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Phosphodiesterase-4 inhibitors for chronic obstructive pulmonary disease (Review)

Janjua S, Fortescue R, Poole P

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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, no other treatments that slow lung function decline are available. Roflumilast and cilomilast are oral phosphodiesterase-4 (PDE_4) inhibitors proposed to reduce the airway inflammation and bronchoconstriction seen in COPD. This Cochrane Review was first published in 2011, and was updated in 2017 and 2020.

Objectives

To evaluate the efficacy and safety of oral PDE_4 inhibitors for management of stable COPD.

Search methods

We identified randomised controlled trials (RCTs) from the Cochrane Airways Trials Register (date of last search 9 March 2020). We found other trials at web-based clinical trials registers.

Selection criteria

We included RCTs if they compared oral PDE_4 inhibitors with placebo in people with COPD. We allowed co-administration of standard COPD therapy.

Data collection and analysis

We used standard Cochrane methods. Two independent review authors selected trials for inclusion, extracted data, and assessed risk of bias. We resolved discrepancies by involving a third review author. We assessed our confidence in the evidence by using GRADE recommendations. Primary outcomes were change in lung function (minimally important difference (MID) = 100 mL) and quality of life (scale 0 to 100; higher score indicates more limitations).

Main results

We found 42 RCTs that met the inclusion criteria and were included in the analyses for roflumilast (28 trials with 18,046 participants) or cilomilast (14 trials with 6457 participants) or tetomilast (1 trial with 84 participants), with a duration between six weeks and one year or longer. These trials included people across international study centres with moderate to very severe COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades II to IV), with mean age of 64 years.

We judged risks of selection bias, performance bias, and attrition bias as low overall amongst the 39 published and unpublished trials.

Lung function

Treatment with a PDE_4 inhibitor was associated with a small, clinically insignificant improvement in forced expiratory volume in one second (FEV_1) over a mean of 40 weeks compared with placebo (mean difference (MD) 49.33 mL, 95% confidence interval (CI) 44.17 to 54.49; participants = 20,815; studies = 29; moderate-certainty evidence). Forced vital capacity (FVC) and peak expiratory flow (PEF) were also improved over 40 weeks (FVC: MD 86.98 mL, 95% CI 74.65 to 99.31; participants = 22,108; studies = 17; high-certainty evidence; PEF: MD 6.54 L/min, 95% CI 3.95 to 9.13; participants = 4245; studies = 6; low-certainty evidence).

Quality of life

Trials reported improvements in quality of life over a mean of 33 weeks (St George's Respiratory Questionnaire (SGRQ) MD -1.06 units, 95% CI -1.68 to -0.43; participants = 7645 ; moderate-certainty evidence).

Incidence of exacerbations

Treatment with a PDE_4 inhibitor was associated with a reduced likelihood of COPD exacerbation over a mean of 40 weeks (odds ratio (OR) 0.78, 95% CI 0.73 to 0.84; participants = 20,382; studies = 27; high-certainty evidence), that is, for every 100 people treated with PDE_4 inhibitors, five more remained exacerbation-free during the study period compared with those given placebo (number needed to treat for an additional beneficial outcome (NNTB) 20, 95% CI 16 to 27). No change in COPD-related symptoms nor in exercise tolerance was found.

Adverse events

More participants in the treatment groups experienced an adverse effect compared with control participants over a mean of 39 weeks (OR 1.30, 95% CI 1.22 to 1.38; participants = 21,310; studies = 30; low-certainty evidence). Participants experienced a range of gastrointestinal symptoms such as diarrhoea, nausea, vomiting, or dyspepsia. Diarrhoea was more commonly reported with PDE_4 inhibitor treatment (OR 3.20, 95% CI 2.74 to 3.50; participants = 20,623; studies = 29; high-certainty evidence), that is, for every 100 people treated with PDE_4 inhibitors, seven more suffered from diarrhoea during the study period compared with those given placebo (number needed to treat for an additional harmful outcome (NNTH) 15, 95% CI 13 to 17). The likelihood of psychiatric adverse events was higher with roflumilast 500 µg than with placebo (OR 2.13, 95% CI 1.79 to 2.54; participants = 11,168; studies = 15 (COPD pool data); moderate-certainty evidence). Roflumilast in particular was associated with weight loss during the trial period and with an increase in insomnia and depressive mood symptoms.

Participants treated with PDE_4 inhibitors were more likely to withdraw from trial participation; on average, 14% in the treatment groups withdrew compared with 8% in the control groups.

Mortality

No effect on mortality was found (OR 0.98, 95% CI 0.77 to 1.24; participants = 19,786; studies = 27; moderate-certainty evidence), although mortality was a rare event during these trials.

Authors' conclusions

For this current update, five new studies from the 2020 search contributed to existing findings but made little impact on outcomes described in earlier versions of this review.

PDE_4 inhibitors offered a small benefit over placebo in improving lung function and reducing the likelihood of exacerbations in people with COPD; however, they had little impact on quality of life or on symptoms. Gastrointestinal adverse effects and weight loss were common, and the likelihood of psychiatric symptoms was higher, with roflumilast 500 µg.

The findings of this review provide cautious support for the use of PDE_4 inhibitors in COPD. In accordance with GOLD 2020 guidelines, they may have a place as add-on therapy for a subgroup of people with persistent symptoms or exacerbations despite optimal COPD management (e.g. people whose condition is not controlled by fixed-dose long-acting $beta_2$-agonist (LABA) and inhaled corticosteroid (ICS) combinations). More longer-term trials are needed to determine whether or not PDE_4 inhibitors modify FEV_1 decline, hospitalisation, or mortality in COPD.

PLAIN LANGUAGE SUMMARY

Phosphodiesterase-4 inhibitors for people with chronic obstructive pulmonary disease (COPD)

Background

COPD is a progressive lung condition caused by damage from harmful chemicals breathed in and is predominantly seen in people who smoke tobacco. These chemicals cause inflammation and lung damage and increase mucus production in the lungs. This leads to periods of breathlessness and coughing called exacerbations (or flare-ups). Exacerbations make it harder for people to do their day-to-day tasks. Exacerbations become more frequent and severe over time. People vary in terms of how they are affected by COPD. This is related in part to

the severity of the disease but also to differences in response to medicines, as well as fitness and co-existent conditions. For most people, the only way to prevent further lung damage is to stop smoking.

Medicines prescribed to manage COPD generally aim to improve symptoms, reduce exacerbations, or both. In early stages, taking bronchodilators makes breathing easier by relaxing muscles in the lungs and widening airways, allowing more air to move freely into and out of the lungs.

Some long-acting agents may reduce exacerbations. For example, steroid inhalers reduce inflammation in the lungs and thus modestly reduce the number of exacerbations.

Phosphodiesterase-4 (PDE_4) inhibitors are a relatively new class of medicines marketed to improve COPD. They have both bronchodilator and anti-inflammatory effects. Two currently available medicines - roflumilast and cilomilast - are taken as a tablet. We collated and analysed results of existing trials to define the benefits and risks of PDE_4 inhibitors in COPD.

Key results

Data analysis included 42 studies in 24,587 adults with moderate to very severe disease who discontinued other regular COPD medications. Some trials allowed people to carry on using their usual COPD medicines. Most trials were funded by manufacturers of PDE_4 inhibitors.

PDE_4 inhibitors provided a small benefit in improving lung function measurements (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and peak expiratory flow (PEF)). PDE_4 inhibitors also reduced the likelihood of COPD-related exacerbations. We found that 28 out of 100 people taking PDE_4 inhibitors every day for a year would experience at least one exacerbation, which was five fewer than for people who did not receive these medicines.

PDE_4 inhibitors provided a small benefit in reducing breathlessness and improving quality of life. Around 5% to 10% of people who received roflumilast or cilomilast reported side effects such as diarrhoea, nausea, and vomiting. We expected that 11 out of 100 people taking PDE_4 inhibitors every day for 39 weeks would experience an episode of diarrhoea, which was seven more than for those not receiving PDE_4 inhibitors. We found that 7 people out of 100 were likely to experience a psychiatric event with roflumilast 500 µg. A two- to three-fold increase in risk of sleep or mood disturbance was found with roflumilast 500 µg, although overall the total number of reported incidents was low. There was no effect on death rates. Effects were the same regardless of the severity of COPD, or whether other medicines for COPD were being taken.

Quality of the evidence

We were moderately certain about data for lung function and quality of life. We were highly certain of evidence for side effects such as diarrhoea and of data for exacerbations.

Results seen in trials published in journals by pharmaceutical companies show greater benefit of these medicines than those that were unpublished. Psychiatric adverse effects data remain unpublished.

Conclusions

We support the use of PDE_4 inhibitors for COPD, but with caution. PDE_4 inhibitors provided a small benefit in improving lung function and reducing the likelihood of COPD exacerbations, but they had little impact on quality of life and COPD symptoms. Side effects including diarrhoea and weight loss were common.

PDE_4 inhibitors may be best used as add-on therapy for a subgroup of people with persistent symptoms or exacerbations despite otherwise optimal COPD management (e.g. people whose condition was not controlled on fixed-dose long-acting $beta_2$-agonist (LABA) and inhaled corticosteroid (ICS) combinations). This is in accordance with GOLD 2020 guidelines. Longer-term trials are necessary to get a more accurate estimate of the benefits and safety of these medicines over time, including determining whether they slow COPD disease progression.

Summary of findings 1. 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
Setting: community-based, randomised, parallel, double-blind, placebo-controlled trials
Intervention: phosphodiesterase 4 inhibitors
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with PDE_4 inhibitor				
Change in FEV_1 Follow-up: weighted mean 40 weeks	Mean FEV_1 was -21.37 mL	MD 49.33 mL higher (44.17 higher to 54.49 higher)	-	20815 (29 RCTs)	⊕⊕⊖⊖ Moderate[a,b]	This is an overall analysis of the outcome that includes roflumilast 250 µg, roflumilast 500 µg, cilomilast 15 mg, and tetomilast 50 µg MID for FEV_1 is 100 mL
Change in FVC Follow-up: weighted mean 45 weeks	Mean FVC was -42.47	MD 86.98 higher (74.65 higher to 99.31 higher)	-	22108 (17 RCTs)	⊕⊕⊕⊕ High	This is an overall analysis of the outcome that includes roflumilast and cilomilast studies
Change in PEF Follow-up: weighted mean 42 weeks	Mean PEF was -2.82	MD 6.54 higher (3.95 higher to 9.13 higher)	-	4245 (5 RCTs)	⊕⊕⊖⊖ Low[c]	This is an overall analysis of the outcome that includes roflumilast and cilomilast studies
Change in SGRQ total score Follow-up: weighted mean 33 weeks	Mean SGRQ total score was -2.21 SGRQ units	MD 1.06 SGRQ units lower (1.68 lower to 0.43 lower)	-	7645 (12 RCTs)	⊕⊕⊕⊖ Moderate[a,b]	This is an overall analysis of the outcome that includes roflumilast 500 µg, roflumilast 250 µg, and cilomilast 15 mg. Lower scores on the SGRQ represent improved quality of life. The MID for this scale is a change of 4 units. This result does not reach the MID for this scale (0 to 100; higher scores indicate more limitations)
Number of participants with 1 or more exacerbations Follow-up: weighted mean 40 weeks	33 per 100	27 per 100 (26 to 29)	OR 0.78 (0.73 to 0.84)	20382 (27 RCTs)	⊕⊕⊕⊕ High	This is an overall analysis of the outcome that includes roflumilast 500 µg, cilomilast 15 mg, and tetomilast 50 µg

Number of participants experiencing an adverse event Follow-up: weighted mean 39 weeks	63 per 100	69 per 100 (68 to 71)	OR 1.30 (1.22 to 1.38)	21310 (30 RCTs)	⊕⊕⊖⊖ Low[b,c]	This is an overall analysis of the outcome that includes roflumilast 500 µg, cilomilast 15 mg, and tetomilast 50 µg, and participants who reported COPD exacerbations as an adverse event
Gastrointestinal adverse effects: diarrhoea Follow-up: weighted mean 39 weeks	4 per 100	11 per 100 (10 to 12)	OR 3.10 (2.74 to 3.50)	20623 (29 RCTs)	⊕⊕⊕⊕ High[b]	This is an overall analysis of the outcome that includes roflumilast 500 µg, cilomilast 15 mg, and tetomilast 50 µg. Diarrhoea was the most commonly reported gastrointestinal side effect. See Figure 4. Weight loss was more common and may be a result of diarrhoea
Psychiatric adverse effects (roflumilast 500 µg) Follow-up: 6 to 52 weeks	3 per 100	7 per 100 (6 to 8)	OR 2.13 (1.79 to 2.54)	11168 (14 studies)	⊕⊕⊕⊖ Moderate[d]	Pooled data from FDA website, not individual trial reports
Mortality Follow-up: weighted mean 40 weeks	1 per 100	1 per 100 (1 to 2)	OR 0.98 (0.77 to 1.24)	19786 (27 RCTs)	⊕⊕⊕⊖ Moderate[e]	This is an overall analysis of the outcome that includes roflumilast 500 µg, cilomilast 15 mg, and tetomilast 50 µg

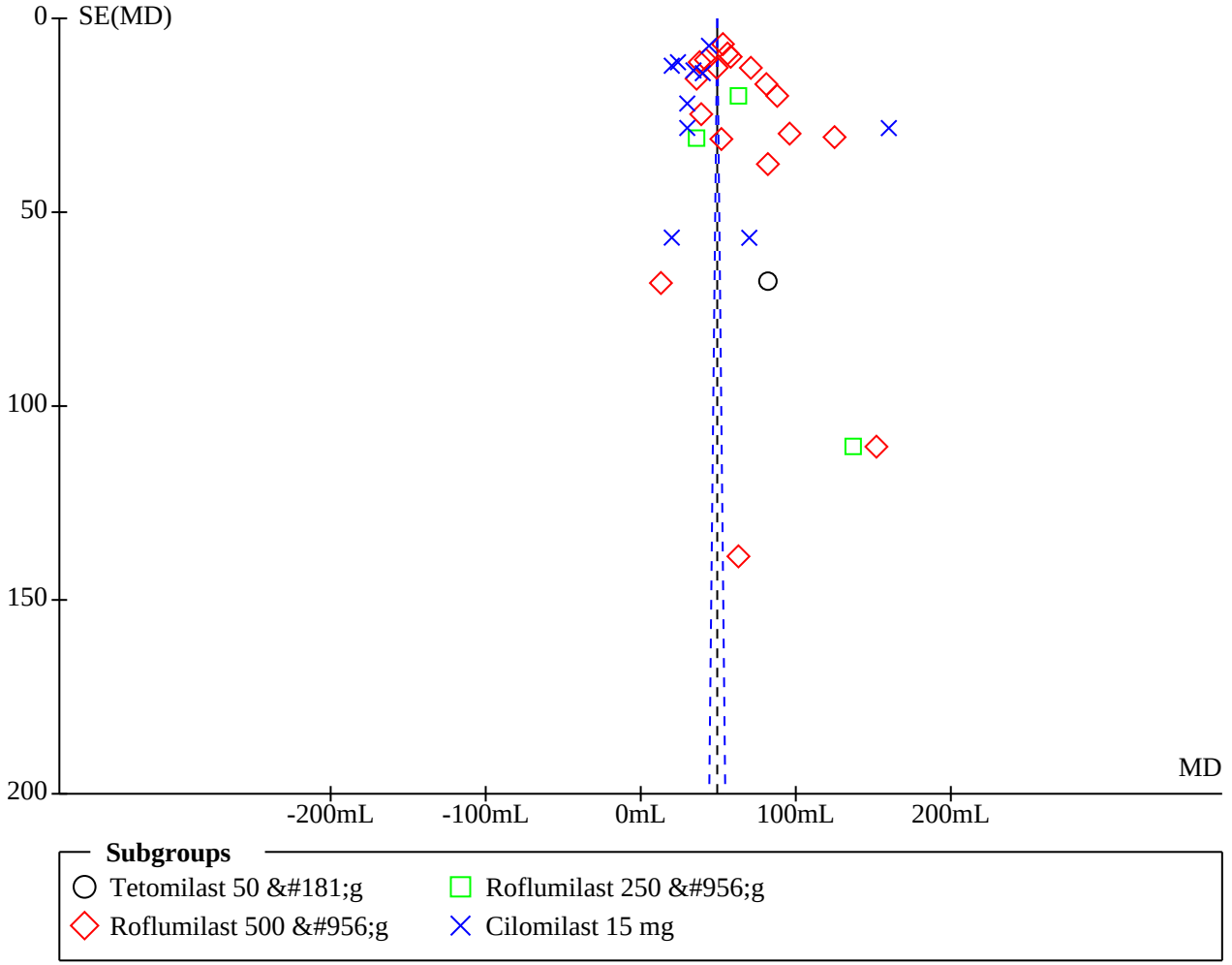
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; COPD: chronic obstructive pulmonary disease; FDA: US Food and Drug Administration; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MD: mean difference; MID: minimally important difference; OR: odds ratio; PEF: peak expiratory flow; PDE_4: phosphodiesterase-4 inhibitor; RCT: randomised controlled trial; RR: risk ratio; SGRQ: St George's Respiratory Questionnaire.

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

[a]The outcome was downgraded by 1 point due to moderate heterogeneity across studies (I^2 = 30% to 60%).
[b]Although some publication bias was found on further investigation through a sensitivity analysis, we did not consider the removal of studies suspected of publication bias to have a large enough impact on the overall effect estimate and CIs. Therefore, we did not downgrade for publication bias.
[c]The outcome was downgraded by 2 points due to substantial heterogeneity across studies (I^2 = 50% to 90%).
[d]Based on data from the combined COPD safety pool. Individual study data not obtained.
[e]The outcome was downgraded by 1 point due to a small number of events, leading to wide confidence intervals.

Figure 4. Funnel plot of comparison: 1 PDE_4 inhibitor versus placebo (2020 update), outcome: 1.1 FEV_1 (by drug) [mL].



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 2020). In 2002, COPD 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).

COPD is an overarching term that includes two lung conditions: chronic bronchitis and emphysema. These lung conditions cause narrowing of the airways and overinflation of the alveoli, leading to difficulty in breathing. Diagnosis of COPD by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) says that it is a "heterogeneous disease that is 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 and influenced by host factors including abnormal lung development" (GOLD 2020). COPD may be punctuated by periods of acute worsening of respiratory symptoms, called exacerbations. Besides exposures, host factors predispose individuals to develop COPD. Comorbidities contribute to overall severity and mortality in individual people (GOLD 2020). Diagnosis is based on a history of exposure to risk factors for this disease and symptoms of cough and sputum production or dyspnoea (shortness of breath). Spirometry is required for diagnosis, with airflow obstruction confirmed by a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) of 0.7 or lower (Celli 2004). Life expectancy is reduced among people diagnosed with COPD, and although prognosis is variable, age and FEV_1 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 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 2020).

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 2020). Mainstays of treatment include short- and long-acting inhaled $beta_2$-agonists (LABAs) and anticholinergics, corticosteroids, and methylxanthines. Triple therapy with inhaled corticosteroids, LABAs, and long-acting muscarinic antagonists (LAMAs) can improve FEV_1, reduce exacerbations, and improve patient-reported outcomes (GOLD 2020). 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 finding 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 results in the need for additional therapy (GOLD 2020). Risk of exacerbation is significantly increased in more severe cases of COPD. Exacerbations have a negative impact on quality of life and lead to more rapid COPD progression, as well as to higher healthcare utilisation and associated costs. A greater impact on health is seen in a subgroup of people with COPD who are more susceptible to exacerbations (defined as "frequent exacerbators"), who have at least two treated exacerbations per year (Le Rouzic 2018).

Common triggers are respiratory viral infection, bacterial infection, and air pollution (Wedzicha 2007; White 2003), which may lead to increased 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 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 (PDE_4). 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 for years for treatment of people with COPD. These are recommended by current international guidelines as part of adjunctive therapy to long-acting bronchodilators (GOLD 2020). 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 increased risks of cardiac arrhythmia and seizure (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 PDE_4 is the predominant isoenzyme involved in metabolising cAMP in immune and inflammatory immune cells, such as neutrophils, macrophages, T cells, and endothelial cells in COPD; and in airway smooth muscle and pulmonary nerves (Agusti 2005; Boswell-Smith 2006; Torphy 1998; Vignola 2004). Inhibition of PDE_4 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, PDE_4 is an attractive target for inhibition in COPD.

Furthermore, central nervous system (CNS) and cardiovascular adverse effects experienced by patients treated with the non-selective PDE inhibitor, theophylline, are the result of adenosine receptor antagonism. This feature is not present with PDE_4-specific inhibitors (Vignola 2004).

Why it is important to do this review

The development of selective PDE_4 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, PDE_4 inhibitors may be easier to use because they provide less pharmacokinetic variability and lower potential for drug interactions compared with theophylline (Barnes 2005).

Several PDE_4 inhibitors have been developed, with some progressing to phase 3 clinical trials. These include the second-generation PDE_4 inhibitors roflumilast (Nycomed, formerly Altana) and cilomilast (GlaxoSmithKline).

Earlier studies of roflumilast have shown significant improvement in pre-bronchodilator FEV_1 and reduced annual rates of exacerbation among people with severe to very severe COPD who also have chronic bronchitis (Calverley 2009). Roflumilast may be considered in people taking triple inhaled therapy who still have exacerbations, FEV_1 less than 50% predicted, and chronic bronchitis, especially if they have had a hospitalisation in the last year (GOLD 2020).

This review update focuses on effects of PDE_4 inhibitors for treatment 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 PDE_4 inhibitors translate into useful clinical effects, and may suggest the potential place of PDE_4 inhibitors within the increasing pharmacopoeia of COPD treatments.

OBJECTIVES

To evaluate the efficacy and safety of oral PDE_4 inhibitors for 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 PDE_4 inhibitors with placebo. We included any long-term treatment trials but excluded single-dose trials, as well as trials in acute exacerbations of COPD. We also excluded cross-over trials to reduce non-random sources of bias between studies.

Types of participants

Adults (over 18 years of age) with COPD, as defined by the American Thoracic Society, the European Respiratory Society, or GOLD, with airflow obstruction evident by spirometry with post-bronchodilator FEV_1/FVC of 0.7 or less (GOLD 2020). 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 PDE_4 inhibitor with those for control participants who received placebo.

Types of outcome measures

Primary outcomes

- Changes in lung function from baseline including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), or peak expiratory flow (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 events (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
- Mortality

Search methods for identification of studies

Electronic searches

The previously published version included searches up to October 2016. We updated the search for this version from 2016 to 9 March 2020.

We identified trials from the Cochrane Airways Trials Register (Cochrane Airways 2019), 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), in the Cochrane Library, through the Cochrane Register of Studies Online (crso.cochrane.org).
- Weekly searches of MEDLINE Ovid SP 2016 to March 2020.
- Weekly searches of Embase Ovid SP 2016 to March 2020.
- Monthly searches of PsycINFO Ovid SP 2016 to March 2020.
- Monthly searches of the Cumulative Index to Nursing and Allied Health Literature (CINAHL) EBSCO 2016 to March 2020.
- Monthly searches of the Allied and Complementary Medicine Database (AMED) EBSCO.
- Handsearches of proceedings of major respiratory conferences.

Studies contained in the Trials 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 provided in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We also searched the following trials registries.

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

We searched the Cochrane Airways Trials Register and additional sources to March 2020, with no restriction on language or type of publication. The original strategy for this review, which was more sensitive but less specific, is provided in Appendix 3.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references and the websites of clinical trials registries for unpublished trial data. We searched relevant manufacturers' websites for study information and PubMed for errata or retractions from included studies published in full text (www.ncbi.nlm.gov/pubmed).

Data collection and analysis

Selection of studies

Two review authors (SJ, RF) independently screened the titles and abstracts of search results and coded them as 'retrieved' (eligible or potentially eligible/unclear) or 'did not retrieve'. We retrieved the full-text study reports of all potentially eligible studies, and two review authors (SJ, RF) independently screened them for inclusion, recording reasons for exclusion of ineligible studies. We resolved any disagreements through discussion. We identified and excluded duplicates and collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table (Moher 2009). We categorised references according to trial name (by drug name and number, or by author and year).

Data extraction and management

For the current update, we used an Excel spreadsheet to extract data and assess risk of bias for each included study. One review author (SJ) extracted data on characteristics of included studies (methods, participants, interventions, outcomes) and results of the included studies. We contacted sponsors of the included studies for unpublished data and searched the sponsor's website for further details of outcomes if needed.

We extracted the following data.

- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study setting, withdrawals, and date of study.
- Participants: N, mean age, severity of condition, baseline lung function, inclusion criteria, and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications, and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Notes: funding for studies and notable conflicts of interest of trial authors.

Two review authors (SJ, RF) independently extracted outcome data from the included studies. We noted in the Characteristics of included studies table if outcome data were not reported in a useable way. We resolved any disagreements by consensus. One review author (SJ) transferred data into the Review Manager 5 file (RevMan 2014). We double-checked that data were entered correctly by comparing data presented in the systematic review against the study reports. A third review author (PP) spot-checked study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (SJ, RF) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We resolved disagreements by discussion. We assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We judged each potential source of bias as high, low, or unclear, and we provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised 'Risk of bias' judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary. When information on risk of bias related to unpublished data or correspondence with trialists, we noted this in the 'Risk of bias' table.

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

Assessment of bias in conducting the systematic review

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

Measures of treatment effect

The outcomes included in this review were either dichotomous or continuous. For dichotomous outcomes, we recorded the number of participants with one or more outcome events by allocated treatment group.

We undertook meta-analyses only when this was meaningful, that is, when treatments, participants, and the underlying clinical question were similar enough for pooling to make sense. We expressed results for pooled outcomes with dichotomous variables using a fixed-effect odds ratio (OR) with 95% confidence interval (CI). Results for continuous variables were expressed as mean differences (MDs) using a fixed-effect or standardised mean difference (SMD), with 95% CI. We considered a P value 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. We used intention-to-treat or 'full analysis set' analyses when they were reported (i.e. analyses for which data had been imputed for participants who were randomly assigned but

did not complete the study) instead of completer or per-protocol analyses.

For change in FEV_1, we used 100 mL as the minimally important difference (MID). For SGRQ, the scale was measured from 0 to 100, with higher scores indicating more limitations. A change in score of 4 units was considered as the MID.

We presented the data as forest plots when possible to show size and direction of effect for treatments with 95% CIs (certainty) using Review Manager 5 (RevMan 2014).

When a single study reported multiple trial arms, we included only the relevant arms. We reported details of the additional arms in the Characteristics of included studies table. When two comparisons (e.g. intervention A versus placebo and intervention B versus placebo) are combined in the same meta-analysis, we will combine the active arms or will halve the control group to avoid double-counting.

If adjusted analyses were available (ANOVA or ANCOVA), we used these as a preference in our meta-analyses. If both change from baseline and endpoint scores were available for continuous data, we used change from baseline unless there was low correlation between measurements among participants. If a study reported outcomes at multiple time points, we used the latest time point. If studies reported post-treatment follow-up, we extracted this information and reported it narratively.

Unit of analysis issues

For dichotomous outcomes, we used participants, rather than events, as the unit of analysis (e.g. number of participants experiencing an adverse event rather than the number of adverse events). However, if a study reported rate ratios, we analysed them on this basis.

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.

We contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study was identified as an abstract only). When this was not possible, and missing data were thought to introduce serious bias, we took this into consideration when performing the GRADE assessment for affected outcomes.

Assessment of heterogeneity

We used the I^2 statistic, along with P values (Higgins 2003), to measure heterogeneity among the trials in each analysis. For I^2, we employed the following criteria.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

In the case of substantial heterogeneity, we reported it and explored possible causes by conducting pre-specified subgroup analysis.

Assessment of reporting biases

We compared available published outcomes with prescribed methods and, when available, original study protocols. If we were able to pool more than 10 studies, we created and examined a funnel plot to explore possible small-study and publication biases.

Data synthesis

We used a fixed-effect model and performed a sensitivity analysis by using a random-effects model.

'Summary of findings' tables

We assessed the certainty of evidence for change in FEV_1 lung function, change in quality of life, COPD exacerbations, adverse events, diarrhoea, and all-cause mortality. We conducted assessments according to recommendations put forth by the GRADE Working Group (Guyatt 2008) and presented in Summary of findings 1 . We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence related to studies that contributed data for the pre-specified outcomes. We used the methods and recommendations described in Higgins 2019, employing GRADEpro GDT software (GRADEpro GDT 2015). We justified all decisions to downgrade the certainty of evidence by using footnotes and made comments to aid the reader's understanding of the review when necessary. We applied the clinical importance of results using published minimal important differences (MIDs), when available (e.g. SGRQ has well-established MIDs in the literature).

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

- Severity of airflow obstruction at baseline (FEV_1 % predicted GOLD grade II 50% to 80%, grade III 30% to 50%, grade IV < 30%) (GOLD 2020).
- Drug (e.g. roflumilast, cilomilast).
- Dose (e.g. roflumilast 250 µg or 500 µg).
- Duration of therapy (≤ 12 weeks; 24 to 26 weeks; 52 weeks; > 52 weeks).
- Concomitant therapy (inhaled or oral corticosteroids, inhaled long-acting $beta_2$-agonists, or anticholinergics, or both).

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

Sensitivity analysis

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

- Studies with high risk of bias in one or more domains.

We planned to compare results from a fixed-effect model by using a random-effects model.

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

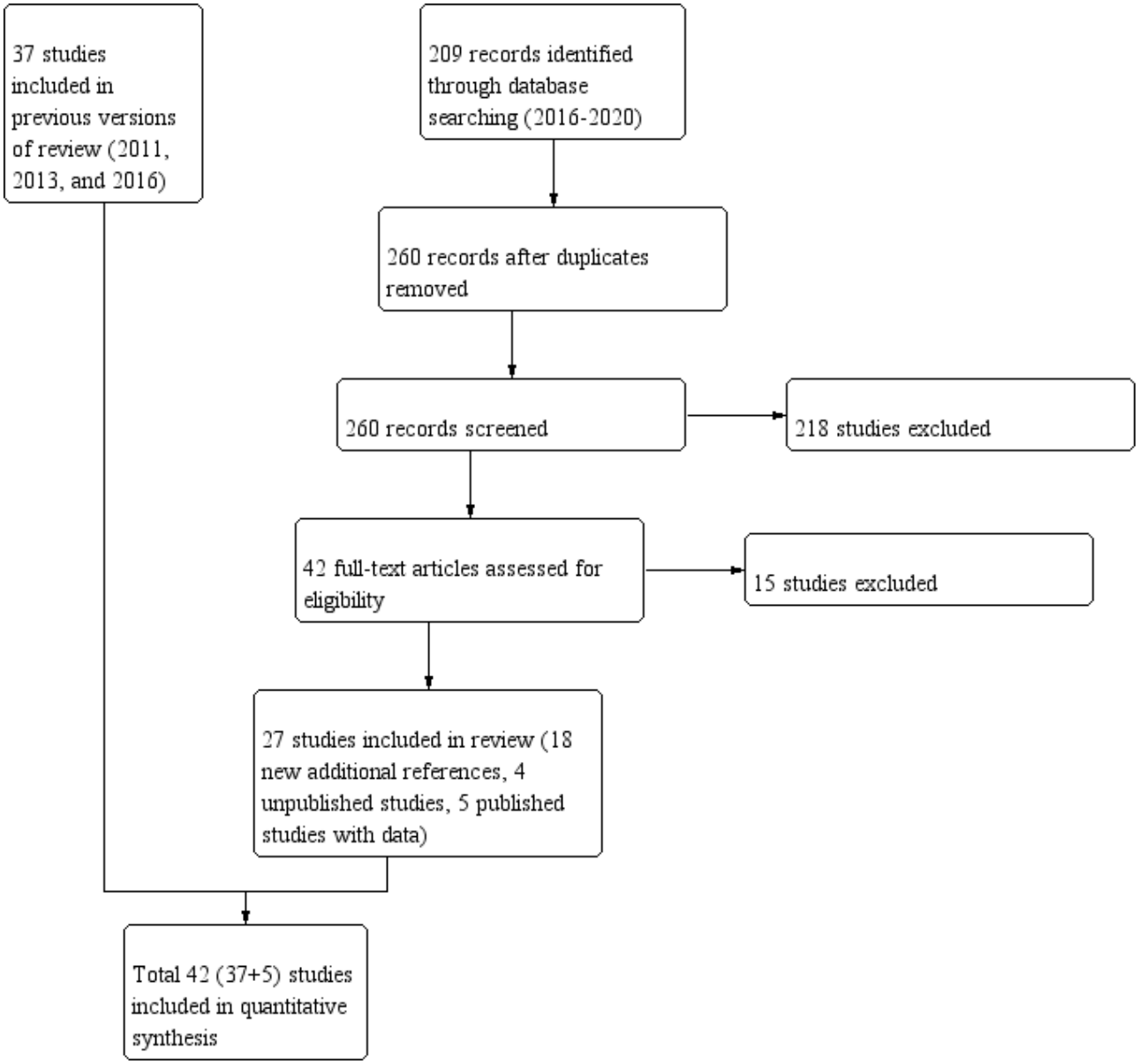
RESULTS

Description of studies

Results of the search

See Figure 1 for study flow diagram (Moher 2009).

Figure 1. Flow diagram.



From the previous updates (2011 to 2016), 37 studies were included in the review (reference to 2011, 2013, and 2016 reviews). From the current database update search (2016-2020), 261 abstracts were identified, one of which was a duplicate and was removed. Full texts for 42 relevant references were assessed further for inclusion (Table 1). Of 27 references that were selected for inclusion, 18 references were new additional references to already included studies, one of which was a new additional reference to an ongoing study that had already been identified previously. Four unpublished trials met the inclusion criteria; however, the data for these trials were not available (NCT01595750; NCT00671073; NCT01701934; EUCTR2004-004442-40-GB). Five new trials were identified that met the inclusion criteria and were included in the analyses (Kavitha 2018; Liu 2018; NCT00874497 (EMPHASIS); RO-2455-402-RD (ROBERT); Urban 2018 (ELASTIC)).

Included studies

Details of the 42 studies included in this review are described in detail in the Characteristics of included studies section.

Of the 42 studies, 27 studies examined roflumilast (COPD safety pool; Kavitha 2018; Liu 2018; RO-2455-301-RD (ACROSS); RO-2455-402-RD (ROBERT); 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; 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); Urban 2018 (ELASTIC)), 14 trials studied cilomilast (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), and one trial explored the use of tetomilast (NCT00874497 (EMPHASIS)).

Most of the roflumilast trials were funded by pharmaceutical companies including AstraZeneca and GlaxoSmithKline. Three trials did not report funding information (Kavitha 2018; Liu 2018; Roflumilast FK1 103). One study was funded by Ludwig Boltzmann Institute (Urban 2018 (ELASTIC)). All cilomilast studies were funded by GlaxoSmithKline, and one tetomilast study was funded by Otsuka Pharmaceutical Development & Commercialization, Inc (NCT00874497 (EMPHASIS)).

Almost all studies used inclusion criteria of spirometry and a history of smoking. Only 6 of the 39 studies mandated a history of exacerbation in the previous year (Cilomilast 103657; Cilomilast 121; NCT00874497 (EMPHASIS); Roflumilast M2-124; Roflumilast M2-125; Urban 2018 (ELASTIC)).

The mean age of participants in these trials ranged from 60 to 70 years, with the proportion of male participants between 49% and 96%. Mean FEV_1 (% predicted) in trials that reported it ranged from 33% to 51%. Most trials included participants at all stages of COPD; however limitation to those with severe and very severe COPD occurred in RO-2455-301-RD (ACROSS), RO-2455-404-RD (REACT), Roflumilast DAL-MD-01, Roflumilast M2-111, Roflumilast M2-112, Roflumilast M2-124, Roflumilast M2-125, and Roflumilast ROF-MD-07(RE2SPOND).

Roflumilast studies

Most of the trials were designed as randomised, double-blind, placebo-controlled studies, apart from Urban 2018 (ELASTIC), which was triple-blinded, and Kavitha 2018, which was assumed to have no blinding. All studies before 2013, apart from Roflumilast JP-706, 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). Combined safety figures also include participants in two other 24-week studies (Roflumilast M2-110; Roflumilast M2-121), for which results have not been published (roflumilast 500 µg: 5970; roflumilast 250 µg: 1002; placebo: 5682).

All studies compared 500 µg of roflumilast in the intervention group with placebo, with the exception of one study, which was an early-dose selection study comparing participants who were given roflumilast 250 µg and 500 µg for 24 weeks (Roflumilast M2-107). The duration of roflumilast treatment in studies ranged from 12 to 52 weeks.

The history of roflumilast studies can be explained in order of publication. The first published PDE_4 inhibitor study for COPD treatment was 52 weeks in duration and allowed concomitant corticosteroid use (Roflumilast M2-112). Subsequently, results of a replicate study were published (Roflumilast M2-111). Another two studies were completed that investigated the effects of roflumilast for 52 weeks in participants with severe to very severe COPD with associated chronic bronchitis who were at risk of exacerbations (Roflumilast M2-124; Roflumilast M2-125).

Two studies evaluated the add-on use of roflumilast with long-acting bronchodilator agents (Roflumilast M2-127; Roflumilast M2-128), the first with salmeterol and the second with tiotropium. Both studies ran for 24 weeks. A further two studies - RO-2455-404-RD (REACT) and Roflumilast ROF-MD-07(RE2SPOND) - added roflumilast or placebo to a fixed-dose ICS/LABA 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. Roflumilast M2-119 investigated pulmonary function and safety in a group of participants recruited at centres across the Asia-Pacific regions. Roflumilast DAL-MD-01 was mainly aimed at investigating effects on sputum and other biomarkers. Roflumilast FLUI-2011-77 explored the airway architecture using imaging techniques.

Three more large RCTs were completed - RO-2455-301-RD (ACROSS), RO-2455-404-RD (REACT), and Roflumilast ROF-MD-07(RE2SPOND). RO-2455-301-RD (ACROSS) was carried out across three centres in mainland China, Hong Kong, and Singapore and investigated the effects and safety of roflumilast over 24 weeks. Both RO-2455-404-RD (REACT) and Roflumilast ROF-MD-07(RE2SPOND) were 52-week multi-centre trials investigating effects on rates of moderate and severe exacerbations.

Four additional trials were completed in 2017 and 2018 - Kavitha 2018, Liu 2018 RO-2455-402-RD (ROBERT), RO-2455-402-RD (ROBERT), and Urban 2018 (ELASTIC). RO-2455-402-RD (ROBERT) was a multi-centre study carried out across Denmark, Germany, Poland, Sweden, and United Kingdom for 16 weeks. The primary aim of this study was to investigate effects on inflammatory markers and changes in lung function. Urban 2018 (ELASTIC) was an Austrian study carried out over 26 weeks, primarily to assess effects of subclinical atherosclerosis and markers of inflammation, but also lung function, exercise, and health impact, in participants with stable COPD. Kavitha 2018, a 12-week single-centre study in India investigating effects of roflumilast on change in pulmonary function of participants with moderate to severe disease taking a combined LABA and tiotropium metered-dose inhaler. Liu 2018 was a 52-week single-centre study in China that primarily investigated change in lung function among participants with moderate to severe disease.

Two trials were 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 with placebo once daily for the following 12 weeks.

Unpublished results were identified for two other 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.

In the three studies that compared 500 µg or 250 µg with placebo, the placebo group was halved to avoid double counting (Roflumilast FK1 101; Roflumilast IN-108; Roflumilast M2-107).

NCT02671942 2016 was identified as an ongoing trial - a Chinese study designed to assess whether altering the standard 500-µg dose improved tolerability of roflumilast. NCT02451540 (reported as ongoing in the 2016 update) was carried out in Belgium to assess effects of roflumilast on lung function (as measured by functional respiratory imaging) in COPD patients taking LABA/LAMA therapy. This study was reported in the trials registry as being terminated early as no new investigational product could be delivered to the study site.

Further information for three unpublished trials could not be found upon contact with authors (NCT00671073; NCT01595750; NCT01701934).

Cilomilast studies

No new studies were identified for the current update.

Data were derived mainly from phase 3 clinical trials and from one phase 2/3 trial. These included unpublished studies. All used a 15-mg dose twice daily, except for Compton 2001.

Compton 2001 was a parallel, six-week, dose-ranging study comparing placebo with 5 mg, 10 mg, and 15 mg of cilomilast, with FEV_1 as the primary outcome. Pivotal efficacy studies included Cilomilast 039, Cilomilast 042, Cilomilast 091, and Cilomilast 156, all of which were 24 weeks in duration. Cilomilast 121 (phase 2/3, 24 weeks), Cilomilast 157 (52 weeks), and Cilomilast 103657 (24 weeks) followed the pivotal efficacy studies and were smaller in sample size.

Cilomilast 039 and Cilomilast 156 were conducted in North America, and Cilomilast 042 and Cilomilast 091 were conducted in the European Union. Here, primary study outcomes were change in FEV_1, lung function, and SGRQ quality of life score. Cilomilast 076, Cilomilast 110, Cilomilast 111, and Cilomilast 168 were supporting studies, all of which lasted less than 24 weeks, with average trial duration of 10.8 weeks, for which neither FEV_1 lung function nor SGRQ was the primary outcome. Cilomilast 180 (18 weeks) had a primary lung function endpoint - functional residual capacity; Cilomilast 181 (13 weeks) assessed the number of inflammatory cells in a bronchial biopsy.

Tetomilast studies

One new tetomilast study was identified - a phase 2a multi-centre, randomised, double-blind, placebo-controlled study that assessed efficacy and safety in patients with emphysema who had at least one previous exacerbation (NCT00874497 (EMPHASIS)). Study duration was 104 weeks, and the dose of tetomilast was 50 µg. The primary outcome was change in FEV_1 (NCT00874497 (EMPHASIS)).

One unpublished study on oglemilast was identified by the search (NCT00671073); however, no further information could be obtained from trial authors on contact.

Excluded studies

We excluded 15 additional references from the 2020 update at full-text review, as they did not meet the inclusion criteria. We have provided reasons for exclusion of these 15 studies (see Excluded studies).

Risk of bias in included studies

An overview of risk of bias in individual studies is provided in Figure 2; support for judgements for individual studies is provided under Characteristics of included studies.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

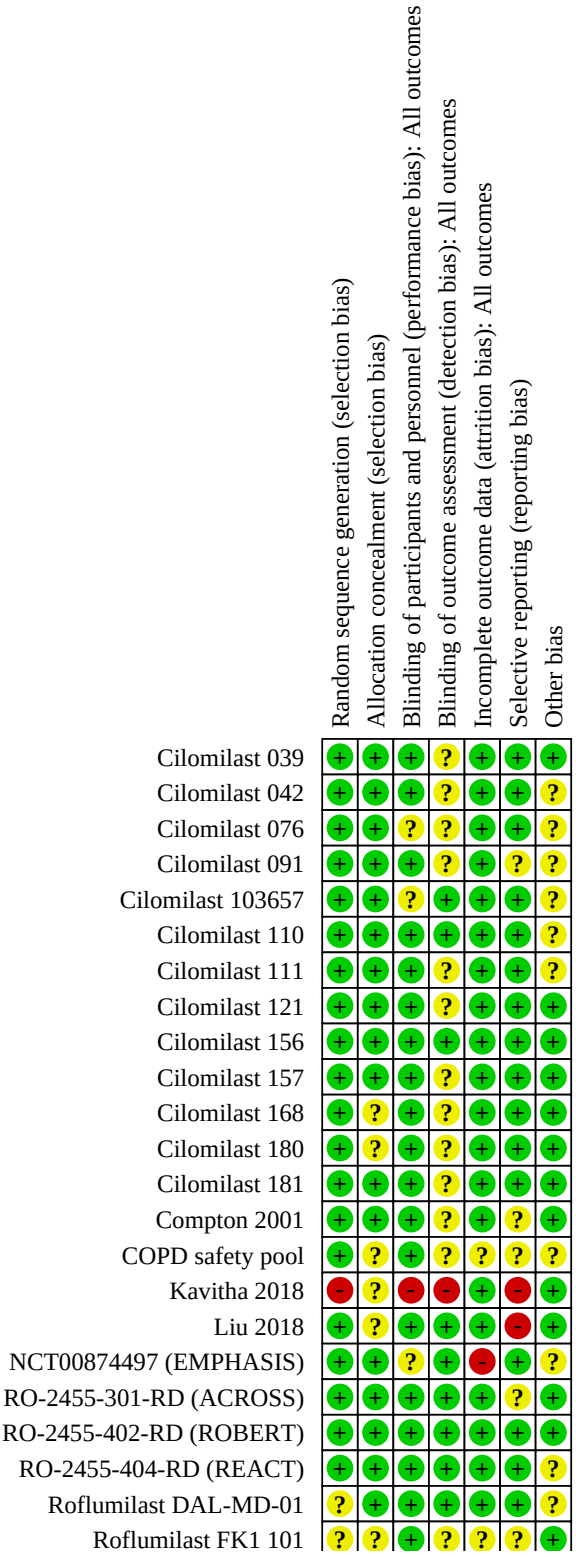
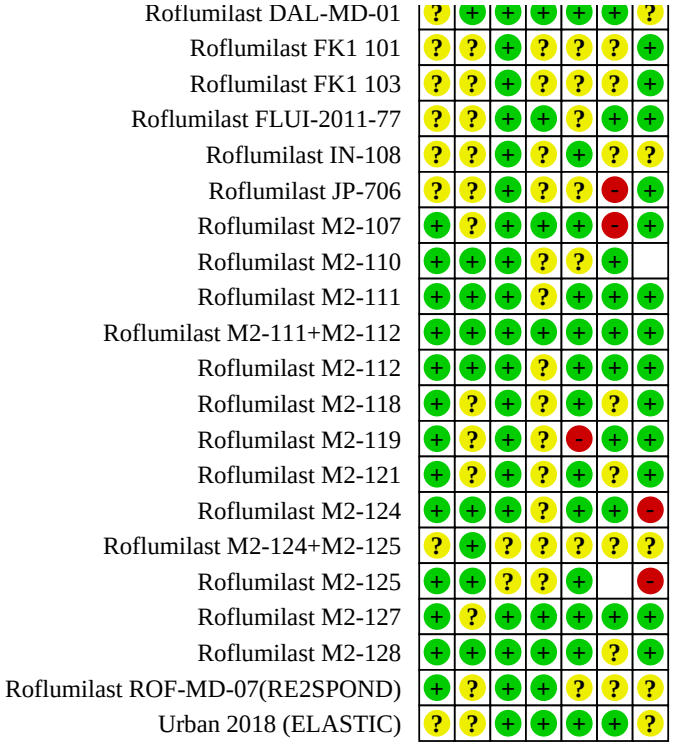


Figure 2. (Continued)



Allocation

We assessed 12 out of 24 roflumilast studies as having low risk of bias for allocation concealment. Information about allocation concealment for cilomilast studies was limited in publications, but we have considered that this is unlikely to be a source of bias because these studies were sponsored, and standard methods would have been used to minimise the risk of selection bias. We therefore judged the risk of selection bias as low, although allocation concealment is marked as unclear in many of these studies. We considered the only study for tetomilast as having low risk of bias for this domain.

