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The safety and effectiveness of the current treatment regimen with or without roflumilast in advanced COPD patients: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease, which reduces the lung function and causes respiratory symptoms over time, and it is primarily associated with shortness of breath, cough and sputum production. Roflumilast, which is a long-acting selective inhibitor, reduces the anti-inflammatory effect of the main symptoms of COPD. The aim of this study was to compare the clinical effectiveness of adding roflumilast to the current treatment regimen of patients with severe COPD.

Methods: To retrieve the marker studies, medical databases were searched up to February 2014. We included studies, which compared the clinical effectiveness and safety of roflumilast as concomitant to Long-acting ß2-agonist/Long-acting muscarinic antagonist (LABA/LAMA) regimen, in adult patients with severe COPD. The number of exacerbations, changes in the lung function FEV1, FEV1/FVC and quality of life were the major predefined outcomes. Meta-analysis of outcomes was performed by the RevMan software, with $I^2 > 50\%$, representing considerable heterogeneity.

Results: Seven randomized controlled trials and two systematic reviews were included. In terms of safety, participants were likely to experience more side effects from roflumilast compared to placebo, particularly gastrointestinal effects (diarrhea, nausea, vomiting), headache and weight loss. There was no significant difference in the risk of cardiac complications or flu-like symptoms or upper respiratory tract infection in the two groups. In terms of effectiveness, only a small improvement was observed in SGRQ (St George's Respiratory Questionnaire) index. Roflumilast reduced moderate to severe attacks, and caused significant improvements in the lung function regardless of the severity of the disease and the concurrent use of other standard COPD therapies.

Conclusion: Roflumilast anti-inflammatory therapy reduces the chronic bronchitis symptoms in patients with moderate to severe COPD, and it can be safely used with other drugs simultaneously.

Keywords: Roflumilast, COPD, Safety, Effectiveness.

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common lung disorders in adults (1-3). COPD is a progressive and chronic respiratory disease (4) with decreased lung function and respiratory symptoms over time such as primarily shortness of breath, cough and sputum production (5) which ultimately lead to limited activities and lower quality of life (6-8).

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COPD is more common in seventh and eighth decades of life and has a low prevalence in people less than 40 years of age. It shows a higher prevalence in those with low socioeconomic status (SES), and it is directly correlated with rates of smoking and air pollution (9). In Iran, it accounts for about 10% of the causes of mortality and morbidity (9). According to the statistics in Iran (1387), of the country's total population of 70 million, 7 million suffer from respiratory diseases, with the prevalence of 25-30% (10), and many of them referred to emergency departments. WHO estimates that COPD is the fourth or fifth most common cause of mortality worldwide (11). Moreover, it is estimated to be promoted to the third cause of mortality in the world by 2020 (9). Currently, there is no cure for COPD (12). There is no intervention to reduce the mortality caused by COPD, except for quitting smoking (13), non-drug treatments such as pulmonary rehabilitation (14) and oxygen therapy in hypoxic patients (11). Disease control is comprised of interventions for smoking cessation (15), drug treatment, training and pulmonary rehabilitation (11). Drug treatment aims to relieve symptoms, improve exercise tolerance (16), promote quality of life, decelerate reduction of the lung function and even improve it, and to prevent and treat attacks. Attacks in COPD patients disturb their quality of life. In addition, the huge economic burden of COPD is attributed to the cost of attacks control (11). Drugs are frequently used to manage COPD as recommended by the World Health Authority (WHO) and GOLD include β2-agonists such as salbutamol and salmeterol, and anti-cholinergic agents (17). Although these drugs have proved to reduce exacerbations and symptoms, there is little evidence to suggest they can reduce the progression of this disease (17). There are no medications to cure inflammation. PDE4 inhibitors provide a novel approach for the treatment of COPD (18). Roflumilast (Daxas) is the most promising compound in pre-clinical and clinical development. It is a long-acting selective inhibitor, which reduces the main symptoms of COPD through its anti-inflammatory effect. The medicine is prescribed as a 500µg pill once a day (19). The aim of this study was to compare the effects of a common treatment regimen with/ without roflumilast on COPD patients.

Objectives

1. To evaluate the safety of roflumilast compared to the current treatment regimen used for advanced COPD patients; the medical side effects of this drug include diarrhea, headache and nausea.
2. To examine the effectiveness of roflumilast compared to the current treatment regimen used for advanced COPD patients by observing the changes in FEV1

Research Questions

1- How is the status of safety (drugs' side effects) of roflumilast compared to common treatment regimen in patients with advanced COPD?

2- How is the status of efficacy (FEV1, reducing attacks) of roflumilast compared to the current treatment regimen in patients with advanced COPD?

Methods

To retrieve the studies that compared the clinical effectiveness of roflumilast with salmeterol, tiotropium and salmeterol/ fluticasone, we searched PubMed, Cochrane, CRD, Scopus, IranMedex, Web of Science, and CINHAL. In addition, a hand search of respiratory journals and meeting abstracts was done up to February 2014. Finally, the search was performed in Google scholar (Table 3). The literature was also examined. In this search, MeSH and Free texts were used. To avoid publication bias, extensive search was done without any language restrictions although the articles were mostly in English (Table 4). We reviewed the reference lists of all the primary trials and review articles for additional references. To obtain the results of the ongoing studies, clinicaltrials.gov websites were searched.

Table 1. Inclusion criteria used in roflumilast-study selection

PICO	Clinical effectiveness
Population	Moderate to severe COPD patients (FEV1 ≤ 50% predicted) over 18 years
Interventions	Roflumilast
Comparition	A Common Treatment Regimen: Laba (Salmeterol), Lama (Tiotropium).
Outcomes	The number of exacerbations, changes in lung function FEV1, FEV1 / FVC, quality of life, adverse events, the frequency of hospitalization, cardiovascular diseases
Study design	Systematic review, randomised controlled trial

Table 2. Exclusion criteria used in roflumilast-study selection

Population	Patients who did not have COPD; healthy subjects; patients with asthma
Study	Pharmacokinetics or cost effectiveness studies; Studies with poor performance; trials outside the natural environment (in vitro)
Language restrictions	Non-English language

Inclusion and Exclusion Criteria

Adults older than 18 years of age with COPD, as defined by the American Thoracic Society, European Respiratory Society or GOLD, with an airflow obstruction evident by spirometry, with post-bronchodilator FEV1/FVC ≤ 0.7 (20) were included in the study.

Interventions that compared outcomes in participants who received placebo and treatment of concomitant oral roflumilast (LABA and LAMA) were examined.

Primary outcomes included changes in the lung function from baseline including forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and COPD exacerbations.

Secondary outcomes were as follows: The incidence of quality of life e.g., the total score on St. George's Respiratory Questionnaire (SGRQ); symptoms (breathlessness on Borg and other scales and Shortness of Breath Questionnaire; composite measures (summary symptom score)); adverse effects (number of participants experiencing one or more adverse event e.g., gastrointestinal, central nervous system (CNS) and cardiovascular adverse events, and changes in weight, and withdrawal rates); and serious adverse events and mortality. Such research included the systematic review of the studies (Systematic Review) and RCTs in which the oral administration of placebo, compared to treatment with roflumilast (LABA and LAMA), was done simultaneously (Table 1 and 2).

Table 3. Summarizes the number of papers and articles on the site entering the final stage of the synthesis

81	Pubmed	Databases
20	Cochrane	
3	CRD	
21	Thoracic	
33	Clinical Trial	
11	Controlled-trial	
3	Chestnet	
2	Informahealth care	
6	Pulsus	
1008	Scholar google	
1118	Total of entered	EndNote software
63	Repeated studies	
1125	The remaining studies	
1125	Documents of Title and Abstract	Title and Abstract
1100	Unrelated documents	
25	The remaining titles and Abstract	
16	Out studies for a reason	
5	Ongoing trials	
9	Full text	Trials entered into the Quality Survey

