

# Roflumilast, an oral, once-daily phosphodiesterase 4 inhibitor, attenuates allergen-induced asthmatic reactions

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**Background:** Asthma is a chronic inflammatory disease with increasing incidence worldwide. Roflumilast is an oral, once-daily inhibitor of phosphodiesterase type 4 that prevents the breakdown of cyclic adenosine monophosphate levels, leading to inhibition of proinflammatory signaling.

**Objective:** The objective of this study was to investigate the effects of repeated doses of 250 or 500 µg of roflumilast on asthmatic airway responses to allergen.

**Methods:** Twenty-three patients with mild asthma with an FEV<sub>1</sub> of 70% of predicted value or greater were enrolled in a randomized, double-blind, placebo-controlled, 3-period crossover study. Patients participated in 3 treatment periods (7-10 days) separated by washout periods (2-5 weeks). Patients received 250 µg of oral roflumilast, 500 µg of roflumilast, or placebo once daily. Allergen challenge was performed at the end of each treatment period, followed by FEV<sub>1</sub> measurements over the ensuing 24 hours.

**Results:** Late asthmatic reactions (LARs) were reduced by 27% ( $P = .0110$ ) and 43% ( $P = .0009$ ) in patients treated with 250 and 500 µg of roflumilast, respectively, versus placebo.

Roflumilast, 250 and 500 µg, also attenuated early asthmatic reactions by 25% ( $P = .0038$ ) and 28% ( $P = .0046$ ), although not to the same extent as LAR attenuation. Roflumilast was well tolerated. No serious adverse events or discontinuations caused by adverse events were reported.

**Conclusion:** Once-daily oral roflumilast modestly attenuated early asthmatic reactions and, to a greater extent, LARs to allergen in patients with mild allergic asthma. Pronounced suppression of late responses in an allergen challenge model suggests that roflumilast might have anti-inflammatory activity, which could provide clinical efficacy in chronic inflammatory

pulmonary diseases, such as asthma. (*J Allergy Clin Immunol* 2005;116:292-8.)

**Key words:** Asthma, roflumilast, phosphodiesterase type 4, allergen provocation, inflammation, late phase

Asthma is a worldwide public health concern that has been increasing in prevalence, particularly in developed countries.<sup>1,2</sup> In the United States approximately 31 million persons have been given a diagnosis of asthma.<sup>3</sup> Furthermore, the economic burden of asthma (eg, prescription drugs, hospitalization, and loss of productivity) has also increased over the past 20 years, with the economic costs associated with asthma estimated to exceed those of tuberculosis and HIV-AIDS combined.<sup>4</sup>

Asthma is characterized by chronic inflammation and airway hyperresponsiveness (AHR), leading to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing.<sup>5</sup> A primary goal of asthma therapy is to achieve and maintain control of clinical symptoms by improving lung function and reducing AHR. In addition, reducing the frequency of asthmatic exacerbations and improving health-related quality of life are important therapeutic goals. There are several therapeutic options for long-term maintenance (ie, controllers) and symptom relief (ie, relievers) available to asthmatic patients. Commonly prescribed fixed-dose combination therapies based on inhaled corticosteroids (ICSs) provide effective relief to many patients with asthma and comprise the current standard of care. Unfortunately, this standard of care does not control asthma in all patients. Long-term use of ICSs can also potentially cause serious systemic side effects,<sup>6</sup> and poor compliance is an additional concern.<sup>7</sup> Furthermore, a small number of patients are unresponsive to ICS therapy and require alternative therapeutic options.<sup>8</sup> Novel therapies that increase the natural anti-inflammatory response in inflammatory target cells have the potential to meet the current unmet medical need for asthmatic patients.

Inhaled allergen challenge in patients with mild allergic asthma results in an early asthmatic reaction (EAR), followed by a late-phase response (the late asthmatic reaction [LAR]). The EAR is a consequence of the activation and degranulation of cells expressing allergen-specific IgE. Mediators are released that induce nerve stimulation, mucus hypersecretion, vasodilation, and microvascular leakage.

