Author's response to reviews

Title: Comparison of vilanterol, a novel long-acting beta2 agonist, with placebo and a salmeterol reference arm in asthma uncontrolled by inhaled corticosteroids

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Author's response to reviews: see over
Dear Professor Olsen,

Please find uploaded to the *Journal of Negative Results in Biomedicine* author site a revised version of our manuscript 4169880581021511, entitled “Comparison of vilanterol, a novel LABA, with placebo and a salmeterol reference arm in asthma uncontrolled by ICS”, together with detailed responses to the reviewers’ comments. We have presented the responses to the comments in the form of a table highlighting the specific comments and have provided a detailed response for each, with reference to the modified sections of the manuscript.

In response to comments made by the reviewers, we have provided in addition to the revised manuscript three supporting tables to be made available as online supplementary information.

We are very grateful for the suggestions provided by the reviewers to improve our manuscript and we hope that we have been able to respond to them satisfactorily. We hope that you find the revised version of our paper improved and more acceptable to the Journal. Many thanks for your work on this paper to date and the interest that you have shown in it.

Yours truly,

Prof. Jan Lötvall
<table>
<thead>
<tr>
<th>Reviewers</th>
<th>Reply to Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVIEWER 1</td>
<td></td>
</tr>
<tr>
<td>1.1</td>
<td>An interesting negative study of adding vilanterol to ICS showing no additional lung function benefit that ICS therapy plus placebo. In general I think this is written very well although some issues seem to be missing.</td>
</tr>
<tr>
<td>1.2</td>
<td>There seems to be large intercountry variation in the results that is not explored in detail which might explain a loss of power.</td>
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<td>1.3</td>
<td>The results seem incomplete for some secondary endpoints such as AM PEF and should be included</td>
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<tr>
<td>1.4</td>
<td>It is stated this is the first trial by the sponsor to show a negative response to salmeterol vs placebo. Does this include all unpublished study results and how was this verified?</td>
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<tr>
<td>1.5</td>
<td>A discussion on how to improve future studies which might increase background ICS compliance and diminish study effects is merited such as longer run-ins, provision of ICS for a background period especially in countries with more limited drug access.</td>
</tr>
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</table>

We have clarified in the Discussion how ICS compliance was assessed: “To confirm compliance, patients in this study were asked daily via the e-diary if they had used their ICS”, and have added some additional discussion of how the experience of this study could help inform the design of future studies, as follows: “In future studies, confirmation of adherence during the run-in period could be addressed by providing single-blind ICS with dose counters, in order to better compare the ICS response with the observed treatment effect following the addition of vilanterol.” |
The primary aim of this study was to show that Vilanterol, a new ultralong acting beta 2 agonist was superior to Salmeterol and Placebo at 24 hour after dosing. 34 centers recruited 347 patients and 298 completed. As main inclusion criteria was patients with asthma, symptomatic and unstable despite being treated with regular ICS.

The study fail to show superiority over placebo or salmeterol. The authors argue that this is because of a very significant placebo effect, probably due to improved ICS adherence after entering the study. I miss information on patient demographics and evaluation of inclusion criterias.

2.1

We thank the reviewer for these very insightful and important comments on our study, with which we concur. To address these comments we have amended the manuscript in several places.

Firstly, data on patient demographics for the total patient population are provided in Table 1. As per our response to one of reviewer 1’s comments (1.2), we have added as an online supplement baseline data by country in a new supplementary table (Supplementary Table 1). This informs a discussion of the possible effects on the results of inter-country variation in the primary endpoint (Table 3), although no clear relationship between baseline data and the magnitude of the placebo effect is apparent. Inclusion criteria are included in the methods (see “Eligibility criteria and interventions”).

Secondly, the study was not necessarily designed to show the superiority of vilanterol over salmeterol, but rather to show the superiority of vilanterol over placebo, as stated in the Methods. The statistical powering of the study was therefore based upon the comparison of vilanterol with placebo. If the vilanterol and salmeterol treatment regimens had both demonstrated a statistically significant difference relative to placebo, the relative effects were to be evaluated by assessing the degree of overlap between the 95% confidence intervals relating to their treatment differences with placebo. The particular point of interest in that situation would have been whether or not the point estimate of the vilanterol-placebo difference fell within the 95% confidence interval for the salmeterol-placebo difference.
| 2.1 | In previous GSK studies evaluating the effect by LABA included patients usually have an FEV of 50-80% of predicted and a minimum reversibility of 15%. Patients in this study had a mean FEV at screening of 66.6% of predicted normal and a mean FEV reversibility of 26.2-30%. All were on ICS treatment at baseline.

Real life feasibility evaluation has shown that this type of very beta-2 responsive patients on regular ICS treatment are very rare. Consequently there is a risk for selection bias where centers having a large fraction of ICS non-adherent patients are being favored.

This problem should be discussed more in detail. |
|---|---|
| | As indicated in the first paragraph of the Results section in the submitted manuscript, the mean % FEV₁ reversibility at screening was high across all treatment groups; although the eligibility threshold of reversibility was just ≥12% and ≥200mL (as in other GSK-sponsored studies), the mean % reversibility at screening was more than twice this in all treatment groups. We concur with the reviewer that this may suggest poor adherence to maintenance ICS therapy prior to study start and subsequent improvement in adherence during the study, and have amended the Discussion to provide additional commentary around ICS adherence in this study compared with a previous parallel-group study of VI versus placebo: “Comparatively, in a previous study of VI versus placebo in which compliance with ICS was required during the 4-week run-in period, a statistically significant improvement in lung function was seen (Lötvall et al, *Eur Respir J*, 2012).”

We have amended the final paragraph of the Discussion to discuss how this could potentially inform future studies:

“The high degree of FEV₁ reversibility observed among the population adds further weight to the suggestion that ICS non-adherence may have affected the outcome of this study. In future studies, confirmation of adherence during the run-in period could be addressed by providing single-blind ICS with dose counters, in order to better compare the ICS response with the observed treatment effect following the addition of vilanterol.” |