Reviewer's report

**Title:** Implementing lessons learned from previous bronchial biopsy trials in a new randomized controlled COPD biopsy trial with roflumilast

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**Reviewer:** JOSÉ LUIS IZQUIERDO ALONSO

**Reviewer's report:**

Roflumilast is a new therapeutic option with an anti-inflammatory mechanism of action that is aimed at treating patients with severe COPD, signs of chronic bronchitis and frequent exacerbations. There is a rationale for the use of this drug in patients with COPD, chronic cough and sputum production since they are considered markers of underlying bronchial inflammation. There is not rationale for its use in patients A and B (without exacerbations).

In vitro, both roflumilast and its active metabolite roflumilast-N-oxide have been demonstrated to affect the functions of many cell types, including neutrophils, monocytes/macrophages, CD4+ and CD8+ T-cells, endothelial and epithelial cells, smooth muscle cells and fibroblasts. In vivo they mitigate key COPD-related disease mechanisms such as tobacco smoke-induced lung inflammation, mucociliary malfunction, lung fibrotic and emphysematous remodelling, oxidative stress, pulmonary vascular remodelling and pulmonary hypertension.

Undoubtedly this study can be very useful to widen our knowledge on the effect of roflumilast on COPD inflammation. However several points should be taken into consideration.

**Mayor limitations.**

1. Is it really necessary to publish in a separate article the methodology of this study?

Such publications may make sense in large clinical trials such as TORCH, UPLIFT, TIOSPIR, etc., but I do not see it as necessary in the current study. In any case, this should be a decision of the publisher.

2. As a result of the foregoing, the introduction is too extensive, more typical of a review article and the information is repetitive with that presented in the discussion.

3. The work that the authors comment from Hogg et al is transversal, and therefore it is very difficult to really know their relevance in the pathogenesis of the events that occur in COPD. Unfortunately, the study design will not allow to correlate possible changes in inflammatory markers with clinically relevant variables.

4. It is difficult to understand the selection of the study population. (A and B).

If the rationale of this drug is to be used in patients with exacerbations on the
basis that these are associated with a greater degree of inflammation, why they choose A and B patients?. They are at low risk of exacerbations. In this situation, what is the value that the authors will give to the results if they can not correlate with changes in exacerbations?. If population has not exacerbacions, what is the meaning of their findings?. What is the clinical value of changes in the values of CD8 or other markers?.

Minor limitations.

1. They need to describe in more detail some aspects

Previous use of inhaled corticosteroids or the use of certain drugs that can potentially interfere with the results (is the run in period enough for that or all patients should be naive?).

2. Comorbidities, including their treatments, should be taken into consideration.

Recommendation:

This study is very interesting and will lead to a publication with high impact factor. However, there is no clear indication to publish the methodology preliminary in an independent paper. The current work, summarized, with final results, and with an addendum if necessary, would be the right way to show this study.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'declare that I have no competing interests related with this study'