Reviewer's report

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

Version: 2 Date: 15 July 2013

Reviewer: Irma Godoy

Reviewer's report:

Roflumilast reduces the rate of exacerbations in patients with a high risk of future exacerbations. The present trial proposes to analyze inflammatory markers in bronchial biopsies, induced sputum and blood serum, to reveal the mechanisms underlying the roflumilast effect on reducing the rate of exacerbations in COPD patients. Bronchial biopsies will provide anatomical detail of airway morphology.

The identification of mechanisms associated with decrease of exacerbation rate is a very important aim. However some points of the trial need to be better specified:

Major compulsory revisions:

1. Since the effect of roflumilast on exacerbation frequency was described in GOLD patients groups C and D, the inclusion of GOLD patients groups A and B probably will not test adequately the study hypothesis. Adverse effects of bronchial and drop outs in these groups will be less frequent; however, the odds of the study results helping to understand mechanisms underlying effects of roflumilast in patients groups C and D are not high.

2. Are there evidences that the primary endpoint of the study (number of CD8+ cells - cell counts per mm2 in bronchial biopsy tissue specimens) is associated with the rate of exacerbation in COPD? In fact, neutrophilic recruitment seems to be more evident during exacerbation of the disease.

3. Since a bronchoscopy will be performed, bronchial specimen cultures should be done to confirm the absence of bronchial infection because it may modify inflammatory markers in bronchial biopsy.

4. Since the study intend to associate changes in inflammation with perceived clinical benefit, and also shed light on which inflammatory pathways are most important with regards to clinically relevant events. What clinical benefits and clinically relevant events will be evaluated? The Table 1 includes only biopsy material, induced sputum, blood serum and pulmonary function changes.

5. What are the scientific foundations to exclude patients with an exacerbation within six months prior to baseline and patients who have had a respiratory tract infection only four weeks before baseline?

Minor essential revisions:

6. If only GOLD patients groups A and B will be included why the section “Inflammatory biomarkers in induced sputum” states: Sputum induction will be
limited to patients with a minimum post-bronchodilator forced expiratory volume in one second (FEV1) \#1L and FEV1 >30% predicted.

7. Why inclusion criteria includes “Post-bronchodilator 30\% FEV1\#80\% predicted” if patients GOLD A and B include those with FEV1 < 50%?

**Level of interest:** An article of importance in its field

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.