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Title: Tiotropium as add-on therapy to inhaled corticosteroids for patients with symptomatic asthma: Lung function and safety

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Body: Background: Asthma is not controlled in some patients, despite using medium-dose ICS. Methods: Two identical Phase III, randomised, double-blind, double-dummy, placebo (pbo)-controlled, parallel-group trials (NCT01172808/821) assessed tiotropium (tio) efficacy/safety. Patients with symptomatic asthma and pre-bronchodilator FEV_1 60-90% predicted, using medium-dose ICS (400-800µg budesonide equivalent), were randomised to once-daily tio 5µg or 2.5µg (via Respimat® Soft Mist™ Inhaler), salmeterol (sal, active comparator without inferential analysis) or pbo. Other LABAs were not permitted. Pre-specified co-primary end points included peak $FEV_{1(0\text{-}3h)}$ and trough FEV_1 response at 24 wks. Results: Baseline characteristics were similar between trials/treatment groups in 2103 randomised patients (2100 treated); mean post-bronchodilator FEV_1 88.8% predicted. Both tio doses showed significant improvements vs pbo: mean change from baseline in peak $FEV_{1(0\text{-}3h)}$ at 24 wks: 236 mL (tio 2.5µg)/198 mL (tio 5µg) greater than pbo in trial 1 (sal 213 mL); 211 mL (tio 2.5µg) or 169 mL (tio 5µg) greater in trial 2 (all $p<0.0001$) (sal 176 mL). FEV_1 trough response at 24 wks: 185 mL (tio 2.5µg)/152 mL (tio 5µg) greater in trial 1 (sal 123 mL); 176 mL (tio 2.5µg)/133 mL (tio 5µg) greater in trial 2 (all $p<0.0001$) (sal 106 mL). Discontinuation due to adverse

events (AEs): pbo, 2.5%; tio 2.5µg, 1.2%; tio 5µg, 1.9%, sal, 1.8%. No fatal events. AEs balanced across treatment groups. Conclusion: In patients with symptomatic asthma and airflow limitation despite medium-dose ICS, addition of once-daily tiotropium provides sustained bronchodilation (efficacy comparable to sal) and is well tolerated.