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<b>Study No.:</b> ADC111114
<b>Title:</b> A Randomized, Double-Blind, Parallel-Group, 24-Week Study to Evaluate the Efficacy and Safety of ADVAIR DISKUS (Fluticasone Propionate/Salmeterol Combination Product 250/50mcg Inhalation Powder) BID Plus Spiriva HandiHaler (Tiotropium Bromide Inhalation Powder 18mcg) QD Versus Spiriva QD Plus Placebo DISKUS BID in Subjects with Chronic Obstructive Pulmonary Disease (COPD)
<b>Rationale:</b> Both Fluticasone Propionate/Salmeterol Combination (FSC) and tiotropium (Tio) are indicated for the maintenance treatment of COPD. FSC contains fluticasone propionate, an inhaled corticosteroid (ICS) and salmeterol, a bronchodilator which is an agonist at beta-adrenergic receptors [long-acting beta-agonist, (LABA)] in a combination inhaler to be administered BID. Tiotropium, like salmeterol, is a long-acting bronchodilator but is an antagonist at muscarinic cholinergic receptors [long-acting muscarinic antagonist (LAMA)] and is administered once-daily. These medications are frequently co-prescribed in clinical practice, but few studies have examined the triple combination therapy of an ICS/LABA and LAMA for the treatment of COPD. Furthermore, few studies have examined the triple combination of the FSC 250/50 strength combined with tiotropium, and FSC 250/50mcg is the only approved dosage for COPD in the United States (US). This study will provide information on the efficacy and safety of add-on therapy with FSC 250/50 to tiotropium compared with tiotropium alone. The results of this study may give health care providers an additional arsenal of combination therapies that are safe and result in better COPD symptom control than tiotropium alone for patients with COPD.
<b>Phase:</b> IV
<b>Study Period:</b> 01Dec2008 -08Dec2009
<b>Study Design:</b> This was a multicenter, randomized, double-blind, parallel group study. Subjects completed a 4-week run-in period in which open-label tiotropium only was given. Albuterol was supplied as rescue medication during run-in and throughout the rest of the study. Following run-in, only subjects who had a modified Medical Research Council (mMRC) dyspnea scale score of $\geq 2$ were eligible for randomization. The run-in period was followed by a 24 week treatment period. Subjects were randomized 1:1 to open-label tiotropium 18mcg once-daily plus double-blind FSC 250/50 mcg BID or open-label tiotropium 18mcg once daily plus double-blind matching Placebo DISKUS BID.  There were a total of 6 study visits Screening, Randomization, and after 4, 8, 16, and 24 weeks of treatment. A follow-up phone contact for collection of adverse event (AE) and pregnancy (if applicable) information was conducted approximately 14 days following the last study visit. Study completion was defined as completion of the follow-up phone call.
<b>Centres:</b> 33 centers in the United States
<b>Indication:</b> COPD
<b>Treatment:</b> Fluticasone propionate/salmeterol 250/50mcg via DISKUS BID plus

