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## Title

# Dual bronchodilation response by exacerbation history and eosinophilia in the FLAME study


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## Author contributions

All authors contributed to the design and conduct of this *post hoc* analysis. The authors take full responsibility for the scope, direction, content of, and editorial decisions relating

to the manuscript, were involved at all stages of development, and have approved the submitted letter to the editor.

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**Running head**: Exacerbation history and eosinophilia in COPD

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## To the Editor

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 strategy notes that exacerbation history is the best predictor of future exacerbations in patients with chronic obstructive pulmonary disease (COPD) (1); in addition, blood eosinophil level has been suggested as a potential biomarker for exacerbation risk and a predictor of efficacy of inhaled corticosteroids (ICS) in preventing exacerbations in COPD patients at a risk of exacerbations (1-3). A long-acting $\beta_2$-agonist (LABA)/long-acting muscarinic antagonist (LAMA) combination is recommended as the preferred treatment for symptomatic COPD patients who are at an increased risk of exacerbations, determined by their exacerbation history (GOLD D) (1). GOLD 2017 recommends ICS use in patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators; of note, long-term ICS use is associated with adverse events (AEs) such as pneumonia, suggesting that their use should be limited to patients with clear benefits from this treatment (1,4). In COPD patients (particularly those with mMRC dyspnea grade ≥2 and a history of exacerbation(s) in the previous year), LABA/LAMA combinations have demonstrated greater improvements in lung function, fewer exacerbations, and a lower risk of pneumonia compared with LABA/ICS (4,5).

The FLAME study (NCT01782326) showed greater exacerbation reduction with the LABA/LAMA indacaterol/glycopyrronium (IND/GLY) than with the LABA/ICS salmeterol/fluticasone (SFC) in symptomatic patients with a history of exacerbations (5). A recently published analysis of the FLAME study revealed that exacerbation prevention with IND/GLY was superior or similar to that with SFC for all tested

ranges of blood eosinophil levels (6), which had to be <600/μl to allow inclusion. However, a recent *post hoc* analysis of the WISDOM study (2) suggested that a small proportion of patients with both history of ≥2 exacerbations and high blood eosinophil counts were at an increased risk of exacerbations during follow-up after ICS withdrawal. Here we report a *post hoc* analysis of the FLAME study that evaluated treatment effects on moderate/severe exacerbations based on absolute blood eosinophil count (tested cutoffs:150 and 300 cells/μL) or blood eosinophil percentage (tested cutoffs: 2%, 3%, and 4%) and exacerbation history (tested cutoffs: 1 exacerbation and ≥2 exacerbations). An analysis of treatment effects in patients with >2 exacerbations or 1 hospitalisation was also conducted but the results (data not shown) were not different from those observed in patients with ≥2 exacerbations.

The rate of exacerbations was analyzed using a negative binomial model. The time-to-event endpoints were analyzed using a Cox proportional hazards regression model. Blood eosinophil cutoff levels were applied to measurements at treatment initiation according to the percentage of total white blood cell count and absolute eosinophil count.

In patients with <150 cells/μL, IND/GLY significantly reduced the rate of moderate/severe exacerbations compared with SFC in patients with 1 and ≥2 exacerbations ($P < 0.001$ and $P = 0.021$, respectively); effects of both treatments were comparable in patients with ≥150 cells/μL, independent of exacerbation history **(Figure 1)**. Similarly, in patients with <300 cells/μL, IND/GLY significantly reduced the rate of moderate/severe exacerbations compared with SFC in patients with 1

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and ≥2 exacerbations (*P* < 0.001 and
*P* = 0.038, respectively), whereas effects of both treatments were comparable in patients with ≥300 cells/μL, independent of exacerbation history **(Figure 1)**. In patients with
<150 cells/μL, IND/GLY significantly improved (i.e., increased) the time-to-first moderate/severe exacerbation, across all groups according to exacerbation history, whereas the two treatments were comparable in patients with ≥150 cells/mL, across all three groups according to exacerbation history **(Figure 2)**. Similarly, in patients with <300 cells/μL, IND/GLY significantly increased the time-to-first moderate/severe exacerbation across all groups according to exacerbation history, whereas both treatments were comparable in patients with ≥300 cells/μL **(Figure 2)**. IND/GLY provided greater or similar exacerbation prevention than SFC across all groups according to blood eosinophil percentage and exacerbation history (data not shown).

