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Study No: AC2105333

Title : A randomised, double-blind, placebo-controlled, dose ascending, three period crossover study to examine the safety, tolerability, pharmacodynamics and pharmacokinetics of repeat inhaled doses of GSK233705B in COPD subjects.

Rationale: This was a multi-centre study to examine the safety, tolerability, pharmacodynamics and pharmacokinetics of GSK233705B in subjects with chronic obstructive pulmonary disease (COPD) under repeat dose conditions (7 days) in order to provide information supporting future development of this long-acting bronchodilator for use in COPD.

Phase: IIA.

Study Period: 16-Aug-2006 - 03-Apr-2007.

Study Design: Randomised, double-blind, placebo-controlled, dose ascending, three period crossover study.

Centres: Three centres in Belgium and two centres in Sweden.

Indication: None.

Treatment: Subjects were randomised to receive the following treatments as a three-way cross-over, in dose-ascending manner (i.e., they did not receive the higher dose before treatment with the lower dose):

- Inhaled dose of GSK233705B (20 μg) dry powder inhaler (DPI) administered twice daily for 7 days.
- Inhaled dose of GSK233705B (50 μg) DPI administered twice daily for 7 days.
- Inhaled dose of matching placebo DPI administered twice daily for 7 days.

Objectives: To assess the safety and tolerability of repeat inhaled doses of GSK233705B (inhaled twice daily for 7 days) in COPD patients.

Statistical Methods: The safety population included all available data on subjects who received at least one dose of study medication. The Pharmacokinetic Concentration Population was defined as all subjects in the Safety Population for whom a pharmacokinetic sample was obtained and analysed. The Pharmacokinetic Parameter Population was defined as all subjects in the Pharmacokinetic Concentration Population who provide PK parameters. The Modified Per Protocol Population (MPP) included all available data on subjects for each period where major deviations from the protocol did not occur.

Power calculations were based on the ability to detect a 0.15 L difference in the forced expiratory volume in 1 second (FEV_1) between placebo and both doses of GSK233705B at the 24 h time point (12 h post-afternoon dose). Using a weighted standard deviation estimate from three previous studies (0.179 L), and assuming 12 subjects on each of the three possible treatment sequences, 36 evaluable subjects would provide at least 89% power to detect a 0.15 L difference in FEV_1 between placebo and the GSK233705B doses using a two sided 5% significance level.

The derived parameters weighted mean and maximum value were calculated over the time period 0–4 h for each of heart rate, systolic and diastolic blood pressure, QTc(B) and QTc(F). Mean (0–24 h), maximum (0–24 h) and minimum (0–24 h) heart rate as measured from Holter monitoring were also calculated. Mixed effect modelling was performed for serial time point analysis as well as analysis of the weighted mean and maximum value parameters.

All specific airway conductance (sGaw) and FEV_1 data in the Modified Per-Protocol (mPP) population were summarised and sGaw and FEV_1 data were analysed across serial time points (up to 25 h for sGaw and up to 24 h for FEV_1) using repeated measures modelling. Specific airways conductance was logarithmatically transformed prior to analysis.

The pharmacokinetic parameters were calculated by standard non-compartmental analysis.

Exploratory dose proportionality analysis was assessed for both plasma and urine pharmacokinetic data using Analysis of Variance (ANOVA).

An exploratory assessment of the accumulation parameters accumulation ratio(Ro)(area under the drug time concentration curve from time 0 to the time of the last quantifiable concentration (AUC(0-t))), and the accumulation ratio of the maximum plasma concentration (Cmax) (RCmax) was made. An assessment of accumulation for the amount of drug excreted unchanged in the urine (Ae) (0-12) after the morning dose was assessed.

Study Population: Male and female subjects with COPD aged 40–75 years with a body weight >50 kg. They had to be smokers or ex-smokers with at least a 10-year pack history and to demonstrate a bronchodilator response to ipratropium bromide. Subjects had to have FEV_1/forced vital capacity (FVC) ratio of <0.7 and FEV_1 ≤80% of predicted normal post-bronchodilator (salbutamol).

