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: SCO100470
Title: A multicentre, randomised, double-blind, parallel group, 24-week study to compare the effect of the salmeterol/fluticasone propionate combination product 50/250mcg, with salmeterol 50mcg both delivered twice daily via the DISKUS/ACCUHALER inhaler on lung function and dyspnoea in subjects with Chronic Obstructive Pulmonary Disease (COPD).
Rationale: Salmeterol/fluticasone propionate combination product (SFC) at a dose of 50/500mcg twice daily is approved in Europe for the treatment of patients with severe COPD (FEV1 <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy. The purpose of the present study was to assess the effects of SFC 50/250mcg in subjects with milder COPD. In this study SFC 50/250mcg was compared with salmeterol 50mcg alone in COPD subjects with a Forced Expiratory Volume in one second (FEV1) of greater than 50% but less than 80% of predicted normal; using lung function (FEV1) and dyspnoea, as measured by the Transitional Dyspnoea Index (TDI) as co-primary endpoints.
Phase: Phase III
Study Period: 22 June 2002 – 25 May 2005
Study Design: The study was a multicentre, randomised, double-blind, double dummy, parallel group design.
Centres: Subjects were randomised by 135 investigators [n] in 20 countries (Australia [10], Bulgaria [5], Croatia [1], Czech Republic [8], France [14], Germany [18], Greece [4], Italy [16], Latvia [5], Lithuania [2], Netherlands [12], Philippines [3], Poland [5], Romania [3], Russian Federation [8], Slovakia [4], Slovenia [4], Sweden [4], Thailand [4] and United Kingdom [5]), One hundred and forty one subjects were enrolled in the Asia Pacific region, and 909 subjects were enrolled in Europe.
Indication: Chronic Obstructive Pulmonary Disease (COPD)
Treatment: Salmeterol 50mcg/ fluticasone propionate 250mcg combination product (SFC50/250) twice daily, or salmeterol 50mcg (Sal 50) twice daily, both taken orally using the DISKUS/ ACCUHALER .
Objectives: To compare the effectiveness of SFC 50/250 combination product with Sal 50 both delivered twice daily via the DISKUS/ACCUHALER inhaler on lung function (FEV_1), and relief of dyspnoea as measured by the TDI, in subjects with COPD, over a 24-week treatment period.
Primary Outcome/Efficacy Variable: The primary efficacy variables were change from baseline in trough FEV_1 and TDI focal score at endpoint (last available on-treatment value).
Secondary Outcome/Efficacy Variable(s): Secondary efficacy variables included: Change from baseline in trough FEV_1 at 4, 8, 12, 16, and 24 weeks. Change from baseline in trough FVC, and FEV_1/FVC ratio (prior to use of VENTOLIN and before the administration of the morning dose of study medication) at 4, 8, 12, 16, 20, and 24 weeks, and endpoint. TDI focal score at 4, 8, 12, 16, 20, and 24 weeks. Percentage of subjects who achieve an improvement or deterioration in TDI focal score of ≥ 1 unit at 4, 8, 12, 16, 20, and 24 weeks, and at endpoint. Change from baseline in post-dose FEV_1, FVC and FEV_1/FVC (measured two hours after inhalation of study medication and prior to use of VENTOLIN) at 4, 8, 12, 16, 20, and 24 weeks and at endpoint. Change from baseline in mean morning PEF as measured by the subject and documented in the Daily Record Card (DRC) over the 24-week treatment period. Number of subjects withdrawn during the 24-week treatment period. Change from baseline in St George's Respiratory Questionnaire (SGRQ) health status score at 4, 8, 12, 16, 20, and 24 weeks, and endpoint.
Statistical Methods: The ITT (Intent to treat) Population (all subjects randomised and confirmed as having received at least one dose of double-blind study medication) was the primary population for analysis of all efficacy and health outcomes variables; the Safety Population (identical to the ITT Population) was used for analysis of all safety variables. The primary efficacy variables (change from baseline at endpoint in trough FEV_1 and TDI focal score at endpoint) were compared between treatments using an analysis of covariance (ANCOVA) model adjusted for factors of country, sex,

