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: MAB104958

Title: A study to assess the pharmacokinetics of single escalating doses of inhaled GSK961081 DPI (a dual pharmacophore) in healthy subjects (Part 1) and a randomised, double-blind, double dummy, crossover (incomplete block) study to assess the safety, tolerability, pharmacodynamics (pulmonary and systemic) and pharmacokinetics of 14 days dosing with inhaled GSK961081 DPI compared with placebo and tiotropium plus salmeterol in patients with COPD (Part 2).

Rationale: GSK961081 is a potent dual pharmacophore that has demonstrated both muscarinic acetylcholine receptor antagonist and β2-adrenergic agonist pharmacology in pre-clinical studies. It is under development as a bronchodilator in chronic obstructive pulmonary disease (COPD).

Phase: I and IIa.

Study Period: 19 June 2007 – 23 May 2008.

Study Design:
Part 1: A randomised, double-blind, placebo controlled, single dose escalating crossover design.
Part 2: A randomised, double-blind, double dummy, placebo and active comparator controlled, crossover (incomplete block) design.

Centres: One study centre in Germany and three study centres in South Africa.

Indication: None.

Treatment: Part 1: Twelve healthy subjects were randomised. At each study period, nine subjects received the active drug and three received placebo.

Part 2: Fifty subjects were randomised: , 41 received tiotropium 18 μg once daily (qd) + salmeterol 50 μg twice daily (bid) and 43 received placebo. Treatments were given qd in the morning except salmeterol which was given bid.

Objectives: Part 1: To assess the systemic pharmacokinetics of GSK961081 DPI after single inhaled doses in healthy male subjects.
Part 2: To investigate the pulmonary pharmacodynamic profile of two doses of GSK961081 DPI (determined from Part 1 of GSK961081) versus placebo and versus tiotropium plus salmeterol given for 14 days in patients with COPD.

Statistical Methods: In Part 1, sample size was based primarily on feasibility. Sample size for Part 2 was calculated based on data from three previous studies in subjects with COPD. Thus, 40 evaluable subjects would provide approximately 90% power to detect a difference of 150 mL in forced expiratory volume in 1 second (FEV1) at 24 h between each active treatment and placebo, using a two-sided 5% significance level.

Assessment of Dose Proportionality and Accumulation Ratio
Part 1:
Part 2: To evaluate the accumulation ratio, a statistical analysis of AUC(0-t) and Cmax was performed after log transformation of the data. A mixed effects model was fitted with day as a fixed effect and subject as a random effect. Day 14 was compared with Day 1 in order to estimate the accumulation ratio. The ratio was calculated by back-transforming the difference between the least square means. Using the pooled estimate of variance, 90% CIs were calculated for the difference and then back-transformed.

Pharmacodynamic Analyses
Part 1:
Part 2: The primary endpoint, serial FEV1 data, was statistically analysed for the modified per protocol (MPP) population using a mixed effects model. Hypothesis testing (superiority) was employed to assess FEV1 for the primary treatment comparisons of tiotropium 18 μg qd + salmeterol 50 μg bid versus placebo at various time points. Point estimates and corresponding 95% CIs were constructed for the estimated differences. A difference would be demonstrated if the two-sided 95% CI for the difference between treatment groups did not include zero. The mixed model fitted treatment, period, time and treatment by time as fixed effects; subject level baseline, period level baseline and period level baseline by time as covariates (fixed effects); and subject as a random effect. Day 1 and Day 14 data were analysed separately using the same mixed effects model as described above.
Serial specific airway conductance (sGaw) data on Day 1 and Day 14 were analysed in the same way as described for FEV1 with the exception that the sGaw data (and baseline covariates) were log-transformed. Results from the statistical

analyses (adjusted geometric means and corresponding two-sided 95% CIs) were presented in tabular form and plotted. Statistical analysis was also conducted on derived heart rate, blood pressure, QT interval corrected for heart rate (Fridericia's formula) (QTc(F)), QT interval corrected for heart rate (Bazett's formula) (QTc(B)), glucose and potassium endpoints using mixed effects models. Treatment, period, day and treatment by day were included as fixed effects; subject level baseline, period level baseline and period level baseline by day as covariates (fixed effects) and subject fitted as random effects.

Safety Analyses

Part 1 and Part 2 safety data were summarised; there was no formal statistical analysis.

Study Population: Inclusion criteria:

Part 1: Healthy adult male subjects aged 18–50 years with a body mass index within the range 18.5–29.9 kg/m^2. An FEV1 ≥80% predicted and a FEV1/ forced vital capacity (FVC) ratio ≥0.7.

Part 2: Subjects were male or female (of non-child bearing potential) ≥40 and ≤75 years of age with body mass index 18–35 kg/m^2. Subjects had a diagnosis of COPD (stage II) in accordance with American Thoracic Society/European Respiratory Society guidelines. Subjects had FEV1 between 50% and 80% after inhalation of salbutamol. Subjects had FEV1/FVC ≤0.7 and FEV1 ≤80% of predicted post-bronchodilator (salbutamol). Subjects showed responses to ipratropium bromide and salbutamol, according to pre-defined FEV1 criteria.

