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<b>Study No.:</b> FFA103096
<b>Title:</b> A randomised, double blind, placebo controlled, incomplete block, five-way cross-over study to investigate the effect of one week repeat dosing of a new chemical entity (NCE) and inhaled fluticasone propionate (FP) on twenty-four hour serum cortisol in healthy subjects.
<b>Rationale:</b> The dose selection of inhaled corticosteroids for Phase IIb studies is often difficult because their clinical efficacy cannot be satisfactorily measured in small studies of short duration. Hypothalamic-pituitary-adrenal (HPA) axis suppression, measured by decreases in levels of serum and urinary cortisol, can be used to assess the potential for systemic side-effects of inhaled corticosteroids. This study investigated the dose-response of a NCE and FP on HPA-axis suppression. The main objective of the study was to guide dose selection for Phase IIb studies.
<b>Phase:</b> I
<b>Study Period:</b> 19 Oct 2004–08 Mar 2005
<b>Study Design:</b> This was a randomised, double blind, placebo controlled, incomplete block, 5-way cross-over, 7-day repeat dose study. Results are presented for the FP arms in this summary. Data for the NCE will be added, if and when the NCE is approved and marketed.
<b>Centres:</b> One centre in the UK.
<b>Indication:</b> None.
<b>Treatment:</b> Inhaled NCE at 5 dose levels; inhaled fluticasone propionate (FP) <i>DISKUS</i> twice daily (b.i.d.) 250, 500, and 1000 µg; and placebo.
<b>Objectives:</b> The primary objective was to estimate the dose of the NCE that has an equivalent effect on the weighted mean 0–24 hour serum cortisol as FP <i>DISKUS</i> 500 µg b.i.d. after 1 week repeat dosing in healthy subjects.
<b>Statistical Methods:</b> All data were listed and summarised. The dose response relationships on weighted mean 0–24 h serum cortisol was characterized using a mixed effects model with terms fitted for subject (random effect), baseline, period, compound, dose (continuous variable) fitted as a quadratic term and a compound by dose interaction term (all fixed effects). Placebo was excluded from this analysis. The weighted means were log <sub>e</sub> -transformed prior to analysis. The daily dose of the NCE predicted to have a similar effect as FP 500 µg b.i.d. was then calculated using the predicted lines of best fit for both compounds. Corresponding 95% confidence intervals (CIs) around the dose were calculated using the 95% CIs for the lines of best fit for both compounds. Estimates of the daily doses of the NCE predicted to have similar effects as FP 250 µg b.i.d. and 1000 µg b.i.d. were also calculated from the same model, along with corresponding 95% CIs. A secondary analysis was conducted to supplement the primary analysis. Weighted mean 0–24 h serum cortisol on Day 7 was log <sub>e</sub> -transformed and then analysed using a mixed effects model with baseline, period and treatment group (indicating compound and dose group combined) fitted as fixed effects, and subject fitted as a random effect. Each active treatment group was compared with placebo. The total amount of cortisol excreted in the urine over 0–24 h (Ae <sub>(0–24)</sub> ) was log <sub>e</sub> -transformed and then analysed using a mixed effects model in which period and treatment group were fitted as fixed effects and subject fitted as a random effect. Each active treatment group was compared with placebo. Population modelling techniques using non-linear mixed effects methods were used to estimate absorption rate constants (ka), apparent clearances (CL/F), apparent volume of distributions (V <sub>ss</sub> /F), and predicted concentration-time courses (from which AUC <sub>(0–1)</sub> , AUC <sub>(0–24)</sub> , C <sub>max</sub> and t <sub>max</sub> could be determined) for FP and the NCE. Relationships between the PK parameters and demographic variables were explored by examining the effects of these variables on the residual error when they were included in the model as covariates. The relationship between weighted mean 0–24 h serum cortisol, urinary cortisol Ae <sub>(0–24)</sub> and systemic exposure (AUC <sub>(0–24)</sub> ) was further investigated in an E <sub>max</sub> model that estimated the potency of the NCE relative to FP. Safety data were listed and summarised only. There was no formal statistical analysis of the safety data. All 44 subjects who entered the study and received at least one dose of study drug were included in the safety listings and summaries. There were 41 out of the total 44 subjects for whom PK and cortisol parameters could be derived. Therefore 41 of the 44 subjects were included in the PK and cortisol analyses.
<b>Study Population:</b> Healthy, men and women (non-childbearing potential only) aged 18–65 years, with body mass index 19–31 kg/m <sup>2</sup> and no history of breathing problems. Non-smokers for past 12 months and pack history ≤5 pack years. Normal ECG at screening and able to use inhalation device satisfactorily. No history or evidence of any disease, condition or allergy that would preclude participation in the study in terms of the subject's health and ability to participate, or that would affect the validity of the study results.