Blinding

All studies included in this review were double-blind RCTs, with the exception of Kavitha 2018, which failed to report blinding. We regarded overall risk of performance bias and detection bias as low.

Incomplete outcome data

The rate of withdrawal and dropout was reported in 28 of the 39 studies and was generally less than 20% for randomly assigned participants. However, two studies reported higher rates of attrition (NCT00874497 (EMPHASIS); Roflumilast M2-119). NCT00874497 (EMPHASIS) reported that 54% of participants in both tetomilast and placebo groups did not complete treatments. In addition, five more participants in the tetomilast group than in the placebo group discontinued treatment due to adverse events. Similarly, in Roflumilast M2-119, more participants in the roflumilast group than in the placebo group discontinued (20% versus 8%). We judged these two studies to be at high risk of bias. We judged the remaining nine studies as having unclear risk of bias due to lack of information about the flow of participants throughout the duration of these studies.

Selective reporting

We identified 27 published and 12 unpublished trials. We performed analyses of differences in treatment effect between published and unpublished treatment groups for primary outcomes and reported this information in the subgroup and sensitivity analyses below.

Other potential sources of bias

We did not consider sponsorship as necessarily increasing the risk of bias when studies were well designed.

For some trials, we noted minor differences in baseline characteristics such as age, gender, FEV_1, and smoking history.

Effects of interventions

See: **Summary of findings 1** Phosphodiesterase-4 inhibitors compared to placebo for chronic obstructive pulmonary disease

Primary outcomes

Change in FEV_1

We included 32 studies in the main analysis (participants = 20,815). Eighteen studies compared roflumilast 500 µg with placebo (RO-2455-301-RD (ACROSS); RO-2455-402-RD (ROBERT); RO-2455-404-RD (REACT); Roflumilast DAL-MD-01; Roflumilast FK1 101; Roflumilast FK1 103; Roflumilast FLUI-2011-77; Roflumilast IN-108; Roflumilast M2-107; Roflumilast M2-111;

Roflumilast M2-112; Roflumilast M2-118; Roflumilast M2-119; Roflumilast M2-124; Roflumilast M2-125; Roflumilast M2-127; Roflumilast M2-128; Roflumilast ROF-MD-07(RE2SPOND), three studies compared roflumilast 250 µg with placebo (Roflumilast FK1 101; Roflumilast IN-108; Roflumilast M2-107), 10 studies compared cilomilast 15 mg with placebo (Cilomilast 039; Cilomilast 042; Cilomilast 076; Cilomilast 091; Cilomilast 103657; Cilomilast 110; Cilomilast 121; Cilomilast 156; Cilomilast 157; Compton 2001), and one study compared tetomilast 50 µg with placebo (NCT00874497 (EMPHASIS)).

For RO-2455-402-RD (ROBERT), we calculated standard deviations (SDs) using the RevMan calculator and the number of participants in each treatment group. We did not have change from baseline data for each treatment group; therefore, we used the reported mean difference value between groups (0.063) as the MD for the roflumilast group and an MD of zero for the placebo group.

Urban 2018 (ELASTIC) was not included in the meta-analysis as the data were skewed and were analysed on a log-scale as a percentage difference. Similarly, Liu 2018 could not be included in the analysis because reporting of standard errors was unclear, and we received no further correspondence from trial authors on request. Kavitha 2018 reported the outcome separately as endpoint data.

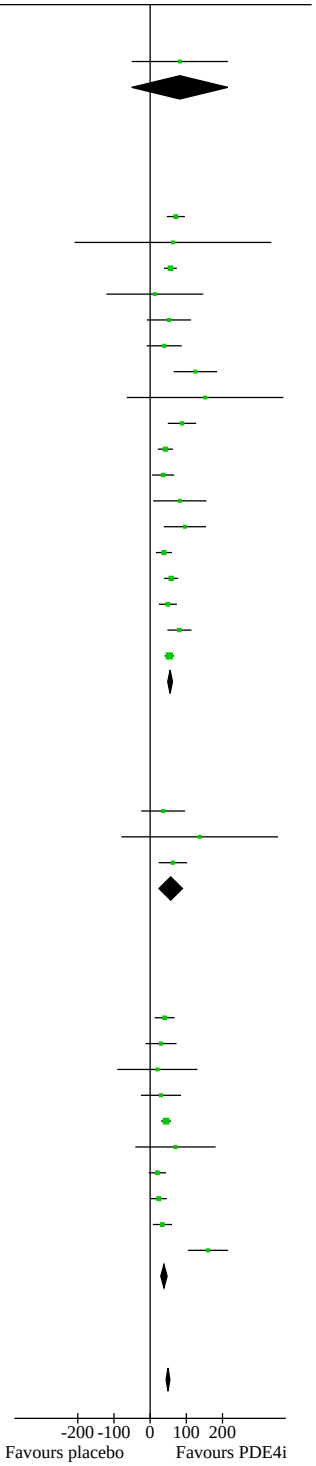
Main analysis

Note that an increase in FEV_1 represents an improvement in lung function.

Based on the 32 trials that reported this outcome, results showed improvement in FEV_1 from baseline among PDE_4 inhibitor-treated participants compared with controls at a mean of 40.17 weeks' duration (mean difference (MD) 49.33 mL, 95% confidence interval (CI) 44.17 to 54.49; participants = 20,815; studies = 32; I^2 = 45%; moderate-certainty evidence) (Analysis 1.1; Figure 3; Summary of findings 1). Effects on FEV_1 with 500 µg or 250 µg roflumilast, respectively, were improved (roflumilast 500 µg: MD 55.18 mL, 95% CI 48.65 to 61.71; participants = 14,384; studies = 18; I^2 = 21%; studies = 17; I^2 = 26%) (roflumilast 250 µg: MD 56.88 mL, 95% CI 24.38 to 89.38; participants = 1033; studies = 3; I^2 = 0%). Similar improvement was observed with cilomilast 15 mg (MD 38.15 mL, 95% CI 29.41 to 46.90; participants = 5322; studies = 10; I^2 = 62%). There was only one small study, with wide uncertainty about effects with tetomilast (MD 82.00 mL, 95% CI -50.84 to 214.84; participants = 76) (Analysis 1.1).

Figure 3. Forest plot of comparison: 1 PDE_4 inhibitor versus placebo (2020 update), outcome: 1.1 FEV_1 (by drug) [mL].

Study or Subgroup	PDE4i treatment Mean [mL]	SD [mL]	Total	Placebo Mean [mL]	SD [mL]	Total	Weight	Mean Difference IV, Fixed, 95% CI [mL]
1.1.1 Tetomilast 50 µg								
NCT00874497 (EMPHASIS)	-1	201.1	48	-83	324.1	28	0.2%	82.00 [-50.84 , 214.84]
Subtotal (95% CI)			**48**			**28**	**0.2%**	**82.00 [-50.84 , 214.84]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.21 (P = 0.23)								
1.1.2 Roflumilast 500 µg								
RO-2455-301-RD (ACROSS)	49	159.5692	313	-22	159.5692	313	4.3%	71.00 [46.00 , 96.00]
RO-2455-402-RD (ROBERT) (1)	63	861	77	0	861	77	0.0%	63.00 [-208.97 , 334.97]
RO-2455-404-RD (REACT)	52	194.9638	928	-4	196.3246	941	8.5%	56.00 [38.26 , 73.74]
Roflumilast DAL-MD-01	41	91	11	28	250	16	0.1%	13.00 [-120.78 , 146.78]
Roflumilast FK1 101 (2)	109	273	169	57	213	86	0.7%	52.00 [-9.00 , 113.00]
Roflumilast FK1 103	78	240	200	39	245	186	1.1%	39.00 [-9.44 , 87.44]
Roflumilast FLUI-2011-77	66	120	30	-59	71	11	0.7%	125.00 [64.96 , 185.04]
Roflumilast IN-108 (2)	28	486	42	-124	281	12	0.1%	152.00 [-64.52 , 368.52]
Roflumilast M2-107 (2)	49	283	555	-39	189	140	1.7%	88.00 [48.83 , 127.17]
Roflumilast M2-111	30	182	545	-12	178	596	6.1%	42.00 [21.08 , 62.92]
Roflumilast M2-112	9	303	760	-27	302	753	2.9%	36.00 [5.52 , 66.48]
Roflumilast M2-118	55	282	127	-27	311	123	0.5%	82.00 [8.34 , 155.66]
Roflumilast M2-119	54	289	189	-42	298	201	0.8%	96.00 [37.74 , 154.26]
Roflumilast M2-124	46	218	745	8	218	745	5.4%	38.00 [15.86 , 60.14]
Roflumilast M2-125	33	189	730	-25	194	766	7.1%	58.00 [38.59 , 77.41]
Roflumilast M2-127	39	192	456	-10	193	460	4.3%	49.00 [24.07 , 73.93]
Roflumilast M2-128	65	229	365	-16	229	364	2.4%	81.00 [47.75 , 114.25]
Roflumilast ROF-MD-07(RE2SPOND)	53	160.836	1178	0	160.836	1174	15.8%	53.00 [40.00 , 66.00]
Subtotal (95% CI)			**7420**			**6964**	**62.5%**	**55.18 [48.65 , 61.71]**
Heterogeneity: Chi² = 21.53, df = 17 (P = 0.20); I² = 21%								
Test for overall effect: Z = 16.56 (P < 0.00001)								
1.1.3 Roflumilast 250 µg								
Roflumilast FK1 101 (2)	93	273	175	57	213	86	0.7%	36.00 [-24.52 , 96.52]
Roflumilast IN-108 (2)	13	492	43	-124	292	13	0.1%	137.00 [-79.38 , 353.38]
Roflumilast M2-107 (2)	24	288	576	-39	189	140	1.7%	63.00 [23.84 , 102.16]
Subtotal (95% CI)			**794**			**239**	**2.5%**	**56.88 [24.38 , 89.38]**
Heterogeneity: Chi² = 1.08, df = 2 (P = 0.58); I² = 0%								
Test for overall effect: Z = 3.43 (P = 0.0006)								
1.1.4 Cilomilast 15 mg								
Cilomilast 039	10	194	378	-30	144	207	3.5%	40.00 [12.30 , 67.70]
Cilomilast 042	30	210	435	0	296	230	1.4%	30.00 [-13.04 , 73.04]
Cilomilast 076	-50	183	21	-70	192	23	0.2%	20.00 [-90.83 , 130.83]
Cilomilast 091	0	417	435	-30	303	230	0.9%	30.00 [-25.40 , 85.40]
Cilomilast 103657	50	86	296	6	89	316	13.9%	44.00 [30.13 , 57.87]
Cilomilast 110	10	179	20	-60	204	26	0.2%	70.00 [-40.92 , 180.92]
Cilomilast 121	14	175	622	-6	181	328	4.6%	20.00 [-3.93 , 43.93]
Cilomilast 156	7	153	364	-17	155	377	5.4%	24.00 [1.82 , 46.18]
Cilomilast 157	32	197	390	-2	182	411	3.8%	34.00 [7.70 , 60.30]
Compton 2001	130	206	107	-30	207	106	0.9%	160.00 [104.53 , 215.47]
Subtotal (95% CI)			**3068**			**2254**	**34.8%**	**38.15 [29.41 , 46.90]**
Heterogeneity: Chi² = 23.75, df = 9 (P = 0.005); I² = 62%								
Test for overall effect: Z = 8.55 (P < 0.00001)								
Total (95% CI)			**11330**			**9485**	**100.0%**	**49.33 [44.17 , 54.49]**
Heterogeneity: Chi² = 56.15, df = 31 (P = 0.004); I² = 45%								
Test for overall effect: Z = 18.73 (P < 0.00001)								
Test for subgroup differences: Chi² = 9.80, df = 3 (P = 0.02), I² = 69.4%								



Footnotes

(1) Units converted from L to mL, standard deviations obtained by imputing participant number in each group in the calculator from GIV analysis. Mean differences for each treatment group were not availa

(2) The participant number in the placebo group was halved to avoid double counting

Moderate and high levels of heterogeneity seen amongst roflumilast 500 µg and cilomilast studies, respectively, can be explained in part by investigation of differences between these two PDE_4 inhibitors (for subgroup analyses, see below).

We investigated publication bias amongst the studies included in the analysis (Figure 4). Four studies were outliers and were investigated further (roflumilast 500 µg: Roflumilast FLUI-2011-77; Roflumilast IN-108; roflumilast 250 µg: Roflumilast IN-108; cilomilast 15 mg: Compton 2001). These studies were small in population size and contributed very little weight to the overall analysis. In addition, removing these studies from the sensitivity analysis did not have a large impact on the overall effect estimate. We did not downgrade the outcome in our GRADE assessment for this reason (Summary of findings 1).

Studies not included in the main analysis

Kavitha 2018 reported FEV_1 at endpoint but did not report the units. It is unclear whether the outcome was reported as litres or millilitres, and trial authors reported much greater improvement compared to authors of another study, which reported improvement of 60 mL (see Kavitha 2018 risk of bias assessment for explanation). Trial authors did not respond when contacted for further information.

Change in FVC from baseline

We included 17 trials in the analysis (Cilomilast 039; Cilomilast 042; Cilomilast 091; Cilomilast 103657; Cilomilast 156; Compton 2001; RO-2455-301-RD (ACROSS); RO-2455-402-RD (ROBERT); RO-2455-404-RD (REACT); Roflumilast M2-107; Roflumilast M2-112; Roflumilast M2-119; Roflumilast M2-124; Roflumilast M2-125; Roflumilast M2-127; Roflumilast M2-128; Roflumilast ROF-MD-07(RE2SPOND)).

Treatment with a PDE_4 inhibitor was associated with greater change in FVC from baseline compared to placebo (MD 86.98, 95% CI 74.65 to 99.31; participants = 22,108; studies = 17; I^2 = 0%; high-certainty evidence) with no heterogeneity amongst the 17 trials (Analysis 1.2; Summary of findings 1).

Studies not included in the main analysis

Kavitha 2018 reported FVC at endpoint but did not report the units. It is unclear whether the outcome was reported as litres or millilitres; therefore, we did not include this study in the analysis. Trial authors did not respond when contacted for further information.

Change in PEF from baseline

We included six studies in the analysis (Compton 2001; Roflumilast FK1 101 (250 µg); Roflumilast FK1 101 (500 µg); Roflumilast M2-119; Roflumilast M2-124; Roflumilast M2-125). Roflumilast FK1 101 compared one placebo group with roflumilast 250 µg or 500 µg; therefore, the number of participants in the placebo group was halved to avoid double counting, and the study was added to the analysis twice to represent higher and lower doses of roflumilast.

Change in PEF was greater with roflumilast treatment overall than with placebo (MD 6.54 L/min, 95% CI 3.95 to 9.13; participants = 4245; studies = 6; I^2 = 74; low-certainty evidence) (Analysis 1.3; Summary of findings 1). On further analysis of doses, we noted improvement in PEF with roflumilast 500 µg but not with roflumilast 250 µg when compared with placebo. Upon further investigation, when Compton 2001 was taken out of the analysis, the heterogeneity was zero.

Change in quality of life

St George's Respiratory Questionnaire (SGRQ)

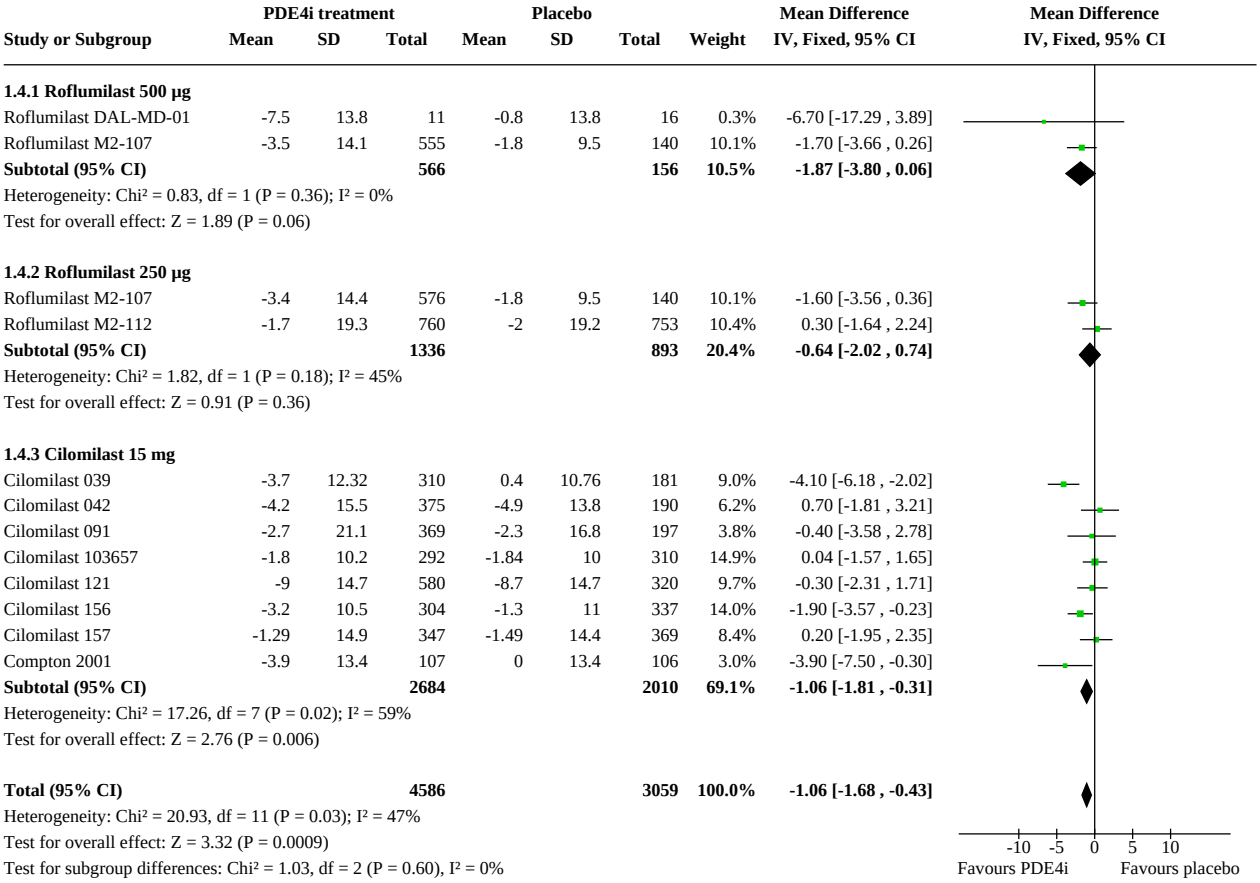
Note that a decrease in SGRQ total score represents improvement in quality of life.

We included 12 studies in the analysis for this outcome (participants = 7645) (Cilomilast 039; Cilomilast 042; Cilomilast 091; Cilomilast 103657; Cilomilast 121; Cilomilast 156; Cilomilast 157; Compton 2001; Roflumilast DAL-MD-01; Roflumilast M2-107 (250 µg); Roflumilast M2-107 (500 µg); Roflumilast M2-112).

Roflumilast M2-107 reported data for 250 µg and for 500 µg roflumilast compared to one placebo group; therefore, the number of participants in the placebo group was halved to avoid double counting, and the study was included in the analysis twice (Analysis 1.4).

We noted a small decrease in total score on the SGRQ from baseline to mean 33 weeks' duration among participants treated with PDE_4 inhibitors compared with those given the control intervention (MD -1.06 units, 95% CI -1.68 to -0.43; participants = 7645; studies = 13; I^2 = 47%; moderate-certainty evidence (Analysis 1.4; Figure 5; Summary of findings 1). Moderate levels of heterogeneity amongst roflumilast and cilomilast studies can be explained further by subgroup analysis (see below).

Figure 5. Forest plot of comparison: 1 PDE$_4$ inhibitor versus placebo (2020 update), outcome: 1.4 SGRQ total score.



Improvement in symptoms (reported as SGRQ symptom score) was uncertain amongst two studies (Roflumilast M2-107; Compton 2001) (MD -1.53 units, 95% CI -4.11 to 1.06; participants = 1048; studies = 2; Analysis 1.5).

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. Liu 2018 was also not included in the analysis due to unclear reporting of standard errors and no response from trial authors.

Secondary outcomes

Incidence of COPD exacerbations

We included 27 trials in the analysis (participants = 20,382) (Cilomilast 039; Cilomilast 042; Cilomilast 076; Cilomilast 091; Cilomilast 111; Cilomilast 121; Cilomilast 156; Cilomilast 157; Cilomilast 168; Cilomilast 180; Liu 2018; NCT00874497 (EMPHASIS); RO-2455-301-RD (ACROSS); RO-2455-402-RD (ROBERT); RO-2455-404-RD (REACT); Roflumilast FK1 101 (500 µg); Roflumilast IN-108; Roflumilast JP-706; Roflumilast M2-107; Roflumilast M2-111+M2-112; Roflumilast M2-119; Roflumilast M2-124; Roflumilast M2-125; Roflumilast M2-127; Roflumilast M2-128; Roflumilast ROF-MD-07(RE2SPOND); Urban 2018 (ELASTIC); .

Use of PDE$_4$ inhibitors was associated with a reduction in the numbers of participants experiencing one or more COPD exacerbations at a mean duration of 40 weeks (odds ratio (OR) 0.78, 95% CI 0.73 to 0.84; high-certainty evidence; Analysis 1.6; Summary of findings 1). This is a relative reduction of more than 20% from a representative risk of 33 per 100 on placebo to 27 per 100 on PDE$_4$ inhibitors over a weighted mean of 40 weeks (Summary of findings 1), and the number needed to treat for an additional beneficial outcome (NNTB) was 20 (95% CI 16 to 27) (Figure 6). There was little heterogeneity among trials (I^2 = 6%), and a reduction in people experiencing COPD exacerbations was seen with both roflumilast and cilomilast. Tetomilast revealed wide uncertainty about the number of participants experiencing one or more COPD exacerbations; only one study contributed to this result (Analysis 1.6).

Figure 6. In the control group, 33 out of 100 people had an exacerbation of COPD over 40 weeks of treatment, compared to 27 (95% CI 26 to 29) out of 100 people in the active treatment group.

Exacerbation rates

Nine studies reported exacerbation rates and the number of exacerbations experienced on average per participant per year (Cilomilast 157; RO-2455-402-RD (ROBERT); Roflumilast M2-111; Roflumilast M2-112; Roflumilast M2-124; Roflumilast M2-125; Roflumilast M2-127; Roflumilast M2-128; Roflumilast ROF-MD-07(RE2SPOND)) (Analysis 1.7). We observed a small benefit with treatment, representing a 12% reduction in the exacerbation rate (0.88, 95% CI 0.83 to 0.93).

Roflumilast FK1 101 reported that the probability of experiencing an exacerbation was reduced by 8% with 250 µg of roflumilast and by 48% with 500 µg, although the absolute value was not reported and it was not stated whether this result was significant.

Four studies reported reduction in severe exacerbation rates per participant per year with PDE_4 inhibitor compared with placebo (Cilomilast 039; RO-2455-404-RD (REACT); Roflumilast M2-124+M2-125; Roflumilast ROF-MD-07(RE2SPOND)). Cilomilast 15 mg resulted in a 45% reduction in severe exacerbations (P = 0.001) (Cilomilast 039). In studies using roflumilast 500 µg, the reduction in the rate of severe exacerbations ranged from 8.5% to 24.3% across studies (Table 2).

Symptoms (breathlessness on Borg or other symptom scales)

We included a total of 14 studies (participants = 10,701) that reported results on the Borg Scale (Analysis 1.8), the Shortness of Breath Questionnaire (Analysis 1.9), the Summary Symptom Scale (Analysis 1.10), or the Breathlessness, Cough, and Sputum Scale (BCSS) (Analysis 1.11) (Borg Scale: Cilomilast 039; Cilomilast 042; Cilomilast 091; Cilomilast 111; Cilomilast 156; Cilomilast 180; Shortness of Breath Questionnaire: Roflumilast M2-127; Roflumilast M2-128; Summary Symptom Scale: Cilomilast 039; Cilomilast 042; Cilomilast 091; RO-2455-404-RD (REACT); Roflumilast ROF-MD-07(RE2SPOND); BCSS: NCT00874497 (EMPHASIS)).

Overall, the mean difference in change from baseline with PDE_4 inhibitor treatment compared with the control intervention on COPD-related symptoms at mean duration of 21 weeks was small, regardless of the scale used to measure it. The only effect was seen in one trial of cilomilast - for breathlessness scored on a Borg Scale (MD -0.19, 95% CI -0.33 to -0.05) (Analysis 1.8). This is a small absolute difference so is of doubtful clinical relevance. Results showed no difference with PDE_4 inhibitor in effects on the Summary Symptom Scale (standardised mean difference (SMD) -0.02, 95% CI -0.07 to 0.03; participants = 6186; studies = 5; I^2 = 19%), the Shortness of Breath Questionnaire (MD -1.09, 95% CI -2.47 to 0.28;

participants = 1633; studies = 2; I^2 = 81%), or the BCSS (Analysis 1.11).

Exercise tolerance (six-minute walk test)

We included six studies that reported the six-minute walk test (6MWT) (participants = 2055) (Cilomilast 039; Cilomilast 042; Cilomilast 091; Cilomilast 111; Roflumilast DAL-MD-01; Urban 2018 (ELASTIC)).

Exercise tolerance was measured on the 6MWT in six trials (two roflumilast and four cilomilast trials). We found uncertainty in walk test distance at a mean duration of 21 weeks between PDE_4 inhibitor and placebo groups (MD 3.50; 95% CI -5.84 to 12.85) (Analysis 1.12).

Adverse events

We included 30 studies in the overall analysis (participants = 21,310) (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; NCT00874497 (EMPHASIS); RO-2455-301-RD (ACROSS); RO-2455-402-RD (ROBERT); RO-2455-404-RD (REACT); Roflumilast DAL-MD-01; Roflumilast FK1 101; Roflumilast IN-108; Roflumilast JP-706; Roflumilast M2-107; Roflumilast M2-111+M2-112; Roflumilast M2-119; Roflumilast M2-124+M2-125; Roflumilast M2-127; Roflumilast M2-128; Roflumilast ROF-MD-07(RE2SPOND); Urban 2018 (ELASTIC)).

Overall, the likelihood of a participant experiencing an adverse event at a mean duration of 38 weeks was higher with PDE_4 inhibitor treatment than with placebo (OR 1.30, 95% CI 1.22 to 1.38; participants = 21,310; studies = 30; I^2 = 64%; low certainty evidence) (Analysis 1.13; Summary of findings 1). This effect was seen for both roflumilast and cilomilast but not for tetomilast, as we found only one study for this PDE_4 inhibitor.

Adverse events: roflumilast 500 µg versus roflumilast 250 µg

The higher dose of roflumilast (500 µg) was associated with more adverse events than the lower dose (250 µg); however, this finding was based on only four trials and confidence intervals were wide (OR 1.21, 95% CI 1.01 to 1.46) (Analysis 1.14).

We found a range of adverse effects that occurred more frequently in PDE_4 inhibitor-treated participants, which are described below.

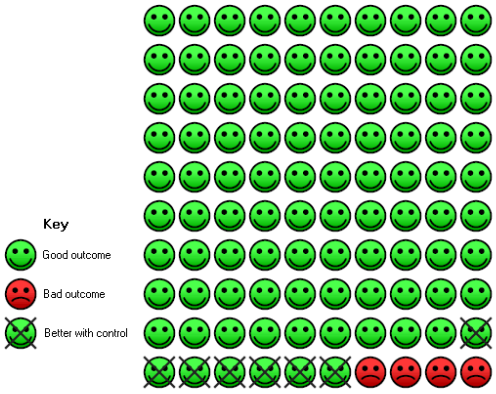
Gastrointestinal adverse effects (diarrhoea, nausea, vomiting, dyspepsia, weight loss)

Diarrhoea was more commonly experienced in PDE_4 inhibitor-treated groups than in placebo groups (OR 3.10, 95% CI 2.74 to 3.50; participants = 20,623; studies = 29; I^2 = 12%; high-certainty evidence) (Analysis 1.15; Summary of findings 1).

Nausea was also reported as an increased side effect (OR 3.79, 95% CI 3.24 to 4.43; participants = 20,949; studies = 28; I^2 = 24%) (Analysis 1.16), as were vomiting (OR 3.95, 95% CI 2.78 to 5.60; participants = 5986; studies = 12; I^2 = 0%) (Analysis 1.17) and dyspepsia (OR 3.17, 95% CI 2.33 to 4.30; participants = 6247; studies = 13; I^2 = 0%) (Analysis 1.18). Weight loss was commonly reported and was an increased adverse effect (OR 3.72, 95% CI 3.09 to 4.47; participants = 12,462; studies = 12; I^2 = 24%) (Analysis 1.19).

More than 10% of participants in the PDE_4 inhibitor group experienced gastrointestinal side effects; diarrhoea was the most frequently reported symptom (Figure 7) (number needed to treat for an additional harmful outcome (NNTH) 14, 95% CI 12 to 17).

Figure 7. In the control group, 4 out of 100 people had a diarrhoea episode over 39 weeks of treatment, compared to 11 (95% CI 10 to 12) out of 100 people in the active treatment group.



Withdrawals

An increase in withdrawals attributed to adverse events was recorded for both roflumilast and cilomilast treatment groups (OR 1.89, 95% CI 1.73 to 2.07; participants = 21,358; studies = 31; I^2 = 21%) (Analysis 1.20).

Headache

We found 23 studies that reported a higher proportion of participants experiencing headache as an adverse effect when taking a PDE_4 inhibitor (OR 1.69, 95% CI 1.46 to 1.94; participants = 19,215; I^2 = 23%) (Analysis 1.21). Participants in the roflumilast 500 µg treatment group were more likely to experience headache than those given placebo (OR 2.13, 95% CI 1.74 to 2.59; participants = 13,565; studies = 12; I^2 = 0%) (Analysis 1.21).

Abdominal pain

Fifteen studies reported abdominal pain as an adverse effect in the PDE_4 inhibitor treatment group (OR 2.02, 95% CI 1.62 to 2.52; participants = 8329; studies = 15; I^2 = 0%) (Analysis 1.22). A greater likelihood of abdominal pain was noted for participants in the roflumilast treatment group compared with the placebo group (OR 2.77, 95% CI 1.38 to 5.56; participants = 2641; studies = 3). Participants were also more likely to experience abdominal pain with cilomilast than with placebo (OR 1.97, 95% CI 1.55 to 2.49; participants = 5604; studies = 11), although the magnitude of effect was smaller compared to that seen with roflumilast (Analysis 1.22).

Influenza-like symptoms

There was uncertainty in the incidence of influenza-like symptoms between PDE_4 inhibitors (OR 1.09, 95% CI 0.87 to 1.36; participants = 11,460; studies = 10), as confidence intervals crossed the line of no effect (Analysis 1.23).

Upper respiratory tract infection

There was uncertainty in the incidence of upper respiratory tract infection between PDE_4 inhibitor and placebo treatment groups (OR 0.91, 95% CI 0.81 to 1.04; participants = 17,022; studies = 23), as confidence intervals crossed the line of no effect (Analysis 1.24).

Psychiatric adverse effects: COPD safety pool

We recorded the number of psychiatric adverse events from pooled data derived 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 results from 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. The likelihood of experiencing a psychiatric adverse event was greater in the roflumilast 500 µg treatment group than in the placebo group (OR 2.13, 95% CI 1.79 to 2.54) (Analysis 1.25; Summary of findings 1). This was reported in three out of 100 people in the placebo group compared to seven out of 100 in the PDE_4 inhibitor-treated group (95% CI 6 to 8) (NNTH 28, 95% CI 21 to 39). The likelihood of experiencing a psychiatric adverse event was uncertain with 250 µg roflumilast compared with placebo, as

the confidence interval crossed the line of no effect (OR 0.87, 95% CI 0.56 to 1.33) (Analysis 1.25).

An increase in symptoms of anxiety (OR 1.81, 95% CI 1.26 to 2.62) (Analysis 1.26) and depression (OR 1.59, 95% CI 1.11 to 2.27) (Analysis 1.27) was associated with roflumilast 500 µg compared with placebo. Uncertainty about symptoms of anxiety (OR 0.94, 95% CI 0.40 to 2.21) or depression (OR 0.56, 95% CI 0.20 to 1.56) was greater with roflumilast 250 µg compared with placebo, as confidence intervals crossed the line of no effect in both analyses (Analysis 1.26; Analysis 1.27).

Three reports described completed suicides and two suicide attempts in roflumilast-treated participants compared to none in participants given placebo (roflumilast COPD safety database, n = 12,054).

In more recent roflumilast trials, the numbers of participants experiencing insomnia and sleep disorders taking roflumilast 500 µg were greater than among those taking placebo (OR 2.67, 95% CI 2.11 to 3.38) (Analysis 1.28), but results with 250 µg roflumilast were uncertain, as the confidence interval crossed the line of no effect (Analysis 1.28).

Serious adverse events

Treatment was found to have no effect on serious adverse events (OR 0.99, 95% CI 0.91 to 1.07; participants = 19,191; studies = 29; I^2 = 54%) (Analysis 1.29).

Mortality

Mortality was a relatively rare event during these trials, results showed no effect of treatment for this outcome (OR 0.98, 95% CI 0.77 to 1.24; participants = 19,786; studies = 27; I^2 = 0%; moderate-certainty evidence) (Analysis 1.30; Summary of findings 1).

Subgroup and sensitivity analyses

Primary outcome: FEV_1

A moderate but significant level of heterogeneity was evidence for the change in FEV_1 outcome when all trials were pooled (I^2 = 45%). We analysed the data further by performing subgroup and sensitivity analyses.

Subgroup analysis: COPD severity

To see whether the size of the treatment effect varied with COPD severity, we conducted subgroup analyses of trials for which the mean per cent predicted FEV_1 at baseline was available (Analysis 1.31). Effects seen in both old GOLD grade I or II ($FEV_1 \geq 50\%$) predicted and old GOLD grade III or IV ($FEV_1 < 50\%$) were statistically significant and of similar magnitude (MD 52.78, 95% CI 46.73 to 58.83; test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.87)).

Subgroup analysis: dose (roflumilast 500 µg versus roflumilast 250 µg)

For dose effects of roflumilast, both roflumilast 500 µg and roflumilast 250 µg were associated with a similar change in FEV_1 (roflumilast 500 µg: MD 55.18, 95% CI 48.65 to 61.71; participants = 14,384; studies = 18; I^2 = 21%; roflumilast 250 µg: MD 56.88, 95% CI 24.38 to 89.38; participants = 1033; studies = 3; I^2 = 0%) (test for subgroup differences: Chi^2 = 0.01, df = 2 (P = 0.92)) (Analysis 1.1; Figure 3).

Subgroup analysis: duration of treatment

For FEV_1, the size of the treatment effect, that is, the mean difference between PDE_4 and placebo groups, was numerically greater in short studies of 6 to 12 weeks (MD 101.71, 95% CI 70.96 to 132.46; participants = 1191; studies = 8) than in studies of 24 to 26 weeks (MD 46.14, 95% CI 38.44 to 53.84; participants = 8086; studies = 13) and studies of 52 weeks (MD 48.77, 95% CI 41.44 to 56.10; participants = 10,662; studies = 7). However this difference between subgroups may be a chance finding (test for subgroup differences: Chi^2 = 5.11, df = 6 (P = 0.53)) (Analysis 1.33).

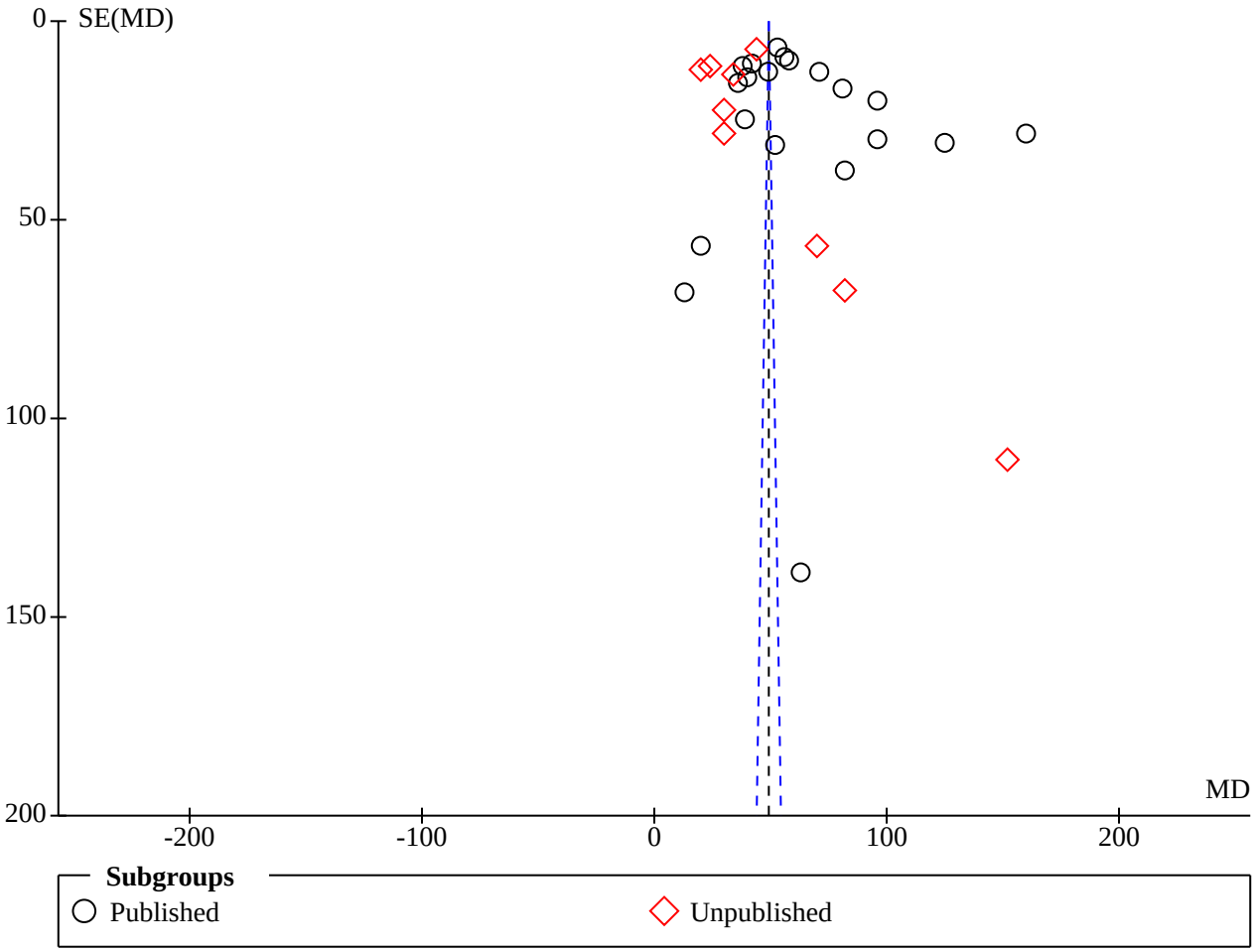
Subgroup analysis: concomitant therapies (roflumilast versus cilomilast)

With respect to PDE_4 inhibitor use with concomitant therapies (Analysis 1.34), the largest increases in FEV_1 were seen in two trials where participants were taking regular, long-acting bronchodilators: in one trial, salmeterol (Roflumilast M2-127), and in the other, tiotropium (Roflumilast M2-128) (MD 60.52 mL, 95% CI 40.57 to 80.46). The next largest improvements were seen in trials for which 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) (Analysis 1.34). A similar improvement in FEV_1 was seen when participants were taking corticosteroids (MD 42.26 mL, 95% CI 25.46 to 59.05) (Analysis 1.34). Improvements in FEV_1 were also noted in trials where only a PDE_4 inhibitor was taken (apart from short-acting $beta_2$ agonists) (MD 44.80 mL, 95% CI 37.69 to 51.91) (test for subgroup differences: Chi^2 = 5.61, df = 3 (P = 0.13) (Analysis 1.34).

Sensitivity analysis

Using a random-effects model made no difference in levels of statistical significance nor degree of heterogeneity for the change in FEV_1 (MD 51.49, 95% CI 42.87 to 60.10; Analysis 1.35). Too many 'Risk of bias' domains were judged to be at 'unclear' risk of bias for subgroup analysis to be conducted according to study quality. Of note, some effect sizes were greater in the published trials, for example, the treatment effect on FEV_1 was MD 55.75 mL (95% CI 49.45 to 62.06) in the 20 published trials, and MD 35.05 (95% CI 25.70 to 44.40) in the nine unpublished trials (Analysis 1.36), which was significantly different (test for subgroup differences: Chi^2 = 12.94, df = 1 (P = 0.0003)). This is illustrated in the funnel plot, with more unpublished studies showing a smaller treatment effect (Figure 8).

Figure 8. Funnel plot of comparison: 2 PDE_4 inhibitor versus placebo (2020 update), outcome: 2.36 FEV_1 (published versus unpublished).



By visual analysis of the forest plot and sequential elimination, we identified the six-week Compton 2001 cilomilast trial as a major contributor to the heterogeneity of pooled FEV_1 results. When this trial was removed, the overall I^2 statistic decreased from 45% to 26%, and in the cilomilast subgroup from 62% to 0%. It is notable that this study had the shortest treatment duration (six weeks) and showed the greatest improvement from baseline in FEV_1 lung function in the treatment group across all studies.

Primary outcome: SGRQ

Subgroup analysis: COPD severity

Although quality of life was improved in participants with GOLD grade I or II COPD severity, and with GOLD grade III or IV COPD severity (MD -1.56 units, 95% CI -2.39 to -0.74; participants = 4851; studies = 8) (test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.89)) (Analysis 1.37), overall heterogeneity was high (I^2 = 55%). Studies in which participants had grade I or II COPD severity were similar (I^2 = 0%), but variation was observed amongst studies in which participants had grade III or IV COPD severity (I^2 = 73%) (Analysis 1.37).

Subgroup analysis: duration of treatment

It is notable that in two trials with a duration of one year that reported total SGRQ, the change in quality of life seen with treatment compared with control was uncertain (MD 0.26, 95% CI -1.18 to 1.69) (Analysis 1.38). However, quality of life was improved among participants taking a PDE_4 inhibitor for less than 12 weeks (MD -4.19, 95% CI -7.60 to -0.78) and for 24 to 26 weeks (MD -1.18, 95% CI -1.94 to -0.42). A significantly greater treatment effect was noted in short studies (6 to 12 weeks) compared with studies of 24 to 52 weeks. A high level of heterogeneity (I^2 = 57%) was observed amongst studies providing 24 to 26 weeks of treatment (test for subgroup differences: Chi^2 = 6.50, df = 2 (P = 0.04)) (Analysis 1.38).

Sensitivity analysis

Analysis revealed a difference in 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: Chi^2 = 4.94, df = 1 (P = 0.03)) (Analysis 1.39).

Secondary outcome: exacerbations

Subgroup analysis: additional medications

When investigating whether other additional medication made any difference, we found similar efficacy for both roflumilast and cilomilast, specifically when use of concomitant long-acting bronchodilators was permitted (OR 0.79, 95% CI 0.73 to 0.85) (test for subgroup differences: $Chi^2 = 1.53$, df = 3 (P = 0.67)) (Analysis 1.40).

DISCUSSION

Summary of main results

This systematic review evaluated randomised controlled trials (RCTs) that assessed the efficacy and safety of oral phosphodiesterase 4 (PDE_4) inhibitors in people with chronic obstructive pulmonary disease (COPD). The conclusions of this review remain unchanged following the addition of new studies for the 2020 update, reporting small improvements in lung function and quality of life and decreased exacerbations.

Lung function

Based on data from 32 trials (low-certainty evidence), we found that both roflumilast and cilomilast led to greater improvements in lung function from baseline, as measured by forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), or peak expiratory flow rate (PEF), compared with placebo (Summary of findings 1). Furthermore, improvement in lung function was seen regardless of the severity of the disease. This improvement in FEV_1 lung function occurred whether or not PDE_4 inhibitor treatment was given in addition to other COPD treatments, such as long-acting $beta_2$-agonists (LABAs) or anticholinergics or inhaled corticosteroids (ICSs).

