Lack of clinically relevant differences between combination therapy and monotherapy in COPD

To the Editor:

BATEMAN *et al.* [1] reported significantly greater mean improvements with indacaterol/glycopyrronium combination therapy, Ultibro Breezhaler (QVA149) compared to monotherapy with either indacaterol (0.07 L), glycopyrronium (0.09 L) or tiotropium (0.08 L) for the primary outcome of trough forced expiratory volume in 1 s (FEV_1) at week 26 in patients with chronic obstructive pulmonary disease (COPD). However, such improvements were all less than the 0.1–0.14 L range that represents the minimal clinically important difference (MCID) for FEV_1 [2]. Pointedly, the mean differences between combination therapy and monotherapy for the secondary outcomes of dyspnoea (transition dyspnoea index score) and health status (St. George's Respiratory Questionnaire score) were also less than the respective MCID values, with a significant difference between Ultibro Breezhaler (QVA149) and tiotropium at week 26. Analysis of individual responders revealed a significantly higher proportion of patients exceeding the MCID for transition dyspnoea index ($\geqslant$1 unit) and St. George's Respiratory Questionnaire ($\geqslant$4 units) with QVA149 *versus* tiotropium but not indacaterol or glycopyrronium. These data do not therefore support the conclusion that QVA149 demonstrated clinically relevant superiority *versus* their respective monotherapy components in COPD.

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Clinically relevant differences not found between combination and monotherapy http://ow.ly/thbE4

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From the authors:

We would like to thank B.J. Lipworth for his letter and interest in the SHINE study. B.J. Lipworth incorrectly describes the conclusion of the SHINE study article. Nowhere in the article is it stated that QVA149 "demonstrated clinically relevant superiority *versus* its respective monotherapy components in COPD". Rather, we concluded that "dual bronchodilation with once-daily QVA149 demonstrated superior and clinically meaningful outcomes *versus* placebo and superiority *versus* treatment with a single bronchodilator" [1]. The conclusion on QVA149 *versus* placebo is justified by improvements in trough forced expiratory volume in 1 s (FEV_1) being twice the accepted minimal clinically important difference (MCID) of 100 mL [2] and that for the transition dyspnoea index (TDI) exceeding the MCID of >1 unit improvement [3]. The improvement in the St George's Respiratory Questionnaire (SGRQ) total score (least squares mean difference *versus* placebo -3.99 units at week 12) fell just short of the MCID of 4 units reduction [4].