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 I² > 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.
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 4. How to find clinical effectiveness studies

| Databases       | Keywords                                                                                                                                                                                                 | N. finding |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| PubMed          | (Crepid 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 or Roflumilast or daxas or daliresp or phosphodisterase4 or phosphodisterase 4 or pde4 or pde 4 or pde four or "phosphodisterase 4**" or "pde4**" or tiotropium or spiriva or fluticasone or flutixode or fluticasone salmeterol or advair or seretid 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*). | 773252     |
|                 | Total                                                                                                                                                                                                     | 5344       |
|                 | (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 chronic obstructive disease: ti, ab, kw or Copd or coad: ti, ab, kw (Word variations have been searched)) | 33302      |
| Cochrane        | (Phosphodisterase4 or phosphodisterase 4 or pde4 or pde 4 or pde four or "phosphodisterase 4**" or "pde4**" or Roflumilast or daxas or daliresp: ti, ab, kw (Word variations have been searched)). | 3011066    |
|                 | Total                                                                                                                                                                                                     | 81         |
|                 | (Word variations have been searched)).                                                                                                                                                                    | 13725      |
| CRD             | (Tiotropium or spiriva or fluticasone or flutixode or fluticasone salmeterol or advair or seretid 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-adrenoceptor agonist or long acting beta agonist or long acting*ti, ab, kw (Word variations have been searched))). | 500687     |
|                 | Total                                                                                                                                                                                                     | 20         |
|                 | (Word variations have been searched)).                                                                                                                                                                    | 815        |
| ClinicalTrials.gov | "Copd" AND "roflumilast"                                                                                                                                                                                | 33         |
| ats journals.org |                                                                                                                                                    | 3          |
| Controlled trials.com | (Roflumilast or daxas) and (salmeterol or serevent or tiotropium or spiriva or Formoterol or Foradil or Oxis or Fluticasone or Flutixode or (Fluticasone and salmeterol) or seretid 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 healthcare.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 flutixode OR fluticasone salmeterol OR advair OR seretid 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*))). | 2          |
| chestnet.org |                                                                                                                                                    | 3          |
| Scholar google |                                                                                                                                                    | 3030       |
Table 5. Principal design features and quality survey for studies

| Study | Type       | Design                                                                 | No. Of Pats. | Duration | Eligibility                                                                                                                                                                                                 | Author, year                        | Quality  |
|-------|------------|------------------------------------------------------------------------|--------------|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|----------|
| M2-111| Earlier    | Double-blind, randomized, placebo-controlled, parallel group          | 1,173        | 52 Weeks | • COPD  
• Post-bronchodilator FEV1 % predicted ≤ 50% and FEV1/FVC ≤ 70%.  
• Current or ex-smoker                                                                                       | Clinial Study Report for trial M2-111 | Low risk |
|       | Phase3     | (roflumilast 500 mcg once daily); four week single-blind placebo run-in followed by a treatment period of 52 weeks. ICS allowed. |              |          |                                                                                                                                                                                                           |                                     |          |
| M2-112| Earlier    | Double-blind, randomized, placebo-controlled, parallel group          | 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 |
|       | Phase3     | (roflumilast 500 mcg once daily); four-week single-blind placebo run-in followed by a treatment period of 52 weeks. ICS allowed. |              |          |                                                                                                                                                                                                           |                                     |          |
| M2-111|            | As described in separate studies above                                | 2,686        | 52 Weeks | As described in separate studies above                                                                                                                               | Rennard 2011                      | Low risk |
| + M2-112|            | The datasets combined in a post-hoc, pooled analysis                  |              |          |                                                                                                                                                                                                           |                                     |          |
| (26)  |            |                                                                        |              |          |                                                                                                                                                                                                           |                                     |          |
| M2-124| Pivotal    | Double-blind, randomized, placebo-controlled, parallel group         | 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 |
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Table 6. Documents list out separately exclusion

| Row | Title                                                                 | 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 metanalysis | 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       |

All patients received salmeterol 50 µg BID as underlying treatment.

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.

FEV1 increase ≤ 12% and/or 200 mL after receiving 400 µg salbutamol.

- 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.

Source: http://mjiri.iums.ac.ir
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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 I² statistic to measure heterogeneity among the trials in each analysis. Cochrane systematic review was conducted according to statistics I²>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 β2 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.

