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Title: Effects of low- vs high-dose fluticasone/formoterol combination therapy on AMP challenge in asthmatic patients

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Body: Background: The ICS fluticasone propionate (FLUT) and the LABA formoterol fumarate (FORM) have now been combined in a single aerosol inhaler (FLUT/FORM; flutiform®). The effect of low- (2 puffs 50/5µg bid) vs high-dose (2 puffs 250/10µg bid) FLUT/FORM on airway responsiveness to AMP was compared in an incomplete block, placebo-controlled, 2-way crossover study. Post hoc data analysis from patients who received both FLUT/FORM doses is presented. Methods: 62 patients (33M, 29F; ≥18yrs; reversible FEV_1 ≥60% pred.) discontinued maintenance ICS medication for 2-3wks; those showing a provocative dose of AMP producing a 20% decline in FEV_1 (AMP PD_{20} FEV_1) of <60mg were randomised to receive 2 of 3 treatments (FLUT/FORM high-, low dose or placebo) during 2 periods of 28±3 days each, separated by 2-3wks. AMP challenges were performed pre-dose and repeated 12h after last dose at the end of each treatment period. The difference in changes in AMP PD_{20} FEV_1 (day 1 vs day 28) between treatments were compared by an ANCOVA. Results: 15 patients were randomised to receive both high- and low-dose FLUT/FORM. The change in AMP PD_{20} FEV_1 was greater with FLUT/FORM high- compared with low-dose (LS means: high dose = 11mg; 95% CI 4.3, 27.9; low dose = 4.6mg, 95% CI 1.8, 11.8), with a statistically significant 2.4 fold difference in AMP PD_{20} FEV_1 (1.2 doubling doses) between doses (LS mean: 2.4; 95% CI 1.3, 4.5; p=0.012). FLUT/FORM was well-tolerated; only few (mild or moderate) AEs occurred. Conclusions: A significant dose-response was found between low- and high-dose FLUT/FORM with the higher dose demonstrating a greater reduction in airway responsiveness to AMP.