

# Response to the Letter to the Editor Regarding “Intraclass Difference in Pneumonia Risk with Fluticasone and Budesonide in COPD: A Systematic Review of Evidence from Direct-Comparison Studies” [Response to Letter]

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## Dear editor

We read with interest the remarks from Barnes et al regarding our recently published work (Lodise et al 2020;15:2889–2900).<sup>1</sup> They raise some observations based on several flawed arguments that we would be glad to address in turn.

First, Barnes et al suggest that as fluticasone furoate (FF) and fluticasone propionate (FP) are molecularly distinct compounds, they should be analyzed separately. However, no head-to-head clinical trial has conclusively demonstrated a lower/different pneumonia risk with FF versus FP, and the grouping of FF and FP in our analysis is consistent with the approach taken by previous independent investigations, including by the European Medicines Agency (EMA, per the 2016 EMA Pharmacovigilance Risk Assessment Committee) and a recent meta-analysis.<sup>2</sup>

Barnes et al also seem to be missing the point that our analysis sought to compare pneumonia risks between fluticasone and budesonide using data from direct-comparison studies only. To our knowledge, our analysis is the first systematic review of direct treatment comparison studies that addresses an evidence gap highlighted in the 2016 EMA assessment. Notably, the 2016 EMA assessment could not account for some important newer publications, including 2 cohort studies,<sup>3,4</sup> a nested case-control study,<sup>5</sup> and a meta-analysis,<sup>2</sup> as well as the FULFIL trial<sup>6</sup> and a post-hoc analysis of the UPLIFT trial.<sup>7</sup> Our inclusion of only direct-comparison studies surmounted many of the limitations associated with previous evaluations that made indirect comparisons of randomized clinical trials. In each of the direct-comparison studies included in our systematic review, treatment groups were highly similar at baseline, mitigating the impact of confounding factors on the observed results. The findings of our analysis are corroborated by numerous long-term population-based cohort and nested case-control studies conducted in several countries across multiple regions,<sup>3–5,8–12</sup> which, taken together, reported either higher pneumonia risk or higher odds of pneumonia, depending on the study design, with fluticasone- versus budesonide-containing therapy.

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Additionally, Barnes et al voice some concerns about data inclusion. For instance, we incorporated partial data from the FULFIL study,<sup>6</sup> excluding the (lack of a difference in) pneumonia rates at 52 weeks. This is correct, as the 52-week data were not included because the safety extension population (EXT) included only 430 out of 1,810 subjects from the intent-to-treat (ITT) population, representing a reduction of >75% of the randomized set. This large difference between the ITT and EXT populations limits meaningful interpretations of the pneumonia-related safety data up to 52 weeks. In addition, event rates, which account for individual patient exposure/multiple events per patient and are therefore commonly used by regulatory authorities to compare safety risks between interventions, are not publicly available for that EXT population. Their letter further cites similar percentages of pneumonia in the ETHOS<sup>13</sup> and IMPACT<sup>14</sup> studies as evidence against an intraclass difference in pneumonia risk among inhaled corticosteroid (ICS) agents. However, this represents an indirect comparison with ICS- and non-ICS-containing treatments that was not relevant to our analysis. Notably, a closer comparison of the ETHOS and IMPACT studies still shows that the incidence and event rates for pneumonia were higher with fluticasone- versus budesonide-containing therapy (Table 1).

Barnes et al further refer to the observational PATHOS<sup>10</sup> study and its associated limitations and emphasize that our findings are highly dependent on this study. As previously described, however, our conclusions were based on the totality of evidence that the difference in pneumonia risk between fluticasone and budesonide observed in FULFIL, a direct-comparison randomized trial, is corroborated by similar findings across a variety of observational studies and is consistent with a large body of evidence. In addition, in our article, we have acknowledged the limitations of observational studies and note that these limitations, including unmeasured

confounders, misclassification of exposures and outcomes, and a lack of lung function data mentioned specifically in their letter, should equally apply to patients receiving fluticasone and budesonide. Furthermore, while systematic errors are always a concern in observational studies, it is important to note that the two treatment groups were extremely well balanced at baseline after matching in the PATHOS study. Therefore, the concerns raised by Barnes et al regarding potential biases present in this article are overstated.

In conclusion, we believe our systematic review represents the totality of current evidence indicating a clinically important intraclass difference in the risk of pneumonia between fluticasone- and budesonide-containing inhaled medications for chronic obstructive pulmonary disease. We hope that our clarifications will be helpful to the readership.

## Disclosure

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**Table 1** Indirect Comparison of Pneumonia Incidence Rates and Event Rates in the ETHOS and IMPACT Studies

Treatment	Incidence Rate (% of Patients)	Event Rate (per 1000 Patient-Years)
Budesonide (320 µg)/glycopyrrolate/formoterol fumarate <sup>13</sup>	4.6	53.3
Glycopyrrolate/formoterol fumarate <sup>13</sup>	2.9	37.3
Rate ratio	1.6	<b>1.4</b>
Fluticasone furoate/umeclidinium/vilanterol <sup>14</sup>	8	95.8
Umeclidinium/vilanterol <sup>14</sup>	5	61.2
Rate ratio	1.6	<b>1.6</b>

**Note:** The bolded values in the table are the rate ratios of the event rates in the ETHOS and IMPACT studies, respectively.

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