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.: AC2110664

Title: Dose-ranging Study for GSK233705 Delivered Once-Daily in Subjects with COPD

Rationale: The information obtained from this study will be used to select the optimal effective and safe once-daily dose of GSK233705 for subsequent clinical development for the treatment of chronic obstructive pulmonary disease (COPD).

Phase: IIb

Study Period: 16 May 2008 through 03 February 2009

Study Design: Randomized, double-blind, placebo-controlled, parallel-group multicenter study

Centres: A total of 79 centers randomized subjects to treatment: 30 in North America (USA and Canada), 28 in Europe (Bulgaria, Germany, Hungary, Netherlands, Romania, and UK), and 21 in international regions (Argentina, Chile, Korea, Philippines, South Africa, and Thailand)

Indication: Chronic obstructive pulmonary disease (COPD)

Treatment: One of five doses of GSK233705 (12.5, 25, 50, 100, or 200 mcg) or placebo once daily for 28 days.

Objectives: The primary objective of this study was to evaluate the dose response, efficacy and safety of five dosage regimens of GSK233705 (12.5, 25, 50, 100, and 200 mcg) over a 28-day period in subjects with COPD to inform the selection of the optimal once daily dose of GSK233705 for subsequent development as a monotherapy product and as a component of fixed dose combination products.

Primary Outcome/Efficacy Variable: The primary efficacy endpoint was the change from baseline in trough forced expiratory volume in one second (FEV_1) on Day 29.

Secondary Outcome/Efficacy Variable(s): Secondary efficacy endpoints included: 1) Time-adjusted area under the curve (AUC, i.e., weighted mean) for 24-hour serial FEV_1 and forced vital capacity (FVC) on Days 1 to 2 and 28 to 29 (serial spirometry obtained 30 minutes pre-dose, immediately pre-dose, and post-dose at 30 minutes, and 1, 2, 4, 8, 10, 12, 23, and 24 hours), and 2) Change from baseline in clinic visit trough FVC on Day 29.

Statistical Methods: The sample size (480 completed subjects; 80 per treatment group) was based on the primary efficacy endpoint of change from baseline in trough FEV_1 on Day 29, which was derived from the mean of the assessments taken 23 and 24 hours after dosing on Day 28. The study was powered at 90% to detect a treatment difference of 130 mL in change from baseline in trough FEV_1 between a GSK233705 dose and placebo, assuming a standard deviation of 250 mL and with significance declared at the 2-sided 5% level. In order to allow for subject withdrawals and missing data, it was planned to randomize 96 subjects per treatment group. The primary analysis was the pair-wise comparison of each of the five doses of GSK23375 with placebo. A step-down closed testing procedure to control multiplicity was applied whereby initially the highest GSK233705 dose with placebo was compared and subsequent comparisons at lower doses continued in a step-down manner only if the preceding comparison was significant at the 5% level. The primary analysis was performed using Analysis of Covariance (ANCOVA) with last observation carried forward (LOCF) to impute missing data. The primary population for this and all other analyses of efficacy measures was the Intent-To-Treat (ITT) Population, comprising all randomized subjects who received at least one dose of study medication. Analysis of secondary efficacy endpoints were performed using repeated measures analyses. Adverse events were summarized by incidence (number of subjects) and preferred terms were categorized by system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA).

Study Population: Male and female subjects 40 to 80 years of age with an established clinical history of COPD and a current or prior history of at least 10 pack-years of cigarette smoking were eligible. At Screening (Visit 1), subjects had to have a post-albuterol/salbutamol FEV_1/ FVC ratio of <=0.70 and a post-albuterol/salbutamol percent predicted FEV_1 of >=35% and <=70%.