Number of Subjects:				
Planned, N	44			
Randomised, N	44			
Completed, n (%)	40 (93.2)			
Total Number Subjects Withdrawn, n (%)	4 (9)			
Withdrawn due to Adverse Events n (%)	0			
Withdrawn due to Lack of Efficacy n (%)	0			
Withdrawn for other reasons n (%)	4 (9)			
Demographics:				
N (All Subjects)	44			
Females:Males	5:39			
Mean Age, years (Range)	35.5 (19-65)			
Caucasian/European heritage, n (%)	37 (84)			
Primary Outcome Results: Only the placebo and FP results are presented				
Summary of weighted mean of 0–24 h serum cortisol ( $\mu\text{g}/\text{dL}$ )				
Treatment	n	Geometric mean	95% CI	
Placebo	21	7.18	6.57–7.84	
FP 250 $\mu\text{g}$ b.i.d.	21	6.36	5.69–7.11	
FP 500 $\mu\text{g}$ b.i.d.	41	5.24	4.72–5.82	
FP 1000 $\mu\text{g}$ b.i.d.	20	2.27	1.57–3.28	
Summary of predicted serum cortisol weighted means and 95% confidence intervals for each FP dose				
Treatment	Predicted weighted mean of 0–24 h serum cortisol ( $\mu\text{g}/\text{dL}$ )		95% CI	
FP 250 $\mu\text{g}$ b.i.d.	6.40		5.29–7.73	
FP 500 $\mu\text{g}$ b.i.d.	5.27		4.58–6.05	
FP 1000 $\mu\text{g}$ b.i.d.	2.24		1.85–2.72	
Ratio of weighted mean 0–24 h serum cortisol after each FP treatment versus placebo, and corresponding 95% confidence intervals				
Treatment comparison	Ratio		95% CI	
FP 250 $\mu\text{g}$ b.i.d. versus placebo	0.85		0.67–1.09	
FP 500 $\mu\text{g}$ b.i.d. versus placebo	0.70		0.57–0.87	
FP 1000 $\mu\text{g}$ b.i.d. versus placebo	0.30		0.23–0.38	
Secondary Outcome Variable(s): Only the placebo and FP results are presented				
Summary of $\text{Ae}_{(0-24)}$ cortisol ( $\mu\text{g}$ )				
Treatment	n	Geometric mean	95% CI	
Placebo	21	31.03	24.66–39.05	
FP 250 $\mu\text{g}$ b.i.d.	21	22.51	18.66–27.15	
FP 500 $\mu\text{g}$ b.i.d.	41	16.93	14.51–19.77	
FP 1000 $\mu\text{g}$ b.i.d.	15 <sup>a</sup>	6.39	3.88–10.51	
a cortisol concentrations were below the limit of quantification in 5 of 20 subjects after FP 1000 $\mu\text{g}$ b.i.d., and $\text{Ae}_{(0-24)}$ could not be calculated in those instances.				
Ratio of $\text{Ae}_{(0-24)}$ cortisol after each FP treatment versus placebo, and corresponding 95% confidence intervals				
Treatment comparison	Ratio		95% CI	
FP 250 $\mu\text{g}$ b.i.d. versus placebo	0.76		0.58–0.99	
FP 500 $\mu\text{g}$ b.i.d. versus placebo	0.54		0.43–0.68	
FP 1000 $\mu\text{g}$ b.i.d. versus placebo	0.20		0.15–0.27	
Population pharmacokinetic parameters for FP, in healthy men and women, after repeat inhaled doses				
Parameter (units)	Estimate	95% CI		Inter-subject variability ( $\eta$ )
$K_a$ ( $\text{h}^{-1}$ )	9.583	5.514–16.655		125%
CL/F (L/h)	498	451–549		32%
V/F (L)	5115.34	4366.13–5993.12		38%
Geometric mean (95% CI) of post-hoc estimates of FP pharmacokinetic parameters, in healthy men and women, after repeat inhaled doses				
Treatment	n	$C_{\text{max}}$ [ $\mu\text{g}/\text{mL}$ ]	$t_{\text{max}}$ [h] <sup>a</sup>	$\text{AUC}_{(0-24)}$ [ $\mu\text{g}\cdot\text{h}/\text{mL}$ ]

FP 250 µg b.i.d.	21	73.37 (64.16–83.91)	1.05 (0.42–2.58)	1030.68 (910.96–1166.14)
FP 500 µg b.i.d.	41	139.19 (122.22–158.52)	0.77 (0.25–2.03)	2001.94 (1825.07–2195.94)
FP 1000 µg b.i.d.	20	267.06 (228.28–312.43)	0.96 (0.33–3.67)	3925.15 (3383.74–4553.18)
a Median (range) of $t_{max}$				
Safety Results: The time periods for collecting adverse events (AEs) and serious adverse events (SAEs) were as follows: SAEs related to study participation were collected from screening until the follow-up visit; all other AEs and SAEs were collected from first dose until the follow-up visit.				
<b>Most Frequent Adverse Events – On-Therapy Number of subjects (%)</b>	Placebo (N=21)	FP 250 µg b.i.d. (N=21)	FP 500 µg b.i.d. (N=42)	FP 1000 µg b.i.d. (N=20)
No. subjects with any AE, n (% of N)	13 (61.9)	4 (19.0)	21 (50.0)	9 (45.0)
Headache	3 (14.3)	2 (9.5)	4 (9.5)	0
Nasopharyngitis	3 (14.3)	1 (4.8)	6 (14.3)	2 (10.0)
Dysphonia	0	1 (4.8)	2 (4.8)	3 (15.0)
Dry throat	1 (4.8)	0	3 (7.1)	0
Pharyngolaryngeal pain	1 (4.8)	0	2 (4.8)	1 (5.0)
Cough	1 (4.8)	0	3 (7.1)	0
Fatigue	1 (4.8)	0	2 (4.8)	0
Joint sprain	1 (4.8)	0	2 (4.8)	0
<b>Serious Adverse Events – On-Therapy, n (%) [n considered related to the study medication by the investigator]</b>				
No. subjects with non-fatal SAE, n (%) [related]	0	1(4.8)[0]	1(2.4)[0]	0
Urinary tract infection *	0	1(4.8)[0]	0	0
Pyelonephritis *	0	0	1(2.4)[0]	0
No. subjects with fatal SAE, n (%)	0	0	0	0
* The urinary tract infection and pyelonephritis occurred sequentially in the same subject.				

Publications:  
No Publication

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