baseline smoking status, and covariates of respective baseline values and age. Change from baseline in trough FEV_1 and TDI focal score at each time point were analysed using a repeated measures model with fixed effects for treatment, study week, treatment by study week, respective baseline by study week, sex, country and baseline smoking status Changes from baseline in pre-dose FVC and FEV_1/FVC ratio, post-dose FEV_1, FVC and FEV_1/FVC ratio, and SGRQ score at endpoint and at each visit were analysed as described for the primary endpoints.
The percentage of subjects achieving a TDI focal score of ≥1 at endpoint was analysed using a logistic regression model. The percentage of subjects achieving a TDI focal score of ≥1 at each time point was analysed using a generalized equation estimation model (GEE) adjusted for factors of country, sex, baseline smoking status, and continuous covariates, BDI focal score, age, study week, treatment by study week, and TDI focal score by study week.
Change from baseline in mean morning PEF as documented in the Daily Record Card (DRC) over the 24-week treatment period was analysed using ANCOVA adjusted for factors of treatment, country, sex, baseline smoking status, and covariates of respective baseline values and age.
The time to withdrawal was compared between treatments using the Log Rank test.

Study Population: Male or female, aged 40-80 years with an established history of GOLD (**G**lobal initiative for chronic **O**bstructive **L**ung **D**isease) stage II COPD; poor reversibility of airflow obstruction (defined as ≤ 10% increase in FEV_1 as a percentage of the normal predicted value); a minimum score of ≥ 2 on the Modified Medical Research Council Dyspnoea Scale, and a smoking history of at least 10 pack years. In addition, subjects had to achieve a composite symptom score of ≥ 120 (out of 400 maximum score, measured using visual analogue scales) on at least 4 of the last 7 days of the run-in period, and to have a Baseline Dyspnoea Index (BDI) score of ≤ 7 units at Visit 2. Subjects would be excluded if they had asthma or atopic disease, had a lung disease likely to confound the drug response other than COPD, had a recent exacerbation (within 4 weeks or screening or during run-in); were receiving long-term oxygen therapy or pulmonary rehabilitation or had taken tiotropium bromide, inhaled corticosteroids or anti-leukotriene medication within 14 days of visit 1.

	Sal 50	**SFC50/250**
Number of Subjects:		
Planned, N	443	443
Randomised, N	532	518
Completed, n (%)	458 (86)	459 (89)
Total Number Subjects Withdrawn, N (%)	74 (14)	59 (11)
Withdrawn due to Adverse Events n (%)	37 (7)	25 (5)
Withdrawn due to Lack of Efficacy n (%)	5 (<1)	2 (<1)
Withdrawn for other reasons n (%)	32 (6)	32 (6)
Demographics	**Sal 50**	**SFC50/250**
N (ITT)	N=532	N=518
Females: Males	121:411	112:406
Mean Age, years (SD)	63.7 (9.02)	63.5 (9.35)
Race, n (%) Caucasian	481 (90)	469 (91)
Current smoker (%)	234 (44)	217 (42)
Primary Efficacy Results		
	Sal 50	**SFC50/250**
	N=532	**N=518**
FEV_1		
N	517	508
Mean Baseline FEV_1 mL [SD]	1681 [465]	1654 [459]
Adjusted mean FEV_1 at endpoint [SE]	1689 [12]	1728 [12]
Difference between treatments in mL [SE]	39mL [18]	
95% Confidence Interval in mL	5, 73	
p-value	0.026	
TDI		
N	516	505
Mean BDI at baseline [SD] units	5.6 [1.26]	5.6 [1.28]
Adjusted mean TDI at endpoint [se]	2.2 [0.12]	2.3 [0.12]
Treatment difference [SE]	0.2 [0.17]	
95% Confidence Interval	-0.2 to 0.5	

