CLINICAL
INVESTIGATION

Roflumilast for the treatment of respiratory disease: review of the Phase II and III trials

Roflumilast (Daxas® [EU], Daliresp® [USA]) is the first phosphodiesterase 4 inhibitor approved in Europe to be used in severe chronic obstructive pulmonary disease (COPD). Its preclinical evaluation streamed its subsequent clinical development towards COPD based on the prominent anti-inflammatory activities demonstrated in various preclinical models of COPD. Its clinical development was based mainly on Phase III studies initially performed in COPD patients with various stages of disease severity and then focused on severe COPD patients with chronic bronchitis. On both a short- and long-term basis, roflumilast was demonstrated to reduce the incidence of moderate to severe COPD exacerbations and to improve lung function. This article discusses the clinical relevance of the data coming from Phase II and III studies and raises some issues related to the use of roflumilast in COPD.

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Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the airways and lung parenchyma caused by various noxious agents, such as smoking, characterized by accelerated lung function decline, and chronic respiratory symptoms, such as dyspnea and productive cough. The existing therapies reduce disease exacerbations, improve disease symptoms and increase QOL, but do not have a significant impact on lung function decline [101]. In particular, the anti-inflammatory therapies represented by inhaled corticosteroids (ICS) have a greater efficacy compared with asthma and are able to sever the airways inflammation especially in more advanced COPD [101].

Asthma is another chronic inflammatory disease of the airways, which is heavily related to allergies and can be diagnosed at all age groups. In asthma, inflammation can be tackled with ICS and cysteinil leukotriene inhibitors but sometimes these medications are not enough to optimally control the disease. Therefore, other more efficacious therapies should be developed in order to appropriately minimize the inflammatory burden of the disease.

Phosphodiesterase (PDE) 4 isoenzymes belong to the larger PDE family that is ubiquitously expressed and hydrolyzes cAMP. PDE4 are expressed in lung structural cells, such as smooth muscle cells and airway epithelium, and inflammatory cells, such as neutrophils, lymphocytes or macrophages [1,2]

PDE4 isoenzymes have emerged over the past two decades as a potential therapeutic target in asthma and COPD, based on the assumption that they have more potent bronchodilating effects. Consequently, PDE4 inhibitors such as rolipram, cilomilast or roflumilast have been developed. Among them, only roflumilast demonstrated subsequently more prominent anti-inflammatory activities, which were demonstrated in various preclinical models of COPD and were developed clinically for this disease [3].

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Roflumilast (Daxas®, Nycomed) has been approved since 2010 in Europe for the treatment of severe COPD (forced expiratory volume in 1 s [FEV_1] % predicted below 50%) associated with chronic bronchitis in adult patients with a history of frequent exacerbations in combination with bronchodilator treatment [102].

This article discusses the results of Phase II and III studies and their relevance for the present therapeutic indication.

Phase II & III studies with roflumilast in asthma

In asthma, the clinical development of roflumilast was initially based on a few clinical studies. In a Phase II/III study, 693 patients were randomized to receive 100, 250 or 500 µg of roflumilast once daily for 12 weeks after a 1- to 3-week placebo run-in period. The primary end point was represented by the change from baseline in FEV_1 whereas the secondary end points included change from baseline in morning and evening peak expiratory flow. Roflumilast significantly increased lung function by 260 ml with 100 µg, 320 ml with 250 µg and 400 ml with 500 µg, as compared with baseline (p < 0.001). Roflumilast 500 µg, was significantly superior to roflumilast 100 µg on morning FEV_1 (p = 0.002). Roflumilast also significantly improved peak expiratory flow. Roflumilast was well tolerated at all doses tested [4].

Initial Phase II studies in COPD

The clinical data supporting roflumilast use in COPD comes from several short- and long-term Phase II and III clinical studies, which focused on its effects on lung function, exacerbations, airways inflammation and health status, as well as on adverse effects.

An earlier clinical crossover Phase II study enrolled 38 patients with COPD and mean age 63.1 years, and postbronchodilator (FEV_1) percent predicted of 61% who received 500 µg roflumilast or placebo once daily for 4 weeks: roflumilast significantly reduced the sputum neutrophils count by 35.5% (p = 0.002) and eosinophils count by 50.0% (p < 0.001), compared with placebo. Sputum neutrophil and eosinophil counts were not found to be significantly influenced by the treatment. Roflumilast significantly improved the postbronchodilator FEV_1 during roflumilast compared with placebo, the mean difference between treatments being found to be 68.7 ml (p = 0.018). Roflumilast significantly reduced IL-8, neutrophil elastase, eosinophil cationic protein and $\alpha(2)$-macroglobulin levels in sputum, as well as the release of TNF-α from blood cells compared with placebo [5].