Number of Subjects	Placebo	12.5mcg	25mcg	50mcg	100mcg	200mcg
Planned, N	96	96	96	96	96	96
Randomized, N	97	96	97	98	96	97
ITT Population, N	96	95	96	97	95	97
Completed, n (%)	87 (91)	88 (93)	90 (94)	92 (95)	89 (94)	91 (94)
Total Number Subjects Withdrawn, N (%)	9 (9)	7 (7)	6 (6)	5 (5)	6 (6)	6 (6)

Withdrawn due to Adverse Events n (%)	0	1 (1)	1 (1)	2 (2)	2 (2)	2 (2)
Withdrawn due to Lack of Efficacy n (%)	2 (2)	2 (2)	1 (1)	1 (1)	2 (2)	1 (1)
Withdrawn for other reasons n (%)	7 (7)	4 (4)	4 (4)	2 (2)	2 (2)	3 (3)
Demographics	Placebo	12.5mcg	25mcg	50mcg	100mcg	200mcg
N (ITT)	96	95	96	97	95	97
Females: Males	46:50	34:61	43:53	45:52	33:62	34:63
Mean Age, years (SD)	61.4 (8.73)	62.2 (9.75)	62.2 (8.70)	62.8 (6.99)	61.7 (8.77)	64.1 (8.30)
White, n (%)	84 (88)	86 (91)	86 (90)	88 (91)	83 (87)	85 (88)
Primary Efficacy Results:						
Trough FEV_1 (L) on Day 29 (ITT – ANCOVA with LOCF)	Placebo N=96	12.5mcg N=95	25mcg N=96	50mcg N=97	100mcg N=95	200mcg N=97
Mean Baseline FEV_1, (SD)	1.291 (0.4169)	1.335 (0.4551)	1.292 (0.4004)	1.269 (0.3874)	1.271 (0.4145)	1.242 (0.4640)
n analyzed	94	94	94	97	94	96
Adjusted mean change from baseline (SE)	-0.009 (0.0181)	0.058 (0.0180)	0.088 (0.0180)	0.060 (0.0178)	0.073 (0.0181)	0.128 (0.0179)
Treatment difference vs. placebo	---	0.067	0.097	0.069	0.082	0.137
95% CI	---	0.017, 0.117	0.047, 0.147	0.019, 0.118	0.032, 0.132	0.086, 0.187
p-value	---	0.009	<0.001	0.007	0.001	<0.001
Secondary Outcome Variables:						
	Placebo N=96	12.5mcg N=95	25mcg N=96	50mcg N=97	100mcg N=95	200mcg N=97
Weighted Mean for 24 hr Serial FEV_1 (L) on Day 1 (ITT- Repeated measures analysis)						
n analyzed (data on 1 or more days)	94	94	95	97	94	97
n analyzed (data on the given day)	93	93	92	96	94	96
Treatment difference vs. placebo	---	0.106	0.107	0.123	0.152	0.176
95% CI	---	0.065, 0.146	0.067, 0.147	0.083, 0.163	0.112, 0.193	0.135, 0.216
Weighted Mean for 24 hr Serial FEV_1 (L) on Day 28 (ITT- Repeated measures analysis)						
n analyzed (data on 1 or more Days)	94	94	95	97	94	97
n analyzed (data on the given day)	86	88	89	90	89	91
Treatment difference vs. placebo	---	0.106	0.142	0.124	0.142	0.170
95% CI	---	0.056, 0.157	0.092, 0.192	0.074, 0.174	0.092, 0.193	0.120, 0.220
Weighted Mean for 24 hr Serial FVC (L) on Day 1 (ITT- Repeated measures analysis)						
n analyzed (data on 1 or more Days)	94	94	95	97	94	97
n analyzed (data on the given day)	93	93	92	96	94	96
Treatment difference vs. placebo	---	0.166	0.186	0.198	0.244	0.301
95% CI	---	0.094, 0.237	0.115, 0.258	0.127, 0.268	0.172, 0.315	0.229, 0.372
Weighted Mean for 24 hr Serial FVC (L) on Day 28 (ITT- Repeated measures analysis)						
n analyzed (data on 1 or more Days)	94	94	95	97	94	97
n analyzed (data on the given day)	86	88	89	90	89	91
Treatment difference vs. placebo	---	0.178	0.219	0.191	0.232	0.294
95% CI	---	0.098, 0.258	0.139, 0.298	0.111, 0.270	0.152, 0.312	0.214, 0.373