Greater improvement in FEV_1 was observed in studies of shorter duration (Analysis 1.33); this could be due to a limited short-term response to PDE_4 inhibitor treatment, as might be seen with tachyphylaxis, and needs further investigation.

The mean change in FEV_1 was less than what is usually considered a minimum clinically important difference (MCID) (100 mL; Donohue 2005), but it was comparable to that seen with other COPD treatments in recent large RCTs. For example, mean improvement in FEV_1 of 49 mL with treatment, as 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 among people with severe COPD.

Quality of life

Data show only a small improvement in quality of life as assessed by 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 PDE_4 inhibitors might outweigh any beneficial COPD-related events. The average change in SGRQ total score was 1.06 units (over a duration between 6 and 12 months) (Summary of findings 1) 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 MCID (Jones 2005). Although symptom scores were marginally better in the treatment groups, no change was seen in exercise tolerance, suggesting that improvements in respiratory symptoms may not necessarily translate into enhanced physical functioning. Fewer trials were assessable for these outcomes, raising the possibility of type 1 or type 2 error.

Exacerbations

A second major finding, based on data from 27 trials (moderate-certainty evidence; Summary of findings 1), was that participants were more likely to be exacerbation-free while being treated with PDE_4 inhibitors compared with those given control interventions. 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% confidence interval (CI) 16 to 26) for one person to be exacerbation-free in the study period (Figure 6; Summary of findings 1). Although the likelihood of an individual experiencing an exacerbation was lowered with PDE_4 inhibitor treatment, the decrease in the overall rate of exacerbations was less marked, with a relative reduction of 13%.

Taken together, results for lung function and exacerbations suggest that PDE_4 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 longer studies, but the reasons for this are unclear. Significant heterogeneity was noted among trials, suggesting that unmeasured differences between trials may be having an impact.

Adverse events

Adverse events were more likely among roflumilast- and cilomilast-treated participants than among those receiving placebo (very low-certainty evidence; Summary of findings 1), particularly gastrointestinal effects such as diarrhoea, nausea, vomiting, and dyspepsia.

Participants in treatment groups were more likely to withdraw from trials because of adverse events; on average, 14% in the treatment groups withdrew compared with 8% in the control groups. Similarly, there was a slight excess in the total numbers of participants in the treatment groups experiencing any adverse event compared with numbers in the control groups (Analysis 1.13). As this analysis included symptoms as well as exacerbations, which were reduced among treatment groups, the analysis will tend to underestimate the excess of non-COPD-related adverse events occurring with PDE_4 inhibitor treatment.

It is notable that treatment with roflumilast was associated with an increased incidence of weight loss. Whether this was due to anorexia from gastrointestinal adverse effects or from another effect is not yet clear. Also not clear is whether cilomilast has the same effect, as this has not been studied. Weight loss may be a beneficial effect for 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 2020). This adverse effect warrants further investigation. It is reassuring that there was no increase in serious adverse events nor in mortality, although trials were of relatively short duration and analyses were underpowered to report on the latter outcome.

Although the lower dose (250 µg) of roflumilast produced similar improvements in FEV_1 (Analysis 1.32) and was associated with

slightly fewer adverse events than the larger dose (Analysis 1.14), the lower dose was associated with a smaller reduction in rates of exacerbation when compared with the higher dose in the only trial that reported this (Roflumilast FK1 101). Moreover, data on the lower dose were available from a limited number of studies, and this has not been studied as add-on therapy to other bronchodilators.

Awareness of the risk of psychiatric adverse events associated with roflumilast treatment is growing (Analysis 1.25; Summary of findings 1), in particular the increased likelihood of experiencing sleep disturbances, anxiety, and depressed mood. It should be noted that we found three reports of completed suicides and two of suicide attempts among roflumilast-treated participants compared to none in participants given placebo (roflumilast COPD safety database).

Mortality

Mortality was a rare event, and there was no difference between participants treated with a PDE_4 inhibitor and those given placebo (Analysis 1.30; Summary of findings 1).

Overall completeness and applicability of evidence

We have reviewed all known published and unpublished trials identified through standard Cochrane searches, as well as those obtained from the trials register for the National Institutes of Health (NIH) and from pharmaceutical websites.

We have not been able to verify the pooled endpoint data for psychiatric (treatment possibly harmful) and cardiovascular adverse events (treatment possibly beneficial), as we obtained this information from reports on the US Food and Drug Administration (FDA) website and from White 2013, respectively.

To ensure that our Cochrane systematic review accurately reflects all known outcomes of roflumilast therapy, for previous updates we approached the manufacturer of roflumilast for study-level data on each of the cardiovascular outcomes (cardiovascular death, non-fatal myocardial infarction, and 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 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 per-study data that would comprise numbers in each treatment arm that were too low for conclusive interpretation.
- In none of the studies was blinded adjudication of events implemented as a prospective analysis, which would have required a data release in terms of transparency for each individual study (this is why it was not mentioned in the original publications of 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 treatment groups were matched at baseline, it cannot be assumed that these groups are equivalent when the focus is only on groups of participants who experienced exacerbations. These concerns could not be assessed in this review, as further study data were not provided.

Certainty of the evidence

For the key outcomes of changes in lung function and quality of life, greater beneficial effects of PDE_4 inhibitors were reported in published than in unpublished studies, raising concerns about publication bias. When investigating publication bias further for each outcome, we found that eliminating from the analyses studies with suspected publication bias did not significantly alter overall effect estimates or confidence intervals for lung function or quality of life. Similarly, this was apparent when adverse events were investigated.

We identified a moderate level of heterogeneity for 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 that unknown factors that may impact effect size have led us to downgrade the quality of evidence and the certainty of our findings (Summary of findings 1). In contrast, the blinded design of studies comparing roflumilast or cilomilast with placebo protected against detection bias in our view. The certainty of evidence for a reduction in exacerbation was therefore higher for this comparison. On balance, we believe the true beneficial effect of PDE_4 inhibitors is likely to be no greater than we have reported and is probably less; equally, the harms of PDE_4 treatment may have been understated (due in part 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 for individual participants, we cannot rule out benefit for individuals of a specific COPD phenotype.

Addition of new trials

The 2020 update of this review included four studies on roflumilast 500 µg and one study on tetomilast (Kavitha 2018; Liu 2018; NCT00874497 (EMPHASIS); RO-2455-402-RD (ROBERT); Urban 2018 (ELASTIC)). Data from these new trials did not affect the results already yielded by analyses. Kavitha 2018 and Liu 2018 were not included in the analyses for lung function, as the units for this endpoint were unclear even though we contacted trial authors for clarification. Data from Liu 2018 were not included in the meta-analysis for SGRQ due to unclear data units in the publication.

Potential biases in the review process

Potential biases in the review process were minimised by double-checking of data extraction and input. The review authors have no conflicts of interest to declare.

Agreements and disagreements with other studies or reviews

Several other meta analyses have been conducted, including Luo 2016, Yuan 2016, and Shen 2018. Each of these included fewer studies than the present review but presented findings and conclusions that were similar. Our findings are also similar to those

presented by Wedzicha 2016 and show effects on exacerbations similar to those described in Rabe 2017.

In a post hoc pooled analysis (n = 5595) of four trials in this review (Rennard 2014), roflumilast was seen to improve transition dyspnoea index (TDI) focal scores of breathlessness versus placebo at week 52 (treatment difference 0.327; P < 0.0001). Roflumilast was associated with more TDI responders and 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 PDE_4 inhibitors have been meta-analysed and reported in White 2013. This review found that 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 the placebo group (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 events individually were statistically different. Cardiovascular events were higher among participants with baseline cardiovascular risk factors than among 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 statistically significant only for the group of participants without baseline risk factors. Event rates in a subgroup of trials that were one year in duration show no significant differences 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 were similar (43.2% and 42.1%, respectively).

AUTHORS' CONCLUSIONS

Implications for practice

Phosphodiesterase-4 (PDE_4) inhibitors are oral medicines that may be taken in combination with other standard chronic obstructive pulmonary disease (COPD) treatments. Most evidence has been gathered for roflumilast at a dose of 500 µg daily and cilomilast at 15 mg twice daily.

PDE_4 inhibitors join an increasing list of treatments for COPD that improve short-term lung function and reduce exacerbations, but they have not been shown to increase life expectancy. Most trials to date have been one year in duration (with the exception of one study of nearly two years' duration). In contrast to long-acting bronchodilators, PDE_4 inhibitors have minimal benefit for symptoms on a day-to-day basis, or for quality of life, and are often associated with adverse effects, especially gastrointestinal effects and headaches. Roflumilast is associated with greater weight loss and increased psychiatric symptoms compared with placebo. Findings of this review provide cautious support for the use of PDE_4 inhibitors in COPD. In accordance with GOLD 2020 guidelines, PDE_4 inhibitors may have a place as add-on therapy for a subgroup of people with persistent symptoms or exacerbations despite optimal COPD management (e.g. people who are not controlled on fixed-dose long-acting $beta_2$-agonist (LABA) and inhaled corticosteroid (ICS) combinations).

Implications for research

This review has highlighted several possible topics for further study.

- Effects of PDE_4 inhibitors on forced expiratory volume in one second (FEV_1) decline and mortality in studies of longer duration.
- Effects of PDE_4 inhibitors at shorter time points in longer-duration studies on FEV_1.
- Subgroup analysis of participants with/without chronic bronchitis and with/without a history of exacerbations.
- Effects of PDE_4 inhibitors among participants with frequent exacerbations.
- Effects of PDE_4 inhibitors on healthcare utilisation, including hospitalisation (incidence and bed days).
- Direct comparison of PDE_4 inhibitors and inhaled corticosteroids (ICSs) when used as add-on therapies to tiotropium, to long-acting $beta_2$-agonists (LABA), or to all three (triple inhaled therapies).
- Direct comparison of tiotropium or LABA, or both, as add-on therapies to PDE_4 inhibitors (± ICS).
- Effects of roflumilast on quality of life.
- Better characterisation of the weight loss seen with PDE_4 inhibitors in COPD.
- Better description of the nature of effects on exacerbations that do occur.
- Use of PDE_4 inhibitors in acute exacerbations.
- Cost-effectiveness of PDE_4 inhibitors.
- Increased exercise tolerance data for roflumilast.
- Increased data on tetomilast.
- Whether there is any benefit on cardiovascular outcomes for PDE_4 inhibitors in COPD.
- Use of effects of PDE_4 inhibitors to better understand the pathophysiology of COPD.
- Further evaluation of roflumilast 250 µg versus 500 µg daily.
- Subgroup analysis of participants based on their weight.
- Use of CAT score as an outcome.
- Responder analyses (e.g. proportion of participants achieving a minimum clinically important difference).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Cilomilast 039

Study characteristics	
Methods	**Study design**: parallel-group study
	Randomisation: randomised, double-blind, placebo-controlled trial
	Trial duration: 24 weeks
	Intention-to-treat analysis: stated

Cilomilast 039 *(Continued)*

Participants	**Setting**: 102 centres in Canada, Mexico, and the USA **Participants**: 647 (15 mg cilomilast: 431, placebo: 216) **Baseline characteristics**: mean age 65 years, 62% male, mean FEV_1 % predicted 49.7%, mean smoking history 59.9 pack-years for cilomilast and 56.1 pack-years for placebo, or current smokers (44% and 47%, respectively) **Inclusion criteria**: $FEV_1/FVC \leq 0.7$, FEV_1 30% to 70% with smoking history > 10 pack-years or current smokers **Exclusion criteria**: active tuberculosis, lung cancer, bronchiectasis **Total numbers of participant withdrawals**: 137 (32%) and 52 (24%) from treatment and control groups, respectively
Interventions	**Run-in**: 4 weeks, single-blind. Placebo tablets to assess suitability • Cilomilast 15 mg twice daily • Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: "the only other permitted medications for the treatment of airways disease were stable doses of Ipratropium, via a metered-dose inhaler, and mucolytic agents" • SABA: "...the short-acting β_2-agonist albuterol, which was administered via a metered-dose inhaler, was supplied for the relief of acute respiratory symptoms" • Corticosteroid: none • LABA: none
Outcomes	**Primary outcomes**: lung function; change in FEV_1; SGRQ averaged over 24 weeks **Secondary outcomes**: incidence rate of COPD exacerbations; adverse events; FVC at trough; 6MWT; post-exercise dyspnoea
Notes	Funded by GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assumed that the randomisation process was adequate due to pharma sponsorship
Allocation concealment (selection bias)	Low risk	Assumed that the allocation concealment method was adequate due to pharmaceutical sponsorship
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	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%).

Cilomilast 039 *(Continued)*

		More subjects receiving cilomilast than placebo withdrew from the double-blind phase of study (31.8% (n = 137) versus 24.1% (n = 52)"
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. Trial information was reported on the GSK website
Other bias	Low risk	Baseline anticholinergic, beta$_2$-agonist, or corticosteroid use 54% in cilomilast, 58% placebo used ipratropium; 99% in cilomilast, 100% placebo used albuterol; 9% in cilomilast, 12% placebo used salmeterol; 7% in cilomilast, 8% placebo used triamcinolone; 6% in cilomilast, 7% placebo used beclomethasone

Cilomilast 042

Study characteristics	
Methods	**Study design**: 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 49% with 5.1% reversibility, DLCO 71% predicted, also with higher rates of chronic bronchitis 80.1%. 45% active smokers **Inclusion criteria**: aged 40 to 80 years, $FEV_1/FVC \leq 0.7$, FEV_1 30% to 70% with smoking history > 10 pack-years **Exclusion criteria**: active tuberculosis, lung cancer, bronchiectasis **Total numbers 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** • Short-acting anticholingeric: 2% in cilomilast, 3% placebo used salbutamol; 3% in cilomilast, 1% placebo used ipratropium • SABA: "albuterol MDI was used as rescue medication" • Corticosteroid: none • LABA: 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 trough; 6MWT; post-exercise dyspnoea
Notes	Funded by GlaxoSmithKline

Cilomilast 042 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assumed that the randomisation method was adequate due to pharma sponsorship
Allocation concealment (selection bias)	Low risk	Assumed that the allocation concealment method was adequate due to pharmaceutical company sponsorship
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total numbers of participants withdrawn 51 (23%) placebo, 122 (26%) cilomilast, primarily due to adverse events, of which most were not from COPD exacerbations
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. Trial information was reported on the GSK website
Other bias	Unclear risk	No information on baseline anticholinergic, beta$_2$-agonist, or corticosteroid use

Cilomilast 076

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 12 weeks Analysis was done on per-protocol population
Participants	**Setting**: not stated **Participants**: 59 (15 mg cilomilast: 29, placebo: 30) **Baseline characteristics**: mean age 61 to 62 years, 81% male, 53% active smokers, mean 46 pack-years, 53% to 58% FEV_1 predicted **Inclusion criteria**: aged 40 to 80 years, fixed airflow obstruction, smoking history > 10 pack-years **Exclusion criteria**: not stated **Total numbers of participant withdrawals**: 4 (14%) and 2 (7%) from treatment and control groups, respectively
Interventions	**Run-in**: 4 weeks, single-blind with placebo • Cilomilast 15 mg twice daily

Cilomilast 076 *(Continued)*

	• Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: "14 of 59 used ipratropium bromide at a constant dosage (8 in the placebo group, 6 in the cilomilast group)" • SABA: "all patients were given albuterol for use as required" • Corticosteroid: none • LABA: none Used alongside SABA (available to all) and anticholingeric drugs (offered to 24%)
Outcomes	**Primary outcome**: change in neutrophil percentage in induced sputum **Secondary outcomes**: FEV_1; numbers of subepithelial CD8+ cells, CD 68+ cells, epithelial, and subepithelial neutrophils
Notes	Funded by GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assumed that the randomisation process was adequate due to pharmaceutical company sponsorship
Allocation concealment (selection bias)	Low risk	Assumed that the allocation concealment method was adequate due to pharmaceutical company sponsorship
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	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"
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. Trial information was reported on the GSK website
Other bias	Unclear risk	No information on baseline anticholinergic, $beta_2$-agonist, or corticosteroid use

Cilomilast 091

Study characteristics

Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 24 weeks

Cilomilast 091 *(Continued)*

	Intention-to-treat analysis: stated
Participants	**Setting**: 110 centres in Belgium, Finland, France, Italy, the Netherlands, Norway, Portugal, Spain, and the UK **Participants**: 711 (15 mg cilomilast: 469, placebo: 242) **Baseline characteristics**: mean age 64.6 years, 86% male, mean FEV_1 % predicted 53% with 5.0% reversibility, 38% active smokers **Inclusion criteria**: $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years **Exclusion criteria**: active tuberculosis, lung cancer, bronchiectasis **Total numbers of participant withdrawals**: 121 (26%) and 63 (26%) 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** • Short-acting anticholingeric: 0.9% in cilomilast, 4% placebo used salbutamol; 1% in cilomilast, 3% placebo used ipratropium • SABA: "albuterol MDI was used as rescue medication" • Corticosteroid: none • LABA: 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 trough; 6MWT; post-exercise dyspnoea
Notes	Funded by GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assumed that the randomisation process was adequate due to pharmaceutical company sponsorship
Allocation concealment (selection bias)	Low risk	Assumed that the allocation concealment method was adequate due to pharmaceutical company sponsorship
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total numbers of participants withdrawn 63 (26%) placebo, 121 (26%) cilomilast, primarily due to adverse events, of which most were not due to COPD exacerbations

Cilomilast 091 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Outcomes were reported as planned. Trial information was reported on the GSK website only
Other bias	Unclear risk	No information on baseline anticholinergic, beta$_2$-agonist, or corticosteroid use

Cilomilast 103657

Study characteristics	
Methods	**Study design**: 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, 63.1 years cilomilast, 47% male placebo, 46% male cilomilast. Mean FEV_1 % predicted not available **Inclusion criteria**: aged ≥ 40 years, FEV_1/FVC ≤ 0.7 with smoking history > 10 pack-years, ≤ 70% post-albuterol reversibility, ≤ 15% or ≤ 200 mL (or both) post-albuterol FEV_1 ≤ 70% of predicted normal, ≥ 1 COPD exacerbation within 12 months before screening **Exclusion criteria**: not stated **Total numbers 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** • Short-acting anticholingeric: no information available • SABA: no information available • Corticosteroid: no information available • LABA: no information available
Outcomes	**Primary outcomes**: change from baseline to endpoint in trough pre-bronchodilator FEV_1; change in total SGRQ score averaged over 24 weeks **Secondary outcomes**: changes from baseline in clinic trough FVC; time to first level 2 or level 3 COPD exacerbation
Notes	Funded by GlaxoSmithKline

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

Cilomilast 103657 *(Continued)*

Random sequence generation (selection bias)	Low risk	Assumed that trialists used a robust method to carry out the randomisation process because of pharmaceutical company sponsorship
Allocation concealment (selection bias)	Low risk	Assumed that trialists used a robust method to carry out the randomisation process because of pharmaceutical company sponsorship
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was double-blinded (participants and investigator). It is not clear if the investigator was administering the treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total numbers of participants withdrawn 76 (24%) placebo, 105 (35%) cilomilast
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. The trial was registered at clinicaltrials.gov
Other bias	Unclear risk	No information on baseline anticholinergic, beta$_2$-agonist, or corticosteroid use

Cilomilast 110

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 12 weeks Analysis was done on 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 to 80 years, $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years, post-salbutamol reversibility ≤ 15% or 200 mL, post-salbutamol $FEV_1 \geq 1.0$ L and between 30% and 70% predicted **Exclusion criteria**: not stated **Total numbers of participant withdrawals**: 1 (3%) and 1 (3%) from treatment and control groups, respectively
Interventions	**Run-in**: not stated • Cilomilast 15 mg twice daily • Placebo twice daily **Concomitant medication**

Cilomilast 110 *(Continued)*

- Short-acting anticholingeric: no information available
- SABA: no information available
- Corticosteroid: no information available
- LABA: no information available

Outcomes	**Primary outcome**: change from baseline at endpoint in neutrophils as a percentage of total cells in induced sputum **Secondary outcomes**: FVC at trough; sputum macrophages, eosinophils, and lymphocytes as a percentage of total cells in induced sputum; total cell counts in induced sputum
Notes	Funded by GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assumed that trialists used a robust method to carry out the randomisation process because of pharmaceutical sponsorship
Allocation concealment (selection bias)	Low risk	Assumed that trialists used a robust method to carry out the randomisation process because of pharmaceutical sponsorship
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total numbers of participants withdrawn 1 (3%) placebo, 1 (3%) cilomilast
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. Trial information was reported on the GSK website only
Other bias	Unclear risk	No information on baseline anticholinergic, beta$_2$-agonist, or corticosteroid use

Cilomilast 111

Study characteristics

Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 12 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 32 centres in the USA, Canada, and Australia **Participants**: 156 (15 mg cilomilast: 79, placebo: 77)

Cilomilast 111 *(Continued)*

	Baseline characteristics: mean age 64.2 years placebo and 65 years cilomilast, 66% male placebo and 65% male cilomilast, mean FEV_1 % predicted not available **Inclusion criteria**: aged 40 to 80 years, $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years, post-salbutamol reversibility ≤ 15% or 200 mL, post-salbutamol $FEV_1 \geq 1.0$ L and between 30% and 70% predicted, baseline RV (from plethysmography) ≥ 120% predicted RV **Exclusion criteria**: not stated **Total numbers of participant withdrawals**: 15 (19%) and 14 (18%) from treatment and control groups, respectively
Interventions	**Run-in**: not stated • Cilomilast 15 mg twice daily • Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: no information available • SABA: no information available • Corticosteroid: no information available • LABA: no information available
Outcomes	**Primary outcome**: change from baseline to endpoint in volume of trapped gas (D) **Secondary outcomes**: lung volume measurements, including SVC and RV; 6MWT; exertional dyspnoea
Notes	Funded by GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assumed that trialists used a robust method to carry out the randomisation process because of pharmaceutical sponsorship
Allocation concealment (selection bias)	Low risk	Assumed that trialists used a robust method to carry out the allocation concealment process because of pharmaceutical sponsorship
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total numbers of participants withdrawn 14 (18%) placebo, 15 (19%) cilomilast
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. Trial information was reported on the GSK website only
Other bias	Unclear risk	No information on baseline anticholinergic, $beta_2$-agonist, or corticosteroid use

Cilomilast 121

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 24 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 22 centres in China **Participants**: 1018 (15 mg cilomilast: 678, placebo: 340) **Baseline characteristics**: mean age 63.9 years placebo and 64.6 years cilomilast, 91% male placebo and 93% male cilomilast, mean FEV_1 % predicted not available **Inclusion criteria**: aged 40 to 75 years, FEV_1/FVC ≤ 0.7 with smoking history > 10 pack-years, documented history of COPD exacerbations each year for 3 years before screening, ≥ 1 exacerbation in the last year that required oral corticosteroids or antibiotics, post-salbutamol reversibility ≤ 15% or 200 mL, post-salbutamol FEV_1 ≥ 1.0 L and between 25% and 70% predicted, % predicted FRC ≥ 120% from plethysmography **Exclusion criteria**: not stated **Total numbers of participant withdrawals:** 124 (18%) and 35 (10%) from treatment and control groups, respectively
Interventions	**Run-in**: not stated • Cilomilast 15 mg twice daily • Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: no information available • SABA: no information available • Corticosteroid: no information available • LABA: no information available
Outcomes	**Primary outcome**: change from baseline to endpoint in trough pre-bronchodilator FEV_1 **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 on SGRQ
Notes	Funded by GlaxoSmithKline

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Assumed that trialists used a robust method to carry out the randomisation process because of pharmaceutical company sponsorship
Allocation concealment (selection bias)	Low risk	Assumed that trialists used a robust method to carry out the allocation concealment process because of pharmaceutical company sponsorship

Cilomilast 121 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total numbers of participants withdrawn 35 (10%) placebo, 124 (18%) cilomilast
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. Trial information was reported on the GSK website only
Other bias	Low risk	No information on baseline anticholinergic, beta$_2$-agonist, or corticosteroid use

Cilomilast 156

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 24 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 132 centres in USA and Canada **Participants**: 825 (15 mg cilomilast: 418, placebo: 407) **Baseline characteristics**: mean age 64.4 years placebo and 64.5 years cilomilast, 62% male placebo and 56% male cilomilast, > 50% predicted FEV_1 for both groups **Inclusion criteria**: aged 40 to 80 years, FEV_1/FVC ≤ 0.7 with smoking history > 10 pack-years, post-salbutamol reversibility ≤ 15% or 200 mL, post-salbutamol FEV_1 ≥ 1.0 L and between 30% and 70% predicted **Exclusion criteria**: not stated **Total numbers of participant withdrawals**: 143 (34%) and 96 (24%) from treatment and control groups, respectively
Interventions	**Run-in**: not stated • Cilomilast 15 mg twice daily • Placebo twice daily **Concomitant medication** • Short-acting anticholingeric 8.1% in cilomilast, 8.6% placebo used salbutamol; 1.7% in cilomilast, 2% placebo used ipratropium bromide • SABA: "albuterol MDI was used as rescue medication" • Corticosteroid: none • LABA: none

Cilomilast 156 *(Continued)*

Outcomes	**Primary outcomes**: change from baseline to endpoint in trough pre-bronchodilator FEV_1; change in total SGRQ score averaged over 24 weeks **Secondary outcomes**: post-exercise breathlessness; clinic trough FVC; time to first level 2 or level 3 COPD exacerbation
Notes	Funded by GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation code was provided by RAMOS (registration and medication ordering system)
Allocation concealment (selection bias)	Low risk	No further information on allocation concealment method
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and personnel did not know which treatment had been allocated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors did not know which treatment had been allocated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total numbers of participants withdrawn 96 (24%) placebo, 143 (34%) cilomilast
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. Trial information was reported on the GSK website only
Other bias	Low risk	No information on baseline anticholinergic, $beta_2$-agonist, or corticosteroid use

Cilomilast 157

Study characteristics

Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 52 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 137 centres from 18 countries **Participants**: 907 (15 mg cilomilast: 455, placebo: 452) **Baseline characteristics**: mean age 63.3 years placebo and 64.6 years cilomilast, 73% male placebo and 78% male cilomilast, 42% current smokers **Inclusion criteria**: aged 40 to 80 years, $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years, poor reversibility of airway obstruction defined by ≤ 10% predicted normal or ≤ 200 mL (or both) increase in

Cilomilast 157 *(Continued)*

	FEV_1 after administration of salbutamol 400 µg via MDI at screening, post-salbutamol FEV_1 between 30% and 70% predicted normal at screening **Exclusion criteria**: not stated **Total numbers of participant withdrawals**: 167 (37%) and 121 (27%) from treatment and control groups, respectively
Interventions	**Run-in**: not stated • Cilomilast 15 mg twice daily • Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: no information available • SABA: no information available • Corticosteroid: no information available • LABA: no information available
Outcomes	**Primary outcomes**: mean change from baseline in trough pre-bronchodilator FEV_1 averaged over 52 weeks; incidence rate of level 2 (moderate) and level 3 (severe) COPD exacerbations during treatment period **Secondary outcomes**: time to first level 2 or level 3 COPD exacerbation; quality of life determined by SGRQ
Notes	Funded by GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation code was generated via the pharmaceutical company's coding memo system in blocks
Allocation concealment (selection bias)	Low risk	No further information on allocation concealment method
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and investigator were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total numbers of participants withdrawn 121 (27%) placebo, 167 (37%) cilomilast
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. Trial information was reported on the GSK website only
Other bias	Low risk	No information on baseline anticholinergic, $beta_2$-agonist, or corticosteroid use

Cilomilast 168

Study characteristics	
Methods	**Study design**: 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% predicted **Exclusion criteria**: not stated **Total numbers 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** • Short-acting anticholingeric: no information available • SABA: no information available • Corticosteroid: no information available • LABA: no information available
Outcomes	**Primary outcome**: no primary efficacy or safety analyses defined; descriptive statistics of change from baseline in minimum and maximum heart rate via 24-hour Holter monitoring reported **Secondary outcome**: no secondary efficacy or safety analyses defined
Notes	Funded by GlaxoSmithKline

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation sequence was generated by the pharmaceutical company's biometrics unit
Allocation concealment (selection bias)	Unclear risk	No further information on allocation concealment method
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was double-blind

Cilomilast 168 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total numbers of participants withdrawn 14 (14%) placebo, 61 (30%) cilomilast
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. Trial information was reported on the GSK website only
Other bias	Low risk	No information on baseline anticholinergic, beta$_2$-agonist, or corticosteroid use

Cilomilast 180

Study characteristics	
Methods	**Study design**: 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 **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 ≥ 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 BDI focal score ≤ 7, evidence of hyperinflation defined by RFRC ≥ 140% predicted, exercise limitation defined as peak symptom limited VO_2 < 75% **Exclusion criteria**: not stated **Total numbers of participant withdrawals**: 24 (25%) and 13 (13%) from treatment and control groups, respectively
Interventions	**Run-in**: not stated • Cilomilast 15 mg twice daily • Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: no information available • SABA: no information available • Corticosteroid: no information available • LABA: no information available
Outcomes	**Primary outcome**: change from baseline at endpoint in RFRC

Cilomilast 180 *(Continued)*

	Secondary outcomes: change from baseline at endpoint in IC during exercise; exertional dyspnoea as measured by the modified Borg Scale
Notes	Funded by GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised via a call to the sponsor's medication ordering system, during which the patient's subject number was confirmed and the patient was provided with a 6-digit container number for identification of the initial bottle of double-blind medication
Allocation concealment (selection bias)	Unclear risk	No further information on allocation concealment method.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was double blind. Cilomilast and matched placebo tablets were identical in appearance, and only the double-blind medication included the container number
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total numbers of participants withdrawn 13 (13%) placebo, 24 (25%) cilomilast
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. Trial information was reported on the GSK website only
Other bias	Low risk	No information on baseline anticholinergic, beta$_2$-agonist, or corticosteroid use

Cilomilast 181

Study characteristics

Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 13 weeks Analysis was done on the per-protocol population
Participants	**Setting**: 27 centres in Australia, Canada, Finland, Ireland, Lithuania, Norway, Romania, Slovakia, Slovenia, South Africa, Sweden, and the UK **Participants**: 127 (15 mg cilomilast: 65, placebo: 62) **Baseline characteristics**: mean age 63.4 years placebo and 61.4 years cilomilast, 76% male placebo and 72% male cilomilast

Cilomilast 181 *(Continued)*

	Inclusion criteria: aged 40 to 80 years, FEV_1/FVC ≤ 0.7 with smoking history > 10 pack-years, post-bronchodilator FEV_1 between 40% and 80% predicted normal, poor reversibility of ≤ 10% or 200 mL increase in FEV_1 **Exclusion criteria**: not stated **Total numbers of participant withdrawals**: 8 (12%) and 6 (10%) from treatment and control groups, respectively
Interventions	**Run-in**: not stated • Cilomilast 15 mg twice daily • Placebo twice daily **Concomitant medication** • Short-acting anticholingeric: no information available • SABA: no information available • Corticosteroid: no information available • LABA: no information available
Outcomes	**Primary outcomes**: change from baseline at endpoint in CD68+ (macrophages) and CD8+ (cytotoxic T lymphocytes) per unit area of tissue **Secondary outcomes**: change from baseline in numbers of subepithelial cells per unit area in biopsy for neutrophil elastase-positive (ne+) cells, CD4+, IL-8 mRNA-positive cells, TNF-alpha mRNA-positive cells
Notes	Funded by GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A central randomisation schedule that was balanced at site level. An interactive voice response system was used to generate a random number to assign eligible participants
Allocation concealment (selection bias)	Low risk	Assumed that the allocation concealment method was adequate due to pharmaceutical company sponsorship
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was double-blind. Participants and personnel were blind to which treatment they were assigned to. Cilomilast and matched placebo tablets were identical in appearance, and only the double-blind medication included the container number
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total numbers of participants withdrawn 6 (10%) placebo, 8 (12%) cilomilast
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. Trial information was reported on the GSK website only
Other bias	Low risk	No information on baseline anticholinergic, $beta_2$-agonist, or corticosteroid use

Compton 2001

Study characteristics	
Methods	**Study design**: 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 to 63 years, 75% to 78% male, mean FEV_1 % predicted 46.8%, mean smoking history 36 to 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, recent corticosteroid use **Total numbers 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** • Short-acting anticholingeric: 382 (90%) participants were given concomitant treatment for COPD during the study; 267 (70%) salbutamol and 115 (30%) ipratropium bromide • SABA: salbutamol used in 70% • Corticosteroid: none • LABA: none
Outcomes	**Primary outcomes**: lung function: change in FEV_1; SGRQ **Secondary outcomes**: peak expiratory flow and FVC; first dose effect of active treatment on FEV_1
Notes	Post-bronchodilator results not given, so pre-bronchodilator values used in analysis. Funded by GlaxoSmithKline

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised. Assumed that the randomisation method was adequate due to pharmaceutical company sponsorship
Allocation concealment (selection bias)	Low risk	Assumed that the allocation concealment method was adequate due to pharmaceutical company sponsorship
Blinding of participants and personnel (performance bias)	Low risk	The trial was double-blinded. Participants were not aware of which treatment they were receiving because cilomilast and matched placebo tablets were identical in appearance

Compton 2001 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was double-blinded, but it is unclear who assessed the outcomes
Incomplete outcome data (attrition bias) All outcomes	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"
Selective reporting (reporting bias)	Unclear risk	Unclear whether outcomes were assessed as planned; it was not possible to find the trial in the GSK registry
Other bias	Low risk	102 (24%) participants had been taking long-acting β_2-agonists (e.g. salmeterol, formoterol). 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

Study characteristics		
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 µg once daily Roflumilast 250 µg once daily Placebo once daily	
Outcomes		
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Unclear risk	See individual studies
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trials were double-blind
Blinding of outcome assessment (detection bias)	Unclear risk	Assumed that this would be low risk; however, no available information

COPD safety pool *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See individual studies
Selective reporting (reporting bias)	Unclear risk	See individual studies
Other bias	Unclear risk	See individual studies

Kavitha 2018

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised controlled trial **Trial duration**: 12 weeks **Intention-to-treat analysis**: not stated
Participants	**Setting**: 1 pulmonary medicine ward in India **Participants**: 61 (intervention: 31; control: 30) **Baseline characteristics**: mean age 58 years, mean FEV_1 predicted 0.93, current smokers 33% **Inclusion criteria**: Indian ethnicity, age ≥ 40 years with moderate to severe COPD, current or past smokers, other co-existing conditions **Exclusion criteria**: bronchial asthma, other lung diseases, lower respiratory tract infection, pregnant or breastfeeding **Total numbers of participant withdrawals**: not stated; assumed 1 person was not included in the analysis
Interventions	**Run-in**: not stated • Roflumilast 500 µg once daily with 12 µg formoterol and 9 µg tiotropium combination metered-dose inhaler once daily • Formoterol 12 µg and 9 µg tiotropium combination metered-dose inhaler once daily **Concomitant medication** • All study participants were taking formoterol 12 µg and 9 µg tiotropium combination metered-dose inhaler
Outcomes	**Primary outcomes**: lung function (FEV_1 and FVC); change in mean FEV_1 after treatment **Secondary outcomes**: adverse events in the roflumilast treatment group
Notes	Funding not stated

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

Kavitha 2018 *(Continued)*

Random sequence generation (selection bias)	High risk	Reported as a "randomised control study". No further information about randomisation method. Also, groups are not balanced with regards to baseline characteristics. For example, the placebo group includes a high percentage of patients with diabetes
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Assumed that there was no blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assumed that there was no blinding of the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant in the roflumilast group was lost; however, reasons for attrition were not reported
Selective reporting (reporting bias)	High risk	Outcomes not reported in the methods, so unclear whether outcomes reported were what they intended to assess. Adverse event data were not reported for the control group, so it is unclear whether there were no events in this group. Outcome data for FEV_1 were not clear, as no units were reported. If it is assumed that trial authors reported litres, then those in the intervention group improved by 660 mL, which is large in COPD terms, as it indicates 28% improvement, yet in the discussion, trial authors mention that it is similar to the 60 mL reported in the Fabbri study
Other bias	Low risk	No information on baseline anticholinergic, $beta_2$-agonist, or corticosteroid use

Liu 2018

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 52 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: single hospital in Yan'an, China **Participants**: 120 (roflumilast 500 µg: 60, placebo: 60) **Baseline characteristics**: COPD stage II to IV according to GOLD criteria, mean age 65 years, FEV_1 % predicted < 50%, 72% male, smoking history 37 pack-years, 66% current smokers **Inclusion criteria**: aged ≥ 40 years, post-bronchodilator FEV_1 < 50% predicted, FEV1:FVC ratio 70%, post-bronchodilator FEV_1 with 30% to 80% predicted, COPD history > 12 months, no medication change for past 3 months **Exclusion criteria**: asthma, other lung disease, systemic glucocorticosteroids, SABA 1 month before study, severe mental disorder, pregnant or breastfeeding

Liu 2018 *(Continued)*

	Total numbers of participant withdrawals: 5 (8%) and 6 (10%) from treatment and control groups, respectively
Interventions	**Run-in**: not stated • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication** • Anticholingeric: 40% of participants were on anticholinergics • β_2-agonist: 34% of participants were on β_2-agonists • Corticosteroid: 18% of participants were on ICSs • LABA: not stated 23% of participants were on home oxygen therapy
Outcomes	**Primary outcome**: change from baseline in lung function (FEV_1, FVC, and $FEF_{25\%-75\%}$) **Secondary outcomes**: quality of life (SGRQ); adverse events
Notes	Funding not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved via a computerised number programme generated by a statistician who was blinded to treatment allocation
Allocation concealment (selection bias)	Unclear risk	Unclear how the allocation sequence was concealed from patients (i.e. no mention of concealed envelopes or any other method)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were reported to be blinded to treatment allocation; investigators, data analysts, and outcome assessors were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants were reported to be blinded to treatment allocation; investigators, data analysts, and outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, the number of withdrawals was 9%; however there was 1 more withdrawal in the placebo group compared to the intervention group
Selective reporting (reporting bias)	High risk	Reporting of outcome data for lung function and SGRQ is unclear. Data provided consist of mean difference and 95% CI when standard errors should be provided. A check of the data revealed discrepancies in the numbers. Data for adverse events were also unclear. There was no reference to a protocol, so we do not know whether outcomes were reported as planned. The paper includes some confusing statements about follow-up at 12 weeks vs 12 months - probably 12 months - but then follow-up for another 3 months. Abstract states that adverse events were increased, but this is not the same as the data in the paper
Other bias	Low risk	No information on baseline anticholinergic, beta$_2$-agonist, or corticosteroid use

NCT00874497 (EMPHASIS)

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, triple-blind, placebo-controlled trial **Trial duration**: 104 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 12 specialist centres across the USA **Participants**: 84 (tetomilast 25 µg: 51, placebo: 33) **Baseline characteristics**: mean age 58 years, 51% male I**nclusion criteria**: aged 40 to 75 years, rating ≥ 1 on Goddart scale for emphysema, FEV_1:FVC > 70% predicted, ≥ 1 COPD exacerbation in the past 12 months **Exclusion criteria**: asthma, active tuberculosis/bronchiectasis, respiratory tract infection in past month before screening, cancer in past 5 years, cardiovascular/endocrine blood/nervious system disorder, uncontrolled COPD exacerbation (level 2 or 3), recent systemic ICS or immunosuppressant, anticoagulant **Total numbers of participant withdrawals**: 28 (54%) and 18 (54%) from treatment and control groups, respectively
Interventions	**Run-in**: 25 µg dose tetomilast for 2 weeks **Intervention**: 50 µg once daily **Comparator**: placebo once daily **Concomitant medication** • Short-acting anticholingeric: not stated • SABA: not stated • Corticosteroid: not stated • Long-acting $beta_2$-agonist: not stated
Outcomes	**Primary outcomes:** change in FEV_1; rate of change in 20th percentile of lung voxels **Secondary outcomes:** change in trough FEV_1; density mask score based on lung density voxels; rate of change in 20th percentile of lung density voxels expressed in HU units for whole lung; rate of change in emphysema (observed); change in cumulative frequency of HU; change in computed tomography (derived lung volumes); change in trough RV/TLC; change in trough inspiratory capacity; change in trough functional residual capacity; change in carbon monoxide diffusion capacity; changes in mean specific airway resistance and specific conductance; change in 7-day average total symptom score for dyspnoea, cough, and sputum; change in 7-day mean number of actuations of rescue medications; percentage of participants with COPD exacerbations by group; percentage of participants experiencing a COPD exacerbation **Safety outcomes:** adverse events; changes in laboratory parameters, blood pressure, heart rate, physical examination findings, body weight, and BMI
Notes	Clinicaltrials.gov identifier: NCT00874497 Funded by Otsuka Pharmaceutical Development & Commercialization, Inc.
Risk of bias	

NCT00874497 (EMPHASIS) *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assumed that the randomisation method was adequate due to pharmaceutical company sponsorship
Allocation concealment (selection bias)	Low risk	Assumed that the allocation concealment method was adequate due to pharmaceutical company sponsorship
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was double-blind; participants, care providers, and outcome assessors were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was double-blind; participants, care providers, and outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	54% in each group did not complete treatment and discontinued the trial early, but there were 5 more adverse events in the tetomilast group vs the placebo group. 4 more people in the intervention arm discontinued because of early termination of the trial. Other factors included loss to follow-up, withdrawal by either participant, or physician decision. Different numbers were used in different analyses
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. Trial information was reported on the GSK website
Other bias	Unclear risk	No information on baseline anticholinergic, beta$_2$-agonist, or corticosteroid use

RO-2455-301-RD (ACROSS)

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 24 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 43 centres in mainland China, Hong Kong, and Singapore **Participants**: 626 (500 µg roflumilast: 313, placebo: 313) **Baseline characteristics**: mean age 64 years, 91% male, mean FEV_1 % predicted 36%, mean smoking history 37.2 pack-years for roflumilast and 37.5 pack-years for placebo or current smokers (24% and 29%, respectively) **Inclusion criteria**: Chinese, Malaysian, or Indian ethnicity, age 40 to 80 years with severe or very severe COPD, $FEV_1/FVC \leq 0.7$, post-bronchodilator $FEV_1 \leq 50\%$. Current smokers or ex-smokers with smoking history > 10 pack-years or current smokers; 12-month history of COPD and ≥ 14 puffs of rescue medication during the week before randomisation **Exclusion criteria**: primary bronchiectasis, cystic fibrosis, bronchiolitis, lung resection, lung cancer, interstitial lung disease, active TB, lower respiratory tract infection, diagnosis of asthma at < 40 years of age, α_1-antitrypsin deficiency

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

	Total numbers of participant withdrawals: 67 (21.4%) and 50 (16%) from treatment and control groups, respectively
Interventions	**Run-in**: 4 weeks, single-blind. Placebo tablets to assess suitability • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication** 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 before 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 before study inclusion. All other COPD treatments were not allowed
Outcomes	**Primary outcomes**: lung function; change in pre-bronchodilator FEV_1 **Secondary outcomes**: changes in post-bronchodilator FEV_1, FVC, incidence rates of COPD exacerbations, time to first COPD exacerbation, transition dyspnoea index, proportions of participants experiencing a COPD exacerbation, adverse events, changes in body weight, laboratory values, vital signs, and physical examination findings
Notes	Clinicaltrials.gov identifier: NCT01313494 Funded by AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Investigators used an automated, interactive voice-response system to randomly assign participants. The sponsor generated a list of participant numbers using a pseudo-random number generator
Allocation concealment (selection bias)	Low risk	The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was double-blinded, and tablets were identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was double-blinded. The investigator or anyone at the study site was prevented from knowing the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total numbers of participants that discontinued 50 (16%) placebo, 67 (21.4%) roflumilast
Selective reporting (reporting bias)	Unclear risk	Outcomes were reported as planned, and the trial was registered at the NCT website
Other bias	Low risk	LAMA: 17.9% for placebo; 20.4% for roflumilast SAMA: 18.2% for placebo; 17.3% for roflumilast ICS/LABA: 55.9% for placebo; 59.7% for roflumilast No information available. SABA allowed

RO-2455-402-RD (ROBERT)

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 16 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 18 centres in Denmark, Germany, Poland, Sweden, and United Kingdom **Participants**: 158 (500 µg roflumilast: 79; placebo: 79) **Baseline characteristics**: mean age 63 years, 77% male, mean FEV_1 predicted 60%, mean smoking history longer than 20 years or current smokers 54% I**nclusion criteria**: post-bronchodilator 30% ≤ FEV_1 ≤ 8% predicted, post-bronchodilator FEV_1/FVC ratio ≤ 70%, current/former smoker history ≥ 20 pack-years; aged 40 to 80 years with COPD diagnosed at least 12 months before study inclusion, chronic productive cough for 3 months in each of previous 2 years **Exclusion criteria**: recent COPD exacerbation, ongoing upper or lower respiratory tract infection, asthma (with or without other lung disease), alpha-1-antitrypsin deficiency, bleeding disorder, concomitant glucocorticosteroids, theophylline, lipoxygenase inhibitors, antiplatelet therapy, leukotriene antagonists **Total numbers of participant withdrawals**: 3 (4%) and 6 (8%) from treatment and control groups, respectively
Interventions	**Run-in**: 6 weeks, single-blind with placebo to assess compliance. ICS and other non-allowed drugs stopped • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication** • Short-acting anticholingeric: none • SABA: none • Corticosteroid: not permitted. • Long-acting β_2-agonist: 61% in the roflumilast group and 61% in the placebo group, respectively
Outcomes	**Primary outcome**: change in numbers of CD8 inflammatory cells in bronchial biopsy samples **Secondary outcomes**: change in numbers of inflammatory cells measured in submucosa, bronchial epithelium, induced sputum; blood FEV_1, FVC, and FEV_1/FVC ratio **Safety outcomes**: adverse events; changes in laboratory parameters, blood pressure, heart rate, physical examination findings, body weight, and BMI
Notes	Funded by AstraZeneca
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