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*Abbreviations used*

AHR:	Airway hyperresponsiveness
AUC:	Area under the curve
cAMP:	Cyclic adenosine monophosphate
COPD:	Chronic obstructive pulmonary disease
EAR:	Early asthmatic reaction
ICS:	Inhaled corticosteroid
LAR:	Late asthmatic reaction
PC <sub>20</sub> FEV <sub>1</sub> :	Provocative concentration resulting in a 20% decrease in FEV <sub>1</sub>
PDE4:	Phosphodiesterase type 4

The LAR is believed to reflect mechanisms of asthmatic inflammation because in this response activated airway cells release cytokines and chemokines locally and into the circulation, thus stimulating the release of inflammatory leukocytes, particularly eosinophils and their precursors, from the bone marrow into the circulation. Inflammatory cells in the peripheral blood are then recruited into the inflamed airways, where they augment airway inflammation and increase AHR.

Roflumilast (3-cyclo-propylmethoxy-4-difluoromethoxy-N-[3,5-di-chloropyrid-4-yl]-benzamide) is an oral, once-daily phosphodiesterase type 4 (PDE4) inhibitor in clinical development as long-term maintenance therapy for chronic obstructive pulmonary disease (COPD) and asthma. Phosphodiesterases hydrolyze the second messenger cyclic adenosine monophosphate (cAMP) to 5'-adenosine monophosphate, rendering it inactive. The PDE4 isozyme has localized activity in the lung, and PDE4 inhibitors, such as roflumilast, block cAMP hydrolysis in the airways. The inflammatory response is highly sensitive to levels of cAMP, and by preventing the breakdown of cAMP, PDE4 inhibitors are associated with a natural anti-inflammatory activity. As a second messenger, cAMP blocks proliferation and chemotaxis of inflammatory cells (eg, lymphocytes), inhibits proinflammatory cell activity (eg, phagocytosis and respiratory burst), and suppresses the release of inflammatory and cytotoxic mediators (eg, TNF- $\alpha$ ) in the lungs.<sup>9</sup> In previous *in vitro* and *in vivo* studies, roflumilast decreased inflammatory cell infiltration into the airways, total protein levels, and TNF- $\alpha$  release.<sup>10</sup> Thus by maintaining levels of cAMP in key airway inflammatory cells, roflumilast acts as a steroid-free anti-inflammatory agent that might have utility in diseases such as asthma and COPD.<sup>11</sup>

This proof-of-concept study investigated the effect of repeat doses of roflumilast (250 and 500  $\mu$ g) on allergen-induced asthmatic responses and AHR in patients with mild allergic asthma.

## METHODS

### Patients

Patients were included in the study if they had a history of wheezing consistent with mild asthma, had an FEV<sub>1</sub> of 70% of

predicted value or greater, were between 18 and 50 years of age, and were not receiving treatment with asthma medications other than short-acting bronchodilators for symptom relief. Inclusion criteria also required a positive allergen skin prick test response and hyperresponsiveness to methacholine, with a provocative concentration resulting in a 20% decrease in FEV<sub>1</sub> (PC<sub>20</sub>FEV<sub>1</sub>) of 16 mg/mL or less. All patients provided informed written consent, and the Human Research Ethics Committee of the University of Stellenbosch (Cape Town, South Africa) approved the study.

