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: AC2108378

Title : A randomised, double-blind, placebo-controlled, dose ascending, 2-cohort, parallel group study to examine the safety, tolerability, pharmacokinetics and pharmacodynamics of twice-daily inhaled doses of GSK233705B formulated with the excipient Magnesium Stearate in COPD subjects for 7-days.

Rationale: A new formulation of GSK233705 was developed using 0.5% magnesium stearate (MgSt) as the excipient and the safety, pharmacokinetics and pharmacodynamics of this new formulation required assessment in patients.

Phase: I.

Study Period: 29 March 2007 – 11 October 2007.

Study Design: Randomised, double-blind, placebo-controlled, parallel-group, dose-escalating design study.

Centres: Four centres in the Netherlands.

Indication: None.

Treatment: Two cohorts of subjects with chronic obstructive pulmonary disorder (COPD) were dosed. Subjects in Cohort I were randomised to receive either placebo or GSK233705 MgSt 50 μg twice daily (BD) inhaled from a DISKUS inhaler for 7 days of repeat dosing. Subjects in Cohort II were randomised to receive either placebo or GSK233705 MgSt 100 μg BD inhaled from a DISKUS inhaler for 7 days of repeat dosing.

Objectives: To assess the safety, tolerability, pharmacokinetics and pharmacodynamics of repeat inhaled doses of GSK233705B with MgSt (inhaled twice daily for 7 days) in subjects with COPD.

Statistical Methods: No formal sample size calculation was performed for this study. The focus of the study was on estimation rather than hypothesis testing. The All Subjects Population included all available data on subjects who received at least one dose of study medication (including placebo). The Pharmacokinetic Population was defined as all subjects in the All Subjects Population for whom a pharmacokinetic sample was obtained and analysed. For the primary endpoint, all safety data were listed and summarised. Formal statistical analysis was carried out on the weighted mean (0–4 h) and maximum value (0–4 h) for supine vital signs (heart rate, systolic blood pressure, and diastolic blood pressure), QTc(B) and QTc(F) and for the mean and maximum (0–24 h) heart rate from the Holter monitoring using a mixed model with day as a repeated effect and subject as a blocking effect.
Plasma and urine concentrations of GSK233705, and all derived pharmacokinetic plasma and urine parameters were listed and summarised. An assessment of accumulation was done by performing statistical analysis (after log-transformation of the data when necessary) on the plasma pharmacokinetic parameters: area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration (AUC(0–t)) and maximum observed plasma concentration (Cmax) and the urine parameter amount of drug excreted unchanged in urine from 0 to 12 h (Ae (0–12)) based on available data. A mixed effect model was fitted with dose, day and a dose by day interaction as fixed effects, with day as a repeated effect and subject as a blocking effect. For pharmacodynamics, formal statistical analysis was carried out on the derived maximum readings for forced expiratory volume in 1 second (FEV1), and forced vital capacity (FVC) at serial timepoints using a mixed model. Treatment, day, time, baseline, treatment by day by time and baseline by day by time interactions were fitted as fixed effects and subject as a random effect, with time as a repeated effect and subject by day as a blocking effect. Pharmacokinetic / pharmacodynamic exploratory plots were presented for individual plasma concentrations versus corresponding pharmacodynamic variables.

Study Population: Men or women (of non-childbearing potential) aged 40–75 years with a body mass index of 18.0–32.0 kg/m^2 who were diagnosed with COPD were eligible for the study. Subjects were to be smokers, or ex-smokers with a history of ≥10 pack years, who had post-bronchodilator FEV1 of ≥40% to ≤80% of predicted normal and an FEV1/FVC <0.7 post-bronchodilator. Subjects were also to have a 24-h Holter recording that was within normal limits. All subjects provided written informed consent to participate in the study.

Number of Subjects:	**Placebo**	**GSK233705**		**Total**
	(N = 6)	**50 μg (N = 9)**	**100 μg (N = 8)**	**(N = 23)**
Planned N	6	9	9	24
Dosed N	6	9	8	23
Completed n (%)	6 (100)	9 (100)	8 (100)	23 (100)
Total Number Subjects Withdrawn N (%)	0	0	0	0

Demographics				
N (All Subjects)	6	9	8	23
Females: Males	1 : 5	0 : 9	3 : 5	4 : 19
Mean Age in Years (range)	60.0 (43–71)	66.4 (54–75)	59.0 (53–71)	62.2 (43–75)
Mean Weight in Kg (range)	75.1 (61–91)	77.7 (64–87)	77.9 (54–94)	77.1 (54–94)
White n (%)	6 (100)	9 (100)	8 (100)	23 (100)

Safety results: Adverse event (AE) data were collected and recorded on the case report form from screening to follow-up.