Furthermore, the difference in effects between the two treatments decreased with an increase in eosinophil counts and number of past exacerbations (**Figures 1 and 2**). However, while the interaction was significant between treatment effect and blood eosinophil levels, it was not significant between treatment effect and exacerbation history (data not shown). Of note, the size of patient groups reduced significantly as eosinophil counts and number of past exacerbations increased and, therefore, the interaction analyses need to be interpreted with caution. Overall, at no cutoff level was SFC superior to IND/GLY in terms of reduction in moderate/severe exacerbation rate or time-to-first exacerbation. Although high eosinophil counts may identify a group that was more likely to experience exacerbation/s after ICS

withdrawal from triple therapy among patients with history of exacerbations (2), the present analysis suggests that blood eosinophil counts and exacerbation history did not identify a subpopulation of patients where LABA/ICS would be preferable over IND/GLY for exacerbation prevention (4, 5). Moreover, the fact that IND/GLY is always superior in patients with low blood eosinophils but of similar efficacy in the higher eosinophils groups may support indirectly the WISDOM study analysis (2), indicating that blood eosinophils may have a role in identifying patients who benefit from ICS in addition to LABA/LAMA.

The clinical relevance of blood eosinophil cutoff in the management of COPD remains uncertain because blood eosinophils are not stable throughout the disease course (7). A recent publication reported that the association of higher eosinophil count with exacerbations is not consistent (8). In FLAME, slight changes in blood eosinophil levels (<0.5%) were observed during the run-in and treatment phases of the study. Ongoing prospective studies such as TRIBUTE (NCT02579850), IMPACT (NCT02164513) and ETHOS (NCT02465567) may illuminate this issue.

Our results suggest that IND/GLY provided greater or comparable exacerbation prevention than SFC in all groups according to blood eosinophil levels and exacerbation history. These results further support the efficacy of IND/GLY for exacerbation prevention in patients with moderate-to-very severe COPD, particularly in those who are at a risk of exacerbations, and are in line with current GOLD recommendations regarding use of LABA/LAMA over LABA/ICS in COPD patients at risk of exacerbations (1).

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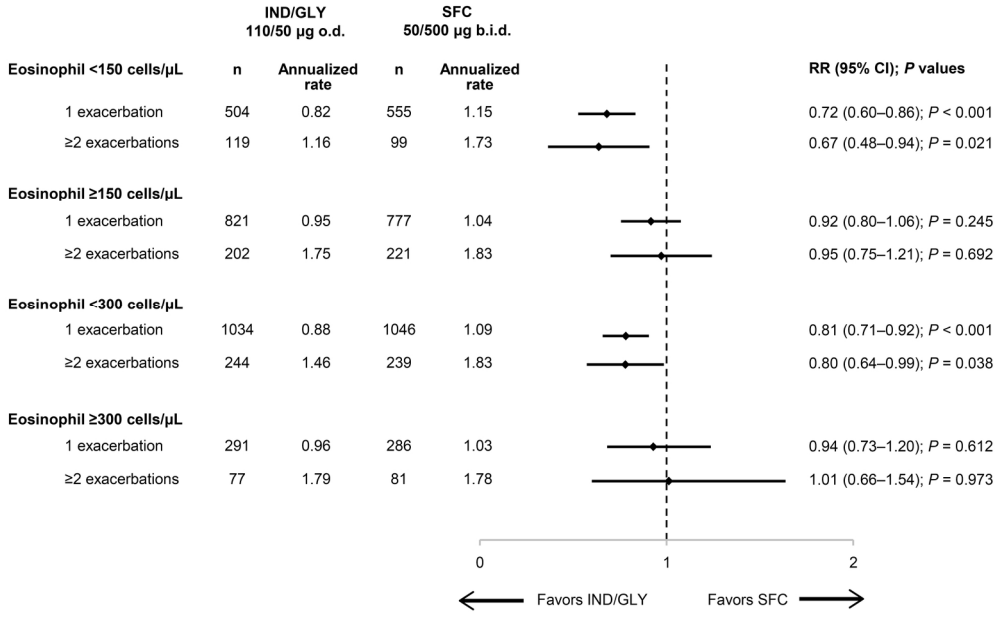
## FIGURES