Trough FVC (L) on Day 29 (ITT – Repeated Measures analysis)						
n analyzed (data on 1 or more Days)	94	94	94	97	94	96
n analyzed (data on the given day)	87	88	90	91	89	91
Treatment difference vs. placebo	---	0.099	0.150	0.094	0.163	0.235
95% CI	---	0.015, 0.182	0.067, 0.233	0.011, 0.177	0.080, 0.247	0.152, 0.319
Most Frequent Adverse Events – On-Therapy (Day 1 through Day 28 or last day of treatment)	Placebo N=96	12.5mcg N=95	25mcg N=96	50mcg N=97	100mcg N=95	200mcg N=97
Subjects with any AE(s), n (%)	27 (28)	30 (32)	24 (25)	30 (31)	31 (33)	27 (28)
Headache	7 (7)	4 (4)	6 (6)	9 (9)	5 (5)	3 (3)
Back pain	1 (1)	1 (1)	4 (4)	2 (2)	3 (3)	2 (2)
Nasopharyngitis	4 (4)	1 (1)	1 (1)	2 (2)	2 (2)	0
Diarrhea	2 (2)	1 (1)	2 (2)	1 (1)	0	1 (1)
Cough	4 (4)	0	1 (1)	0	0	1 (1)
Dyspnea	0	0	2 (2)	2 (2)	1 (1)	1 (1)
Oropharyngeal pain	0	1 (1)	2 (2)	0	2 (2)	1 (1)
Upper respiratory tract infection	0	3 (3)	0	2 (2)	0	1 (1)
Urinary tract infection	1 (1)	1 (1)	2 (2)	0	1 (1)	1 (1)
Chronic obstructive pulmonary disease	0	2 (2)	0	2 (2)	1 (1)	0
Dizziness	0	1 (1)	1 (1)	1 (1)	2 (2)	0
Hypertension	1 (1)	0	1 (1)	1 (1)	1 (1)	1 (1)
Myalgia	0	1 (1)	2 (2)	2 (2)	0	0
Insomnia	1 (1)	0	1 (1)	1 (1)	0	1 (1)
Abdominal pain	0	0	2 (2)	1 (1)	0	0
Arthritis	0	0	0	2 (2)	1 (1)	0
Constipation	0	0	1 (1)	1 (1)	0	1 (1)
Dyspepsia	0	0	1 (1)	0	0	2 (2)
Sinusitis	1 (1)	0	1 (1)	0	0	1 (1)
Wheezing	0	1 (1)	0	0	1 (1)	1 (1)
Arthralgia	0	0	0	1 (1)	0	1 (1)
Blood creatine phosphokinase increased	0	2 (2)	0	0	0	0
Candidiasis	1 (1)	0	0	0	0	1 (1)
Contact dermatitis	1 (1)	1 (1)	0	0	0	0
Dry mouth	0	1 (1)	0	0	1 (1)	0
Erythema	0	0	1 (1)	0	0	1 (1)
Fatigue	0	0	2 (2)	0	0	0
Hyperchlorhydria	0	0	0	2 (2)	0	0
Influenza	1 (1)	0	0	0	1 (1)	0
Muscle strain	0	1 (1)	0	0	0	1 (1)
Edema peripheral	1 (1)	0	0	0	0	1 (1)
Rhinorrhea	0	0	0	1 (1)	0	1 (1)
Sinus headache	0	1 (1)	0	0	1 (1)	0
Toothache	0	1 (1)	1 (1)	0	0	0
Vasomotor rhinitis	1 (1)	0	1 (1)	0	0	0
Vomiting	0	1 (1)	0	0	0	1 (1)
Acute sinusitis	0	1 (1)	0	0	0	0
Alanine aminotransferase increased	0	0	0	0	0	1 (1)
Anemia	0	0	0	0	0	1 (1)
Aphonia	0	0	0	0	0	1 (1)
Arthropod sting	0	0	0	0	0	1 (1)
Aspartate aminotransferase increased	0	0	0	0	0	1 (1)
Bronchitis	0	1 (1)	0	0	0	0