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 exacerbation rates in moderate or severe COPD exacerbation was significantly delayed across all patients and in the subgroups using LABA drugs. In the subgroup not receiving LABAs, only the first 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. Roflurilast 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.

Roflurilast 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? Roflurilast 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 nongovernmental 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

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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)

| Study or Subgroup | Roflumilast | Placebo | Mean Difference | Mean Difference |
|-------------------|-------------|---------|----------------|----------------|
|                   | Mean       | SD      | Total          | Mean           | SD      | Total          | Weight | IV, Fixed, 95% CI |
| Roflumilast M2-111| 30 182 545 | -12 178| 596 21.6%      | 42.00 [21.08, 62.02] |
| Roflumilast M2-112| 49 303 760 | -8 302| 733 10.2%      | 57.00 [26.52, 87.48] |
| Roflumilast M2-124| 46 218 745 | 8 218| 745 19.3%      | 38.00 [15.66, 60.14] |
| Roflumilast M2-125| 33 189 730 | -25 194| 766 25.1%      | 58.00 [38.59, 77.41] |
| Roflumilast M2-127| 39 192 456 | -10 193| 460 15.2%      | 49.00 [24.07, 73.93] |
| Roflumilast M2-128| 65 229 365 | -16 229| 364 8.6%       | 81.00 [47.75, 114.25] |
| Total (95% CI)   | 3601       | 3684   | 100.0%        | 51.18 [41.45, 60.90] |

Heterogeneity: $\chi^2 = 5.84, df = 5 (P = 0.32), I^2 = 14%$

Test for overall effect: $Z = 10.31 (P < 0.00001)$

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

| Study or Subgroup | Roflumilast | Placebo | Mean Difference | Mean Difference |
|-------------------|-------------|---------|----------------|----------------|
|                   | Mean       | SD      | Total          | Mean           | SD      | Total          | Weight | IV, Fixed, 95% CI |
| Roflumilast M2-111| 30 182 545 | -12 178| 596 21.6%      | 42.00 [21.08, 62.02] |
| Roflumilast M2-112| 49 303 760 | -8 302| 733 10.2%      | 57.00 [26.52, 87.48] |
| Roflumilast M2-124| 46 218 745 | 8 218| 745 19.3%      | 38.00 [15.66, 60.14] |
| Roflumilast M2-125| 33 189 730 | -25 194| 766 25.1%      | 58.00 [38.59, 77.41] |
| Subtotal (95% CI) | 2780       | 2860   | 76.2%        | 48.26 [37.12, 59.40] |

Heterogeneity: $\chi^2 = 2.45, df = 3 (P = 0.48), I^2 = 0%$

Test for overall effect: $Z = 8.49 (P < 0.00001)$

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

| Study or Subgroup | Roflumilast | Placebo | Mean Difference | Mean Difference |
|-------------------|-------------|---------|----------------|----------------|
|                   | Mean       | SD      | Total          | Mean           | SD      | Total          | Weight | IV, Fixed, 95% CI |
| Roflumilast M2-111| 30 182 545 | -12 178| 596 21.6%      | 42.00 [21.08, 62.02] |
| Roflumilast M2-112| 49 303 760 | -8 302| 733 10.2%      | 57.00 [26.52, 87.48] |
| Roflumilast M2-124| 46 218 745 | 8 218| 745 19.3%      | 38.00 [15.66, 60.14] |
| Roflumilast M2-125| 33 189 730 | -25 194| 766 25.1%      | 58.00 [38.59, 77.41] |
| Subtotal (95% CI) | 2780       | 2860   | 76.2%        | 48.26 [37.12, 59.40] |

Heterogeneity: $\chi^2 = 5.84, df = 5 (P = 0.32), I^2 = 14%$

Test for overall effect: $Z = 10.31 (P < 0.00001)$

Test for subgroups: $\chi^2 = 1.11, df = 1 (P = 0.29), I^2 = 9.5%$
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### Analysis 4. Comparison 1 Roflumilast versus placebo, Outcome 4 FEV1 (Concomitant medications)

| Study or Subgroup | roflumilast | placebo | Mean Difference IV, Fixed, 95% CI |
|-------------------|-------------|---------|----------------------------------|
| Corticosteroids   |             |         |                                  |
| Roflumilast M2-111| 30          | 182     | 545                              |
| Roflumilast M2-112| 49          | 303     | 760                              |
| Subtotal (95% CI)| 1305        |         | 1349                             |
| Heterogeneity: Chi² = 0.63, df = 1 (P = 0.43); I² = 0% |
| Test for overall effect: Z = 5.32 (P < 0.00001) |