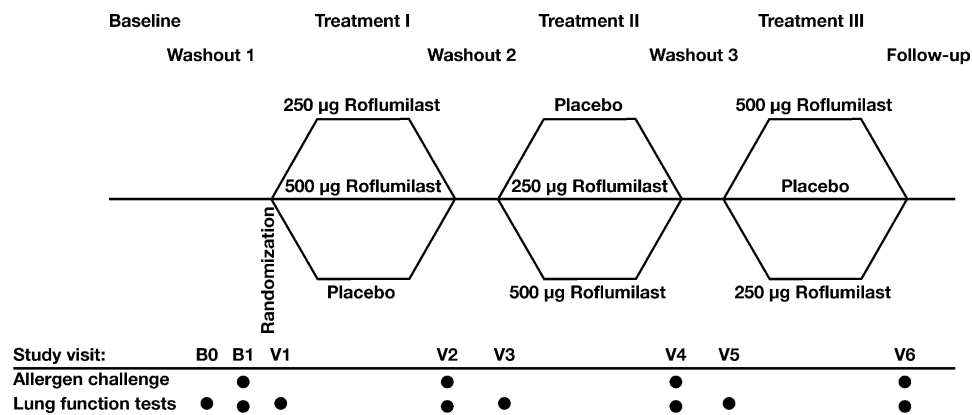
### Study design and measurements

In a double-blind, placebo-controlled, 3-period crossover study, patients were randomized to 250  $\mu$ g of roflumilast, 500  $\mu$ g of roflumilast, or placebo once daily for 7 to 10 days, with washout periods of 2 to 5 weeks before each treatment period (Fig 1). Randomization was performed after the first washout period at the first treatment visit. Study medication was taken between 7 AM and 10 AM daily.

At the first baseline visit, FEV<sub>1</sub> was measured with a mobile spirometer (Vitalograph, Hamburg, Germany), and AHR to methacholine challenge was assessed for each patient. At the second baseline visit, allergen challenge was done to determine a provocative concentration causing an early response to allergen (FEV<sub>1</sub>  $\geq$ 25% decrease) and late response (FEV<sub>1</sub>  $\geq$ 15% decrease), as detailed below. During the baseline visits, patients were assessed for adherence to inclusion and exclusion criteria. In eligible patients methacholine challenge was performed on the first treatment visit, and allergen challenge was performed on the second treatment visit (ie, after taking study medication for 7-10 days). The FEV<sub>1</sub> measurements were done over the ensuing 24 hours at 5, 10, 15, 30, 45, and 60 minutes; subsequently at 1-hour intervals for the next 11 hours; and at 4.5, 5.5, and 24 hours after allergen challenge. At the conclusion of the 24-hour period after allergen challenge, methacholine challenge was repeated.

Allergen and methacholine challenges were performed according to the bronchial provocation technique described by Chai et al,<sup>12</sup> as previously published by Bardin et al.<sup>13</sup> The challenge tests were performed by using a Spira Elektra breath-actuated inhalation dosimeter (SPIRA OY; Hämeenlinna, Finland). The duration of delivery per actuation was 0.6 seconds, and the flow of compressed air was 8 L/min. Each inhalation was controlled to result in an inspiratory flow of 0.6 to 0.8 L/s. Provocation began with 5 breaths of saline inhalation, each lasting 5 seconds, followed by holding the breath for 2 seconds (from functional residual capacity to total lung capacity). Challenges were performed only if baseline FEV<sub>1</sub> was 70% of predicted value or greater, if it was within 12% of the initial value measured at baseline, and if, after saline inhalation, the decrease in FEV<sub>1</sub> was 10% or less. At initial assessment, a decrease in FEV<sub>1</sub> of 25% or greater from the postsaline value within the first 2 hours after the challenge defined the EAR, whereas the LAR was characterized by a decrease of 15% or greater in FEV<sub>1</sub> from the postsaline value at 2 or more time points after spontaneous reversal of the EAR (>2-12 hours after challenge) and with a typical gradual deterioration in FEV<sub>1</sub>.

Each patient was challenged with a single allergen identified on the basis of reactivity during the skin prick test. The allergens used in this study were house dust mite, cat hair, South African grass pollen, and Bermuda grass pollen (dilutions: 10<sup>-2</sup>, 10<sup>-3</sup>, 10<sup>-4</sup>, 10<sup>-5</sup>, and 10<sup>-6</sup> SQU/mL; Bayer Miles, Inc, Cape Town, South Africa). Patients always started with the lowest allergen concentration, and FEV<sub>1</sub> was recorded 5, 10, and 15 minutes after inhalation. If the decrease in FEV<sub>1</sub> was less than 10% of the postsaline FEV<sub>1</sub>, a 10-fold higher allergen concentration was administered; if the decrease was 10% to 15%, a 5-fold higher concentration was administered; and if the



**FIG 1.** Study design. In this randomized, double-blind, 3-period crossover study, each treatment period lasted 7 to 10 days and was preceded by a 2- to 5-week washout period.

