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.: B2C108562
Title: A multi-centre, randomised, placebo-controlled, double-blind, 4-arm parallel-group, 2-week study to evaluate the safety, tolerability, pharmacodynamics and pharmacokinetics of a NCE (2 dosage strengths, administered once-daily in the morning via DISKUS™ dry-powder inhaler) compared with salmeterol (50mcg administered twice-daily via DISKUS dry-powder inhaler) and placebo in subjects with moderate COPD
Rationale: The present study tested the safety, tolerability, pharmacodynamics and pharmacokinetics of a new chemical entity (NCE) (dosed once daily) at single and repeat inhaled doses in male and female subjects with COPD, compared with salmeterol (50mcg, dosed twice daily) and placebo
Phase: II
Study Period: 03Nov2006 - 10May2007
Study Design: This was a multi-centre, randomised, placebo-controlled, double-blind, 4-arm, parallel-group study, evaluating 2 dosage strengths of a NCE (administered once-daily) versus a positive control group (salmeterol 50mcg twice-daily) and placebo. Subjects were screened (Visit 1) within 3-7 days of the first dose of study medication to check if they met the eligibility criteria. At the end of the run-in period (Visit 2) they were randomised to enter a 2 week double-blind treatment period. At the end of the treatment period subjects attended a follow-up visit within 48 hours of the final administration of study medication. After follow-up subjects left the study to return to their conventional therapy.
Centres: Fourteen (14) centres in 6 countries participated in this study (10 centres in Europe, 2 centres in Australia and 2 centres in New Zealand).
Indication: COPD
Treatment: Subjects were randomised to a 2 week treatment period in which they administered one of two dosage strengths of the NCE or 50mcg salmeterol or placebo.
Objectives: The primary objective was to evaluate the safety and tolerability of 2 dosage strengths of the NCE (administered once-daily for 2 weeks) versus salmeterol and placebo in subjects with moderate COPD.
Primary Outcome: Incidence of Adverse Events (AEs) reported prior to, throughout and after the 15-day treatment period as recorded by subjects on daily record cards (DRCs) and investigators (during clinical assessments).
Secondary Outcomes: 1. Summary measures for Heart Rate (HR) and Systolic and Diastolic Blood Pressure (BP), derived from 28.5h ambulatory blood pressure monitoring starting on Days 1, 7 and 14. 2. Summary measures for QTc(F) and QTc(B) values derived from clinical visit 12-lead ECGs recorded at several time points at Days 1 and 2, 7 and 8 and 14 and 15. 3. Summary measures for QTc(F) and QTc(B), premature ventricular beats, premature supraventricular beats and ventricular runs derived from 24h 3-lead Holter ECG monitoring at Days 1, 7 and 14. 4. Change in haematological and clinical chemistry parameters from baseline at Days 7 and 14 5. Summary measures for clinic visit FEV1 recorded at several time points at Days 1 and 2, 7 and 8 and 14 and 15. 6. Summary measures for PEFR (AM and PM) and use of rescue medication as recorded daily from run-in to follow-up by subjects on Diary Record Cards (DRCs), and averaged over the run-in, week 1, week 2 and follow-up periods. 7. Summary measures of fasting glucose and potassium recorded at several time points at Days 1 and 2, 7 and 8 and 14 and 15. 8. PK parameters AUC_{0-4}, C_{max}, t_{max} and accumulation ratios (C_{max} and AUC_{0-4}) on Days 1, 7 and 14 for the derived NCE, its counter-ion and metabolites and salmeterol. 9. PK parameters AUC_{0-2} (for NCE dose 1 only), $AUC_{0\text{-}tlast}$, t_{last} and accumulation ratios for AUC_{0-2} on Days 1, 7 and 14 for the NCE.

Statistical Methods:

No formal statistical analysis was planned for this study. Inferences regarding relative safety, tolerability and PD of the NCE, salmeterol and placebo were intended to be made based upon summary measures of recorded data. However, in order to further support future studies with the NCE in a broader COPD population, additional exploratory statistical analyses were performed for weighted mean and maximum 0-4h heart rate and glucose, weighted mean and minimum 0-4h potassium and weighted mean 22-24h FEV_1. Using ANCOVA an estimate of the difference between each active treatment and placebo was presented together with 95% confidence intervals for the treatment difference; p-values were not presented. These analyses were defined before the database was frozen and the study unblinded.