Tiotropium 18 mcg QD or Tiotropium 18 mcg QD plus Placebo DISKUS BID		
<b>Objectives:</b> The primary objective was to evaluate the effectiveness and safety of FSC 250/50mcg plus tiotropium 18mcg compared to tiotropium 18mcg alone in patients with COPD.		
<b>Primary Outcome/Efficacy Variable:</b> The primary efficacy measure was AM pre-dose FEV <sub>1</sub> at Endpoint.		
<b>Secondary Outcome/Efficacy Variable(s):</b> 2 hour post-dose FEV <sub>1</sub> at Endpoint AM Pre-dose FVC at Endpoint 2 hour post-dose FVC at Endpoint AM Pre-Dose IC at Endpoint Scores on the CRQ-SAS at Endpoint		
<p><b>Statistical Methods:</b> : It was estimated that 133 subjects per treatment group would provide approximately 90% power for detection of a significant difference of 100 mL in pre-dose FEV<sub>1</sub> change from baseline at Endpoint with a significance level of 0.05 based on a two-sample two-sided t-test with a standard deviation estimate of 250 mL. Approximately 350 subjects were to be randomized to allow for a 30% study withdrawal rate. The analysis population for this study was the Intent-to-Treat (ITT) Population which included all subjects randomized to study drug.</p> <p>The primary efficacy measure (change from baseline in pre-dose FEV<sub>1</sub> at Endpoint) and secondary efficacy measures of pre-dose FVC and IC, 2-hour post-dose FEV<sub>1</sub> and FVC, and CRQ-SAS scores were compared between treatment groups using analysis of covariance (ANCOVA).</p> <p>The Hochberg method was used at the 0.05 significance level to control the overall type I error rate across the secondary efficacy measures. Other efficacy measures were nested under a secondary efficacy measure, and the secondary efficacy measure served as a gatekeeper for the other measures.</p> <p>The proportion of subjects reporting AEs was summarized for each treatment group using the Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class (SOC) and preferred term.</p>		
<b>Study Population:</b> Subjects were males and non-pregnant females age 40 years or older who were current or previous smokers with at least a 10 pack-year history of cigarette smoking. Subjects must have had an established clinical history of COPD. All subjects provided written informed consent prior to study participation. Subjects must have had a post-albuterol forced expiratory volume in one second (FEV <sub>1</sub> ) of $\geq 40$ to $\leq 80\%$ of predicted normal and a post-albuterol FEV <sub>1</sub> /forced vital capacity (FVC) ratio of $\leq 0.70$ . Subjects were excluded from study participation if they had a current diagnosis of asthma or any respiratory disorder other than COPD.		
	<b>FSC + Tio</b>	<b>Tio</b>
Number of Subjects:		
Planned, N	175	175

Randomised, N	173	169
Completed, n (%)	137 (79)	127 (75)
Total Number Subjects Withdrawn, N (%)	36 (21)	42 (25)
Withdrawn due to Adverse Events n (%)	12 (7)	10 (6)
Withdrawn due to Lack of Efficacy n (%)	0	1 (<1)
Withdrawn for other reasons n (%)	24 (14)	31 (18)
<b>Demographics</b>		
	<b>FSC + Tio N=173</b>	<b>Tio N=169</b>
N (ITT)	173	169
Females: Males	86:87	96:73
Mean Age, years (SD)	61.3 (8.56)	61.0 (9.41)
White, n (%)	165 (95)	162 (96)
<b>Primary Efficacy Results:</b>		
	<b>FSC + Tio N=173</b>	<b>Tio N=169</b>
<b>AM Pre-Dose FEV<sub>1</sub> at Endpoint</b>		
Mean change from baseline at Endpoint, mL (SE)	101 (21.8)	-16 (20.4)
LS Mean difference, (SE)	115 (29.5)	
p-value	<0.001	
<b>Secondary Outcome Variable(s):</b>		
	<b>FSC + Tio N=173</b>	<b>Tio N=169</b>
<b>2 hour post-dose FEV<sub>1</sub> at Endpoint</b>		
Mean change from baseline at Endpoint, mL (SE)	233 (23.1)	77 (20.6)
LS Mean difference, (SE)	154 (30.1)	
p-value	<0.001	
	<b>FSC + Tio N=173</b>	<b>Tio N=169</b>
<b>AM Pre-Dose FVC at Endpoint</b>		
Mean change from baseline at Endpoint, mL (SE)	95 (32.7)	-28 (30.6)
LS Mean difference, (SE)	122 (44.0)	
p-value	0.006	
	<b>FSC + Tio N=173</b>	<b>Tio N=169</b>
<b>2 Hour Post-Dose FVC at Endpoint</b>		
Mean change from baseline at Endpoint, mL (SE)	265 (35.9)	87 (31.2)
LS Mean difference, (SE)	175 (46.4)	
p-value	<0.001	
	<b>FSC + Tio N=173</b>	<b>Tio N=169</b>
<b>AM Pre-Dose IC at Endpoint</b>		
Mean change from baseline at Endpoint, mL (SE)	107 (28.4)	-8 (28.1)
LS Mean difference, (SE)	141 (41.0)	
p-value	<0.001	
	<b>FSC + Tio N=173</b>	<b>Tio N=169</b>
<b>CRQ-SAS Scores at Endpoint</b>		