Table 4. How to find clinical effectiveness studies

Databases	Keywords	N. finding
PubMed	Copd or coad or pulmonary disease, chronic obstructive or chronic obstructive pulmonary disease or chronic airway disorder or chronic airway limitation or chronic obstructive respiratory disease or chronic obstructive lung disease or pulmonary disease	773252
	Roflumilast or daxas or daliresp or phosphodisterase4 or phosphodisterase 4 or pde4 or pde 4 or pde four or "phosphodisterase 4*" or "pde4*"	5344
	tiotropium or spiriva or fluticasone or flixotide or fluticasone salmeterol or advair or seretide or salmeterol or serevent or ICS or inhaled corticosteroid* or LAMA or long acting muscarinic receptor antagonist or long acting muscarinic antagonist or LABA or long acting* agonist or long acting beta-adrenoceptor agonist or long acting beta agonist or long acting*	33302
	Randomized controlled trial or controlled clinical trial or randomized or clinical trial or randomly or trial or systematic review or placebo	3011066
Cochrane	Total	81
	Pulmonary disease or chronic obstructive lung disease or chronic obstructive respiratory disease: ti, ab, kw or chronic airway limitation or chronic airway disorder or chronic obstructive pulmonary disease or pulmonary disease, chronic obstructive: ti, ab, kw or Copd or coad: ti, ab, kw (Word variations have been searched)	13725
	Phosphodisterase4 or phosphodisterase 4 or pde4 or pde 4 or pde four or "phosphodisterase 4*" or "pde4*":ti, ab, kw or roflumilast or daxas or daliresp: ti, ab, kw (Word variations have been searched)	266
	Tiotropium or spiriva or fluticasone or flixotide or fluticasone salmeterol or advair or seretide or salmeterol or serevent: ti,ab,kw or ICS or inhaled corticosteroid* or LAMA or long acting muscarinic receptor antagonist or long acting muscarinic antagonist or LABA or long acting* agonist or long acting beta-adernoceptor agonist or long acting beta agonist or long acting*:ti, ab, kw (Word variations have been searched)	10238
	Randomized controlled trial or controlled clinical trial or randomized or clinical trial or randomly or trial or systematic review or placebo	500687
CRD	Total	20 E.E = 1
	Copd or coad or pulmonary disease, chronic obstructive or chronic obstructive pulmonary disease or chronic airway disorder or chronic airway limitation or chronic obstructive respiratory disease or chronic obstructive lung disease or pulmonary disease	815
	Phosphodisterase4 or phosphodisterase 4 or pde4 or pde 4 or pde four or "phosphodisterase 4*" or "pde4*":ti,ab,kw or roflumilast or daxas or daliresp:ti,ab,kw (Word variations have been searched)	14
	Tiotropium or spiriva or fluticasone or flixotide or fluticasone salmeterol or advair or seretide or salmeterol or serevent:ti,ab,kw or ICS or inhaled corticosteroid* or LAMA or long acting muscarinic receptor antagonist or long acting muscarinic antagonist or LABA or long acting* agonist or long acting beta-adernoceptor agonist or long acting beta agonist or long acting*:ti,ab,kw (Word variations have been searched)	422
	Randomized controlled trial or controlled clinical trial or randomized or clinical trial or randomly or trial or systematic review or placebo	44998
ClinicalTrials.gov	Total	3
	"Copd" AND "roflumilast"	33
atsjournals.org		21
Controlled trials.com	(Roflumilast or daxas) and (salmeterol or serevent or tiotropium or spriva or Formoterol or Foradil or Oxis or Fluticasone or Flixotide or (Fluticasone and salmeterol) or seretide or Advair or LABA or long acting* or LAMA or ICS or inhaled*)and (chronic*)	11
pulsus.com	(roflumilast or daxas or daliresp)	6
Inform ahealthcare.com	(((roflumilast OR daxas OR daliresp OR phosphodisterase4 OR phosphodisterase 4 OR pde4 OR pde 4 OR pde four OR "phosphodisterase 4*" OR "pde4*") AND (Copd OR coad OR pulmonary disease, chronic obstructive OR chronic obstructive pulmonary disease OR chronic airway disorder OR chronic airway limitation OR chronic obstructive respiratory disease OR chronic obstructive lung disease OR pulmonary disease)) AND (tiotropium OR spiriva OR fluticasone OR flixotide OR fluticasone salmeterol OR advair OR seretide OR salmeterol OR serevent OR ICS OR inhaled corticosteroid* OR LAMA OR long acting muscarinic receptor antagonist OR long acting muscarinic antagonist OR LABA OR long acting* agonist OR long acting beta-adernoceptor agonist OR long acting beta agonist OR long acting*))	2
chestnet.org		3
Scholar google		3030

Table 5. Principal design features and quality survey for studies

Study	Type	Design	No. Of Pats.	Dura-tion	Eligibility	Author, year	Quality
M2-111	Earlier Phase3	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 mcg once daily); four week single-blind placebo run-in followed by a treatment period of 52 weeks. ICS allowed.	1,173	52 Weeks	• COPD • Age ≥ 40 years. • Post-bronchodilator FEV1 % predicted ≤ 50% and FEV1/FVC ≤ 70%. • Current or ex-smoker	Clinial Study Report for trial M2-111	Low risk
M2-112	Earlier Phase3	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 mcg once daily); four-week single-blind placebo run-in followed by a treatment period of 52 weeks. ICS allowed.	1,513	52 Weeks	• COPD • Age ≥ 40 years. • Post-bronchodilator FEV1 % predicted ≤ 50% and FEV1/FVC ≤ 70%.Available for Public Disclosure Without Redaction • Current or ex-smoker • Fixed airway obstruction (FEV1 increase ≤15% and/or 200 mL after inhalation of salbutamol.	Calverley 2007	Low risk
M2-111 + M2-112 (26)		As described in separate studies above The datasets combined in a post-hoc, pooled analysis	2,686	52 Weeks	As described in separate studies above	Rennard 2011	Low risk
M2-124	Pivotal	Double-blind, randomized, placebocontrolled, parallel group (roflumilast 500 µg once daily); four-week single-blind placebo run-in followed by a treatment period of 52 weeks. LABA allowed; Use of ICS terminated at randomization	1523	52 Weeks	• COPD for at least 12 months. • Age ≥ 40 years. • Post-bronchodilator FEV1 % predicted ≤ 50% and FEV1/FVC ≤ 70%. • Chronic bronchitis (chronic productive cough for three months in each of last 2 yrs prior to the study). • History of COPD exacerbations. • Current or ex-smoker • Symptomatic patients: total cough/sputum score ≥ 14 during last week prior to randomization.	Calverley 2009	Low risk

M2-125	Pivotal	Double-blind, randomized, placebocontrolled, parallel group (roflumilast 500 µg once daily); four-week single-blind placebo run-in followed by a treatment period of 52 weeks. LABA allowed; Use of ICS terminated at randomization	1568	52 Weeks	• COPD for at least 12 months. • Age ≥ 40 years. • Post-bronchodilator FEV1 % predicted ≤ 50% and FEV1/FVC ≤ 70%. • Chronic bronchitis (chronic productive Cough for three months in each of last 2 yrs prior to the study). • History of COPD exacerbations. • Current or ex-smoker • Symptomatic patients: total cough/sputum score ≥ 14 during last week prior to randomization.	Calverley 2009	Low risk
M2-124 + M2-125		As described in separate studies above Concomitant medication • Short-acting anticholingeric: 31%, 38% of those in the roflumilast group and 32%, 41% on placebo (M2-124, M2-125 respectively) • Short-acting ß2 agonist: "Patients could use short acting ß2 agonists as needed" • Corticosteroid: none • Long-acting ß2 bronchodilator: "Eligible patients were stratified according to their use of long acting ß2 agonists and smoking status." Roflumilast 49%, 48% (M2-124, M2-125 respectively) placebo 51% in bothe them.	3091	52 Weeks	As described in separate studies above	E.D. Bateman 2011	Low risk
M2-127	Supportive	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 mcg once daily); four-week single blind placebo run-in followed by a treatment period	933	24 Weeks	• COPD for at least 12 months. • Age ≥ 40 years. • Post-bronchodilator FEV1 % predicted between 40% and 70%. FEV1/ FVC ≤ 70%. • Current or ex-smoker • Fixed airway obstruction (defined as an	Fabbri 2009	Low risk

		of 24 weeks. All patients received salmeterol 50 µg BID as underlying treatment.			FEV1 increase ≤ 12% and/or 200 mL after receiving 400 µg salbutamol).		
M2-128	Supportive	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 µg once daily); four-week single-blind placebo run-in followed by a treatment period of 24 weeks. All patients received tiotropium 18 µg once daily as underlying treatment.	743	24 Weeks	• COPD for at least 12 months. • Age ≥ 40 years. • Post-bronchodilator FEV1 % predicted between 40% and 70%. And FEV1/FVC ≤70%. • Chronic bronchitis at enrollment (chronic productive cough for 3 months in each of the last 2 years prior to the study. • Current or former smoker • Fixed airway obstruction (defined as an FEV1 increase≤12% and/or 200 mL after receiving 400 µg salbutamol. • Pretreated with tiotropium for at least 3 months before baseline visit. • Use ≥ 28 puffs of rescue medication during week before randomization..	Fabbri 2009	Low risk

