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Study No: FFA10027
Title: A randomised, double-blind, placebo-controlled, 6-way cross-over design study to investigate the effect of 250 µg single inhaled doses of GW685698X and FP on airway responsiveness to adenosine 5'-monophosphate (AMP) challenge in mild asthmatic patients
Rationale: The rationale for the current study was to assess long-term activity of a new chemical entity (GW685698X (GW)) in subjects undergoing adenosine 5'-monophosphate (AMP) challenge compared with placebo (PBO) and using FP as a positive control. Results are presented for the FP and PBO arms only.
Phase: I
Study Period: 23 April 2004 to 03 September 2004
Study Design: A multicentre, randomised, double-blind, placebo-controlled, 6-way crossover study. Results are presented for the FP and PBO arms only. Results for the GW will be added if and when it is approved and marketed.
Centres: Five centres in 3 countries: Australia (3), New Zealand (1), South Africa (1)
Indication: Asthma
Treatment: All eligible subjects who completed the screening and run-in AMP challenge (AMP PC ₂₀ within 1.25 doubling doses [DD] of each other) received the following treatments (via <i>DISKHALER™</i>) in a random order. Treatments were administered twice daily on Day 1 and in the morning on Day 2. PBO on days 1–2 GW (single dose) and matching PBO on days 1–2, with AMP challenge 2 hours after final active dose GW (single dose) and matching PBO on days 1–2, with AMP challenge 14 hours after final active dose GW (single dose) and matching PBO on days 1–2, with AMP challenge 26 hours after final active dose FP (250µg single dose) and matching PBO on days 1–2, with AMP challenge 2 hours after final active dose FP (250µg single dose) and matching PBO on days 1–2, with AMP challenge 14 hours after final active dose Treatment periods lasted 2 days, with a post-treatment AMP challenge on Day 2. Periods were separated by ≥5 days (from Day 2) and ≤10 days. A post-study visit was held within 8–12 days of the last dose.
Objectives: To investigate the effect of a single dose of GW and a single dose of 250µg FP in the AMP challenge model when delivered 2, 14 and 26 hours prior to the challenge in subjects with mild asthma. To investigate the pharmacokinetics of GW and FP using a population pharmacokinetic (PK) approach To investigate FVC at PC ₂₀ .
Statistical Methods: The sample size calculations were based on the number of subjects needed to detect a difference of 1.5 doubling doses between any of the active doses and placebo. This difference was approximately equal to the (average) previously observed effect of FP 250 µg 2 h prior to challenge. Twenty-four subjects were to be recruited into this study. Subjects who were withdrawn were not to be replaced. Based on this sample size it was anticipated that at least 18 subjects would complete the clinical phase of the study (i.e., complete all treatment periods). The All Subjects Population included all subjects randomised to treatment who received at least 1 dose of study medication. The AMP PC ₂₀ on day 2 was adjusted for screening and run-in values. The recalculated AMP PC ₂₀ was log transformed (base 2) and then analysed using a mixed model with period and treatment group as fixed effects and subject as a random effect. Treatment differences and 95% confidence intervals (CIs; using pooled estimates of variance) were presented in terms of Doubling Doses (DDs). The lowest post-saline FEV ₁ was used as the baseline in the calculations of post-treatment AMP PC ₂₀ ; however, this was not a 'true' baseline as study drug could affect this measure. Population modelling techniques using non-linear mixed effects methods (NONMEN) were used to estimate PK parameters. No formal analysis was performed on safety data. Summary statistics only were produced.
Study Population: Males or females (of non-child-bearing potential), aged 18–55 years, with mild allergic asthma

(FEV ₁ ≥70% of predicted and taking short-acting beta-agonists only) and bronchoconstriction (>20% fall in FEV ₁ after inhaled AMP [AMP PC ₂₀ <50 mg/ml] at screening). Subjects were excluded if they had life-threatening asthma or a disease (past or present) that could affect the study outcome.				
Number of Subjects:		All Subjects Population		
Planned N	24			
Dosed N	24			
Completed n (%)	18 (75)			
Total Number Subjects Withdrawn N (%)	6 (25)			
Withdrawn due to Adverse Events n (%)	0			
Withdrawn due to Lack of Efficacy n (%)	0			
Withdrawn for Other Reasons n (%)	6 (25)			
Demographics:		All Subjects Population		
N	24			
Females: Males	0:24			
Mean Age in Years (sd)	27.9 (7.7)			
Mean Weight in Kg (sd)	81.05 (14.38)			
Caucasian n (%)	24 (100)			
Primary PD outcome:				
Summary of AMP PC₂₀ data (mg/mL) (All Subjects Population)				
	PBO	FP (2 h pre-AMP)	FP (14 h pre-AMP)	
Geometric mean (n)	5.49 (19)	33.94 (21)	11.33 (19)	
(95% CI)	(2.82, 10.67)	(14.66, 78.56)	(5.21, 24.63)	
Summary of AMP PC₂₀ data (mg/mL) (subjects with screening / run-in AMP PC₂₀ within 1.25 DDs)				
	FP (2 h pre-AMP) vs PBO		FP (14 h pre-AMP) vs PBO	
DD difference	2.29		1.07	
(95% CI)	(1.50, 3.08)		(0.28, 1.87)	
Summary of AMP PC₂₀ data (mg/mL) (adjustment for post-saline FEV₁)				
	FP (2 h pre-AMP) vs PBO		FP (14 h pre-AMP) vs PBO	
DD difference	2.32		1.02	
(95% CI)	(1.56, 3.08)		(0.22, 1.81)	
Secondary PD outcome:				
Summary of FVC data				
	PBO, pre-challenge FVC		PBO, 15-minutes post-challenge FVC	
Median (L) (n)	-0.130 (19)		-0.227 (19)	
Range (L)	-0.38, 0.74		-1.41, 0.14	
	FP (2 h pre-AMP), pre-challenge FVC	FP (2 h pre-AMP), 15-minutes post-challenge FVC	FP (14 h pre-AMP), pre-challenge FVC	FP (14 h pre-AMP), 15-minutes post-challenge FVC
Median (L) (n)	0.003 (21)	-0.047 (21)	0.065 (19)	-0.282 (19)
Range (L)	-0.41, 0.42	-0.89, 0.44	-0.38, 1.46	-1.48, 0.42
Secondary PK outcomes:				
PK parameters for FP				
	FP (2 h pre-AMP), geometric mean*	FP (2 h pre-AMP), (95% CI) †	FP (14 h pre-AMP), geometric mean*	FP (14 h pre-AMP), (95% CI) †
n	21	21	19	19
C _{max} (pg/mL)	61.4	(50.0, 75.3)	70.2	(57.7, 85.5)
T _{max} (hours)	0.67	(0.42, 1.00)	0.75	(0.50, 1.00)
AUC(0-∞) (pg.h/mL)	703	(580, 853)	915	(756, 1108)
* = median for T _{max} ; † = (minimum, maximum) for T _{max}				
Safety Results: On-therapy adverse events (AEs) were collected at each visit starting from Day 1 of the first treatment period through to the post-study visit.				
Adverse Events:	PBO	FP		

		2 h pre-AMP	14 h pre-AMP
N (All subjects population)	19	21	19
No. subjects with AEs, n (%)	3 (16)	5 (24)	4 (21)
Most frequent AEs			
Headache	0	1 (5)	2 (11)
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:			
	PBO	FP 2 h pre-AMP	14 h pre-AMP
Subjects with non-fatal SAEs	0	0	0
Subjects with fatal SAEs	0	0	0

Publications: No Publication
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