p-value	0.374	
Secondary Outcome Variable(s):	**SAL 50**	**SFC50/250**
Change from baseline in Trough FEV_1		
Baseline raw mean mL [sd]	1681 [465]	1654 [459]
Adjusted mean change from baseline in mL [sd] at		
Week 4	32 [11]	78 [11]
Week 8	30 [11]	65 [11]
Week 12	47 [12]	74 [12]
Week 16	20 [13]	77 [13]
Week 20	18 [12]	85 [12]
Week 24	24 [13]	60 [13]
Endpoint	21 [12]	60 [12]
Change from baseline in trough FVC		
Baseline raw mean FVC in mL [sd]	2869 [752]	2870 [733]
Adjusted mean change from baseline in mL [se] at		
Week 4	39 [17]	66 [17]
Week 8	47 [19]	34 [19]
Week 12	59 [21]	52 [21]
Week 16	2 [20]	52 [20]
Week 20	23 [19]	28 [19]
Week 24	9 [20]	5 [20]
Endpoint	-2 [19]	4 [19]
Change from baseline in trough FEV_1/FVC ratio		
Baseline raw mean FEV_1:FVC ratio [sd]	0.59 [0.096]	0.58 [0.097]
Adjusted mean change from baseline [se] at		
Week 4	0.01 [0.003]	0.01 [0.003]
Week 8	0.00 [0.003]	0.01 [0.003]
Week 12	0.01 [0.003]	0.02 [0.003]
Week 16	0.01 [0.003]	0.01 [0.003]
Week 20	0.01 [0.004]	0.02 [0.004]
Week 24	0.01 [0.004]	0.02 [0.004]
Endpoint	0.01 [0.003]	0.02 [0.003]
TDI focal score at 4, 8, 12, 16, 20, and 24 weeks		
Baseline raw mean BDI units [sd]	5.6 [1.26]	5.6 [1.28]
Mean TDI focal score units [sd] at		
Week 4	1.1 [0.10]	1.5 [0.11]
Week 8	1.7 [0.10]	1.9 [0.10]
Week 12	1.9 [0.12]	1.9 [0.12]
Week 16	2.0 [0.12]	2.0 [0.12]
Week 20	2.1 [0.12]	2.2 [0.12]
Week 24	2.4 [0.12]	2.5 [0.12]
Endpoint	2.2 [0.12]	2.3 [0.12]
Percentage of subjects who achieve an improvement or deterioration in TDI focal score of ≥ 1 unit at 4, 8, 12, 16, 20, and 24 weeks and at endpoint		
Number (percentage) of subjects achieving TDI focal score >=1 at Week 4		
Week 8	263 (57%)	277 (55%)
Week 12	292 (59%)	306 (62%)
Week 16	280 (57%)	290 (60%)
Week 20	290 (61%)	280 (59%)
Week 24	281 (60%)	282 (61%)
Endpoint	290 (65%)	284 (63%)
	309 (60%)	310 (61%)
Change from baseline in post-dose FEV_1, (measured two hours after inhalation of study medication and prior to use of VENTOLIN) at 4, 8, 12, 16, 20, and 24 weeks and at endpoint		