RO-2455-402-RD (ROBERT) *(Continued)*

Random sequence generation (selection bias)	Low risk	A computerised central randomisation system stratified by concomitant use of LABA was used
Allocation concealment (selection bias)	Low risk	Both roflumilast and placebo were given as identical yellow, triangular tablets; blinding was maintained via an interactive voice-response system and an interactive web-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded to group assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall the total % of participants who discontinued was 5.7%. In the roflumilast group, 3.7% discontinued compared to 7.59% in the placebo group. The number of adverse events was the same in each group; the numbers not completing were 6 in the placebo group and 3 in the roflumilast group
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. Some of the outcome data were reported in the NCT and EU clinical trials registers
Other bias	Low risk	No information on baseline anticholinergic, beta$_2$-agonist, or corticosteroid use

RO-2455-404-RD (REACT)

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 52 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 203 centres in 21 countries (see online appendix) **Participants**: 1945 (500 µg roflumilast: 969; placebo: 966) **Baseline characteristics**: mean age 65 years, 75% male, mean FEV_1 predicted 35%, mean smoking history 48 pack-years for roflumilast and 48 pack-years for placebo or current smokers (42% and 45%, respectively) **Inclusion criteria**: ≥ 40 years of age with a smoking history ≥ 20 pack-years and a diagnosis of COPD with severe airflow limitation (confirmed by post-bronchodilator FEV_1/FVC ratio < 0.70 and post-bronchodilator FEV_1 ≤ 50% predicted), symptoms of chronic bronchitis, history of ≥ 2 exacerbations in the previous year. 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% to 125% during the 4-week baseline observation period, and with a total cough and sputum score ≥ 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

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

	Exclusion criteria: COPD exacerbation that was ongoing during the baseline period, diagnosis of asthma or other major lung disease **Total numbers of participant withdrawals**: 269 (28%) and 192 (20%) from treatment and control groups, respectively
Interventions	**Run-in**: 4 weeks, single-blind. Placebo tablets to assess suitability • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication** All participants used a fixed-dose ICS–LABA combination during baseline and treatment periods. If a participant had an exacerbation that needed additional treatment during the study, the investigator could give up to 40 mg prednisolone, administered systemically, per day for 7 to 14 days. In the case of purulent sputum or suspected bacterial infection, additional antibiotic therapy was allowed. Use of the following treatments was not allowed: oral and parenteral glucocorticosteroids (except to treat acute exacerbations), LABA or ICS monotherapy, SAMA, and any SABA (with the exception of salbutamol) or oral β_2-agonists. Participants already taking inhaled tiotropium bromide (a LAMA) were allowed to continue this treatment
Outcomes	**Primary outcomes**: rate of moderate or severe COPD exacerbations per patient per year **Secondary outcomes**: change from baseline in post-bronchodilator FEV_1, rate of severe COPD exacerbations per patient per year, rate of COPD exacerbations per patient per year (all categories), percentage of participants experiencing ≥ 1 COPD exacerbation, time to first COPD exacerbation (all categories), time to second moderate or severe COPD exacerbation, time to third moderate or severe COPD exacerbation, number of participants needed to treat to avoid 1 moderate or severe COPD exacerbation derived from exacerbation per patient per year, number of moderate or severe COPD exacerbation days, duration of moderate or severe COPD exacerbations per participant, change from baseline in post-bronchodilator FVC, change from baseline in post-bronchodilator FEF (25% to 75% vital capacity), change from baseline in post-bronchodilator FEV_6, change from baseline in post-bronchodilator FEV_1/FVC, change from baseline in rescue medication use, change from baseline in COPD symptom score, percentage symptom-free days, percentage rescue medication-free days, change from baseline in CAT total score, percentage participants with CAT score improvement, time to mortality (all-cause and COPD exacerbation-related), time to withdrawal (all-cause and COPD exacerbation-related), percentage of participants with major adverse cardiovascular event, time to first major adverse cardiovascular event, percentage of participants with hospitalisation (all-cause), time to first hospitalisation, time to withdrawal due to adverse event, percentage of participants experiencing ≥ 1 adverse event (treatment-related), change from baseline in body weight, change from baseline in BMI
Notes	Clinicaltrials.gov identifier: NCT01329029 Funded by AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	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)
Allocation concealment (selection bias)	Low risk	All parties involved in the study were masked to treatment assignment
Blinding of participants and personnel (performance bias)	Low risk	Roflumilast and placebo were supplied as identical yellow triangular tablets in wallet cards containing 40 tablets; all parties involved in the study were masked to treatment assignment

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

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All parties involved in the study were masked to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	269 participants (28%) in the roflumilast group discontinued from the study and 192 (20%) from the placebo group discontinued
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. The trial was registered at the NCT website
Other bias	Unclear risk	LAMA: 69% for placebo; 70% for roflumilast. No group differences stated; however 1900 (98%) of 1935 participants were using a combination of ICS–LABA according to the protocol

Roflumilast DAL-MD-01

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 12 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: single centre in USA **Participants**: 27 (500 µg roflumilast: 11, placebo: 16) **Baseline characteristics**: mean age 62 years, 64% male, mean FEV_1 % predicted 45%, mean smoking history 44 pack-years for roflumilast and 47 pack-years for placebo or current smokers (63% and 55%, respectively) **Inclusion criteria**: > 40 years old with a diagnosis of moderate to severe COPD as defined by GOLD 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 ≥ 3 months for 2 consecutive years **Exclusion criteria**: asthma as defined by ATS/ERS guidelines, clinically significant bronchiectasis, known sensitivity to roflumilast, use of other methylxanthines (specifically theophylline) within 1 month of screening, changes to maintenance COPD therapy within 1 month of screening **Total numbers of participant withdrawals**: 1 (9%) and 1 (6%) from treatment and control groups, respectively
Interventions	**Run-in**: no run-in • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication** 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%) and 6 (55%)

Roflumilast DAL-MD-01 *(Continued)*

Outcomes	**Primary outcome**: change in induced sputum AcPGP at 12 weeks post randomisation in an intention-to-treat analysis **Secondary outcomes**: changes in plasma AcPGP, sputum neutrophil counts, additional sputum biomarkers, 6MWT, Breathlessness Cough and Sputum Scale, SGRQ scores, changes in post-bronchodilator FEV_1 at 12-week visit
Notes	Clinicaltrials.gov identifier NCT01572948. Funded by Forest Laboratories Inc., University of Alabama at Birmingham

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was reported as block randomised with a 1:1 allocation, stratified by current smoking status and ICS use, but no information about the sequence generation was provided
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was triple-blinded (participant, care provider, and investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was triple-blinded (participant, care provider, and investigator)
Incomplete outcome data (attrition bias) All outcomes	Low risk	At follow-up, only 1 participant in each group was lost because of refusal to attend the final visit or inability to be contacted for the final visit
Selective reporting (reporting bias)	Low risk	Outomes were reported as planned; the trial was registered at clinicaltrials.gov
Other bias	Unclear risk	None

Roflumilast FK1 101

Study characteristics

Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 26 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: not stated **Participants**: 516 (roflumilast 250 µg: 175, roflumilast 500 µg: 169, placebo: 172) **Baseline characteristics**: median age 61 to 62 years, 72% male, mean 38 to 63 pack-years, 53% current smokers

Roflumilast FK1 101 *(Continued)*

	Inclusion criteria: aged 40 to 75 years, $FEV_1/FVC \leq 0.7$ with smoking history > 10 pack-years, reversibility < 12% or 200 mL, post-bronchodilator FEV_1 35% to 75% predicted **Exclusion criteria**: not stated **Total numbers of participant withdrawals**: not stated
Interventions	**Run-in**: 2 weeks with placebo • Roflumilast 500 µg once daily • Roflumilast 250 µg once daily • Placebo once daily **Concomitant medication** • Short-acting anticholinergic: allowed at a constant daily dose for those treated before with anticholinergics on a constant dosage • SABA: salbutamol was allowed as rescue medication • Corticosteroid: none • LABA: none
Outcomes	**Primary outcomes**: post-bronchodilator FEV_1 and FEF between 25% and 75% of vital capacity **Secondary outcomes**: numbers of moderate or severe COPD exacerbations that required treatment with OCS
Notes	Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised. No further information
Allocation concealment (selection bias)	Unclear risk	No available information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No available information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No available information
Selective reporting (reporting bias)	Unclear risk	Unpublished study; no available information
Other bias	Low risk	None

Roflumilast FK1 103

Study characteristics	
Methods	**Study design**: 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 µg: 200, placebo: 186) **Baseline characteristics**: mean age 60 years, 75% male, 62% current smokers, average 35 pack-years **Inclusion criteria**: aged 40 to 75 years, $FEV_1/FVC \leq 0.7$, post-bronchodilator FEV_1 35% to 75% predicted, FEV_1 reversibility ≤ 12% and ≤ 200 mL, pre-bronchodilator $FEV_1/FVC \leq 70\%$ **Exclusion criteria**: not stated **Total numbers of participant withdrawals**; not stated
Interventions	**Run-in**: 2 weeks with placebo • Roflumilast 500 µg once daily for 24 weeks • Roflumilast 500 µg once daily for 12 weeks. Placebo once daily for following 12 weeks **Concomitant medication** • Short-acting anticholinergic: all medications were withdrawn except constant-dose short-acting anticholinergics • SABA: as rescue medication • Corticosteroid: none • LABA: none Used alongside short-acting β_2-agonists (available to all)
Outcomes	**Primary outcomes**: results for 12/24-week post-bronchodilator FEV_1
Notes	Funding not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	No information available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available

Roflumilast FK1 103 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Low risk	None

Roflumilast FLUI-2011-77

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 26 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 numbers of participant withdrawals**: not stated
Interventions	**Run-in**: not stated • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication**: not stated
Outcomes	**Primary outcomes**: post bronchodilation: spirometry, body plethysmography, 6MWT, patient-reported outcomes **Secondary outcomes**: not stated
Notes	Clinicaltrials.gov identifier NCT01480661 Funded by Takeda

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported as block randomised in a 3:1 ratio of roflumilast to placebo, respectively; no further information about sequence generation

Roflumilast FLUI-2011-77 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was reported as triple-blind (participant, care provider, and investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was reported as triple-blind (participant, care provider, and investigator)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Selective reporting (reporting bias)	Low risk	Outcomes reported as intended; trial registered at clinicaltrials.gov
Other bias	Low risk	None

Roflumilast IN-108

Study characteristics	
Methods	**Study design**: 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 µg: 47, roflumilast 200 µg: 46, placebo: 25) **Baseline characteristics**: mean age 60 years, 98% male, 41% current smokers, post-bronchodilator FEV_1 57% to 61%, average 25 pack-years **Inclusion criteria**: not stated **Exclusion criteria**: not stated **Total numbers of participant withdrawals**: roflumilast 500 µg: 13 (28%); roflumilast 200 µg: 7 (15%); control 10 (40%)
Interventions	**Run-in**: none • Roflumilast 250 µg once daily • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication** • Short-acting anticholinergic: not stated • SABA: not stated • Corticosteroid: none

Roflumilast IN-108 *(Continued)*

- LABA: not stated

Outcomes	**Primary outcome**: post-bronchodilator FEV_1 **Secondary outcomes**: COPD exacerbations, adverse events
Notes	Funded by Forest Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised. No further information available
Allocation concealment (selection bias)	Unclear risk	No information available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was reported as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data as above
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Unclear risk	None

Roflumilast JP-706

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 24 weeks **Intention-to-treat analysis**: not stated
Participants	**Setting**: Japan **Participants**: 600 (roflumilast 250 µg: 205, roflumilast 500 µg: 204, placebo: 191) **Baseline characteristics**: mean age 70 years, 96% male, post-bronchodilator FEV_1 not stated, average 56 pack-years, 37% current smokers **Inclusion criteria**: not stated **Exclusion criteria**: not stated

Roflumilast JP-706 *(Continued)*

	Total numbers of participant withdrawals: not stated
Interventions	**Run-in**: single-blind 4 weeks with placebo • Roflumilast 500 µg once daily • Roflumilast 250 µg once daily • Placebo once daily **Concomitant medication** • Short-acting anticholinergic: used at a constant daily dose • SABA: not stated • Corticosteroid: not stated • LABA: not stated
Outcomes	**Primary outcomes**: pulmonary function (FEV_1 pre-bronchodilator, FVC pre- and post-bronchodilator, MMEF pre- and post-bronchodilator) **Secondary outcomes**: number of COPD exacerbations, number of days to first COPD exacerbation, adverse events (all-cause and drug-related), serious adverse events (all-cause and drug-related)
Notes	Funded by Mitsubishi-Tanabe

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised; no further information about randomisation process
Allocation concealment (selection bias)	Unclear risk	No information available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was reported as double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	High risk	No further information available about the trial. No trial registry information found
Other bias	Low risk	None

Roflumilast M2-107

Study characteristics

Methods	**Study design**: parallel-group study

Roflumilast M2-107 *(Continued)*

	Randomisation: randomised, double-blind, placebo-controlled trial **Trial duration**: 24 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 159 centres in Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, South Africa, Spain, and the UK **Participants**: 1411 (roflumilast 250 µg: 576, roflumilast 500 µg: 555, placebo: 280) **Baseline characteristics**: median age 64 years, 74% male, post-bronchodilator FEV_1 51% for both groups, average 42 pack-years, 45% current smokers **Inclusion criteria**: aged ≥ 40 with history of COPD > 12 months, FEV_1 < 50% predicted, FEV_1/FVC ≤ 0.7 with smoking history > 10 pack-years, reversibility < 12% or 200 mL, mean post-bronchodilator FEV_1 30% to 80% predicted **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 run-in period **Total numbers of participant withdrawals**: 124 (22%) and 32 (11%) from treatment and control groups, respectively
Interventions	**Run-in**: 4 weeks with placebo • Roflumilast 500 µg once daily • Roflumilast 250 µg once daily • Placebo once daily **Concomitant medication** • Short-acting anticholinergic: used at a constant daily dose • SABA: salbutamol as rescue medication • Corticosteroid: none • LABA: none
Outcomes	**Primary outcomes**: post-bronchodilator FEV_1; SGRQ total score **Secondary outcomes**: change from baseline in pre-bronchodilator FEV_1; post-bronchodilator FVC; post-bronchodilator FEV in 6 seconds and FVC; FEF rate between 25% and 75% of vital capacity; number of moderate or severe COPD exacerbations
Notes	Funded by ALTANA Pharma AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation sequence was generated by the sponsor in a blind manner
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment method, but "no person involved in data analysis had knowledge of the randomisation sequence"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was double-blind. Roflumilast and placebo tablets and packaging were identical, so neither participants nor study personnel were aware of either medication allocation

Roflumilast M2-107 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No person involved in data analysis had knowledge of the randomisation sequence" Roflumilast and placebo tablets and packaging were identical, so the investigator was not aware of either medication allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	100 participants discontinued from the roflumilast 250 µg group, 124 from the roflumilast 500 µg group, and 32 from the placebo group
Selective reporting (reporting bias)	High risk	There was inconsistency in the quoting of statistical errors. Within the text and in 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 results represented SE, not SD. Trial registration was not found
Other bias	Low risk	None

Roflumilast M2-110

Study characteristics	
Methods	**Study design**: 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**: 909 participants randomised (roflumilast 500 µg: 449; placebo: 460) **Baseline characteristics**: aged between 55 and 74 years (mean age 64.2 years in the roflumilast group and 64.6 years in the placebo group), 88% participants were white, roflumilast group included 51% males and the placebo group 55% males **Inclusion criteria**: clinical diagnosis of COPD based on ATS criteria, post-bronchodilator $FEV_1/FVC \leq 70\%$, post-bronchodilator $FEV_1 \geq 30\%$ and $\leq 80\%$ predicted, post-bronchodilator FEV_1 increase $\leq 12\%$ or ≤ 200 mL compared to pre-bronchodilator value, score grade ≥ 1 on the MRC Dyspnea Scale, currently stable COPD with no change in COPD treatment in the prior 4 weeks **Exclusion criteria**: clinical diagnosis of asthma, poorly controlled COPD, regular need for daily oxygen therapy **Total numbers of participant withdrawals**: roflumilast group: 15.4% withdrew due to adverse events, 10.5% withdrew consent, 2.9% withdrew due to lack of efficacy; placebo group: 7.6% withdrew due to adverse events, 8.5% withdrew consent, 3% withdrew due to protocol violation
Interventions	**Run-in**: 4-week single-blind period during which respiratory medication (including ICS, LABA, and long-acting anticholinergics) was withdrawn • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication** • Short-acting anticholinergic: none • SABA: none

Roflumilast M2-110 *(Continued)*

- Corticosteroid: none
- LABA: none

Outcomes	**Primary outcomes**: pulmonary function tests (FEV_1, FVC, FEF, PEF, FIV_1, FVC_{in}) **Secondary outcomes**: exacerbation rate; quality of life; symptoms; use of rescue medication; safety and tolerability
Notes	ClinicalTrials.gov Identifier: NCT00062582. Funded by ALTANA Pharma AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported as randomised. Assumed that the randomisation method was adequate due to pharmaceutical company sponsorship
Allocation concealment (selection bias)	Low risk	Assumed that the allocation concealment method was adequate due to pharmaceutical company sponsorship
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was reported as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Roflumilast group: 15.4% withdrew due to adverse events, 10.5% withdrew consent, 2.9% withdrew due to lack of efficacy; placebo group: 7.6% withdrew due to adverse events, 8.5% withdrew consent, 3% withdrew due to protocol violation
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. The trial was registered at clinicaltrials.gov

Roflumilast M2-111

Study characteristics

Methods	**Study design**: 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 at 188 centres in 6 countries, and M2-112 at 159 centres in 14 countries **Participants**: 1176 participants were randomised in this study (roflumilast: 500 µg: 568; placebo: 608) **Baseline characteristics**: severe COPD according to GOLD criteria grades III and IV, mean age 64 to 65 years, 72% male **Inclusion criteria**: aged ≥ 40 years, post-bronchodilator FEV_1 < 50% predicted, reversibility < 15%, mean post-bronchodilator FEV_1 42%, FEV_1/FVC ≤ 0.7 with smoking history > 10 pack-years, 40% current smokers, 60% ex-smokers, average 46 to 48 pack-years

Roflumilast M2-111 *(Continued)*

	Exclusion criteria: history of asthma, lung cancer, or bronchiectasis; need for long-term oxygen therapy; known α_1-antitrypsin deficiency, clinically significant cardiopulmonary comorbidity **Total numbers of participant withdrawals**: data combined with M2-112 showing 433 (33%) and 348 (26%) from treatment and control groups, respectively
Interventions	**Run-in**: 4 weeks with placebo • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication** • Short-acting anticholingeric: 891 patients on short-acting anticholinergics • SABA: salbutamol as rescue medication • Corticosteroid: 943 patients continued corticosteroid use • LABA: none Used alongside corticosteroids, anticholinergics, and rescue short-acting β_2-agonists 54% overall (available to all)
Outcomes	**Primary outcomes**: change from baseline to endpoint in post-bronchodilator FEV_1; number of moderate or severe exacerbations per patient per year **Secondary outcomes**: change from baseline in SGRQ total score; change from baseline in pre-bronchial FEV_1, post-bronchodilator FEV in 6 seconds and in FVC; FEF rate between 25% and 75% vital capacity; number of moderate or severe COPD exacerbations requiring systemic corticosteroid treatment per patient per year
Notes	NCT00076089/BY217/M2-111. Funded by AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation sequence was generated by a multiplicative congruent pseudo-random numbers generator programme (programme RANDOM, based on Fishman and Moore)
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"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data combined with M2-112
Selective reporting (reporting bias)	Low risk	Trial registered at clinicaltrials.gov; outcomes reported as planned. M2-111 and M2-112 data combined

Roflumilast M2-111 *(Continued)*

Other bias	Low risk	None

Roflumilast M2-111+M2-112

Study characteristics		
Methods	As described in separate studies above and below	
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	See individual trials
Allocation concealment (selection bias)	Low risk	See individual trials
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See individual trials
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See individual trials
Incomplete outcome data (attrition bias) All outcomes	Low risk	See individual trials
Selective reporting (reporting bias)	Low risk	See individual trials
Other bias	Low risk	

Roflumilast M2-112

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 52 weeks

Roflumilast M2-112 *(Continued)*

	Intention-to-treat analysis: stated
Participants	**Setting**: 159 centres in 14 countries **Participants**: 1514 (roflumilast 500 µg: 761, placebo: 753) **Baseline characteristics**: severe COPD according to GOLD criteria grades III and IV, mean age 65 years, 75% male **Inclusion criteria**: aged ≥ 40 years, post-bronchodilator FEV_1 < 50% predicted, reversibility < 15%, mean post-bronchodilator FEV_1 41%, FEV_1/FVC ≤ 0.7 with smoking history > 10 pack-years, 37% current smokers, 63% ex-smokers, average 44 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 comorbidity **Total numbers of participant withdrawals**: 217 (29%) and 163 (22%) from treatment and control groups, respectively
Interventions	**Run-in**: 4 weeks with placebo • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication** • Short-acting anticholinergic: 891 participants on short-acting anticholinergics • SABA: salbutamol as rescue medication • Corticosteroid: 943 participants continued corticosteroid use • LABA: none Used alongside corticosteroids, anticholinergics, and rescue short-acting β_2-agonists 54% overall (available to all)
Outcomes	**Primary outcomes**: change from baseline to endpoint in post-bronchodilator FEV_1 and in the number of moderate or severe exacerbations per patient per year **Secondary outcomes**: change from baseline in SGRQ total score; change from baseline in pre-bronchial FEV_1; post-bronchodilator FEV in 6 seconds and FVC; FEF rate between 25% and 75% of vital capacity; number of moderate or severe COPD exacerbations requiring systemic corticosteroid treatment per patient per year
Notes	NCT00430729/BY217/M2-112. Funded by AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation list was generated using a multiplicative congruent pseudo-random number generator (program RANDOM, based on Fishman and Moore)"
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"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was double-blinded

Roflumilast M2-112 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	"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" "Withdrawal due to COPD exacerbations was reported in 3.5 and 3.2% of patients in roflumilast and placebo groups, respectively"
Selective reporting (reporting bias)	Low risk	None
Other bias	Low risk	None

Roflumilast M2-118

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 12 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 22 centres in 4 countries **Participants**: 250 (roflumilast 500 µg: 127, placebo: 123) **Baseline characteristics**: mean age 60 years, 73% (roflumilast) vs 84% (placebo) male, post-bronchodilator FEV_1 55% predicted, average 41 pack-years, 53% current smokers **Inclusion criteria**: clinically stable patients ≥ 40 years of age with smoking history > 10 pack-years and 12-month history of COPD. Other inclusion criteria included post-bronchodilator FEV_1 30% to 80% predicted, FEV_1/forced vital capacity (FVC) < 0.7, and set plethysmographic FRC and peak oxygen uptake requirements **Exclusion criteria**: asthma or lung disease other than COPD, α_1-antitrypsin deficiency, participation in pulmonary rehabilitation programme within 2 months, supplemental oxygen therapy, significant medical comorbidity that may influence exercise tolerance **Total numbers of participant withdrawals**: 16 (13%) and 12 (10%) from treatment and control groups, respectively
Interventions	**Run-in**: 2- to 3-week baseline period consisting of 2 familiarisation visits during which a symptom-limited constant work rate cycle exercise test was performed at 75% of maximum incremental work rate. If a constant work rate endurance time was not produced within 2 minutes at both visits, a third visit was performed. If reproducibility was not achieved at the third visit, the patient was not randomised • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication** • Short-acting anticholingeric: participants could use ipratropium bromide in regular stable doses as needed

Roflumilast M2-118 *(Continued)*

- SABA: participants could use short-acting β_2-agonists as needed
- Corticosteroid: ICSs were permitted throughout the study if taken at a constant dosage for > 3 months before the start of the study
- LABA: none

Outcomes	**Primary outcomes**: activity-related dyspnoea (TDI); spirometry and body plethysmography; symptom-limited exercise tests
Notes	Funded by Nycomed GmbH (Konstanz, Germany)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported as randomised. Assumed that the randomisation method was adequate due to pharmaceutical company sponsorship
Allocation concealment (selection bias)	Unclear risk	No available information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 250 randomised participants, 16 from the roflumilast group and 12 from the placebo group discontinued prematurely
Selective reporting (reporting bias)	Unclear risk	Outcomes reported, but no trial protocol found on trial registry websites
Other bias	Low risk	None

Roflumilast M2-119

Study characteristics

Methods	**Study design**: 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 **Participants**: 410 (roflumilast 500 µg: 203, placebo: 207) **Baseline characteristics**: mean age 68 years, 93% male, post-bronchodilator FEV_1 50.5% predicted, average 44 pack-years, 69% current smokers

Roflumilast M2-119 *(Continued)*

	Inclusion criteria: former or current smokers with pack-year history ≥ 10, aged ≥ 40 years, post-bronchodilator $FEV_1/FVC \leq 0.7$, FEV_1 30% to 80% predicted, clinically stable COPD within 4 weeks before baseline **Exclusion criteria**: history of asthma or other relevant lung disease, COPD exacerbation within 4 weeks before baseline, need for long-term oxygen therapy, known α_1-antitrypsin deficiency, clinically significant cardiopulmonary comorbidity **Total numbers of participant withdrawals**: 40 (20%) and 18 (9%) from treatment and control groups, respectively
Interventions	**Run-in**: 4 weeks with placebo • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication** • Short-acting anticholingeric: "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" • SABA: patients could use SABAs as needed • Corticosteroid: none • LABA: none
Outcomes	**Primary outcome**: mean change in post-bronchodilator FEV_1 from baseline **Secondary outcomes**: mean change in pre-bronchodilator FEV_1 from baseline; change in other lung function measures, time to COPD exacerbation; proportion of participants experiencing exacerbations; time to study withdrawal; adverse effects
Notes	Clinicaltrials.gov identifier: NCT00242320; BY217/M2-119. Funded by Nycomed GmbH, Konstanz, Germany

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list used
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 411 randomised participants, 41 from the roflumilast group and 18 from the placebo group discontinued during the treatment period (20% compared with 8%, respectively)
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned. The protocol was registered at clincaltrials.gov

Roflumilast M2-119 *(Continued)*

Other bias	Low risk	None

Roflumilast M2-121

Study characteristics

Methods	**Study design**: 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**: 600 participants (full analysis set; roflumilast 500 µg: 301, placebo: 299) **Baseline characteristics**: median age 65 years, 74% male, FEV_1 46% predicted, 48 mean pack-years **Inclusion criteria**: history of COPD ≥ 12 months as defined by GOLD criteria, age ≥ 40 years, FEV_1/FVC ratio (post-bronchodilator) ≤ 70%, FEV_1 (post-bronchodilator) ≤ 65% predicted, FRC (post-bronchodilator) ≤ 120% predicted **Exclusion criteria**: COPD exacerbation indicated by treatment with systemic glucocorticosteroids not stopped ≥ 4 weeks before baseline visit; non-smoker, current smoker, or ex-smoker (smoking cessation ≥ 1 year ago) with smoking history < 10 pack-years; any concomitant disease that might interfere with study procedures or evaluation **Total numbers of participant withdrawals**: 32 participants withdrew due to COPD exacerbations
Interventions	**Run-in**: 4-week single-blind placebo tablet once daily in the morning and all disallowed concomitant medications withdrawn • Roflumilast 500 µg once daily • Placebo **Concomitant medication** • Short-acting anticholinergic: none • SABA: none • Corticosteroid: none • LABA: none
Outcomes	**Primary outcome**: lung function parameters indicative of hyperinflation in people with COPD **Secondary outcomes**: mean change from randomisation to endpoint in additional pre- and post-bronchodilator spirometric and lung volume parameters; measurement of quality of life parameters; dyspnoea
Notes	ClinicalTrials.gov Identifier: NCT00108823; BY217/M2-121. Funded by AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported as randomised. Assumed that the randomisation method was adequate due to pharmaceutical company sponsorship

Roflumilast M2-121 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No available information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 600 randomised participants, 13 from the roflumilast group and 19 from the placebo group withdrew due to exacerbations
Selective reporting (reporting bias)	Unclear risk	A publication was not found for this trial; however, study results were obtained from the trial registry website
Other bias	Low risk	None

Roflumilast M2-124

Study characteristics	
Methods	**Study design**: 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 µg: 760, placebo: 753) **Baseline characteristics**: mean age 64 years, 71% male, post-bronchodilator FEV_1 37.6% predicted, average 47 pack-years, 48% current smokers **Inclusion criteria**: former or current smokers with ≥ 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, ≥ 1 recorded COPD exacerbation requiring systemic glucocorticosteroids or treatment in hospital in previous year **Exclusion criteria**: available in the online web appendix (p 11) **Total numbers of participant withdrawals**: 264 (34%) and 234 (31%) from treatment and control groups, respectively
Interventions	**Run-in**: 4 weeks with placebo • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication** • Short-acting anticholingeric: 31% of those in the roflumilast group and 32% in the placebo group • SABA: "patients could use short acting β_2-agonists as needed"

Roflumilast M2-124 *(Continued)*

- Corticosteroid: none
- LABA: "eligible patients were stratified according to their use of long acting β_2-agonists and smoking status"; roflumilast 49%, placebo 51%

Outcomes	**Primary outcomes**: mean change in pre-bronchodilator FEV_1; mean rate of COPD exacerbations requiring oral or parenteral glucocorticosteroids or requiring hospitalisation or leading to death (per patient per year) **Secondary outcomes**: mean change in post-bronchodilator FEV_1; time to mortality for any reason; natural log-transformed CRP (mg/L); mean TDI focal score
Notes	Clinicaltrials.gov identifier: NCT00297102. Funded by AstraZeneca Adverse event data are pooled with numbers from study M2-125, which followed an identical study design

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation list was generated via a pseudo-random numbers generator, and an automated interactive voice-response system was used to randomly assign participants
Allocation concealment (selection bias)	Low risk	All individuals involved in the studies were unaware of treatment assignment
Blinding of participants and personnel (performance bias) All outcomes	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"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	264 participants discontinued from the roflumilast group and 234 discontinued from the placebo group
Selective reporting (reporting bias)	Low risk	Outcomes reported as planned. Trial registered at clinicaltrials.gov
Other bias	High risk	44% of participants in both roflumilast and placebo groups received corticosteroid pre-treatment

Roflumilast M2-124+M2-125

Study characteristics	
Methods	As described in separate studies above and below
Participants	
Interventions	

Roflumilast M2-124+M2-125 *(Continued)*

Outcomes
Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See individual studies
Allocation concealment (selection bias)	Low risk	See individual studies
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See individual studies
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See individual studies
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See individual studies
Selective reporting (reporting bias)	Unclear risk	See individual studies
Other bias	Unclear risk	See individual studies

Roflumilast M2-125

Study characteristics

Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 52 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 221 centres in 8 countries **Participants**: 1571 (roflumilast 500 µg: 773, placebo: 798) **Baseline characteristics**: mean age 64 years, 80% male, average 48 pack-years, 35% current smokers **Inclusion criteria**: former or current smokers with pack-year history ≥ 20 years, aged ≥ 40 years, post-bronchodilator $FEV_1/FVC \leq 0.7$, chronic cough and sputum production, post-bronchodilator $FEV_1 < 50\%$ predicted, ≥ 1 recorded COPD exacerbation requiring systemic glucocorticosteroids or treatment in hospital in previous year **Exclusion criteria**: available in the online web appendix (p 11)

Roflumilast M2-125 *(Continued)*

	Total numbers of participant withdrawals: 246 (32%) and 248 (31%) from treatment and control groups, respectively
Interventions	**Run-in**: 4 weeks with placebo • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication** • Short-acting anticholingeric: 38% of those in the roflumilast group and 41% of the placebo group • SABA: "patients could use short acting β_2-agonists as needed" • Corticosteroid: none • LABA: "eligible patients were stratified according to their use of long acting β_2-agonists and smoking status"; roflumilast 48%, placebo 51%
Outcomes	**Primary outcomes**: mean change in pre-bronchodilator FEV_1; mean rate of COPD exacerbations (moderate or severe) requiring oral or parenteral glucocorticosteroids or requiring hospitalisation or leading to death (per patient per year) **Secondary outcomes**: mean change in post-bronchodilator FEV_1; time to mortality for any reason; natural log-transformed CRP (mg/L); mean TDI focal score during treatment period
Notes	Clinicaltrials.gov identifier: NCT00297115; BY217/M2-125. Funded by AstraZeneca Adverse event data are pooled with numbers from study M2-124, which followed an identical study design

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation list was generated via a pseudo-random numbers generator, and an automated interactive voice-response system was used to randomly assign participants
Allocation concealment (selection bias)	Low risk	All individuals involved in the studies were unaware of treatment assignment
Blinding of participants and personnel (performance bias) All outcomes	Unclear 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"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assumed that this would be low risk; however, no available information
Incomplete outcome data (attrition bias) All outcomes	Low risk	246 patients discontinued from the roflumilast group and 248 discontinued from the placebo group
Other bias	High risk	40% of participants in both roflumilast and placebo groups received corticosteroid pre-treatment

Roflumilast M2-127

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 24 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 135 centres in 10 countries **Participants**: 1221 (roflumilast 500 µg: 467, placebo: 468) **Baseline characteristics**: mean age 65 years, 71% male, post-bronchodilator FEV_1 54.7% and 55.3% predicted (roflumilast and placebo), average 43 pack-years, 39% current smokers **Inclusion criteria**: former or current smokers with ≥ 1 year smoking cessation and a pack-year history ≥ 10, aged ≥ 40 years, post-bronchodilator FEV_1/FVC ≤ 0.7, post-bronchodilator FEV_1 40% to 70% predicted, partial reversibility to albuterol with increase from baseline FEV_1 ≤ 12% or 200 mL **Exclusion criteria**: available in the online web appendix (p 10) **Total numbers of participant withdrawals**: 107 (23%) and 82 (18%) from treatment and control groups, respectively
Interventions	**Run-in**: 4 weeks with placebo once a day • Roflumilast 500 µg and salmeterol once daily • Placebo once daily **Concomitant medication** • Short-acting anticholingeric: none • SABA: participants used short-acting β_2 as rescue medication • Corticosteroid: none • LABA: none
Outcomes	**Primary outcomes**: change in mean pre-bronchodilator FEV_1 from baseline to each post-randomisation visit **Secondary outcomes**: post-bronchodilator FEV_1 and FVC; TDI score; SOBQ; rate of COPD exacerbations; use of rescue medication
Notes	ClinicalTrials.gov identifier NCT00313209; BY217/M2-127; 2005-005080-28 (EudraCT Number). Funded by Nycomed GmbH, Konstanz, Germany

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The sponsor generated a randomisation list of patient random numbers using a pseudo-random number generator. The investigator used an automated, interactive voice response system to randomly assign patients"
Allocation concealment (selection bias)	Unclear risk	No available information
Blinding of participants and personnel (performance bias)	Low risk	All individuals involved in the studies were unaware of treatment assignment

Roflumilast M2-127 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All individuals involved in the studies were unaware of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	107 participants discontinued from the roflumilast group and 82 discontinued from the placebo group
Selective reporting (reporting bias)	Low risk	Outcomes reported as planned. Trial registered at clincialtrials.gov
Other bias	Low risk	None

Roflumilast M2-128

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 24 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 85 centres in 7 countries **Participants**: 910 (roflumilast 500 µg: 372, placebo: 372) **Baseline characteristics**: mean age 64 years, 71% male, post-bronchodilator FEV_1 56.0% and 56.2% predicted (roflumilast and placebo), average 44 pack-years, 40% current smokers **Inclusion criteria**: former or current smokers with ≥ 1 year smoking cessation and a pack-year history ≥ 10, aged ≥ 40 years, post-bronchodilator FEV_1/FVC ≤ 0.7, post-bronchodilator FEV_1 40% to 70% predicted, partial reversibility to albuterol with increase from baseline FEV_1 ≤ 12% or 200 mL **Exclusion criteria**: available in the online web appendix (p 10) **Total numbers of participant withdrawals**: 62 (17%) and 39 (11%) from treatment and control groups, respectively
Interventions	**Run-in**: 4 weeks with placebo once a day • Roflumilast 500 µg and tiotropium once daily • Placebo once daily **Concomitant medication** • Short-acting anticholingeric: none • SABA: participants used short-acting β_2 as rescue medication • Corticosteroid: none • LABA: none
Outcomes	**Primary outcomes**: change in mean pre-bronchodilator FEV_1 from baseline to each post-randomisation visit

Roflumilast M2-128 *(Continued)*

	Secondary outcomes: post-bronchodilator FEV_1 and FVC; TDI score; SOBQ; rate of COPD exacerbations; use of rescue medication
Notes	Clinicaltrials.gov identifier: NCT0042468; BY217/M2-128. Funded by Nycomed GmbH, Konstanz, Germany

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The sponsor generated a randomisation list of patient random numbers using a pseudo-random number generator. The investigator used an automated, interactive voice response system to randomly assign patients"
Allocation concealment (selection bias)	Low risk	The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling
Blinding of participants and personnel (performance bias) All outcomes	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"
Blinding of outcome assessment (detection bias) All outcomes	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"
Incomplete outcome data (attrition bias) All outcomes	Low risk	62 participants discontinued from the roflumilast group and 39 discontinued from the placebo group
Selective reporting (reporting bias)	Unclear risk	Outcomes reported as planned. Trial protocol registered at clincialtrials.gov and at European trial registry
Other bias	Low risk	None

Roflumilast ROF-MD-07(RE2SPOND)

Study characteristics

Methods	**Study design**: parallel-group study **Randomisation**: randomised, double-blind, placebo-controlled trial **Trial duration**: 52 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 338 locations across Australia, Argentina, Canada, Chile, Columbia, Italy, Malaysia, Peru, Phillippines, Romania, Russia, Serbia, Spain, Taiwan, and Ukraine **Participants**: 2354 (500 µg roflumilast: 1178; placebo: 1176) **Baseline characteristics**: mean age 64 years, 68% male, mean FEV_1 % predicted 33%, mean smoking history 52.2 pack-years for roflumilast and 53.1 pack-years for placebo or current smokers (39% and 40%, respectively)

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

	Inclusion criteria: ≥ 40 years with severe or very severe COPD, chronic bronchitis, ≥ 2 exacerbations and/or hospitalisations in the previous year, receiving ICS/LABA with or without LAMA daily for ≥ 3 months **Exclusion criteria**: within the 4 weeks before enrolment, had a moderate or severe COPD exacerbation and/or a COPD exacerbation treated with antibiotics or systemic corticosteroids or a lower respiratory tract infection. Other exclusionary criteria included diagnoses of other 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, clinically significant cardiovascular condition, resting QTc interval > 470 ms, BMI ≥ 45 kg/m^2 **Total numbers of participant withdrawals**: 337 (29%) and 254 (21%) from treatment and control groups, respectively
Interventions	**Run-in**: 2 weeks, single-blind. Placebo tablets to assess suitability • Roflumilast 500 µg once daily • Placebo once daily **Concomitant medication** 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)). 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 ≥ 3 months before screening, with no dose change. Those not on LAMA were allowed a SAMA
Outcomes	**Primary outcome**: rate of moderate or severe COPD exacerbations per patient per year **Secondary outcomes**: rate of COPD exacerbations leading to hospitalisation or death (severe COPD exacerbations); rate of moderate or severe exacerbations; rate of moderate or severe COPD exacerbations or COPD exacerbations treated with antibiotics; rate of moderate or severe COPD exacerbations treated with antibiotics during the treatment period; mean change in pre-dose FEV_1; mean change in pre-dose FEV_1 from randomisation over 52 weeks; adverse events; mortality (all-cause); serious adverse events; other adverse events (not including serious events)
Notes	Clinicaltrials.gov identifier: NCT01443845. Funded by Astra Zeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported as randomised. Assumed that the randomisation method was adequate due to pharmaceutical company sponsorship
Allocation concealment (selection bias)	Unclear risk	No available information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as triple-blind (participant, investigator and outcome assessor)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reported as triple-blind (participant, investigator and outcome assessor)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	337 participants (29%) discontinued from the roflumilast group and 254 (22%) discontinued from the placebo group

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

Selective reporting (reporting bias)	Unclear risk	Outcomes reported as planned. Trial registered at clinicaltrials.gov
Other bias	Unclear risk	47% in each treatment group were taking LAMAs. Participants were also using combined LABA/ICS. 65% in the placebo group were taking fluticasone propionate/salmeterol FDC, and 65% in the roflumilast group. 35% of participants in each treatment group were taking budesonide/formoterol FDC

Urban 2018 (ELASTIC)

Study characteristics	
Methods	**Study design**: parallel-group study **Randomisation**: randomised, triple-blind, placebo-controlled trial **Trial duration**: 24 weeks **Intention-to-treat analysis**: stated
Participants	**Setting**: 1 specialist respiratory and critical care medicine centre at a hospital in Austria **Participants**: 80 (roflumilast 500 µg: 40, placebo: 40) **Baseline characteristics**: median age 64, 52% male, median 50 smoking pack-years **Inclusion criteria**: 40 years of age and over, history of ≥ 2 COPD exacerbation requiring systemic corticosteroid treatment or hospitalisation in the last year **Exclusion criteria**: inability to comply with study medication, history of acute exacerbation, alpha$_1$-antitrypsin deficiency, asthma, acute/severe respiratory infection, lung cancer, bronchiectasis, ILD, acute MI, systolic left ventricular dysfunction, CHF, cardiac arrhythmia/heart valve deformation, peripheral arterial occlusive disease, acute or chronic hepatic failure, autoimmune disease, active malignancy, pregnant/breastfeeding, hypersensitivity to study medication or placebo, mental or neurological disorder, history of depression **Total numbers of participant withdrawals**: 7 (17%) and 6 (15) in the roflumilast and placebo groups, respectively
Interventions	**Run-in**: 4 weeks • Roflumilast 500 µg, once daily • Placebo once daily **Concomitant medication** • Short-acting anticholinergic: not stated • SABA: not stated • Corticosteroid: not stated • LABA: not stated
Outcomes	**Primary outcome**: change in carotid femoral-pulse wave velocity **Secondary outcomes**: change in reactive hyperaemia index; change in augmentation index; change in matrix metalloproteinase-9; change in asymmetrical dimethylamine; change in tumour necrosis factor-alpha; change in FEV$_1$; change in 6-minute walk test; change in COPD assessment test

Urban 2018 (ELASTIC) *(Continued)*

Notes	Clincaltrials.gov identifier: NCT01630200. Funded by Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised; no further information
Allocation concealment (selection bias)	Unclear risk	No available information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All responsible persons, those administering interventions or assessing the outcomes, and elementally all experimental and control patients were blinded to group assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All responsible persons, those administering interventions or assessing the outcomes, and elementally all experimental and control patients were blinded to group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 randomised in each group. In the roflumilast group 33/40 completed (82.5%), in the placebo arm 34/40 completed (85%), so similar attrition. Similar numbers of non-fatal and serious fatal adverse events in each group
Selective reporting (reporting bias)	Low risk	Study authors reported outcomes as planned; methods and results were published on EU trials registry
Other bias	Unclear risk	Criteria for COPD not well defined apart from exacerbations

6MWT: 6-minute walk test; AcPGP: plasma acetyl-proline-glycine-proline; ATS: American Thoracic Society; BDI: Baseline Dyspnoea Index; BMI: body mass index; BORG Scale: rating of perceived exertion; CAT: COPD Assessment Test; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DLCO: diffusing capacity of the lung for carbon monoxide; EU: European Union; ERS: European Respiratory Society; FDC: fixed dose combination; FEF: forced expiratory flow; FEV_1: forced expiratory volume in one second; FEV_6: forced expiratory volume in six seconds; FIV_1: forced expiratory volume in one second; FRC: functional residual capacity; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HU: Hounsfield unit; HIV: human immunodeficiency virus; IC: inspiratory capacity; ICS: inhaled corticosteroid; ILD: interstitial lung disease; LABA: long-acting beta$_2$-agonist; LAMA:long-acting muscarinic antagonist; MDI: metered-dose inhaler; MI: myocardial infarction; MMEF: maximal mid-expiratory flow; NCT: national clinical trial; PEF: peak expiratory flow; QTc: corrected Q wave and T wave; RFRC: resting functional residual capacity; RV: residual volume; SABA: short-acting beta$_2$-agonist; 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; TLC: total lung capacity VO_2: oxygen uptake.

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

Study	Reason for exclusion
Borker 2003	Insufficient data; only RR of QoL improvement provided
CTRI/2012/09/002961	No placebo group
CTRI/2014/01/004370	No placebo group
Ferguson 2003	Integrated results from four 24-week cilomilast trials

Study	Reason for exclusion
Fischer 2003	Analysis focused on participants with baseline SGRQ score ≥ 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 2 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 3 cilomilast trials
NCT00246935	Different regimens of roflumilast; no placebo group
NCT01849341	Different regimens of roflumilast; no placebo group
NCT01973998	Patients were diagnosed with AECOPD
NCT02018432	Different regimens of roflumilast; no placebo group
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
Rabe 2017	Editorial letter
Reisner 2003	Combined results; individual studies already included in review
Rennard 2008	Systematic review; relevant individual studies already included in review
Roflumilast JP708	JP108 is an extension study of APTA-2217-06. After the key open of APTA-2217-06, administration to placebo group would be terminated. Not all participants enrolled in JP106 continued onto the JP108 study
Sadigov 2014	No placebo group
Sadigov 2015	Open-label; no placebo group
SB207499/040	Open-label study; men or women with COPD who successfully completed study 042 or 091 in which 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 in which 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

Study	Reason for exclusion
Spencer 2002	No study identification 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
Watz 2016	Different regimens of roflumilast

AECOPD: acute exacerbation of COPD; COPD: chronic obstructive pulmonary disease; QoL: quality of life; RR: risk ratio; SD: standard deviation; SE: standard error; SGRQ: St George's Respiratory Questionnaire.

