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<b>Study No.:</b> SCO100250		
<b>Title:</b> A Randomized, Double-Blind, Parallel-Group, 52-Week Study to Compare the Effect of Fluticasone Propionate/Salmeterol DISKUS 250/50mcg BID with Salmeterol DISKUS 50mcg BID on the Annual Rate of Moderate/Severe Exacerbations in Subjects with Chronic Obstructive Pulmonary Disease (COPD)		
<b>Rationale:</b> COPD exacerbations are an important cause of the morbidity and mortality associated with COPD, and frequent exacerbations are associated with quality of life impairment. In subjects with COPD, the 500/50mcg strength of fluticasone propionate/salmeterol combination product (FSC) has been shown to reduce the rate of COPD exacerbations compared to salmeterol alone. Since the 250/50mcg strength of FSC is the only approved dose for treatment of COPD in the United States (US), the primary objective of this study was to compare the effect of FSC 250/50 with salmeterol on the annual rate of moderate/severe COPD exacerbations.		
<b>Phase:</b> IV		
<b>Study Period:</b> 27 December 2004 to 14 June 2007		
<b>Study Design:</b> Randomized, double-blind, parallel-group study		
<b>Centres:</b> 98 centers; 85 centers in the US and 13 centers in Canada		
<b>Indication:</b> COPD		
<b>Treatment:</b> FSC 250/50 twice-daily (BID) or Salmeterol 50mcg BID. Subjects were instructed to administer study medication one inhalation in the morning and one inhalation in the evening approximately 12 hours apart		
<b>Objectives:</b> The primary objective was to compare the effect of FSC 250/50 BID with salmeterol 50mcg BID on the annual rate of moderate/severe exacerbations in subjects with COPD over a 52-week treatment period.		
<b>Primary Outcome/Efficacy Variable:</b> The annual rate of moderate/severe COPD exacerbations		
<b>Secondary Outcome/Efficacy Variable(s):</b> The time to first moderate/severe exacerbation, the annual rate of exacerbations requiring oral corticosteroids, and AM forced expiratory volume in one second (FEV1).		
<b>Statistical Methods:</b> Using rate estimates of 1.9 and 1.5 for salmeterol and FSC 250/50 from previous GlaxoSmithKline (GSK) studies and Poisson regression with an over-dispersion factor of 1.5, it was estimated that 337 subjects per treatment group would provide 90% power to detect the 21% reduction in the rate of moderate/severe exacerbations between FSC 250/50 and salmeterol at the 0.05 significance level. A total of approximately 775 subjects were planned for randomization. The primary analysis method for the primary efficacy measure was amended in the protocol from Poisson regression to the negative binomial model. The negative binomial regression model included terms for baseline disease severity, pooled investigator, reversibility stratum and treatment group. The primary analysis population was the Intent-to-Treat (ITT) population which included all subjects who had been randomized to study drug. During the conduct of the study, two investigative sites were closed and subjects randomized at these sites (19 subjects total) were not included in the ITT efficacy or health outcome analyses.		
<b>Study Population:</b> Study subjects were males and non-pregnant females aged 40 years or older with an established clinical history of COPD, a pre-bronchodilator FEV1 $\leq$ 50% of predicted normal, a pre-bronchodilator FEV1/forced vital capacity (FVC) ratio of $\leq$ 0.70, a cigarette smoking history of $\geq$ 10 pack-years, and a documented history of at least one COPD exacerbation in the past year prior to screening that required treatment with oral corticosteroids, antibiotics, or hospitalization. Both current and former cigarette smokers were enrolled. Key exclusion criteria included a current diagnosis of asthma, other respiratory disorders other than COPD, a moderate/severe exacerbation that had not resolved prior to Visit 1, and concurrent use of long-acting anticholinergics, theophylline preparations, and leukotriene modifiers.		
	<b>FSC 250/50</b>	<b>Salmeterol</b>
Number of Subjects:		
Planned, N	388	388
Randomised, N	394	403
Completed, n (%)	269 (68)	247 (61)
Total Number Subjects Withdrawn, n (%)	125 (32)	156 (39)

