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.: MAB115032

Title: A Four Week Dose Ranging, Dose Interval, Efficacy, Safety, Tolerability Study of GSK961081 in subjects with COPD

Rationale: The purpose of this study was to evaluate the safety and efficacy of GSK961081 administered both once- and twice-daily over a 28 day period to allow the selection of an optimal safe and efficacious dose and dosing interval.

Phase: IIb

Study Period: 13 December 2010 – 02 September 2011

Study Design: A multi-centre, randomised, double-blind, double-dummy, placebo- and active-controlled, parallel-group, dose-ranging and dose-interval study

Centres: 49 centres in 9 countries (Europe and South Africa)

Indication: COPD

Treatment: Dry powder formulations of GSK961081 delivered via DISKUS™ administered once-daily,in the morning (100mcg, 400mcg, 800mcg) or twice-daily in the morning and evening (100mcg, 200mcg, 400mcg). Matching placebo delivered via DISKUS once-daily (in the evening) or twice-daily (morning and evening).Salmeterol 50mcg delivered via DISKUS administered twice-daily (morning and evening).

Objectives: The primary objective of this study was to evaluate the dose response, dose interval, efficacy, and safety of GSK961081 by studying three QD doses and three BID doses and salmeterol compared with placebo delivered by DISKUS in subjects with COPD.

Primary Outcome/Efficacy Variable: Change from baseline in AM trough forced expiratory volume in 1 second (FEV_1) on Day 29 (defined as the mean of the values recorded 11 H and 12 H after the PM dose on Day 28).

Secondary Outcome/Efficacy Variable(s):

- Weighted mean for 0 to 24 H serial FEV_1 in the subset of subjects with overnight spirometry on Day 28 (pre-dose and post-AM dose after 15, 30 and 60 min and 2, 4, 6, 11 and 12 H; post-PM dose after 15, 30 and 60 min and 2, 4, 6, 11 and 12 H).
- Serial AM FEV_1 on Day 1 and Day 28 at each time point up to 12 H post AM dose.
- Serial FEV_1 on Day 28 at each time point up to 24H post AM dose in the subset of subjects performing overnight spirometry.

Other Efficacy Outcomes:

- Weighted mean for AM 0 to 12 H serial FEV_1 on Days 1 and 28 (pre-dose and post AM dose after 15, 30 and 60 Min and 2, 4, 6, 11 and 12 H).
- Change from baseline in pre AM dose trough FEV_1 on Days 2, 14 and 28.
- Proportion of subjects reaching 100mL and 150mL increase in FEV_1 from baseline on Days 1 and 28 (0-24 H).
- Time to achieve an increase of 100mL above baseline in FEV_1 on Day 1 (0-6 H post AM dose).
- Time above 100mL and 150mL change from baseline over dosing interval on Day 1 and Day 28
- Change from baseline in pre PM dose trough FEV_1 on Days 1 and 28 (defined as the mean of the values recorded 11 and 12 H after the AM dose).
- Peak AM FEV_1 on Day 1 and Day 28 (0-6 H post AM dose).
- Peak PM FEV_1 on Day 28 (0-6 H post PM dose) (in the subset of subjects performing overnight spirometry only).
- Weighted mean for PM 0 to 12 H serial FEV_1 on Day 28 (pre-dose and post PM dose after 15, 30 and 60 Min and 2, 4, 6, 11 and 12 H) in the subset of subjects who are undergoing overnight spirometry.

- Time to peak AM FEV_1 on Day 1 and Day 28 (0-6 H post AM dose).
- Time to peak PM FEV_1 on Day 28 (0-6 H post PM dose) in the subset of subjects performing overnight spirometry.
- Change from baseline in clinic visit pre-dose trough FVC on Days 2, 14, 28 and 29.
- Serial FVC on Day 1 and Day 28 (at each time point).
- Salbutamol use (occasions/day), averaged over each week of treatment and over the 28-day treatment period.
- The percentage of salbutamol rescue-free 24 H periods during each week of treatment and over the 28-day treatment period.

Statistical Methods: Forty-two evaluable subjects in each of the GSK961081 treatment groups and 63 evaluable subjects in the placebo treatment group were deemed necessary to provide greater than 90% power (across all strata combined) to detect a difference between a GSK961081 dose regimen and placebo of 150mL in change from baseline clinic trough FEV_1 at endpoint, assuming a standard deviation of 200mL and a 2.5% significance level. An uneven ratio of subjects on GSK961081 arms and the placebo arm was used in order to increase the precision of the estimate of placebo effect.

