Name of Sponsor/Company
University of Dundee

Title of Study
A Proof of Concept Study to Evaluate the Additive Effects of HFA-BDP (Qvar) to fluticasone/salmeterol (Seretide) on Surrogate Markers of Small and Large Airway Inflammation in Refractory Asthma

Investigators
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Publication (reference)
WILLIAMSON P, SHORT P, VAIDYANATHAN S, LIPWORTH BJ. Inhaled and systemic corticosteroid response in severe asthma assessed by alveolar nitric oxide: a randomized crossover pilot study of add-on therapy. Br J Clin Pharmacol 2013;75:93-102

Date of first enrolment	**Phase of development**
31.03.2009 **Date of last completed** 09.07.2010	Phase IV

Objectives
To establish whether addition of extra-fine particle BDP (Qvar) or coarse particle inhaled corticosteroids achieve additional suppression of small airways inflammation when added to Fluticasone/Salmeterol (*Seretide*) combination therapy in refractory asthma.

Methodology
A randomised open-label crossover study.

6 week dose-ramp run-in of Fluticasone/Salmeterol (FPSM) 250/50µg BID for 3 weeks, then 500/50 µg BID for 3 weeks. Patients then received additional HFA-BDP 200 µg BID or FP 250µg BID for 3 weeks in a cross-over. Participants then received prednisolone (PRED) 25mg/day for 1 week. Nitric oxide, lung function, mannitol challenge, systemic inflammatory markers and urinary cortisol were measured.

Number of patients planned
24 enrolled to complete 14 adults

Number of patients analysed
15

Diagnosis and main criteria for inclusion
Asthma diagnosis, prescribed ≥1000 µg day fluticasone or 1600 µg day budesonide in the previous year, non-smokers or ex-smokers with <10 pack years, FEV_1<80%, gas trapping and CANO $\geq$ 2ppb.

Test product dose

HFA-BDP 100mcg 2 puff b.i.d. (3 weeks)

Fluticasone Accuhaler 250 mcg b.i.d (3 weeks)

Prednisolone 25mg od (1 week)

Duration of treatment
7 weeks (2 treatment periods of 3 weeks, and 1 treatment period of 1 week)

Reference therapy
Fluticasone/Salmeterol (FPSM) 500/50 µg BID

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Criteria for evaluation

Primary Endpoint
CA_{NO}

Secondary Endpoints
Spirometry, IOS, body plethysmography, PEF diary cards, exhaled oxide levels, PD10 to mannitol in subgroup with $FEV_1 \geq 50\%$), Juniper mini-AQLQ and Juniper ACQ), peripheral eosinophils, serum ECP, ICAM-1, and E-selectin, overnight urinary cortisol/creatinine ratio and 8am serum cortisol.

Statistical methods
Data were assessed for normality using the Shapiro-Wilk test and inspection of boxplots.

Non-Gaussian data were log-transformed prior to analysis. Values for baseline (FPSM), treatment limbs (FPSM/FP and FPSM/FP) and positive control limb (FPSM/PRED) were compared using an ANOVA of repeated measures followed by Bonferroni correction for multiple comparisons.

Analyses were performed using SPSS version 17.0 (Chicago, Illinois, USA) or GraphPad PRISM version 5.01 (San Diego, California, USA).

Summary Conclusions

Results
Fifteen completed per protocol: mean (SD) age 51 (12) years,

FEV_1 58 (13)% predicted, residual volume 193 (100)% predicted and $mannitol_{PD10}$ 177 (2.8) µg.

There was no significant difference between FPSM and add-on therapy for CA_{NO}. FPSM/BDP and FPSM/PRED suppressed bronchial flux (Jaw_{NO}) and FE_{NO} compared with FPSM alone, but there was no significant difference between FPSM/BDP and FPSM/FP.

ECP, e-selectin and ICAM-1 were suppressed by FPSM/PRED compared with FPSM and FPSM/FP but not FPSM/BDP. Plasma cortisol was significantly suppressed by FPSM/PRED.

Conclusion
In severe asthma, CA_{NO} is insensitive to changes in dose and delivery of inhaled corticosteroids and is not suppressed by systemic corticosteroids. Additional inhaled HFA-BDP reduced FE_{NO} and Jaw_{NO} without adrenal suppression. There was a trend to reduction in FE_{NO} and Jaw_{NO} with additional FP but this did not reach statistical significance. PRED reduced FE_{NO} and Jaw_{NO} with suppression of systemic inflammatory markers and urinary cortisol.

Date of the report: 30/03/2016