All summary measures and statistical analyses (excluding those for PK endpoints) were performed on the safety population. The safety population comprised all subjects who were randomized and received at least one dose of study treatment. All summary measures and statistical analyses of the PK data were performed on the PK Concentration or PK Parameter population. The PK Concentration Population included those subjects in the Safety Population for whom a PK sample was obtained and analysed. The PK Parameter Population included all subjects in the PK Concentration Population who provided any PK parameter information (i.e. AUC_{0-4}, C_{max} or T_{max}).The main comparisons of interest were between each dose of the NCE and placebo and these were considered of equal importance. The comparisons of salmeterol with placebo were secondary to establish a benchmark response

The study randomisation was planned for equal allocation of subjects among the four treatment groups. The sample size of 20 subjects per treatment group (80 subjects in total) was planned to provide sufficient numbers of subjects in each treatment arm to provide information for the next phase of clinical development. There were no formal powering calculations that underpinned the sample size for this study. However, for this study, it was considered that if no occurrences of a specific AE were observed in 20 subjects receiving a given dose of the NCE in this study, there was a 95% probability that the true population incidence of that AE was no more than 15% at that dose. Similarly, if no occurrences of a specific AE were observed in any of the 40 patients projected to be dosed with the NCE in this study, there was a 95% probability that the true population incidence was no more than 7.5% across the NCE dose range.

Statistical analysis of C_{max}, $AUC_{(0-2)}$ and $AUC_{(0-4)}$ for each analyte (salmeterol, NCE and metabolites) was performed using a mixed effects model after a log transformation of the data from Days 1, 7 and 14 to evaluate the accumulation ratio provided that the analyte was detected in at least 75% of subjects on an active treatment.

Four populations were analysed in this study: the All Subjects Enrolled Population (145 subjects), the Safety Population (68 subjects), the PK Concentration Population (50 subjects) and the PK Parameter Population (49 subjects).

Study Population:

1. Male or female subjects of non child bearing potential (i.e. post-menopausal or surgically sterile) ≥ 40 years of age at screening (Visit 1)
2. COPD Diagnosis: subjects with a clinical history of COPD were enrolled.
3. Tobacco Use: Subjects with a current or prior history of >10 pack years of cigarette smoking at screening (Visit 1).
4. Severity of Disease: Subjects who conformed to the GOLD severity classification for Stage II disease in terms of post-bronchodilator spirometry (either confirmed within 3 months of screening (Visit 1) or at screening (Visit 1).
5. Patients with a primary diagnosis of asthma were excluded.

Data regarding the NCE will be provided in the event the NCE is marketed. Data regarding salmeterol and placebo is provided at this time.

	Placebo BID	Salmeterol 50mcg BID
Number of Subjects:		
Planned, N	20	20
Randomised, N	17	18
Completed, n (%)	16 (94)	14 (78)
Total Number Subjects Withdrawn, n (%)	1 (6)	4 (22)
Withdrawn due to Adverse Events, n (%)	0	1 (6)
Subject decided to withdraw, n (%)	0	1 (6)
Subject withdrew due to exacerbation, n (%)	0	1 (6)
Withdrawn for other reasons, n (%)	1(6)	1(6)
Demographics	Placebo BID	Salmeterol 50mcg BID