Adjusted mean change from baseline in FEV_1 in mL [se] at		
Week 4	184 [31]	177 [31]
Week 8	130 [14]	180 [14]
Week 12	149 [13]	180 [13]
Week 16	134 [14]	178 [14]
Week 20	121 [13]	181 [13]
Week 24	115 [13]	161 [13]
Endpoint	112 [13]	156 [13]
Change from baseline in post-dose FVC (measured two hours after inhalation of study medication and prior to use of VENTOLIN) at 4, 8, 12, 16, 20 and 24 weeks, and at endpoint.		
Adjusted mean change from baseline in FVC in mL [se] at		
Week 4	225 [35]	198 [35]
Week 8	147 [23]	202 [23]
Week 12	191 [24]	193 [24]
Week 16	134 [23]	177 [23]
Week 20	121 [20]	165 [20]
Week 24	121 [20]	119 [20]
Endpoint	112 [19]	116 [19]
Change from baseline in post-dose FEV_1/FVC (measured two hours after inhalation of study medication and prior to use of VENTOLIN) at 4, 8, 12, 16, 20 and 24 weeks and at endpoint.		
Adjusted mean change from baseline in FEV_1/FVC ratio [se] at		
Week 4	0.01 [0.003]	0.02 [0.003]
Week 8	0.01 [0.004]	0.02 [0.004]
Week 12	0.01 [0.003]	0.02 [0.003]
Week 16	0.02 [0.005]	0.02 [0.005]
Week 20	0.02 [0.004]	0.03 [0.004]
Week 24	0.02 [0.004]	0.03 [0.004]
Endpoint	0.02 [0.003]	0.03 [0.004]
Change from baseline in mean morning PEF as measured by the subject and documented in the Daily Record Card (DRC) over the 24-week treatment period.		
Baseline morning mean PEF L/min [sd]	276.5 [82.6]	273.6 [85.0]
Adjusted mean change from baseline in morning PEF over 24 weeks L/min [se]	17.6 [1.71]	28.0 [1.72]
Number of subjects withdrawn during the 24-week treatment period		
Subjects withdrawn during treatment period n (%)		
Week 0- <4	10 (2%)	2 (0%)
Week 4- <8	16 (3%)	11 (2%)
Week 8- <12	13 (2%)	13 (3%)
Week 12- <16	9 (2%)	7 (1%)
Week 16- <20	12 (2%)	11 (2%)
Week 20- <24	8 (2%)	9 (2%)
Change from baseline in St George's Respiratory Questionnaire (SGRQ) health status score at 4, 8, 12, 16, 20, and 24 weeks and at endpoint.		
Baseline raw mean SGRQ Total score [sd]	48.2 [16.55]	48.0 [17.10]
Adjusted mean change from baseline in SGRQ Total score [se] at		
Week 4	-4.3 [0.48]	-6.0 [0.48]
Week 8	-6.9 [0.56]	-7.9 [0.57
Week 12	-7.8 [0.58]	-8.8 [0.58]
Week 16	-8.6 [0.60]	-10.4 [0.61]
Week 20	-8.9 [0.64]	-10.1 [0.65]
Week 24	-9.7 [0.66]	-10.3 [0.67]
Endpoint	-9.0 [0,.63]	-9.8 [0.64]

Safety Results:
All AEs and SAEs that were collected during the study were documented. On-therapy adverse events are defined as an AE with an onset date on or after the start of study medication until one day after the last dose of study medication. An on therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication.

	Sal50	SFC50/250
	N= 532 (%)	**N= 518(%)**
Most Frequent Adverse Events – On-Therapy ITT population		
Subjects with any AE(s), n(%)	200 (38)	225 (43)
Nasopharyngitis	39 (7)	56 (11)
Headache	25 (5)	23 (4)
Upper respiratory tract infection	15 (3)	20 (4)
Chronic obstructive airways disease exacerbated	15 (3)	12 (2)
Dizziness	7 (1)	13 (3)
Influenza	6 (1)	14 (3)
Cough	10 (2)	11 (2)
Dysphonia	6 (1)	10 (2)
Hypertension	9 (2)	5 (<1)
Diarrhoea	8 (2)	6 (1)
Non-fatal Serious Averse Events –with onset on Therapy N (%) [number considered by the investigator to be related to study medication]		
Subjects with any SAE(s), n (%)	24 (5) [0]	32 (6) [0]
Chronic obstructive airways disease exacerbation	9 (2) [0]	5 (<1) [0]
Pneumonia	4 (<1) [0]	2 (<1) [0]
Cardiac failure	0 (0) [0]	3 (<1) [0]
Pulmonary embolism	2 (<1) [0]	0
Abdominal pain	1 (<1) [0]	0
Anaemia	0	1 (<1) [0]
Iron deficiency anaemia	1 (<1) [0]	0
Angle closure glaucoma	0	1 (<1) [0]
Aortic aneurysm	1 (<1) [0]	0
Ruptured aortic aneurysm	0	1 (<1) [0]
Aortic stenosis	1 (<1) [0]	0
Carotid artery stenosis	1 (<1) [0]	0
Cerebrovascular accident	1 (<1) [0]	1 (<1) [0]
Colon cancer	0	1 (<1) [0]
Colon neoplasm	0	1 (<1) [0]
Cyst	0	1 (<1) [0]
Deep vein thrombosis	0	1 (<1) [0]
Femur fracture	0	1 (<1) [0]
Gastritis	0	1 (<1) [0]
Granuloma	1 (<1) [0]	0
Hepatic cancer metastatic	1 (<1) [0]	0
Inguinal hernia	0	1 (<1) [0]
Intermittent claudication	0	1 (<1) [0]
Intervertebral disc protrusion	0	1 (<1) [0]
Lacunar infarction	0	1 (<1) [0]
Lung neoplasm malignant	0	1 (<1) [0]
Metastases to bone	1 (<1) [0]	0
Metastases to liver	0	1 (<1) [0]
Non-cardiac chest pain	1 (<1) [0]	0
Oesophageal varices haemorrhage	0	1 (<1) [0]
Orthostatic hypotension	1 (<1) [0]	0