Early 6-month Phase III study: the RECORD study

A subsequent Phase III, multicenter, double-blind randomized, placebo-controlled study (The RECORD, M 2–107) enrolled 1411 patients to receive roflumilast 250 µg (n = 576), roflumilast 500 µg (n = 555) or placebo (n = 280) orally once daily for 24 weeks. Primary end points were represented by postbronchodilator FEV_1 and health-related QOL, whereas secondary end points included other lung function parameters and COPD exacerbations. A total of 32 (11%) patients withdrew from the placebo group, 100 (17%) from the roflumilast 250 µg group, and 124 (22%) from the roflumilast 500 µg group. In the intention-to-treat analysis, which included 1157 (82%) patients who completed the study, roflumilast at both dosages was found to improve the postbronchodilator FEV_1 at the end of treatment; roflumilast 250 µg by 74 ml and roflumilast 500 µg by 97 ml when each compared with placebo (p < 0.0001). Roflumilast 250 and 500 µg improved the health status when compared with placebo (-3.4 and 3.5 units respectively compared with -1.8 units), but these effects were neither statistically nor clinically significant. Roflumilast 500 µg had the most significant effect on the exacerbation rate; the patients in this treatment group had the lowest number of COPD exacerbations (1.13 in placebo group; 1.03 in roflumilast 250 µg and 0.75 in roflumilast 500 µg), mainly due to the reduction of the number of mild exacerbations (42% reduction of the number of mild exacerbations in roflumilast 500 µg as compared with placebo) [6].

The adverse events most commonly reported were moderate and severe COPD exacerbations and nasopharyngitis, which, however, had comparable incidences in the active treatment groups and in placebo. Diarrhea (2–6%), nausea (1–3%) and headache (1–2%) were the most common medication-related adverse events reported in roflumilast-treated patients [6].

Other Phase II/III or Phase III studies were performed with roflumilast (Table 1). These studies were performed in various populations and most of them evaluated the effects of 24 weeks roflumilast therapy mainly on lung function, exacerbation rate, QOL and respiratory symptoms, but their results are not known.

The following studies were all Phase III trials evaluating a single dosage of roflumilast 500 µg (the dosage subsequently put forward as a therapeutic dose) in 24 or 52 week duration periods against placebo or against bronchodilators, such as salmeterol or tiotropium.

Early 1-year Phase III studies: the OPUS & RATIO studies

The OPUS (M2-111) and the RATIO (M2-112) were two replicate, randomized, double-blind, placebo controlled Phase III studies evaluating the effects of oral roflumilast 500 µg versus placebo once daily for 52 weeks in COPD patients with severe to very severe disease [7,8].

Table 1. Other completed clinical trials with roflumilast in chronic obstructive pulmonary disease and asthma.					
Study	Phase	Duration (weeks)	Primary end point	Roflumilast dose (µg)	Estimated enrollment
The HERO study: effects of roflumilast in patients with COPD (BY217/M2-121)	III	24	Lung hyperinflation	500	550
Efficacy and safety of roflumilast in Japanese patients older than 40 years with COPD (APTA-2217-06)	II/III	24	Change in post bronchodilator FEV_1	n/a	570
Effect of roflumilast on pulmonary function and respiratory symptoms in patients with COPD (BY217/M2-110)	III	24	Pulmonary function	500	1000
Long-term study of safety and efficacy of roflumilast in Japanese patients older than 40 years with COPD (APTA-2217-08)	III	52	Long-term safety after 28 weeks treatment of roflumilast	n/a	150
The JADE Study. Efficacy and safety of oral roflumilast taken once daily in patients older than 40 years with COPD (BY217/M2-119)	III	12	Mean change from randomization to end point in lung function (postbronchodilator)	500	551
Efficacy and safety of roflumilast taken in the morning or evening in patients with stable asthma (12–70 years) (BY217/M2-015)	III	6	Mean change from randomization to end point in FEV_1	500	511
The FLASH Study: a study of roflumilast versus placebo in patients with asthma (BY217/M2-023)	III	n/a	Change in lung function	250, 500	822
Efficacy and safety of oral roflumilast taken with low dose inhaled corticosteroids in patients with asthma (12–70 years) (BY217/M2-013)	III	24	Change in FEV_1 from baseline to final visit	500	2054
Long-term study of safety and efficacy of roflumilast in Japanese patients with bronchial asthma (20–71 years) (APTA-2217-07)	III	28	Long-term safety after 28 weeks treatment of roflumilast at (total 52 weeks, 24 weeks of study APTA-2217–05 followed by 28 weeks)	n/a	150