Table 6. Documents list out separately exclusion

Row	Exit reason	published	Author
1	Title: Cardiovascular safety in patients receiving roflumilast for the treatment of COPD Exit reason: lack of access to the full text, the study were only examined the cardiovascular safety	2013	White, W. B
2	Title: Roflumilast: a phosphodiesterase-4 inhibitor for the treatment of severe chronic obstructive pulmonary disease Exit reason: lack of access to the full text (systematic review)	2012	Pinner
3	Title: Efficacy and safety of roflumilast in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis Exit reason: lack of access to the full text (systematic review)	2013	Oba
4	Title: Efficacy and safety of roflumilast in patients with stable chronic obstructive pulmonary disease: A meta-analysis Exit reason: lack of access to the full text (meta-analysis)	2013	Yan
5	Title: Pharmacotherapies for chronic obstructive pulmonary disease: a multiple treatment comparison meta-analysis Exit reason: meta-analysis, out of our PICO	2011	Mills, E. J
6	Title: Roflumilast Treatment In COPD Patients Taking A Fixed-Dose Combination Of Long-Acting {superscript 2} 2 Agonist (LABA) And Inhaled Corticosteroid (ICS): Rationale And Design Of A Prospective Randomized Controlled Trial [Abstract] Exit reason: lack of access to the full text	2012	Ferguson, G. T
7	Title: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease Exit reason: it is a strategy	2013	Vestbo

8	Title: No relevant cardiac, pharmacokinetic or safety interactions between roflumilast and inhaled formoterol in healthy subjects: an open-label, randomized, actively controlled study Exit reason: Pharmacokinetic Study	2011	de Mey, C
9	Title: Effect of 1-Year Treatment with Roflumilast in Severe Chronic Obstructive Pulmonary Disease Exit reason: FEV_1 41%	2007	Calverley
10	Title: Effects of Roflumilast in Patients With COPD (Chronic Obstructive Pulmonary Disease) (BY217/M2-121) Exit reason: FEV1 ≤65%	2013	The HERO-study M2-121
11	Title: Roflumilast in Asian patients with COPD: A randomized placebo-controlled trial [Abstract] Exit reason: FEV1 30-80%	2011	Hui D M2-119
12	Title: Efficacy and Safety of Roflumilast in Japanese Patients Older Than 40 Years With Chronic Obstructive Pulmonary Disease (APTA-2217-06) Exit reason: FEV1 30-80%	2005	APTA-06
13	Title: Long-term Study of Safety and Efficacy of Roflumilast in Japanese Patients Older Than 40 Years With Chronic Obstructive Pulmonary Disease (APTA-2217-08) Exit reason: FEV1 30-80%	2005	APTA-08
14	Title: Roflumilast—an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomized controlled trial Exit reason: FEV1 30-80%	2005	Klaus F Rabe
15	Title: A Chronic Obstructive Pulmonary Disease (COPD) Trial Investigating Roflumilast on Safety and Effectiveness in China, Hong Kong and Singapore Exit reason: The comparison group differed	2012	ACROSS
16	Title: Effect of Roflumilast on Pulmonary Function and Respiratory Symptoms in Patients With Chronic Obstructive Pulmonary Disease (COPD) (BY217/M2-110) Exit reason: : lack of access to the full text	2003	M2-110

Two reviewers independently screened the search results to select citations to retrieve the full texts, and they also screened the full-texts of the articles to identify the appropriate studies for inclusion. One reviewer extracted data from the eligible studies, and the second one checked the data. Data were entered into RevMan 5.2, and the following data were extracted:

• Methods: Trial design, and duration of follow-up

• Participants: Age, gender, smoking status, study setting, inclusion and exclusion criteria

• Intervention: Drug name, dose, duration of treatment, control and/or standard therapy

• Outcome measures

References were classified according to the trial name (by drug name and number or by author and year). We obtained data on additional outcomes from other references. Also, to conduct the meta-analysis, we considered the changes in the pre-bronchodilator FEV1 for all trials. Lung function is reported in milliliters (mL). The “total adverse events” outcome involved the participants in each group experiencing one or more adverse events, including an acute exacerbation of COPD. Serious adverse events included conditions requiring hospital- level treatment and more serious COPD exacerbations.

To assess the risk of bias in the included studies, trials were evaluated as low, unclear or high, using the "risk of bias" methods outlined in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions.

Measures of Treatment Effect

We used the results of RCT studies to analyze the pooled effect estimates of the outcomes. We pooled continuous variables using a fixed-effect mean difference or standardized mean difference (SMD), with 95% confidence intervals (CI) as well as outcomes with dichotomous variables using a fixed-effect odds ratio (OR) with 95% CI. We considered a p-value of less than 0.05 as statistically significant. Rate ratios were combined on a natural logarithm scale and weighted by the inverse of the variance of the log rate ratio. Because the number of the included studies was not sufficient (n=10), we could not assess the publication bias of the studies according to the Cochrane recommendation (21).

When more than ten studies were included in the reviews, we used the I^2 statistic to measure heterogeneity among the trials in each analysis. Cochrane systematic review was conducted according to statistics I^2>50%, indicating considerable heterogeneity. Sensitivity analysis of the results was performed to explore heterogeneity. In addition, subgroup differences in pooled estimates were analyzed according to the following variables:

- Severity of airflow obstruction at baseline
- Drug (e.g., roflumilast)
- Duration of therapy (6- 12 months)
- Concomitant therapy (inhaled or oral corticosteroids, inhaled long-acting ß2 agonists, anticholinergics or both)

Results

Primary Findings

Two reviewers assessed the full-text versions of the trials to determine whether they met the inclusion criteria. We resolved any differences by discussion. Then trials that met the inclusion criteria were assessed for methodological quality (Fig. 1). After evaluating and assessing the quality of the articles, we found 7 RCTs studies that met our inclusion criteria. Two one-year-long studies (M2-111, M2-112) assessed the therapeutic effect of roflumilast 500 mcg once-daily in patients with severe and very severe COPD; in these two studies the patients were not required to have a history of chronic bronchitis or previous exacerbations, and concomitant corticosteroids were allowed during the study period (22).

Two one-year-long studies (M2-124, M2-125) that investigated the therapeutic effect of roflumilast in a specific subgroup, severe to very severe COPD, were associated with chronic bronchitis in patients at risk of exacerbations (23).

one study considered the findings of two studies (M2-124 + M2-125) in which the add-on use of roflumilast with long acting bronchodilator agents was examined (Roflumilast + LABA) (24).

Two six-month studies (M2-127, M2-128) evaluated the add-on use of roflumilast with long acting bronchodilator agents, the first with salmeterol and the second with tiotropium (25).

Three systematic reviews were also included, but their full texts were not available. One study (Chong J. 2013) that evaluated the efficacy and safety of oral PDE4 inhibitors (Roflumilast and Cilomilast) in the management of stable COPD, in a review of 29 studies which met the inclusion criteria, 15 trials were associated with roflumilast (26). We took an advantage of our results and those related to roflumilast, which were consistent with our study criteria. In an Evidence Review Group (ERG) report by Rob Riemsma (2011) on the medication review of the manufacturers' published studies that presented the results for the two sets of data, the data for adults with severe COPD (FEV1 post bronchodilator less than 50% predicted)" and the data for adults with moderate to severe COPD (FEV1 post bronchodilator, were less than 65%) were obtained (27). Characteristics

and quality assessment of the studies are presented in Table 5.

We excluded 16 studies due to inconsistency and lack of access to their full text (Table 6).

Overall, the methodological quality of all the published trials was acceptable. There were adequate descriptions of allocation concealment and method of blinding in all the trials.

All studies included in this review were double-blind randomized controlled trials, with inclusion and exclusion criteria and withdrawal of the participants. Withdrawals occurred mostly due to adverse events, particularly in PDE4 inhibitor-treated participants. Information on the use of β-agonists and anticholinergics (M2-124, M2-125, M2-127, M2-128), and corticosteroids at baseline trials (M2-127, M2-128) was not available.