Adverse Events:	**Placebo**	**GSK233705 50 μg**	**GSK233705 100 μg**
N (All Subjects)	6	9	8
No. subjects with AEs n (%)	4 (67)	4 (44)	4 (50)
Most Frequent AEs			
Dyspnoea	1 (17)	1 (11)	2 (25)
Headache	1 (17)	1 (11)	2 (25)
Nasopharyngitis	0	0	2 (25)
Serious Adverse Events, n (%)			
No. subjects with AEs n (%)	0	0	0

A summary of results from the statistical analysis of derived heart rate parameters is presented in the following table:

Derived parameter	Difference in adjusted mean (95% confidence interval)			
	GSK233705 50 μg – placebo		GSK233705 100 μg – placebo	
	Day 1	Day 7	Day 1	Day 7
Heart rate (bpm)				
Maximum (0–4 h)	2.26 (-5.58, 10.10)	2.62 (-5.30, 10.54)	0.16 (-8.17, 8.48)	-5.44 (-13.86, 2.97)
Weighted mean (0–4 h)	0.14 (-5.52, 5.79)	2.39 (-3.50, 8.28)	-2.67 (-8.67, 3.34)	-3.84 (-10.10, 2.41)

A summary of results from the statistical analysis of derived systolic blood pressure parameters is presented in the following table:

Derived parameter	Difference in adjusted mean (95% confidence interval)			
	GSK233705 50 μg – placebo		GSK233705 100 μg – placebo	
	Day 1	Day 7	Day 1	Day 7
Systolic blood pressure (mmHg)				
Maximum (0–4 h)	-0.97 (-12.68, 10.75)	-4.10 (-12.92, 4.72)	6.21 (-5.78, 18.19)	-4.76 (-13.79, 4.27)
Weighted mean (0–4 h)	-2.78 (-12.43, 6.87)	-1.88 (-10.07, 6.31)	3.01 (-6.87, 12.88)	-3.50 (-11.88, 4.89)

A summary of the results of the statistical analysis of derived systolic blood pressure parameters is presented in the following table:

	Difference in adjusted mean (95% confidence interval)			
	GSK233705 50 μg – placebo		GSK233705 100 μg – placebo	
	Day 1	Day 7	Day 1	Day 7
Diastolic blood pressure (mmHg)				
Maximum (0–4 h)	0.58 (-3.89, 5.06)	-6.64 (-11.62, -1.65)	0.98 (-3.73, 5.68)	-10.81 (-16.05, -5.57)
Weighted mean (0–4 h)	-0.28 (-4.09, 3.54)	-3.89 (-8.32, 0.54)	-1.75 (-5.76, 2.26)	-9.39 (-14.04, -4.73)

A summary of the results of statistical analysis of derived QTc(B) parameters is presented in the following table.

	Difference in adjusted mean (95% confidence interval)			
	GSK233705 50 μg – placebo		GSK233705 100 μg – placebo	
	Day 1	Day 7	Day 1	Day 7
QTc(B) (msec)				
Maximum (0–4 h)	4.42 (-12.66, 21.49)	9.02 (-5.13, 23.17)	10.57 (-7.24, 28.38)	16.50 (1.74, 31.26)
Weighted mean (0–4 h)	9.55 (-1.46, 20.57)	8.39 (-3.97, 20.74)	11.47 (-0.02, 22.96)	15.28 (2.39, 28.17)

A summary of the results of the statistical analysis of derived QTc(F) parameters is presented in the following table.

	Difference in adjusted mean (95% confidence interval)			
	GSK233705 50 μg – placebo		GSK233705 100 μg – placebo	
	Day 1	Day 7	Day 1	Day 7
QTc(F) (msec)				
Maximum (0–4 h)	2.13 (-16.51, 20.78)	12.29 (1.20, 23.38)	17.66 (-1.53, 36.85)	22.32 (10.90, 33.73)
Weighted mean (0–4 h)	8.32 (-1.35, 18.00)	8.75 (-2.21, 19.72)	16.83 (6.87, 26.79)	20.46 (9.17, 31.75)

A summary of the results of the statistical analysis of derived heart rate parameters from Holter data is presented in the following table:

	Difference in adjusted mean (95% confidence interval)			
	GSK233705 50 μg – placebo		GSK233705 100 μg – placebo	
	Day 1	Day 7	Day 1	Day 7
Heart rate from 24 h Holter data (bpm)				
Maximum heart rate (0–24 h)	2.233 (-4.743, 9.210)	5.730 -11.200, 22.664)	-1.272 (-8.051, 5.507)	0.988 (-15.470, 17.443)
Mean heart rate (0–24 h)	2.734 (-4.468, 9.936)	4.783 (-1.4372, 10.938)	-1.074 (-8.003, 5.854)	1.569 (-4.353, 7.490)