N (Safety Population)	1717	18
Females: Males	4:13	9:9
Mean Age, years (SD)	61.4 (8.79)	60.2 (7.37)
Race, n (%)		
White	16 (94)	18 (100)
Native Hawaiian or other Pacific Islander	1 (6)	0
Primary Efficacy Results: See Safety Results below.		
Safety Results: The key safety data are listed below.		
	Placebo BID	Salmeterol 50mcg, BID
All Adverse Events started During/Post Treatment	n (%)	n (%)
Subjects with any AE(s), n (%)	4 (24)	6 (33)
Nervous System Disorders, n (%)		
Headache	2 (12)	3 (17)
Dizziness	0	2 (11)
Respiratory, Thoracic and Mediastinal Disorders, n(%)		
Cough	1 (6)	1 (6)
Pharyngolaryneal pain	0	1 (6)
Haemoptysis	1 (6)	0
Gastrointestinal Disorders, n (%)		
Nausea	0	1 (6)
General Disorders and administration site conditions, n (%)		
Chest discomfort	2 (12)	0
Chest pain	1 (6)	1 (6)
Application site rash	1 (6)	0
Infections and Infestations, n (%)		
Oral herpes	1(6)	0
Cardiac Disorders, n (%)		
Ventricular extrasystoles	0	1(6)
Investigations, n (%)		
White blood cell count decreased	1 (6)	0
Skin and subcutaneous tissue disorders, n (%)		
Skin reaction	1 (6)	0
Psychiatric Disorders, n (%)		
Insomnia	1 (6)	0
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]		
	Placebo BID	Salmeterol 50mcg, BID
	n (%)[n related]	n (%)[n related]
Subjects with any non-fatal SAEs, n (%)	0	1 (6) [1]
Cardiac Disorders:		
Ventricular extrasystoles	0	1(6) [1]
Subjects with any fatal SAEs, n (%)	0	0
Secondary Safety Results:		
Change from Baseline and Treatment Difference in weighted mean HR (bpm) (0-4 hrs)		
	Placebo BID	Salmeterol 50mcg, BID
Day 1		
LS Mean change (SE)	2.14 (2.134)	4.63 (2.020)
LS Mean Difference (salmeterol – placebo)	2.49	
95% CI	-3.35, 8.33	
Day 2		
LS Mean change (SE)	1.01 (2.208)	5.61 (2.138)
LS Mean Difference (salmeterol – placebo)	4.60	

95% CI	-1.45, 10.65	
Day 7		
LS Mean change (SE)	8.21 (2.357)	6.75 (2.324)
LS Mean Difference (salmeterol – placebo)	-1.46	
95% CI	-8.25, 5.33	
Day 8		
LS Mean change (SE)	1.11 (2.341)	4.94 (2.317)
LS Mean Difference (salmeterol – placebo)	3.82	
95% CI	-2.85, 10.50	
Day 14		
LS Mean change (SE)	3.64 (2.307)	6.92 (2.476)
LS Mean Difference (salmeterol – placebo)	3.29	
95% CI	-3.58, 10.15	
Day 15		
LS Mean change (SE)	2.17 (2.460)	4.28 (2.440)
LS Mean Difference (salmeterol – placebo)	2.11	
95% CI	-4.96, 9.18	
Change from Baseline and Treatment Difference in Maximum HR (bpm) (0-4 hrs)		
	Placebo BID	Salmeterol 50mcg, BID
Day 1		
LS Mean change (SE)	20.6 (3.71)	20.5 (3.51)
LS Mean Difference (salmeterol – placebo)	0.0	
95% CI	-10.2, 10.1	
Day 2		
LS Mean change (SE)	9.7 (3.17)	11.3 (2.90)
LS Mean Difference (salmeterol – placebo)	1.6	
95% CI	-6.9, 10.1	
Day 7		
LS Mean change (SE)	26.8 (4.21)	22.0 (4.36)
LS Mean Difference (salmeterol – placebo)	-4.8	
95% CI	-17.1, 7.5	
Day 8		
LS Mean change (SE)	9.0 (2.85)	12.1 (2.95)
LS Mean Difference (salmeterol – placebo)	3.1	
95% CI	-5.2, 11.4	
Day 14		
LS Mean change (SE)	26.1 (3.730	23.2 (3.86)
LS Mean Difference (salmeterol – placebo)	-2.9	
95% CI	-13.8, 8.0	
Day 15		
LS Mean change (SE)	10.2 (3.04)	14.6 (3.13)
LS Mean Difference (salmeterol – placebo)	4.4	
95% CI	-4.5, 13.3	
Change from Baseline in weighted mean HR (bpm) (0-24 hrs)		
	Placebo BID	Salmeterol 50mcg, BID
Day 7		
Mean change (SD)	6.50 (6.696)	6.47 (6.885)
Day 14		
Mean change (SD)	2.77 (7.495)	5.87 (6.420)
Change from baseline and treatment difference in weighted mean FEV_1 (L) (22-24 hrs)		
	Placebo BID	Salmeterol 50mcg, BID
Day 1		