Withdrawn due to Adverse Events n (%)	37(9)	39(10)
Withdrawn due to Lack of Efficacy n (%)	7(2)	14(3)
Withdrawn for other reasons n (%)	81(21)	103(26)
<b>Demographics</b>	<b>FSC 250/50</b>	<b>Salmeterol</b>
N (ITT)	394	403
Females: Males	193: 201	173: 230
Mean Age, years (range)	65.4(43-87)	65.3(42-86)
White/Caucasian, n (%)	371(94)	382(95)
<b>Primary Efficacy Results:</b>		
<b>Annual Rate of Moderate/Severe Exacerbations</b>	<b>FSC 250/50 N=385</b>	<b>Salmeterol N=393</b>
Mean Exacerbation Rate	1.10	1.59
FSC 250/50 vs. Salmeterol Treatment Ratio	0.696	
95% Confidence Interval	0.583, 0.831	
p-value	<0.001	
<b>Secondary Outcome Variable(s):</b>		
<b>Time to First Moderate/Severe Exacerbation</b>	<b>FSC 250/50 N=385</b>	<b>Salmeterol N=393</b>
Overall probability of having an Exacerbation	59.7%	68.4%
Hazard Ratio	0.726	
95% Confidence Interval	0.602, 0.876	
<b>Rate of COPD Exacerbations Requiring Oral Corticosteroids</b>	<b>FSC 250/50 N=385</b>	<b>Salmeterol N=393</b>
Mean Exacerbation Rate	0.81	1.23
FSC 250/50 vs Salmeterol Treatment Ratio	0.657	
95% CI	0.530, 0.814	
<b>Pre-dose AM FEV<sub>1</sub></b>	<b>FSC 250/50 N=385</b>	<b>Salmeterol N=393</b>
Mean Change from Baseline at Endpoint, mL(SE)	-29(16.9)	-105(16.5)

95% CI	n/a	
<b>Safety Results:</b> “On therapy” AEs and SAEs were defined as those with onset on or after the start date of study medication but not later than the last date of study medication.		
	<b>FSC 250/50 N=394</b>	<b>Salmerterol N=403</b>
<b>Most Frequent Adverse Events – On-Therapy</b>	<b>n (%)</b>	<b>n (%)</b>
Subjects with any AE(s), n(%)	344 (87)	343 (85)
Nasopharyngitis	133 (34)	133 (33)
Pharyngolaryngeal pain	129 (33)	135 (33)
Pyrexia	70 (18)	77 (19)
Headache	52 (13)	53 (13)
COPD	42 (11)	45 (11)
Rhinorrhoea	43 (11)	37 (9)
Upper respiratory tract infection	41 (10)	30 (7)
Nausea	33 (8)	22 (5)
Nasal congestion	32 (8)	22 (5)
Back pain	32 (8)	21 (5)
Sinusitis	30 (8)	22 (5)
Diarrhoea	27 (7)	25 (6)
Muscle spasms	25 (6)	19 (5)
Dizziness	23 (6)	19 (5)
Fatigue	24 (6)	13 (3)
Pneumonia	23 (6)	9 (2)

<b>Serious Adverse Events - On-Therapy</b> n (%) [n considered by the investigator to be related to study medication]		
	<b>FSC 250/50</b> <b>N=394</b>	<b>Salmerterol</b> <b>N=403</b>
<b>Subjects with non-fatal SAEs, n (%)</b>	82(21)	71(18)
	<b>n (%) [related]</b>	<b>n (%) [related]</b>
Chronic obstructive pulmonary disease	34 (9) [0]	38 (9) [0]
Respiratory failure	3 (<1) [0]	1 (<1) [0]
Acute respiratory failure	0	2 (<1) [0]
Bronchitis chronic	1 (<1) [0]	1 (<1) [0]
Dyspnoea	1 (<1) [0]	1 (<1) [0]
Broncholithiasis	0	1 (<1) [0]
Haemoptysis	0	1 (<1) [0]
Pleural effusion	0	1 (<1) [0]
Pleurisy	0	1 (<1) [0]
Pneumonia aspiration	1 (<1) [0]	0
Respiratory distress	1 (<1) [0]	0
Pneumonia	11 (3) [0]	7 (2) [0]
Bronchitis	4 (1) [0]	4 (<1) [0]
Appendicitis	1 (<1) [0]	0
Bronchopneumonia	0	1 (<1) [0]
Cellulitis	0	1 (<1) [0]
Cellulitis staphylococcal	0	1 (<1) [0]
Diverticulitis	1 (<1) [0]	0
Lobar pneumonia	1 (<1) [0]	0
Lung infection	1 (<1) [0]	0
Obstructive chronic bronchitis with acute exacerbation	0	1 (<1) [0]
Pilonidal cyst	0	1 (<1) [0]
Sepsis	1 (<1) [0]	0
Sinusitis	1 (<1) [0]	0
Urosepsis	1 (<1) [0]	0
Viraemia	1 (<1) [0]	0
Cardiac failure congestive	2 (<1) [0]	3 (<1) [0]
Atrial fibrillation	1 (<1) [0]	2 (<1) [1]
Coronary artery disease	2 (<1) [1]	1 (<1) [0]
Angina pectoris	2 (<1) [0]	0
Myocardial infarction	2 (<1) [0]	0
Acute myocardial infarction	0	1 (<1) [0]
Arrhythmia	1 (<1) [0]	0
Arteriospasm coronary	0	1 (<1) [0]
Bundle branch block right	1 (<1) [0]	0
Cardiomyopathy	0	1 (<1) [0]
Cor pulmonale	1 (<1) [0]	0
Coronary artery occlusion	0	1 (<1) [0]
Palpitations	0	1 (<1) [0]
Right ventricular failure	1 (<1) [0]	0
Supraventricular tachycardia	0	1 (<1) [0]
Chest pain	3 (<1) [0]	6 (1) [0]
Chest discomfort	0	1 (<1) [0]
Non-cardiac chest pain	1 (<1) [0]	0
Rectal haemorrhage	2 (<1) [0]	0
Abdominal pain upper	0	1 (<1) [0]
Abdominal strangulated hernia	1 (<1) [0]	0