**TABLE I.** Baseline patient demographics and characteristics

Parameter	Patients (n = 23)
Median age, y (range)	28 (20-44)
Mean height $\pm$ SD, cm	168 $\pm$ 10.7
Mean weight $\pm$ SD, kg	76 $\pm$ 19.3
Sex distribution, n (%)	
Female	12 (52)
Male	11 (48)
Smoking habits, n (%)	
Never smoked	19 (83)
Exsmokers	3 (13)
Current smokers	1 (4)
Mean FEV <sub>1</sub> $\pm$ SD, L	3.17 $\pm$ 0.82
Mean FEV <sub>1</sub> $\pm$ SD, % predicted	89 $\pm$ 10
Mean PC <sub>20</sub> FEV <sub>1</sub> $\pm$ SD, mg/mL	4.09 $\pm$ 3.79

decrease in FEV<sub>1</sub> was greater than 15% to 25%, the same allergen concentration was administered a second time. The concentration of allergen causing a decrease in postsaline FEV<sub>1</sub> of greater than 25% was used in each patient for allergen provocation on subsequent study days. If needed, patients received single doses of inhaled beclomethasone or budesonide (800 µg) for stabilization of their condition after allergen challenge.

For methacholine challenge, if the decrease in postsaline FEV<sub>1</sub> was 10% or less, 5 breaths of the lowest methacholine concentration (0.03 mg/mL) were inhaled. Doubling concentrations of methacholine were then administered until either FEV<sub>1</sub> decreased to 20% or greater of the postsaline value or the highest available methacholine concentration (16 mg/mL) was reached. The PC<sub>20</sub>FEV<sub>1</sub> was calculated by means of linear interpolation of the FEV<sub>1</sub> dose-response curve.<sup>13</sup>

Clinical laboratory evaluations, electrocardiography, vital signs measurement, and physical examinations were performed at the beginning and end of the study. Adverse events were assessed throughout the study.

## Statistical methods

The primary efficacy variable of this study was inhibition of the LAR. Attenuation of the EAR and AHR were secondary end points. Pairwise tests were used to compare the effects of the 3 treatments on the area under the curve (AUC) from 2 to 12 hours of the FEV<sub>1</sub>,

corresponding to the primary variable, LAR, and on the AUC from 0 to 2 hours of the FEV<sub>1</sub>, corresponding to the EAR. The AUC of the FEV<sub>1</sub> decrease over time was compared by using ANOVA for the 3-period crossover design for both the LAR and EAR. Geometric means and 95% CIs were calculated for the differences between population means. Point estimates and 95% CIs were calculated for the maximum decrease analysis. Percentage reductions in the EAR and LAR were calculated for the differences between population least-squares means for the per-protocol population. Other secondary end points were analyzed in a descriptive manner with geometric means, and 95% CIs were calculated where appropriate.

## RESULTS

### Patients

Patient demographics and characteristics at baseline are summarized in Table I. A total of 23 patients were randomized in this study; 2 patients terminated the study prematurely because of nonmedical reasons. The per-protocol population varied among the different efficacy analyses because of missing or invalid data. Safety data are reported for the intent-to-treat population that was actually exposed to each treatment. The numbers of patients exposed to 500 µg of roflumilast, 250 µg of roflumilast, and placebo were 23, 21, and 22, respectively. Three patients were exsmokers, and 1 patient was a current smoker. Median age was 28 years. At baseline, the mean FEV<sub>1</sub> was 3.17 L (SD, 0.82), 89% of the predicted value.

