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: MAB110123

Title : A randomised, double-blind, crossover study to investigate the bronchodilatation post-inhalation of GSK961081 alone and with the addition of cumulative doses of short acting bronchodilators (salbutamol and ipratropium bromide) in patients with COPD.

Rationale: This study aimed to measure the bronchodilatation after inhalation of GSK961081 (400 μg or 1200 μg) as a single dose alone (via DISKUS™ metered dose powder inhaler) and in the presence of supratherapeutic doses of the short-acting β_2-adrenergic agonist, salbutamol, and the short-acting muscarinic antagonist, ipratropium bromide.

Phase: II

Study Period: 25 APR 2008–19 OCT 2008

Study Design: This was a randomised, double-blind, complete crossover design

Centres: Four centres in New Zealand, Thailand and the United Kingdom

Indication: Chronic obstructive pulmonary disease (COPD)

Treatment: Each subject participated in six treatment sessions and received the following:

- GSK961081 400 μg single dose followed by cumulative doses (3 x 200 μg at 20 minute intervals) of salbultamol (salb) at 1 h, 12 h and 24
- GSK961081 1200 μg single dose followed by cumulative doses (3 x 200 μg at 20 minute intervals) of salbultamol at 1 h, 12 h and 24 h
- GSK961081 400 μg single dose followed by cumulative doses (20 μg, 20 μg and 40 μg at 20 minute intervals) of ipratropium bromide (ipr) at 1 h, 12 h and 24 h
- GSK961081 1200 μg single dose followed by cumulative doses (20 μg, 20 μg and 40 μg at 20 minute intervals) of ipratropium bromide at 1 h, 12 h and 24 h
- GSK961081 400 μg single dose followed by placebo (pbo) (3 doses at 20 minute intervals) at 1 h, 12 h and 24 h
- GSK961081 1200 μg single dose followed by placebo at (3 doses at 20 minute intervals) 1 h, 12 h and 24 h

Lung function measurements were made during the 27-h period following dosing. The total duration of the study was approximately 11–12 weeks for each subject.

Objectives: To assess the pulmonary pharmacodynamic profile of single doses of GSK961081 in combination with cumulative doses of short acting bronchodilators (salbutamol or ipratropium bromide) in COPD patients.

Statistical Methods: Pharmacodynamic analyses: Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) data were listed and summarised.

For serial maximal change following dosing a repeated measures analysis was performed using a mixed effect model with treatment, period, time, treatment by time interaction, subject level baseline, period level baseline and period level baseline by time fitted as fixed effects. Subject was fitted as a random effect.

Adjusted means and treatment differences between GSK961081 + short acting bronchodilators (salbutamol or ipratropium bromide) and GSK961081 + pbo and the corresponding two-sided 90% confidence intervals (CIs) were summarised together with one-sided p-values for the treatment differences. Adjusted means by treatment were presented with 90% CIs.

Study Population: Subjects with COPD, in accordance with American Thoracic Society/European Respiratory Society guidelines, were enrolled. Subjects were aged 40–75 years old and were smokers or ex-smokers.

Number of Subjects:	
Planned N	45
Dosed N	44
Completed n (%)	38 (86)
Total Number Subjects Withdrawn N (%)	6 (14)
Withdrawn due to Adverse Events n (%)	2 (5)
Withdrawn for Other Reasons n (%)	4 (9)
Demographics	
N (All Subjects)	44
Females: Males	8:36
Mean Age in Years (range)	63.1 (48–74)
Mean Weight in Kg (range)	68.32 (41.0–108.5)
White n (%)	21 (48)

Pharmacodynamics (PD):
A summary of the results from the statistical analysis of maximal change in FEV1 from pre-dosing with short-acting bronchodilators is presented below.