The Intent-To-Treat (ITT) Population, which comprised all subjects randomised to treatment and who had received at least one dose of double-blind study medication, was the primary population for all analyses of efficacy, safety and pharmacodynamic measures. The primary endpoint was analysed for each dose regimen of GSK961081 vs. placebo, using a repeated measures model with effects due to baseline trough FEV_1, reversibility, concomitant ICS use, site type (overnight/non-overnight), sex, age, smoking status and dose regimen. Inferences were made as dictated by two step-down closed testing procedures (one for the QD dose interval vs. placebo and one for the BID dose interval vs. placebo). Comparisons for each dosing interval used a 2.5% significance level (preserving the overall alpha level of 5%).

The secondary endpoints were analysed using ANCOVA models with the same covariates as used for the primary analysis. Pairwise treatment comparisons of each dose regimen of GSK961081 to placebo were used with inferences made at a 5% significance level without adjustment for multiplicity.

Study Population: Male and female subjects, ≥ 40 years old, with a current COPD diagnosis: post-salbutamol $FEV_1/FVC<0.70$ and %predicted $FEV_1 \geq 30\%$ and $\leq 70\%$, with no other respiratory disorders diagnosed, including asthma. Subjects were randomised if they had no clinically significant abnormalities, COPD exacerbations or lower respiratory infections during run-in. Use of oral corticosteroids or antibiotics were not allowed within 6 weeks prior to Visit 1 (Screening).

	Placebo	**Salmeterol (50mcg BID)**	**GSK961081 BID**			**GSK961081 QD**		
			100 mcg	**200 mcg**	**400 mcg**	**100 mcg**	**400 mcg**	**800 mcg**
Number of Subjects:								
Planned, N	75	50	50	50	50	50	50	50
Randomised, N	81	47	52	50	54	50	50	52
Completed, n (%)	71 (88)	43 (91)	47 (90)	45 (90)	49 (91)	45 (90)	41 (82)	48 (92)
Total Number Subjects Withdrawn, N (%)	10 (12)	4 (9)	5 (10)	5 (10)	5 (9)	5 (10)	9 (18)	4 (8)
Withdrawn due to Adverse Events n (%)	2 (2)	0	1 (2)	2 (4)	2 (4)	2 (4)	0	1 (2)
Withdrawn due to Lack of Efficacy n (%)	2 (2)	0	0	0	1 (2)	0	0	0
Withdrawn for other reasons n (%)	6 (7)	4 (9)	4 (8)	3 (6)	2 (4)	3 (6)	9 (18)	3 (6)

Demographics	Placebo	Salmeterol (50mcg BID)	GSK961081 BID			GSK961081 QD		
			100 mcg	200 mcg	400 mcg	100 mcg	400 mcg	800 mcg
N (ITT)	81	47	52	50	54	50	50	52
Males	57 (70)	29 (62)	37 (71)	32 (64)	38 (70)	32 (64)	26 (52)	35 (67)
Mean Age, years (SD)	63 (7)	61 (7)	62 (9)	61 (9)	63 (8)	63 (9)	62 (7)	61 (9)
White, n (%)	79 (98)	46 (98)	52 (100)	50 (100)	53 (98)	50 (100)	50 (100)	51 (98)
Not hispanic/latino, n(%)	81 (100)	46 (98)	52 (100)	50 (100)	54 (100)	50 (100)	50 (100)	52 (100)
Mean Body Mass Index, kg/m2 (SD)	26 (4)	26 (4)	26 (4)	26 (4)	26 (4)	26 (4)	27 (4)	25 (4)

Primary Efficacy Results:

Change from baseline in AM trough FEV_1 on Day 29	Placebo	Salmeterol (50mcg BID)	GSK961081 BID			GSK961081 QD		
			100 mcg	200 mcg	400 mcg	100 mcg	400 mcg	800 mcg
n	71	43	47	46	49	45	41	48
LS Mean (SE) (L)	-0.01 (0.02)	0.07 (0.03)	0.17 (0.03)	0.24 (0.03)	0.25 (0.03)	0.15 (0.03)	0.21 (0.03)	0.27 (0.03)
LS Mean Difference from Placebo (L)	-	0.077	0.173	0.249	0.258	0.155	0.215	0.277
95% Confidence Interval	-	0.00, 0.15	0.10, 0.25	0.17, 0.32	0.19, 0.33	0.08, 0.23	0.14, 0.29	0.20, 0.35
p-value	-		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Secondary Outcome Variable(s):

For this study, one secondary endpoint (weighted mean FEV_1 (0-24h) on Day 28) and one other endpoint (weighted mean FEV_1 (0-12h) on Day 28) are reported to give a brief but representative summary of the efficacy outcomes.

