## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Computerized lung sound analysis to improve the specificity of pediatric pneumonia diagnosis in resource-poor settings: Protocol and methods for an observational study |
| **AUTHORS** | Laura E Ellington, Robert H Gilman, James M Tielsch, Mark Steinhoff, Dante Figueroa, Shalim Rodriguez, Brian Caffo, Brian Tracey, Mounya Elhilali, James West and William Checkley |

## VERSION 1 - REVIEW

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| **REVIEWER** | Mario Cazzola, Unit of Respiratory Clinical Pharmacology, Department of Internal Medicine, University of Rome Tor Vergata, Rome, Italy.<br><br>I am a friend of Jan Lotvall (we have also published a paper and a book chapter together)and Leif Bjermer (I was an Associate Editor of Respiratory Medicine when he was Editor-in-chief of the journal and now we are both officiers at the ERS School). |
| **REVIEW RETURNED** | 07/09/2011 |

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| **GENERAL COMMENTS** | This paper is the first to present clinical data on inhaled vilanterol/fluticasone furoate combination therapy in patients with chronic obstructive lung disease. In patients with moderate-to-severe COPD, vilanterol/fluticasone furoate 25/400 mcg once daily improved lung function with ICS/LABA-associated side effects generally similar to placebo.<br>An important limitation that must be mentioned is the fact that the study lasted only 4 weeks and based on the rate of disease progression and the frequency of exacerbations, it is now recognised that pharmacological trials in stable chronic obstructive pulmonary disease should be ≥6 months in order to examine potential outcomes or support claims of treatment response, particularly for regulatory submissions (Cazzola et al, ERJ, 2008;31:416-469). In any case, due to seasonal variation, an evaluation of exacerbation frequency requires a period of ≥1 yr and, in any case, the timing of the study treatment may prove important (e.g. capturing winter cold season in the majority of patients).<br>Another important issue is the fact that even patients that could be classified as suffering from moderate COPD were treated with the combination therapy and no data was presented on the effect of vilanterol alone in this type of population in order to understand the real advantage offered by this type of therapy. The authors should at least present data in patients with severe COPD separating them from those in patients with moderate COPD.<br>In this article the Authors do not mention tremor as a side effect. This seems strange to me because tremor has been noted when oral corticosteroids are added to an inhaled long acting β2-adrenergic agonist (Tan et al, Chest 1998;113;34-41), possibly because corticosteroids reverse the tolerance that is known to |

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| | develop to this side effect with long-term β2-adrenergic agonist treatment.<br>The Authors should add more information on vilanterol and fluticasone furoate. In particular, the Authors should mention the pharmacological differences between vilanterol and salmeterol and fluticasone furoate and fluticasone propionate. |

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| **REVIEWER** | Dave Singh<br>Professor of Clinical Pharmacology & Respiratory Medicine<br>University of Manchester |
| **REVIEW RETURNED** | 18/09/2011 |

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| **THE STUDY** | It is not clear what medication the patients were taking during the run in period. |
| **RESULTS & CONCLUSIONS** | This is a safety study of the novel ICS/LABA combination (FF/VI). Efficacy is a secondary endpoint. The study is not designed to tell us much novel about efficacy of ICS/LABA combinations in COPD: the comparison is active vs placebo, and there are plenty of studies that have already shown us thet ICS/LABA vs placebo is superior in terms of lung function. |
| **GENERAL COMMENTS** | This is principally a safety study that merits publication in a specialist journal, rather than the wide readership of the BMJ. The secondary efficacy endpoints only contain limited novel data. |

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| **REVIEWER** | Winston Banya<br>Statistician<br><br>Royal Brompton & Harefield NHS Foundation Trust<br>Clinical Trials and Evaluation Unit<br>Sydney Street<br>London SW3 6NP<br><br>I have no conflict of Interest |
| **REVIEW RETURNED** | 08/11/2011 |

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| **RESULTS & CONCLUSIONS** | I would like to see Table 2 presented in a slightly different way i.e<br><br>Baseline Day 28<br>Placebo Active Placebo Active<br><br>For the second part of that table rather than list the change in mean at the different time points on day 28, may be a regression analysis to give one overall score for unit change in time might be useful. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer: Mario Cazzola, Unit of Respiratory Clinical Pharmacology, Department of Internal Medicine, University of Rome Tor Vergata, Rome, Italy.

I am a friend of Jan Lotvall (we have also published a paper and a book chapter together)and Leif Bjermer (I was an Associate Editor of Respiratory Medicine when he was Editor-in-chief of the journal and now we are both officiers at the ERS School).