Treatment comparison: test minus reference	Planned time	Adjusted means		Difference	90% CI of difference	One-sided p-value
		Test	Reference			
GSK961081 400 μg + salb – GSK961081 400 μg + pbo	1 h	0.111	0.072	0.039	(0.008, 0.069)	0.020*
	12 h	0.141	0.002	0.139	(0.101, 0.176)	<0.001*
	24 h	0.161	0.039	0.123	(0.080, 0.158)	<0.001*
GSK961081 400 μg + ipr – GSK961081 400 μg + pbo	1 h	0.087	0.072	0.014	(-0.016, 0.045)	0.217
	12 h	0.127	0.002	0.124	(0.087, 0.161)	<0.001*
	24 h	0.179	0.039	0.141	(0.105, 0.176)	<0.001*
GSK961081 1200 μg + salb – GSK961081 1200 μg + pbo	1 h	0.113	0.094	0.019	(-0.012, 0.050)	0.155
	12 h	0.134	0.043	0.091	(0.053, 0.129)	0.001*
	24 h	0.175	0.049	0.126	(0.090, 0.162)	<0.001*
GSK961081 1200 μg + ipr – GSK961081 1200 μg + pbo	1 h	0.111	0.094	0.017	(-0.015, 0.048)	0.187
	12 h	0.098	0.043	0.055	(0.017, 0.093)	0.029*
	24 h	0.172	0.049	0.122	(0.086, 0.159)	<0.001*

CI = confidence interval; * indicates statistically significant at the one-sided 5% significance level.

Compared with GSK96181 + placebo, additional bronchodilatory effects in terms of FVC were observed for GSK961081 + ipratropium bromide and GSK961081 + salbutamol at 12 h and 24 h ($p < 0.05$ for all, except GSK961081 400 μg + salbutamol at 24 h [$p = 0.099$]).

Pharmacokinetics (PK):
A summary of derived GSK961081 plasma pharmacokinetic parameters is presented below.

Treatment	Cmax[1] (pg/mL)	AUC(0–t)[2] (pg.h/mL)	tmax[2] (h)	tlast[2] (h)
GSK961081 400 μg + salb	66.93 (56.65, 79.07)	NC (NC–327.2)	0.920 (0.90–1.97)	0.960 (0.90–4.02)
GSK961081 1200 μg + salb	169.05 (139.77, 204.47)	223.58 (NC–1944.4)	0.930 (0.90–2.08)	2.000 (0.92–23.95)
GSK961081 400 μg + ipr	70.77 (60.20, 83.19)	56.46 (NC–629.1)	0.925 (0.90–1.97)	1.930 (0.92–11.95)
GSK961081 1200 μg + ipr	153.59 (132.14, 178.52)	201.53 (NC–1841.5)	0.920 (0.90–1.97)	3.920 (0.92–23.97)
GSK961081 400 μg + pbo	70.52 (58.92, 84.40)	NC (NC–735.7)	0.920 (0.83–2.02)	1.920 (0.83–4.00)
GSK961081 1200 μg + pbo	176.92 (152.70, 204.98)	215.83 (NC–1420.2)	0.920 (0.83–1.93)	2.050 (0.92–11.98)

1. Geometric mean (95% confidence interval);
2. Median (range);

NC=not calculable due to non-quantifiable concentration.

Safety results:
Adverse event (AE) and serious adverse event (SAE) data were collected and recorded on the electronic case report form starting on Day 1 and continuing until the end of the confinement period. A summary of the most frequently reported AEs (experienced in 3 or more subjects; all subjects population) is presented below.

Adverse Events:	**GSK961081 400 µg + salb**	**GSK961081 1200 µg + salb**	**GSK961081 400 µg + ipr**	**GSK961081 1200 µg + ipr**	**GSK961081 400 µg + pbo**	**GSK961081 1200 µg + pbo**
N (ITT)	39	41	41	41	40	39
No. subjects with AEs n (%)	13 (33)	13 (32)	15 (37)	9 (22)	6 (15)	11 (28)
Most Frequent AEs n (%)						
Headache	5 (13)	5 (12)	4 (10)	4 (10)	1 (3)	3 (8)
Cough	1 (3)	1 (2)	3 (7)	0	0	0
Nasopharyngitis	0	0	1 (2)	0	1 (3)	2 (5)
Hypokalaemia	0	3 (7)	0	0	0	1 (3)
Diarrhoea	0	1 (2)	0	1 (2)	1 (3)	0
Dysguesia	0	1 (2)	0	1 (2)	0	1 (3)
Tremor	1 (3)	2 (5)	1 (2)	1 (2)	0	0

Serious Adverse Events: There were two serious adverse events, as follows: 1) angina pectoris of severe intensity which resulted in hospitalization, judged by the investigator as not related to study drug; and 2) loss of vision diagnosed as migraine of moderate intensity, judged by the investigator as not related to study drug.

Publications: None.