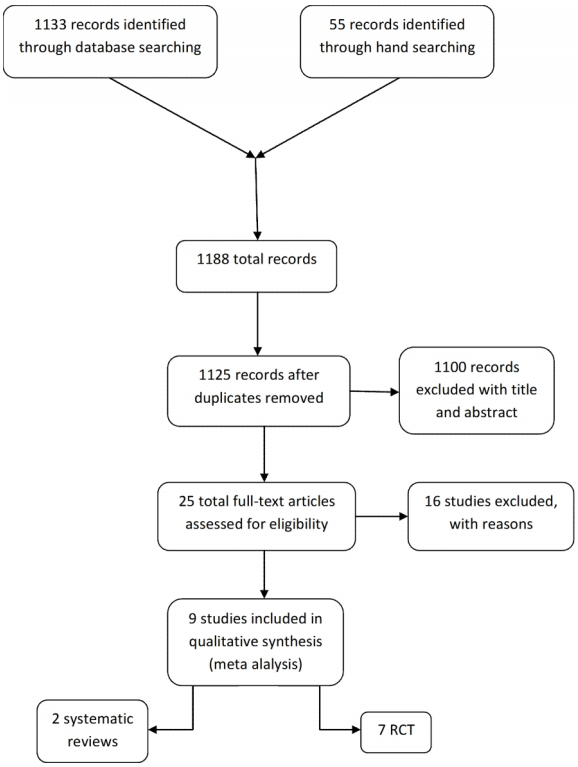

Fig. 1. Study flow diagram

Secondary Findings

Change in the Lung Function from Baseline

Based on the seven trials that reported this outcome, there was a statistically significant improvement in FEV1 from baseline in the roflumilast treated participants compared to controls (MD 51.18 mL; 95%CI 41.45 to 60.90) over the study period (Analysis 1). With respect to roflumilast use with concomitant therapies (Analysis 4), the largest increases in FEV1 were observed in the two trials in which participants were taking regular long-acting bronchodilators: In one trial, the participants took salmeterol (roflumilast M2-127) and in the other, they took tiotropium (Roflumilast M2-128) (overall MD 60.52 mL; 95% CI 40.57 to 80.46). The next largest improvements were found in trials in which all other medications apart from the short-acting beta- 2 agonists were stopped (MD 49.31 mL; 95%CI 34.71 to 63.90). Moreover, similar improvements were observed in three trials (Roflumilast M2-111+M2-112) in which both treatment and control groups continued on an inhaled corticosteroid (ICS) (MD 46.80 mL; 95% CI 29.55 to 64.05). Treatment with roflumilast was associated with a statistically greater change in FVC from baseline than placebo (MD 86.60 mL; 95%CI 66.08 to 107.13) with minimal heterogeneity among the 5 trials (Analysis 5). Change in PEF was measured in only two of the seven trials, but it was significantly higher in the treatment group than in controls (MD 4.65 L/min; 95%CI 1.74 to 7.55) (Analysis 6).

Exacerbations

Use of roflumilast was associated with a statistically significant reduction in the numbers of participants experiencing one or more COPD exacerbations. This chong j (2013) (26) meta-analysis of six studies with RCT revealed that in terms of exacerbation rate and the number of exacerbations experienced on average per patient per year (Analysis 9), a small but significant benefit of treatment was observed, representing a 13% reduction in the rate ratio.

Quality of Life

In the subgroup analysis of M2-112 and M2-111 studies, significant improvement in

SGRQ total score was observed for patients with chronic bronchitis (p= 0.0265). The difference in patients with chronic bronchitis was treated concurrently with ICS. (p=0.0397). In patients with chronic bronchitis, the difference of -1.073 units, compared to placebo, did not achieve the conventional minimum important difference of 4 units (Jones 2005), but it was statistically significant and similar to differences observed between therapies in other one-year trials. In studies of M2-124 and M2-125 for EQ-5D, the difference between the treatments was -0.0047 (p= 0.5331) and -0.0106 (p=0.1715), respectively and in the combined analysis, the difference was statistically significant 0.0034 (p= 0.06712), indicating a little change in quality of life.

Shortness of Breath Questionnaire (SOBQ)

In a study conducted by Chong J. (2013), in the meta-analysis of M2-127 and M2-128 studies, it was revealed that in the M2-127 study no significant difference was found between the placebo and roflumilast group, but a significant difference versus placebo was seen in the study of M2-128 in favor of roflumilast (Analysis 7) (26).

Use of Rescue Medication

For this outcome, the meta-analysis of five studies was examined. The meta-analysis results revealed that the concurrent treatment of roflumilast with corticosteroids or long-acting β-agonists did not seem to have such beneficial effects on more people who experienced exacerbation during the study period (Analysis 8).

Adverse Events

The likelihood of a participant experiencing an adverse event was higher with roflumilast than with placebo (OR 1.21; 95% CI 1.09 to 1.34; Analysis 10). A range of adverse effects occurred more frequently in participants treated with roflumilast. The most frequently reported side effects were as follows: Diarrhea (OR 3.71; 95% CI 2.97 to 4.63; Analysis 11); nausea (OR 3.37; 95%CI 2.48 to 4.58; Analysis 12); headache (OR 2.42; 95%CI 1.82 to 3.21; Analysis 13); and weight loss (OR 3.85; 95% CI 3.03 to 4.90; Analysis 14). There were no significant differences in the incidence of either influenza-like symptoms (Analysis 15) or upper respiratory tract infections (Analysis 16) between treatment and control groups. Most adverse events generally occurred within the first four weeks of therapy, particularly in the drug group and were resolved with continued treatment. More patients withdrew from the study due to adverse effects, and withdrawal was higher in the roflumilast 500 mcg group than the placebo group (OR 1.68; 95%CI 1.46 to 1.93; Analysis 17). However, the treatment did not significantly affect the non-fatal serious adverse events (OR 0.95; 95% CI 0.83 to 1.07; Analysis 18) or mortality (OR 0.92; 95% CI 0.66 to 1.27; Analysis 19), although mortality was relatively rare in the trials. Weight loss caused the most concern. Those patients in the roflumilast group who reported diarrhea, nausea, vomiting, or headache had a greater weight loss compared to those not reporting these symptoms. The largest absolute weight loss with roflumilast occurred in obese patients (BMI> 30), but a significant reduction in body weight was observed between patients with low weight. Physical examinations, routine laboratory tests, C-reactive protein concentrations, and ECGs did not show any clinically significant changes after administration of roflumilast in patients concomitantly treated with salmeterol or tiotropium. Moreover, patients with chronic bronchi who were more likely to benefit from roflumilast did not experience an increased incidence of adverse events. Furthermore, these individuals had fewer side effects (nausea, diarrhea, and weight loss) associated with PDE4 inhibitors.

Discussion

In accordance with ICH Guideline for Industry: “Extent of Population Exposure to Assess Clinical Safety” (March 1995) (28)

and in accordance with the FDA Draft Guidance for Industry: "Chronic Obstructive Pulmonary Disease: Development of Drugs for Treatment" (November 2007) (29), most patients were treated with roflumilast for six months to one year. Diarrhea, nausea, decreased appetite, headaches, dizziness, insomnia and weight decrease were observed more in the roflumilast arm compared to the placebo arm. It was notable that treatment with roflumilast was associated with a significant chance of weight loss. It is not yet clear whether or not this was due to anorexia caused by gastrointestinal adverse effects. Weight loss may be a beneficial effect in patients 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 2013) (30). This adverse effect warrants further investigation. There was no increase in serious adverse effects or mortality, although trials were of relatively short duration and analyses were underpowered to report on the latter outcome. The magnitude of the treatment effect on exacerbation is comparable for all currently available COPD treatments when using similar definitions of exacerbation. The reported reduction in the rate of exacerbations in three of the largest COPD trials conducted to date, ranged from 14% (tiotropium in UPLIFT) (31) to 20% (salmeterol in TRISTAN) (32) and from 5% to 18% (fluticasone in TRISTAN and TORCH) (32, 33) for single agents and up to 25% for combination products (fluticasone/salmeterol in TRISTAN and TORCH) (32, 33). The effect size of roflumilast, as a single agent, was 15% to 19% in the pivotal studies. To best characterize the improvements observed with roflumilast, the effect size should not be compared to the -25%, a fixed combination of LABA-ICS achieved compared to placebo, but rather to what is achieved when adding an ICS to a LABA. For example, salmeterol alone improved the exacerbation rate in the TRISTAN study by 20% compared to placebo (32). Adding ICS increased the effect size by just 5%, resulting in a total of 25% reduction in exacerbation for the fixed combination of fluticasone and salmeterol compared to placebo. Another large trial, TORCH, showed that salmeterol versus placebo reduced exacerbation by 15% when compared to placebo (32); adding fluticasone to salmeterol in a fixed combination demonstrated an additional reduction in exacerbation by 12% versus salmeterol alone. The roflumilast studies showed that the effect of adding roflumilast to a LABA background treatment improved the exacerbation rate by 21% (p= 0.001), an effect that compares favorably to that of an ICS added to LABA treatment. Although not powered to test for exacerbations, M2-127 and M2-128 studies indicated that roflumilast may substantially reduce exacerbations in patients taking salmeterol or tiotropium in a moderate to severe COPD population by 37% (p= 0.0315, post-hoc analysis) or 23% (p= 0.1957). In the M2-124 + M2-125 study, the relative reduction in moderate or severe exacerbation rates in roflumilast + LABA group was 20.7%. Moreover, the absolute rate reduction exacerbation per patient per year was 0.322. In this study, roflumilast significantly reduced the mean rate of moderate or severe exacerbations in both frequent (i.e., more than two exacerbations per year), and infrequent (i.e., fewer than two exacerbations per year), exacerbators (respectively, RR=0.78, p= 0.0017 and RR= 0.84, p= 0.0062). The time to onset the first, second and third moderate or severe COPD exacerbation was significantly delayed across all patients and in the subgroups using LABAs. In the subgroup not receiving LABAs, only the time to onset the second exacerbation was significantly delayed. In frequent exacerbators, time to onset for the second (p=0.0017) and third exacerbation (p=0.0074) was delayed, and in infrequent exacerbators to onset, the second exacerbation (p= 0.0245) was delayed. In conclusion, roflumilast consistently demonstrated a clinically meaningful reduction in exacerbations in the acute COPD patient popu-

