Dear editor

We read the article by Porpodis et al.1 with great interest. In this study, the authors have evaluated the effect of roflumilast on the phagocytic activity of systemic phagocytes in severe and very severe COPD patients by measuring the oxidative burst post-bacterial stimulation. The study group for this study involved 21 severe or very severe COPD patients who were administered roflumilast in addition to other COPD treatments such as long-acting beta-adrenoceptor agonists (LABA) + inhaled corticosteroids (ICS) + long-acting anti-muscarinic agent (LAMA) or ICS + LABA.

Prior animal studies have reported that ICS impairs Klebsiella pneumoniae phagocytosis and decreases oxidative stress post-infection with bacteria.2 It would have been interesting to know the phagocytic efficacy of roflumilast in combination with other therapeutic drugs for instance, whether the phagocytic efficacy of the combination of roflumilast and ICS is more as compared to other combinations. This could have been possibly achieved by dividing the study group into subgroups such as ICS + roflumilast or LABA + roflumilast or LAMA + roflumilast or ICS + LABA + roflumilast. Porpodis et al.1 also reported that roflumilast increases phagocytic activity, and this anti-inflammatory effect contributes toward increase in lung function parameters among COPD subjects.3 Previous studies have reported that ICS + LABA or ICS + LABA + LAMA improves the lung function. However, in this study there is no control group (group without roflumilast treatment) therefore, the improvement seen in lung function could be a combined effect of ICS + LABA, ICS + LABA + LAMA and roflumilast and not roflumilast alone.

Additionally, it would have been interesting to know whether increase in phagocytosis by roflumilast can contribute toward improvement of exacerbations. It has been reported by Calverley et al.4 that roflumilast decreases exacerbations among mild to moderate COPD patients, but there are no data available with reference to severe COPD patients. Lastly, the authors should have presented the lung function data in terms of actual values along with the percent predicted format, this would have made the results easy to comprehend.

Disclosure

The authors have no conflicts of interest to disclose.

References

1. Porpodis K, Domvri K, Zarogoulidis P, et al. Roflumilast, a phosphodiesterase-4 inhibitor, induces phagocytic activity in Greek COPD patients. Int J Chron Obstruct Pulmon Dis. 2015;10:1123–1128.
2. Patterson CM, Morrison RL, D’Souza A, Teng XS, Happel KI. Inhaled fluticasone propionate impairs Klebsiella pneumoniae clearance in mice. Respir Rev. 2012;13(1):40.
3. Tashkin DP, Ferguson GT. Combination bronchodilator therapy in the management of chronic obstructive pulmonary disease. *Respir Res.* 2013;14(1):49.

4. Calverley PM, Rabe KF, Goehring UM, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet.* 2009;374(9691):685–694.
Authors’ reply
Paul Zarogoulidis
Konstantinos Zarogoulidis
Pulmonary Department, Oncology Unit, “G Papanikolaou” General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

Correspondence: Paul Zarogoulidis
Pulmonary Department, Oncology Unit, “G Papanikolaou” General Hospital, Aristotle University of Thessaloniki, 57010, Thessaloniki 57010, Greece
Tel +30 697 727 1974
Fax +30 231 099 2424
Email pzarog@hotmail.com

Dear editor
We chose outpatients from our clinic who were stable for at least a month. Seven days before roflumilast treatment these patients were monitored more frequently. They all had a history of exacerbations but no one was recovering from an acute exacerbation.

We included a table with patients’ characteristics (Table 1). No patient was taking oral steroids during the study period. Patients were treated according to TORCH (Towards a Revolution in Chronic Obstructive Pulmonary Disease Health) and UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) studies. Our hypothesis was that the addition of an anti-inflammatory regimen such as roflumilast, in patients who experience frequent exacerbations, would have beneficial influence on lung function and exacerbations. This is the only way to be sure that the PDE-4 inhibitor induces phagocytic activity and to what degree. If an oral corticosteroid had been used we would not be sure if PDE-4 would assist in the treatment of an exacerbations. Due to the small number of patients, statistical analysis by subgrouping the patients was not possible. Every patient was a control to himself and every spirometry value or phagocytic activity was compared to the first values before roflumilast treatment. Our study is an on-going pilot study. Although COPD care has improved over the last decade, there is still a huge unmet burden of disease. Exacerbations

Table 1 Patients’ characteristics
| Characteristics                          | No % of patients |
|-----------------------------------------|------------------|
| Age, years (mean)                       | 67.4             |
| Sex (male, female)                      | (86%, 14%)       |
| Groups (C, D)                           | (72%, 28%)       |
| LABA + ICS + LAMA, LABA + ICS           | (28%, 72%)       |
| Frequency of exacerbations (1, 2)       | (80%, 20%)       |
| FEV₁ % pred (mean)                      | 42.3%            |
| FVC % pred (mean)                       | 63.5%            |

Abbreviations: LABA, long-acting beta-adrenoceptor agonists; ICS, inhaled corticosteroids; LAMA, long-acting anti-muscarinic agent; pred, predicted; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

Figure 1 Mean change of stimulation index (phagocytic activity). FEV₁ % predicted, FVC % predicted, per indicated periods (0: before receiving roflumilast, 3 months and 6 months after).

Notes: Vertical bars represent the 95% confidence intervals of means calculated from analysis of variance error mean square. The pooled standard deviation was used to calculate the intervals.

Abbreviations: pred, predicted; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; CI, confidence interval; stim, stimulation.
in particular can be distressing for patients and have serious consequences on their long-term health, such as increased disease progression, increased risk of cardiovascular events, and increased mortality rates. Roflumilast is an oral PDE-4 inhibitor that targets inflammatory cells involved in triggering COPD exacerbations. It includes the only PDE-4 inhibitor approved by the US Food and Drug Administration and is available in 500 μg tablets to be administered once daily. As stated in our publication although this was a small study, the anti-inflammatory activity of roflumilast was shown to provide incremental benefits on top of existing therapies. Future randomized studies will further confirm the impact of roflumilast on COPD and beyond. The authors believe that the lung function values would not clearly present the changes and therefore we chose to present this information with the variability of the values (Figure 1).

Disclosure
The authors have no conflicts of interest to disclose.

References
1. Almagro P, Salvado M, Garcia-Vidal C, et al. Recent improvement in long-term survival after a COPD hospitalisation. Thorax. 2010;65(4):298–302.
2. Kessler R, Stahl E, Vogelmeier C, et al. Patient understanding, detection, and experience of COPD exacerbations: an observational, interview-based study. Chest. 2006;130(1):133–142.
3. Decramer M, Cooper CB. Treatment of COPD: the sooner the better? Thorax. 2010;65(9):837–841.
4. Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. Chest. 2010;137(5):1091–1097.
5. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. Lancet. 2007;370(9589):786–796.
6. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005;60(11):925–931.