Colonic polyp	1 (<1) [0]	0
Gastrointestinal haemorrhage	0	1 (<1) [0]
Nausea	1 (<1) [0]	0
Pancreatitis	0	1 (<1) [0]
Upper gastrointestinal haemorrhage	1 (<1) [0]	0
Vomiting	1 (<1) [0]	0
Arthralgia	0	1 (<1) [0]
Back pain	0	1 (<1) [0]
Flank pain	0	1 (<1) [0]
Groin pain	0	1 (<1) [0]
Myalgia	0	1 (<1) [0]
Osteoarthritis	1 (<1) [0]	0
Osteonecrosis	0	1 (<1) [0]
Pain in extremity	0	1 (<1) [0]
Spinal column stenosis	0	1 (<1) [0]
Bladder cancer	1 (<1) [0]	0
Colon cancer	0	1 (<1) [0]
Lung neoplasm malignant	1 (<1) [0]	0
Non-Hodgkin's lymphoma	1 (<1) [0]	0
Prostate cancer	0	1 (<1) [0]
Renal cell carcinoma stage unspecified	0	1 (<1) [0]
Transitional cell carcinoma	0	1 (<1) [0]
Syncope	1 (<1) [0]	1 (<1) [0]
Carotid artery stenosis	0	1 (<1) [0]
Cerebrovascular accident	1 (<1) [0]	0
Depressed level of consciousness	0	1 (<1) [0]
Loss of consciousness	0	1 (<1) [0]
Drug toxicity	0	1 (<1) [0]
Incisional hernia	1 (<1) [0]	0
Pelvic fracture	1 (<1) [0]	0
Sternal fracture	1 (<1) [0]	0
Upper limb fracture	1 (<1) [0]	0
Cholelithiasis	3 (<1) [0]	0
Gallbladder disorder	1 (<1) [0]	0
Hyperkalaemia	0	1 (<1) [0]
Hyperlipidaemia	1 (<1) [0]	0
Hypovolaemia	0	1 (<1) [0]
Arterial occlusive disease	1 (<1) [0]	0
Arterial thrombosis limb	1 (<1) [0]	0
Hypertension	1 (<1)[1]	0
Anxiety	1 (<1) [0]	0
Depression	0	1 (<1) [0]
Benign prostatic hyperplasia	0	2 (<1) [0]
Blood pressure increased	1 (<1)[1]	0
Dysuria	0	1 (<1) [0]
Haematuria	0	1 (<1) [0]
Swelling face	0	1 (<1) [0]
	<b>FSC 250/50</b>	<b>Salmeterol</b>
	<b>N=394</b>	<b>N=403</b>
<b>Subjects with fatal SAEs, n (%)</b>	4(1)	6(1)
	<b>n (%) [related]</b>	<b>n (%) [related]</b>
COPD	2 (<1) [0]	1 (<1) [0]
Respiratory failure	1 (<1) [0]	2 (<1) [0]
Cardio-respiratory arrest	1 (<1) [0]	1 (<1) [0]
Cardiac failure congestive	1 (<1) [0]	0

Chronic myeloid leukaemia	0	1 (<1) [0]
Lung carcinoma cell type unspecified stage IV	1 (<1)[0]	0
Renal failure chronic	0	1 (<1)[0]

**Conclusion:** This study showed a statistically significant difference between FSC 250/50 and salmeterol on the primary efficacy variable (annual rate of moderate/severe exacerbations) and each of the secondary efficacy variables (time to first moderate/severe exacerbation, annual rate of exacerbations requiring oral corticosteroids, and pre-dose AM FEV<sub>1</sub>). In the FSC 250/50 and salmeterol groups, 344 and 343 subjects, respectively, reported adverse events with the most frequently reported events in both groups being nasopharyngitis and pharyngolaryngeal pain. In the FSC 250/50 and salmeterol groups, 82 and 71 subjects, respectively, reported a non-fatal SAE with the most frequently reported non-fatal SAEs being COPD and pneumonia in both groups. There were a total of 4 fatalities in the FSC 250/50 group and 6 fatalities in the salmeterol group. The results of this study replicate the findings of an identical study (SCO40043) which also showed a significant reduction in the annual rate of moderate/severe exacerbations with FSC 250/50 compared with salmeterol.

**Publication:**

Anzueto A, Ferguson GT, Feldman G, Chinsky K, Seibert A, Emmett A, Knobil K, O'Dell D, Kalberg C, Crater G. (2009). Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes. *Journal of Chronic Obstructive Pulmonary Disease*. 2009; 6:320-329

Date Updated: 30-Sep-2009