Number of Subjects:	Placebo	GSK233705B 20 μg	GSK233705B 50 μg
Planned N	45	45	45

Dosed N	39	39	37
Completed n (%)	38 (97)	37 (95)	37 (100)
Total Number Subjects Withdrawn N (%)	1 (3)	2 (5)	0
Withdrawn due to Adverse Events n (%)	1 (3)	2(5)	0
Withdrawn for Other Reasons n (%)	0	0	0

Note: Withdrawals are assigned to the treatment with which the subject was last dosed, prior to withdrawal.

Demographics	**All subjects**
N (Safety population)	40
Females: Males	10:30
Mean Age in Years (sd)	61.0 (7.74)
Mean Weight in Kg (sd)	78.33 (13.548)
White n (%)	100

Pharmacokinetics (PK),pharmacodynamics (PD) Endpoints: A summary of the FEV_1 treatment difference between active and placebo from the statistical analysis on Days 1 and 7 is presented in the following table:

Comparison with placebo	**Day**	**Timepoint (hours)**	**Treatment difference (active-placebo) (L)**	**95% confidence interval for difference**
GSK233705B 20μg (N=39)	1	12	0.179	(0.093, 0.266)
		24	0.232	(0.158, 0.307)
GSK233705B 50μg (N=37)	1	12	0.178	(0.090, 0.265)
		24	0.215	(0.139, 0.291)
GSK233705B 20μg (N=39)	7	12	0.200	(0.105, 0.296)
		24	0.163	(0.079, 0.247)
GSK233705B 50μg (N=37)	7	12	0.150	(0.054, 0.246)
		24	0.173	(0.089, 0.257)

A summary of the sGaw treatment difference between active and placebo on Days 1 and 7 from the statistical analysis is presented in the following table:

Comparison with placebo	**Day**	**Timepoint (hours)**	**Treatment ratio (active/placebo)**	**95% confidence interval for ratio**
GSK233705B 20 μg (N=39)	1	11	1.412	(1.270,1.569)
		25	1.380	(1.245, 1.528)
GSK233705B 50 μg (N=37)	1	11	1.419	(1.276, 1.579)
		25	1.336	(1.204, 1.483)
GSK233705B 20 μg (N=39)	7	11	1.516	(1.365, 1.685)
		25	1.305	(1.176, 1.448)
GSK233705B 50 μg (N=37)	7	11	1.474	(1.326, 1.638)
		25	1.412	(1.275, 1.565)

A summary of plasma Cmax and tmax are presented in the following table:

Parameter	**GSK233705B dose (morning)**	**N**	**n**	**n#**	**Geometric mean**	**95% Confidence interval**	**CVb(%)**
Cmax_high (ng/mL)	20 μg	39	39	27	0.0110	(0.0104, 0.0116)	17.3
	50 μg	37	36	3	0.0319	(0.0256, 0.0397)	72.1
tmax (h)[1]	20 μg	39	12	0	0.08	(0.07, 0.33)	NA
	50 μg	37	33	0	0.08	(0.08, 0.25)	NA
Cmax_high (ng/mL) (Day 7)	20 μg AM	39	37	15	0.0138	(0.0122, 0.0156)	38.1
	20 μg PM	39	36	16	0.0135	(0.0119, 0.0153)	37.6
	50 μg AM	37	36	1	0.0529	(0.0419, 0.0667)	77.5

	50 µg PM	37	36	2	0.0493	(0.0398, 0.0610)	70.0
tmax (h)[1] (Day 7)	20 µg AM	39	22	0	0.08	(0.07, 0.28)	NA
	20 µg PM	39	20	0	0.08	(0.07, 0.25)	NA
	50 µg AM	37	35	0	0.08	(0.00, 11.98)	NA
	50 µg PM	37	34	0	0.08	(0.00, 0.25)	NA