Pancreatitis acute	0	1 (<1) [0]
Peripheral vascular disorder	1 (<1) [0]	0
Tendon rupture	0	1 (<1) [0]
Urinary retention	0	1 (<1) [0]
Acute respiratory distress syndrome	1 (<1) [0]	0
Acute respiratory failure	1 (<1) [0]	0
Angina unstable	0	1 (<1) [0]
Arrhythmia	0	1 (<1) [0]
Cardiogenic shock	1 (<1) [0]	
Coronary artery stenosis	1 (<1) [0]	0
Diverticulitis	0	1 (<1) [0]
Epistaxis	0	1 (<1) [0]
Eye infection	0	1 (<1) [0]
Haemoptysis	0	1 (<1) [0]
Loss of consciousness	1 (<1) [0]	0
Pulmonary haemorrhage	0	1 (<1) [0]
Pyelonephritis acute	0	1 (<1) [0]
Tachyarrhythmia	0	1 (<1) [0]
Tachycardia	0	1 (<1) [0]
Urinary tract infection	0	1 (<1) [0]
Fatal Serious Averse Events –post randomisation N (%) [number considered by the investigator to be related to study medication]Subjects with fatal SAEs, n (%)	SAL 50	SFC50/250
	N (%) [related]	N (%) [related]
No. subjects with fatal SAEs	3 (<1)	3 (<1)
Cardiogenic shock	1 (<1) [0]	0
Colon cancer metastatic	0	1 (<1) [0]
Aortic aneurysm rupture	0	1 (<1) [0]
Chronic obstructive airways disease exacerbation	1 (<1) [0]	0
Pulmonary haemorrhage	0	1 (<1) [0]
Myocardial infarction	1 (<1) [0]	0

Conclusion:
This study showed that SFC 50/250 increased the FEV_1 change from baseline at endpoint significantly more than salmeterol 50mcg, although the two treatments produced similar improvements in dyspnoea assessed using the TDI at endpoint. Adverse experiences occurred in 43% of the subjects taking SFC 50/250 and 38% of subjects taking salmeterol. Within the SFC50/250 group the most commonly reported AEs were nasopharyngitis (11%), headache (4%), upper respiratory tract infection (4%), dizziness (3%) and influenza (3%). Within the salmeterol 50mcg group the most commonly reported AEs were nasopharyngitis (7%), headache (5%), upper respiratory tract infection (3%) and chronic obstructive airways disease exacerbated (3%). Serious adverse events were reported in 56 subjects (24 [5%] in the salmeterol 50mcg group and 32 (6%) of subjects in the SFC50/250 group, with the most frequently reported being COPD exacerbation in both groups (9 [2%] in the salmeterol group and 5 [<1%] in the SFC50/250 group). Six subjects died during the treatment phase of this study, three in each randomised treatment group.

Publications: No publication

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