory tract infection	20	16902	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.79, 1.02]
33.1 Roflumilast 500 µg	10	11419	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.75, 1.07]
33.2 Roflumilast 250 µg	2	1203	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.54, 1.31]
33.3 Cilomilast 15 mg	10	4280	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.13]
34 Withdrawals due to adverse events	28	20996	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [1.74, 2.09]
34.1 Roflumilast 500 µg	14	14451	Odds Ratio (M-H, Fixed, 95% CI)	1.91 [1.71, 2.13]
34.2 Cilomilast 15 mg	14	6545	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [1.61, 2.24]
35 Non-fatal serious adverse events	24	18689	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.07]
35.1 Roflumilast 500 µg	10	12144	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.11]
35.2 Cilomilast 15 mg	14	6545	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.72, 1.06]
36 Mortality	23	19344	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.76, 1.23]
36.1 Roflumilast	10	13012	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.78, 1.29]
36.2 Cilomilast	13	6332	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.34, 1.45]
37 All psychiatric disorders (roflumilast)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
37.1 Roflumilast 500 µg	1	11168	Odds Ratio (M-H, Fixed, 95% CI)	2.13 [1.79, 2.54]
37.2 Roflumilast 250 µg	1	6288	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.56, 1.33]
38 Insomnia and sleep disorders (roflumilast)	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
38.1 Roflumilast 500 µg	4	15482	Odds Ratio (M-H, Fixed, 95% CI)	2.67 [2.11, 3.38]
38.2 Roflumilast 250 µg	1	6288	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.81, 2.70]
39 Anxiety or anxiety disorder (roflumilast)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
39.1 Roflumilast 500 µg	1	11168	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [1.26, 2.62]
39.2 Roflumilast 250 µg	1	6288	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.40, 2.21]
40 Depression (roflumilast)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
40.1 Roflumilast 500 µg	1	11168	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [1.11, 2.27]
40.2 Roflumilast 250 µg	1	6288	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.20, 1.56]

Analysis 1.1. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 1 FEV₁ (by drug).

Analysis 1.2. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 2 FEV₁ (by mean COPD severity).

Analysis 1.3. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 3 FEV₁ (Roflumilast 500 µg by mean COPD severity).

Analysis 1.4. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 4 FEV₁ (by study duration).

Analysis 1.5. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 5 FEV₁ (additional medication).

Study or subgroup	PDE4i treatment		Placebo		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			

Test for overall effect: $Z=18.38$ ($P<0.0001$)
Test for subgroup differences: $\text{Chi}^2=5.61$, $\text{df}=1$ ($P=0.13$), $I^2=46.55\%$

Favours placebo -200 -100 0 100 200 Favours PDE4i

Analysis 1.6. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 6 FEV₁ (published versus unpublished).

Study or subgroup	PDE4i treatment		Placebo		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			

1.6.1 Published

Cilomilast 039	378	10 (194)	207	-30 (144)		3.57%	40[12.3,67.7]
Cilomilast 076	21	-50 (183)	23	-70 (192)		0.22%	20[-90.83,130.83]
Compton 2001	107	130 (206)	106	-30 (207)		0.89%	160[104.53,215.47]
RO-2455-301-RD (ACROSS)	313	49 (159.6)	313	-22 (159.6)		4.38%	71[46,96]
RO-2455-404-RD (REACT)	928	52 (195)	941	-4 (196.3)		8.71%	56[38.26,73.74]
Roflumilast DAL-MD-01	11	41 (91)	16	28 (250)		0.15%	13[-120.78,146.78]
Roflumilast FK1 101	169	109 (273)	172	57 (302)		0.73%	52[-9.08,113.08]
Roflumilast FK1 103	200	78 (240)	186	39 (245)		1.17%	39[-9.44,87.44]
Roflumilast FLUI-2011-77	30	66 (120)	11	-59 (71)		0.76%	125[64.96,185.04]
Roflumilast M2-107	555	51 (283)	280	-45 (268)		1.78%	96[56.76,135.24]
Roflumilast M2-111	545	30 (182)	596	-12 (178)		6.26%	42[21.08,62.92]
Roflumilast M2-112	760	9 (303)	753	-27 (302)		2.95%	36[5.52,66.48]
Roflumilast M2-118	127	55 (282)	123	-27 (311)		0.5%	82[8.34,155.66]
Roflumilast M2-119	189	54 (289)	201	-42 (298)		0.81%	96[37.74,154.26]
Roflumilast M2-124	745	46 (218)	745	8 (218)		5.59%	38[15.86,60.14]
Roflumilast M2-125	730	33 (189)	766	-25 (194)		7.27%	58[38.59,77.41]
Roflumilast M2-127	456	39 (192)	460	-10 (193)		4.41%	49[24.07,73.93]
Roflumilast M2-128	365	65 (229)	364	-16 (229)		2.48%	81[47.75,114.25]
Roflumilast ROF-MD-07(RE2SPOND)	1178	53 (160.8)	1174	0 (160.8)		16.21%	53[40,66]
Subtotal ***	7807		7437			68.84%	55.75[49.44,62.06]

Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=37.44$, $\text{df}=18$ ($P=0$); $I^2=51.93\%$
Test for overall effect: $Z=17.32$ ($P<0.0001$)

1.6.2 Unpublished

Cilomilast 042	440	30 (210)	219	0 (296)		1.43%	30[-13.84,73.84]
Cilomilast 091	435	0 (417)	230	-30 (303)		0.89%	30[-25.4,85.4]
Cilomilast 103657	296	50 (86)	316	6 (89)		14.25%	44[30.13,57.87]
Cilomilast 110	20	10 (179)	26	-60 (204)		0.22%	70[-40.92,180.92]
Cilomilast 121	622	14 (175)	328	-6 (181)		4.78%	20[-3.93,43.93]
Cilomilast 156	364	7 (153)	377	-17 (155)		5.57%	24[1.82,46.18]
Cilomilast 157	390	32 (197)	411	-2 (182)		3.96%	34[7.7,60.3]
Roflumilast IN-108	42	28 (486)	25	-124 (405)		0.06%	152[-64.35,368.35]
Subtotal ***	2609		1932			31.16%	34.82[25.44,44.19]

Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=5.66$, $\text{df}=7$ ($P=0.58$); $I^2=0\%$
Test for overall effect: $Z=7.28$ ($P<0.0001$)

Total ***

	10416		9369			100%	49.23[43.99,54.46]
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Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=56.29$, $\text{df}=26$ ($P=0$); $I^2=53.81\%$
Test for overall effect: $Z=18.43$ ($P<0.0001$)

Favours placebo -200 -100 0 100 200 Favours PDE4i

Study or subgroup	PDE4i treatment		Placebo		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			

Test for subgroup differences: $\chi^2=13.18$, $df=1$ ($P=0$), $I^2=92.41\%$

Favours placebo -200 -100 0 100 200 Favours PDE4i

Analysis 1.7. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 7 FEV₁ (random-effects model).

Study or subgroup	PDE4i treatment		Placebo		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Cilomilast 039	378	10 (194)	207	-30 (144)		4.78%	40[12.3,67.7]
Cilomilast 042	440	30 (210)	219	0 (296)		2.79%	30[-13.84,73.84]
Cilomilast 076	21	-50 (183)	23	-70 (192)		0.59%	20[-90.83,130.83]
Cilomilast 091	435	0 (417)	230	-30 (303)		1.97%	30[-25.4,85.4]
Cilomilast 103657	296	50 (86)	316	6 (89)		7.4%	44[30.13,57.87]
Cilomilast 110	20	10 (179)	26	-60 (204)		0.59%	70[-40.92,180.92]
Cilomilast 121	622	14 (175)	328	-6 (181)		5.43%	20[-3.93,43.93]
Cilomilast 156	364	7 (153)	377	-17 (155)		5.75%	24[1.82,46.18]
Cilomilast 157	390	32 (197)	411	-2 (182)		5.01%	34[7.7,60.3]
Compton 2001	107	130 (206)	106	-30 (207)		1.97%	160[104.53,215.47]
RO-2455-301-RD (ACROSS)	313	49 (159.6)	313	-22 (159.6)		5.24%	71[46,96]
RO-2455-404-RD (REACT)	928	52 (195)	941	-4 (196.3)		6.63%	56[38.26,73.74]
Roflumilast DAL-MD-01	11	41 (91)	16	28 (250)		0.41%	13[-120.78,146.78]
Roflumilast FK1 101	169	109 (273)	172	57 (302)		1.69%	52[-9.08,113.08]
Roflumilast FK1 103	200	78 (240)	186	39 (245)		2.42%	39[-9.44,87.44]
Roflumilast FLUI-2011-77	30	66 (120)	11	-59 (71)		1.74%	125[64.96,185.04]
Roflumilast IN-108	42	28 (486)	25	-124 (405)		0.16%	152[-64.35,368.35]
Roflumilast M2-107	555	49 (283)	280	-39 (268)		3.23%	88[48.76,127.24]
Roflumilast M2-111	545	30 (182)	596	-12 (178)		6%	42[21.08,62.92]
Roflumilast M2-112	760	9 (303)	753	-27 (302)		4.34%	36[5.52,66.48]
Roflumilast M2-118	127	55 (282)	123	-27 (311)		1.23%	82[8.34,155.66]
Roflumilast M2-119	189	54 (289)	201	-42 (298)		1.82%	96[37.74,154.26]
Roflumilast M2-124	745	46 (218)	745	8 (218)		5.76%	38[15.86,60.14]
Roflumilast M2-125	730	33 (189)	766	-25 (194)		6.29%	58[38.59,77.41]
Roflumilast M2-127	456	39 (192)	460	-10 (193)		5.25%	49[24.07,73.93]
Roflumilast M2-128	365	65 (229)	364	-16 (229)		3.95%	81[47.75,114.25]
Roflumilast ROF-MD-07(RE2SPOND)	1178	53 (160.8)	1174	0 (160.8)		7.57%	53[40,66]
Total ***	10416		9369			100%	51.47[42.68,60.26]