This paper is the first to present clinical data on inhaled vilanterol/fluticasone furoate combination therapy in patients with chronic obstructive lung disease. In patients with moderate-to-severe COPD, vilanterol/fluticasone furoate 25/400 mcg once daily improved lung function with ICS/LABA-associated side effects generally similar to placebo.

An important limitation that must be mentioned is the fact that the study lasted only 4 weeks and based on the rate of disease progression and the frequency of exacerbations, it is now recognised that pharmacological trials in stable chronic obstructive pulmonary disease should be ≥6 months in order to examine potential outcomes or support claims of treatment response, particularly for regulatory submissions (Cazzola et al, ERJ, 2008;31:416-469). In any case, due to seasonal variation, an evaluation of exacerbation frequency requires a period of ≥1 yr and, in any case, the timing of the study treatment may prove important (e.g. capturing winter cold season in the majority of patients).
• We have expanded upon this limitation in the discussion, with particular reference to interpretation of the efficacy data from this Phase IIa study, which was primarily a safety study.

Another important issue is the fact that even patients that could be classified as suffering from moderate COPD were treated with the combination therapy and no data was presented on the effect of vilanterol alone in this type of population in order to understand the real advantage offered by this type of therapy. The authors should at least present data in patients with severe COPD separating them from those in patients with moderate COPD.
• We have clarified in the discussion that one limitation of this study is that it lacks a VI arm. With respect to breaking out the data by stage of severity we feel that this would not be viable for a study of this nature and size. In part this is because the study (a Phase IIa study) was not powered, nor designed to investigate such a difference in efficacy, and certainly the number of severe patients will be very low. Additionally, and to the point about the 4-week duration of the study we feel that over-analysis of the efficacy data, from what was primarily a safety study would be inappropriate.

In this article the Authors do not mention tremor as a side effect. This seems strange to me because tremor has been noted when oral corticosteroids are added to an inhaled long acting β2-adrenergic agonist (Tan et al, Chest 1998;113;34-41), possibly because corticosteroids reverse the tolerance that is known to develop to this side effect with long-term β2-adrenergic agonist treatment.
• We have made no mention of tremor as no incidences were recorded during the study. For the reviewers reference 5% of patients in the FF/VI group were receiving LABA monotherapy prior to initiating therapy. As such we feel that this population is not sufficiently 'LABA experienced' to warrant discussion of the potential un-masking LABA-related tremor by the addition of ICS.

The Authors should add more information on vilanterol and fluticasone furoate. In particular, the Authors should mention the pharmacological differences between vilanterol and salmeterol and fluticasone furoate and fluticasone propionate.
• We have provided further detail on both agents in the introduction

Reviewer: Dave Singh

Professor of Clinical Pharmacology & Respiratory Medicine

University of Manchester

It is not clear what medication the patients were taking during the run in period .

- We have clarified this in the first part of the results section

This is a safety study of the novel ICS/LABA combination (FF/VI). Efficacy is a secondary endpoint. The study is not designed to tell us much novel about efficacy of ICS/LABA combinations in COPD: the comparison is active vs placebo, and there are plenty of studies that have already shown us thet ICS/LABA vs placebo is superior in terms of lung function.

• We agree that the study does not feature any novel efficacy design however we do feel that the first data on the combination of FF/VI in COPD patients does provide novel data, similarly we agree that it is well established that the combination of ICS/LABA is superior to placebo in terms of lung function, but would again suggest that it is the specific ICS/LABA (FF/VI, not FP/SAL or BUD/FORM) and it's frequency of dosing (once-daily versus twice-daily) which is of interest

This is principally a safety study that merits publication in a specialist journal, rather than the wide readership of the BMJ. The secondary efficacy endpoints only contain limited novel data

• Per the previous point, we feel that the data are novel as they relate to a novel, once-daily combination of ICS/LABA

**VERSION 2 – REVIEW**

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| **REVIEWER** | Mario Cazzola, Unit of Respiratory Clinical Pharmacology, Department of Internal Medicine, University of Rome Tor Vergata, Rome, Italy.<br><br>I am a friend of Jan Lotvall (we have also published a paper and a book chapter together)and Leif Bjermer (I was an Associate Editor of Respiratory Medicine when he was Editor-in-chief of the journal and now we are both officiers at the ERS School). |
| **REVIEW RETURNED** | 08/12/2011 |

The reviewer filled out the checklist but made no further comments.