lation. The pivotal roflumilast studies enrolled a severe to very severe patient population with a mean pre-bronchodilator FEV1 of about 1 liter and a low mean reversibility of 10% to 12%. The Cochrane review (Appleton, 2006) (34) showed that even bronchodilators like formoterol and salmeterol increased FEV1 by an average of only 51 mL in patients with poorly reversible COPD. The pivotal roflumilast study pool demonstrated a mean FEV1 improvement of 48 mL in a similar population. In all the studies discussed above, roflumilast improved FEV1 values from baseline, whereas placebo treatment showed no change or decrease in FEV1 values from baseline. The importance of the reversibility on treatment related FEV1 improvement was demonstrated in a corresponding subgroup analysis of the pooled data of M2-124 and M2-125 studies in which larger treatment effects (72 mL) were found in severe to very severe COPD patients with less fixed airway obstruction (higher reversibility) compared to those with fixed airway obstruction. Roflumilast exerts its effects in addition to the treatment effects of long-acting bronchodilators. In particular, improvements in pre-bronchodilator FEV1 with roflumilast on top of concomitant LABA or SAMA treatment in patients with severe to very severe COPD were 46 mL and 58 mL in the pivotal studies of M2-124 and M2-125, respectively.

In a study, M2-124 + M2-125, those patients receiving LABAs had similar pre-bronchodilator FEV1 values to those not receiving LABAs, but had a smaller increase after administration of a SABA (data not available). Both pre- and post-bronchodilator FEV1 significantly improved with roflumilast compared to placebo, irrespective of concomitant treatment with LABAs, SAMAs or previous ICS use or previous exacerbation frequency.

The effect of roflumilast on the lung function, on top of salmeterol or tiotropium treatment in patients with moderate to severe COPD, was 49 mL and 80 mL (M2-127 and M2-128, respectively). The effect size of roflumilast on the lung function is similar to what is achieved by inhaled corticosteroids alone or when added to a LABA treatment. In a large three-year study [TORCH] (33), fluticasone alone improved lung function by 47 mL over placebo, salmeterol alone by 42 mL, and a fixed combination of salmeterol/fluticasone improved the lung function by 92 mL. In conclusion, the effect size measured with roflumilast on the lung function was in a severe, poorly reversible COPD population similar to what is achieved with LABAs in similar populations and it is also comparable to the effect size of inhaled corticosteroids, which are currently the only available anti-inflammatory treatments for COPD. Roflumilast represents a significant addition to the armamentarium of prescribing physicians for the following reasons: Demonstrating clinically relevant efficacy in reducing the rate of moderate and severe exacerbations and in improving the lung function; having an additive effect on top of the background bronchodilator therapy; having a novel mechanism of action that reduces inflammation with a mechanism different from corticosteroids; an easy oral administration once-a-day with no clinically significant interactions with drugs commonly used by COPD patients; acceptable tolerability and safety profile; and rapid absorption after oral administration

Conclusion

Phosphodiesterase 4 inhibitors are oral medicines that can be used in combination with other standard COPD treatments. Clinical studies have demonstrated higher pharmacologic activity and better tolerability of roflumilast as compared to earlier PDE4-inhibitor. Roflumilast has been developed as an innovative once-daily oral treatment for COPD, targeting the inflammatory processes that are relevant to the disease. Most evidence exists for roflumilast at a dose of 500 µg. Phosphodiesterase 4 inhibitors join an increasing list of treatments for COPD that im-

prove short-term lung function and reduce exacerbations, but have not been shown to increase life expectancy.

To date, the trials which have been done on this topic have taken one year or less to conduct. In contrast to long-acting bronchodilators, PDE4 inhibitors have minimal benefits on symptoms on a day-to-day basis, or quality of life, and are often associated with adverse effects, particularly gastrointestinal system and headaches. Roflumilast is associated with significant weight loss compared to placebo treatment. Thus, their use may best be limited to add-on therapy in a subgroup of patients with persistent symptoms or exacerbations despite optimal COPD management. If they are not well- tolerated, they may be discontinued.

COPD is a major, growing health care problem causing significant morbidity and mortality. Treatment of COPD is mostly based on inhaled bronchodilators (long and short acting beta agonists and muscarinic agents), and inhaled corticosteroids with the objective of improving the lung function and decreasing exacerbations.

Roflumilast represents a significant addition to the armamentarium of prescribing physicians for the following reasons:

• A demonstrated clinically relevant efficacy in reducing the rate of moderate and severe exacerbations and in improving the lung function

• An Additive effect in addition to the background bronchodilator therapy

• A novel mechanism of action that reduces inflammation with a mechanism different from corticosteroids

• An easy oral administration once a day with no clinically significant interactions with drugs commonly used by COPD patients

• Acceptable tolerability and safety profile

• Rapid absorption after oral administration (35)

Longer-term trials are necessary to obtain a more accurate estimate of the benefits and ensure the safety of these medicines over time including whether they slow the progression of COPD.

Limitations of the Study

- Lack of access to some databases including EMBASE due to the closure of the base in Iran

- Lack of a systematic review of the studies that have been done on this topic

The Message of the Research

What is the message of this research? Roflumilast has been approved as an effective and safe drug and is known as an anti-inflammatory medicine for patients with moderate to severe COPD and chronic bronchitis symptoms. This medicine decreases the attacks, improves the lung function and significantly reduces weight. Moreover, this drug can be used safely in conjunction with other COPD drugs.

To whom is the message sent? The results of this study may be used by health policy makers, the Food and Drug Administration (FDA), insurance agencies, researchers, clinicians, immunologists, professional groups, the Committee on asthma, allergies and chronic lung diseases, the non-governmental organizations and factories, as well as companies importing and manufacturing drugs.

Who sends the message? The messenger's credit, scientific and social prestige is important. Therefore, the Office of HTA, FDA, the Committee on asthma, allergies and chronic lung diseases, and insurance organizations are proposed as the messengers.

What is the process of transition? (How)

To transfer of HTA is reported to the FDA to publish articles in national and international journals.

What is the impact of the transition? (Evaluation)

It is expected that the transition of research-based knowledge brings about some changes in the knowledge, attitude and behavior of the related stakeholders, which can be subject of further assessments, and they are as follows:

1. The importation and/ or production of the drug in the country
2. Drug coverage by insurance
3. Arranging and planning to use the drug information in the preparation of national guidelines

Adding this medication to the country's drug list

Role of the Funding Source: The sponsor did not place any restrictions on authors about the statements made in the final report.