Number of Subjects	Part 1	Part 2
Planned, N	12	40
Randomised, N	12	50
Completed, n (%)	12 (100)	47 (94)
Total Withdrawn (any reason), n (%)		
Withdrawn due to adverse events, n (%)		
Withdrawn due to other reason n (%)		
All subjects population, N	12	50
Modified per protocol population (part 2 only), N	Not applicable	48
Pharmacokinetic population, N	9, 9, 9[1]	29, 32[2]
Demographics		
Age in years, mean [range]	43.7 [27–57]	58.3 [41–74]
Sex, n (%)		
Female:	0	16 (32)
Male:	12 (100)	34 (68)
Ethnicity, n (%)		
Not Hispanic/Latino	12 (100)	50 (100)
Race, n (%)		
White - White Caucasian/European Heritage	12 (100)	49 (98)
African American/African Heritage	0	1 (2)
Height in cm, mean [range]	179.0 [168–192]	178.1 [166–191]
Weight in kg, mean [range]	81.13 [61.3–101.4]	73.09 [53.3–93.3]
Body mass index in kg/m^2, mean [range]	25.20 [21.7–29.8]	25.71 [18.2–35.0]
Smoking history (n%)		
Former smoker	-	18 (36)
Current smoker	-	32 (64)
Years smoked, mean [range]	-	35.3 [11–62]
Number of cigarettes/day, mean [range]	-	24.3 [8–60]
Smoking pack years, mean [range]	-	43.7 [11–138]

1.

Pharmacokinetic results: Part 1: Selected plasma pharmacokinetic parameters are summarised in the following table.

GSK961081 dose	N/n/n*	Cmax[1] (pg/mL)	tmax[2] (h)	tlast[2] (h)	AUC(0-t)[1] (pg·h/mL)	AUC(0-2)[1] (pg·h/mL)

Statistical analysis of AUC(0-t) and Cmax (dose proportionality using the power model) is summarised in the following table:

Parameter	Slope log (parameter) versus log	90% confidence interval of slope

	(dose)	
AUC(0-t) (h.pg.mL)		
Cmax (pg/mL)		

Part 2: Selected Day 1 plasma pharmacokinetic parameters are summarised below:

GSK961081 dose	N/n/n*	Cmax[1] (pg/mL)	tmax[2] (h)	tlast[2] (h)	AUC(0-t)[1] (pg·h/mL)	AUC(0-2)[1] (pg·h/mL)

Selected Day 7 plasma pharmacokinetic parameters are summarised below:

GSK961081 dose	N/n/n*	Cmax[1] (pg/mL)	tmax[2] (h)	tlast[2] (h)	AUC(0-t)[1] (pg·h/mL)	AUC(0-2)[1] (pg·h/mL)

Selected Day 14 plasma pharmacokinetic parameters are summarised below:

GSK961081 dose	N/n/n*	Cmax[1] (pg/mL)	tmax[2] (h)	tlast[2] (h)	AUC(0-t)[1] (pg·h/mL)	AUC(0-2)[1] (pg·h/mL)

Statistical analysis of AUC(0-t) and Cmax (accumulation over 14 days) is summarised below.

Parameter	Treatment	N/n	Day	Adjusted geometric mean	Ratio of adjusted geometric means	90% CI

Pharmacodynamic results: Forced expiratory volume in 1 second:

Part 1:

Part 2: Serial time point analysis for tiotropium 18 μg qd + salmeterol 50 μg bid compared with placebo is presented in the following table.

Treatment comparison	Day	Time point (h)	Treatment difference	95% CI	p-value
Tiotropium 18 μg qd + salmeterol 50 μg bid – placebo	1	12	0.266	0.182, 0.351	<0.001
		24	0.162	0.092, 0.231	<0.001
	14	12	0.214	0.129, 0.300	<0.001
		24	0.103	0.026, 0.180	0.009

Part 2: Specific airway conductance: Serial time point analysis for tiotropium 18 μg qd + salmeterol 50 μg bid compared with placebo are presented in the table below.

Treatment comparison	Day	Time point (h)	Treatment ratio	95% CI	p-value

Tiotropium 18 μg qd + salmeterol 50 μg bid – placebo	1	12	1.445	1.289, 1.620	<0.001
		24	1.258	1.139, 1.390	<0.001
	14	12	1.401	1.269, 1.547	<0.001
		24	1.210	1.087, 1.346	<0.001

Other pharmacodynamic endpoints:
Part 1:
Part 2: There were no clinically relevant changes in heart rate, systolic and diastolic blood pressure, QTc(B), QTc(F), glucose and potassium over the first 4 h in the Tiotropium & Salmeterol treatment group compared with placebo.

Safety results:
Part 1: A summary of all AEs irrespective of causality are presented in the following table:

Preferred term	Placebo N = 9 n (%)				Total
Any event	1 (11)				
Headache	1 (11)				

Part 2: A summary of most frequently reported adverse events irrespective of causality (experienced by at least two subjects per treatment group) is presented in the following table:

Preferred term	Placebo N = 43 n (%)			Tiotropium 18 μg qd + salmeterol 50 μg bid N = 41 n (%)	
Any event	23 (53)			20 (49)	
Headache	6 (14)			3 (7)	
Nasopharyngitis	3 (7)			2 (5)	
Diarrhoea	1 (2)			2 (5)	
Nausea	1 (2)			1 (2)	
Dizziness	2 (5)			1 (2)	
Upper respiratory tract infection	1 (2)			2 (5)	
Vomiting	2 (5)			1 (2)	
Constipation	1 (2)			2 (5)	
Application site reaction	0			1 (2)	

Serious Adverse Events, n (%) [# considered by the investigator to be related, possibly related, or probably related to study medication]: There were no SAE's in Part 1 or Part 2 of the study.

Publications: None.