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Title: A randomized, crossover study to examine the pharmacodynamics and safety of a new antimuscarinic (TD-4208) in COPD

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Body: Background: TD-4208 is a potent and selective inhaled muscarinic antagonist with functional lung selectivity and long duration in preclinical models of bronchoconstriction. Aims: To investigate the bronchodilatory profile, safety and tolerability of nebulized TD-4208 in patients with COPD. Methods: Thirty-two patients aged 45-75 years with moderate or severe COPD were randomized in a double blind, complete 4-way crossover study. Single doses of 350 µg or 700 µg TD-4208, ipratropium (500 µg) or placebo were administered using a PARI LC Plus nebulizer in each period. Baseline and serial post-dose spirometry assessments (0-25 hrs) were performed. Safety evaluation included AEs, vital signs, ECGs, and clinical lab results. Results: A statistically significant improvement in peak FEV1 versus placebo of 174 mL (95% CI: 112, 235), 169 mL (95% CI: 108, 231) and 176 mL (95% CI: 114, 237), for TD-4208 350 µg, 700 µg, and ipratropium, respectively, was observed ($p<0.001$ for each comparison). Similar to ipratropium, onset of action of TD-4208 was rapid and bronchodilation was sustained over the 25-hr monitoring period. FEV1 difference from placebo at 12 hrs was 112.5 mL, 123.4 mL, and 15.3 mL; $p <0.001$; <0.001 and 0.669, and at 24 hrs was 102.8 mL, 136.6 mL, and -24.2 mL; $p <0.001$; <0.001 and 0.327, for TD-4208 350 µg, 700 µg, and ipratropium, respectively. AEs were generally mild and occurred with similar frequencies in all groups, with the most common being headache and dyspnea. No SAEs occurred. Conclusions: TD-4208 was well tolerated and demonstrated significant peak bronchodilation with rapid onset that was sustained over 24 hrs suggesting a once daily dosing regimen.