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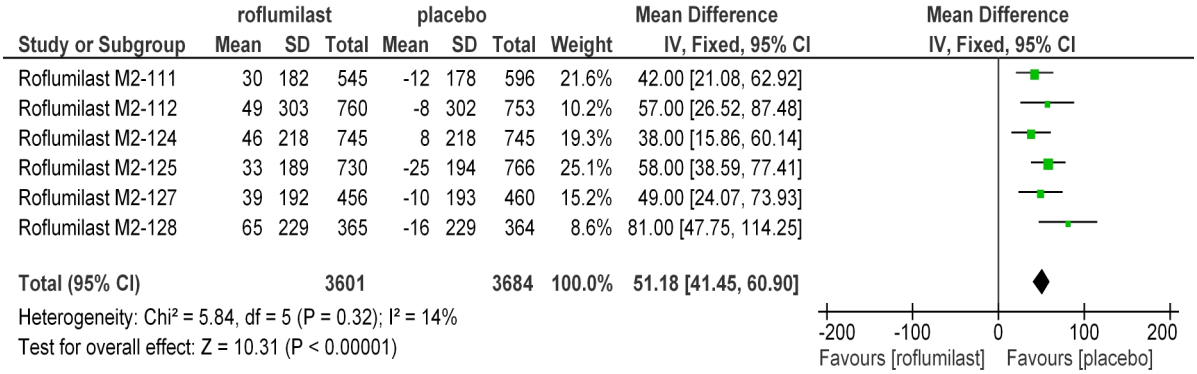
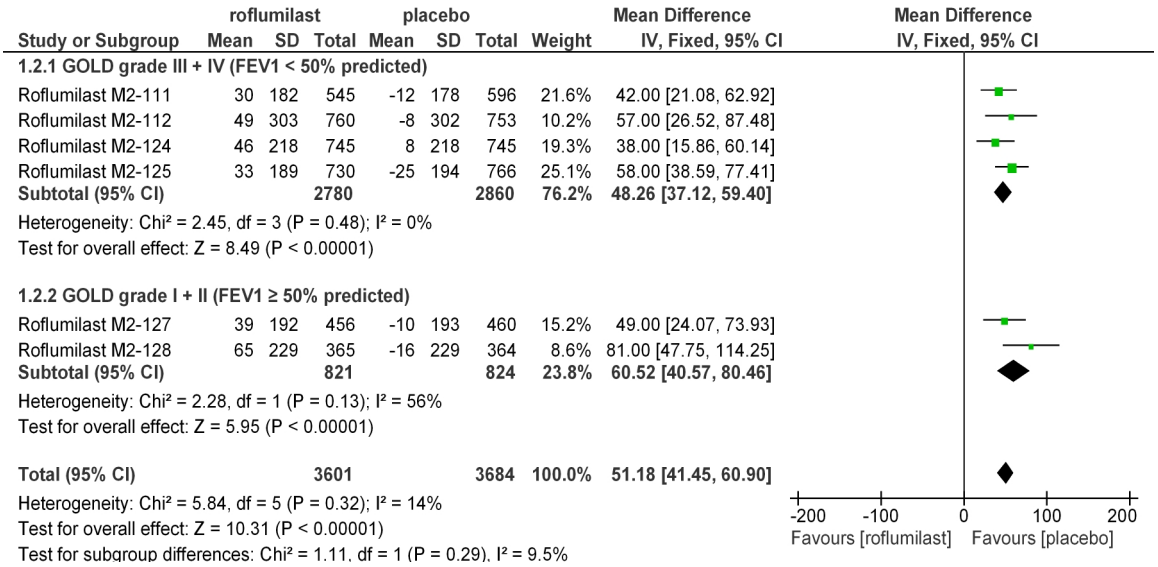
Appendix

The results of a meta-analysis of effectiveness:

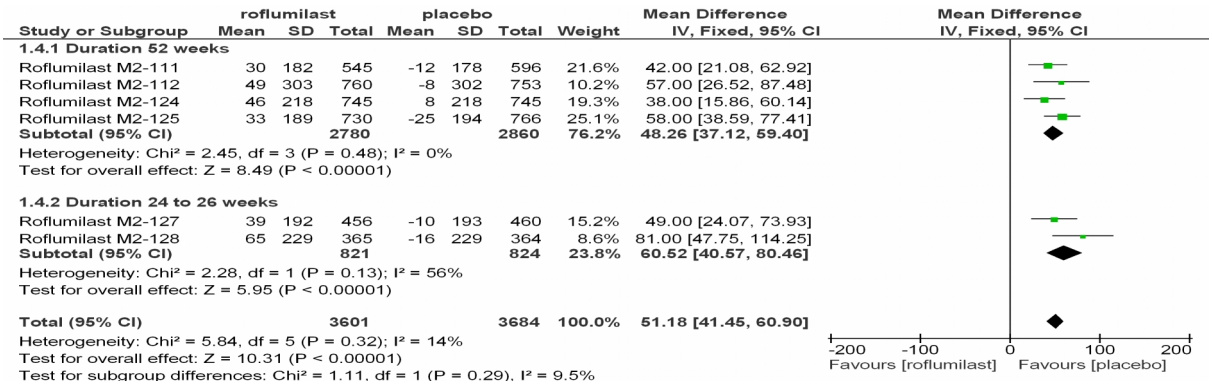
Analysis 1. Comparison 1 Roflumilast versus placebo, Outcome 1 FEV1 (by drug)



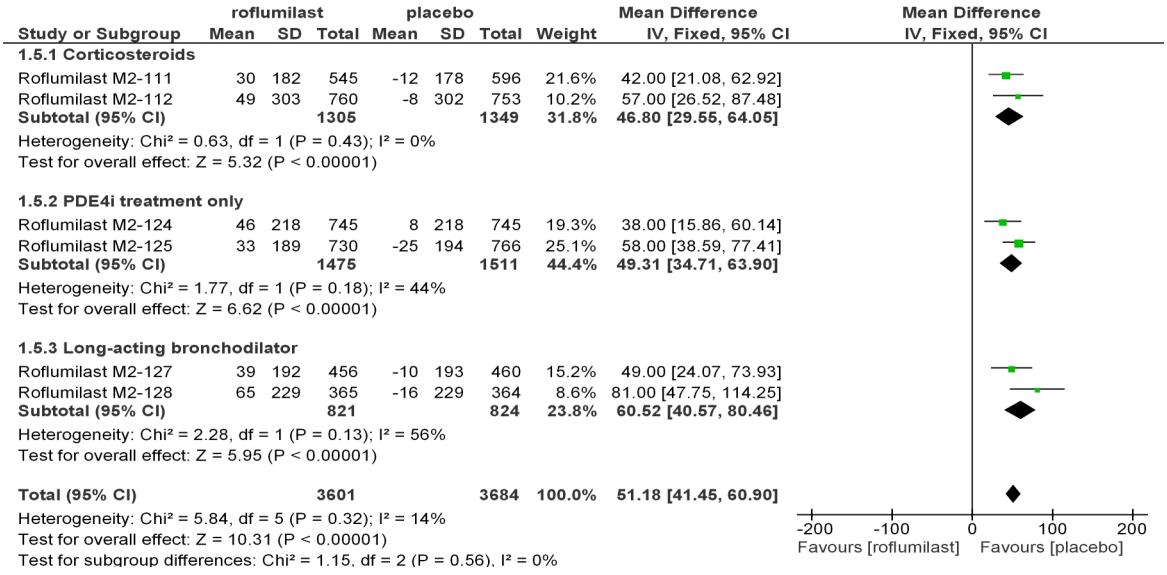
Analysis 2. Comparison 1 Roflumilast versus placebo, Outcome 2 FEV1 (by mean COPD severity)



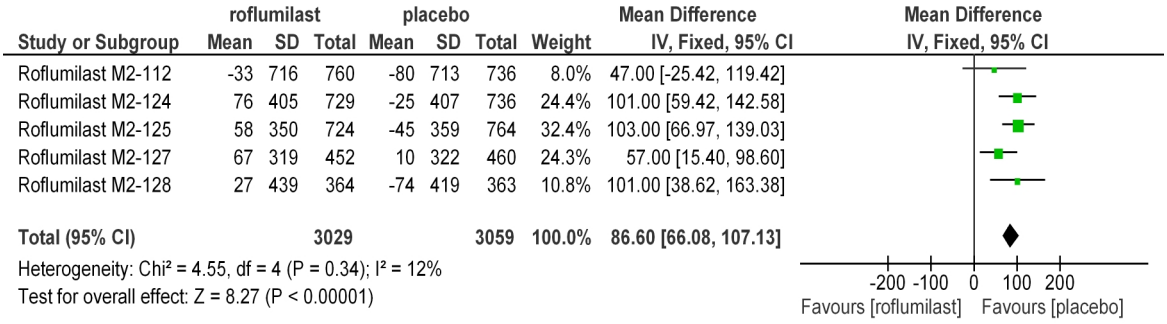
Analysis 3. Comparison 1 Roflumilast versus placebo, Outcome 3 FEV1 (by study duration)



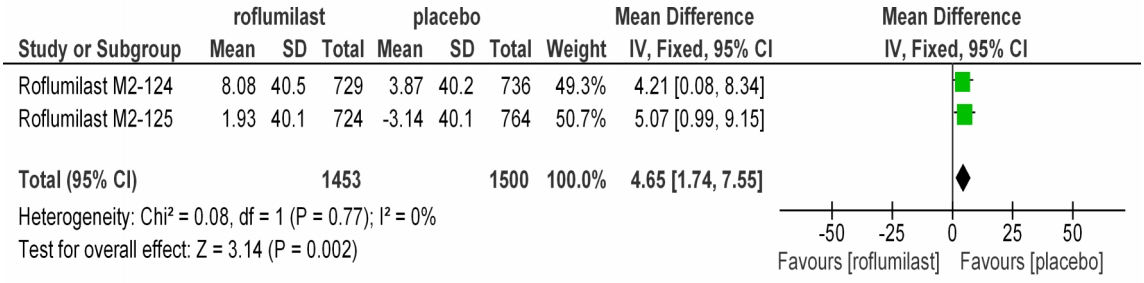
Analysis 4. Comparison 1 Roflumilast versus placebo, Outcome 4 FEV1 (Concomitant medications)