Dental caries	1 (1)	0	0	0	0	0
Diabetes mellitus	1 (1)	0	0	0	0	0
Dry throat	0	0	0	0	0	1 (1)
Erectile dysfunction	0	1 (1)	0	0	0	0
Flushing	0	0	0	0	0	1 (1)
Gamma-glutamyltransferase increased	0	0	0	0	0	1 (1)
Gastrointestinal infection	0	1 (1)	0	0	0	0
Hemorrhoids	0	1 (1)	0	0	0	0
Hordeolum	0	0	0	0	0	1 (1)
Hypercholesterolemia	0	1 (1)	0	0	0	0
Hypoesthesia	0	1 (1)	0	0	0	0
Influenza-like illness	0	1 (1)	0	0	0	0
Joint injury	0	1 (1)	0	0	0	0
Joint swelling	0	0	0	0	0	1 (1)
Limb injury	0	1 (1)	0	0	0	0
Local swelling	0	0	0	0	0	1 (1)
Mouth cyst	0	1 (1)	0	0	0	0
Mouth ulceration	0	0	0	0	0	1 (1)
Muscle injury	1 (1)	0	0	0	0	0
Oral candidiasis	0	0	0	0	0	1 (1)
Osteopenia	0	0	0	0	0	1 (1)
Paronychia	1 (1)	0	0	0	0	0
Post procedural hemorrhage	0	1 (1)	0	0	0	0
Prostatitis	0	1 (1)	0	0	0	0
Pulmonary congestion	0	0	0	0	0	1 (1)
Acute renal failure	0	0	0	0	0	1 (1)
Respiratory tract congestion	0	0	0	0	0	1 (1)
Restless legs syndrome	0	0	0	0	0	1 (1)
Rhinitis	0	0	0	0	0	1 (1)
Shoulder operation	1 (1)	0	0	0	0	0
Sinus bradycardia	0	0	0	0	0	1 (1)
Stomach discomfort	0	0	0	0	0	1 (1)
Syncope	0	1 (1)	0	0	0	0
Tension headache	0	1 (1)	0	0	0	0
Vessel puncture site hematoma	0	0	0	0	0	1 (1)
Viral sinusitis	1 (1)	0	0	0	0	0
Serious Adverse Events - On-Therapy (Day 1 through 7 days post-treatment) n (%) [n considered by the investigator to be related to study medication]	Placebo N=96	12.5mcg N=95	25mcg N=96	50mcg N=97	100mcg N=95	200mcg N=97
Subjects with non-fatal SAEs, n (%)	0	0	2 (2) [0]	1 (1) [0]	1 (1) [0]	0
Colitis	0	0	1 (1) [0]	0	0	0
Pancreatitis	0	0	0	0	1 (1) [0]	0
Chronic obstructive pulmonary disease (exacerbation)	0	0	0	1 (1) [0]	0	0
Uterine leiomyoma	0	0	1 (1) [0]	0	0	0
Subjects with fatal SAEs, n (%)	0	0	0	0	0	1 (1) [0]
Acute renal failure	0	0	0	0	0	1 (1) [0]
Congestive cardiac failure	0	0	0	0	0	1 (1) [0]

Conclusion: The primary efficacy endpoint (change from baseline in trough FEV_1 on Day 29) demonstrated statistically significant differences in favor of all five doses of GSK233705 compared with placebo. The differences were ≥130 mL for the 200 mcg dose. Statistically significant differences were observed in favor of GSK233705 over placebo for the secondary efficacy endpoints. The most frequently reported AEs across the treatment groups (GSK233705 and placebo) were headache, back pain, and nasopharyngitis. The incidence of these AEs was similar

across the treatment groups. Non-fatal SAEs were reported for 4 subjects in the GSK233705 treatment groups and included colitis, pancreatitis, COPD exacerbation, and uterine leiomyoma. One fatality due to acute renal failure and congestive cardiac failure was reported.
Publication: None