### Lung function and response to allergen challenge

Patients treated with 250 and 500 µg of roflumilast experienced a significant attenuation of the LAR after allergen challenge compared with those treated with placebo. Treatment with 250 µg of roflumilast led to a 27% reduction in the LAR by means of AUC analysis ( $P = .0110$ ) compared with placebo, whereas 500 µg of roflumilast led to a 43% ( $P = .0009$ ) reduction compared with placebo (Table II). Therefore roflumilast-induced attenuation of the LAR showed a dose-related trend. Significant attenuation of the LAR compared with placebo was maintained for 12 hours after allergen challenge

**TABLE II.** Treatment differences in the LAR and EAR with AUC analysis

Roflumilast dose	Patients,* n	LAR AUC <sub>2-12h</sub>			EAR AUC <sub>0-2h</sub>		
		Point estimate (95% CI)	P value	Reduction, %	Point estimate (95% CI)	P value	Reduction, %
Roflumilast, 250 μg, † vs placebo ‡	21	-0.148 (-0.272 to -0.024)	.0110	27	-0.146 (-0.248 to -0.044)	.0038	25
Roflumilast, 500 μg, † vs placebo ‡	19	-0.243 (-0.382 to -0.104)	.0009	43	-0.179 (-0.307 to -0.050)	.0046	28
Roflumilast, 500 μg, † vs roflumilast, 250 μg ‡	19	-0.084 (-0.223 to 0.056)	.1113	21	-0.015 (-0.118 to 0.089)	.3851	3

AUC<sub>2-12hr</sub>, Area under the curve for FEV<sub>1</sub> between 2 and 12 hours; AUC<sub>0-2hr</sub>, area under the curve for FEV<sub>1</sub> between 0 and 2 hours.

\*This summarizes the per-protocol population. Data for the comparisons between 500 μg of roflumilast versus placebo or 500 μg of roflumilast versus 250 μg of roflumilast were only available for 19 patients.

†Test.

‡Reference.

(Fig 2). Treatment with 250 and 500 μg of roflumilast resulted in a modest yet statistically significant inhibition of the maximum decrease in FEV<sub>1</sub> during the LAR of 17% ( $P = .0321$ ) and 33% ( $P = .0002$ ), respectively, compared with placebo (Table III). Both measures of lung function (AUC and maximum decrease) demonstrated that roflumilast inhibits bronchoconstriction associated with antigen challenge.

On the basis of the analysis of the AUC of FEV<sub>1</sub>, patients treated with 250 and 500 μg of roflumilast also experienced a statistically significant attenuation in the EAR compared with placebo. Treatment with 250 μg of roflumilast reduced the EAR by 25% ( $P = .0038$ ) and 500 μg of roflumilast reduced the EAR by 28% ( $P = .0046$ ) versus placebo, respectively (Fig 2). There were no statistically significant differences between the 250- and 500-μg roflumilast doses with respect to LAR and EAR attenuation (Table II). There was a modest reduction of 14% in the maximum decrease in FEV<sub>1</sub> during the EAR for both 250 and 500 μg of roflumilast compared with placebo (Table III).

AHR was only slightly modified by roflumilast. During roflumilast treatment, the PC<sub>20</sub>FEV<sub>1</sub> ratio was 1.0 or greater, indicating that airway responsiveness did not increase despite the preceding allergen challenge (1.03 for 250 μg of roflumilast and 1.11 for 500 μg of roflumilast). The PC<sub>20</sub>FEV<sub>1</sub> ratio was less than 1.0 (0.87) in patients treated with placebo, which reflects an increase in AHR (Table IV). There was an apparent trend in doubling doses between roflumilast and placebo treatment, but the difference between treatments did not reach statistical significance.

