Name of Sponsor/Company
University of Dundee

Title of Study
A Randomised, Double-Blind, Double-Dummy Cross-Over Study to demonstrate Superiority of Fluticasone/ Salmeterol pMDI over double the dose of Fluticasone pMDI on Methacholine Hyper-Reactivity in Patients with Persistent, Mild to Moderate Asthma (as defined by GINA guidelines).

Investigators
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Study centre(s)
Asthma & Allergy Research Group

Publication (reference)
CLEARIE K, McKINLAY L, WILIAMSON P, LIPWORTH BJ. Fluticasone/Salmeterol combination confers benefits in smoking asthmatics. Chest 2012;141:330-338

Date of first enrolment	**Phase of development**
15.04.2009 **Date of last completed** 04.05.2010	Phase III

Objectives
The objective of this study was to evaluate the effects on airway hyper-responsiveness of adding salmeterol to fluticasone vs doubling the dose of fluticasone in patients with asthma who smoked and patients with asthma who did not smoke.

Methodology
Sixteen patients with mild to moderate persistent asthma who did not smoke and 15 such patients who smoked completed a double-blind, randomized, placebo-controlled crossover study. They received either a fluticasone/salmeterol combination (FP/SM) (125/25 mcg) two puffs bid (plus fluticasone placebo), or active fluticasone (250 mcg) two puffs bid (plus FP/SM placebo), for 2 weeks each, with baselines after 1-week to 2-week run-in and washout periods.

Number of patients planned
32 patients randomized to achieve 26 evaluable patients.

Number of patients analysed
31

Diagnosis and main criteria for inclusion
Asthma diagnosis. Inclusion criteria: aged 18 – 65 years, $FEV_1 \geq 60\%$, <30% PEF variability, $\leq$ 1000 mcg BDP or equivalent, $PC_{20} < 4$ mg/mL.

Test product dose
Arm A
FP 250 mcg MDI, 2 puffs bid (via Volumatic spacer)
+
Placebo to FP/SM, 2 puffs bid (via Synchro-breathe spacer)

Arm B
FP/SM 125/25 mcg MDI, 2 puffs bid (via Synchro-breathe spacer)
+
Placebo to FP, 2 puffs bid (via Volumatic spacer)

Duration of treatment
Approximately 4 weeks (2 treatment periods of 2 weeks, plus up to 3 days)

Reference therapy
None

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Primary Endpoint
Change from baseline in the provocative concentration of methacholine required to produce a 20% fall in FEV_1 (PC_{20}).

Secondary Endpoints
Mannitol, FEV_1, FeNO, ACQ, Overnight Urinary Cortisol Creatinine Clearance

Statistical methods
The SPSS version 16 software (SPSS Inc) was used to carry out the statistical analysis. A sample size of 13 completed patients was estimated to give > 80% power to detect a one-dd difference (minimal important difference) in methacholine PC_{20}. Data were analyzed within each group for patients who completed the crossover study per protocol. Any non-Gaussian data were log transformed prior to analysis. Gaussian data were assessed using Bonferroni-corrected paired and unpaired *t* tests. Post-run-in and post-washout data were compared with a paired *t* test to demonstrate no carry-over effect. Response-dose ratios (RDRs) and asthma control questionnaire (ACQ) data were subjected to nonparametric analysis. Median differences were calculated within groups using the Wilcoxon rank-sum test for paired data, and between groups using the Mann-Whitney test.

Summary Conclusions

Results
In the patients who did not smoke, there were similar improvements in the methacholine PC_{20} with the use of fluticasone and FP/SM. The patients who smoked gained a benefit from FP/SM but not fluticasone, amounting to a PC 20 difference of 1.6 doubling dilutions (95% CI, 1.0-2.2), $P < .01$. The provocative dose of mannitol required to produce a 15% fall in FEV_1 (PD_{15}) showed greater improvements with FP/SM than fluticasone in both patients who smoked and did not smoke. Similar differences in airway calibre between those who smoked and did not smoke were observed in FEV_1 and airway resistance.

Conclusion
FP/SM confers greater improvements in airway hyper-responsiveness and airway calibre in patients with asthma who smoke compared with double the dose of fluticasone. We hypothesize that in the presence of relative steroid resistance, the smooth muscle stabilization conferred by salmeterol is of greater clinical importance in patients who smoke than in those who do not smoke.

Date of the report: 12.05.2016