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Study No: FFA10028																																			
Title: A randomised, double-blind, placebo-controlled, balanced incomplete block, multiple dose crossover study to investigate the effect of 3 Days repeat dosing of GW685698X and fluticasone propionate (1000 µg) on exhaled nitric oxide in mild to moderate asthmatic patients.																																			
Rationale: The purpose of the current study was to investigate the effect of a new chemical entity (NCE), which is currently not marketed, and FP on a surrogate marker for efficacy in asthma (exhaled nitric oxide [exNO]).																																			
Phase: I																																			
Study Period: 24 March 2003 to 07 August 2003																																			
Study Design: This was a randomised, double-blind, placebo-controlled, balanced incomplete block, multiple-dose, 3-period crossover study. Data are reported here for the group who received FP and placebo. Data for the NCE will be added to this summary if the NCE is approved and marketed.																																			
Centres: Two centres in Germany																																			
Indication: Asthma																																			
<p>Treatment: Subjects were randomised to one of the following sequence groups:</p> <table border="1"> <thead> <tr> <th>Sequence</th> <th>period 1</th> <th>period 2</th> <th>period 3</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>A</td> <td>B</td> <td>C</td> </tr> <tr> <td>2</td> <td>B</td> <td>D</td> <td>A</td> </tr> <tr> <td>3</td> <td>C</td> <td>A</td> <td>D</td> </tr> <tr> <td>4</td> <td>D</td> <td>C</td> <td>B</td> </tr> </tbody> </table> <p>Each subject received 3 of the 4 treatments</p> <table border="1"> <thead> <tr> <th>Treatment Group</th> <th>Compound</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>PBO</td> <td>-</td> </tr> <tr> <td>B</td> <td>NCE</td> <td>n/a µg</td> </tr> <tr> <td>C</td> <td>NCE</td> <td>n/a µg</td> </tr> <tr> <td>D</td> <td>FP</td> <td>1000µg</td> </tr> </tbody> </table> <p>Inhalations were taken every 30 seconds (total dose administered over 2 minutes).</p>	Sequence	period 1	period 2	period 3	1	A	B	C	2	B	D	A	3	C	A	D	4	D	C	B	Treatment Group	Compound	Dose	A	PBO	-	B	NCE	n/a µg	C	NCE	n/a µg	D	FP	1000µg
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<p>Objectives:</p> <p>To investigate the effect of repeated inhaled doses of NCE (given once-daily for 3 days) on exNO.</p> <p>To investigate the effect of repeated inhaled doses of FP (1000 µg given once daily for 3 Days) on exhaled nitric oxide.</p> <p>To study the pharmacokinetics of repeat inhaled doses of NCE and FP in mild to moderate asthmatic subjects.</p> <p>To investigate the effect of repeat doses of NCE on the HPA-axis.</p>																																			
<p>Primary Outcome Variable(s):</p> <p>The primary (PD) endpoint was exNO weighted mean (0–24 hours) on Day 3.</p>																																			
<p>Secondary Outcome Variable(s):</p> <p>The secondary PD endpoints were exNO weighted mean (0–24 hours) on Day 1; other derived exNO parameters (minimum 0–24 hours, trough) on Days 1 and 3; serum cortisol weighted mean (0–24 hours) on Day 3 only</p> <p>The pharmacokinetic (PK) evaluations included plasma concentrations of NCE and FP on Day 3 to 72 hours post-dose.</p>																																			
<p>Statistical Methods: Twenty-eight subjects were recruited into this study. Subjects who were withdrawn were not replaced. Based on this sample size it was anticipated that at least 24 subjects would have to complete the clinical phase of the study (i.e. complete all treatment periods).</p> <p>Data from previous studies suggest that the effect on reductions in exNO of FP 1000 µg once daily after 3 days of dosing is likely to be in the region of 35-50%. Therefore the sample size calculations were based on the number of subjects needed to detect a reduction of 35% between any of the active doses and placebo. For each of the comparisons, a difference was demonstrated if the two-sided 95% confidence interval for the difference between treatment groups did not contain zero.</p> <p>In previous studies, the observed within-subject standard deviation (on the loge scale) ranged from 0.23 to 0.54. The average of these estimates (weighted by the residual degrees of freedom) was 0.32. Based on this estimate of variability, this study had more than 90% power to detect a difference of 35% between any two treatment groups.</p> <p><u>Populations analysed:</u></p> <p>The All Subjects Population included all subjects randomised to treatment who received ≥1 dose of study medication.</p>																																			