### Safety

Roflumilast was well tolerated at both dose levels tested. No serious adverse events or discontinuations because of adverse events occurred during the study. Most adverse events were mild to moderate in intensity and were related to the digestive tract (eg, diarrhea and gastrointestinal disorder) or the nervous system (eg, headache). Headache was the most common adverse event. During baseline, 6 (26%) of 23 patients reported headaches. During the

treatment period, headache was reported by 4 (18%) of 22 patients, 6 (29%) of 21 patients, and 8 (35%) of 23 patients treated with placebo, 250 μg of roflumilast, and 500 μg of roflumilast, respectively. The majority of headaches reported during the treatment period (73%) were considered by the investigator to be unlikely or not related to study medication. The 6 adverse events associated with the digestive tract were considered by the investigator to be likely related to study medication, but no adverse events were judged definitely related. There were no clinically relevant changes in vital signs, electrocardiographic results, or clinical laboratory parameters.

### DISCUSSION

Asthma is characterized by chronic inflammation of the airways that might be responsive to treatment with PDE4 inhibitors. We have assessed the benefits of the PDE4 inhibitor roflumilast in patients with mild asthma using an allergen challenge model. Roflumilast had only a modest effect on the EAR but demonstrated a more pronounced effect on the LAR. This suggests a potential anti-inflammatory role for roflumilast because it is believed that allergen-induced LARs are linked to an influx of inflammatory cells and mediators associated with an inflammatory response.<sup>14-16</sup>

In several *in vivo* and *in vitro* animal models, roflumilast has demonstrated multiple anti-inflammatory effects, including inhibition of inflammatory cell infiltration and reduction of TNF-α release in the lungs.<sup>11</sup> In a previous study in patients with exercise-induced asthma, 500 μg of roflumilast reduced the decrease in FEV<sub>1</sub> after exercise challenge by 41% and the median TNF-α levels by 21% versus placebo.<sup>17</sup> Exercise-induced bronchoconstriction is regarded as an asthmatic airway reaction to nonspecific stimuli.<sup>18,19</sup> As a common characteristic of asthma, exercise-induced bronchoconstriction is an appropriate model in which to study the efficacy of roflumilast; however, alternative models are needed to elucidate the mechanism of action of roflumilast in patients with asthma. The allergen challenge model (particularly the LAR) is a