Weighted mean FEV_1 (0-24h) on Day 28 (subset analysis)	Salmeterol (50mcg BID)	GSK961081 BID			GSK961081 QD		
		100 mcg	200 mcg	400 mcg	100 mcg	400 mcg	800 mcg
n	19	22	21	24	18	18	23
LS Mean difference from placebo (L)	0.085	0.226	0.325	0.307	0.246	0.300	0.335
95% CI (if appropriate)	-0.02, 0.19	0.12, 0.33	0.22, 0.43	0.21, 0.40	0.14, 0.35	0.19, 0.41	0.24, 0.43
Weighted mean FEV_1 (0-12h) on Day 28	**Salmeterol (50mcg BID)**	**GSK961081 BID**			**GSK961081 QD**		
		100 mcg	**200 mcg**	**400 mcg**	**100 mcg**	**400 mcg**	**800 mcg**
n	43	47	46	49	45	42	48
LS Mean difference from placebo (L)	0.104	0.213	0.283	0.277	0.183	0.287	0.343
95% CI (if appropriate)	0.03, 0.18	0.14, 0.29	0.21, 0.36	0.20, 0.35	0.11, 0.26	0.21, 0.37	0.27, 0.42

AEs were collected from the start of Investigational Product (Visit 2) and until the follow-up contact. SAEs were collected over the same time period as stated above for AEs unless they were assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication. If this was the case, SAEs were recorded from the time a subject consented to participate in the study up to and including any follow-up contact.

	Placebo	Salmeterol (50mcg BID)	GSK961081 BID			GSK961081 QD		
			100 mcg	200 mcg	400 mcg	100 mcg	400 mcg	800 mcg
	N=81	N=47	N=52	N=50	N=54	N=50	N=50	N=52

Most Frequent Adverse Events – On-Therapy, n (%)								
Subjects with any AE(s)	20 (25)	8 (17)	12 (23)	12 (24)	16 (30)	16 (32)	15 (30)	13 (25)
Headache	5 (6)	2 (4)	2 (4)	0	5 (9)	5 (10)	5 (10)	2 (4)
Cough	2 (2)	0	2 (4)	4 (8)	1 (2)	5 (10)	5 (10)	4 (8)
Dysguesia	0	0	2 (4)	3 (6)	3 (6)	2 (4)	1 (2)	0
Nasopharyngitis	3 (4)	0	1 (2)	0	0	3 (6)	1 (2)	0
Back Pain	2 (2)	0	1 (2)	0	0	0	2 (4)	0
Dysphonia	2 (2)	0	0	0	0	0	1 (2)	2 (4)
Muscle spasms	0	1 (2)	1 (2)	0	2 (4)	0	0	1 (2)
Nausea	2 (2)	0	0	0	0	1 (2)	2 (4)	0
Myalgia	1 (1)	1 (2)	0	0	0	0	2 (4)	0
Palpitations	0	1 (2)	0	0	2 (4)	0	0	0
Upper respiratory tract infection	2 (2)	0	0	0	0	0	0	0

Serious Adverse Events - On-Therapy

One non-fatal SAE was reported during the study. This was an incidence of biliary colic which was reported in one subject (2%) in the 400mcg QD GSK961081 treatment group and was not considered to be related to the study drug).

Conclusion:

All doses of GSK961081 demonstrated statistically significant differences from placebo for pre-dose trough FEV1 on Day 29. Between 23-32% of subjects in the GSK961081 treatment groups reported adverse events, with the most frequently reported being headache and cough. In the placebo treated group, 25% of subjects reported adverse events with the most frequently reported being headache and nasopharyngitis. One serious adverse event, biliary colic, was reported in the GSK961081 400mcg QD treatment group. There were no deaths reported during the study.