LS Mean change (SE)	0.0191 (0.04224)	0.0955 (0.04043)
LS Mean Difference (salmeterol – placebo)	0.0764	
95% CI	-0.0375, 0.1903	
Day 7		
LS Mean change (SE)	-0.0174 (0.05640)	0.1204 (0.05723)
LS Mean Difference (salmeterol – placebo)	0.1377	
95% CI	-0.0233, 0.2987	
Day 14		
LS Mean change (SE)	-0.0225 (0.05719)	0.0732 (0.05827)
LS Mean Difference (salmeterol – placebo)	0.0956	
95% CI	-0.0686, 0.2599	

Other Safety Results:

One subject from the salmeterol group had reported abnormal liver function parameters starting on Day 8. High, out of range values were flagged for alanine amino transferase, aspartate amino transferase, lactate dehydrogenase and total bilirubin. Additional liver function tests plus immunology and virology investigations were conducted. The immunology and virology assessment results were negative. All the liver function parameters returned to within normal range without treatment after Day 8 except for aspartate amino transferase levels and alanine amino transferase levels which returned to normal range after Visit 8 (follow-up) and by Day 33. The subject continued in the study.

PD Results:

Change in Baseline and Treatment Difference in Weighted Mean Glucose (0-4 hrs) (mMol/L)

	Placebo BID	Salmeterol 50mcg, BID
Day 1		
LS Mean change (SE)	0.048 (0.2097)	0.140 (0.1946)
LS Mean Difference (salmeterol – placebo)	0.093	
95% CI	-0.469, 0.654	
Day 2		
LS Mean change (SE)	-0.137 (0.2749)	-0.072 (0.2550)
LS Mean Difference (salmeterol – placebo)	0.065	
95% CI	-0.667, 0.797	
Day 7		
LS Mean change (SE)	-0.002 (0.1978)	0.078 (0.1929)
LS Mean Difference (salmeterol – placebo)	0.080	
95% CI	-0.471, 0.631	
Day 8		
LS Mean change (SE)	-0.183 (0.3111)	-0.039 (0.3097)
LS Mean Difference (salmeterol – placebo)	0.144	
95% CI	-0.742, 1.030	
Day 14		
LS Mean change (SE)	0.193 90.2104)	0.006 (0.1956)
LS Mean Difference (salmeterol – placebo)	-0.187	
95% CI	-0.765, 0.391	
Day 15		
LS Mean change (SE)	-0.100 (0.2505)	0.078 (0.2413)
LS Mean Difference (salmeterol – placebo)	0.178	
95% CI	-0.522, 0.877	

Change in Baseline and Treatment Difference in Maximum Glucose (0-4 hrs) (mMol/L)

	Placebo BID	Salmeterol 50mcg, BID
Day 1		
LS Mean change (SE)	0.65 (0.361)	0.48 (0.336)
LS Mean Difference (salmeterol – placebo)	-0.17	
95% CI	-1.15, 0.80	
Day 2		