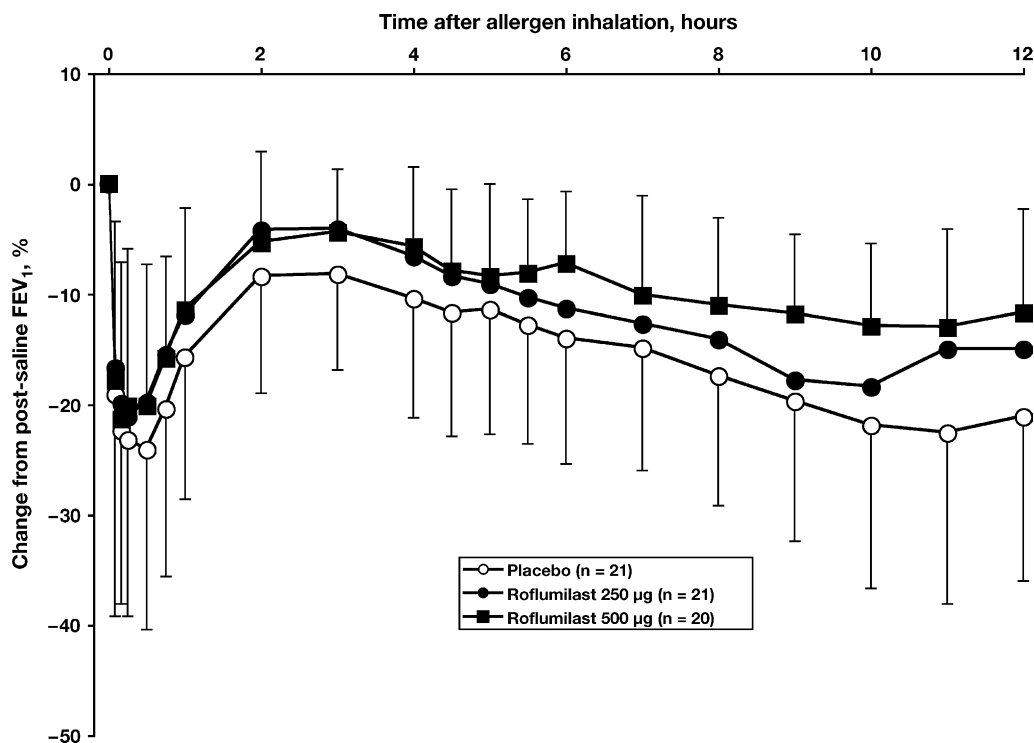


FIG 2. Mean percentage decrease of FEV<sub>1</sub> from postsaline value after allergen challenge. Roflumilast, 250 and 500 µg, significantly attenuated the EAR (0-2 hours) and LAR (2-12 hours) compared with placebo. Data are presented for the intent-to-treat population.

TABLE III. Treatment differences in the LAR and EAR with maximum decrease analysis\*

Roflumilast dose	LAR			EAR		
	Point estimate (95% CI)	P value	Reduction, %	Point estimate (95% CI)	P value	Reduction, %
Roflumilast, 250 µg,† vs placebo‡	4.712 (0.427 to 8.997)	.0321	17	4.015 (0.082 to 7.948)	.0457	14
Roflumilast, 500 µg,† vs placebo‡	8.901 (4.507 to 13.294)	.0002	33	3.909 (-0.140 to 7.958)	.0580	14
Roflumilast, 500 µg,† vs roflumilast 250 µg‡	4.118 (-0.209 to 8.586)	.0613	18	-0.106 (-4.161 to 3.949)	.9580	0

\*This summarizes the per-protocol population (n = 20, 21, and 21 for patients administered 500 µg of roflumilast, 250 µg of roflumilast, and placebo, respectively).

†Test.

‡Reference.

validated technique used to reproduce amplified asthmatic airway inflammation and has previously been used to assess the influence of anti-inflammatory medications on the EAR and LAR.<sup>20</sup> The significant inflammatory component of the LAR has been attributed to an influx of activated eosinophils and the release of cytokines and chemokines that lead to the recruitment of additional inflammatory cells, such as basophils, lymphocytes, and monocytes. In a similar challenge model montelukast and budesonide demonstrated a partial reduction of inflammation, as judged by changes in sputum inflammatory cells; however, budesonide did not significantly reduce the EAR.<sup>21</sup> As a targeted PDE4 inhibitor with anti-inflamma-

tory actions, roflumilast might confer earlier benefits compared with corticosteroids and more comprehensive anti-inflammatory benefits compared with a cysteinyl leukotriene receptor antagonist.

The objective of this study was to evaluate the effect of roflumilast by assessing its effect on the EAR and LAR in patients with allergen-induced asthma. Roflumilast at daily doses of 250 µg and 500 µg significantly diminished the LAR, confirming attenuation of allergen-induced responses to single-dose administration of roflumilast found in early studies.<sup>22</sup> Roflumilast attenuation of the LAR showed a dose-related trend: compared with placebo, 250 µg of roflumilast resulted in a mean attenuation

**TABLE IV.** PC<sub>20</sub>FEV<sub>1</sub> ratios\* by dose group†

	Placebo (n = 15)	Roflumilast, 250 µg (n = 18)	Roflumilast, 500 µg (n = 18)
Mean PC <sub>20</sub>	0.87	1.03	1.11
FEV <sub>1</sub> ratio			
95% CI	0.55 to 1.36	0.59 to 1.81	0.67 to 1.85
Mean doubling factor	-0.20	0.04	0.15
95% CI	-0.85 to 0.45	-0.77 to 0.86	-0.59 to 0.89

\*Ratio of second visit of treatment period versus first visit of treatment period.

