Author's response to reviews

Title: Efficacy of Once-daily Indacaterol 75ug Relative to Alternative Bronchodilators in COPD: a study level and a patient level Network meta-analysis

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Author's response to reviews: see over
April 5th, 2012

Dear Editor-in-Chief,

Enclosed is a manuscript submitted for your consideration for publication in BMC Pulmonary Medicine as an original report entitled: “EFFICACY OF ONCE-DAILY INDACATEROL 75µg RELATVIE TO ALTERNATIVE BRONCHODILATORS IN COPD: A STUDY LEVEL AND PATIENT LEVEL NETWORK META-ANALYSIS”.

The manuscript has been revised based on the suggestions and comments from the Reviewers, which have been described below on pages 2-5. In addition to a clean version of the manuscript, we have also attached a track-changes version

This manuscript presents mixed treatment comparison (MTC) meta-regression models using two methods to adjust for potential effect modifiers based on either individual patient data or study level aggregate data to remove bias due to similarity and consistency violations. The results of this analysis allow for the comparison of indacaterol 75ug to alternative monotherapies for COPD.

The individual patient data for this study is proprietary to Novartis. However, the models and methodology used in the research are not proprietary. This work has not been previously published, nor is it under consideration for publication elsewhere. However, the methodology for the individual patient analysis has been submitted for publication based on a subset of the data included in the current manuscript.

This research project was sponsored by Novartis. Jie Zhang and James Williams are employees of Novartis. Shannon Cope and Jeroen P Jansen prepared this manuscript in collaboration with the other authors based on funding from Novartis. The publication of study results was not contingent on the sponsor's approval or censorship of the manuscript.

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I look forward to receiving your feedback.

Sincerely yours,
Jeroen Jansen
Reviewer #1: Mark Weatherall

The authors present a complex pooled analysis of a number of different placebo controlled randomized controlled trials of inhaler use in COPD with the aim of estimating the possible differences between indacaterol and other agents used in COPD based on FEV1 and the St Georges Respiratory Questionnaire.

The literature review seems comprehensive and the authors also had access to individual patient data from a company research program about indacaterol. The analysis was by a Bayesian model as implemented in WinBUGS and I think the authors could usefully present, as a supplement, an example of their code so that the hierarchical structure, statistical distributions, and priors are more obvious than in the text description of their methods.

Author response:

The code was specifically designed for the evidence base and is a combination of WinBugs and R. Currently we are working on a methods paper and prefer to add a more transparent code to that paper.

In the event there was little evidence found in a difference in 12 week FEV1 and St Georges Respiratory Questionnaire between the multiple different agents examined.

I felt the authors gave a balanced description of the strengths and weaknesses of their study in the discussion.

Reviewer #2: Luis Nannini

- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1) I found two recent and outstanding publications; but unfortunately the authors closed the search in 2010: indacaterol versus tiotroium. [ERJ Express. Published on May 26, 2011 as doi: 10.1183/09031936.00191810] Excellent review from Renard et al. Respiratory Research 2011, 12:54 http://respiratory-research.com/content/12/1/54. Novartis Pharma AG, Basel, Switzerland.

Author response:

Between 2010 when the search was performed and September 2011 when the manuscript was submitted to this journal the systematic review of the literature and the analyses were performed and the manuscript was written. Consequently, this lag between the search and the publication reflects a pragmatic limitation of such a project.
On Pg. 14 we have expanded the second paragraph to acknowledge that the study by Buhl et al. 2011 was not included in the current study:

“Furthermore, results from a blinded RCT by Buhl et al. 2011 [38] are also comparable to earlier unblinded results from Donohue et al. for the comparison of indacaterol 150ug versus tiotropium. This RCT was not included in the current study as it was published after the search was performed and no individual patient data were available for this study at the time of the analysis.”

2) The former author showed that 75 mcg indacaterol dose was less effective than 150 and that the plateau occurred beyond 300 mcg. Novartis Switzerland also had experience in network meta-analysis.

Author response:

The objective of this study was to evaluate the comparative efficacy of indacaterol 75µg, tiotropium 18µg, salmeterol 50µg, formoterol 12µg, and placebo for the treatment of COPD. Therefore, the comparison of alternative indacaterol doses is not of interest. The aim of this study was to generate evidence for decision makers in the United States, where indacaterol 75µg is the only dose approved. Given this decision space, results for indacaterol 150 and 300 are not relevant. Moreover, approval decisions from FDC and EMA are based on an overall evaluation of a treatment, whereas the current study focusses on the efficacy of the treatments in terms of trough FEV1 and SGRQ.