### Figure 1. Rate ratios (95% CI) of moderate/severe chronic obstructive pulmonary disease exacerbations based on blood eosinophil cutoff and exacerbation history

b.i.d., twice daily; CI, confidence interval; IND/GLY, indacaterol/glycopyrronium; o.d., once daily; RR, rate ratio; SFC, salmeterol/fluticasone

### Figure 2. Hazard ratios (95% CI) and estimated time-to-first moderate/severe chronic obstructive pulmonary disease exacerbation by blood eosinophil cutoff and exacerbation history

b.i.d., twice daily; CI, confidence interval; HR, hazard ratio; IND/GLY, indacaterol/glycopyrronium; o.d., once daily; SFC, salmeterol/fluticasone

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b.i.d., twice daily; CI, confidence interval; IND/GLY, indacaterol/glycopyrronium; o.d., once daily; RR, rate ratio; SFC, salmeterol/fluticasone

90x57mm (600 x 600 DPI)

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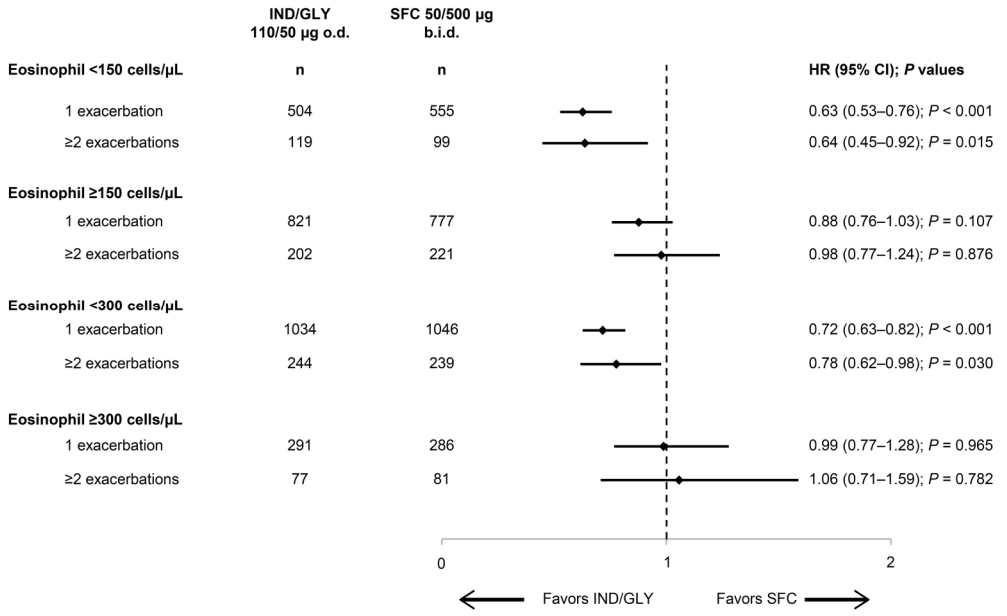


Figure 2. Hazard ratios (95% CI) and estimated time-to-first moderate/severe chronic obstructive pulmonary disease exacerbation by blood eosinophil cutoff and exacerbation history
b.i.d., twice daily; CI, confidence interval; HR, hazard ratio; IND/GLY, indacaterol/glycopyrronium; o.d., once daily; SFC, salmeterol/fluticasone

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