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

Barnes 2014

Methods	international, 16-week, randomised, double-blind, placebo-controlled, parallel-group study investigating effects of roflumilast 500 µg once daily vs 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 randomised in a 1:1 ratio to receive either roflumilast or placebo
Interventions	Roflumilast and placebo
Outcomes	Primary endpoint will be number of CD8+ cells in bronchial biopsy tissue specimens (submucosa) Key secondary endpoint will be number of CD68+ cells assessed by indirect immunohistochemistry
Notes	Completed; awaiting results

EUCTR2004-004442-40-GB

Methods	Randomised controlled trial
Participants	Participants with history of moderate to severe COPD for at least 12 months
Interventions	Roflumilast and placebo
Outcomes	Primary outcome variable will be mean change in post-bronchodilator FEV_1 from baseline
Notes	No data provided; awaiting results

Mahmud 2013

Methods	Single-blind, randomised, placebo-controlled study carried out in the Department of Respiratory Medicine at National Institute of Diseases of the Chest and Hospital (NIDCH), Dhaka, Bangladesh

Mahmud 2013 *(Continued)*

Participants	130 participants were recruited initially and were randomly distributed into Group A, where they received conventional therapy (inhaled salmeterol + fluticasone and tiotropium) and roflumilast (0.5 mg once daily), and Group B, where participants were given placebo with conventional therapy Study duration was 3 months
Interventions	As above
Outcomes	Primary outcome variable was change in mean FEV_1 Secondary outcome variable was change in mean CAT score from baseline
Notes	No data provided; study authors contacted

NCT00671073

Methods	Multi-centre double-blind randomised controlled trial over 12 weeks across USA investigating the safety and efficacy of various doses of oglemilast
Participants	427 participants with COPD, post-bronchodilator FEV_1/FVC < 70%, post-bronchodilator FEV_1 > 30% and < 80%
Interventions	Oglemilast and placebo
Outcomes	Primary outcome variable will be pre-bronchodilator morning (trough) FEV_1 at 12 weeks Secondary endpoint will be pre-bronchodilator FVC at 12 weeks
Notes	No data provided; awaiting results

NCT01595750

Methods	Single-centre, double-blind randomised controlled trial over 12 weeks in Spain
Participants	150 participants with a diagnosis of COPD, FEV_1 < 70%; current and former smokers
Interventions	Roflumilast and placebo
Outcomes	Primary outcome variable will be endothelial function at 12 weeks Secondary endpoints include arterial stiffness; serum and plasma inflammation markers; serum oxidative stress markers; serum endothelial dysfunction markers at 12 weeks
Notes	No data provided; awaiting results

NCT01701934

Methods	Triple-blind randomised controlled trial for 26 weeks investigating whether roflumilast could improve metabolic profiles and reduce visceral adiposity in people with COPD

NCT01701934 *(Continued)*

Participants	14 participants with moderate to severe COPD, assigned to either 500 µg roflumilast or placebo for 26 weeks
Interventions	Roflumilast and placebo
Outcomes	Primary outcome variables will be change in body mass index; change in waist circumference; change in hip-to-waist ratio; change in metabolic profiles; change in body composition; change in subcutaneous adiposity; change in liver fat
Notes	No data provided; awaiting results

CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

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

NCT02451540 2015

Study name	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

Study name	A multicenter randomised 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
Outcomes	Area under the plasma concentration after vs drug dose Percentage of participants with adverse events of interest Change in pre-bronchodilator FEV_1 during the down-titration period

NCT02671942 2016 *(Continued)*

Starting date	March 2016
Contact information	Contact: Zheng Jinping
Notes	Estimated enrolment: 120 Estimated study completion date: August 2017

COPD: chronic obstructive pulmonary disease; CT: computed tomography; FEV_1: forced expiratory volume in one second; LABA: long-acting $beta_2$-agonist; LAMA:long-acting muscarinic antagonist; RCT: randomised controlled trial.

DATA AND ANALYSES

Comparison 1. PDE_4 inhibitor versus placebo (2020 update)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 FEV_1 (by drug)	29	20815	Mean Difference (IV, Fixed, 95% CI)	49.33 [44.17, 54.49]
1.1.1 Tetomilast 50 µg	1	76	Mean Difference (IV, Fixed, 95% CI)	82.00 [-50.84, 214.84]
1.1.2 Roflumilast 500 µg	18	14384	Mean Difference (IV, Fixed, 95% CI)	55.18 [48.65, 61.71]
1.1.3 Roflumilast 250 µg	3	1033	Mean Difference (IV, Fixed, 95% CI)	56.88 [24.38, 89.38]
1.1.4 Cilomilast 15 mg	10	5322	Mean Difference (IV, Fixed, 95% CI)	38.15 [29.41, 46.90]
1.2 FVC	17	22108	Mean Difference (IV, Fixed, 95% CI)	86.98 [74.65, 99.31]
1.3 PEF	5	4245	Mean Difference (IV, Fixed, 95% CI)	6.54 [3.95, 9.13]
1.3.1 Roflumilast 500 µg	4	3685	Mean Difference (IV, Fixed, 95% CI)	5.46 [2.74, 8.17]
1.3.2 Roflumilast 250 µg	1	347	Mean Difference (IV, Fixed, 95% CI)	7.00 [-4.05, 18.05]
1.3.3 Cilomilast 15 mg	1	213	Mean Difference (IV, Fixed, 95% CI)	34.00 [20.14, 47.86]
1.4 SGRQ total score	11	7645	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-1.68, -0.43]
1.4.1 Roflumilast 500 µg	2	722	Mean Difference (IV, Fixed, 95% CI)	-1.87 [-3.80, 0.06]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.4.2 Roflumilast 250 µg	2	2229	Mean Difference (IV, Fixed, 95% CI)	-0.64 [-2.02, 0.74]
1.4.3 Cilomilast 15 mg	8	4694	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-1.81, -0.31]
1.5 SGRQ symptom score	2	1048	Mean Difference (IV, Fixed, 95% CI)	-1.53 [-4.11, 1.06]
1.5.1 Roflumilast	1	835	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-3.78, 1.78]
1.5.2 Cilomilast	1	213	Mean Difference (IV, Fixed, 95% CI)	-4.80 [-11.73, 2.13]
1.6 Number of participants with 1 or more exacerbations (by drug)	27	20382	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.73, 0.84]
1.6.1 Roflumilast 500 µg	16	14778	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.73, 0.86]
1.6.2 Cilomilast	10	5528	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.67, 0.85]
1.6.3 Tetomilast 50 µg	1	76	Odds Ratio (M-H, Fixed, 95% CI)	2.45 [0.26, 23.13]
1.7 Exacerbation rate (inverse variance)	9		Rate Ratio (IV, Fixed, 95% CI)	0.88 [0.83, 0.93]
1.7.1 Roflumilast	8		Rate Ratio (IV, Fixed, 95% CI)	0.87 [0.82, 0.92]
1.7.2 Cilomilast	1		Rate Ratio (IV, Fixed, 95% CI)	0.95 [0.78, 1.17]
1.8 Borg Scale	6	2860	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.33, -0.05]
1.8.1 Cilomilast	6	2860	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.33, -0.05]
1.9 Shortness of Breath Questionnaire	2	1633	Mean Difference (IV, Fixed, 95% CI)	-1.09 [-2.47, 0.28]
1.10 Summary symptom score	5	6186	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.07, 0.03]
1.10.1 Roflumilast	2	4287	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.08, 0.04]
1.10.2 Cilomilast	3	1899	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.13, 0.06]
1.11 Breathlessness Cough and Sputum Scale (BCSS) (tetomilast 50 µg)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.11.1 Breathlessness	1	22	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.77, 0.63]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.11.2 Cough	1	22	Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.54, 1.00]
1.11.3 Sputum	1	22	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.97, 0.65]
1.12 6-minute walk test	6	2055	Mean Difference (IV, Fixed, 95% CI)	3.50 [-5.84, 12.85]
1.12.1 Roflumilast	2	107	Mean Difference (IV, Fixed, 95% CI)	52.61 [-0.21, 105.42]
1.12.2 Cilomilast	4	1948	Mean Difference (IV, Fixed, 95% CI)	1.92 [-7.58, 11.41]
1.13 Number of participants experiencing an adverse event	30	21310	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [1.22, 1.38]
1.13.1 Roflumilast 500 µg	15	14684	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [1.24, 1.43]
1.13.2 Cilomilast 15 mg	14	6542	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [1.08, 1.36]
1.13.3 Tetomilast 50 µg	1	84	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.25, 1.57]
1.14 Number of participants experiencing an adverse event (roflumilast 500 µg vs 250 µg)	4	1977	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [1.01, 1.46]
1.15 Diarrhoea	29	20623	Odds Ratio (M-H, Fixed, 95% CI)	3.10 [2.74, 3.50]
1.15.1 Roflumilast	14	13997	Odds Ratio (M-H, Fixed, 95% CI)	3.65 [3.10, 4.28]
1.15.2 Cilomilast	14	6542	Odds Ratio (M-H, Fixed, 95% CI)	2.47 [2.05, 2.98]
1.15.3 Tetomilast	1	84	Odds Ratio (M-H, Fixed, 95% CI)	1.68 [0.31, 9.24]
1.16 Nausea	27	20949	Odds Ratio (M-H, Fixed, 95% CI)	3.79 [3.24, 4.43]
1.16.1 Roflumilast 500 µg	12	13467	Odds Ratio (M-H, Fixed, 95% CI)	3.25 [2.60, 4.07]
1.16.2 Roflumilast 250 µg	1	856	Odds Ratio (M-H, Fixed, 95% CI)	3.97 [0.91, 17.39]
1.16.3 Cilomilast 15 mg	14	6542	Odds Ratio (M-H, Fixed, 95% CI)	4.37 [3.49, 5.47]
1.16.4 Tetomilast 50 µg	1	84	Odds Ratio (M-H, Fixed, 95% CI)	2.00 [0.20, 20.09]
1.17 Vomiting	12	5986	Odds Ratio (M-H, Fixed, 95% CI)	3.95 [2.78, 5.60]
1.17.1 Roflumilast	2	993	Odds Ratio (M-H, Fixed, 95% CI)	2.32 [0.53, 10.23]
1.17.2 Cilomilast	10	4993	Odds Ratio (M-H, Fixed, 95% CI)	4.06 [2.83, 5.82]
1.18 Dyspepsia	13	6247	Odds Ratio (M-H, Fixed, 95% CI)	3.17 [2.33, 4.30]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.18.1 Roflumilast	1	626	Odds Ratio (M-H, Fixed, 95% CI)	7.07 [0.36, 137.40]
1.18.2 Cilomilast	12	5621	Odds Ratio (M-H, Fixed, 95% CI)	3.13 [2.30, 4.27]
1.19 Weight loss	12	12462	Odds Ratio (M-H, Fixed, 95% CI)	3.72 [3.09, 4.47]
1.19.1 Roflumilast	11	12378	Odds Ratio (M-H, Fixed, 95% CI)	3.80 [3.15, 4.58]
1.19.2 Tetomilast 50 µg	1	84	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 2.63]
1.20 Withdrawals due to adverse events	31	21358	Odds Ratio (M-H, Fixed, 95% CI)	1.89 [1.73, 2.07]
1.20.1 Roflumilast 500 µg	16	14729	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [1.70, 2.12]
1.20.2 Cilomilast 15 mg	14	6545	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [1.61, 2.24]
1.20.3 Tetomilast 50 mg	1	84	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.20, 3.18]
1.21 Headache	23	19215	Odds Ratio (M-H, Fixed, 95% CI)	1.69 [1.46, 1.94]
1.21.1 Roflumilast 500 µg	12	13565	Odds Ratio (M-H, Fixed, 95% CI)	2.13 [1.74, 2.59]
1.21.2 Roflumilast 250 µg	1	347	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.24, 3.99]
1.21.3 Cilomilast 15 mg	11	5303	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [1.08, 1.62]
1.22 Abdominal pain	15	8329	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [1.62, 2.52]
1.22.1 Roflumilast	3	2641	Odds Ratio (M-H, Fixed, 95% CI)	2.77 [1.38, 5.56]
1.22.2 Cilomilast	11	5604	Odds Ratio (M-H, Fixed, 95% CI)	1.97 [1.55, 2.49]
1.22.3 Tetomilast 50 µg	1	84	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.15, 6.13]
1.23 Influenza-like symptoms	9	11460	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.87, 1.36]
1.23.1 Roflumilast 500 µg	7	10147	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.87, 1.41]
1.23.2 Roflumilast 250 µg	1	347	Odds Ratio (M-H, Fixed, 95% CI)	1.98 [0.18, 22.00]
1.23.3 Cilomilast 15 mg	2	966	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.44, 1.75]
1.24 Upper respiratory tract infection	21	17022	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.81, 1.04]
1.24.1 Roflumilast 500 µg	11	11539	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.77, 1.09]
1.24.2 Roflumilast 250 µg	2	1203	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.54, 1.31]
1.24.3 Cilomilast 15 mg	10	4280	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.13]
1.25 Psychiatric adverse events (roflumi-last)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.25.1 Roflumilast 500 µg	1	11168	Odds Ratio (M-H, Fixed, 95% CI)	2.13 [1.79, 2.54]
1.25.2 Roflumilast 250 µg	1	6288	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.56, 1.33]
1.26 Anxiety or anxiety disorder (roflumilast)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.26.1 Roflumilast 500 µg	1	11168	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [1.26, 2.62]
1.26.2 Roflumilast 250 µg	1	6288	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.40, 2.21]
1.27 Depression (roflumilast)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.27.1 Roflumilast 500 µg	1	11168	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [1.11, 2.27]
1.27.2 Roflumilast 250 µg	1	6288	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.20, 1.56]
1.28 Insomnia and sleep disorders (roflumilast)	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.28.1 Roflumilast 500 µg	4	15482	Odds Ratio (M-H, Fixed, 95% CI)	2.67 [2.11, 3.38]
1.28.2 Roflumilast 250 µg	1	6288	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.81, 2.70]
1.29 Serious adverse events	29	19191	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.07]
1.29.1 Roflumilast 500 µg	14	12562	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.12]
1.29.2 Cilomilast 15 mg	14	6545	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.72, 1.06]
1.29.3 Tetomilast 50 µg	1	84	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.23, 1.55]
1.30 Mortality	27	19786	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.77, 1.24]
1.30.1 Roflumilast	13	13370	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.79, 1.30]
1.30.2 Cilomilast	13	6332	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.34, 1.45]
1.30.3 Tetomilast	1	84	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.31 FEV_1 (by mean COPD severity)	22	16813	Mean Difference (IV, Fixed, 95% CI)	52.78 [46.73, 58.83]
1.31.1 GOLD grade I + II (FEV_1 ≥ 50% predicted)	10	4801	Mean Difference (IV, Fixed, 95% CI)	51.82 [39.03, 64.60]
1.31.2 GOLD grade III + IV (FEV_1 < 50% predicted)	12	12012	Mean Difference (IV, Fixed, 95% CI)	53.06 [46.19, 59.92]
1.32 FEV_1 (roflumilast 500 µg vs 250 µg)	3	1560	Mean Difference (IV, Fixed, 95% CI)	22.61 [-5.95, 51.16]

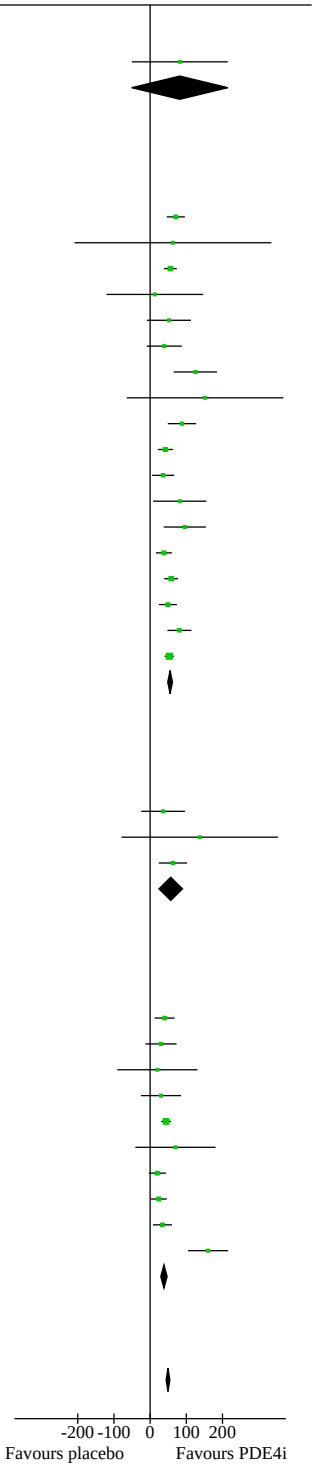
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.32.1 Roflumilast 250 ug	3	1560	Mean Difference (IV, Fixed, 95% CI)	22.61 [-5.95, 51.16]
1.33 FEV_1 (by study duration)	28	19939	Mean Difference (IV, Fixed, 95% CI)	49.09 [43.86, 54.32]
1.33.1 Duration ≤ 12 weeks	8	1191	Mean Difference (IV, Fixed, 95% CI)	101.71 [70.96, 132.46]
1.33.2 Duration 24 to 26 weeks	13	8086	Mean Difference (IV, Fixed, 95% CI)	46.14 [38.44, 53.84]
1.33.3 Duration 52 weeks	7	10662	Mean Difference (IV, Fixed, 95% CI)	48.77 [41.44, 56.10]
1.34 FEV_1 (additional medication)	28	19719	Mean Difference (IV, Fixed, 95% CI)	49.08 [43.85, 54.31]
1.34.1 Long-acting bronchodilator	2	1645	Mean Difference (IV, Fixed, 95% CI)	60.52 [40.57, 80.46]
1.34.2 Corticosteroids	3	2904	Mean Difference (IV, Fixed, 95% CI)	42.26 [25.46, 59.05]
1.34.3 PDE_4i treatment only	20	10323	Mean Difference (IV, Fixed, 95% CI)	44.80 [37.69, 51.91]
1.34.4 Various concomitant treatments	3	4847	Mean Difference (IV, Fixed, 95% CI)	56.58 [46.91, 66.25]
1.35 FEV_1 (random-effects model)	29	20015	Mean Difference (IV, Random, 95% CI)	51.49 [42.87, 60.10]
1.36 FEV_1 (published vs unpublished)	29	20015	Mean Difference (IV, Fixed, 95% CI)	49.28 [44.05, 54.51]
1.36.1 Published	20	15398	Mean Difference (IV, Fixed, 95% CI)	55.75 [49.45, 62.06]
1.36.2 Unpublished	9	4617	Mean Difference (IV, Fixed, 95% CI)	35.05 [25.70, 44.40]
1.37 SGRQ total score (by mean COPD severity)	8	4851	Mean Difference (IV, Fixed, 95% CI)	-1.56 [-2.39, -0.74]
1.37.1 GOLD grade I + II	3	2042	Mean Difference (IV, Fixed, 95% CI)	-1.62 [-2.80, -0.44]
1.37.2 GOLD grade III + IV	5	2809	Mean Difference (IV, Fixed, 95% CI)	-1.51 [-2.67, -0.34]
1.38 SGRQ total score (by duration)	11	7069	Mean Difference (IV, Fixed, 95% CI)	-0.99 [-1.65, -0.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.38.1 Duration < 12 weeks	2	240	Mean Difference (IV, Fixed, 95% CI)	-4.19 [-7.60, -0.78]
1.38.2 Duration 24 to 26 weeks	7	4600	Mean Difference (IV, Fixed, 95% CI)	-1.18 [-1.94, -0.42]
1.38.3 Duration 52 weeks	2	2229	Mean Difference (IV, Fixed, 95% CI)	0.26 [-1.18, 1.69]
1.39 SGRQ total score (by published vs unpublished)	11	7069	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-1.65, -0.34]
1.39.1 Published	5	3079	Mean Difference (IV, Fixed, 95% CI)	-1.98 [-3.07, -0.89]
1.39.2 Unpublished	6	3990	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-1.26, 0.40]
1.40 Number of participants on roflumilast with 1 or more exacerbations (additional medication)	15	14698	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.73, 0.85]
1.40.1 Long-acting bronchodilators	3	1834	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.54, 0.88]
1.40.2 Corticosteroids	1	2686	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.70, 0.95]
1.40.3 Treatment only	7	5145	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.67, 0.93]
1.40.4 Various concomitant treatments	4	5033	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.72, 0.91]
1.41 FVC ML (roflumilast 500 µg, endpoint)	1	60	Mean Difference (IV, Fixed, 95% CI)	0.52 [0.25, 0.79]
1.42 FEV_1 (by unknown COPD severity)	1	76	Mean Difference (IV, Fixed, 95% CI)	82.00 [-50.84, 214.84]
1.43 FEV_1 (by duration, endpoint)	1	60	Mean Difference (IV, Fixed, 95% CI)	0.52 [0.25, 0.79]
1.44 FEV_1 (random-effects model, endpoint data)	1	60	Mean Difference (IV, Random, 95% CI)	0.43 [0.31, 0.55]
1.45 FEV_1 (by moderate to severe COPD severity, endpoint)	1	60	Mean Difference (IV, Fixed, 95% CI)	0.52 [0.25, 0.79]
1.46 FEV_1 (roflumilast 500 µg, endpoint)	1	60	Mean Difference (IV, Fixed, 95% CI)	0.43 [0.31, 0.55]
1.47 FEV_1 ML (additional medication (PDE_4i only) endpoint)	1	60	Mean Difference (IV, Fixed, 95% CI)	0.52 [0.25, 0.79]
1.48 FEV_1 (published, endpoint)	1	60	Mean Difference (IV, Fixed, 95% CI)	0.52 [0.25, 0.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.49 FEV_1 (roflumilast 500 µg by mean COPD severity)	16	13896	Mean Difference (IV, Fixed, 95% CI)	55.51 [48.88, 62.14]
1.49.1 GOLD grade I + II (FEV_1 ≥ 50% predicted)	7	3341	Mean Difference (IV, Fixed, 95% CI)	69.83 [53.34, 86.33]
1.49.2 GOLD grade III + IV (FEV_1 < 50% predicted)	9	10555	Mean Difference (IV, Fixed, 95% CI)	52.75 [45.52, 59.99]
1.50 FEV_1 (unknown additional medication)	1	76	Mean Difference (IV, Fixed, 95% CI)	82.00 [-50.84, 214.84]
1.51 FEV_1 (by moderate to severe COPD severity, roflumilast 500 µg endpoint)	1	60	Mean Difference (IV, Fixed, 95% CI)	0.52 [0.25, 0.79]
1.52 FEV_1 (by unknown COPD severity, roflumilast 500 µg)	1	76	Mean Difference (IV, Fixed, 95% CI)	82.00 [-50.84, 214.84]

Analysis 1.1. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 1: FEV_1 (by drug)

Study or Subgroup	PDE4i treatment Mean [mL]	SD [mL]	Total	Placebo Mean [mL]	SD [mL]	Total	Weight	Mean Difference IV, Fixed, 95% CI [mL]
1.1.1 Tetomilast 50 µg								
NCT00874497 (EMPHASIS)	-1	201.1	48	-83	324.1	28	0.2%	82.00 [-50.84 , 214.84]
Subtotal (95% CI)			**48**			**28**	**0.2%**	**82.00 [-50.84 , 214.84]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.21 (P = 0.23)								
1.1.2 Roflumilast 500 µg								
RO-2455-301-RD (ACROSS)	49	159.5692	313	-22	159.5692	313	4.3%	71.00 [46.00 , 96.00]
RO-2455-402-RD (ROBERT) (1)	63	861	77	0	861	77	0.0%	63.00 [-208.97 , 334.97]
RO-2455-404-RD (REACT)	52	194.9638	928	-4	196.3246	941	8.5%	56.00 [38.26 , 73.74]
Roflumilast DAL-MD-01	41	91	11	28	250	16	0.1%	13.00 [-120.78 , 146.78]
Roflumilast FK1 101 (2)	109	273	169	57	213	86	0.7%	52.00 [-9.00 , 113.00]
Roflumilast FK1 103	78	240	200	39	245	186	1.1%	39.00 [-9.44 , 87.44]
Roflumilast FLUI-2011-77	66	120	30	-59	71	11	0.7%	125.00 [64.96 , 185.04]
Roflumilast IN-108 (2)	28	486	42	-124	281	12	0.1%	152.00 [-64.52 , 368.52]
Roflumilast M2-107 (2)	49	283	555	-39	189	140	1.7%	88.00 [48.83 , 127.17]
Roflumilast M2-111	30	182	545	-12	178	596	6.1%	42.00 [21.08 , 62.92]
Roflumilast M2-112	9	303	760	-27	302	753	2.9%	36.00 [5.52 , 66.48]
Roflumilast M2-118	55	282	127	-27	311	123	0.5%	82.00 [8.34 , 155.66]
Roflumilast M2-119	54	289	189	-42	298	201	0.8%	96.00 [37.74 , 154.26]
Roflumilast M2-124	46	218	745	8	218	745	5.4%	38.00 [15.86 , 60.14]
Roflumilast M2-125	33	189	730	-25	194	766	7.1%	58.00 [38.59 , 77.41]
Roflumilast M2-127	39	192	456	-10	193	460	4.3%	49.00 [24.07 , 73.93]
Roflumilast M2-128	65	229	365	-16	229	364	2.4%	81.00 [47.75 , 114.25]
Roflumilast ROF-MD-07(RE2SPOND)	53	160.836	1178	0	160.836	1174	15.8%	53.00 [40.00 , 66.00]
Subtotal (95% CI)			**7420**			**6964**	**62.5%**	**55.18 [48.65 , 61.71]**
Heterogeneity: Chi² = 21.53, df = 17 (P = 0.20); I² = 21%								
Test for overall effect: Z = 16.56 (P < 0.00001)								
1.1.3 Roflumilast 250 µg								
Roflumilast FK1 101 (2)	93	273	175	57	213	86	0.7%	36.00 [-24.52 , 96.52]
Roflumilast IN-108 (2)	13	492	43	-124	292	13	0.1%	137.00 [-79.38 , 353.38]
Roflumilast M2-107 (2)	24	288	576	-39	189	140	1.7%	63.00 [23.84 , 102.16]
Subtotal (95% CI)			**794**			**239**	**2.5%**	**56.88 [24.38 , 89.38]**
Heterogeneity: Chi² = 1.08, df = 2 (P = 0.58); I² = 0%								
Test for overall effect: Z = 3.43 (P = 0.0006)								
1.1.4 Cilomilast 15 mg								
Cilomilast 039	10	194	378	-30	144	207	3.5%	40.00 [12.30 , 67.70]
Cilomilast 042	30	210	435	0	296	230	1.4%	30.00 [-13.04 , 73.04]
Cilomilast 076	-50	183	21	-70	192	23	0.2%	20.00 [-90.83 , 130.83]
Cilomilast 091	0	417	435	-30	303	230	0.9%	30.00 [-25.40 , 85.40]
Cilomilast 103657	50	86	296	6	89	316	13.9%	44.00 [30.13 , 57.87]
Cilomilast 110	10	179	20	-60	204	26	0.2%	70.00 [-40.92 , 180.92]
Cilomilast 121	14	175	622	-6	181	328	4.6%	20.00 [-3.93 , 43.93]
Cilomilast 156	7	153	364	-17	155	377	5.4%	24.00 [1.82 , 46.18]
Cilomilast 157	32	197	390	-2	182	411	3.8%	34.00 [7.70 , 60.30]
Compton 2001	130	206	107	-30	207	106	0.9%	160.00 [104.53 , 215.47]
Subtotal (95% CI)			**3068**			**2254**	**34.8%**	**38.15 [29.41 , 46.90]**
Heterogeneity: Chi² = 23.75, df = 9 (P = 0.005); I² = 62%								
Test for overall effect: Z = 8.55 (P < 0.00001)								
Total (95% CI)			**11330**			**9485**	**100.0%**	**49.33 [44.17 , 54.49]**
Heterogeneity: Chi² = 56.15, df = 31 (P = 0.004); I² = 45%								
Test for overall effect: Z = 18.73 (P < 0.00001)								
Test for subgroup differences: Chi² = 9.80, df = 3 (P = 0.02), I² = 69.4%								



Footnotes

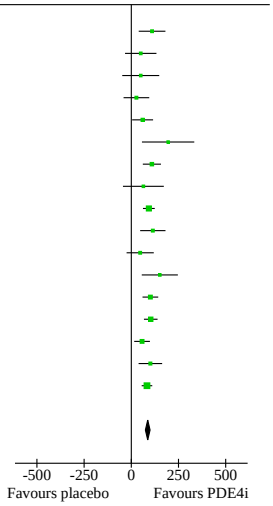
(1) Units converted from L to mL, standard deviations obtained by imputing participant number in each group in the calculator from GIV analysis. Mean differences for each treatment group were not availa

(2) The participant number in the placebo group was halved to avoid double counting

Analysis 1.2. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 2: FVC

Study or Subgroup	PDE4i treatment Mean [mL]	SD [mL]	Total	Placebo Mean [mL]	SD [mL]	Total	Weight	Mean Difference IV, Fixed, 95% CI [mL]
Cilomilast 039	-10	397	394	-120	433	208	3.0%	110.00 [39.29 , 180.71]
Cilomilast 042	30	635	448	-20	445	220	2.2%	50.00 [-33.16 , 133.16]
Cilomilast 091	-20	631	443	-70	609	232	1.6%	50.00 [-47.95 , 147.95]
Cilomilast 103657	25	447	296	-2	409	316	3.3%	27.00 [-41.02 , 95.02]
Cilomilast 156	20	388	377	-40	391	383	5.0%	60.00 [4.62 , 115.38]
Compton 2001	180	517	107	-15	515	106	0.8%	195.00 [56.41 , 333.59]
RO-2455-301-RD (ACROSS)	100	306.3729	313	-9	306.3729	313	6.6%	109.00 [61.00 , 157.00]
RO-2455-402-RD (ROBERT) (1)	64	342.5	77	0	342.5	77	1.3%	64.00 [-44.19 , 172.19]
RO-2455-404-RD (REACT)	36	347.2793	928	-57	941	7187	15.6%	93.00 [61.81 , 124.19]
Roflumilast M2-107	39	495	555	-75	452	280	3.4%	114.00 [46.93 , 181.07]
Roflumilast M2-112	-33	716	760	-80	713	753	2.9%	47.00 [-25.00 , 119.00]
Roflumilast M2-119	51	481	189	-100	483	202	1.7%	151.00 [55.40 , 246.60]
Roflumilast M2-124	76	405	729	-25	407	736	8.8%	101.00 [59.42 , 142.58]
Roflumilast M2-125	58	350	724	-45	359	764	11.7%	103.00 [66.97 , 139.03]
Roflumilast M2-127	67	319	452	10	322	460	8.8%	57.00 [15.40 , 98.60]
Roflumilast M2-128	27	439	364	-74	419	363	3.9%	101.00 [38.62 , 163.38]
Roflumilast ROF-MD-07(RE2SPOND)	83	346.416	1178	0	346.416	1174	19.4%	83.00 [55.00 , 111.00]
Total (95% CI)			**8334**			**13774**	**100.0%**	**86.98 [74.65 , 99.31]**

Heterogeneity: Chi² = 16.06, df = 16 (P = 0.45); I² = 0%
Test for overall effect: Z = 13.82 (P < 0.00001)
Test for subgroup differences: Not applicable

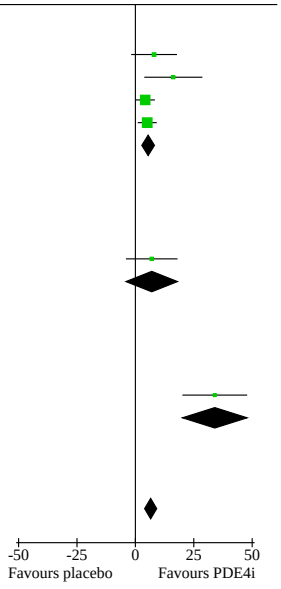


Footnotes
(1) Imputed participant numbers and calculated SDs in RevMan calculator

Analysis 1.3. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 3: PEF

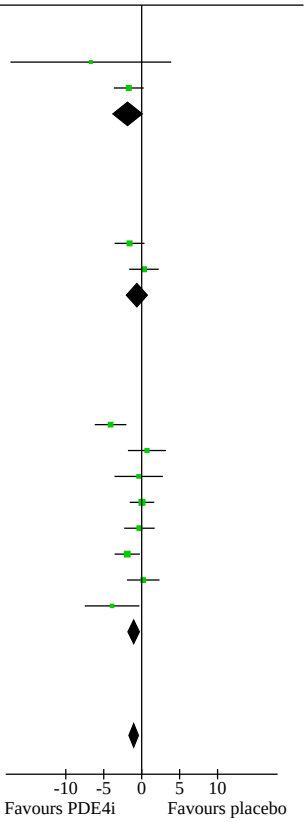
Study or Subgroup	PDE4i treatment Mean [L/min]	SD [L/min]	Total	Placebo Mean [L/min]	SD [L/min]	Total	Weight	Mean Difference IV, Fixed, 95% CI [L/min]
1.3.1 Roflumilast 500 µg								
Roflumilast FK1 101	10	39	169	2	52.5	172	7.0%	8.00 [-1.80 , 17.80]
Roflumilast M2-119	3.06	61.7	189	-13.19	63.7	202	4.3%	16.25 [3.82 , 28.68]
Roflumilast M2-124	8.08	40.5	729	3.87	40.2	736	39.3%	4.21 [0.08 , 8.34]
Roflumilast M2-125	1.93	40.1	724	-3.14	40.1	764	40.4%	5.07 [0.99 , 9.15]
Subtotal (95% CI)			**1811**			**1874**	**91.0%**	**5.46 [2.74 , 8.17]**
Heterogeneity: Chi² = 3.54, df = 3 (P = 0.32); I² = 15%								
Test for overall effect: Z = 3.94 (P < 0.0001)								
1.3.2 Roflumilast 250 µg								
Roflumilast FK1 101	9	52.5	175	2	52.5	172	5.5%	7.00 [-4.05 , 18.05]
Subtotal (95% CI)			**175**			**172**	**5.5%**	**7.00 [-4.05 , 18.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.24 (P = 0.21)								
1.3.3 Cilomilast 15 mg								
Compton 2001	25.5	51.7	107	-8.5	51.5	106	3.5%	34.00 [20.14 , 47.86]
Subtotal (95% CI)			**107**			**106**	**3.5%**	**34.00 [20.14 , 47.86]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.81 (P < 0.00001)								
Total (95% CI)			**2093**			**2152**	**100.0%**	**6.54 [3.95 , 9.13]**

Heterogeneity: Chi² = 19.24, df = 5 (P = 0.002); I² = 74%
Test for overall effect: Z = 4.95 (P < 0.00001)
Test for subgroup differences: Chi² = 15.70, df = 2 (P = 0.0004), I² = 87.3%



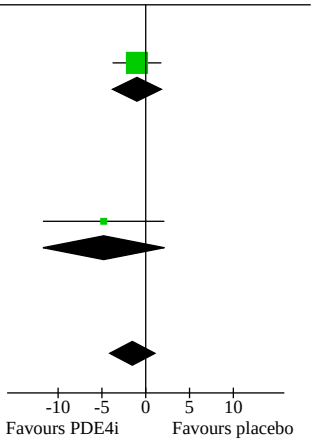
Analysis 1.4. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 4: SGRQ total score

Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 Roflumilast 500 µg								
Roflumilast DAL-MD-01	-7.5	13.8	11	-0.8	13.8	16	0.3%	-6.70 [-17.29 , 3.89]
Roflumilast M2-107	-3.5	14.1	555	-1.8	9.5	140	10.1%	-1.70 [-3.66 , 0.26]
Subtotal (95% CI)			**566**			**156**	**10.5%**	**-1.87 [-3.80 , 0.06]**
Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%								
Test for overall effect: Z = 1.89 (P = 0.06)								
1.4.2 Roflumilast 250 µg								
Roflumilast M2-107	-3.4	14.4	576	-1.8	9.5	140	10.1%	-1.60 [-3.56 , 0.36]
Roflumilast M2-112	-1.7	19.3	760	-2	19.2	753	10.4%	0.30 [-1.64 , 2.24]
Subtotal (95% CI)			**1336**			**893**	**20.4%**	**-0.64 [-2.02 , 0.74]**
Heterogeneity: Chi² = 1.82, df = 1 (P = 0.18); I² = 45%								
Test for overall effect: Z = 0.91 (P = 0.36)								
1.4.3 Cilomilast 15 mg								
Cilomilast 039	-3.7	12.32	310	0.4	10.76	181	9.0%	-4.10 [-6.18 , -2.02]
Cilomilast 042	-4.2	15.5	375	-4.9	13.8	190	6.2%	0.70 [-1.81 , 3.21]
Cilomilast 091	-2.7	21.1	369	-2.3	16.8	197	3.8%	-0.40 [-3.58 , 2.78]
Cilomilast 103657	-1.8	10.2	292	-1.84	10	310	14.9%	0.04 [-1.57 , 1.65]
Cilomilast 121	-9	14.7	580	-8.7	14.7	320	9.7%	-0.30 [-2.31 , 1.71]
Cilomilast 156	-3.2	10.5	304	-1.3	11	337	14.0%	-1.90 [-3.57 , -0.23]
Cilomilast 157	-1.29	14.9	347	-1.49	14.4	369	8.4%	0.20 [-1.95 , 2.35]
Compton 2001	-3.9	13.4	107	0	13.4	106	3.0%	-3.90 [-7.50 , -0.30]
Subtotal (95% CI)			**2684**			**2010**	**69.1%**	**-1.06 [-1.81 , -0.31]**
Heterogeneity: Chi² = 17.26, df = 7 (P = 0.02); I² = 59%								
Test for overall effect: Z = 2.76 (P = 0.006)								
Total (95% CI)			**4586**			**3059**	**100.0%**	**-1.06 [-1.68 , -0.43]**
Heterogeneity: Chi² = 20.93, df = 11 (P = 0.03); I² = 47%								
Test for overall effect: Z = 3.32 (P = 0.0009)								
Test for subgroup differences: Chi² = 1.03, df = 2 (P = 0.60), I² = 0%								



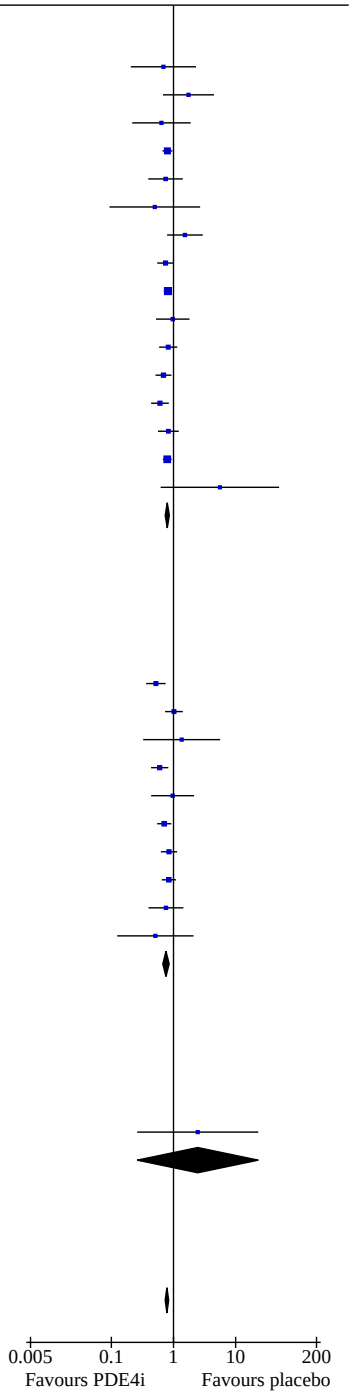
Analysis 1.5. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 5: SGRQ symptom score

Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 Roflumilast								
Roflumilast M2-107	-4.6	21.2	555	-3.6	18.4	280	86.1%	-1.00 [-3.78 , 1.78]
Subtotal (95% CI)			**555**			**280**	**86.1%**	**-1.00 [-3.78 , 1.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.70 (P = 0.48)								
1.5.2 Cilomilast								
Compton 2001	-7.2	25.9	107	-2.4	25.7	106	13.9%	-4.80 [-11.73 , 2.13]
Subtotal (95% CI)			**107**			**106**	**13.9%**	**-4.80 [-11.73 , 2.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.36 (P = 0.17)								
Total (95% CI)			**662**			**386**	**100.0%**	**-1.53 [-4.11 , 1.06]**
Heterogeneity: Chi² = 0.99, df = 1 (P = 0.32); I² = 0%								
Test for overall effect: Z = 1.16 (P = 0.25)								
Test for subgroup differences: Chi² = 0.99, df = 1 (P = 0.32), I² = 0%								



Analysis 1.6. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 6: Number of participants with 1 or more exacerbations (by drug)

Study or Subgroup	PDE4i treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 Roflumilast 500 µg						
Liu 2018 (1)	5	60	7	60	0.3%	0.69 [0.21 , 2.30]
RO-2455-301-RD (ACROSS)	12	313	7	313	0.3%	1.74 [0.68 , 4.49]
RO-2455-402-RD (ROBERT) (1)	6	79	9	79	0.4%	0.64 [0.22 , 1.89]
RO-2455-404-RD (REACT)	380	969	432	966	12.5%	0.80 [0.67 , 0.96]
Roflumilast FK1 101	19	169	25	172	1.0%	0.74 [0.39 , 1.41]
Roflumilast IN-108	3	47	3	25	0.2%	0.50 [0.09 , 2.68]
Roflumilast JP-706	25	204	16	191	0.7%	1.53 [0.79 , 2.96]
Roflumilast M2-107	157	555	97	280	4.4%	0.74 [0.55 , 1.01]
Roflumilast M2-111+M2-112	569	1327	652	1359	17.5%	0.81 [0.70 , 0.95]
Roflumilast M2-119	22	203	23	207	1.0%	0.97 [0.52 , 1.81]
Roflumilast M2-124	70	769	82	755	3.6%	0.82 [0.59 , 1.15]
Roflumilast M2-125	87	778	122	790	5.1%	0.69 [0.51 , 0.93]
Roflumilast M2-127	74	466	111	467	4.4%	0.61 [0.44 , 0.84]
Roflumilast M2-128	58	374	67	369	2.7%	0.83 [0.56 , 1.22]
Roflumilast ROF-MD-07(RE2SPOND)	539	1178	605	1174	15.6%	0.79 [0.67 , 0.93]
Urban 2018 (ELASTIC) (2)	5	40	1	40	0.0%	5.57 [0.62 , 50.03]
Subtotal (95% CI)		**7531**		**7247**	**69.8%**	**0.79 [0.73 , 0.86]**
Total events:	2031		2259			
Heterogeneity: Chi² = 14.27, df = 15 (P = 0.51); I² = 0%						
Test for overall effect: Z = 5.91 (P < 0.00001)						
1.6.2 Cilomilast						
Cilomilast 039	95	431	76	216	3.8%	0.52 [0.36 , 0.75]
Cilomilast 042	176	474	83	226	3.4%	1.02 [0.73 , 1.41]
Cilomilast 076	5	29	4	30	0.2%	1.35 [0.33 , 5.64]
Cilomilast 091	151	469	107	242	4.6%	0.60 [0.44 , 0.82]
Cilomilast 111	15	79	15	77	0.6%	0.97 [0.44 , 2.15]
Cilomilast 121	297	678	178	340	6.3%	0.71 [0.55 , 0.92]
Cilomilast 156	114	418	125	407	4.4%	0.85 [0.63 , 1.14]
Cilomilast 157	191	455	209	452	5.8%	0.84 [0.65 , 1.09]
Cilomilast 168	28	203	18	103	1.0%	0.76 [0.40 , 1.44]
Cilomilast 180	3	97	6	102	0.3%	0.51 [0.12 , 2.10]
Subtotal (95% CI)		**3333**		**2195**	**30.2%**	**0.76 [0.67 , 0.85]**
Total events:	1075		821			
Heterogeneity: Chi² = 12.00, df = 9 (P = 0.21); I² = 25%						
Test for overall effect: Z = 4.64 (P < 0.00001)						
1.6.3 Tetomilast 50 µg						
NCT00874497 (EMPHASIS) (3)	4	48	1	28	0.1%	2.45 [0.26 , 23.13]
Subtotal (95% CI)		**48**		**28**	**0.1%**	**2.45 [0.26 , 23.13]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.43)						
Total (95% CI)		**10912**		**9470**	**100.0%**	**0.78 [0.73 , 0.84]**
Total events:	3110		3081			
Heterogeneity: Chi² = 27.71, df = 26 (P = 0.37); I² = 6%						
Test for overall effect: Z = 7.45 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.43, df = 2 (P = 0.49), I² = 0%						