LS Mean change (SE)	0.21 (0.363)	0.44 (0.337)
LS Mean Difference (salmeterol – placebo)	0.23	
95% CI	-0.74, 1.20	
Day 7		
LS Mean change (SE)	0.52 (0.367)	0.65 (0.359)
LS Mean Difference (salmeterol – placebo)	0.13	
95% CI	-0.89, 1.15	
Day 8		
LS Mean change (SE)	0.28 (0.431)	0.60 (0.429)
LS Mean Difference (salmeterol – placebo)	0.32	
95% CI	-0.90, 1.54	
Day 14		
LS Mean change (SE)	0.37 (0.434)	0.37 (0.433)
LS Mean Difference (salmeterol – placebo)	0.00	
95% CI	-1.23, 1.23	
Day 15		
LS Mean change (SE)	0.21 (0.348)	0.70 (0.346)
LS Mean Difference (salmeterol – placebo)	0.49	
95% CI	-0.50, 1.48	
Change in Baseline and Treatment Difference in Weighted Mean Potassium (0-4 hrs) (mMol/L)		
	Placebo BID	Salmeterol 50mcg, BID
Day 1		
LS Mean change (SE)	0.183 (0.0999)	0.030 (0.1063)
LS Mean Difference (salmeterol – placebo)	-0.153	
95% CI	-0.440, 0.133	
Day 2		
LS Mean change (SE)	0.376 (0.1575)	0.358 (0.1576)
LS Mean Difference (salmeterol – placebo)	-0.018	
95% CI	-0.452, 0.416	
Day 7		
LS Mean change (SE)	0.267 (0.1318)	0.077 (0.1415)
LS Mean Difference (salmeterol – placebo)	-0.190	
95% CI	-0.575, 0.196	
Day 8		
LS Mean change (SE)	0.247 (0.1051)	0.350 (0.1154)
LS Mean Difference (salmeterol – placebo)	0.103	
95% CI	-0.213, 0.418	
Day 14		
LS Mean change (SE)	0.218 (0.1140)	0.123 (0.1224)
LS Mean Difference (salmeterol – placebo)	-0.095	
95% CI	-0.432, 0.243	
Day 15		
LS Mean change (SE)	0.155 (0.1120)	0.293 (0.1234)
LS Mean Difference (salmeterol – placebo)	0.139	
95% CI	-0.198, 0.475	
Change in Baseline and Treatment Difference in Minimum Potassium (0-4 hrs) (mMol/L)		
	Placebo BID	Salmeterol 50mcg, BID
Day 1		
LS Mean change (SE)	-0.12 (0.094)	-0.32 (0.096)
LS Mean Difference (salmeterol – placebo)	-0.19	
95% CI	-0.46, 0.07	
Day 2		
LS Mean change (SE)	0.07 (0.127)	0.05 (0.130)

LS Mean Difference (salmeterol – placebo)	-0.02		
95% CI	-0.37, 0.34		
Day 7			
LS Mean change (SE)	0.07 (0.143)	-0.27 (0.156)	
LS Mean Difference (salmeterol – placebo)	-0.34		
95% CI	-0.76, 0.08		
Day 8			
LS Mean change (SE)	0.09 (0.099)	0.13 (0.113)	
LS Mean Difference (salmeterol – placebo)	0.04		
95% CI	-0.26, 0.34		
Day 14			
LS Mean change (SE)	-0.06 (0.091)	-0.12 (0.103)	
LS Mean Difference (salmeterol – placebo)	-0.06		
95% CI	-0.34, 0.21		
Day 15			
LS Mean change (SE)	-0.02 (0.099)	0.02 (0.113)	
LS Mean Difference (salmeterol – placebo)	0.04		
95% CI	-0.26, 0.34		
PK Results:			
Derived PK parameters for Salmeterol			
$AUC_{(0-4)}$ pg.h/mL	Day 1	Day 7	Day 14
Geometric mean (CV%)	225.334 (14.83)	226.708 (34.42)	178.656 (33.47)
C_{max} pg/mL			
Geometric mean (CV%)	50.218 (45.71)	59.943 (49.73)	51.983 (29.13)
C_{max} pg/mL (LLQ imputed with 25 pg/mL)			
Geometric mean (CV%)	46.262 (49.57)	56.044 (54.66)	51.983 (29.13)
C_{max} pg/mL (LLQ imputed with 0.01 pg/mL)			
Geometric mean (CV%)	18.428 (5958.94)	30.701 (2029.28)	51.983 (29.13)
T_{max} (h)			
Median (range)	1.000 (0.08-2.00)	1.000 (0.08-2.00)	1.000 (0.08-4.05)
Publications: No Publications			

Date updated: 20-Nov-2007