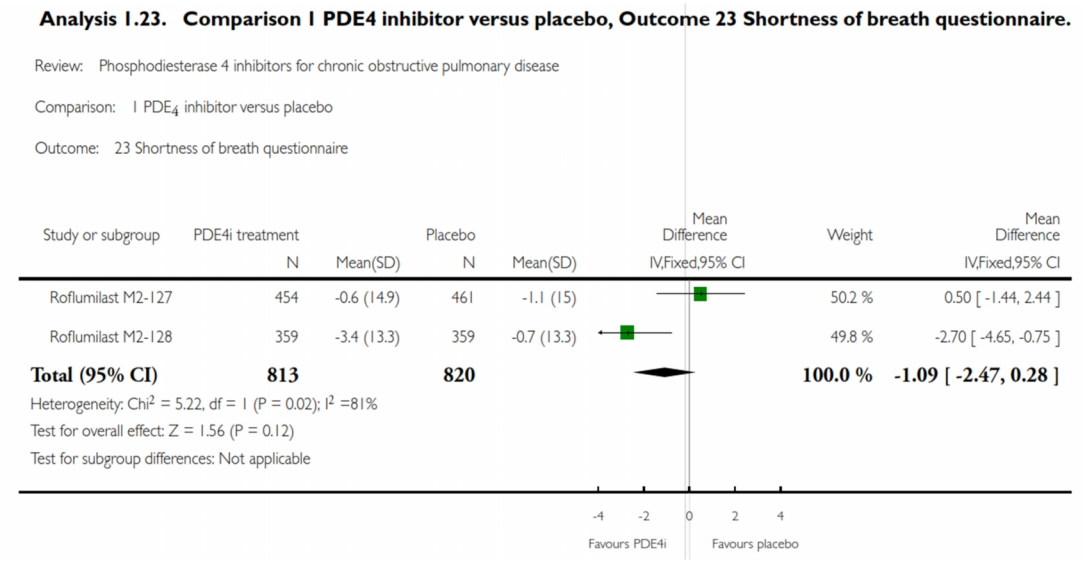
Analysis 5. Comparison 1 Roflumilast versus placebo, Outcome 5 FVC



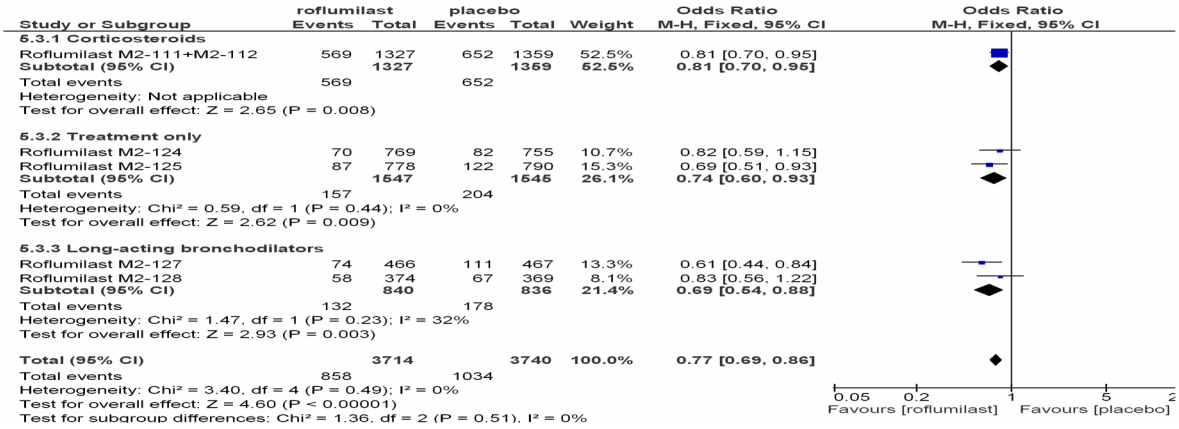
Analysis 6. Comparison 1 Roflumilast versus placebo, Outcome 6 PEF



Analysis 7. Comparison 1 Roflumilast versus placebo, Outcome 7 SOBQ

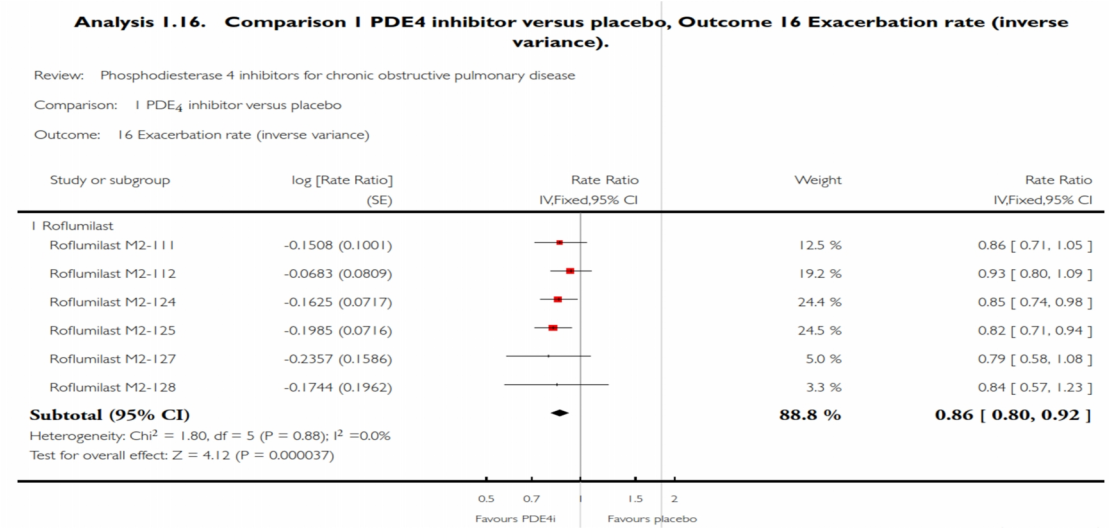


Analysis 8. Comparison 1 Roflumilast versus placebo, Outcome 8 rescue medications



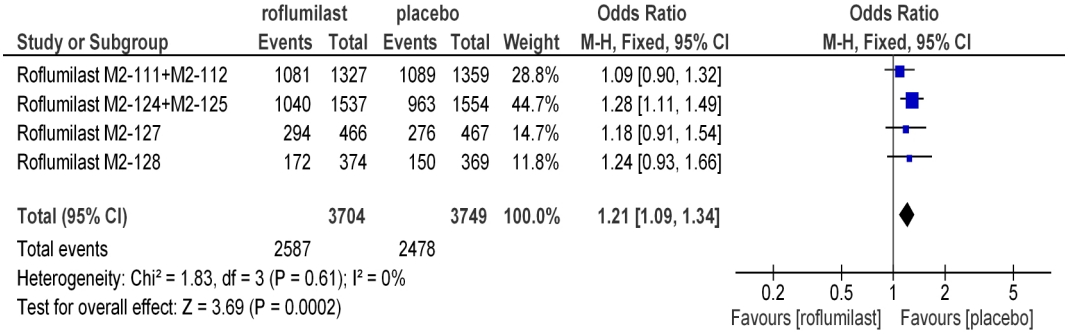
The results of a meta-analysis of safeaty:

Analysis 9. Comparison 1 Roflumilast versus placebo, Outcome 9 Exacerbation rate

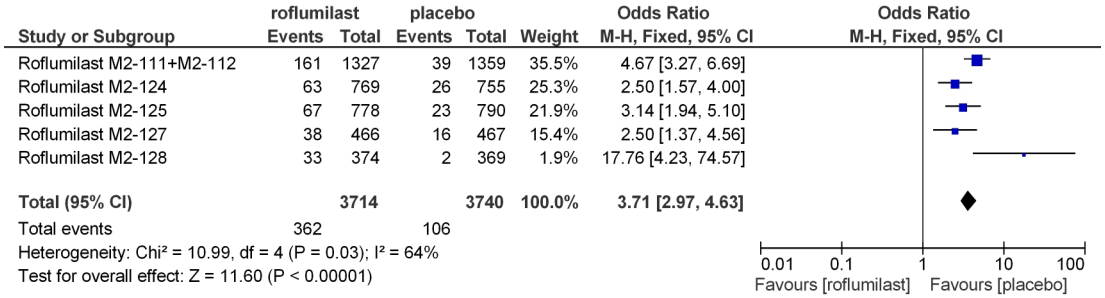


The results of a meta-analysis:

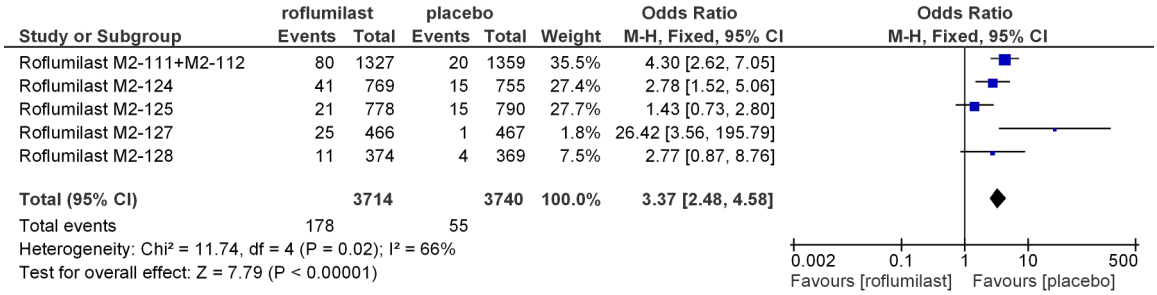
Analysis 10. Comparison 1 Roflumilast versus placebo, Outcome 10 No of patients experiencing an adverse event



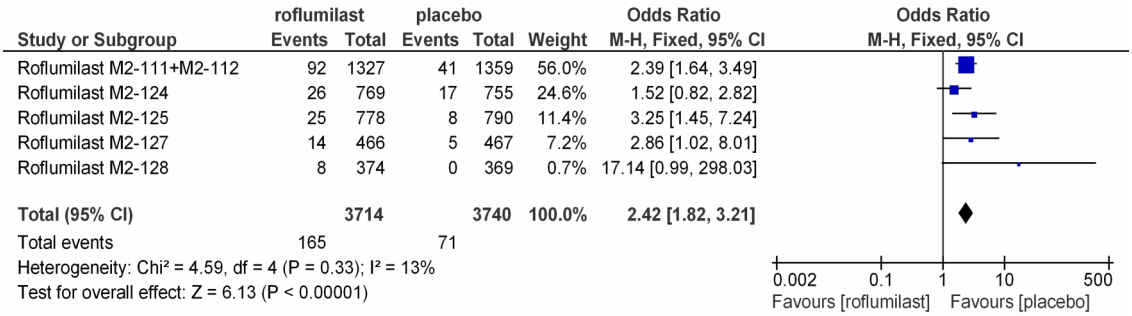
Analysis 11. Comparison 1 Roflumilast versus placebo, Outcome 11 Diarrhoea



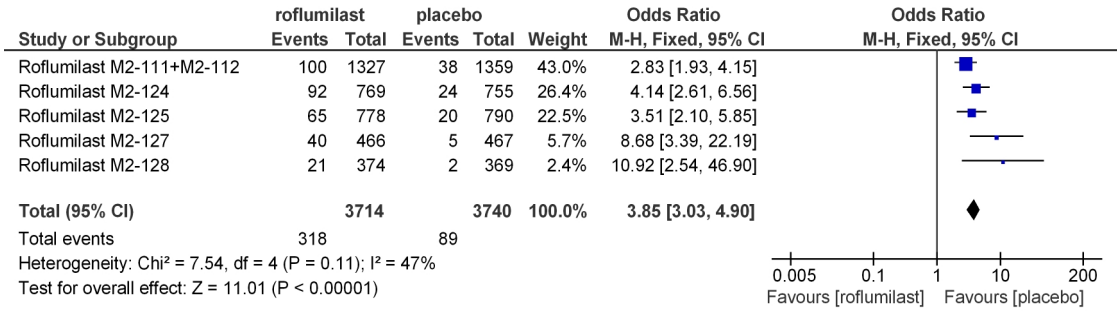
Analysis 12. Comparison 1 Roflumilast versus placebo, Outcome 12 Nausea



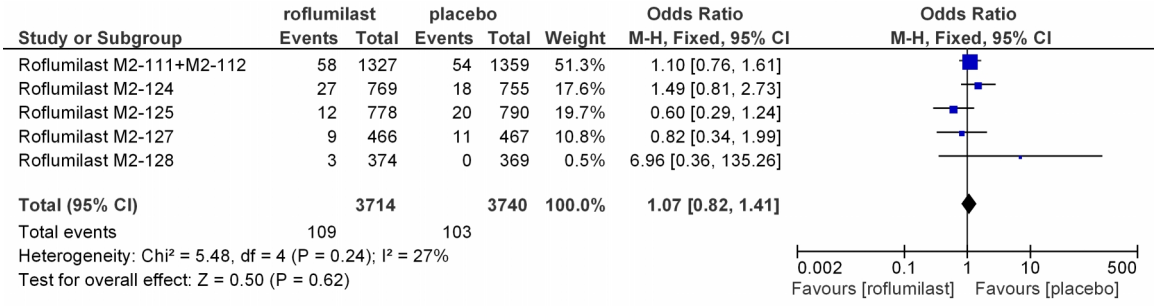
Analysis 13. Comparison 1 Roflumilast versus placebo, Outcome 13 Headache



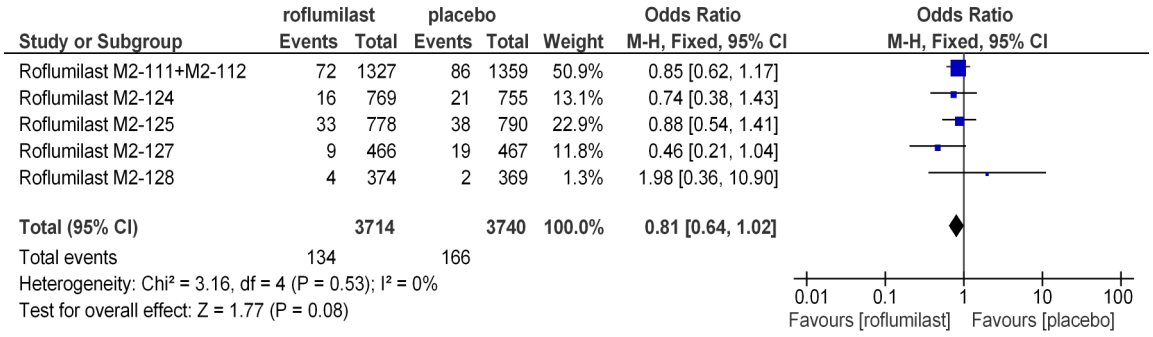
Analysis 14. Comparison 1 Roflumilast versus placebo, Outcome 14 Weight loss



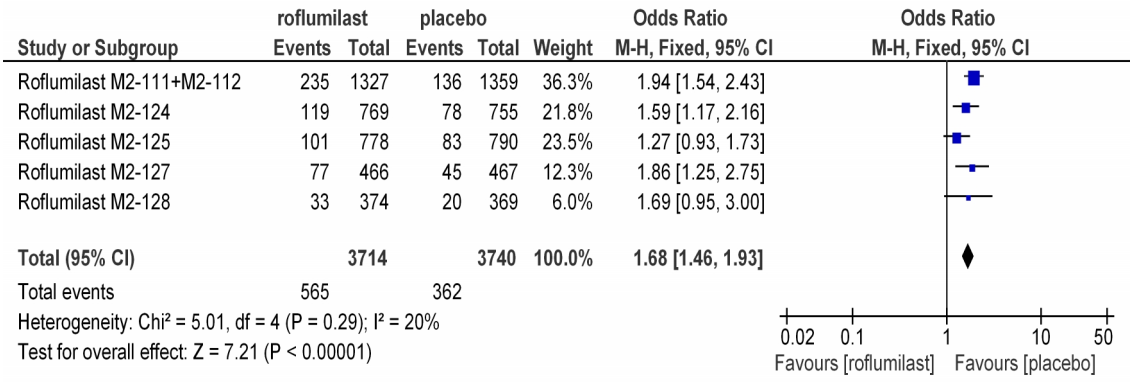
Analysis 15. Comparison 1 Roflumilast versus placebo, Outcome 15 Influenza-like symptoms



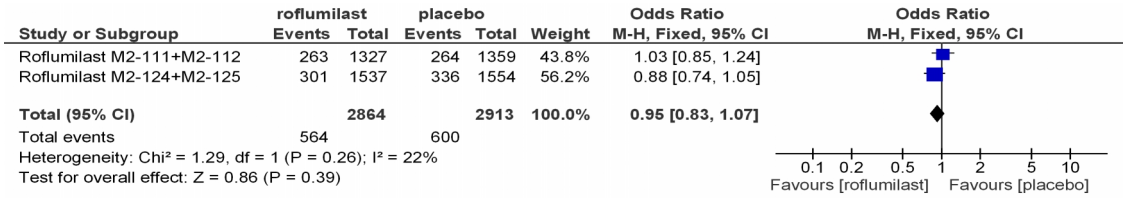
Analysis 16. Comparison 1 Roflumilast versus placebo, Outcome 16 Upper respiratory tract infection



Analysis 17. Comparison 1 Roflumilast versus placebo, Outcome 17 Withdrawals due to adverse events



Analysis 18. Comparison 1 Roflumilast versus placebo, Outcome 18 Non-fatal serious adverse events



Analysis 19. Comparison 1 Roflumilast versus placebo, Outcome 19 Mortality