†This table summarizes PC<sub>20</sub>FEV<sub>1</sub> data for the per-protocol population.

of 27%, whereas treatment with 500 µg of roflumilast compared with placebo resulted in a mean attenuation of 43%. There was a greater degree of protection against decreases in FEV<sub>1</sub> during the LAR than the EAR, supported by both AUC and maximum decrease analyses. There was a more modest 14% reduction of the EAR with 250 and 500 µg of roflumilast, as determined by means of maximum decrease analysis; however, these data support the AUC analysis, which is a more comprehensive examination of the entire EAR and LAR. Roflumilast also has a modest effect on the EAR, which is mediated principally by mast cell degranulation. Corticosteroids do not have a significant effect on the EAR, which is likely because of their lack of effect on mast cell degranulation.<sup>21,23</sup> The early effect of roflumilast on the EAR might suggest a different onset of anti-inflammatory effect than is achieved with corticosteroids. Although modest, the reduction of the EAR by roflumilast might result from mast cell stabilization, mediator release, or both. Roflumilast had more pronounced effects on the LAR, and the higher dose reduced responses by almost half. Because of the inflammatory processes underpinning the LAR, PDE4 inhibitors might be particularly suitable to prevent cellular recruitment and mediator activity in this phase. In line with these known characteristics, roflumilast had a more pronounced effect on the LAR than the EAR, possibly because of its ability to reduce inflammation. Roflumilast did not significantly attenuate AHR, although there was a trend toward reduction of AHR after allergen.

Roflumilast-induced attenuation of the LAR in this study is similar in magnitude to that achieved with ICS treatment, the primary controller therapy used by patients with asthma. For example, 200 µg of budesonide attenuates the LAR by approximately 44%,<sup>24</sup> and ciclesonide, a novel ICS under clinical development, attenuates the LAR by approximately 47% versus placebo.<sup>25</sup> Thus in this study roflumilast appears to offer anti-inflammatory effects comparable with those achieved with ICSs in this model. Additionally, long-acting β-agonists do not express anti-inflammatory activity and have been shown to inhibit the LAR after a single dose.<sup>26,27</sup> This effect is lost after multiple doses.<sup>28</sup> In this study roflumilast maintained its inhibitory effect after multiple doses. This adds credence to the hypothesis that the effect on the LAR with roflumilast in this study is more likely caused by anti-inflammatory mechanisms rather than a direct effect on

airway muscle tone. Indeed, previous studies have shown that roflumilast does not have direct bronchodilatory effects.<sup>29</sup>

Side effects have restricted the use of PDE inhibitors in asthma.<sup>20</sup> Because the PDE4 inhibitors are more targeted, they also tend to produce fewer adverse effects, such as nausea and headache. Roflumilast was well tolerated in this study. Most side effects were mild to moderate in intensity. Headache, diarrhea, and mild nausea were the most common adverse events and appeared to be dose dependent. All were transient and did not result in treatment discontinuation. In the current study the frequency of headache is likely to be affected by the considerable proportion of patients who reported headache at baseline (26%) and the high incidence of headaches in the placebo group (18%). The incidence of adverse events in this study, notably headache, was higher than that reported by studies of the safety and efficacy of roflumilast conducted in larger populations.<sup>30,31</sup>

In conclusion, the current study demonstrates that roflumilast, a targeted PDE4 inhibitor, inhibits the LAR, which might result from the anti-inflammatory activity of roflumilast. Further clinical studies with surrogate markers of inflammation (eg, induced sputum) are needed to confirm the anti-inflammatory effects of roflumilast. Additionally, these data suggest that roflumilast shows promise as an oral, once-daily, steroid-free treatment for asthma. Additional studies to determine the clinical benefits of roflumilast in asthma and COPD are needed.

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## Correction

With regard to the May 2005 article entitled "Physical activity and exercise in asthma: Relevance to etiology and treatment" (2005;115:928-34): In the abstract, the seventh sentence should have appeared as follows:

The allergy community has placed emphasis on medical therapy and allergen avoidance; in addition, exercise has not been formally incorporated into the National Asthma Education and Prevention Program guidelines.