Pharmacokinetics Endpoints: A summary of estimated pharmacokinetic parameters on Day 1 is presented in the following table:

Parameter	GSK233705 dose	N	n	Geometric mean	95% confidence interval	CVb(%)
AUC(0-t) (h.ng/mL)	50 μg BD PM	9	9	0.016	(0.010, 0.025)	68.5
	100 μg BD PM	8	8	0.053	(0.037, 0.075)	43.1
AUC(0-τ) (h.ng/mL)	50 μg BD AM	9	4	0.044	(0.028, 0.068)	28.2
	100 μg BD AM	8	7	0.147	(0.100, 0.215)	43.0
Cmax (ng/mL)	50 μg BD AM	9	9	0.035	(0.021, 0.058)	74.0
	50 μg BD PM	9	9	0.052	(0.029, 0.094)	89.5
	100 μg BD AM	8	8	0.160	(0.100, 0.254)	60.2
	100 μg BD PM	8	8	0.186	(0.120, 0.289)	56.6
t½ (h)	50 μg BD AM	9	4	0.678	(0.403, 1.142)	33.6
	100 μg BD AM	8	7	1.310	(0.878, 1.953)	45.3
tmax (h)[1]	50 μg BD AM	9	9	0.080	(0.08, 1.98)	N/A
	50 μg BD PM	9	9	0.080	(0.08, 0.47)	N/A
	100 μg BD AM	8	8	0.080	(0.08, 0.10)	N/A
	100 μg BD PM	8	8	0.080	(0.08, 0.10)	N/A
tlast (h)[1]	50 μg BD AM	9	9	1.000	(0.48, 2.00)	N/A
	50 μg BD PM	9	9	0.500	(0.25, 0.50)	N/A
	100 μg BD AM	8	8	2.025	(2.00, 6.00)	N/A
	100 μg BD PM	8	8	0.500	(0.48, 0.52)	N/A

1. Presented as median (range)

CVb = between-subject coefficient of variation; AUC(0-t) = area under concentration-time curve from time 0 to time of last quantifiable concentration; AUC(0-τ) = area under the plasma concentration-time curve over the dosing interval; BD = twice daily; AM = morning dosing, PM = evening dosing, Cmax = maximum observed plasma concentration; tmax = time of maximum observed plasma concentration; N/A = not applicable; t½ = half-life; tlast= last timepoint where the concentration is above the limit of quantification, CI = confidence interval

A summary of estimated pharmacokinetic parameters on Day 7 is presented in the following table:

Parameter	GSK233705 dose	N	n	Geometric mean	95% confidence interval	CVb(%)
AUC(0-t) (h.ng/mL)	50 μg BD PM	9	9	0.018	(0.010, 0.030)	77.2
	100 μg BD PM	8	8	0.056	(0.039, 0.079)	43.8
AUC(0-τ) (h.ng/mL)	50 μg BD AM	9	9	0.189	(0.141, 0.253)	39.3
	100 μg BD AM	8	8	0.430	(0.302, 0.614)	44.5
Cmax (ng/mL)	50 μg BD AM	9	9	0.049	(0.026, 0.095)	104
	50 μg BD PM	9	9	0.051	(0.025, 0.102)	113
	100 μg BD AM	8	8	0.190	(0.106, 0.340)	79.0
	100 μg BD PM	8	8	0.191	(0.118, 0.310)	62.7
t½ (h)	50 μg BD AM	9	5	3.844	(1.979, 7.466)	57.5
	100 μg BD AM	8	5	8.304	(5.691, 12.116)	31.1
tmax (h)[1]	50 μg BD AM	9	9	0.230	(0.08, 6.00)	N/A
	50 μg BD PM	9	9	0.080	(0.08, 0.48)	N/A
	100 μg BD AM	8	8	0.080	(0.08, 0.10)	N/A
	100 μg BD PM	8	8	0.080	(0.08, 0.12)	N/A
tlast (h)[1]	50 μg BD AM	9	9	11.920	(2.00, 12.03)	N/A
	50 μg BD PM	9	9	0.500	(0.48, 0.53)	N/A
	100 μg BD AM	8	8	11.920	(11.92, 12.08)	N/A
	100 μg BD PM	8	8	0.500	(0.50, 0.53)	N/A