Heterogeneity: $\tau^2=221.76$; $\chi^2=54.58$, $df=26$ ($P=0$); $I^2=52.36\%$
Test for overall effect: $Z=11.47$ ($P<0.0001$)

Favours placebo -200 -100 0 100 200 Favours PDE4i

Analysis 1.8. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 8 FEV₁ (roflumilast 500 µg versus 250 µg).

Study or subgroup	Roflumilast 500 µg		Roflumilast 250 µg		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Roflumilast FK1 101	169	109 (273)	175	93 (273)		24.49%	16[-41.71,73.71]
Roflumilast IN-108	42	28 (486)	43	13 (492)		1.89%	15[-192.91,222.91]

Favours 250 µg -100 -50 0 50 100 Favours 500 µg

Analysis 1.9. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 9 FVC.

Analysis 1.10. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 10 PEF.

Analysis 1.11. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 11 SGRQ total score.

**Analysis 1.12. Comparison 1 PDE₄ inhibitor versus placebo,
Outcome 12 SGRQ total score (by published versus unpublished).**

Analysis 1.13. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 13 SGRQ total score (by duration).

Analysis 1.14. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 14 SGRQ total score (by mean COPD severity).

Analysis 1.15. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 15 SGRQ symptom score.

Analysis 1.16. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 16 Number of participants with one or more exacerbations (by drug).

Analysis 1.17. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 17 Number of participants on roflumilast with one or more exacerbations (additional medication).

Analysis 1.18. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 18 Exacerbation rate (inverse variance).

Analysis 1.19. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 19 Borg Scale.

Analysis 1.20. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 20 Summary symptom score.

Analysis 1.21. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 21 Shortness of breath questionnaire.

Analysis 1.22. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 22 6-minute walk test.

Analysis 1.23. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 23 Number of participants experiencing an adverse effect.

Analysis 1.24. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 24 Number of participants experiencing an adverse event (Roflumilast 500 µg versus 250 µg).

Analysis 1.25. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 25 Diarrhoea.

Analysis 1.26. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 26 Nausea.

Analysis 1.27. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 27 Headache.

Analysis 1.28. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 28 Vomiting.

Analysis 1.29. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 29 Dyspepsia.

Analysis 1.30. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 30 Abdominal pain.

Analysis 1.31. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 31 Weight loss.

Analysis 1.32. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 32 Influenza-like symptoms.

Analysis 1.33. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 33 Upper respiratory tract infection.

Analysis 1.34. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 34 Withdrawals due to adverse events.

Analysis 1.35. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 35 Non-fatal serious adverse events.

Analysis 1.36. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 36 Mortality.

Analysis 1.37. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 37 All psychiatric disorders (roflumilast).

Analysis 1.38. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 38 Insomnia and sleep disorders (roflumilast).

Analysis 1.39. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 39 Anxiety or anxiety disorder (roflumilast).

