

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: FFA10022	
Title: A randomised, double-blind, placebo-controlled, incomplete block, 3-way cross-over study to investigate the effect of repeat inhaled doses of GW685698X and FP on airway responsiveness to adenosine 5'-monophosphate (AMP) in mild asthmatic patients	
Rationale: This study was conducted on an new chemical entity, GW685698X. Fluticasone propionate (FP) was included as a positive control.	
Phase: II	
Study Period: 11 September 2003 to 08 March 2004	
Study Design: A multicentre, randomised, double-blind, placebo-controlled, incomplete block, 3-way cross-over study. This summary includes data for the marketed products and placebo. Data for GW685698X will be added if and when GW685698X is approved and marketed.	
Centres: Five centres in 4 countries; Germany (2), the Netherlands (1), Sweden (1) and the UK (1)	
Indication: Asthma	
Treatment: Eligible subjects who completed the screening and run-in AMP challenges were randomised to one of 18 possible combinations of 3 of the 5 treatment periods listed below; each period was separated by ≥ 10 days, and a post-study visit was conducted within 10–15 days of the last dose. Subjects were dosed twice daily on Days 1 – 5 and in the morning on Day 6. Placebo (PBO) on Days 1–6, with AMP challenge 2 hours after final dose PBO and GW685698X FP (500mcg BD) on days 1–5 and FP (500mcg OD) on Day 6, with AMP challenge 2 hours after final active dose All treatments were Inhaled via <i>DISKHALER</i> TM	
Objectives: The object will be added when and if GW685698X is approved and marketed. Investigate the effect of repeat inhaled doses of GW685698X and FP on airway responsiveness in AMP challenge model after 5 days of OD dosing.	
Primary Outcome Variable: AMP PC ₂₀ (the concentration of AMP to cause a 20% fall in FEV ₁ compared to baseline [saline] values).	
Secondary Outcome Variable(s): Serum cortisol weighted mean (0–24 hours) Exhaled nitric oxide Plasma concentrations of	
Statistical Methods: Two populations were defined in this study. The All Subjects Population was defined as all subjects randomised to treatment who received ≥ 1 dose of study treatment, and formed the basis for all demography, lung function, and adverse events summaries. The 'Modified Per Protocol Population was defined as all subjects randomised to treatment who received ≥ 1 dose of study treatment and were compliant with study treatment, and formed the basis for all analyses of all PK measures. AMP PC ₂₀ was log transformed (base 2), serum cortisol weighted mean (0–24hours) on Day 5 was log transformed (base e), and exhaled nitric oxide was log transformed (base e); these variables were then analysed using a mixed model with treatment group and period as fixed effects and subject as a random effect. Baseline exhaled nitric oxide (pre-dose measurement on Day 1) was also included as a fixed effect in the analysis of exhaled nitric oxide. FEV ₁ was used as the baseline in the primary outcome analysis; however, this was not a 'true' baseline: sensitivity analysis was, therefore, repeated using the mixed model with log FEV ₁ (lowest post-saline value) as a fixed effect.	
Study Population: Subjects with mild allergic asthma (FEV ₁ $\geq 70\%$ of predicted) and demonstrated bronchoconstriction in response to inhaled AMP between screening and Day 1 and at the run-in visit. Subjects were excluded if they had life-threatening asthma or a disease (past or present) that could affect the study outcome, had taken oral contraceptives less than 8 weeks before screening, or taken inhaled, intranasal or topical steroids less than 4 weeks before screening.	
	All Subjects Population
Number of Subjects:	
Planned, N	36
Randomised, N	40
Completed, n (%)	38 (95)

Total Number Subjects Withdrawn, N (%)	2 (5)	
Withdrawn due to Adverse Events n (%)	1 (2.5)	
Withdrawn due to Lack of Efficacy n (%)	0	
Withdrawn for other reasons n (%)	1 (2.5)	
Demographics:	All Subjects Population	
N	40	
Females: Males	8: 32	
Mean Age, years (SD)	31.7 (8.69)	
Caucasian, n (%)	39 (98)	
Primary Efficacy Results: (Modified Per Protocol Population)		
Summary of AMP PC₂₀ data (mg/ml) on Day 6 (test vs. ref)		
	500mcg FP vs. PBO	
Adjusted mean (mg/ml)		
Test	13.3	
Reference	4.2	
Difference in dose doubling (DD)	1.66	
95% CI)	(0.53, 2.80)	
Secondary Outcome Variable(s): (Modified Per Protocol Population)		
Summary of serum cortisol weighted mean (0–24 hours) data on Day 5 (test vs. ref)		
	500mcg FP vs. PBO	
Test / ref (nmol/L)	232.81 / 270.21	
Ratio	0.86	
(95% CI)	(0.73, 1.02)	
Summary of exhaled nitric oxide data on Day 6 (test vs. ref)		
	500mcg FP vs. PBO	
Test / ref (ppb)	24.06 / 30.66	
Ratio	0.78	
(95% CI)	(0.61, 1.01)	
Summary of plasma concentration-time data for FP		
	500mcg FP	
	N=12	
C _{max} (pg/mL), geometric mean	144.7	
(95% CI)	(119.2, 175.7)	
T _{max} (hours), geometric mean	0.50	
(95% CI)	(0.33, -0.63)	
AUC _(0-t) (pg.h/ml), geometric mean	753.7	
(95% CI)	(608.9, 932.8)	
Safety Results: An 'on-therapy' AE was one that was collected from Day 1 of the first treatment period through to the post-study visit (all subjects population).		
Most Frequent Adverse Events - On-Therapy	PBO	500mcg FP
	N=16	N=12
Subjects with any AE(s), n(%)	7 (44)	6 (50)
Headache	1 (6)	2 (17)
Nasopharyngitis	1 (6)	2 (17)
Serious Adverse Events - On-Therapy		
n (%) [n considered by the investigator to be related to study medication]		
	PBO	500mcg FP
	N=16	N=12

Subjects with any SAE (fatal or non-fatal)	0	0
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Publications: No Publication.

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