

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 (FEV₁) 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 FEV₁ [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 (≥ 1 unit) and St. George's Respiratory Questionnaire (≥ 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 (FEV₁) 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].

Further, we acknowledged in the discussion section of the article, that a limitation of the study is the “difficulty in evaluating the clinical significance of spirometric and other clinical end-points (e.g. TDI and SGRQ total scores) *versus* active (*i.e.* monocomponent) treatments” [1]. Current standards for MCID thresholds were proposed for comparisons *versus* placebo or for improvements *versus* baseline, but have not been confirmed to be applicable or attainable in comparisons either between active comparators, or between combination products and their monotherapy components [2].

Based on this, and as recommended in the new European Medicines Agency’s Committee for Medicinal Products for Human Use guidance [5], a predefined clinically relevant mean treatment difference of 0.06 L for trough FEV₁ was set in the SHINE study protocol for QVA149 monotherapy comparisons. This is consistent with published data comparing free long-acting β_2 -agonist (LABA)+long-acting muscarinic antagonist (LAMA) combinations with individual LABA or LAMA therapies [6, 7]. Along with the statistical significance seen for QVA149 *versus* all monotherapies, the observed treatment differences for trough FEV₁ also met, and exceeded, the predefined clinically relevant threshold of 0.06 L (QVA149 *versus* indacaterol, 0.07 L, glycopyrronium, 0.09 L, and tiotropium, 0.08 L). It is also important to note that the MCID is defined as the smallest difference that patients can perceive (at the individual level) as beneficial. The focus should not only be on mean differences between treatments but, therefore, also on the number and percentage of patients who experience relevant improvement (*i.e.* responder analyses). Responder analyses carried out for this study also corroborate the clinical relevance of these data. A significantly higher proportion of patients on QVA149 demonstrated an improvement of >100 mL in trough FEV₁ from baseline (64.3%) than all the monotherapies (indacaterol 46.2%, glycopyrronium 43.2% and tiotropium 46.6%) and placebo 18.9% ($p < 0.001$ for all treatment comparisons).

Because no published consensus on MCID thresholds between active comparators exists, we did not predefine clinically relevant differences in TDI or SGRQ total scores when comparing QVA149 with its monotherapy components or tiotropium. The reduction in SGRQ total score in the placebo group was unusually high after 26 weeks of treatment (>7 units, two to three times the placebo effect seen in most clinical trials), which may have diminished the opportunity to observe MCID differences between QVA149 and active comparators. Despite this, QVA149 demonstrated the greatest mean reduction in SGRQ total score out of all the active treatments tested; 64% of patients achieved an improvement of ≥ 4 units and >50% an improvement of ≥ 8 units, compared with baseline values. Furthermore, a greater proportion of patients achieved the MCID in TDI focal score of >1 unit with QVA149 (68.1%), compared with indacaterol (64.6%), glycopyrronium (63.7%), tiotropium (59.2%) and placebo (57.5%). Therefore, we believe that our original summary is both accurate and justified.



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Dual bronchodilation with once-daily QVA149 provides superior treatment outcomes in COPD *versus* single bronchodilators <http://ow.ly/sne7T>

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