Analysis 1.40. Comparison 1 PDE₄ inhibitor versus placebo, Outcome 40 Depression (roflumilast).

ADDITIONAL TABLES

Table 1. Number of references for which we sought full text

Search date:	No. of references for which we sought full text
December 2008	53
January 2010	5
August 2010	12
June 2013	20
October 2016	28

APPENDICES

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

Electronic searches: core databases

Database	Frequency of search
CENTRAL (<i>the Cochrane Library</i>)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly

(Continued)

CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respiriology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the Cochrane Airways Trials Register

COPD search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema\$.mp.
4. (chronic\$ adj3 bronchiti\$).mp.
5. (obstruct\$ adj3 (pulmonary or lung\$ or airway\$ or airflow\$ or bronch\$ or respirat\$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

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

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

- #1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
- #2 MeSH DESCRIPTOR Bronchitis, Chronic
- #3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
- #4 COPD:MISC1
- #5 (COPD OR COAD OR COBD):TI,AB,KW
- #6 #1 OR #2 OR #3 OR #4 OR #5
- #7 MeSH DESCRIPTOR Phosphodiesterase 4 Inhibitors
- #8 Phosphodiesterase*
- #9 PDE4*
- #10 roflumilast
- #11 rolipram
- #12 cilomilast
- #13 ariflo
- #14 SB207499
- #15 Tetomilast
- #16 ORIC485
- #17 Oglemilast
- #18 GRC-3886
- #19 QAK423
- #20 Arofylline
- #21 AWD12-281
- #22 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
- #23 #6 and #22

Appendix 3. Airways Group Trials Register search strategy (sensitive search)

PDE* or phosphodiesterase* or isoenzyme* or theophylline or rolipram or pentoxifylline or papaverine or milrinone or etazolate or etazolate or dyphylline or dipyridamole or caffeine or amrinone or aminophylline or isobutylxanthine or cilomilast or ariflo or cilostazol or enoximone or milrinone or olprinone or roflumilast or sb207499 or zardaverine or cilostamide or enoximone or trequinsin or Telomilast or IC485 or Oglemilast or QAK423 or GRC-3886 or Arofylline or AWD12-281

WHAT'S NEW

Date	Event	Description
11 October 2016	New citation required but conclusions have not changed	Five new eligible studies of roflumilast 500 µg included RO-2455-301-RD (ACROSS) ; RO-2455-404-RD (REACT) ; Roflumilast DAL-MD-01 ; Roflumilast FLUI-2011-77 ; Roflumilast ROF-MD-07(RE2SPOND) . No substantive changes to findings.

Date	Event	Description
11 October 2016	New search has been performed	New literature search run.

HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 5, 2011

Date	Event	Description
17 December 2013	Amended	Typo in plain language summary title amended
4 November 2013	Amended	Risk of bias for Cilomilast 076 added.
6 June 2013	New citation required and conclusions have changed	We included seven new studies in this update and excluded one cross-over trial. FDA report on psychiatric adverse events and suicides included. Text revised to take account of Cochrane reporting standards. 'Summary of findings' table added.
6 June 2013	New search has been performed	New literature search run.

CONTRIBUTIONS OF AUTHORS

Jimmy Chong: study selection, data extraction, review write up, leading update of review.

Phillippa Poole: protocol initiation and development, study selection, data extraction, review write up, all stages of update, corresponding author.

Bonnie Leung: study selection, data extraction, review write up.

DECLARATIONS OF INTEREST

Jimmy Chong: none known

Phillippa Poole: none known

Bonnie Leung: none known

SOURCES OF SUPPORT

Internal sources

- University of Auckland provided salary support for Professor Phillippa Poole, New Zealand.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added the comparison between published and unpublished results when we discovered the large number of unpublished studies, but before we extracted the data from the studies and carried out the analysis.

We have excluded cross-over trials as carry-over effects and disease progression cannot be adequately controlled for in people with chronic obstructive pulmonary disease.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Aminopyridines [*administration & dosage] [adverse effects]; Benzamides [*administration & dosage] [adverse effects]; Cyclohexanecarboxylic Acids [*administration & dosage] [adverse effects]; Cyclopropanes [administration & dosage] [adverse effects]; Disease Progression; Forced Expiratory Volume [drug effects]; Nitriles [*administration & dosage] [adverse effects]; Phosphodiesterase 4 Inhibitors [*administration & dosage] [adverse effects]; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans