Efficacy of indacaterol 75 µg versus fixed-dose combinations of formoterol-budesonide or salmeterol-fluticasone for COPD: a network meta-analysis

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Introduction
Chronic obstructive pulmonary disease (COPD) is a progressive disorder characterized by airway obstruction and reduced lung function. Symptoms include deteriorating health status and breathlessness, and treatments aim to prevent and control symptoms, reduce exacerbations, improve health status, and increase exercise tolerance.1
It has been found that a significant number of patients receive fixed-dose combinations as a first-line treatment despite recommendations by the Global Initiative for Chronic Obstructive Lung Disease to use a fixed-dose combination of a long-acting beta-agonist plus an inhaled steroid only for patients with a greater degree of airway obstruction or for patients who experience repeated exacerbations. This evidence and the absence of head-to-head, randomized, controlled trials between indacaterol and fixed-dose combinations led to an indirect comparison of indacaterol 150/300 µg with fixed-dose combinations in a previously published systematic review and network meta-analysis by Cope et al in 2011.

Indacaterol 75 µg, a novel once-daily inhaled long-acting beta-agonist recently approved in the US, is indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The objective of the current study is to compare the efficacy of indacaterol 75 µg with that of fixed-dose formoterol and budesonide twice daily (FOR/BUD) and fixed-dose salmeterol and fluticasone twice daily (SAL/FP) for the treatment of COPD patients using the same approach as Cope et al in 2011. The evidence base in the current analysis is consistent with the previous publication but includes two additional indacaterol 75 µg randomized clinical trials. The outcomes were lung function as measured by trough forced expiratory volume in 1 second (FEV₁) and breathlessness as assessed by transition dyspnea index total score at 12 weeks. At the 12-week time point, there were insufficient data available across the included randomized clinical trials to assess St George’s Respiratory Questionnaire total score.

Materials and methods

Because patients were permitted to use stable inhaled corticosteroids during the indacaterol studies, only data for patients not using inhaled corticosteroids were included in the analyses for all treatment arms in order to ensure the placebo patients in the indacaterol trials were sufficiently similar to those in the fixed-dose combination studies (where inhaled corticosteroids were not permitted).

The systematic literature review published by Cope et al identified 11 randomized clinical trials on search of Medline and Embase, including two Novartis studies of indacaterol by Dahl et al (B2334) and Feldman et al (B2346). This review also included four randomized clinical trials from the indacaterol clinical trial program (Novartis studies B2355S2 published by Donohue et al, B2356 published by Kornmann et al, B1302 and B2333). The current analyses was based on the same evidence base, except that two studies evaluating indacaterol 75 µg versus placebo (Novartis studies B2354 and B2355) were added to the network and two studies by Calverley et al in 2003 and 2007 were excluded because no data were available for the current outcomes of interest. The updated network of evidence is presented in Figure 1.

All studies were multicenter, randomized, placebo-controlled trials with a parallel design and included adult patients with COPD. The studies included patients 40 years of age or older with FEV₁/forced vital capacity ≤ 0.70 and FEV₁ percent predicted <80%, while the indacaterol trials required patients to have a predicted FEV₁ ≥ 30%. Most studies included patients who were current or exsmokers with a smoking history of at least 10 years, although some studies included patients with a smoking history of at least 20 years (Hanania et al, Mahler et al, B2334, B2346, B2355S2, and B2356). Three studies included predominantly Asian patients (Zheng et al, and studies B1302 and B2333), whereas the remaining studies included mostly Caucasian patients or reported study centers in Europe and the US. For additional detail regarding the study and patient characteristics, please see Cope et al.

For the two additional randomized clinical studies of indacaterol 75 µg (B2354 and B2355), details were extracted on study design, population characteristics, and interventions. For the subgroup of patients included in the analysis who did not receive concomitant inhaled corticosteroids, data on file were provided by Novartis for the average results per treatment subgroup. The difference and associated standard error (SE) in trough FEV₁ change from baseline at 12 weeks between indacaterol 75 µg and placebo were extracted for B2354 (difference 0.14 L, SE 0.025 L) and B2355 (difference 0.18 L, SE 0.026 L), as well as for transitional dyspnea index at 12 weeks from both studies (B2354, difference 1.44 points, SE 0.46 points; B2355, difference 0.49 points, SE 0.41 points).

Bayesian network meta-analysis was performed to synthesize the results of the included studies simultaneously regarding change from baseline in FEV₁, and the transitional dyspnea index total score at 12 weeks to obtain relative efficacy estimates for indacaterol 75 µg versus FOR/BUD, SAL/FP, and placebo.

A Bayesian network meta-analysis includes data, a likelihood distribution, a model with parameters, and prior distributions. The model links the data from the individual studies to basic parameters, which represent the (pooled) relative treatment effect of each treatment versus placebo.
The relative efficacy between each of the competing interventions was estimated as a function of the basic parameters. A regression model with a normal likelihood distribution was used and both fixed and random effect models were tested. The residual deviance was used to select a fixed or random effects model.

Since randomization only holds within a trial and not across trials in a network meta-analysis, there is the risk that patients assessed in different comparisons are not similar, which leads to consistency violations. Therefore treatment-by-covariate interactions were incorporated in the models to minimize confounding bias.

Since randomization only holds within a trial and not across trials in a network meta-analysis, there is the risk that patients assessed in different comparisons are not similar, which leads to consistency violations. Therefore treatment-by-covariate interactions were incorporated in the models to minimize confounding bias. Covariates potentially causing bias were selected based on the most influential covariates in the previous analyses, which were included simultaneously, ie, the proportion of patients who are current smokers (as opposed to ex-smokers), and the proportion of patients with severe or very severe COPD (as opposed to mild or moderate COPD). The results of the network meta-analysis provide relative treatment effects of each treatment versus a competing intervention. Noninformative prior distributions were used to avoid prior beliefs influencing the results of the model, consistent with previous analyses.

WinBUGS 1.4.1 software was used for the statistical analysis. Summary statistics are presented for the relative treatment effects (ie, differences in transitional dyspnea index or the differences in the change from baseline for FEV₁) and the 95% credible intervals, which reflects the range of true underlying effects with 95% probability. Since the posterior distribution can be directly interpreted in terms of probabilities, it was also possible to calculate the probability that indacaterol 75 µg is better than a certain regimen, which is one advantage of the Bayesian framework over the frequentist approach. Results are presented with and without adjustment for covariates for the change from baseline in FEV₁ and transitional dyspnea index total score at 12 weeks.
Results
For trough FEV$_1$ at 12 weeks, all treatments were more efficacious than placebo for the analyses without covariates, and results for indacaterol 150 µg versus placebo (difference in change from baseline 0.18 L [95% credible interval, 0.15–0.20]) and indacaterol 300 µg versus placebo (difference in change from baseline 0.17L [95% credible interval, 0.14–0.20]) were consistent with previous results. Based on the results without adjustment for covariates (Table 1), indacaterol 75 µg resulted in a greater change from baseline in FEV$_1$ at 12 weeks compared with FOR/BUD 9/160 µg (0.09 L [0.04–0.13]) and FOR/BUD 9/320 µg (0.07 L [0.03–0.11]), and a comparable change from baseline for SAL/FP 50/250 µg (0.00 L [–0.07–0.07]) and SAL/FP 50/500 µg (0.01 L [–0.04–0.05]). Adjusting for differences in the proportion of current smokers and patients with severe or very severe COPD only had a minor impact on the point estimates for FEV$_1$ at 12 weeks for indacaterol 75 µg versus the alternatives, although credible intervals were wider.

As with previous analyses of transitional dyspnea index at 6 months, SAL/FP 50/500 µg was more efficacious than placebo in terms of transitional dyspnea index at 12 weeks. Indacaterol 75 µg was at least as efficacious as placebo, with higher point estimates in the analyses without covariates (difference 0.90 [–0.01–1.81]) and with covariates (difference 0.81 [–0.37–2.00]). Comparative estimates versus FOR/BUD and SAL/FP 50/250 were not possible given the lack of data at 12 weeks. Indacaterol 75 µg had numerically lower transitional dyspnea index scores compared with SAL/FP 50/500 µg (difference 0.49 [–1.87–0.89]), but the credible interval included zero (Table 1). When results were adjusted for covariates, results were less favorable for indacaterol, reducing the point estimate to −1.80 versus SAL/FP 50/500 µg. A strong interpretation is not possible due to the large amount of uncertainty in these estimates, suggesting the results are inconclusive.

Discussion
The objective of this study was to update a previously published network meta-analysis by Cope et al. in order to compare the efficacy of indacaterol 75 µg once a day versus fixed-dose combinations of FOR/BUD and SAL/FP twice daily for COPD in terms of trough FEV$_1$ and transitional dyspnea index total score. In the US, SAL/FP 50/250 µg twice daily and FOR/BUD 4.5/160 µg x two inhalations (ie, 9/320 µg) twice daily are the approved doses for COPD. Indacaterol 75 µg was at least as efficacious as FOR/BUD (9/160 µg and 9/320 µg) in terms of FEV$_1$, and comparable with SAL/FP (50/250 µg and 50/500 µg). In terms of transitional dyspnea index total score at 12 weeks, results for indacaterol 75 µg versus SAL/FP 50/500 µg do not permit a strong interpretation given the uncertainty in the estimates. Moreover, there was no transitional dyspnea index data available at 12 weeks in order to compare indacaterol 75 µg with the approved fixed-dose combinations in the US. Indacaterol 150 µg and 300 µg estimates were consistent with the previous analysis for FEV$_1$ at 12 weeks, suggesting that these doses are expected to be at least as good as FOR/BUD (9/320 µg and 9/160 µg) and comparable with SAL/FP (50/250 µg and 50/500 µg). There were some differences in the results for transitional dyspnea index at 12 weeks as compared with transitional dyspnea index at 6 months in the previous analyses, although indacaterol 150 µg and 300 µg are still expected to provide comparable improvements to those of SAL/FP 50/500 µg.

Randomized clinical trials form the basis of the network and allow for indirect comparisons in the absence of

Table 1 Results of network meta-analysis for FEV$_1$ and TDI at 12 weeks: indacaterol 75 µg versus alternatives without and with covariates

<table>
<thead>
<tr>
<th></th>
<th>Without adjustment for covariates</th>
<th>With adjustment for covariates</th>
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<tbody>
<tr>
<td></td>
<td>Difference in change from baseline (95% CrI)</td>
<td>Probability of IND 75 being better</td>
</tr>
<tr>
<td><strong>FEV, at 12 weeks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.16 (0.12–0.20)</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td>SAL/FP 50/500</td>
<td>0.01 (–0.04–0.05)</td>
<td>62%</td>
</tr>
<tr>
<td>SAL/FP 50/250</td>
<td>0.00 (–0.07–0.07)</td>
<td>52%</td>
</tr>
<tr>
<td>FOR/BUD 9/320</td>
<td>0.07 (0.03–0.11)</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>FOR/BUD 9/160</td>
<td>0.09 (0.04–0.13)</td>
<td>&gt;99%</td>
</tr>
<tr>
<td><strong>TDI at 12 weeks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.90 (–0.01–1.81)</td>
<td>97%</td>
</tr>
<tr>
<td>SAL/FP 50/500</td>
<td>–0.49 (–1.87–0.89)</td>
<td>25%</td>
</tr>
</tbody>
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**Abbreviations:** 95% CrI, 95% credible interval; SAL/FP, fixed-dose combination salmeterol and fluticasone; FOR/BUD, fixed-dose combination of formoterol and budesonide; IND, indacaterol; TDI, transitional dyspnea; FEV$_1$, forced expiratory volume in 1 second.
head-to-head comparisons. However, to yield meaningful results, the trials must be sufficiently similar. If there are systematic differences in study and patient characteristics across the different direct comparisons, and these differences are modifiers of the relative treatment effects, then the estimate of the indirect and mixed comparisons is biased.\textsuperscript{10} In the indacaterol studies, patients were allowed to continue receiving concurrent inhaled corticosteroids, which was not the case in the FOR/BUD and SAL/FP studies. To avoid biased estimates of indacaterol versus FOR/BUD and SAL/FP, only a subgroup of patients who did not receive concurrent inhaled corticosteroids in the indacaterol studies were evaluated in the network meta-analysis. Meta-regression models were used to adjust for possible differences across studies in terms of the proportion of current smokers and the proportion of patients with severe or very severe COPD. Differences between adjusted and unadjusted models were not greater than the amount of uncertainty in the estimates and therefore lead to consistent interpretation. However, it was not possible to assess the similarity of the studies in terms of all patient characteristics. For example, limited information was presented with respect to the ethnicity of patients across the trials, although previous analyses suggest ethnicity was not an important factor. Similarly, there were insufficient data presented to evaluate the comorbidities of patients across the trials. Therefore, it has to be accepted that with aggregate level data there is the risk of residual confounding bias.

The current analysis focuses on the efficacy of indacaterol 75 \( \mu \text{g} \) in terms of FEV\(_1\), and transitional dyspnea index at 12 weeks. However, decision-makers should also consider additional patient-relevant endpoints. It was not possible to perform a network meta-analysis for St George’s Respiratory Questionnaire (as was performed previously at 6 months) or for rescue medication use given the data available for the current evidence base, although indacaterol 75 \( \mu \text{g} \) was associated with significant improvements in comparison to placebo at 12 weeks for both of these outcomes. Given the existing trials for indacaterol 75 \( \mu \text{g} \) are 12 weeks long, it is not possible to evaluate efficacy beyond this time point. Finally, treatments should also be assessed in terms of their safety, which was not evaluated in the current study.

In conclusion, based on results of a network meta-analysis with and without covariates, indacaterol 75 \( \mu \text{g} \) is expected to be at least as efficacious as FOR/BUD (9/320 \( \mu \text{g} \) and 9/160 \( \mu \text{g} \)) and comparable with SAL/FP (50/250 \( \mu \text{g} \) and 50/500 \( \mu \text{g} \)) in terms of lung function (trough FEV\(_1\)). In terms of breathlessness (transitional dyspnea index) at 12 weeks, results are inconclusive given the limited data.