Author’s response to reviews

Title: Bronchodilatory effect of inhaled budesonide/formoterol and budesonide/salbutamol in acute asthma: A double-blind, randomized controlled trial.

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Title: Rapid bronchodilatory effect of formoterol and salbutamol in acute asthma: A double-blind, randomized controlled trial.

Responses to the Editorial comments:
We thank the Journal for the opportunity to revise the manuscript.
1. The name of the Ethics body which granted approval to the study is highlighted in the ‘Methods’ section.
2. The statements on ‘Competing interests’ and Authors’ contributions have been added.
3. We have structured the abstract as instructed.
We are providing point-by-point responses to the Reviewers’ comments. The changes made in the manuscript are highlighted in red font.

Responses to Reviewers’ comments
We thank the reviewers for their comments and suggestions to improve the manuscript. We have modified the manuscript as suggested. The responses to the comments are as follows:

Reviewer: Tim Harrison
This paper describes a randomised controlled trial of the acute bronchodilator effects of salbutamol and formoterol given via an MDI in children presenting with a mild exacerbation of asthma. The study design is appropriate and the study appears to have been well performed.

RESPONSE: We thank the reviewer for the comments and suggestions.

Major revisions:
1. It is not clear why all the data is described as the median rather than mean?

RESPONSE: As the data for some of the variables were not distributed normally, we had used median (IQR). However, as suggested by both reviewers, we have now shown the mean along with SD.

2. I would like to see a figure of the FEV1 results.

RESPONSE: We have added a figure showing the FEV1 results.

3. With equivalence studies it usual to have greater power than 80%.
RESPONSE: We had calculated the sample size for a power of 80%, as guided by a biostatistician; however we enrolled 90 children in the study.

Minor revisions –

I think the word "rapid" should be removed from the title and throughout the manuscript (ie page 3 "the objective of this study was to compared the "acute" bronchodilator effects" or just "the bronchodilator effects").

RESPONSE: We have deleted the word ‘rapid’ from the title and the manuscript.

In the conclusion, I think the authors should state "may improve compliance" rather than "will..."

RESPONSE: The sentence has been modified as suggested.

Reviewer: Edward Kerwin

Reviewer's report:

Authors J.J.A, R.L. and S.K.K. provide an original clinical trial report of a randomized, masked, parallel group trial of BUD/FOR 200/10 fixed dose combination MDI versus BUD 200 and SAL 200 (separate dosed MDIs) for some 90 children with acute mild asthma exacerbation presenting to a tertiary care emergency room. These data and results are helpful in clarifying the potential role of formoterol in fixed dose combination with BUD in treating acute asthma exacerbations in children. However, several major revisions are needed before this article should be published.

RESPONSE: We thank the reviewer for the comments and suggestions. We have tried to incorporate the changes to address the issues highlighted.

Three major revisions are needed (1 and 2 are considered mandatory, while 3 is recommended) before this MS should be accepted.

1. The Introduction and the Conclusion both should be strengthened to clearly state that FORMOTEROL and LABA monotherapy are not indicated for only patients with asthma, and these LABAs should only be used in combination
with ICS. Formoterol-containing medicines currently contain a Black Box warning (in the U.S.), and international guidelines indicate these medicines should be used in combination with ICS for moderate and persistent asthma patients who cannot be well controlled with ICS and SABA treatments. Since there is actual danger in prescribing FOR or LABA as a monotherapy in asthma (without ICS), the article should clarify this precaution, both in the Introduction, and again in the Discussion and Conclusion, so readers are not mislead to prescribe formoterol as monotherapy.

**RESPONSE:** We agree with the comments and have highlighted the need to avoid monotherapy in the Introduction, Discussion and Conclusions.

2. Secondly, the authors very appropriately dosed an ICS/LABA fixed dose combination inhaler plus a placebo inhaler, versus the same ICS dose and salbutamol in this trial. They did not dose FOR versus SAL, but in fact did something much more appropriate in including ICS doses for all patients.

This is better because:

A.) it correctly evaluates the use of fixed dose ICS/LABA (like BUD/FOR) as a controller and reliever in a single device, and

B.) it also provides a best practice in the ER that acute asthma exacerbations should not be treated with LABA or SABA alone, but should be treated with ICS or steroids plus SABA or LABA for best ER outcomes.

Since the authors did in fact compare a fixed dose ICS/LABA (BUD/FOR) to a conventional ICS plus salbutamol (in separate MDI), the Title, Abstract, and Introduction should all be recast to define this as a trial of ICS/LABA combination versus ICS and SABA for acute asthma exacerbations in children. The fact that formoterol and salbutamol were studied in combination with budesonide must be included in the Title, Introduction, Methods and Conclusion, etc. This article only supports dosing of a BUD/FOR fixed dose combination MDI in the ER, not any dosing of formoterol as a monotherapy.

**RESPONSE:** We did compare a fixed dose combination of Budesonide/ Formoterol with Budesonide with Salbutamol; we have made necessary changes in the manuscript as suggested. We have also highlighted that LABA monotherapy should not be used.

3. (This is a relative major revision to be completed if feasible). The authors
report their statistical data for baseline data, primary efficacy data, and secondary efficacy data in terms of medians and interquartile range in the Methods section, and in Tables 1, 2 and 3. It would be much preferable, if feasible, to re-report these data in terms of means and standard errors of the means, or 95% confidence intervals, if the authors’ data analysis software can report the mean + SE and mean + 95% CI data. Mean data is more precise than the median, and reporting SE + 95% CI allows much better statistical analysis of data, than reporting interquartile range. In addition, nearly all reported data on FOR and on BUD/FOR reports these data in mean + SE. So these authors should also report their data in mean + SE and mean + 95% CI range, if at all feasible, if this is consistent with their pre-specified statistical analysis approach.

RESPONSE: As the data for some of the variables were not distributed normally, we used median (IQR). However, as suggested by both reviewers, we have now shown the mean along with SD (as SD is more appropriate to represent the study data).

Minor revisions:

1. In the Introduction section, explain that this study was designed to only observe children for one hour after treatment, even though the advantages of formoterol + ICS versus salbutamol + ICS are more likely to be seen with longer follow-up periods, such as out to 3-12 hours post-dosing.

RESPONSE: We have highlighted that we observed the enrolled subjects only for 1 hour. Also we have added this aspect to the Discussion section.

2. In the Methods section, under sample size, please clarify how the difference in FEV1 of 10% was selected as a non-inferiority threshold. Were other studies consulted to determine the appropriate range of FEV1 comparability and to set the SD of 15?

RESPONSE: We chose FEV1 (% predicted) difference of 10% as this appeared to be clinically relevant difference. The SD of 15 was chosen based on our previous studies; also similar figure had been reported in a study by Bussamra et al (Ref 8).

3. In the Methods section, please specify whether a rescue medication (such as additional doses of salbutamol, inhaled or nebulized) was allowed if the children had not improved after a single dose of bronchodilator.

RESPONSE: We have clarified this issue in the methods. However, no child required any additional dose.
4. In the Methods section, clarify that the study was only partially blinded, where patients were blinded, but study staff may have been unblinded since the masked canisters used had different designs and sizes, etc.

**RESPONSE:** The study was double blinded; we arranged for similar appearing canisters. The labels of the canisters were removed. These and the subsequent labelling were performed by staff not involved in the administration of medications. The study staff were blinded.

5. In the Methods section, clarify whether the structured “performa” questionnaire was administered on arrival at the ER (before study medication was given), or was it given after bronchodilator treatments were administered.

**RESPONSE:** The children with mild exacerbations were enrolled from out-patient department or Pediatric Chest Clinic which provides follow up services to children with asthma. The children were diagnosed to have mild exacerbations based on clinical criteria and MPIS. The children then performed spirometry. Thereafter, the study medications were administered. The other details of history were then recorded. This aspect has been added to the Methods.

6. Please clarify the time required to administer the MPIS scoring test. Was there adequate time to perform the MPIS between the 1 (one) minute and 5 (five) minute spirometry tests, etc.? Also, briefly summarize how many questions are asked in the MPIS, and whether it is administered by an interviewer or completed by patients, etc.

**RESPONSE:** The scoring (MPIS) took approximately 60 seconds. There was adequate time to perform the MPIS at 1 and 5 minutes after administration of the study medication. The MPIS has 5 components: SpO₂ at room air, use of accessory muscles, inhalational: exhalation ratio; wheezing; Heart rate and respiratory rate. These parameters were scored by the investigator.

7. In the Results section, please detail whether any children failed to stabilize with the dosing of study inhalers and hour long follow-up. Please provide the percentages of children who required prolonged stays in the ER, and the percentage of children who required rescue therapy or additional doses of bronchodilator in the study population.

**RESPONSE:** No child failed to stabilize during the study observation period or needed additional doses of bronchodilator during the observation period.

8. In the Results section, there is a Table 1 provided, but no prompt in the text to “see Table 1”. Please add to text a reference to prompt the reader to view
Table 1.
RESPONSE: We have added the reference to table 1 in the text.

9. In the Results section, Table 2 correctly presents the percent of predicted FEV1 data for each group. Please also include the change from baseline in percent of FEV1 for each time point, and include p values to show which changes reached statistical significance in the table.
RESPONSE: We have added this information in a table.

10. In the Results section, peak expiratory flow rate (PEFR) is helpful data to confirm the changes seen with FEV1. This is also important since many rural practices may only have PEFR equipment, and not spirometry equipment. Please, if possible, include a Table 3 similar to Table 2, that lists PEFR levels and change from baseline PEFR seen at various time points.
RESPONSE: We have added 2 tables to show this data.

11. In the Discussion section, the entire paragraph beginning “Physiochemical properties...” and ending with “…efficient signal transduction,” should be deleted. This is not directly relevant to the study data cited, and refers to references that are 15-18 years old, which may no longer be the most recent information on molecular mechanisms.
RESPONSE: We have deleted this para.

12. In the Discussions and Conclusions, a cautionary statement should be added that LABAs like formoterol, are not to be used as monotherapies for children or adults with asthma, and should only be used in combination with ICS when ICS treatments alone fail to control asthma.
RESPONSE: We have added this cautionary statement.