| PDE4i treatment only |
|----------------------|
| Roflumilast M2-124   | 46          | 218     | 745                              |
| Roflumilast M2-125   | 33          | 189     | 730                              |
| Subtotal (95% CI)    | 1475        |         | 1611                             |
| Heterogeneity: Chi² = 1.77, df = 1 (P = 0.19); I² = 44% |
| Test for overall effect: Z = 6.62 (P < 0.00001) |

| Long-acting bronchodilator |
|----------------------------|
| Roflumilast M2-127         | 39          | 192     | 466                              |
| Roflumilast M2-128         | 65          | 229     | 365                              |
| Subtotal (95% CI)          | 821         |         | 834                              |
| Heterogeneity: Chi² = 2.28, df = 1 (P = 0.13); I² = 56% |
| Test for overall effect: Z = 5.95 (P < 0.00001) |

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

| Study or Subgroup | roflumilast | placebo | Mean Difference IV, Fixed, 95% CI |
|-------------------|-------------|---------|----------------------------------|
| Roflumilast M2-111| -33         | 716     | 760                              |
| Roflumilast M2-124| 76          | 405     | 729                              |
| Roflumilast M2-125| 58          | 350     | 724                              |
| Roflumilast M2-127| 67          | 319     | 452                              |
| Roflumilast M2-128| 27          | 439     | 364                              |
| Total (95% CI)    | 3029        |         | 3059                             |
| Heterogeneity: Chi² = 4.55, df = 4 (P = 0.34); I² = 12% |
| Test for overall effect: Z = 8.27 (P < 0.00001) |

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

| Study or Subgroup | roflumilast | placebo | Mean Difference IV, Fixed, 95% CI |
|-------------------|-------------|---------|----------------------------------|
| Roflumilast M2-124| 8.08        | 40.5    | 729                              |
| Roflumilast M2-125| 1.93        | 40.1    | 724                              |
| Total (95% CI)    | 1453        |         | 1500                             |
| Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² = 0% |
| Test for overall effect: Z = 3.14 (P = 0.002) |

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

The results of a meta-analysis of safety:
Analysis 9. Comparison 1 Roflumilast versus placebo, Outcome 9 Exacerbation rate
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Analysis 14. Comparison 1 Roflumilast versus placebo, Outcome 14 Weight loss

| Study or Subgroup       | roflumilast Events | placebo Events | Total Events | M-H Fixed, 95% CI | Odds Ratio     |
|-------------------------|--------------------|----------------|--------------|-------------------|----------------|
| Roflumilast M2-111+M2-112 | 100                | 38             | 1359         | 43.0%             | 2.83 [1.93, 4.15] |
| Roflumilast M2-124       | 92                 | 24             | 755          | 26.4%             | 4.14 [2.61, 6.56] |
| Roflumilast M2-126       | 65                 | 20             | 790          | 22.5%             | 3.51 [2.10, 5.85] |
| Roflumilast M2-127       | 40                 | 5              | 467          | 5.7%              | 8.68 [3.36, 22.19] |
| Roflumilast M2-128       | 21                 | 2              | 369          | 2.4%              | 10.92 [2.54, 46.90] |
| Total (95% CI)           | 3714               | 3740           | 100.0%       |                   | 3.85 [3.03, 4.90] |
| Total events             | 318                | 89             |              |                   |                |

Heterogeneity: Chi² = 7.54, df = 4 (P = 0.11); I² = 47%
Test for overall effect: Z = 11.01 (P < 0.00001)

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

| Study or Subgroup       | roflumilast Events | placebo Events | Total Events | M-H Fixed, 95% CI | Odds Ratio     |
|-------------------------|--------------------|----------------|--------------|-------------------|----------------|
| Roflumilast M2-111+M2-112 | 58                 | 54             | 1359         | 51.3%             | 1.10 [0.76, 1.61] |
| Roflumilast M2-124       | 27                 | 18             | 755          | 17.6%             | 1.49 [0.81, 2.73] |
| Roflumilast M2-125       | 12                 | 20             | 790          | 19.7%             | 0.60 [0.26, 1.24] |
| Roflumilast M2-127       | 9                  | 11             | 467          | 10.8%             | 0.82 [0.34, 1.99] |
| Roflumilast M2-128       | 3                  | 0              | 369          | 0.5%              | 6.96 [0.36, 135.26] |
| Total (95% CI)           | 3714               | 3740           | 100.0%       |                   | 1.67 [0.82, 1.41] |
| Total events             | 100                | 103            |              |                   |                |