COPD: Chronic obstructive pulmonary disease; FEV_1: Forced expiratory volume in 1 s; n/a: Not available.
Data taken from [107].

In the RATIO study a total of 1513 patients with a mean postbronchodilator FEV_1% predicted of 41% were enrolled. The primary efficacy end points were represented by postbronchodilator FEV_1 and by exacerbation rate, whereas the secondary end point was the health status (QOL measured with the Saint George Respiratory Questionnaire scores) [7,103]. Roflumilast significantly increased the postbronchodilator FEV_1 (39 ml; p = 0.001) but failed to significantly improve the exacerbation rate and the health status. However, in the subset of patients with the GOLD IV stage of the disease, roflumilast was found to significantly reduce the exacerbation rate (1.01 vs 1.59; p = 0.024) [7]. Diarrhea, nausea and headache were adverse events found to be related to roflumilast therapy, but these were reported to diminish with treatment continuation.

In a *post hoc* pooled analysis performed on the total sample of 2686 patients enrolled in the OPUS and the RATIO studies (1327 receiving roflumilast and 1359 receiving placebo) having a mean postbronchodilator FEV_1 of 37.1% in roflumilast population and 36.8% in placebo population, roflumilast was found to have the maximum therapeutic benefit in the 'clinical' COPD phenotype of chronic bronchitis, who were frequent exacerbators and had a postbronchodilator FEV_1 <50%. In this subset, roflumilast was found to reduce the exacerbation rate by approximately 26% (p = 0.001) as compared with placebo, whereas in the subset with emphysema its effect was comparable to that of placebo [8,9,103,104].

Given that in each of the aforementioned studies roflumilast was found to have no significant effect on exacerbation rate, the *post hoc* analysis previously mentioned

was performed in order to better document the overall potential of reducing the exacerbation rate – roflumilast significantly decreased exacerbations by 14.3% compared with placebo (p = 0.026). Features associated with this reduction were presence of chronic bronchitis with or without emphysema (26.2% decrease; p = 0.001), presence of cough (20.9% decrease; p = 0.006), presence of sputum (17.8% decrease; p = 0.03) and concurrent use of ICS (18.8% decrease; p = 0.014) [8,9,103,104].

Roflumilast had no significant therapeutic effect on the median time to first moderate or severe exacerbation when compared with placebo (120 and 126 days, respectively; p = 0.236). Roflumilast was found to significantly reduce the moderate or severe exacerbation rate as compared with placebo in males (0.495 with roflumilast vs 0.609 with placebo; p = 0.018), in patients receiving short-acting anticholinergics (0.706 with roflumilast vs 0.86 with placebo; p = 0.012), ICS (0.72 with roflumilast vs 0.886 with placebo; p = 0.014), in patients with chronic bronchitis with or without emphysema (0.486 with roflumilast vs 0.659 with placebo; p = 0.001), in patients with chronic bronchitis with or without emphysema and who used ICS concomitantly (0.608 with roflumilast vs 0.871; p = 0.001), cough score ≥1 (average/day) at baseline (0.560 with roflumilast vs 0.708 with placebo; p = 0.006), sputum score ≥1 (average/day) at baseline (0.576 with roflumilast vs 0.700 with placebo; p = 0.030) and in patients who completed the study (0.453 with roflumilast vs 0.573 with placebo; p = 0.004) [8].