1. presented as median and range;
NA: not applicable; NC: not calculable; Cmax = maximum observed plasma concentration; tmax = time of maximum observed plasma concentration; Cmax high was derived by substituting all NQ Cmax values with the LLQ (0.01ng/mL), CI = confidence interval; CVb = between-subject coefficient of variance, n=number of subjects with non-missing values, n# = number of subjects with Non quantifiable values, N=number of subjects in treatment group

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

Parameter	**GSK233705B dose**	**N**	**n**	**Geometric mean**	**95% confidence interval**	**CVb(%)**
Ae(0-12) (ng) (Day 1)	20 µg AM	39	23	626	(546, 717)	32.3
	20 µg PM	39	32	784	(679, 905)	41.6
	50 µg AM	37	37	1488	(1199, 1847)	72.3
	50 µg PM	37	36	1890	(1496, 2387)	78.2
CLr (L/h) (Day 1)	20 µg AM	39	0	NC	(NC, NC)	NC
	50 µg AM	37	1	NC	(NC, NC)	NC
Ae(0-12) (ng) (Day 7 AM)	20 µg	39	34	1454	(1267, 1668)	40.9
	50 µg	37	37	3595	(3101, 4169)	46.7
CLr (L/h) (Day 7 AM)	20 µg	39	0	NC	(NC, NC)	NC
	50 µg	37	7	16.6	(11.2, 24.6)	44.8
Fe(0-12) (%)[1] (Day 7 AM)	20 µg	39	34	7.78	(2.63, 13.1)	NA
	50 µg	37	37	7.85	(2.04, 15.2)	NA
Ae(0-12) (ng) (Day 7 PM)	20 µg	39	34	1257	(1030, 1534)	62.1
	50 µg	37	35	3405	(2988, 3881)	39.4
CLr (L/h) (Day 7 PM)	20 µg	39	0	NC	(NC, NC)	NC
	50 µg	37	7	18.4	(13.6, 25.1)	34.0
Fe (0-12)(%)[1] (Day 7 PM)	20 µg	39	35	6.90	(0.00, 14.9)	NA
	50 µg	37	35	7.28	(3.07, 14.4)	NA
t½ (h)	20 µg	39	15	15.6	(12.9, 18.9)	35.3
	50 µg	37	22	14.3	(12.6, 16.3)	29.6

1 arithmetic mean value (range)
NA = not applicable; NC = not calculated; Ae = amount of drug excreted unchanged in urine, AEUR = Area under the excretion rate curve; CLr = renal clearance; Fe = fraction of dose excreted unchanged in urine; t½ = terminal phase half life; CVb = between-subject coefficient of variance

A summary of dose proportionality for Ae(0–12): assessed using the analysis of variance method is presented in the following table:

Parameter	**GSK233705B dose comparison**	**Day**	**Ratio of adjusted geometric means**	**90% confidence interval of means**
Ae(0–12) (ng)	20 µg versus 50 µg	1 (AM)	1.02	(0.84, 1.24)
	20 µg versus 50 µg	7(AM)	1.00	(0.88, 1.13)

Ae = amount of drug excreted unchanged in urine

An assessment of accumulation for Ae(0–12) is presented in the following table:

Parameter	**GSK233705B dose**	**Ratio of adjusted geometric means (Day 7 AM versus Day 1 AM)**	**90% confidence interval**
Ae(0-12) (ng)	20 µg	2.42	(2.03, 2.88)
	50 µg	2.42	(2.09, 2.79)

Ae = amount of drug excreted unchanged in urine

Safety results: All adverse events (AEs) and serious AEs (SAEs) were recorded from first dose until follow up. Serious adverse events related to study treatment were recorded from the time the subject consented until follow up.