Statistical tests used:		
PD endpoints		
Concentrations of exNO were summarised by treatment group and nominal time; the weighted mean was then calculated by dividing AUC (determined via linear trapezoidal method) over the 24-hour period by the time period. The following summary statistics were calculated for each treatment group, median, maximum, minimum, arithmetic mean, standard deviation, coefficient of variation, geometric mean, 95% confidence interval (CI) for the geometric mean and standard deviation of logarithmically transformed data.		
Separate statistical analyses were conducted on the derived parameters. Each parameter was logarithmically transformed prior to analysis. A mix model was fitted with baseline (log _e transformed), period, Day, treatment group and treatment group by Day interaction as fixed effects and subject as a random effect. Baseline was defined as pre-dose measurement on Day 1. Treatment ratios of all comparisons were calculated by taking the anti-log of the difference between the LS (least square) means. Using pooled estimates of variance, 95% CIs were calculated for the difference and then anti-logged.		
Concentrations of serum cortisol were listed and summarised by treatment group and nominal time. The serum cortisol weighted mean (0–24 hours) was determined for each subject on Day 3. A formal statistical analysis for serum cortisol compared to placebo was performed.		
PK endpoints:		
PK parameters were calculated by standard non-compartmental analysis according to current method sheets and using WinNonlin. Summary statistics were also produced.		
Safety:		
No formal analysis was performed on safety data. Summary statistics only were produced.		
Study Population: Atopic subjects with mild to moderate allergic asthma (screening forced expiratory flow volume, 1 second [FEV ₁] ≥60% of predicted and exNO threshold above 30ppb), who could correctly use a <i>DISKHALER™</i> . Subjects were excluded if they had life-threatening asthma or a disease (past or present) that could affect the study outcome. All subjects provided written informed consent.		
Number of Subjects:		All subjects population
Planned N	24	
Dosed N	28	
Completed n (%)	27	
Total Number Subjects Withdrawn N (%)	1 (4)	
Withdrawn due to Adverse Events n (%)	1 (4)	
Withdrawn due to Lack of Efficacy n (%)	0	
Withdrawn for Other Reasons n (%)	0	
Demographics:		All subjects population
N (all subjects population)	28	
Females: Males	1: 27	
Mean Age in Years (SD)	36.4 (9.3)	
Mean Weight in Kg (SD)	84.64 (11.52)	
White n (%)	27 (96)	
Primary PD(s) outcome:		
Summary of exNO values (ppb) on Day 3	PBO N=21	FP 1000µg N=20
Pre-dose mean (SD)	77.07 (59.68)	56.34 (33.20)
24-hour follow-up mean (SD)	77.91 (53.23)	47.21 (29.79)
72-hour follow-up mean (SD)	71.31 (49.97)	48.70 (33.66)
exNO weighted mean (0–24 hours) on Day 3	FP 1000µg vs. PBO	
Ratio	0.71	
(95% CI)	(0.64, 0.78)	
Secondary PD outcomes:		
exNO weighted mean (0–24 hours) on Day 1	FP 1000µg vs. PBO	
Ratio	1.04	
(95% CI)	(0.94, 1.14)	
exNO minimum (0–24 hours) on Days 1 and 3	FP 1000µg vs. PBO	

Ratio, Day 1	1.03	
(95% CI), Day 1	(0.93, 1.14)	
Ratio, Day 3	0.68	
(95% CI), Day 3	(0.62, 0.76)	
exNO weighted mean (0–24 hours) Day 3 / Day 1 comparison	PBO N=21	FP 1000µg N=20
Ratio	1.08	0.73
(95% CI)	(0.98, 1.18)	(0.67, 0.80)
exNO minimum (0–24 hours) Day 3 / Day 1 comparison	PBO N=21	FP 1000µg N=20
Ratio	1.12	0.75
(95% CI)	(1.01, 1.24)	(0.67, 0.83)
Serum cortisol weighted mean (0–24 hours) on Day 3	FP 1000µg vs. PBO	
Ratio	0.82	
(95% CI)	(0.72, 0.94)	
Secondary PK outcomes:		
Parameter (units)	FP 1000µg N=20	
C _{max} (pg/ml), geometric mean (95% CI)	169.4 (121.5, 236.1)	
T _{max} (hours), median (range)	0.56 (0.10, 2.05)	
AUC _(0–7) (pg.h/ml), geometric mean (95% CI)	784.8 (551.8, 1116.1)	
AUC _(0–t) (pg.h/ml), geometric mean (95% CI)	784.8 (551.8, 1116.1)	
T _½ (hours), geometric mean (95% CI)	6.45*** (5.18, 8.03)	
*n=8; **n=16; ***n=17		
Safety Results: All AEs were collected at each visit starting from Day 1 of the first treatment period through to the post-study visit (all subjects population).		
Adverse Events:	PBO N=21	FP 1000 µg N=20
No. subjects with AEs n (%)	11 (52)	7 (35)
Dyspnoea	11 (20)	10 (18)
Nasal congestion	1 (2)	1 (2)
Headache	2 (4)	2 (4)
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:		
	PBO N=21	FP 1000 µg N=20
Subjects with non-fatal SAEs	1 (2) [0]	0
Abdominal pain	1 (2) [0]	0
Subjects with fatal SAEs	0	0
Publications: No Publication		

Date Updated: 28-Sep-2005