In the same analysis, roflumilast was also found to significantly improve the prebronchodilator FEV_1 when compared with placebo, this effect being evident initially at week 4 and being maintained throughout the whole study period [8]. The change in prebronchodilator FEV_1 at 52 weeks as compared with baseline roflumilast versus placebo was 51 ml (p < 0.0001), whereas the similar change in postbronchodilator FEV_1 with roflumilast versus placebo was 53 ml (p < 0.0001). Unlike exacerbations, prebronchodilator and postbronchodilator FEV_1 were found to be significantly improved with roflumilast compared with placebo in all subgroups. In the group of patients with COPD, chronic bronchitis or combined emphysema and chronic bronchitis, the greatest effect of roflumilast on prebronchodilator FEV_1 as compared with placebo was found in patients receiving ICS and was 53 ml (p < 0.0001) [8].

In this analysis, roflumilast had no significant effect on health status as compared with placebo. In patients with chronic bronchitis, however, and in patients with concomitant therapy with ICS, roflumilast significantly improved the health status as compared with placebo (p = 0.0265 for chronic bronchitis and p = 0.0397) [7].

Phase III studies: the AURA & HERMES studies

The AURA (M-124) and the HERMES (M-125) studies were two paired placebo-controlled, double-blind, multicenter Phase III studies performed in patients with severe and very severe COPD (postbronchodilator FEV_1 <50%) with a chronic bronchitis phenotype, having cough and sputum production and at least one exacerbation requiring systemic corticosteroids in the previous year [8].

These studies are the most recently performed and the population selected is very similar to the disease subset for which roflumilast was subsequently approved to be used on the market.

During the initial 4 week run-in period, eligible patients were given a placebo tablet once a day and had the use of short-acting bronchodilators, as well as cough and sputum production recorded. Subsequently, they were randomized to receive either roflumilast 500 μg or placebo once daily for the next 52 weeks and were allowed to take short- and long-acting β2 agonists, but not long-acting anticholinergics or ICS. The primary end points were represented by the change from baseline in prebronchodilator FEV_1 and the rate of moderate and severe COPD exacerbations. Among the secondary end points, change from baseline in postbronchodilator FEV_1, time to death, systemic inflammation (assessed with C reactive protein [CRP]), health utility scores and dyspnea change over study the period were other efficacy end points. Safety end points were also considered [10,105,106].

In the AURA study there were 1523 patients: 765 in roflumilast arm and 758 in placebo arm, whereas in the HERMES study there were 1568 patients: 772 in the roflumilast arm and 796 in the placebo arm. A total of 1537 patients received roflumilast and 1554 received placebo (pooled analysis) in both studies. Roflumilast was found to improve the primary end points in each study and in pooled analysis of both studies: prebronchodilator FEV_1 39 ml (p = 0.0003) in AURA study, 58 ml (p < 0.0001) in HERMES study and 48 ml (p < 0.0001) in both studies, moderate or severe exacerbation rate 1.08 versus 1.27 (p = 0.0278) in the AURA study, 1.21 versus 1.49 (p = 0.0035) in the HERMES study and 1.14 versus 1.37 (p = 0.0003) in both studies [10]. The therapeutic effect of roflumilast on exacerbations was manifested mainly on the moderately severe COPD exacerbations, whereas the therapeutic effect on the severe type was not significant compared with that of placebo. Roflumilast also significantly improved the postbronchodilator FEV_1 and reduced dyspnea severity but there were no significant changes in systemic inflammation (CRP), time to death or health utility scores [10].

In the pooled analysis, adverse events were reported in 1040 patients (67%) receiving roflumilast and 963 patients (62%) receiving placebo and the most frequent adverse events leading to roflumilast discontinuation were represented by nausea, diarrhea and headache [10].

Another pooled analysis evaluated the efficacy and safety of roflumilast in the elderly, specifically age >65 years patients with COPD [11]. Main outcome measures were represented by moderate or severe exacerbations and by changes from baseline in pre- and postbronchodilator FEV_1. In the total sample of 3091 patients there were 878 patients aged ≤65 years ('younger') and 659 aged >65 years ('older') who were randomized to receive roflumilast and 883 patients aged ≤65 years and 671 aged >65 years who were randomized to receive placebo. Roflumilast significantly reduced moderate or severe exacerbation rates compared with placebo in both younger (15.3%; p = 0.0128) and older patients (21.2%; p = 0.0035). Similarly, it improved pre- and postbronchodilator FEV_1 at all time points versus placebo in both age groups (p < 0.0001). Prebronchodilator FEV_1 increase at the end of the study was of 50 ml and 49 ml over placebo (both p < 0.0001) in younger and older patients treated with roflumilast. Postbronchodilator FEV_1, increased with 55 ml and 57 ml over placebo (both p < 0.0001) in younger and older patients. The incidence of each adverse event reported throughout the study was higher in older than with younger patients, but differences between the roflumilast and placebo arms remained consistent for both age groups [11].