Footnotes

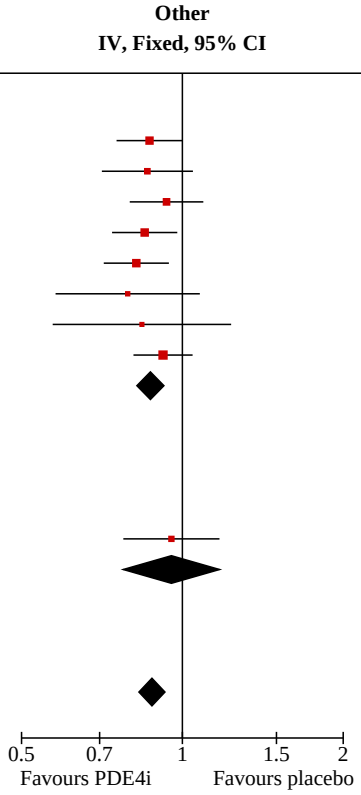
(1) New study data added 2019

(2) New data added 2019

(3) New data 2019: level 2 or more; requiring physician visit or admission to hospital

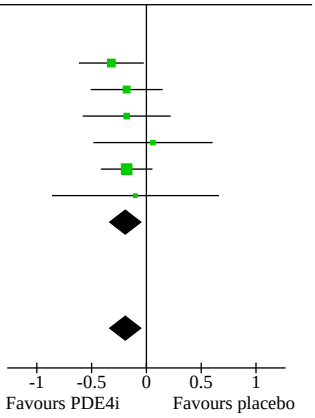
Analysis 1.7. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 7: Exacerbation rate (inverse variance)

Study or Subgroup	log[Other]	SE	Weight	Other IV, Fixed, 95% CI
1.7.1 Roflumilast				
RO-2455-404-RD (REACT)	-0.1416	0.0725	15.5%	0.87 [0.75 , 1.00]
Roflumilast M2-111	-0.1508	0.1001	8.2%	0.86 [0.71 , 1.05]
Roflumilast M2-112	-0.0683	0.0809	12.5%	0.93 [0.80 , 1.09]
Roflumilast M2-124	-0.1625	0.0717	15.9%	0.85 [0.74 , 0.98]
Roflumilast M2-125	-0.1985	0.0716	15.9%	0.82 [0.71 , 0.94]
Roflumilast M2-127	-0.2357	0.1586	3.2%	0.79 [0.58 , 1.08]
Roflumilast M2-128	-0.1744	0.1962	2.1%	0.84 [0.57 , 1.23]
Roflumilast ROF-MD-07(RE2SPOND)	-0.0834	0.065	19.3%	0.92 [0.81 , 1.04]
Subtotal (95% CI)			**92.7%**	**0.87 [0.82 , 0.92]**
Heterogeneity: Chi² = 2.71, df = 7 (P = 0.91); I² = 0%				
Test for overall effect: Z = 4.64 (P < 0.00001)				
1.7.2 Cilomilast				
Cilomilast 157	-0.0473	0.1057	7.3%	0.95 [0.78 , 1.17]
Subtotal (95% CI)			**7.3%**	**0.95 [0.78 , 1.17]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.45 (P = 0.65)				
Total (95% CI)			**100.0%**	**0.88 [0.83 , 0.93]**
Heterogeneity: Chi² = 3.39, df = 8 (P = 0.91); I² = 0%				
Test for overall effect: Z = 4.59 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.68, df = 1 (P = 0.41), I² = 0%				



Analysis 1.8. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 8: Borg Scale

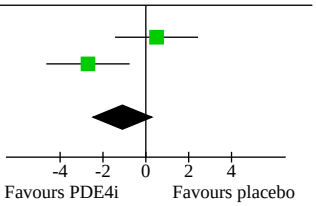
Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.8.1 Cilomilast								
Cilomilast 039	-0.13	1.7	357	0.19	1.7	196	22.8%	-0.32 [-0.62 , -0.02]
Cilomilast 042	-0.29	2.1	422	-0.11	1.9	206	18.6%	-0.18 [-0.51 , 0.15]
Cilomilast 091	0.03	2.9	417	0.21	2.2	223	12.4%	-0.18 [-0.58 , 0.22]
Cilomilast 111	0.03	1.6	73	-0.03	1.7	69	6.8%	0.06 [-0.48 , 0.60]
Cilomilast 156	-0.16	1.7	347	0.02	1.5	369	36.0%	-0.18 [-0.42 , 0.06]
Cilomilast 180	-0.1	2.7	84	0	2.5	97	3.4%	-0.10 [-0.86 , 0.66]
Subtotal (95% CI)			**1700**			**1160**	**100.0%**	**-0.19 [-0.33 , -0.05]**
Heterogeneity: Chi² = 1.62, df = 5 (P = 0.90); I² = 0%								
Test for overall effect: Z = 2.68 (P = 0.007)								
Total (95% CI)			**1700**			**1160**	**100.0%**	**-0.19 [-0.33 , -0.05]**
Heterogeneity: Chi² = 1.62, df = 5 (P = 0.90); I² = 0%								
Test for overall effect: Z = 2.68 (P = 0.007)								
Test for subgroup differences: Not applicable								



Analysis 1.9. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 9: Shortness of Breath Questionnaire

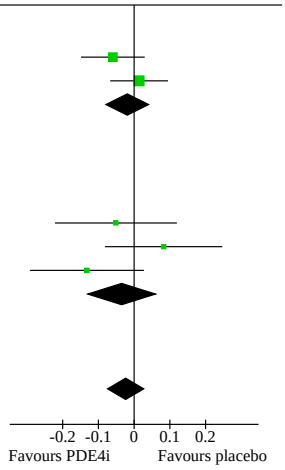
Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Roflumilast M2-127	-0.6	14.9	454	-1.1	15	461	50.2%	0.50 [-1.44 , 2.44]
Roflumilast M2-128	-3.4	13.3	359	-0.7	13.3	359	49.8%	-2.70 [-4.65 , -0.75]
Total (95% CI)			**813**			**820**	**100.0%**	**-1.09 [-2.47 , 0.28]**

Heterogeneity: Chi² = 5.22, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable



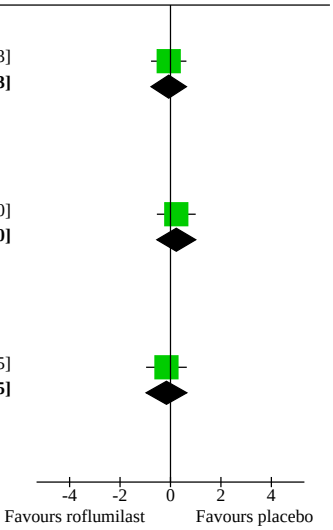
Analysis 1.10. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 10: Summary symptom score

Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.10.1 Roflumilast								
RO-2455-404-RD (REACT)	-1.27	4.8436	969	-0.985	4.718	966	32.3%	-0.06 [-0.15 , 0.03]
Roflumilast ROF-MD-07(RE2SPOND)	0	4.3302	1178	-0.06	4.3302	1174	39.3%	0.01 [-0.07 , 0.09]
Subtotal (95% CI)			**2147**			**2140**	**71.6%**	**-0.02 [-0.08 , 0.04]**
Heterogeneity: Chi² = 1.43, df = 1 (P = 0.23); I² = 30%								
Test for overall effect: Z = 0.63 (P = 0.53)								
1.10.2 Cilomilast								
Cilomilast 039	-0.21	1.8	382	-0.12	1.7	202	8.8%	-0.05 [-0.22 , 0.12]
Cilomilast 042	-0.41	2.3	435	-0.59	1.9	212	9.5%	0.08 [-0.08 , 0.25]
Cilomilast 091	-0.3	2.7	437	0.04	2.3	231	10.1%	-0.13 [-0.29 , 0.03]
Subtotal (95% CI)			**1254**			**645**	**28.4%**	**-0.04 [-0.13 , 0.06]**
Heterogeneity: Chi² = 3.43, df = 2 (P = 0.18); I² = 42%								
Test for overall effect: Z = 0.72 (P = 0.47)								
Total (95% CI)			**3401**			**2785**	**100.0%**	**-0.02 [-0.07 , 0.03]**
Heterogeneity: Chi² = 4.93, df = 4 (P = 0.29); I² = 19%								
Test for overall effect: Z = 0.92 (P = 0.36)								
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%								



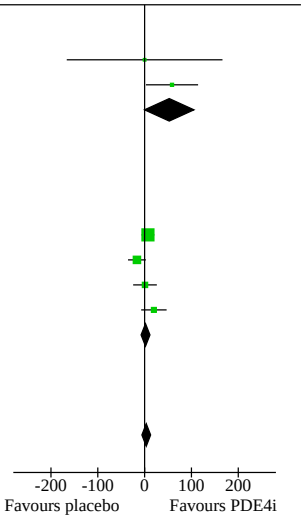
Analysis 1.11. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 11: Breathlessness Cough and Sputum Scale (BCSS) (tetomilast 50 µg)

Study or Subgroup	Roflumilast Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.11.1 Breathlessness								
NCT00874497 (EMPHASIS)	0.13	0.6	13	0.2	0.95	9	100.0%	-0.07 [-0.77 , 0.63]
Subtotal (95% CI)			**13**			**9**	**100.0%**	**-0.07 [-0.77 , 0.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.20 (P = 0.84)								
1.11.2 Cough								
NCT00874497 (EMPHASIS)	0.1	0.4	13	-0.13	1.13	9	100.0%	0.23 [-0.54 , 1.00]
Subtotal (95% CI)			**13**			**9**	**100.0%**	**0.23 [-0.54 , 1.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.59 (P = 0.56)								
1.11.3 Sputum								
NCT00874497 (EMPHASIS)	0.15	0.74	13	0.31	1.07	9	100.0%	-0.16 [-0.97 , 0.65]
Subtotal (95% CI)			**13**			**9**	**100.0%**	**-0.16 [-0.97 , 0.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.39 (P = 0.70)								
Test for subgroup differences: Chi² = 0.53, df = 2 (P = 0.77), I² = 0%								



Analysis 1.12. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 12: 6-minute walk test

Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.12.1 Roflumilast								
Roflumilast DAL-MD-01	0	142	11	0	293	16	0.3%	0.00 [-166.29 , 166.29]
Urban 2018 (ELASTIC) (1)	59.2	127.8862	40	0.69	126.2916	40	2.8%	58.51 [2.81 , 114.21]
Subtotal (95% CI)			**51**			**56**	**3.1%**	**52.61 [-0.21 , 105.42]**
Heterogeneity: Chi² = 0.43, df = 1 (P = 0.51); I² = 0%								
Test for overall effect: Z = 1.95 (P = 0.05)								
1.12.2 Cilomilast								
Cilomilast 039	16.1	79	356	9	77	194	47.3%	7.10 [-6.49 , 20.69]
Cilomilast 042	5.8	125	423	22.2	109	207	24.1%	-16.40 [-35.44 , 2.64]
Cilomilast 091	5.4	178	408	4.6	139	218	13.7%	0.80 [-24.47 , 26.07]
Cilomilast 111	16.1	82	73	-3.7	83	69	11.8%	19.80 [-7.35 , 46.95]
Subtotal (95% CI)			**1260**			**688**	**96.9%**	**1.92 [-7.58 , 11.41]**
Heterogeneity: Chi² = 5.79, df = 3 (P = 0.12); I² = 48%								
Test for overall effect: Z = 0.40 (P = 0.69)								
Total (95% CI)			**1311**			**744**	**100.0%**	**3.50 [-5.84 , 12.85]**
Heterogeneity: Chi² = 9.64, df = 5 (P = 0.09); I² = 48%								
Test for overall effect: Z = 0.74 (P = 0.46)								
Test for subgroup differences: Chi² = 3.43, df = 1 (P = 0.06), I² = 70.8%								

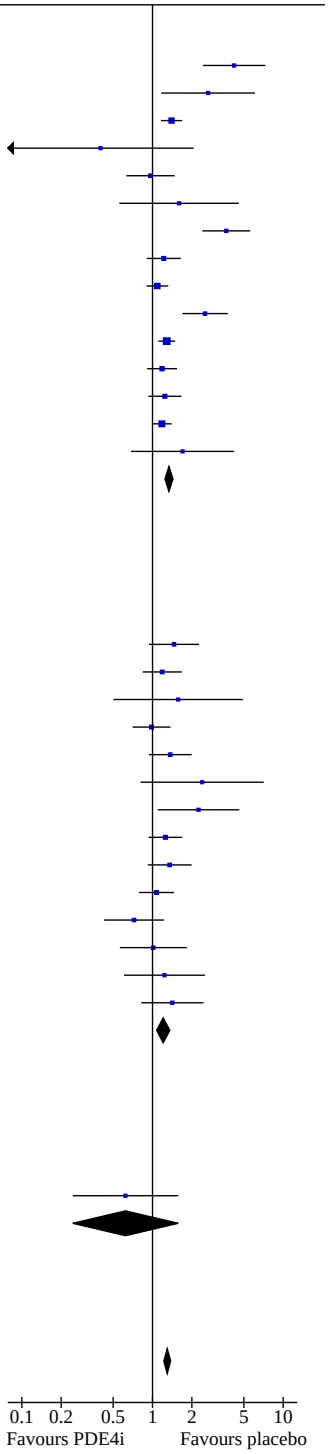


Footnotes

(1) New data 2019

Analysis 1.13. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 13: Number of participants experiencing an adverse event

Study or Subgroup	PDE4i treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.13.1 Roflumilast 500 µg						
RO-2455-301-RD (ACROSS)	64	313	18	313	0.8%	4.21 [2.43 , 7.30]
RO-2455-402-RD (ROBERT) (1)	69	79	57	79	0.4%	2.66 [1.17 , 6.08]
RO-2455-404-RD (REACT)	648	968	572	967	10.2%	1.40 [1.16 , 1.68]
Roflumilast DAL-MD-01	4	16	5	11	0.2%	0.40 [0.08 , 2.06]
Roflumilast FK1 101	82	169	85	172	2.3%	0.96 [0.63 , 1.48]
Roflumilast IN-108	18	47	7	25	0.3%	1.60 [0.56 , 4.57]
Roflumilast JP-706	118	204	52	191	1.2%	3.67 [2.40 , 5.60]
Roflumilast M2-107	370	555	174	280	4.1%	1.22 [0.90 , 1.64]
Roflumilast M2-111+M2-112	1081	1327	1089	1359	10.7%	1.09 [0.90 , 1.32]
Roflumilast M2-119	134	203	90	207	1.6%	2.52 [1.69 , 3.77]
Roflumilast M2-124+M2-125	1040	1537	963	1554	16.6%	1.28 [1.11 , 1.49]
Roflumilast M2-127	294	466	276	467	5.5%	1.18 [0.91 , 1.54]
Roflumilast M2-128	172	374	150	369	4.4%	1.24 [0.93 , 1.66]
Roflumilast ROF-MD-07(RE2SPOND)	804	1178	758	1174	12.9%	1.18 [0.99 , 1.40]
Urban 2018 (ELASTIC) (1)	27	40	22	40	0.4%	1.70 [0.68 , 4.22]
Subtotal (95% CI)		**7476**		**7208**	**71.7%**	**1.34 [1.24 , 1.43]**
Total events:	4925		4318			
Heterogeneity: Chi² = 64.11, df = 14 (P < 0.00001); I² = 78%						
Test for overall effect: Z = 8.04 (P < 0.00001)						
1.13.2 Cilomilast 15 mg						
Cilomilast 039	373	431	176	216	1.7%	1.46 [0.94 , 2.27]
Cilomilast 042	340	474	154	226	3.2%	1.19 [0.84 , 1.67]
Cilomilast 076	22	29	20	30	0.3%	1.57 [0.50 , 4.91]
Cilomilast 091	320	469	166	242	3.7%	0.98 [0.70 , 1.37]
Cilomilast 103657	234	296	232	316	2.5%	1.37 [0.94 , 1.99]
Cilomilast 110	24	31	20	34	0.2%	2.40 [0.81 , 7.10]
Cilomilast 111	63	79	49	77	0.5%	2.25 [1.10 , 4.62]
Cilomilast 121	518	678	245	340	4.1%	1.26 [0.93 , 1.69]
Cilomilast 156	364	418	339	407	2.4%	1.35 [0.92 , 1.99]
Cilomilast 157	351	455	343	452	4.2%	1.07 [0.79 , 1.46]
Cilomilast 168	136	203	76	103	1.8%	0.72 [0.43 , 1.22]
Cilomilast 180	65	97	68	102	1.2%	1.02 [0.56 , 1.83]
Cilomilast 181	41	65	36	62	0.7%	1.23 [0.60 , 2.52]
Compton 2001	64	105	55	105	1.2%	1.42 [0.82 , 2.45]
Subtotal (95% CI)		**3830**		**2712**	**27.7%**	**1.21 [1.08 , 1.36]**
Total events:	2915		1979			
Heterogeneity: Chi² = 12.53, df = 13 (P = 0.48); I² = 0%						
Test for overall effect: Z = 3.19 (P = 0.001)						
1.13.3 Tetomilast 50 µg						
NCT00874497 (EMPHASIS) (1)	30	51	23	33	0.6%	0.62 [0.25 , 1.57]
Subtotal (95% CI)		**51**		**33**	**0.6%**	**0.62 [0.25 , 1.57]**
Total events:	30		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
Total (95% CI)		**11357**		**9953**	**100.0%**	**1.30 [1.22 , 1.38]**
Total events:	7870		6320			
Heterogeneity: Chi² = 80.86, df = 29 (P < 0.00001); I² = 64%						
Test for overall effect: Z = 8.45 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.55, df = 2 (P = 0.10), I² = 56.1%						



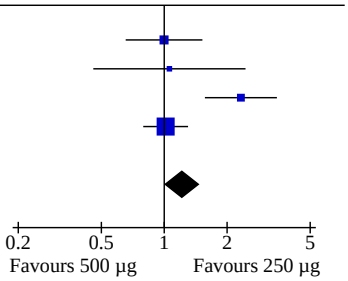
Footnotes

(1) New study data added 2019

Analysis 1.14. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 14: Number of participants experiencing an adverse event (roflumilast 500 µg vs 250 µg)

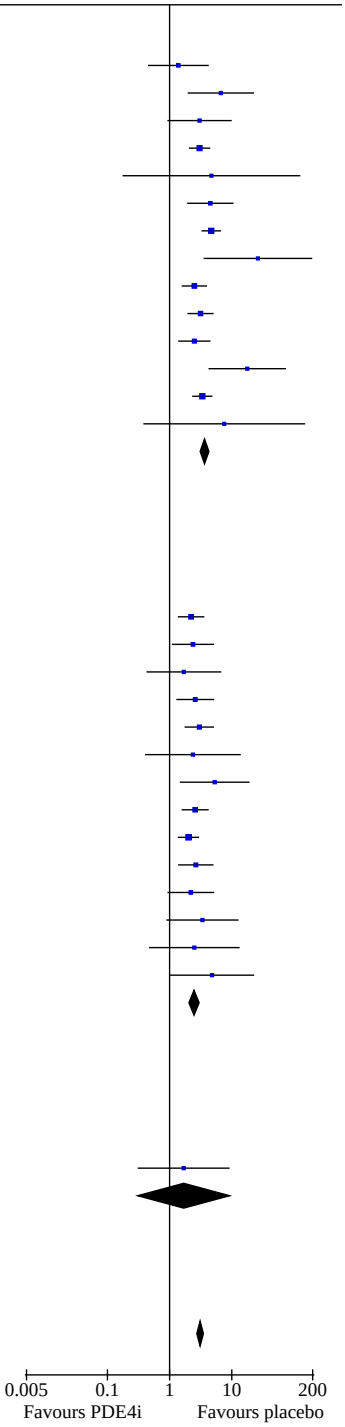
Study or Subgroup	Roflumilast 500 µg Events	Total	Roflumilast 250 µg Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Roflumilast FK1 101	82	169	85	175	20.4%	1.00 [0.65 , 1.52]
Roflumilast IN-108	18	47	17	46	5.0%	1.06 [0.46 , 2.45]
Roflumilast JP-706	118	204	76	205	15.2%	2.33 [1.57 , 3.46]
Roflumilast M2-107	370	555	382	576	59.4%	1.02 [0.79 , 1.30]
Total (95% CI)		**975**		**1002**	**100.0%**	**1.21 [1.01 , 1.46]**
Total events:	588		560			

Heterogeneity: $Chi^2 = 13.28$, df = 3 (P = 0.004); $I^2 = 77\%$
Test for overall effect: Z = 2.08 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 15: Diarrhoea

Study or Subgroup	PDE4i treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.15.1 Roflumilast						
Liu 2018 (1)	8	60	6	60	1.5%	1.38 [0.45 , 4.26]
RO-2455-301-RD (ACROSS)	19	313	3	313	0.8%	6.68 [1.96 , 22.80]
RO-2455-402-RD (ROBERT) (1)	11	79	4	79	1.0%	3.03 [0.92 , 9.98]
RO-2455-404-RD (REACT)	99	968	35	967	9.3%	3.03 [2.04 , 4.51]
Roflumilast DAL-MD-01	1	11	0	16	0.1%	4.71 [0.18 , 126.90]
Roflumilast M2-107	50	555	6	280	2.1%	4.52 [1.91 , 10.68]
Roflumilast M2-111+M2-112	161	1327	39	1359	10.0%	4.67 [3.27 , 6.69]
Roflumilast M2-119	23	203	1	207	0.3%	26.32 [3.52 , 196.86]
Roflumilast M2-124	63	769	26	755	7.1%	2.50 [1.57 , 4.00]
Roflumilast M2-125	67	778	23	790	6.2%	3.14 [1.94 , 5.10]
Roflumilast M2-127	38	466	16	467	4.3%	2.50 [1.37 , 4.56]
Roflumilast M2-128	33	374	2	369	0.5%	17.76 [4.23 , 74.57]
Roflumilast ROF-MD-07(RE2SPOND)	119	1178	38	1174	10.1%	3.36 [2.31 , 4.89]
Urban 2018 (ELASTIC) (1)	3	40	0	40	0.1%	7.56 [0.38 , 151.28]
Subtotal (95% CI)		**7121**		**6876**	**53.6%**	**3.65 [3.10 , 4.28]**
Total events:	695		199			
Heterogeneity: Chi² = 19.96, df = 13 (P = 0.10); I² = 35%						
Test for overall effect: Z = 15.69 (P < 0.00001)						
1.15.2 Cilomilast						
Cilomilast 039	90	431	23	216	7.2%	2.21 [1.36 , 3.62]
Cilomilast 042	38	474	8	226	2.9%	2.38 [1.09 , 5.18]
Cilomilast 076	6	29	4	30	0.9%	1.70 [0.42 , 6.77]
Cilomilast 091	47	469	10	242	3.5%	2.58 [1.28 , 5.21]
Cilomilast 103657	50	296	20	316	4.8%	3.01 [1.74 , 5.19]
Cilomilast 110	4	31	2	34	0.5%	2.37 [0.40 , 13.96]
Cilomilast 111	14	79	3	77	0.7%	5.31 [1.46 , 19.31]
Cilomilast 121	94	678	20	340	6.8%	2.58 [1.56 , 4.25]
Cilomilast 156	82	418	44	407	10.6%	2.01 [1.36 , 2.99]
Cilomilast 157	33	455	13	452	3.6%	2.64 [1.37 , 5.09]
Cilomilast 168	28	203	7	103	2.4%	2.19 [0.92 , 5.21]
Cilomilast 180	9	97	3	102	0.8%	3.38 [0.89 , 12.86]
Cilomilast 181	5	65	2	62	0.6%	2.50 [0.47 , 13.39]
Compton 2001	9	105	2	105	0.5%	4.83 [1.02 , 22.91]
Subtotal (95% CI)		**3830**		**2712**	**45.7%**	**2.47 [2.05 , 2.98]**
Total events:	509		161			
Heterogeneity: Chi² = 4.44, df = 13 (P = 0.99); I² = 0%						
Test for overall effect: Z = 9.40 (P < 0.00001)						
1.15.3 Tetomilast						
NCT00874497 (EMPHASIS) (2)	5	51	2	33	0.6%	1.68 [0.31 , 9.24]
Subtotal (95% CI)		**51**		**33**	**0.6%**	**1.68 [0.31 , 9.24]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
Total (95% CI)		**11002**		**9621**	**100.0%**	**3.10 [2.74 , 3.50]**
Total events:	1209		362			
Heterogeneity: Chi² = 31.97, df = 28 (P = 0.28); I² = 12%						
Test for overall effect: Z = 18.13 (P < 0.00001)						
Test for subgroup differences: Chi² = 9.92, df = 2 (P = 0.007), I² = 79.8%						



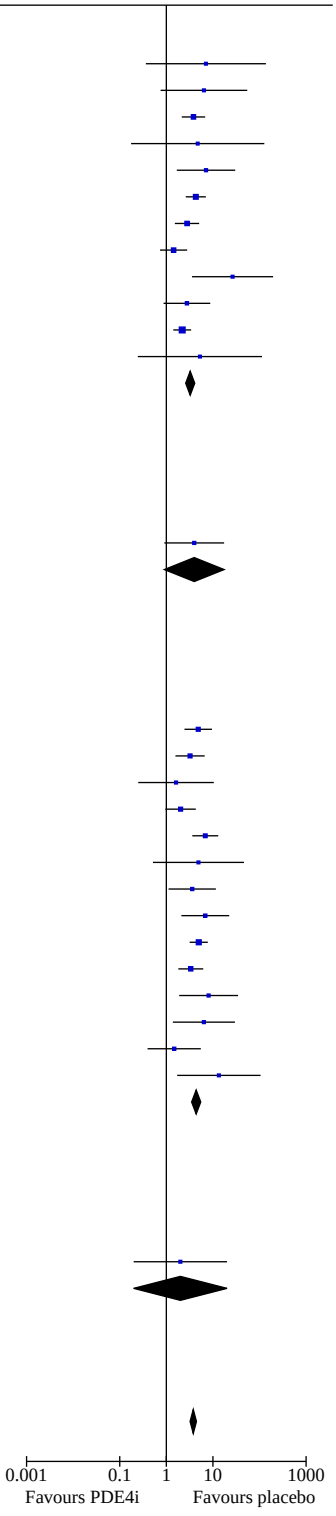
Footnotes

(1) New data 2019

(2) New study data 2019

Analysis 1.16. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 16: Nausea

Study or Subgroup	PDE4i treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.16.1 Roflumilast 500 µg						
RO-2455-301-RD (ACROSS)	3	313	0	313	0.3%	7.07 [0.36 , 137.40]
RO-2455-402-RD (ROBERT) (1)	6	79	1	79	0.5%	6.41 [0.75 , 54.54]
RO-2455-404-RD (REACT)	55	968	15	967	7.2%	3.82 [2.14 , 6.82]
Roflumilast DAL-MD-01	1	11	0	16	0.2%	4.71 [0.18 , 126.90]
Roflumilast M2-107	27	555	2	280	1.3%	7.11 [1.68 , 30.11]
Roflumilast M2-111+M2-112	80	1327	20	1359	9.5%	4.30 [2.62 , 7.05]
Roflumilast M2-124	41	769	15	755	7.3%	2.78 [1.52 , 5.06]
Roflumilast M2-125	21	778	15	790	7.4%	1.43 [0.73 , 2.80]
Roflumilast M2-127	25	466	1	467	0.5%	26.42 [3.56 , 195.79]
Roflumilast M2-128	11	374	4	369	2.0%	2.77 [0.87 , 8.76]
Roflumilast ROF-MD-07(RE2SPOND)	64	1178	30	1174	14.5%	2.19 [1.41 , 3.41]
Urban 2018 (ELASTIC) (1)	2	40	0	40	0.2%	5.26 [0.24 , 113.11]
Subtotal (95% CI)		**6858**		**6609**	**50.7%**	**3.25 [2.60 , 4.07]**
Total events:	336		103			
Heterogeneity: Chi² = 16.80, df = 11 (P = 0.11); I² = 35%						
Test for overall effect: Z = 10.36 (P < 0.00001)						
1.16.2 Roflumilast 250 µg						
Roflumilast M2-107	16	576	2	280	1.3%	3.97 [0.91 , 17.39]
Subtotal (95% CI)		**576**		**280**	**1.3%**	**3.97 [0.91 , 17.39]**
Total events:	16		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.83 (P = 0.07)						
1.16.3 Cilomilast 15 mg						
Cilomilast 039	82	431	10	216	5.5%	4.84 [2.46 , 9.54]
Cilomilast 042	56	474	9	226	5.5%	3.23 [1.57 , 6.65]
Cilomilast 076	3	29	2	30	0.9%	1.62 [0.25 , 10.45]
Cilomilast 091	34	469	9	242	5.6%	2.02 [0.95 , 4.29]
Cilomilast 103657	63	296	12	316	4.7%	6.85 [3.61 , 13.00]
Cilomilast 110	4	31	1	34	0.4%	4.89 [0.52 , 46.36]
Cilomilast 111	13	79	4	77	1.7%	3.59 [1.12 , 11.57]
Cilomilast 121	39	678	3	340	1.9%	6.86 [2.10 , 22.35]
Cilomilast 156	109	418	27	407	10.3%	4.96 [3.17 , 7.76]
Cilomilast 157	44	455	14	452	6.5%	3.35 [1.81 , 6.20]
Cilomilast 168	28	203	2	103	1.2%	8.08 [1.89 , 34.63]
Cilomilast 180	11	97	2	102	0.9%	6.40 [1.38 , 29.65]
Cilomilast 181	6	65	4	62	1.9%	1.47 [0.40 , 5.50]
Compton 2001	12	105	1	105	0.5%	13.42 [1.71 , 105.19]
Subtotal (95% CI)		**3830**		**2712**	**47.4%**	**4.37 [3.49 , 5.47]**
Total events:	504		100			
Heterogeneity: Chi² = 14.16, df = 13 (P = 0.36); I² = 8%						
Test for overall effect: Z = 12.87 (P < 0.00001)						
1.16.4 Tetomilast 50 µg						
NCT00874497 (EMPHASIS) (1)	3	51	1	33	0.6%	2.00 [0.20 , 20.09]
Subtotal (95% CI)		**51**		**33**	**0.6%**	**2.00 [0.20 , 20.09]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
Total (95% CI)		**11315**		**9634**	**100.0%**	**3.79 [3.24 , 4.43]**
Total events:	859		206			
Heterogeneity: Chi² = 35.58, df = 27 (P = 0.12); I² = 24%						
Test for overall effect: Z = 16.65 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.64, df = 3 (P = 0.30), I² = 17.6%						



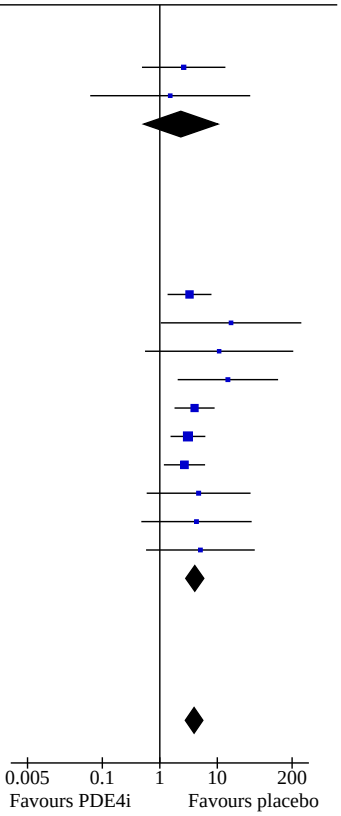
Footnotes

Analysis 1.16. (Continued)

Footnotes
(1) New data 2019

Analysis 1.17. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 17: Vomiting

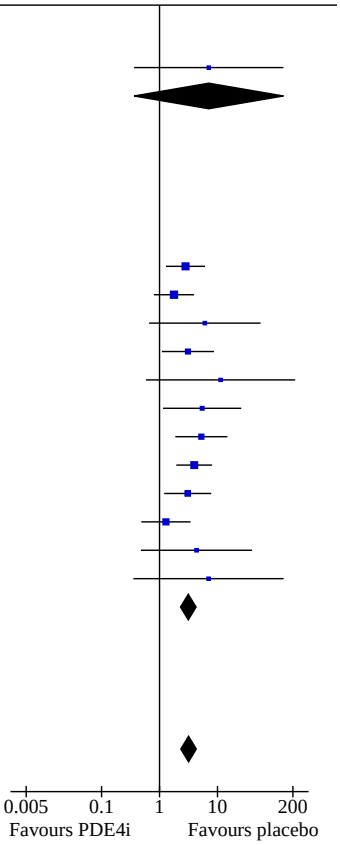
Study or Subgroup	PDE4i treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.17.1 Roflumilast						
RO-2455-402-RD (ROBERT) (1)	5	79	2	79	4.7%	2.60 [0.49 , 13.83]
Roflumilast M2-107	1	555	0	280	1.7%	1.52 [0.06 , 37.37]
Subtotal (95% CI)		**634**		**359**	**6.3%**	**2.32 [0.53 , 10.23]**
Total events:	6		2			
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 1.11 (P = 0.27)						
1.17.2 Cilomilast						
Cilomilast 039	37	431	6	216	18.2%	3.29 [1.37 , 7.91]
Cilomilast 042	17	474	0	226	1.6%	17.33 [1.04 , 289.44]
Cilomilast 076	4	29	0	30	1.0%	10.76 [0.55 , 209.55]
Cilomilast 091	22	369	1	242	2.8%	15.28 [2.05 , 114.12]
Cilomilast 103657	28	296	8	316	17.5%	4.02 [1.80 , 8.98]
Cilomilast 156	33	418	11	407	25.6%	3.09 [1.54 , 6.19]
Cilomilast 157	21	455	8	452	19.1%	2.69 [1.18 , 6.13]
Cilomilast 168	9	203	1	103	3.2%	4.73 [0.59 , 37.87]
Cilomilast 180	4	97	1	102	2.3%	4.34 [0.48 , 39.57]
Cilomilast 181	5	65	1	62	2.4%	5.08 [0.58 , 44.81]
Subtotal (95% CI)		**2837**		**2156**	**93.7%**	**4.06 [2.83 , 5.82]**
Total events:	180		37			
Heterogeneity: Chi² = 4.95, df = 9 (P = 0.84); I² = 0%						
Test for overall effect: Z = 7.60 (P < 0.00001)						
Total (95% CI)		**3471**		**2515**	**100.0%**	**3.95 [2.78 , 5.60]**
Total events:	186		39			
Heterogeneity: Chi² = 5.39, df = 11 (P = 0.91); I² = 0%						
Test for overall effect: Z = 7.68 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.51, df = 1 (P = 0.47), I² = 0%						



Footnotes
(1) New data 2019

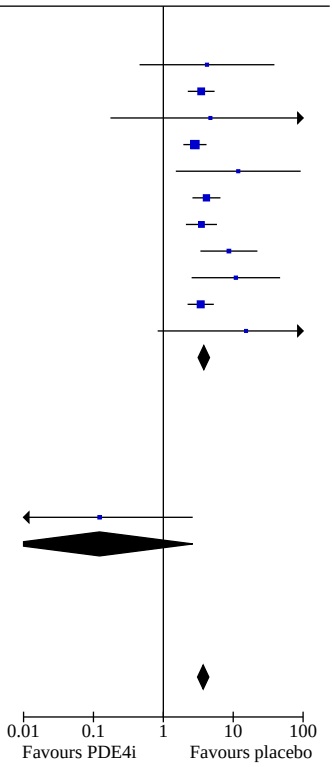
Analysis 1.18. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 18: Dyspepsia

Study or Subgroup	PDE4i treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.18.1 Roflumilast						
RO-2455-301-RD (ACROSS)	3	313	0	313	0.9%	7.07 [0.36 , 137.40]
Subtotal (95% CI)		**313**		**313**	**0.9%**	**7.07 [0.36 , 137.40]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
1.18.2 Cilomilast						
Cilomilast 039	42	431	8	216	17.0%	2.81 [1.29 , 6.09]
Cilomilast 042	29	474	8	226	17.9%	1.78 [0.80 , 3.95]
Cilomilast 076	5	29	1	30	1.4%	6.04 [0.66 , 55.30]
Cilomilast 103657	14	296	5	316	8.1%	3.09 [1.10 , 8.68]
Cilomilast 110	4	31	0	34	0.7%	11.29 [0.58 , 218.85]
Cilomilast 111	10	79	2	77	3.1%	5.43 [1.15 , 25.68]
Cilomilast 121	40	678	4	340	8.8%	5.27 [1.87 , 14.84]
Cilomilast 156	38	418	10	407	16.3%	3.97 [1.95 , 8.08]
Cilomilast 157	18	455	6	452	10.2%	3.06 [1.20 , 7.79]
Cilomilast 168	15	203	6	103	13.0%	1.29 [0.49 , 3.43]
Cilomilast 180	4	97	1	102	1.6%	4.34 [0.48 , 39.57]
Cilomilast 181	3	65	0	62	0.9%	7.00 [0.35 , 138.35]
Subtotal (95% CI)		**3256**		**2365**	**99.1%**	**3.13 [2.30 , 4.27]**
Total events:	222		51			
Heterogeneity: Chi^2 = 8.48, df = 11 (P = 0.67); I^2 = 0%						
Test for overall effect: Z = 7.26 (P < 0.00001)						
Total (95% CI)		**3569**		**2678**	**100.0%**	**3.17 [2.33 , 4.30]**
Total events:	225		51			
Heterogeneity: Chi^2 = 8.80, df = 12 (P = 0.72); I^2 = 0%						
Test for overall effect: Z = 7.37 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 0.29, df = 1 (P = 0.59), I^2 = 0%						



Analysis 1.19. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 19: Weight loss

Study or Subgroup	PDE4i treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.19.1 Roflumilast						
Liu 2018 (1)	4	60	1	60	0.7%	4.21 [0.46 , 38.86]
RO-2455-404-RD (REACT)	88	968	27	967	18.0%	3.48 [2.24 , 5.41]
Roflumilast DAL-MD-01	1	11	0	16	0.3%	4.71 [0.18 , 126.90]
Roflumilast M2-111+M2-112	100	1327	38	1359	25.4%	2.83 [1.93 , 4.15]
Roflumilast M2-119	11	203	1	207	0.7%	11.80 [1.51 , 92.28]
Roflumilast M2-124	92	769	24	755	15.6%	4.14 [2.61 , 6.56]
Roflumilast M2-125	65	778	20	790	13.3%	3.51 [2.10 , 5.85]
Roflumilast M2-127	40	466	5	467	3.3%	8.68 [3.39 , 22.19]
Roflumilast M2-128	21	374	2	369	1.4%	10.92 [2.54 , 46.90]
Roflumilast ROF-MD-07(RE2SPOND)	91	1178	28	1174	18.9%	3.43 [2.23 , 5.28]
Urban 2018 (ELASTIC) (1)	6	40	0	40	0.3%	15.26 [0.83 , 280.72]
Subtotal (95% CI)		**6174**		**6204**	**97.8%**	**3.80 [3.15 , 4.58]**
Total events:	519		146			
Heterogeneity: Chi² = 9.92, df = 10 (P = 0.45); I² = 0%						
Test for overall effect: Z = 14.00 (P < 0.00001)						
1.19.2 Tetomilast 50 µg						
NCT00874497 (EMPHASIS) (1)	0	51	2	33	2.2%	0.12 [0.01 , 2.63]
Subtotal (95% CI)		**51**		**33**	**2.2%**	**0.12 [0.01 , 2.63]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.34 (P = 0.18)						
Total (95% CI)		**6225**		**6237**	**100.0%**	**3.72 [3.09 , 4.47]**
Total events:	519		148			
Heterogeneity: Chi² = 14.56, df = 11 (P = 0.20); I² = 24%						
Test for overall effect: Z = 13.88 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.80, df = 1 (P = 0.03), I² = 79.2%						

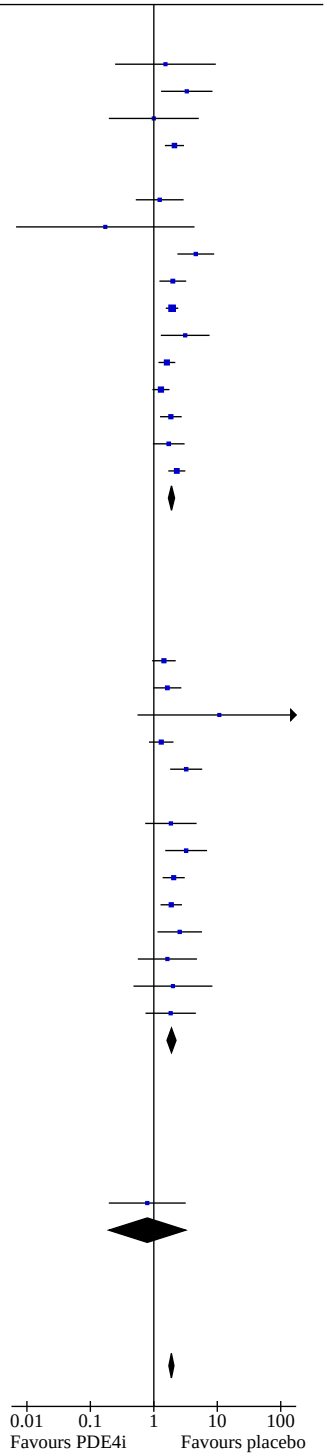


Footnotes

(1) New data

Analysis 1.20. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 20: Withdrawals due to adverse events

Study or Subgroup	PDE4i treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.20.1 Roflumilast 500 µg						
Liu 2018 (1)	3	60	2	60	0.3%	1.53 [0.25 , 9.48]
RO-2455-301-RD (ACROSS)	19	313	6	313	0.8%	3.31 [1.30 , 8.39]
RO-2455-402-RD (ROBERT) (1)	3	79	3	79	0.4%	1.00 [0.20 , 5.11]
RO-2455-404-RD (REACT)	104	969	52	966	6.7%	2.11 [1.50 , 2.99]
Roflumilast DAL-MD-01	0	11	0	16		Not estimable
Roflumilast FK1 101	12	169	10	172	1.3%	1.24 [0.52 , 2.95]
Roflumilast IN-108	0	47	1	25	0.3%	0.17 [0.01 , 4.38]
Roflumilast JP-706	48	204	12	191	1.4%	4.59 [2.35 , 8.95]
Roflumilast M2-107	84	555	23	280	3.7%	1.99 [1.23 , 3.24]
Roflumilast M2-111+M2-112	235	1327	136	1359	15.8%	1.94 [1.54 , 2.43]
Roflumilast M2-119	20	203	7	207	0.9%	3.12 [1.29 , 7.56]
Roflumilast M2-124	119	766	78	759	9.5%	1.61 [1.18 , 2.18]
Roflumilast M2-125	101	773	83	798	10.2%	1.29 [0.95 , 1.76]
Roflumilast M2-127	77	466	45	467	5.4%	1.86 [1.25 , 2.75]
Roflumilast M2-128	33	371	20	372	2.6%	1.72 [0.97 , 3.05]
Roflumilast ROF-MD-07(RE2SPOND)	138	1178	64	1174	8.1%	2.30 [1.69 , 3.13]
Subtotal (95% CI)		**7491**		**7238**	**67.3%**	**1.90 [1.70 , 2.12]**
Total events:	996		542			
Heterogeneity: Chi² = 22.10, df = 14 (P = 0.08); I² = 37%						
Test for overall effect: Z = 11.34 (P < 0.00001)						
1.20.2 Cilomilast 15 mg						
Cilomilast 039	94	431	35	216	5.2%	1.44 [0.94 , 2.21]
Cilomilast 042	71	474	22	226	3.6%	1.63 [0.98 , 2.71]
Cilomilast 076	4	29	0	30	0.1%	10.76 [0.55 , 209.55]
Cilomilast 091	78	469	32	242	5.0%	1.31 [0.84 , 2.04]
Cilomilast 103657	46	296	17	316	2.0%	3.24 [1.81 , 5.79]
Cilomilast 110	0	31	0	34		Not estimable
Cilomilast 111	14	79	8	77	1.0%	1.86 [0.73 , 4.72]
Cilomilast 121	49	678	8	340	1.4%	3.23 [1.51 , 6.91]
Cilomilast 156	80	418	42	407	4.9%	2.06 [1.38 , 3.07]
Cilomilast 157	80	455	46	452	5.4%	1.88 [1.28 , 2.78]
Cilomilast 168	36	203	8	103	1.3%	2.56 [1.14 , 5.73]
Cilomilast 180	9	97	6	102	0.8%	1.64 [0.56 , 4.78]
Cilomilast 181	6	65	3	62	0.4%	2.00 [0.48 , 8.38]
Compton 2001	14	107	8	106	1.0%	1.84 [0.74 , 4.60]
Subtotal (95% CI)		**3832**		**2713**	**32.1%**	**1.90 [1.61 , 2.24]**
Total events:	581		235			
Heterogeneity: Chi² = 11.81, df = 12 (P = 0.46); I² = 0%						
Test for overall effect: Z = 7.72 (P < 0.00001)						
1.20.3 Tetomilast 50 mg						
NCT00874497 (EMPHASIS)	5	51	4	33	0.6%	0.79 [0.20 , 3.18]
Subtotal (95% CI)		**51**		**33**	**0.6%**	**0.79 [0.20 , 3.18]**
Total events:	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
Total (95% CI)		**11374**		**9984**	**100.0%**	**1.89 [1.73 , 2.07]**
Total events:	1582		781			
Heterogeneity: Chi² = 35.41, df = 28 (P = 0.16); I² = 21%						
Test for overall effect: Z = 13.67 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.52, df = 2 (P = 0.47), I² = 0%						