Heterogeneity: Chi² = 5.48, df = 4 (P = 0.24); I² = 27%
Test for overall effect: Z = 0.50 (P = 0.62)

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

| Study or Subgroup       | roflumilast Events | placebo Events | Total Events | M-H Fixed, 95% CI | Odds Ratio     |
|-------------------------|--------------------|----------------|--------------|-------------------|----------------|
| Roflumilast M2-111+M2-112 | 72                 | 86             | 1359         | 50.9%             | 0.85 [0.62, 1.17] |
| Roflumilast M2-124       | 16                 | 21             | 755          | 13.1%             | 0.74 [0.38, 1.43] |
| Roflumilast M2-125       | 33                 | 38             | 790          | 22.9%             | 0.88 [0.54, 1.41] |
| Roflumilast M2-127       | 9                  | 19             | 467          | 11.8%             | 0.46 [0.21, 1.04] |
| Roflumilast M2-128       | 4                  | 2              | 369          | 1.3%              | 1.98 [0.36, 10.90] |
| Total (95% CI)           | 3714               | 3740           | 100.0%       |                   | 0.81 [0.64, 1.02] |
| Total events             | 134                | 166            |              |                   |                |

Heterogeneity: Chi² = 3.16, df = 4 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)
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Analysis 17. Comparison 1 Roflumilast versus placebo, Outcome 17 Withdrawals due to adverse events

| Study or Subgroup | roflumilast | placebo | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|------------|---------|-------------------------------|
| Roflumilast M2-111+M2-112 | 235 (1327, 136) | 1359 (36.3%) | 1.94 [1.54, 2.43] |
| Roflumilast M2-124 | 119 (769, 78) | 755 (21.8%) | 1.59 [1.17, 2.16] |
| Roflumilast M2-125 | 101 (778, 83) | 790 (23.5%) | 1.27 [0.93, 1.73] |
| Roflumilast M2-127 | 77 (466, 45) | 467 (12.3%) | 1.66 [1.25, 2.76] |
| Roflumilast M2-128 | 33 (374, 20) | 369 (6.0%) | 1.69 [0.95, 3.00] |
| Total (95% CI) | 3714 (3740, 100.0%) | | 1.68 [1.46, 1.93] |

Total events 565 362
Heterogeneity: Chi² = 5.01, df = 4 (P = 0.28); I² = 20%
Test for overall effect: Z = 7.21 (P < 0.00001)

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

| Study or Subgroup | roflumilast | placebo | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|------------|---------|-------------------------------|
| Roflumilast M2-111+M2-112 | 263 (1327, 264) | 1559 (43.8%) | 1.03 [0.85, 1.24] |
| Roflumilast M2-124+M2-125 | 301 (1537, 336) | 1554 (56.2%) | 0.88 [0.74, 1.05] |
| Total (95% CI) | 2864 (2913, 100.0%) | | 0.98 [0.83, 1.17] |

Total events 564 600
Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² = 22%
Test for overall effect: Z = 0.86 (P = 0.39)

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

| Study or Subgroup | roflumilast | placebo | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|------------|---------|-------------------------------|
| Roflumilast M2-111+M2-112 | 22 (1327, 32) | 1259 (40.7%) | 0.70 [0.40, 1.21] |
| Roflumilast M2-124 | 17 (769, 17) | 755 (22.0%) | 0.98 [0.50, 1.94] |
| Roflumilast M2-125 | 25 (778, 25) | 790 (31.5%) | 1.02 [0.58, 1.78] |
| Roflumilast M2-127 | 5 (466, 4) | 467 (5.2%) | 1.26 [0.34, 4.76] |
| Roflumilast M2-128 | 2 (374, 0) | 369 (0.7%) | 4.96 [0.24, 103.66] |
| Total (95% CI) | 3714 (3740, 100.0%) | | 0.92 [0.66, 1.27] |

Total events 71 79
Heterogeneity: Chi² = 2.51, df = 4 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.60)