The same outcome measures as above were compared between current and ex-smokers. In the total sample of 3091 patients, 635 current and 902 ex-smokers received roflumilast, whereas 643 current and 911 ex-smokers received placebo [12]. The current smokers group had more younger patients, fewer males, fewer patients with very severe disease and fewer patients treated during the study with long-acting β2 agonists or prior to the study with ICS as compared with the ex-smokers. Roflumilast therapy significantly reduced the rate of moderate or severe exacerbations by 17.7% (p = 0.0180) in the current smokers group. In the ex-smokers group, roflumilast treatment also reduced the rate of exacerbations by 18.4% (p = 0.0023) versus placebo. Treatment with roflumilast significantly improved both pre- and postbronchodilator FEV_1 at all time points versus placebo (p < 0.001), regardless of smoking status. The increase in prebronchodilator FEV_1 was 44 ml (p = 0.0002) in current smokers and 52 ml (p < 0.0001) in ex-smokers compared with placebo. Postbronchodilator FEV_1, increased with 57 ml in current smokers and with 54 ml in ex-smokers compared with placebo (both p < 0.0001). The incidences of adverse events of any category were higher in ex-smokers compared with current smokers. Differences between roflumilast and placebo arms remained consistent for both groups [12].

Phase III studies: the EOS & HELIOS studies

The EOS and HELIOS were 6-month supplementary Phase III studies evaluating the efficacy and safety of roflumilast versus placebo in patients with moderate to severe COPD receiving long-acting bronchodilators, such as salmeterol (EOS, M2-127) or tiotropium (HELIOS, M2-128). Included were patients with stable COPD, current or ex-smokers with a smoking history of at least ten packs per year and postbronchodilator FEV_1 % predicted 40–70%. Other, more specific inclusion criteria for M2-128 were the presence of respiratory symptoms of chronic bronchitis, such as chronic cough and sputum production, and by the frequent use of β2 agonists while being on tiotropium therapy at least during the last 3 months [13].

During the initial 4-week run-in period, patients received a placebo tablet once daily and if no moderate to severe COPD exacerbation developed during this period, the eligible patients were randomized to either roflumilast 500 μg once daily in the morning or placebo for 24 weeks [13].

The primary end point in both studies was represented by change from baseline in prebronchodilator FEV_1, whereas among the secondary end points included were postbronchodilator FEV_1, FVC, TDI score, the Shortness of Breath Questionnaire, exacerbation rate and the use of rescue medications. Safety was also assessed. The EOS study enrolled 933 patients, 466 in the treatment and 467 in the placebo arms, whereas the HELIOS study enrolled 743 patients 371 in the treatment and 372 in the placebo arm. In both studies the COPD populations evaluated were uniform in terms of age, male predominance, the higher prevalence of ex-smokers and the adherence rate. The two populations differed only in terms of use of rescue medication which was higher at baseline in the HELIOS study. Furthermore, in the HELIOS study all patients presented with chronic cough and sputum [13].

In both trials the probability of withdrawal from the study was higher in patients receiving roflumilast and was significantly higher in patients receiving concomitant therapy with salmeterol. Roflumilast was demonstrated to improve lung function overall by increasing the pre- and postbronchodilator FEV_1 and pre- and postbronchodilator FVC. The FEV_1 improvements were demonstrated to be produced in all disease severity subsets and irrespective of the smoking status.

In the EOS study, roflumilast was also found to significantly increase the median time to first moderate or severe COPD exacerbation, and to significantly reduce

the proportion of patients experiencing an exacerbation of any severity throughout the study period in general, and the proportion of patients with moderate or severe exacerbation in particular.

In the HELIOS study, roflumilast significantly reduced the overall proportion of patients with an exacerbation of any severity and significantly prolonged the median time to first exacerbation; it also decreased dyspnea severity, also significantly reducing the use of rescue medication [13].

Clinical safety data

Digestive side effects, such as nausea and diarrhea, have been described with PDE4 inhibitors so far. These effects are usually mild or moderate in intensity, occur within the first weeks and commonly disappear while the treatment continues [1].