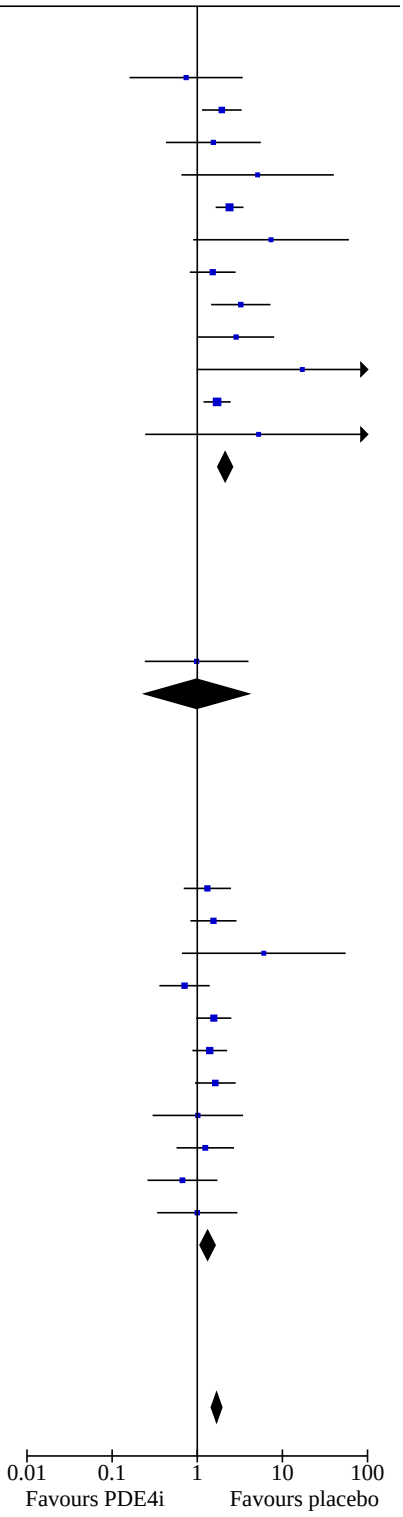


Footnotes

(1) New data added 2019

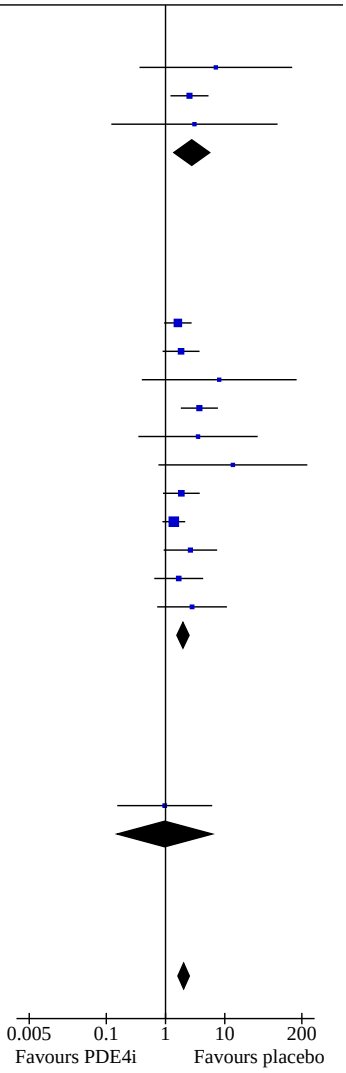
Analysis 1.21. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 21: Headache

Study or Subgroup	Favours PDE4i Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.21.1 Roflumilast 500 µg						
RO-2455-402-RD (ROBERT)	3	79	4	79	1.2%	0.74 [0.16 , 3.42]
RO-2455-404-RD (REACT)	40	968	21	967	6.5%	1.94 [1.14 , 3.32]
Roflumilast FK1 101	6	169	4	172	1.2%	1.55 [0.43 , 5.58]
Roflumilast M2-107	10	555	1	280	0.4%	5.12 [0.65 , 40.19]
Roflumilast M2-111+M2-112	92	1327	41	1359	12.1%	2.39 [1.64 , 3.49]
Roflumilast M2-119	7	203	1	207	0.3%	7.36 [0.90 , 60.34]
Roflumilast M2-124	26	769	17	755	5.3%	1.52 [0.82 , 2.82]
Roflumilast M2-125	25	778	8	790	2.5%	3.25 [1.45 , 7.24]
Roflumilast M2-127	14	466	5	467	1.6%	2.86 [1.02 , 8.01]
Roflumilast M2-128	8	374	0	369	0.2%	17.14 [0.99 , 298.03]
Roflumilast ROF-MD-07(RE2SPOND)	80	1178	48	1174	14.4%	1.71 [1.18 , 2.47]
Urban 2018 (ELASTIC)	2	40	0	40	0.2%	5.26 [0.24 , 113.11]
Subtotal (95% CI)		**6906**		**6659**	**45.7%**	**2.13 [1.74 , 2.59]**
Total events:	313		150			
Heterogeneity: Chi² = 10.85, df = 11 (P = 0.46); I² = 0%						
Test for overall effect: Z = 7.46 (P < 0.00001)						
1.21.2 Roflumilast 250 µg						
Roflumilast FK1 101	4	175	4	172	1.3%	0.98 [0.24 , 3.99]
Subtotal (95% CI)		**175**		**172**	**1.3%**	**0.98 [0.24 , 3.99]**
Total events:	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
1.21.3 Cilomilast 15 mg						
Cilomilast 039	36	431	14	216	5.5%	1.32 [0.69 , 2.49]
Cilomilast 042	44	474	14	226	5.5%	1.55 [0.83 , 2.89]
Cilomilast 076	5	29	1	30	0.3%	6.04 [0.66 , 55.30]
Cilomilast 091	21	469	15	242	6.1%	0.71 [0.36 , 1.40]
Cilomilast 103657	47	296	34	316	8.9%	1.57 [0.98 , 2.51]
Cilomilast 156	46	418	33	407	9.5%	1.40 [0.88 , 2.24]
Cilomilast 157	35	455	22	452	6.5%	1.63 [0.94 , 2.82]
Cilomilast 168	8	203	4	103	1.6%	1.02 [0.30 , 3.45]
Cilomilast 180	16	97	14	102	3.7%	1.24 [0.57 , 2.70]
Cilomilast 181	9	65	12	62	3.4%	0.67 [0.26 , 1.72]
Compton 2001	7	105	7	105	2.1%	1.00 [0.34 , 2.96]
Subtotal (95% CI)		**3042**		**2261**	**53.0%**	**1.32 [1.08 , 1.62]**
Total events:	274		170			
Heterogeneity: Chi² = 8.82, df = 10 (P = 0.55); I² = 0%						
Test for overall effect: Z = 2.69 (P = 0.007)						
Total (95% CI)		**10123**		**9092**	**100.0%**	**1.69 [1.46 , 1.94]**
Total events:	591		324			
Heterogeneity: Chi² = 29.69, df = 23 (P = 0.16); I² = 23%						
Test for overall effect: Z = 7.28 (P < 0.00001)						
Test for subgroup differences: Chi² = 11.37, df = 2 (P = 0.003), I² = 82.4%						



Analysis 1.22. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 22: Abdominal pain

Study or Subgroup	PDE4i treatment Events	PDE4i treatment Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.22.1 Roflumilast						
RO-2455-301-RD (ACROSS)	3	313	0	313	0.4%	7.07 [0.36 , 137.40]
RO-2455-404-RD (REACT)	25	968	10	967	8.0%	2.54 [1.21 , 5.31]
Urban 2018 (ELASTIC) (1)	1	40	0	40	0.4%	3.08 [0.12 , 77.80]
Subtotal (95% CI)		**1321**		**1320**	**8.8%**	**2.77 [1.38 , 5.56]**
Total events:	29		10			
Heterogeneity: Chi² = 0.44, df = 2 (P = 0.80); I² = 0%						
Test for overall effect: Z = 2.87 (P = 0.004)						
1.22.2 Cilomilast						
Cilomilast 039	61	431	20	216	18.8%	1.62 [0.95 , 2.76]
Cilomilast 042	37	474	10	226	10.3%	1.83 [0.89 , 3.75]
Cilomilast 076	3	29	0	30	0.4%	8.06 [0.40 , 163.21]
Cilomilast 091	59	469	9	242	8.5%	3.73 [1.81 , 7.65]
Cilomilast 110	3	31	1	34	0.7%	3.54 [0.35 , 35.93]
Cilomilast 111	6	79	0	77	0.4%	13.71 [0.76 , 247.65]
Cilomilast 121	36	678	10	340	10.4%	1.85 [0.91 , 3.78]
Cilomilast 156	52	418	38	407	27.7%	1.38 [0.89 , 2.15]
Cilomilast 157	13	455	5	452	4.0%	2.63 [0.93 , 7.44]
Cilomilast 168	19	203	6	103	5.9%	1.67 [0.65 , 4.32]
Compton 2001	8	105	3	105	2.3%	2.80 [0.72 , 10.88]
Subtotal (95% CI)		**3372**		**2232**	**89.3%**	**1.97 [1.55 , 2.49]**
Total events:	297		102			
Heterogeneity: Chi² = 9.58, df = 10 (P = 0.48); I² = 0%						
Test for overall effect: Z = 5.63 (P < 0.00001)						
1.22.3 Tetomilast 50 µg						
NCT00874497 (EMPHASIS) (1)	3	51	2	33	1.9%	0.97 [0.15 , 6.13]
Subtotal (95% CI)		**51**		**33**	**1.9%**	**0.97 [0.15 , 6.13]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.97)						
Total (95% CI)		**4744**		**3585**	**100.0%**	**2.02 [1.62 , 2.52]**
Total events:	329		114			
Heterogeneity: Chi² = 11.50, df = 14 (P = 0.65); I² = 0%						
Test for overall effect: Z = 6.22 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.45, df = 2 (P = 0.48), I² = 0%						

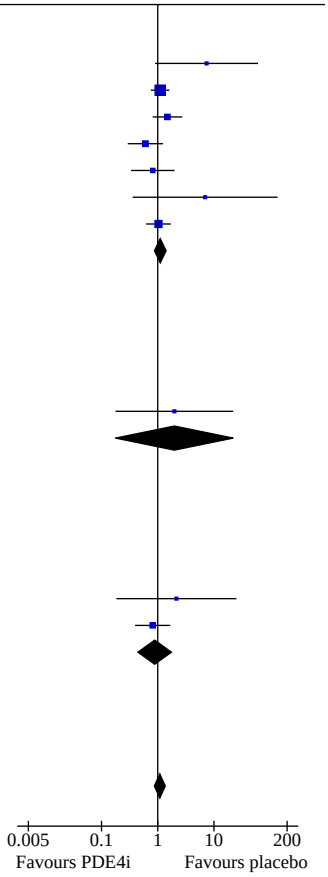


Footnotes

(1) New data added 2019

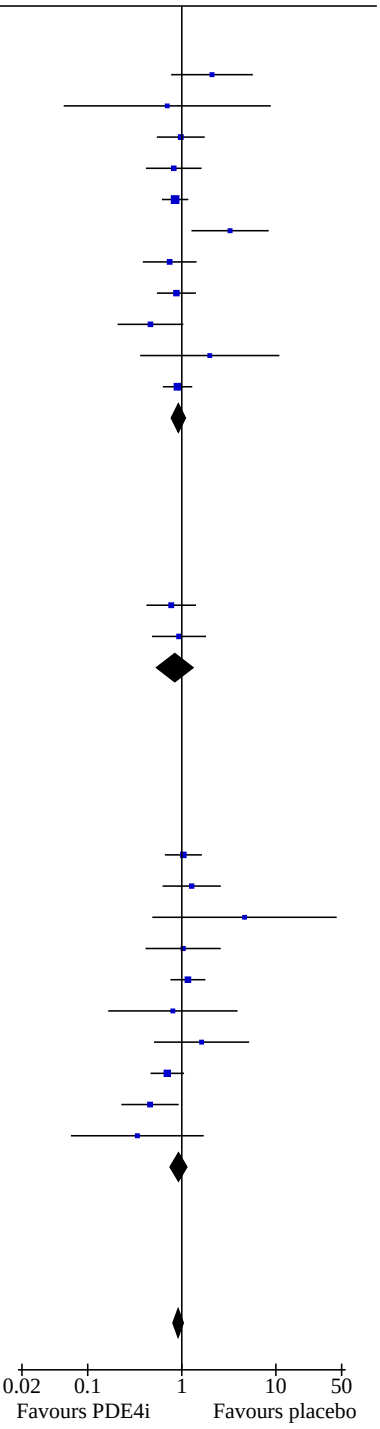
Analysis 1.23. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 23: Influenza-like symptoms

Study or Subgroup	PDE4i treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.23.1 Roflumilast 500 µg						
Roflumilast FK1 101	7	169	1	172	0.6%	7.39 [0.90 , 60.72]
Roflumilast M2-111+M2-112	58	1327	54	1359	34.5%	1.10 [0.76 , 1.61]
Roflumilast M2-124	27	769	18	755	11.8%	1.49 [0.81 , 2.73]
Roflumilast M2-125	12	778	20	790	13.2%	0.60 [0.29 , 1.24]
Roflumilast M2-127	9	466	11	467	7.3%	0.82 [0.34 , 1.99]
Roflumilast M2-128	3	374	0	369	0.3%	6.96 [0.36 , 135.26]
Roflumilast ROF-MD-07(RE2SPOND)	31	1178	30	1174	19.8%	1.03 [0.62 , 1.71]
Subtotal (95% CI)		**5061**		**5086**	**87.5%**	**1.11 [0.87 , 1.41]**
Total events:	147		134			
Heterogeneity: Chi² = 8.77, df = 6 (P = 0.19); I² = 32%						
Test for overall effect: Z = 0.85 (P = 0.39)						
1.23.2 Roflumilast 250 µg						
Roflumilast FK1 101	2	175	1	172	0.7%	1.98 [0.18 , 22.00]
Subtotal (95% CI)		**175**		**172**	**0.7%**	**1.98 [0.18 , 22.00]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
1.23.3 Cilomilast 15 mg						
Cilomilast 076	2	29	1	30	0.6%	2.15 [0.18 , 25.07]
Cilomilast 157	14	455	17	452	11.2%	0.81 [0.40 , 1.67]
Subtotal (95% CI)		**484**		**482**	**11.8%**	**0.88 [0.44 , 1.75]**
Total events:	16		18			
Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
Total (95% CI)		**5720**		**5740**	**100.0%**	**1.09 [0.87 , 1.36]**
Total events:	165		153			
Heterogeneity: Chi² = 9.89, df = 9 (P = 0.36); I² = 9%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Test for subgroup differences: Chi² = 0.62, df = 2 (P = 0.73), I² = 0%						



Analysis 1.24. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 24: Upper respiratory tract infection

Study or Subgroup	PDE4i treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.24.1 Roflumilast 500 µg						
Liu 2018 (1)	13	60	7	60	1.1%	2.09 [0.77 , 5.69]
Roflumilast DAL-MD-01	1	11	2	16	0.3%	0.70 [0.06 , 8.82]
Roflumilast FK1 101	26	169	27	172	4.5%	0.98 [0.54 , 1.75]
Roflumilast M2-107	23	555	14	280	3.5%	0.82 [0.42 , 1.62]
Roflumilast M2-111+M2-112	72	1327	86	1359	15.9%	0.85 [0.62 , 1.17]
Roflumilast M2-119	18	203	6	207	1.1%	3.26 [1.27 , 8.39]
Roflumilast M2-124	16	769	21	755	4.1%	0.74 [0.38 , 1.43]
Roflumilast M2-125	33	778	38	790	7.1%	0.88 [0.54 , 1.41]
Roflumilast M2-127	9	466	19	467	3.7%	0.46 [0.21 , 1.04]
Roflumilast M2-128	4	374	2	369	0.4%	1.98 [0.36 , 10.90]
Roflumilast ROF-MD-07(RE2SPOND)	60	1178	66	1174	12.4%	0.90 [0.63 , 1.29]
Subtotal (95% CI)		**5890**		**5649**	**54.1%**	**0.92 [0.77 , 1.09]**
Total events:	275		288			
Heterogeneity: Chi² = 13.93, df = 10 (P = 0.18); I² = 28%						
Test for overall effect: Z = 0.96 (P = 0.34)						
1.24.2 Roflumilast 250 µg						
Roflumilast FK1 101	22	175	27	172	4.7%	0.77 [0.42 , 1.42]
Roflumilast M2-107	27	576	14	280	3.6%	0.93 [0.48 , 1.81]
Subtotal (95% CI)		**751**		**452**	**8.3%**	**0.84 [0.54 , 1.31]**
Total events:	49		41			
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.76 (P = 0.45)						
1.24.3 Cilomilast 15 mg						
Cilomilast 039	68	431	33	216	7.3%	1.04 [0.66 , 1.63]
Cilomilast 042	29	474	11	226	2.8%	1.27 [0.62 , 2.60]
Cilomilast 076	4	29	1	30	0.2%	4.64 [0.49 , 44.27]
Cilomilast 091	14	469	7	242	1.8%	1.03 [0.41 , 2.59]
Cilomilast 103657	52	296	49	316	7.7%	1.16 [0.76 , 1.78]
Cilomilast 110	3	31	4	34	0.7%	0.80 [0.17 , 3.91]
Cilomilast 111	8	79	5	77	0.9%	1.62 [0.51 , 5.20]
Cilomilast 156	46	418	61	407	10.9%	0.70 [0.47 , 1.06]
Cilomilast 168	18	203	18	103	4.3%	0.46 [0.23 , 0.93]
Cilomilast 180	2	97	6	102	1.1%	0.34 [0.07 , 1.71]
Subtotal (95% CI)		**2527**		**1753**	**37.7%**	**0.92 [0.75 , 1.13]**
Total events:	244		195			
Heterogeneity: Chi² = 12.11, df = 9 (P = 0.21); I² = 26%						
Test for overall effect: Z = 0.78 (P = 0.44)						
Total (95% CI)		**9168**		**7854**	**100.0%**	**0.91 [0.81 , 1.04]**
Total events:	568		524			
Heterogeneity: Chi² = 26.33, df = 22 (P = 0.24); I² = 16%						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: Chi² = 0.14, df = 2 (P = 0.93), I² = 0%						

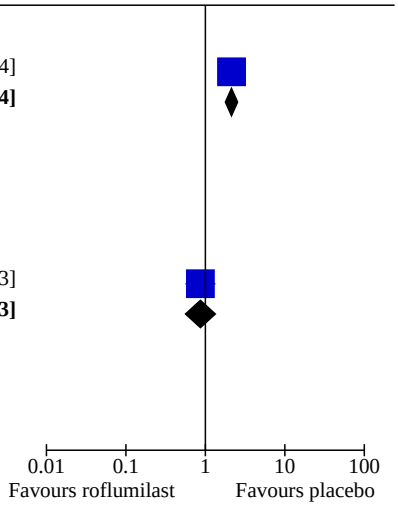


Footnotes

(1) New data added 2019

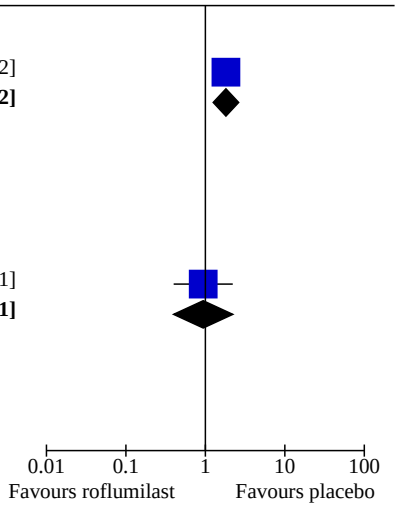
Analysis 1.25. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 25: Psychiatric adverse events (roflumilast)

Study or Subgroup	Roflumilast Events	Roflumilast Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.25.1 Roflumilast 500 µg						
COPD safety pool	403	5677	190	5491	100.0%	2.13 [1.79 , 2.54]
Subtotal (95% CI)		**5677**		**5491**	**100.0%**	**2.13 [1.79 , 2.54]**
Total events:	403		190			
Heterogeneity: Not applicable						
Test for overall effect: Z = 8.40 (P < 0.00001)						
1.25.2 Roflumilast 250 µg						
COPD safety pool	24	797	190	5491	100.0%	0.87 [0.56 , 1.33]
Subtotal (95% CI)		**797**		**5491**	**100.0%**	**0.87 [0.56 , 1.33]**
Total events:	24		190			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.51)						
Test for subgroup differences: Chi² = 14.35, df = 1 (P = 0.0002), I² = 93.0%						



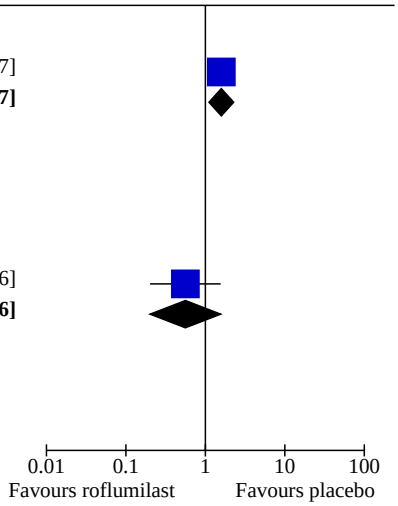
Analysis 1.26. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 26: Anxiety or anxiety disorder (roflumilast)

Study or Subgroup	Roflumilast Events	Roflumilast Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.26.1 Roflumilast 500 µg						
COPD safety pool	82	5677	44	5491	100.0%	1.81 [1.26 , 2.62]
Subtotal (95% CI)		**5677**		**5491**	**100.0%**	**1.81 [1.26 , 2.62]**
Total events:	82		44			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.17 (P = 0.002)						
1.26.2 Roflumilast 250 µg						
COPD safety pool	6	797	44	5491	100.0%	0.94 [0.40 , 2.21]
Subtotal (95% CI)		**797**		**5491**	**100.0%**	**0.94 [0.40 , 2.21]**
Total events:	6		44			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
Test for subgroup differences: Chi² = 1.92, df = 1 (P = 0.17), I² = 47.9%						



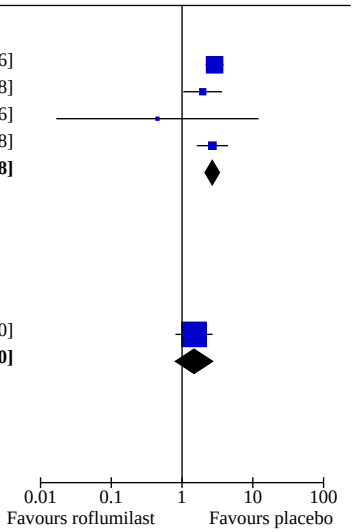
Analysis 1.27. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 27: Depression (roflumilast)

Study or Subgroup	Roflumilast Events	Roflumilast Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.27.1 Roflumilast 500 µg						
COPD safety pool	80	5677	49	5491	100.0%	1.59 [1.11 , 2.27]
Subtotal (95% CI)		**5677**		**5491**	**100.0%**	**1.59 [1.11 , 2.27]**
Total events:	80		49			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.53 (P = 0.01)						
1.27.2 Roflumilast 250 µg						
COPD safety pool	4	797	49	5491	100.0%	0.56 [0.20 , 1.56]
Subtotal (95% CI)		**797**		**5491**	**100.0%**	**0.56 [0.20 , 1.56]**
Total events:	4		49			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
Test for subgroup differences: Chi² = 3.56, df = 1 (P = 0.06), I² = 71.9%						



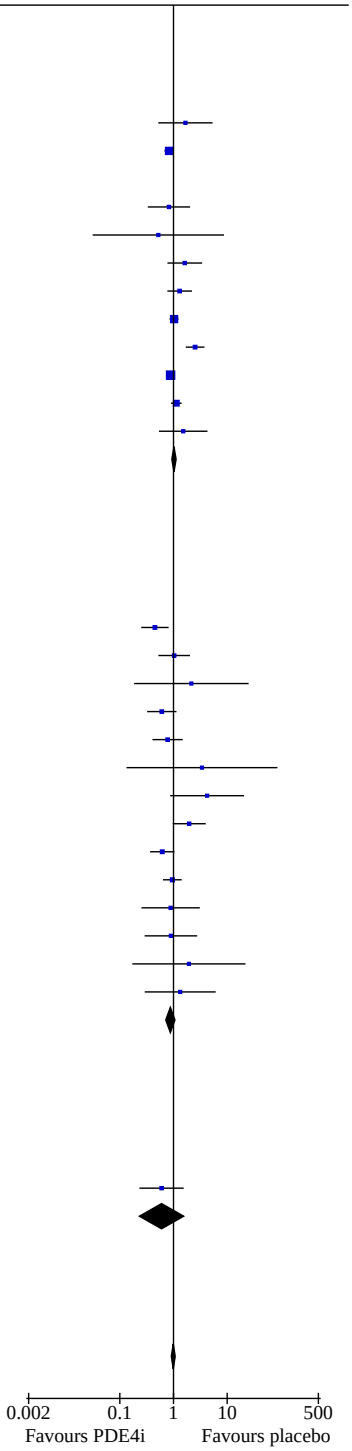
Analysis 1.28. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 28: Insomnia and sleep disorders (roflumilast)

Study or Subgroup	Roflumilast Events	Roflumilast Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.28.1 Roflumilast 500 µg						
COPD safety pool	178	5677	61	5491	62.7%	2.88 [2.15 , 3.86]
RO-2455-404-RD (REACT)	29	968	15	967	15.2%	1.96 [1.04 , 3.68]
Roflumilast DAL-MD-01	0	11	1	16	1.2%	0.45 [0.02 , 12.06]
Roflumilast ROF-MD-07(RE2SPOND)	55	1178	21	1174	20.9%	2.69 [1.62 , 4.48]
Subtotal (95% CI)		**7834**		**7648**	**100.0%**	**2.67 [2.11 , 3.38]**
Total events:	262		98			
Heterogeneity: Chi² = 2.31, df = 3 (P = 0.51); I² = 0%						
Test for overall effect: Z = 8.23 (P < 0.00001)						
1.28.2 Roflumilast 250 µg						
COPD safety pool	13	797	61	5491	100.0%	1.48 [0.81 , 2.70]
Subtotal (95% CI)		**797**		**5491**	**100.0%**	**1.48 [0.81 , 2.70]**
Total events:	13		61			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.26 (P = 0.21)						
Test for subgroup differences: Chi² = 3.23, df = 1 (P = 0.07), I² = 69.0%						



Analysis 1.29. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 29: Serious adverse events

Study or Subgroup	PDE4i treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.29.1 Roflumilast 500 µg						
Kavitha 2018 (1)	0	30	0	30		Not estimable
Liu 2018 (1)	0	60	0	60		Not estimable
RO-2455-402-RD (ROBERT) (1)	8	79	5	79	0.4%	1.67 [0.52 , 5.34]
RO-2455-404-RD (REACT)	249	969	285	966	18.7%	0.83 [0.68 , 1.01]
Roflumilast DAL-MD-01	0	16	0	11		Not estimable
Roflumilast FK1 101	9	169	11	172	0.9%	0.82 [0.33 , 2.04]
Roflumilast IN-108	1	47	1	25	0.1%	0.52 [0.03 , 8.71]
Roflumilast JP-706	20	204	12	191	1.0%	1.62 [0.77 , 3.41]
Roflumilast M2-107	53	555	21	280	2.2%	1.30 [0.77 , 2.21]
Roflumilast M2-111+M2-112	263	1327	264	1359	18.4%	1.03 [0.85 , 1.24]
Roflumilast M2-119	134	203	90	207	2.7%	2.52 [1.69 , 3.77]
Roflumilast M2-124+M2-125	301	1537	336	1554	23.7%	0.88 [0.74 , 1.05]
Roflumilast ROF-MD-07(RE2SPOND)	180	1178	162	1174	12.1%	1.13 [0.90 , 1.42]
Urban 2018 (ELASTIC) (1)	11	40	8	40	0.5%	1.52 [0.54 , 4.29]
Subtotal (95% CI)		**6414**		**6148**	**80.6%**	**1.02 [0.93 , 1.12]**
Total events:	1229		1195			
Heterogeneity: Chi² = 31.35, df = 10 (P = 0.0005); I² = 68%						
Test for overall effect: Z = 0.43 (P = 0.66)						
1.29.2 Cilomilast 15 mg						
Cilomilast 039	24	431	25	216	2.8%	0.45 [0.25 , 0.81]
Cilomilast 042	28	474	13	226	1.5%	1.03 [0.52 , 2.03]
Cilomilast 076	2	29	1	30	0.1%	2.15 [0.18 , 25.07]
Cilomilast 091	23	469	19	242	2.1%	0.61 [0.32 , 1.13]
Cilomilast 103657	17	296	23	316	1.8%	0.78 [0.41 , 1.48]
Cilomilast 110	1	31	0	34	0.0%	3.39 [0.13 , 86.43]
Cilomilast 111	8	79	2	77	0.2%	4.23 [0.87 , 20.58]
Cilomilast 121	38	678	10	340	1.1%	1.96 [0.96 , 3.98]
Cilomilast 156	25	418	38	407	3.2%	0.62 [0.37 , 1.04]
Cilomilast 157	53	455	55	452	4.3%	0.95 [0.64 , 1.42]
Cilomilast 168	7	203	4	103	0.5%	0.88 [0.25 , 3.09]
Cilomilast 180	6	97	7	102	0.6%	0.89 [0.29 , 2.76]
Cilomilast 181	2	65	1	62	0.1%	1.94 [0.17 , 21.91]
Compton 2001	4	107	3	106	0.3%	1.33 [0.29 , 6.11]
Subtotal (95% CI)		**3832**		**2713**	**18.4%**	**0.87 [0.72 , 1.06]**
Total events:	238		201			
Heterogeneity: Chi² = 19.12, df = 13 (P = 0.12); I² = 32%						
Test for overall effect: Z = 1.34 (P = 0.18)						
1.29.3 Tetomilast 50 µg						
NCT00874497 (EMPHASIS) (1)	13	51	12	33	1.0%	0.60 [0.23 , 1.55]
Subtotal (95% CI)		**51**		**33**	**1.0%**	**0.60 [0.23 , 1.55]**
Total events:	13		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**10297**		**8894**	**100.0%**	**0.99 [0.91 , 1.07]**
Total events:	1480		1408			
Heterogeneity: Chi² = 54.01, df = 25 (P = 0.0007); I² = 54%						
Test for overall effect: Z = 0.25 (P = 0.80)						
Test for subgroup differences: Chi² = 3.04, df = 2 (P = 0.22), I² = 34.2%						

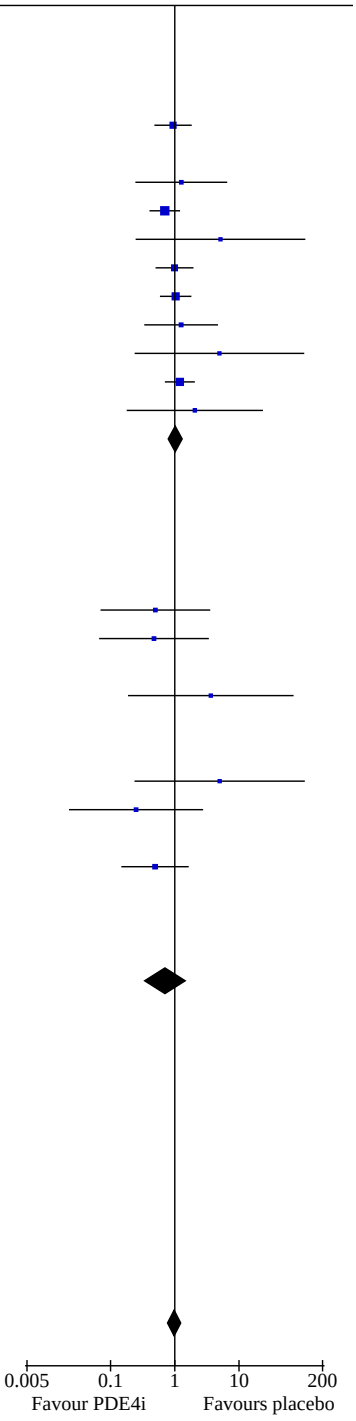


Footnotes

(1) New study data added 2019

Analysis 1.30. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 30: Mortality

Study or Subgroup	PDE4i treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.30.1 Roflumilast						
Liu 2018 (1)	0	60	0	60		Not estimable
RO-2455-402-RD (ROBERT) (1)	0	79	0	79		Not estimable
RO-2455-404-RD (REACT)	17	969	18	966	12.7%	0.94 [0.48 , 1.84]
Roflumilast DAL-MD-01	0	16	0	11		Not estimable
Roflumilast M2-107	5	555	2	280	1.9%	1.26 [0.24 , 6.55]
Roflumilast M2-111+M2-112	22	1327	32	1359	22.3%	0.70 [0.40 , 1.21]
Roflumilast M2-119	2	203	0	207	0.4%	5.15 [0.25 , 107.91]
Roflumilast M2-124	17	765	17	758	12.0%	0.99 [0.50 , 1.96]
Roflumilast M2-125	25	772	25	796	17.1%	1.03 [0.59 , 1.81]
Roflumilast M2-127	5	466	4	467	2.8%	1.26 [0.34 , 4.70]
Roflumilast M2-128	2	374	0	369	0.4%	4.96 [0.24 , 103.66]
Roflumilast ROF-MD-07(RE2SPOND)	30	1178	25	1174	17.5%	1.20 [0.70 , 2.05]
Urban 2018 (ELASTIC) (1)	2	40	1	40	0.7%	2.05 [0.18 , 23.59]
Subtotal (95% CI)		**6804**		**6566**	**87.7%**	**1.01 [0.79 , 1.30]**
Total events:	127		124			
Heterogeneity: Chi² = 4.84, df = 9 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.91)						
1.30.2 Cilomilast						
Cilomilast 039	2	431	2	216	1.9%	0.50 [0.07 , 3.57]
Cilomilast 042	2	474	2	226	1.9%	0.47 [0.07 , 3.39]
Cilomilast 076	0	29	0	30		Not estimable
Cilomilast 091	3	469	0	242	0.5%	3.64 [0.19 , 70.73]
Cilomilast 103657	0	296	0	316		Not estimable
Cilomilast 110	0	31	0	34		Not estimable
Cilomilast 111	2	79	0	77	0.4%	5.00 [0.24 , 105.86]
Cilomilast 121	1	678	2	340	1.9%	0.25 [0.02 , 2.76]
Cilomilast 156	0	418	0	407		Not estimable
Cilomilast 157	4	455	8	452	5.7%	0.49 [0.15 , 1.65]
Cilomilast 168	0	203	0	103		Not estimable
Cilomilast 180	0	97	0	102		Not estimable
Cilomilast 181	0	65	0	62		Not estimable
Subtotal (95% CI)		**3725**		**2607**	**12.3%**	**0.70 [0.34 , 1.45]**
Total events:	14		14			
Heterogeneity: Chi² = 4.08, df = 5 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
1.30.3 Tetomilast						
NCT00874497 (EMPHASIS) (2)	0	51	0	33		Not estimable
Subtotal (95% CI)		**51**		**33**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**10580**		**9206**	**100.0%**	**0.98 [0.77 , 1.24]**
Total events:	141		138			
Heterogeneity: Chi² = 10.18, df = 15 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
Test for subgroup differences: Chi² = 0.88, df = 1 (P = 0.35), I² = 0%						



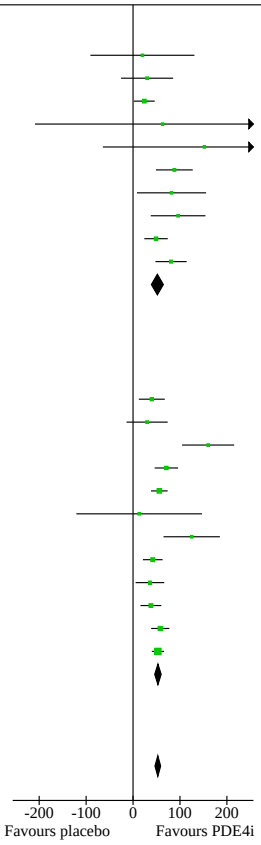
Footnotes

(1) New study data added 2019

(2) New data added 2019

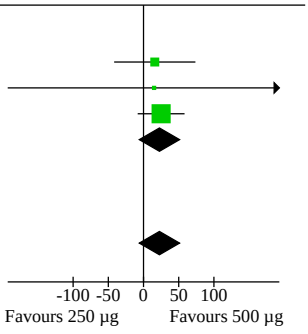
Analysis 1.31. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 31: FEV_1 (by mean COPD severity)

Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.31.1 GOLD grade I + II (FEV_1 # 50% predicted)								
Cilomilast 076	-50	183	21	-70	192	23	0.3%	20.00 [-90.83 , 130.83]
Cilomilast 091	-30	421	443	-60	305	232	1.2%	30.00 [-25.47 , 85.47]
Cilomilast 156	7	153	364	-17	155	377	7.4%	24.00 [1.82 , 46.18]
RO-2455-402-RD (ROBERT)	63	861	77	0	861	77	0.0%	63.00 [-208.97 , 334.97]
Roflumilast IN-108	28	486	42	-124	405	25	0.1%	152.00 [-64.35 , 368.35]
Roflumilast M2-107	49	283	555	-39	268	280	2.4%	88.00 [48.76 , 127.24]
Roflumilast M2-118	55	282	127	-27	311	123	0.7%	82.00 [8.34 , 155.66]
Roflumilast M2-119	54	289	189	-42	298	201	1.1%	96.00 [37.74 , 154.26]
Roflumilast M2-127	39	192	456	-10	193	460	5.9%	49.00 [24.07 , 73.93]
Roflumilast M2-128	65	229	365	-16	229	364	3.3%	81.00 [47.75 , 114.25]
Subtotal (95% CI)			**2639**			**2162**	**22.4%**	**51.82 [39.03 , 64.60]**
Heterogeneity: Chi² = 16.91, df = 9 (P = 0.05); I² = 47%								
Test for overall effect: Z = 7.94 (P < 0.00001)								
1.31.2 GOLD grade III + IV (FEV_1 < 50% predicted)								
Cilomilast 039	10	194	378	-30	144	207	4.8%	40.00 [12.30 , 67.70]
Cilomilast 042	30	210	440	0	296	219	1.9%	30.00 [-13.84 , 73.84]
Compton 2001	130	206	107	-30	207	106	1.2%	160.00 [104.53 , 215.47]
RO-2455-301-RD (ACROSS)	49	159.5692	313	-22	159.5692	313	5.9%	71.00 [46.00 , 96.00]
RO-2455-404-RD (REACT)	52	194.9638	928	-4	196.3246	941	11.6%	56.00 [38.26 , 73.74]
Roflumilast DAL-MD-01	41	91	11	28	250	16	0.2%	13.00 [-120.78 , 146.78]
Roflumilast FLUI-2011-77	66	120	30	-59	71	11	1.0%	125.00 [64.96 , 185.04]
Roflumilast M2-111	30	182	545	-12	178	596	8.4%	42.00 [21.08 , 62.92]
Roflumilast M2-112	9	303	760	-27	302	753	3.9%	36.00 [5.52 , 66.48]
Roflumilast M2-124	46	218	745	8	218	745	7.5%	38.00 [15.86 , 60.14]
Roflumilast M2-125	33	189	730	-25	194	766	9.7%	58.00 [38.59 , 77.41]
Roflumilast ROF-MD-07(RE2SPOND)	53	160.836	1178	0	160.836	1174	21.6%	53.00 [40.00 , 66.00]
Subtotal (95% CI)			**6165**			**5847**	**77.6%**	**53.06 [46.19 , 59.92]**
Heterogeneity: Chi² = 28.44, df = 11 (P = 0.003); I² = 61%								
Test for overall effect: Z = 15.15 (P < 0.00001)								
Total (95% CI)			**8804**			**8009**	**100.0%**	**52.78 [46.73 , 58.83]**
Heterogeneity: Chi² = 45.39, df = 21 (P = 0.002); I² = 54%								
Test for overall effect: Z = 17.11 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%								



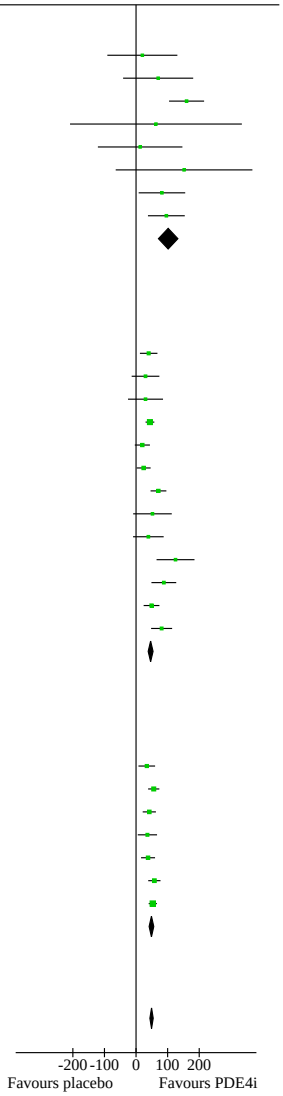
Analysis 1.32. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 32: FEV_1 (roflumilast 500 µg vs 250 µg)

Study or Subgroup	Roflumilast 500 µg Mean	SD	Total	Roflumilast 250 µg Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.32.1 Roflumilast 250 ug								
Roflumilast FK1 101	109	273	169	93	273	175	24.5%	16.00 [-41.71 , 73.71]
Roflumilast IN-108	28	486	42	13	492	43	1.9%	15.00 [-192.91 , 222.91]
Roflumilast M2-107	49	283	555	24	288	576	73.6%	25.00 [-8.28 , 58.28]
Subtotal (95% CI)			**766**			**794**	**100.0%**	**22.61 [-5.95 , 51.16]**
Heterogeneity: Chi² = 0.08, df = 2 (P = 0.96); I² = 0%								
Test for overall effect: Z = 1.55 (P = 0.12)								
Total (95% CI)			**766**			**794**	**100.0%**	**22.61 [-5.95 , 51.16]**
Heterogeneity: Chi² = 0.08, df = 2 (P = 0.96); I² = 0%								
Test for overall effect: Z = 1.55 (P = 0.12)								
Test for subgroup differences: Not applicable								



Analysis 1.33. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 33: FEV_1 (by study duration)

Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.33.1 Duration # 12 weeks								
Cilomilast 076	-50	183	21	-70	192	23	0.2%	20.00 [-90.83 , 130.83]
Cilomilast 110	10	179	20	-60	204	26	0.2%	70.00 [-40.92 , 180.92]
Compton 2001	130	206	107	-30	207	106	0.9%	160.00 [104.53 , 215.47]
RO-2455-402-RD (ROBERT) (1)	63	861	77	0	861	77	0.0%	63.00 [-208.97 , 334.97]
Roflumilast DAL-MD-01	41	91	11	28	250	16	0.2%	13.00 [-120.78 , 146.78]
Roflumilast IN-108	28	486	42	-124	405	25	0.1%	152.00 [-64.35 , 368.35]
Roflumilast M2-118	55	282	127	-27	311	123	0.5%	82.00 [8.34 , 155.66]
Roflumilast M2-119	54	289	189	-42	298	201	0.8%	96.00 [37.74 , 154.26]
Subtotal (95% CI)			**594**			**597**	**2.9%**	**101.71 [70.96 , 132.46]**
Heterogeneity: Chi² = 8.93, df = 7 (P = 0.26); I² = 22%								
Test for overall effect: Z = 6.48 (P < 0.00001)								
1.33.2 Duration 24 to 26 weeks								
Cilomilast 039	10	194	378	-30	144	207	3.6%	40.00 [12.30 , 67.70]
Cilomilast 042	30	210	440	0	296	219	1.4%	30.00 [-13.84 , 73.84]
Cilomilast 091	0	417	435	-30	303	230	0.9%	30.00 [-25.40 , 85.40]
Cilomilast 103657	50	86	296	6	89	316	14.2%	44.00 [30.13 , 57.87]
Cilomilast 121	14	175	622	-6	181	328	4.8%	20.00 [-3.93 , 43.93]
Cilomilast 156	7	153	364	-17	155	377	5.6%	24.00 [1.82 , 46.18]
RO-2455-301-RD (ACROSS)	49	159.5692	313	-22	159.5692	313	4.4%	71.00 [46.00 , 96.00]
Roflumilast FK1 101	109	273	169	57	302	172	0.7%	52.00 [-9.08 , 113.08]
Roflumilast FK1 103	78	240	200	39	245	186	1.2%	39.00 [-9.44 , 87.44]
Roflumilast FLUI-2011-77	66	120	30	-59	71	11	0.8%	125.00 [64.96 , 185.04]
Roflumilast M2-107	49	283	555	-39	268	280	1.8%	88.00 [48.76 , 127.24]
Roflumilast M2-127	39	192	456	-10	193	460	4.4%	49.00 [24.07 , 73.93]
Roflumilast M2-128	65	229	365	-16	229	364	2.5%	81.00 [47.75 , 114.25]
Subtotal (95% CI)			**4623**			**3463**	**46.2%**	**46.14 [38.44 , 53.84]**
Heterogeneity: Chi² = 28.73, df = 12 (P = 0.004); I² = 58%								
Test for overall effect: Z = 11.74 (P < 0.00001)								
1.33.3 Duration 52 weeks								
Cilomilast 157	32	197	390	-2	182	411	4.0%	34.00 [7.70 , 60.30]
RO-2455-404-RD (REACT)	52	194.9638	928	-4	196.3246	941	8.7%	56.00 [38.26 , 73.74]
Roflumilast M2-111	30	182	545	-12	178	596	6.3%	42.00 [21.08 , 62.92]
Roflumilast M2-112	9	303	760	-27	302	753	2.9%	36.00 [5.52 , 66.48]
Roflumilast M2-124	46	218	745	8	218	745	5.6%	38.00 [15.86 , 60.14]
Roflumilast M2-125	33	189	730	-25	194	766	7.3%	58.00 [38.59 , 77.41]
Roflumilast ROF-MD-07(RE2SPOND)	53	160.836	1178	0	160.836	1174	16.2%	53.00 [40.00 , 66.00]
Subtotal (95% CI)			**5276**			**5386**	**50.9%**	**48.77 [41.44 , 56.10]**
Heterogeneity: Chi² = 5.11, df = 6 (P = 0.53); I² = 0%								
Test for overall effect: Z = 13.03 (P < 0.00001)								
Total (95% CI)			**10493**			**9446**	**100.0%**	**49.09 [43.86 , 54.32]**
Heterogeneity: Chi² = 54.59, df = 27 (P = 0.001); I² = 51%								
Test for overall effect: Z = 18.39 (P < 0.00001)								
Test for subgroup differences: Chi² = 11.82, df = 2 (P = 0.003), I² = 83.1%								