Adverse Events:	**Placebo**	**GSK233705B 20 µg**	**GSK233705B 50 µg**
N (Safety population)	39	39	37

No. subjects with AEs n (%)	13 (33)	27 (69)	19 (51)
Most Frequent AEs			
Headache	4 (10)	13 (33)	11 (30)
Nasopharyngitis	2 (5)	3 (8)	3 (8)
Cough	2 (5)	2 (5)	2 (5)
Constipation	1 (3)	1 (3)	1 (3)
Fatigue	1 (3)	2 (5)	0
Pharyngolaryngeal pain	1 (3)	0	2 (5)
AST increased	1 (3)	0	1 (3)
COPD	1 (3)	1 (3)	0
Leukocyturia	0	1 (3)	1 (3)
Palpitations	0	2 (5)	0
Pyrexia	0	1 (3)	1 (3)
Ventricular extrasystole	0	1 (3)	1 (3)
Vertigo	1 (3)	1 (3)	0
Vomiting	0	1 (3)	1 (3)
AST = aspartate transaminase, COPD = chronic obstructive pulmonary disease			
Serious Adverse Events	**Placebo (N=39)**	**GSK233705B 20 μg (N=39)**	**GSK233705B 50 μg (N=37)**
No. subjects with SAEs n (%)	0	1 (3)	0
Most Frequent SAEs			
Pneumonia	0	1 (3)	0
A summary of results of statistical analysis of maximum, minimum and mean heart rate data from holter (0-24hrs) (adjusted means) is presented in the following table:			

Treatment	Day 1				Day 7			
	n	Maximum bpm (CI)	Minimum bpm (CI)	Mean bpm (CI)	n	Maximum bpm (CI)	Minimum bpm (CI)	Mean bpm (CI)
Placebo (N=39)	37	121.656 (117.523, 125.788)	53.939 (51.863, 56.016)	74.937 (71.938, 77.937)	36	119.971 (115.737, 124.205)	53.122 (51.062, 55.182)	73.740 (70.770, 76.709)
GSK233705 20 μg (N=39)	37	121.814 (117.532, 126.095)	53.343 (51.226, 55.460)	74.700 (71.657, 77.744)	35	120.462 (116.035, 124.888)	53.294 (51.175, 55.414)	73.545 (70.520, 76.570)
GSK233705 50 μg (N=37)	34	121.800 (117.482, 126.119)	53.021 (50.888, 55.154)	74.850 (71.797, 77.903)	35	122.443 (118.075, 126.811)	51.463 (49.364, 53.562)	74.035 (71.026, 77.044)

CI = confidence interval

A summary of results of statistical analysis of derived 12-lead electrocardiogram parameters (QTc(B) and QTc(F)) is presented in the following table.

Endpoint	Treatment comparison (versus placebo)	Day	Difference	Standard error	95% confidence interval
Maximum QTc(B) (0–4 h) (msec)	GSK233705 20 μg	1	4.26	2.889	-1.47,10.00
	GSK233705 50 μg	1	-2.29	2.884	-8.02,3.43
	GSK233705 20 μg	7	-1.84	2.434	-6.69, 3.01
	GSK233705 50 μg	7	-3.53	2.387	-8.29, 1.23
Weighted mean QTc(B) (0–4 h) (msec)	GSK233705 20 μg	1	0.78	1.571	-2.34, 3.90
	GSK233705 50 μg	1	-0.05	1.559	-3.15, 3.05
	GSK233705 20 μg	7	-1.85	1.757	-5.34, 1.65
	GSK233705 50 μg	7	-1.42	1.729	-4.86, 2.03
Maximum QTc(F) (0–4 h) (msec)	GSK233705 20 μg	1	4.21	2.079	0.09, 8.34
	GSK233705 50 μg	1	-1.21	2.062	-5.31, 2.89
	GSK233705 20 μg	7	-1.82	2.012	-5.82, 2.14
	GSK233705 50 μg	7	-1.78	1.968	-5.82, 2.14
Weighted mean QTc(F) (0–4 h) (msec)	GSK233705 20 μg	1	1.60	1.294	-0.97, 4.17
	GSK233705 50 μg	1	0.30	1.279	-2.24, 2.84
	GSK233705 20 μg	7	-1.44	1.509	-4.44, 1.56
	GSK233705 50 μg	7	-0.46	1.479	-3.40, 2.49

Publications: None