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<b>Study No:</b> B2F100819	
<b>Title:</b> A randomised, double-blind, three-way crossover study to investigate the effects of nebulised sterile water for injection on beta-agonist induced bronchodilation in healthy male and female volunteers.	
<b>Rationale:</b> Inhaled beta2 agonists used to treat asthma and chronic obstructive pulmonary disease (COPD) may be administered in a nebulised formulation in sterile water for injection (WFI). Low osmolarity solutions are known to provoke cough, although not bronchoconstriction, in healthy subjects. Previous studies have shown that de-sensitisation to cough develops rapidly following inhalation of nebulised distilled water, and that tachyphylaxis persists for over 30 minutes. This study was conducted to determine whether pre-administration of nebulised sterile WFI affects the bronchodilatory response to salmeterol 50 µg assessed by specific airways conductance (sGaw) in healthy subjects.	
<b>Phase:</b> I.	
<b>Study Period:</b> 25 November 2003 – 23 December 2003.	
<b>Study Design:</b> A randomised, double-blind, three-way crossover study.	
<b>Centres:</b> One centre in the UK.	
<b>Indication:</b> None.	
<b>Treatment:</b> Subjects received each of the following three treatments on separate study days: Treatment A = saline (PariNebuliser), saline (ProDose), salmeterol 50 µg Treatment B = saline (PariNebuliser), sterile WFI (ProDose), salmeterol 50 µg Treatment C = sterile WFI (PariNebuliser), sterile WFI (ProDose), salmeterol 50 µg Saline or sterile WFI was administered for 3 minutes via a PariNebuliser, then after 21 minutes saline or sterile WFI for 5 minutes via a ProDose nebuliser. After a further minute, salmeterol 50 µg was administered via an MDI device attached to a VOLUMATIC spacer. There was a minimum washout period of 48 hours between treatments. Order of administration was randomly allocated.	
<b>Objectives:</b> To determine whether pre-administration of nebulised sterile WFI for 3 and 5 minutes alters bronchodilation following a 50 µg dose of salmeterol in healthy male and female subjects.	
<b>Statistical Methods:</b> The primary analyses were performed on the following pharmacodynamic parameters: maximum sGaw, weighted mean sGaw, and serial sGaw measurements from 1 to 10 hours post-salmeterol. Weighted means were determined by first calculating the Area under the curve (AUC) using a trapezoidal rule and then dividing by the relevant time interval. Weighted mean, maximum and serial sGaw data were analysed following a natural logarithmic transformation of the data by analysis of covariance (ANCOVA). Treatment ratios were obtained by taking the anti-log of difference between least squares means and the 95% confidence intervals (95%CI) of the difference was anti-logged to get the 95%CI of the ratios. Secondary analyses were performed on cough-count data measured at 30-second intervals during nebulisation with the PariNebuliser and ProDose nebulisers.	
<b>Study Population:</b> Healthy male and female subjects aged 18 – 45 years, with body mass index of 18.5 – 29.9 kg/m <sup>2</sup> , who were non-smokers for at least 6 months prior to study entry with a pack history of ≤10 pack years Subject were excluded if they had a history of Asthma	
<b>Number of Subjects:</b>	
Planned N	12
Dosed N	12
Completed n (%)	12 (100)
Total Number Subjects Withdrawn N (%)	0
Withdrawn due to Adverse Events n (%)	0
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for Other Reasons n (%)	0
<b>Demographics</b>	
N (ITT)	12
Females : Males	7 : 5
Mean Age in Years (Range)	34 (21 - 41)
Mean Weight in kg (SD)	70.8 (13.7)
White n (%)	12 (100)

**Pharmacodynamic Endpoints:** Comparisons of adjusted geometric means of sGaw between groups for Treatments A, B and C showed no significant differences between treatment groups in the degree of bronchodilation obtained after administration of salmeterol for maximum, weighted mean or serial sGaw data. Secondary analysis of cough incidence was not performed, as treatment did not elicit a sufficient level of coughing after nebulised WFI to distinguish between treatment with low osmolarity WFI or iso-osmolar saline.

**Primary analysis: Statistical Comparison for Maximum sGaw Data Across Treatment Groups**

Treatment Comparison	Adjusted geometric means	Ratio	95% CI
Treatment C/Treatment A	1.92/1.93	1.00	(0.89, 1.11)
Treatment B/Treatment A	1.94/1.93	1.01	(0.90, 1.13)
Treatment C/Treatment B	1.92/1.94	0.99	(0.88, 1.11)

**Primary analysis: Statistical Comparison For Weighted Mean sGaw Data Across Treatment Groups**

Treatment Comparison	Adjusted geometric means	Ratio	95% CI
Treatment C/Treatment A	1.61/1.63	0.98	(0.91, 1.07)
Treatment B/Treatment A	1.60/1.63	0.98	(0.91, 1.06)
Treatment C/Treatment B	1.61/1.60	1.00	(0.92, 1.09)

**Safety results:** Adverse events were collected throughout the study by standard questioning. No adverse events lead to premature discontinuation of the study.

Adverse events:	Treatment A	Treatment B	Treatment C
N (ITT)	12		
No. subjects with AEs n (%)	5 (42)		
Most Frequent AEs			
Headache	0	4	2

**Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: No serious adverse events occurred during the study.**

No. subjects with SAEs n (%) -includes fatal and non-fatal events	0	0
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**Publications:**

No Publication.

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