1. Presented as median (range)

CVb = between-subject coefficient of variation; AUC (0-t)= area under concentration-time curve from time 0 to time of last quantifiable concentration; AUC(0-τ) = area under the plasma concentration-time curve over the dosing interval; BD = twice daily; AM = morning dosing, PM = evening dosing, Cmax = maximum observed plasma concentration; tmax = time of maximum observed plasma concentration; N/A = not applicable; t½ = half-life; tlast= last timepoint where the concentration is above the limit of quantification, CI = confidence interval

A summary of results of the statistical analysis of accumulation for plasma pharmacokinetic parameters is presented in the following table:

Parameter	Dose time	Treatment group	Ratio of adjusted geometric means Day 7 versus Day 1	90% confidence interval
AUC(0-t)	PM	GSK233705 50 μg BD	1.139	(0.811, 1.601)
AUC(0-t)	PM	GSK233705 100 μg BD	1.060	(0.739, 1.520)
Cmax	AM	GSK233705 50 μg BD	1.408	(0.934, 2.122)
Cmax	PM	GSK233705 50 μg BD	0.979	(0.658, 1.457)
Cmax	AM	GSK233705 100 μg BD	1.190	(0.770, 1.838)
Cmax	PM	GSK233705 100 μg BD	1.028	(0.674, 1.568)

AUC (0-t)= area under concentration-time curve from time 0 to time of last quantifiable concentration; AM = morning dosing; PM = evening dosing; Cmax = maximum observed plasma concentration

A summary of urine pharmacokinetic parameters on Day 1 is presented in the following table:

Parameter	GSK233705 dose	N	n	Geometric mean	95% confidence interval	CVb(%)
Ae(0-12) (ng)	50 μg BD AM	9	9	1432.6	(1138.2, 1803.1)	30.6
	50 μg BD PM	9	9	2080.2	(1665.7, 2597.8)	29.5
	100 μg BD AM	8	8	3977.1	(3054.7, 5178.0)	32.4
	100 μg BD PM	8	8	4913.3	(3586.0, 6731.9)	39.0
Fe(0-12) (%)[1]	50 μg BD AM	9	9	3.0	(2, 4)	N/A
	50 μg BD PM	9	9	4.3	(2, 6)	N/A
	100 μg BD AM	8	8	4.2	(2, 6)	N/A
	100 μg BD PM	8	8	5.2	(2, 7)	N/A
CLr (L/h)	50 μg BD AM	9	4	36.2	(24.7, 53.2)	24.5
	100 μg BD AM	8	7	27.5	(17.7, 42.6)	50.2

1. Presented as median (range)

CVb = between-subject coefficient of variation; NA = not applicable; CLr = renal clearance; Ae = amount of drug excreted unchanged in urine; Fe = fraction of dose excreted unchanged in urine; BD = twice daily

A summary of urine pharmacokinetic parameters on Day 7 is presented in the following table:

Parameter	GSK233705 dose	N	n	Geometric mean	95% confidence interval	CVb(%)
Ae(0-12) (ng)	50 μg BD AM	9	9	3661.2	(2977.1, 4502.5)	27.4
	50 μg BD PM	9	9	3344.7	(2157.7, 5184.7)	62.0
	100 μg BD AM	8	8	6538.3	(3942.3, 10843.8)	66.5
	100 μg BD PM	8	8	7328.5	(5448.2, 9857.6)	36.6
Fe(0-12) (%)[1]	50 μg BD AM	9	9	7.5	(5, 10)	N/A
	50 μg BD PM	9	9	7.5	(2, 14)	N/A
	100 μg BD AM	8	8	7.5	(2, 12)	N/A
	100 μg BD PM	8	8	7.7	(4, 12)	N/A
CLr (L/h)	50 μg BD AM	9	9	19.4	(13.6, 27.7)	49.1
	100 μg BD AM	8	8	15.2	(9.10, 25.5)	68.4

CVb = between-subject coefficient of variation; Ae = amount of drug excreted unchanged in urine; BD = twice daily; AM = morning dose; PM = evening dose; Fe = fraction of dose excreted unchanged in urine; N/A = not applicable; CLr = renal clearance

A summary of results of the statistical analysis of accumulation for urine pharmacokinetic parameters is presented in the following table:

Parameter	Treatment group	Ratio of adjusted geometric means (Day 7 AM versus Day 1 AM)	90% confidence interval
Ae(0-12) (ng)	GSK233705 50 μg	2.556	(2.033, 3.213)
	GSK233705 100 μg	1.644	(1.290, 2.095)

Ae = amount of drug excreted in the urine

Pharmacodynamics Endpoints: Values of FEV1 were higher for both treatment groups compared with placebo, with the largest values seen in the highest dose group (GSK233705 100 μg). Values of FVC were higher for both treatment groups compared with placebo, with the largest values seen in the highest dose group (GSK233705 100 μg).

Publications: None.