In clinical studies with roflumilast, the incidence of adverse events was found to be approximately 16% with roflumilast compared with 5% with placebo. Among the adverse reactions, the most commonly reported were: diarrhea (5.9%), weight loss (3.4%), nausea (2.9%), abdominal pain (1.9%) and headache (1.7%) [102]. Roflumilast therapy was reported to be associated with an increased risk of psychiatric disorders such as insomnia, anxiety, nervousness and depression [102]. Suicidal ideation and behavior as well as mood changes were also rarely detected in clinical trials, and based on these findings roflumilast is not recommended in patients with a history of depression associated with suicidal ideation or behavior [102].

In terms of cardiovascular safety, a pooled analysis of the safety data from the 14 placebo-controlled trials of 12–52 weeks duration performed in patients with moderate to severe COPD found that, in the 12,054 patients included (6563 roflumilast, 5491 placebo), the rate of the major adverse cardiovascular events including altogether CV death, nonfatal myocardial infarction and nonfatal stroke was lower with roflumilast than with placebo (hazard ratio: 0.66; 95% CI: 0.46–0.95; $p = 0.0235$). The individual hazard of first nonfatal myocardial infarction, nonfatal stroke and CV death were reduced with roflumilast compared with placebo [14] .

Future perspective

Roflumilast was evaluated in a large range of clinical studies in various populations including very severe COPD, elderly with COPD or current smokers with COPD. It demonstrated its beneficial therapeutic effect on lung function and moderate or severe exacerbations. The fact that it was authorized as an add on to bronchodilator therapy reflects the benefit in lung function, which was the highest in patients taking concomitantly long-acting bronchodilators, such as LABAs or LAMAs. Such results support its current therapeutic indication for which roflumilast is approved in Europe, as well as its subsequent authorization in the USA.

However, there are still some issues related to its use in a COPD clinical setting. For example, given that COPD is a chronic disease in which airways inflammation also becomes systemic, it would be very useful to know if roflumilast (as an anti-inflammatory therapy) is able to tackle the systemic inflammation as well.

Another issue is represented by the appropriateness of the use of roflumilast as a standalone therapy in milder COPD patients, or in patients with chronic bronchitis only. In the latter case, demonstration of the delay in COPD development would be a strong argument in favor of roflumilast use in patients without COPD.

PDE4 inhibitors were initially evaluated in parallel for both asthma and COPD as bronchodilating agents, but the subsequent demonstration of potent anti-inflammatory activities in the airways and the heavier inflammatory burden associated with COPD, led these drugs to be further developed towards this disease. This does not mean that in asthma PDE4 inhibitors cannot be used effectively. A disease subset might potentially be represented by refractory to usual therapies, for example, the non-atopic asthma that shares more similar pathogenic features with COPD than with atopic asthma. However, the evaluation of roflumilast as a potential therapy in asthma is at its early clinical stages and its clinical efficacy and safety in asthma subjects has to be further documented.

Inhaled PDE4 inhibitors are also a potential therapy in both COPD and asthma, their major advantage being represented by the targeted administration in the airways with a lower likelihood of side effects, including digestive and cardiovascular ones.

Several inhaled PDE4 inhibitors are currently under development and roflumilast might also be assessed subsequently with this formulation.

Until then, roflumilast remains the newest and most promising oral therapy for more advanced COPD, which in its clinical development program in COPD benefited by one of the most extensive panel of trials performed in various populations.

Executive summary

- Roflumilast (Daxas®) is the newest therapy approved for chronic obstructive pulmonary disease (COPD) in Europe.
- Roflumilast is approved in Europe to be used as an add-on to bronchodilator therapy in severe COPD with chronic bronchitis phenotype.
- Phase II and III clinical trials with roflumilast demonstrated its therapeutic effects on lung function, disease exacerbations and its excellent cardiovascular safety profile.
- The gastrointestinal side effects associated with roflumilast use are nausea and diarrhea, which are mainly mild to moderate in intensity and usually disappear with treatment continuation.
- The most relevant clinical effects for the current therapeutic indication were demonstrated in the Phase III studies performed in severe COPD with chronic bronchitis phenotype.
- COPD is also associated with systemic inflammation and demonstration of a therapeutic effect of roflumilast on it would further support its use in COPD.
- The possibility of topic formulation of PDE4 inhibitors, such as roflumilast, should also be explored.

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