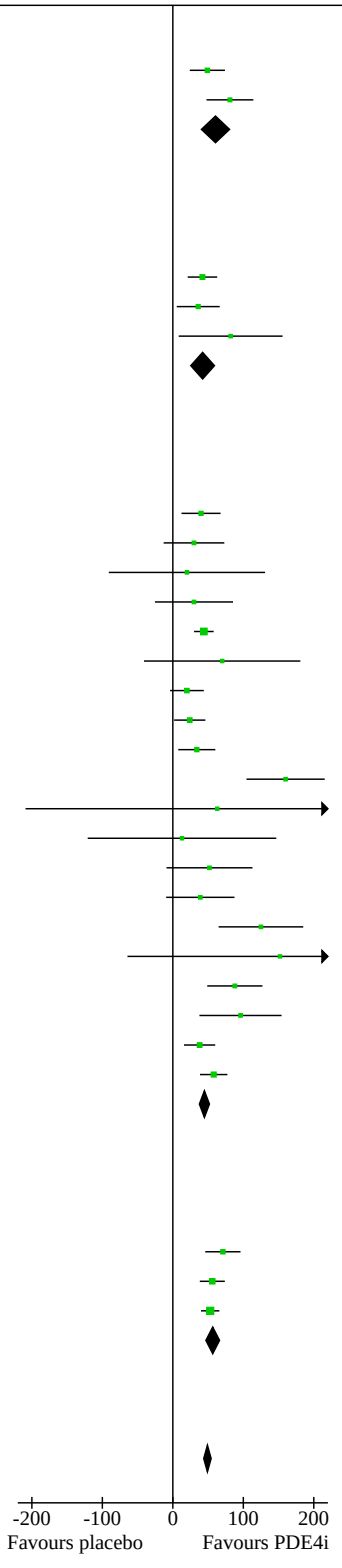


Footnotes

(1) Converted L to mL, SDs obtained from imputing participants in each group, mean for each group obtained from difference in mean between roflumilast and placebo and standard error reported i

Analysis 1.34. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 34: FEV_1 (additional medication)

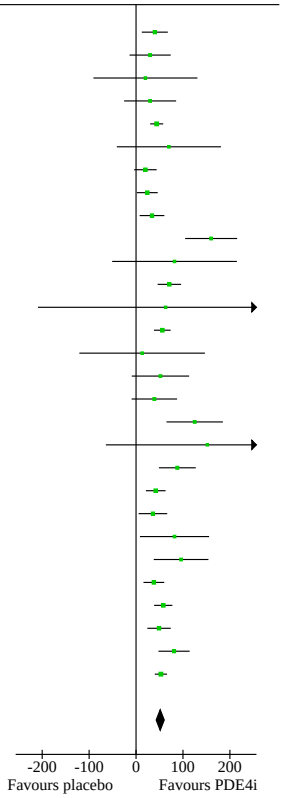
Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
34.1 Long-acting bronchodilator								
oflumilast M2-127	39	192	456	-10	193	460	4.4%	49.00 [24.07 , 73.93]
oflumilast M2-128	65	229	365	-16	229	364	2.5%	81.00 [47.75 , 114.25]
ubtotal (95% CI)			**821**			**824**	**6.9%**	**60.52 [40.57 , 80.46]**
eterogeneity: Chi² = 2.28, df = 1 (P = 0.13); I² = 56%								
est for overall effect: Z = 5.95 (P < 0.00001)								
34.2 Corticosteroids								
oflumilast M2-111	30	182	545	-12	178	596	6.3%	42.00 [21.08 , 62.92]
oflumilast M2-112	9	303	760	-27	302	753	2.9%	36.00 [5.52 , 66.48]
oflumilast M2-118	55	282	127	-27	311	123	0.5%	82.00 [8.34 , 155.66]
ubtotal (95% CI)			**1432**			**1472**	**9.7%**	**42.26 [25.46 , 59.05]**
eterogeneity: Chi² = 1.28, df = 2 (P = 0.53); I² = 0%								
est for overall effect: Z = 4.93 (P < 0.00001)								
34.3 PDE_4 i treatment only								
ilomilast 039	10	194	378	-30	144	207	3.6%	40.00 [12.30 , 67.70]
ilomilast 042	30	210	435	0	296	230	1.5%	30.00 [-13.04 , 73.04]
ilomilast 076	-50	183	21	-70	192	23	0.2%	20.00 [-90.83 , 130.83]
ilomilast 091	0	417	435	-30	303	230	0.9%	30.00 [-25.40 , 85.40]
ilomilast 103657	50	86	296	6	89	316	14.2%	44.00 [30.13 , 57.87]
ilomilast 110	10	179	20	-60	204	26	0.2%	70.00 [-40.92 , 180.92]
ilomilast 121	14	175	622	-6	181	328	4.8%	20.00 [-3.93 , 43.93]
ilomilast 156	7	153	364	-17	155	377	5.6%	24.00 [1.82 , 46.18]
ilomilast 157	32	197	390	-2	182	411	4.0%	34.00 [7.70 , 60.30]
ompton 2001	130	206	107	-30	207	106	0.9%	160.00 [104.53 , 215.47]
O-2455-402-RD (ROBERT)	63	861	77	0	861	77	0.0%	63.00 [-208.97 , 334.97]
oflumilast DAL-MD-01	41	91	11	28	250	16	0.2%	13.00 [-120.78 , 146.78]
oflumilast FK1 101	109	273	169	57	213	86	0.7%	52.00 [-9.00 , 113.00]
oflumilast FK1 103	78	240	200	39	245	186	1.2%	39.00 [-9.44 , 87.44]
oflumilast FLUI-2011-77	66	120	30	-59	71	11	0.8%	125.00 [64.96 , 185.04]
oflumilast IN-108	28	486	42	-124	405	25	0.1%	152.00 [-64.35 , 368.35]
oflumilast M2-107	49	283	555	-39	189	140	1.8%	88.00 [48.83 , 127.17]
oflumilast M2-119	54	289	189	-42	298	201	0.8%	96.00 [37.74 , 154.26]
oflumilast M2-124	46	218	745	8	218	745	5.6%	38.00 [15.86 , 60.14]
oflumilast M2-125	33	189	730	-25	194	766	7.3%	58.00 [38.59 , 77.41]
ubtotal (95% CI)			**5816**			**4507**	**54.2%**	**44.80 [37.69 , 51.91]**
eterogeneity: Chi² = 43.89, df = 19 (P = 0.0010); I² = 57%								
est for overall effect: Z = 12.35 (P < 0.00001)								
34.4 Various concomitant treatments								
O-2455-301-RD (ACROSS)	49	159.5692	313	-22	159.5692	313	4.4%	71.00 [46.00 , 96.00]
O-2455-404-RD (REACT)	52	194.9638	928	-4	196.3246	941	8.7%	56.00 [38.26 , 73.74]
oflumilast ROF-MD-07(RE2SPOND)	53	160.836	1178	0	160.836	1174	16.2%	53.00 [40.00 , 66.00]
ubtotal (95% CI)			**2419**			**2428**	**29.3%**	**56.58 [46.91 , 66.25]**
eterogeneity: Chi² = 1.57, df = 2 (P = 0.46); I² = 0%								
est for overall effect: Z = 11.47 (P < 0.00001)								
otal (95% CI)			**10488**			**9231**	**100.0%**	**49.08 [43.85 , 54.31]**
eterogeneity: Chi² = 54.63, df = 27 (P = 0.001); I² = 51%								
est for overall effect: Z = 18.39 (P < 0.00001)								
est for subgroup differences: Chi² = 5.61, df = 3 (P = 0.13), I² = 46.5%								



Analysis 1.35. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 35: FEV_1 (random-effects model)

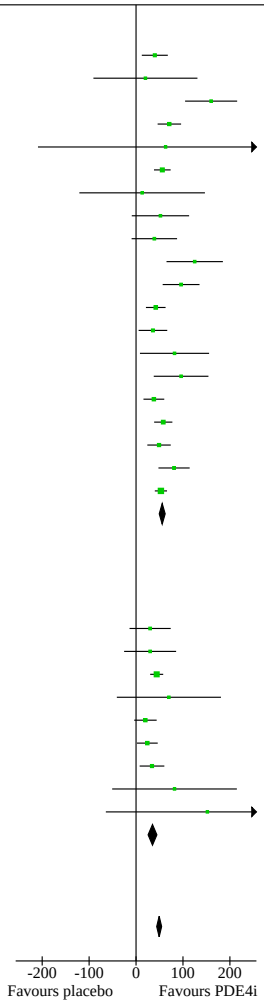
Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cilomilast 039	10	194	378	-30	144	207	4.7%	40.00 [12.30 , 67.70]
Cilomilast 042	30	210	440	0	296	219	2.7%	30.00 [-13.84 , 73.84]
Cilomilast 076	-50	183	21	-70	192	23	0.6%	20.00 [-90.83 , 130.83]
Cilomilast 091	0	417	435	-30	303	230	1.9%	30.00 [-25.40 , 85.40]
Cilomilast 103657	50	86	296	6	89	316	7.5%	44.00 [30.13 , 57.87]
Cilomilast 110	10	179	20	-60	204	26	0.6%	70.00 [-40.92 , 180.92]
Cilomilast 121	14	175	622	-6	181	328	5.4%	20.00 [-3.93 , 43.93]
Cilomilast 156	7	153	364	-17	155	377	5.8%	24.00 [1.82 , 46.18]
Cilomilast 157	32	197	390	-2	182	411	5.0%	34.00 [7.70 , 60.30]
Compton 2001	130	206	107	-30	207	106	1.9%	160.00 [104.53 , 215.47]
NCT00874497 (EMPHASIS)	-1	201.1	48	-83	324.1	28	0.4%	82.00 [-50.84 , 214.84]
RO-2455-301-RD (ACROSS)	49	159.5692	313	-22	159.5692	313	5.2%	71.00 [46.00 , 96.00]
RO-2455-402-RD (ROBERT)	63	861	77	0	861	77	0.1%	63.00 [-208.97 , 334.97]
RO-2455-404-RD (REACT)	52	194.9638	928	-4	196.3246	941	6.7%	56.00 [38.26 , 73.74]
Roflumilast DAL-MD-01	41	91	11	28	250	16	0.4%	13.00 [-120.78 , 146.78]
Roflumilast FK1 101	109	273	169	57	302	172	1.6%	52.00 [-9.08 , 113.08]
Roflumilast FK1 103	78	240	200	39	245	186	2.4%	39.00 [-9.44 , 87.44]
Roflumilast FLUI-2011-77	66	120	30	-59	71	11	1.7%	125.00 [64.96 , 185.04]
Roflumilast IN-108	28	486	42	-124	405	25	0.2%	152.00 [-64.35 , 368.35]
Roflumilast M2-107	49	283	555	-39	268	280	3.2%	88.00 [48.76 , 127.24]
Roflumilast M2-111	30	182	545	-12	178	596	6.0%	42.00 [21.08 , 62.92]
Roflumilast M2-112	9	303	760	-27	302	753	4.3%	36.00 [5.52 , 66.48]
Roflumilast M2-118	55	282	127	-27	311	123	1.2%	82.00 [8.34 , 155.66]
Roflumilast M2-119	54	289	189	-42	298	201	1.8%	96.00 [37.74 , 154.26]
Roflumilast M2-124	46	218	745	8	218	745	5.8%	38.00 [15.86 , 60.14]
Roflumilast M2-125	33	189	730	-25	194	766	6.3%	58.00 [38.59 , 77.41]
Roflumilast M2-127	39	192	456	-10	193	460	5.2%	49.00 [24.07 , 73.93]
Roflumilast M2-128	65	229	365	-16	229	364	3.9%	81.00 [47.75 , 114.25]
Roflumilast ROF-MD-07(RE2SPOND)	53	160.836	1178	0	160.836	1174	7.7%	53.00 [40.00 , 66.00]
Total (95% CI)			**10541**			**9474**	**100.0%**	**51.49 [42.87 , 60.10]**

Heterogeneity: $Tau^2 = 207.68$; $Chi^2 = 54.82$, df = 28 (P = 0.002); $I^2 = 49\%$
Test for overall effect: Z = 11.72 (P < 0.00001)
Test for subgroup differences: Not applicable



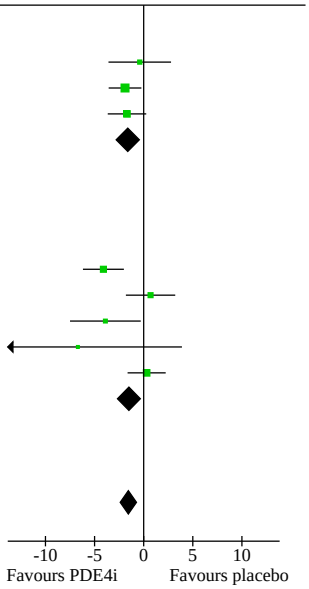
Analysis 1.36. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 36: FEV_1 (published vs unpublished)

Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.36.1 Published								
Cilomilast 039	10	194	378	-30	144	207	3.6%	40.00 [12.30 , 67.70]
Cilomilast 076	-50	183	21	-70	192	23	0.2%	20.00 [-90.83 , 130.83]
Compton 2001	130	206	107	-30	207	106	0.9%	160.00 [104.53 , 215.47]
RO-2455-301-RD (ACROSS)	49	159.5692	313	-22	159.5692	313	4.4%	71.00 [46.00 , 96.00]
RO-2455-402-RD (ROBERT)	63	861	77	0	861	77	0.0%	63.00 [-208.97 , 334.97]
RO-2455-404-RD (REACT)	52	194.9638	928	-4	196.3246	941	8.7%	56.00 [38.26 , 73.74]
Roflumilast DAL-MD-01	41	91	11	28	250	16	0.2%	13.00 [-120.78 , 146.78]
Roflumilast FK1 101	109	273	169	57	302	172	0.7%	52.00 [-9.08 , 113.08]
Roflumilast FK1 103	78	240	200	39	245	186	1.2%	39.00 [-9.44 , 87.44]
Roflumilast FLUI-2011-77	66	120	30	-59	71	11	0.8%	125.00 [64.96 , 185.04]
Roflumilast M2-107	51	283	555	-45	268	280	1.8%	96.00 [56.76 , 135.24]
Roflumilast M2-111	30	182	545	-12	178	596	6.2%	42.00 [21.08 , 62.92]
Roflumilast M2-112	9	303	760	-27	302	753	2.9%	36.00 [5.52 , 66.48]
Roflumilast M2-118	55	282	127	-27	311	123	0.5%	82.00 [8.34 , 155.66]
Roflumilast M2-119	54	289	189	-42	298	201	0.8%	96.00 [37.74 , 154.26]
Roflumilast M2-124	46	218	745	8	218	745	5.6%	38.00 [15.86 , 60.14]
Roflumilast M2-125	33	189	730	-25	194	766	7.3%	58.00 [38.59 , 77.41]
Roflumilast M2-127	39	192	456	-10	193	460	4.4%	49.00 [24.07 , 73.93]
Roflumilast M2-128	65	229	365	-16	229	364	2.5%	81.00 [47.75 , 114.25]
Roflumilast ROF-MD-07(RE2SPOND)	53	160.836	1178	0	160.836	1174	16.2%	53.00 [40.00 , 66.00]
Subtotal (95% CI)			**7884**			**7514**	**68.7%**	**55.75 [49.45 , 62.06]**
Heterogeneity: Chi² = 37.45, df = 19 (P = 0.007); I² = 49%								
Test for overall effect: Z = 17.33 (P < 0.00001)								
1.36.2 Unpublished								
Cilomilast 042	30	210	440	0	296	219	1.4%	30.00 [-13.84 , 73.84]
Cilomilast 091	0	417	435	-30	303	230	0.9%	30.00 [-25.40 , 85.40]
Cilomilast 103657	50	86	296	6	89	316	14.2%	44.00 [30.13 , 57.87]
Cilomilast 110	10	179	20	-60	204	26	0.2%	70.00 [-40.92 , 180.92]
Cilomilast 121	14	175	622	-6	181	328	4.8%	20.00 [-3.93 , 43.93]
Cilomilast 156	7	153	364	-17	155	377	5.6%	24.00 [1.82 , 46.18]
Cilomilast 157	32	197	390	-2	182	411	4.0%	34.00 [7.70 , 60.30]
NCT00874497 (EMPHASIS)	-1	201.1	48	-83	324.1	28	0.2%	82.00 [-50.84 , 214.84]
Roflumilast IN-108	28	486	42	-124	405	25	0.1%	152.00 [-64.35 , 368.35]
Subtotal (95% CI)			**2657**			**1960**	**31.3%**	**35.05 [25.70 , 44.40]**
Heterogeneity: Chi² = 6.15, df = 8 (P = 0.63); I² = 0%								
Test for overall effect: Z = 7.34 (P < 0.00001)								
Total (95% CI)			**10541**			**9474**	**100.0%**	**49.28 [44.05 , 54.51]**
Heterogeneity: Chi² = 56.53, df = 28 (P = 0.001); I² = 50%								
Test for overall effect: Z = 18.47 (P < 0.00001)								
Test for subgroup differences: Chi² = 12.94, df = 1 (P = 0.0003), I² = 92.3%								



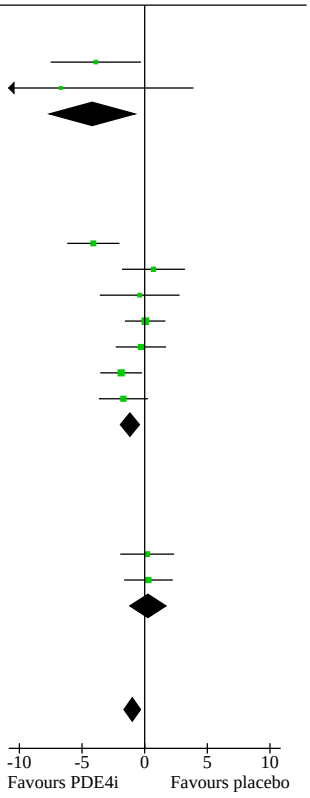
Analysis 1.37. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 37: SGRQ total score (by mean COPD severity)

Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.37.1 GOLD grade I + II								
Cilomilast 091	-2.7	21.1	369	-2.3	16.8	197	6.8%	-0.40 [-3.58 , 2.78]
Cilomilast 156	-3.2	10.5	304	-1.3	11	337	24.7%	-1.90 [-3.57 , -0.23]
Roflumilast M2-107	-3.5	14.1	555	-1.8	13.4	280	17.8%	-1.70 [-3.66 , 0.26]
Subtotal (95% CI)			**1228**			**814**	**49.3%**	**-1.62 [-2.80 , -0.44]**
Heterogeneity: Chi² = 0.68, df = 2 (P = 0.71); I² = 0%								
Test for overall effect: Z = 2.70 (P = 0.007)								
1.37.2 GOLD grade III + IV								
Cilomilast 039	-3.7	12.32	310	0.4	10.76	181	15.8%	-4.10 [-6.18 , -2.02]
Cilomilast 042	-4.2	15.5	375	-4.9	13.8	190	10.8%	0.70 [-1.81 , 3.21]
Compton 2001	-3.9	13.4	107	0	13.4	106	5.3%	-3.90 [-7.50 , -0.30]
Roflumilast DAL-MD-01	-7.5	13.8	11	-0.8	13.8	16	0.6%	-6.70 [-17.29 , 3.89]
Roflumilast M2-112	-1.7	19.3	760	-2	19.2	753	18.2%	0.30 [-1.64 , 2.24]
Subtotal (95% CI)			**1563**			**1246**	**50.7%**	**-1.51 [-2.67 , -0.34]**
Heterogeneity: Chi² = 14.87, df = 4 (P = 0.005); I² = 73%								
Test for overall effect: Z = 2.54 (P = 0.01)								
Total (95% CI)			**2791**			**2060**	**100.0%**	**-1.56 [-2.39 , -0.74]**
Heterogeneity: Chi² = 15.57, df = 7 (P = 0.03); I² = 55%								
Test for overall effect: Z = 3.70 (P = 0.0002)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%								



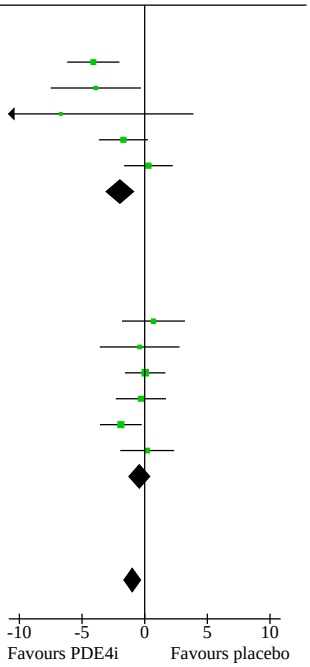
Analysis 1.38. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 38: SGRQ total score (by duration)

Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.38.1 Duration < 12 weeks								
Compton 2001	-3.9	13.4	107	0	13.4	106	3.3%	-3.90 [-7.50 , -0.30]
Roflumilast DAL-MD-01	-7.5	13.8	11	-0.8	13.8	16	0.4%	-6.70 [-17.29 , 3.89]
Subtotal (95% CI)			**118**			**122**	**3.7%**	**-4.19 [-7.60 , -0.78]**
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%								
Test for overall effect: Z = 2.41 (P = 0.02)								
1.38.2 Duration 24 to 26 weeks								
Cilomilast 039	-3.7	12.32	310	0.4	10.76	181	10.0%	-4.10 [-6.18 , -2.02]
Cilomilast 042	-4.2	15.5	375	-4.9	13.8	190	6.9%	0.70 [-1.81 , 3.21]
Cilomilast 091	-2.7	21.1	369	-2.3	16.8	197	4.3%	-0.40 [-3.58 , 2.78]
Cilomilast 103657	-1.8	10.2	292	-1.84	10	310	16.6%	0.04 [-1.57 , 1.65]
Cilomilast 121	-9	14.7	580	-8.7	14.7	320	10.8%	-0.30 [-2.31 , 1.71]
Cilomilast 156	-3.2	10.5	304	-1.32	11	337	15.6%	-1.88 [-3.55 , -0.21]
Roflumilast M2-107	-3.5	14.1	555	-1.8	13.4	280	11.3%	-1.70 [-3.66 , 0.26]
Subtotal (95% CI)			**2785**			**1815**	**75.4%**	**-1.18 [-1.94 , -0.42]**
Heterogeneity: Chi² = 13.81, df = 6 (P = 0.03); I² = 57%								
Test for overall effect: Z = 3.05 (P = 0.002)								
1.38.3 Duration 52 weeks								
Cilomilast 157	-1.29	14.9	347	-1.49	14.4	369	9.4%	0.20 [-1.95 , 2.35]
Roflumilast M2-112	-1.7	19.3	760	-2	19.2	753	11.5%	0.30 [-1.64 , 2.24]
Subtotal (95% CI)			**1107**			**1122**	**20.9%**	**0.26 [-1.18 , 1.69]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%								
Test for overall effect: Z = 0.35 (P = 0.73)								
Total (95% CI)			**4010**			**3059**	**100.0%**	**-0.99 [-1.65 , -0.33]**
Heterogeneity: Chi² = 20.56, df = 10 (P = 0.02); I² = 51%								
Test for overall effect: Z = 2.96 (P = 0.003)								
Test for subgroup differences: Chi² = 6.50, df = 2 (P = 0.04), I² = 69.2%								



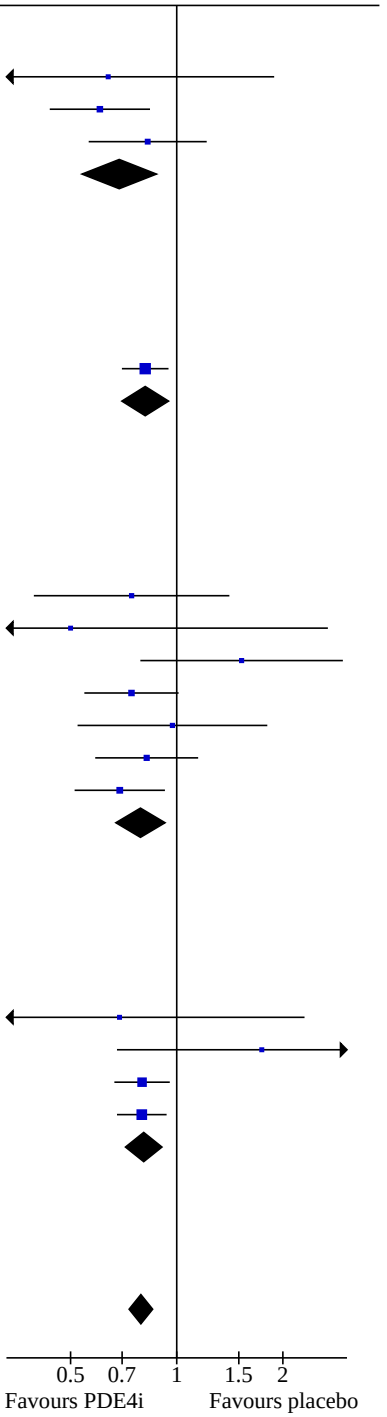
Analysis 1.39. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 39: SGRQ total score (by published vs unpublished)

Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.39.1 Published								
Cilomilast 039	-3.7	12.32	310	0.4	10.76	181	10.0%	-4.10 [-6.18 , -2.02]
Compton 2001	-3.9	13.4	107	0	13.4	106	3.3%	-3.90 [-7.50 , -0.30]
Roflumilast DAL-MD-01	-7.5	13.8	11	-0.8	13.8	16	0.4%	-6.70 [-17.29 , 3.89]
Roflumilast M2-107	-3.5	14.1	555	-1.8	13.4	280	11.3%	-1.70 [-3.66 , 0.26]
Roflumilast M2-112	-1.7	19.3	760	-2	19.2	753	11.5%	0.30 [-1.64 , 2.24]
Subtotal (95% CI)			**1743**			**1336**	**36.5%**	**-1.98 [-3.07 , -0.89]**
Heterogeneity: Chi² = 11.22, df = 4 (P = 0.02); I² = 64%								
Test for overall effect: Z = 3.56 (P = 0.0004)								
1.39.2 Unpublished								
Cilomilast 042	-4.2	15.5	375	-4.9	13.8	190	6.9%	0.70 [-1.81 , 3.21]
Cilomilast 091	-2.7	21.1	369	-2.3	16.8	197	4.3%	-0.40 [-3.58 , 2.78]
Cilomilast 103657	-1.8	10.2	292	-1.84	10	310	16.6%	0.04 [-1.57 , 1.65]
Cilomilast 121	-9	14.7	580	-8.7	14.7	320	10.8%	-0.30 [-2.31 , 1.71]
Cilomilast 156	-3.2	10.5	304	-1.3	11	337	15.6%	-1.90 [-3.57 , -0.23]
Cilomilast 157	-1.29	14.9	347	-1.49	14.4	369	9.4%	0.20 [-1.95 , 2.35]
Subtotal (95% CI)			**2267**			**1723**	**63.5%**	**-0.43 [-1.26 , 0.40]**
Heterogeneity: Chi² = 4.44, df = 5 (P = 0.49); I² = 0%								
Test for overall effect: Z = 1.02 (P = 0.31)								
Total (95% CI)			**4010**			**3059**	**100.0%**	**-1.00 [-1.65 , -0.34]**
Heterogeneity: Chi² = 20.61, df = 10 (P = 0.02); I² = 51%								
Test for overall effect: Z = 2.96 (P = 0.003)								
Test for subgroup differences: Chi² = 4.94, df = 1 (P = 0.03), I² = 79.8%								



Analysis 1.40. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 40: Number of participants on roflumilast with 1 or more exacerbations (additional medication)

Study or Subgroup	PDE4i treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.40.1 Long-acting bronchodilators						
RO-2455-402-RD (ROBERT) (1)	6	79	9	79	0.6%	0.64 [0.22 , 1.89]
Roflumilast M2-127	74	466	111	467	6.4%	0.61 [0.44 , 0.84]
Roflumilast M2-128	58	374	67	369	3.9%	0.83 [0.56 , 1.22]
Subtotal (95% CI)		**919**		**915**	**10.8%**	**0.69 [0.54 , 0.88]**
Total events:	138		187			
Heterogeneity: Chi² = 1.48, df = 2 (P = 0.48); I² = 0%						
Test for overall effect: Z = 3.03 (P = 0.002)						
1.40.2 Corticosteroids						
Roflumilast M2-111+M2-112	569	1327	652	1359	25.1%	0.81 [0.70 , 0.95]
Subtotal (95% CI)		**1327**		**1359**	**25.1%**	**0.81 [0.70 , 0.95]**
Total events:	569		652			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.65 (P = 0.008)						
1.40.3 Treatment only						
Roflumilast FK1 101	19	169	25	172	1.5%	0.74 [0.39 , 1.41]
Roflumilast IN-108	3	47	3	25	0.3%	0.50 [0.09 , 2.68]
Roflumilast JP-706	25	204	16	191	1.0%	1.53 [0.79 , 2.96]
Roflumilast M2-107	157	555	97	280	6.3%	0.74 [0.55 , 1.01]
Roflumilast M2-119	22	203	23	207	1.4%	0.97 [0.52 , 1.81]
Roflumilast M2-124	70	769	82	755	5.1%	0.82 [0.59 , 1.15]
Roflumilast M2-125	87	778	122	790	7.3%	0.69 [0.51 , 0.93]
Subtotal (95% CI)		**2725**		**2420**	**22.9%**	**0.79 [0.67 , 0.93]**
Total events:	383		368			
Heterogeneity: Chi² = 5.59, df = 6 (P = 0.47); I² = 0%						
Test for overall effect: Z = 2.89 (P = 0.004)						
1.40.4 Various concomitant treatments						
Liu 2018 (1)	5	60	7	60	0.4%	0.69 [0.21 , 2.30]
RO-2455-301-RD (ACROSS)	12	313	7	313	0.5%	1.74 [0.68 , 4.49]
RO-2455-404-RD (REACT)	380	969	432	966	17.9%	0.80 [0.67 , 0.96]
Roflumilast ROF-MD-07(RE2SPOND)	540	1178	605	1174	22.4%	0.80 [0.68 , 0.94]
Subtotal (95% CI)		**2520**		**2513**	**41.2%**	**0.81 [0.72 , 0.91]**
Total events:	937		1051			
Heterogeneity: Chi² = 2.66, df = 3 (P = 0.45); I² = 0%						
Test for overall effect: Z = 3.55 (P = 0.0004)						
Total (95% CI)		**7491**		**7207**	**100.0%**	**0.79 [0.73 , 0.85]**
Total events:	2027		2258			
Heterogeneity: Chi² = 11.23, df = 14 (P = 0.67); I² = 0%						
Test for overall effect: Z = 5.98 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.53, df = 3 (P = 0.67), I² = 0%						



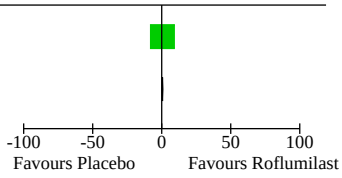
Footnotes

(1) New study data added 2019

Analysis 1.41. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 41: FVC ML (roflumilast 500 µg, endpoint)

Study or Subgroup	Roflumilast Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kavitha 2018	2.56	0.44	30	2.04	0.61	30	100.0%	0.52 [0.25 , 0.79]
Total (95% CI)			**30**			**30**	**100.0%**	**0.52 [0.25 , 0.79]**

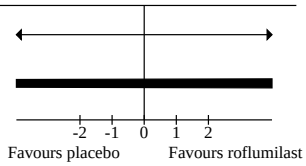
Heterogeneity: Not applicable
Test for overall effect: Z = 3.79 (P = 0.0002)
Test for subgroup differences: Not applicable



Analysis 1.42. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 42: FEV$_1$ (by unknown COPD severity)

Study or Subgroup	Roflumilast Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NCT00874497 (EMPHASIS)	-1	201.1	48	-83	324.1	28	100.0%	82.00 [-50.84 , 214.84]
Total (95% CI)			**48**			**28**	**100.0%**	**82.00 [-50.84 , 214.84]**

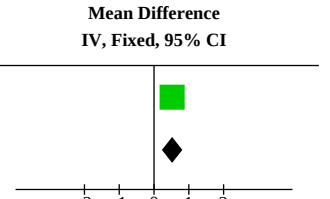
Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 1.43. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 43: FEV$_1$ (by duration, endpoint)

Study or Subgroup	Roflumilast Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kavitha 2018 (1)	2.56	0.44	30	2.04	0.61	30	100.0%	0.52 [0.25 , 0.79]
Total (95% CI)			**30**			**30**	**100.0%**	**0.52 [0.25 , 0.79]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.79 (P = 0.0002)
Test for subgroup differences: Not applicable

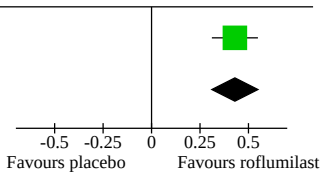


Footnotes
(1) Roflumilast 500 µg, duration 12 weeks

Analysis 1.44. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 44: FEV$_1$ (random-effects model, endpoint data)

Study or Subgroup	Roflumilast Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kavitha 2018 (1)	1.58	0.21	30	1.15	0.257	30	100.0%	0.43 [0.31 , 0.55]
Total (95% CI)			**30**			**30**	**100.0%**	**0.43 [0.31 , 0.55]**

Heterogeneity: Not applicable
Test for overall effect: Z = 7.10 (P < 0.00001)
Test for subgroup differences: Not applicable

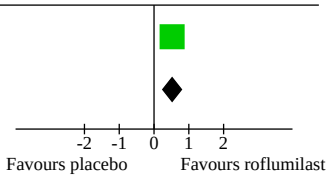


Footnotes
(1) Roflumilast 500 µg

Analysis 1.45. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 45: FEV_1 (by moderate to severe COPD severity, endpoint)

Study or Subgroup	Roflumilast Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kavitha 2018 (1)	2.56	0.44	30	2.04	0.61	30	100.0%	0.52 [0.25 , 0.79]
Total (95% CI)			**30**			**30**	**100.0%**	**0.52 [0.25 , 0.79]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.79 (P = 0.0002)
Test for subgroup differences: Not applicable

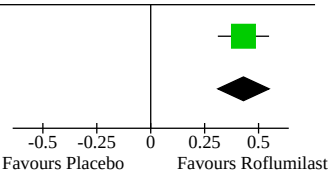


Footnotes
(1) Roflumilast 500 µg, duration 12 weeks

Analysis 1.46. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 46: FEV_1 (roflumilast 500 µg, endpoint)

Study or Subgroup	Roflumilast Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kavitha 2018	1.58	0.21	30	1.15	0.257	30	100.0%	0.43 [0.31 , 0.55]
Total (95% CI)			**30**			**30**	**100.0%**	**0.43 [0.31 , 0.55]**

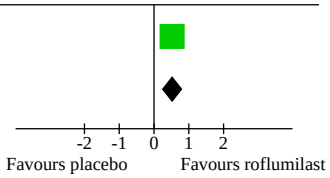
Heterogeneity: Not applicable
Test for overall effect: Z = 7.10 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.47. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 47: FEV_1 ML (additional medication (PDE_4i only) endpoint)

Study or Subgroup	Roflumilast Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kavitha 2018 (1)	2.56	0.44	30	2.04	0.61	30	100.0%	0.52 [0.25 , 0.79]
Total (95% CI)			**30**			**30**	**100.0%**	**0.52 [0.25 , 0.79]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.79 (P = 0.0002)
Test for subgroup differences: Not applicable

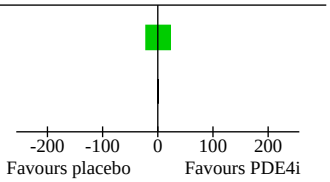


Footnotes
(1) Roflumilast 500 µg only

Analysis 1.48. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 48: FEV_1 (published, endpoint)

Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kavitha 2018 (1)	2.56	0.44	30	2.04	0.61	30	100.0%	0.52 [0.25 , 0.79]
Total (95% CI)			**30**			**30**	**100.0%**	**0.52 [0.25 , 0.79]**

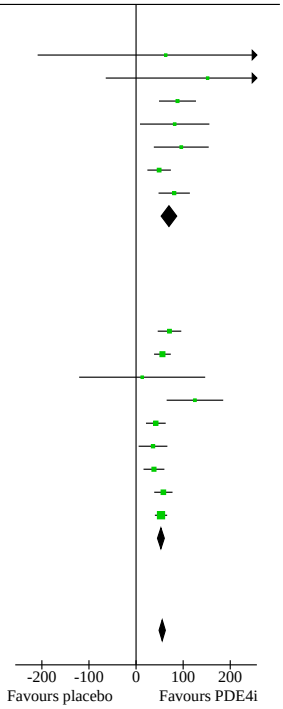
Heterogeneity: Not applicable
Test for overall effect: Z = 3.79 (P = 0.0002)
Test for subgroup differences: Not applicable



Footnotes
(1) Roflumilast 500 µg, duration 12 weeks

Analysis 1.49. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 49: FEV_1 (roflumilast 500 µg by mean COPD severity)

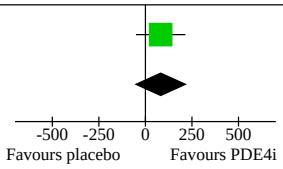
Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.49.1 GOLD grade I + II (FEV_1 # 50% predicted)								
RO-2455-402-RD (ROBERT)	63	861	77	0	861	77	0.1%	63.00 [-208.97 , 334.97]
Roflumilast IN-108	28	486	42	-124	405	25	0.1%	152.00 [-64.35 , 368.35]
Roflumilast M2-107	49	283	555	-39	268	280	2.9%	88.00 [48.76 , 127.24]
Roflumilast M2-118	55	282	127	-27	311	123	0.8%	82.00 [8.34 , 155.66]
Roflumilast M2-119	54	289	189	-42	298	201	1.3%	96.00 [37.74 , 154.26]
Roflumilast M2-127	39	192	456	-10	193	460	7.1%	49.00 [24.07 , 73.93]
Roflumilast M2-128	65	229	365	-16	229	364	4.0%	81.00 [47.75 , 114.25]
Subtotal (95% CI)			**1811**			**1530**	**16.2%**	**69.83 [53.34 , 86.33]**
Heterogeneity: Chi² = 5.38, df = 6 (P = 0.50); I² = 0%								
Test for overall effect: Z = 8.30 (P < 0.00001)								
1.49.2 GOLD grade III + IV (FEV_1 < 50% predicted)								
RO-2455-301-RD (ACROSS)	49	159.5692	313	-22	159.5692	313	7.0%	71.00 [46.00 , 96.00]
RO-2455-404-RD (REACT)	52	194.9638	928	-4	196.3246	941	14.0%	56.00 [38.26 , 73.74]
Roflumilast DAL-MD-01	41	91	11	28	250	16	0.2%	13.00 [-120.78 , 146.78]
Roflumilast FLUI-2011-77	66	120	30	-59	71	11	1.2%	125.00 [64.96 , 185.04]
Roflumilast M2-111	30	182	545	-12	178	596	10.0%	42.00 [21.08 , 62.92]
Roflumilast M2-112	9	303	760	-27	302	753	4.7%	36.00 [5.52 , 66.48]
Roflumilast M2-124	46	218	745	8	218	745	9.0%	38.00 [15.86 , 60.14]
Roflumilast M2-125	33	189	730	-25	194	766	11.7%	58.00 [38.59 , 77.41]
Roflumilast ROF-MD-07(RE2SPOND)	53	160.836	1178	0	160.836	1174	26.0%	53.00 [40.00 , 66.00]
Subtotal (95% CI)			**5240**			**5315**	**83.8%**	**52.75 [45.52 , 59.99]**
Heterogeneity: Chi² = 12.24, df = 8 (P = 0.14); I² = 35%								
Test for overall effect: Z = 14.28 (P < 0.00001)								
Total (95% CI)			**7051**			**6845**	**100.0%**	**55.51 [48.88 , 62.14]**
Heterogeneity: Chi² = 21.07, df = 15 (P = 0.13); I² = 29%								
Test for overall effect: Z = 16.41 (P < 0.00001)								
Test for subgroup differences: Chi² = 3.45, df = 1 (P = 0.06), I² = 71.0%								



Analysis 1.50. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 50: FEV_1 (unknown additional medication)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NCT00874497 (EMPHASIS)	-1	201.1	48	-83	324.1	28	100.0%	82.00 [-50.84 , 214.84]
Total (95% CI)			**48**			**28**	**100.0%**	**82.00 [-50.84 , 214.84]**

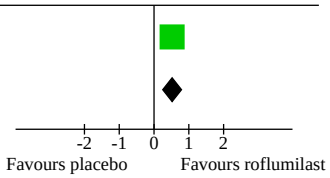
Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 1.51. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 51: FEV_1 (by moderate to severe COPD severity, roflumilast 500 µg endpoint)

Study or Subgroup	Roflumilast Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kavitha 2018 (1)	2.56	0.44	30	2.04	0.61	30	100.0%	0.52 [0.25 , 0.79]
Total (95% CI)			**30**			**30**	**100.0%**	**0.52 [0.25 , 0.79]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.79 (P = 0.0002)
Test for subgroup differences: Not applicable

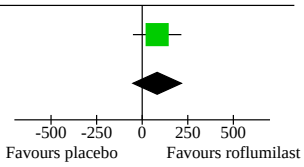


Footnotes
(1) Roflumilast 500 µg, duration 12 weeks

Analysis 1.52. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 52: FEV_1 (by unknown COPD severity, roflumilast 500 µg)

Study or Subgroup	Roflumilast Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NCT00874497 (EMPHASIS)	-1	201.1	48	-83	324.1	28	100.0%	82.00 [-50.84 , 214.84]
Total (95% CI)			**48**			**28**	**100.0%**	**82.00 [-50.84 , 214.84]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable



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
April 2020	42

Table 2. Studies reporting severe exacerbation rates per patient per year

Study ID	Percentage reduction (treatment vs placebo)	Rate ratio (95% CI)	P value
Cilomilast 039	45	-	0.001

Table 2. Studies reporting severe exacerbation rates per patient per year *(Continued)*

RO-2455-404-RD (REACT)	24.3	0.757 (0.601 to 0.952)	0.0175
Roflumilast M2-124+M2-125	17	0.82 (0.63 to 1.06)	0.163
Roflumilast ROF-MD-07(RE2SPOND)	8.5	0.95 (0.75 to 1.19)	0.635

APPENDICES

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

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*The Cochrane Library*)	Monthly
MEDLINE (Ovid SP) ALL	Weekly
Embase (Ovid SP)	Weekly
PsycINFO (Ovid SP)	Monthly
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 Respirology (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
9 March 2020	New citation required but conclusions have not changed	The 2020 update of this review includes 4 new trials of roflumilast - Kavitha 2018; Liu 2018; RO-2455-402-RD (ROBERT); Urban 2018 (ELASTIC) - and 1 new trial of tetomilast - NCT00874497 (EMPHASIS). Two new review authors (SJ and RF) were added, and 2 review authors (JC and BL) stepped down
9 March 2020	New search has been performed	Literature search was run

HISTORY

Protocol first published: Issue 4, 2000
Review first published: Issue 5, 2011

Date	Event	Description
11 October 2016	New search has been performed	New literature search was run
11 October 2016	New citation required but conclusions have not changed	Five new eligible studies of roflumilast 500 µg were 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 were made to review findings
17 December 2013	Amended	Typo in plain language summary title was amended
4 November 2013	Amended	Risk of bias for Cilomilast 076 was added
6 June 2013	New search has been performed	New literature search was run
6 June 2013	New citation required and conclusions have changed	We included 7 new studies in this update and excluded 1 cross-over trial. FDA report on psychiatric adverse events and suicides was included

Date	Event	Description
		Text was revised to take account of Cochrane reporting standards 'Summary of findings' table was added

CONTRIBUTIONS OF AUTHORS

Phillippa Poole: protocol initiation and development, checking of content of current update, corresponding author.

Sadia Janjua: screening, data extraction, risk of bias assessment, and write-up of the 2020 review update.

Rebecca Fortescue: data extraction and risk of bias assessment.

Contributions of editorial team

Chris Cates (Co-ordinating Editor): checked data entry before the full write-up of the review, edited the protocol, advised on methods, and approved the updated review prior to publication.

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

Emma Jackson (Assistant Managing Editor): conducted peer review and edited various sections and references in the protocol and in the review.

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

DECLARATIONS OF INTEREST

Phillippa Poole: none known.

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Rebecca Fortescue is Co-ordinating Editor for Cochrane Airways.

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Internal sources

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External sources

- The authors declare that no such funding was received for this systematic review, Other

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 data from the studies and carried out the analysis.

We excluded cross-over trials, as carry-over effects and disease progression cannot be adequately controlled for in people with COPD.

We updated the methods section in accordance with MECIR standards.

We separated mortality from non-fatal serious adverse events in the methods section for clarity of presentation in the 'Summary of findings' table and in other sections of the review.

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