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)
  1) At one Atlantic coast 75 mcg indacaterol was enough; but in Europe no. I need author´s comments. FDA was wrong or EMEA?

Author response:

It seems that this comment relates to the previous section regarding the comparison of indacaterol 150ug and 75ug, which is not the aim of this study. Please see FDA commentary article of the indacaterol risk and benefit (Chowdhury et al. 2011).


2) The lack of consistency regarding best dose 75-300 was not observed with the other LABA and tiotropium.

Author response:
The network meta-analysis included the approved dose for salmeterol, formoterol, and tiotropium with the objective to evaluate the comparative efficacy of indacaterol 75µg, tiotropium 18µg, salmeterol 50µg, and formoterol 12µg.

3) Discussion: 3rd page of discussion; 2nd paragraph. FEV1 was an important outcome not only due to “regulatory perspective”. It has a prognostic value and despite the current tendency to minimize its relevance in COPD, FEV1 means severity, exacerbation rate, survival, and irreversible decline natural history of COPD.

Author response:

This section of the discussion has been updated to emphasize the importance of FEV1 (Discussion Pg. 16, 2nd paragraph):

“The outcomes in this study are considered relevant to treatments for COPD. FEV1 was the primary endpoint in all of the studies and is also required from a regulatory perspective. Spirometry reflects an important prognostic factor that is used to define severity for COPD, which is considered the most reproducible and objective measurement of airflow limitation available [1].”


3) Since no pharmacologic intervention could modify the FEV1 decline; the authors should also focus in exacerbation rates in future reviews.

Author response:

The authors agree that exacerbation rates are an important outcome for future studies.

4) The authors might change the title in order to obviate the dose 75 mcg because only 2 studies against 5 with other doses were included.

Author response:

The title reflects the main objective of this study, which is to compare indacaterol 75mcg with the alternative bronchodilators for COPD. In order to develop a network of evidence based on individual patient data (IPD), all trials within the indacaterol trial program were included. The alternative bronchodilators (i.e. tiotropium, salmeterol, formoterol) provided the comparators of interest, whereas evidence regarding the different indacaterol doses (i.e. 150 and 300ug) was included to strengthen the network.

5) Could it be done a comparison between indacaterol doses?
Author response:

It is possible to perform a comparison between indacaterol doses. However, as mentioned above this is not the aim of the current study, which is intended to generate evidence that can be used by decision-makers in the United States.

Reviewer #3: Fabrizio Luppi
Based on the evidence available, Cope and colleagues showed that indacaterol 75µg is expected to be at least as efficacious as formoterol and comparable to tiotropium and salmeterol regarding FEV1. Furthermore, indacaterol 75µg shows comparable level of improvement in health-related quality of life to tiotropium, salmeterol, and formoterol, as measured by the SGRQ. The manuscript is interesting, but I think that some issues need to be better addressed
1. Indacaterol 75µg should be compared directly with active comparator and not through an indirect comparison, using Bayesian analysis.

Author response:

The authors agree that a high quality randomized trial directly comparing indacaterol 75µg to all the alternative bronchodilators simultaneously would reflect the highest level of evidence. However, given that such a trial is not available and is also unlikely to be performed in the near future, the current study provides estimates for the relative treatment effects to facilitate decision-making.

2. More globally the methodology utilized in this manuscript, arise doubts about the possibly of a real comparison between different trials.

Author response:

Network meta-analyses reflect an extension of the traditional meta-analysis (where all included studies compare the same intervention with the same comparator) by including multiple different pairwise comparisons across a range of different interventions [Jansen 2008]. As an alternative to head to head trials, indirect treatment comparisons or network meta-analyses are advocated to provide estimates of the relative treatment effects [Glenny 2005, NICE 2008, PBAC 2008, Wells 2009].

The discussion emphasizes the importance of the similarity and consistency assumptions in a network meta-analysis and explains how this potential bias was limited by adjusting for differences in the studies by incorporating treatment by covariate interactions in the statistical models used.

3. The manuscript is well written and accurately edited.