<b>Mastery</b>		
Mean change from baseline at Endpoint, (SE)	0.28 (0.078)	0.04 (0.090)
LS Mean difference, (SE)	0.20 (0.112)	
p-value	0.069	
<b>Fatigue</b>		
Mean change from baseline at Endpoint, (SE)	0.23 (0.094)	0.17 (0.091)
LS Mean difference, (SE)	0.09 (0.123)	
p-value	0.470	
<b>Emotional Function</b>		
Mean change from baseline at Endpoint, (SE)	0.24 (0.072)	0.16 (0.073)
LS Mean difference, (SE)	0.08 (0.096)	
p-value	0.394	
<b>Dyspnea</b>		
Mean change from baseline at Endpoint, (SE)	0.21 (0.091)	0.19 (0.091)
LS Mean difference, (SE)	0.02 (0.119)	
p-value	0.879	
	<b>FSC + Tio N=173</b>	<b>Tio N=169</b>
<b>Most Frequent Adverse Events – On-Therapy</b>		
Subjects with any AE(s), n (%)	100 (58)	87 (51)
Chronic obstructive pulmonary disease	24 (14)	26 (15)
Headache	11 (6)	9 (5)
Nasopharyngitis	7 (4)	6 (4)
Oropharyngeal pain	6 (3)	4 (2)
Bronchitis	6 (3)	4 (2)
Oral candidiasis	5 (3)	2 (1)
Back pain	5 (3)	9 (5)
Dyspnea	0	5 (3)
Hypertension	0	5 (3)
<b>Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]</b>		
	<b>FSC + Tio N=173</b>	<b>Tio N=169</b>
Subjects with non-fatal SAEs, n (%)	7 (4)	13 (8)
	<b>n (%) [related]</b>	<b>n (%) [related]</b>
Chronic obstructive pulmonary disease	1 (<1) [0]	5 (3) [0]
Ileus	0	1 (<1) [0]
Lower gastrointestinal hemorrhage	0	1 (<1) [0]
Esophagitis	0	1 (<1) [0]
Gastric infection	0	1 (<1) [0]
Gastroenteritis	1 (<1) [0]	0
Gastroenteritis viral	0	1 (<1) [0]
Bladder transitional cell carcinoma recurrent	1 (<1) [0]	0
Bone neoplasm malignant	0	1 (<1) [0]
Non-small cell lung cancer	0	1 (<1) [0]
Non-cardiac chest pain	1 (<1) [0]	1 (<1) [0]
Spinal compression fracture	1 (<1) [0]	0
Splenic rupture	0	1 (<1) [0]
Hypokalemia	1 (<1) [0]	1 (<1) [0]

Cerebrovascular accident	0	1 (<1) [0]
Transient ischemic attack	0	1 (<1) [0]
Calculus ureteric	1 (<1) [0]	0
Urinary retention	1 (<1) [1]	0
Finger amputation	0	1 (<1) [0]
Shoulder operation	0	1 (<1) [0]
Aortic aneurysm	1 (<1) [0]	0
Hemorrhage	0	1 (<1) [0]
Hemolytic anemia	0	1 (<1) [0]
Thrombocytopenia	0	1 (<1) [0]
Coronary artery disease	0	1 (<1) [0]

	FSC + Tio N=173	Tio N=169
Subjects with fatal SAEs, n (%)	n (%) [related]	n (%) [related]
Bronchial asthma This fatal SAE occurred prior to randomization.	1 (<1) [0]	

**Conclusion:**

Triple therapy with FSC 250/50 DISKUS + Tiotropium (FSC + Tio) resulted in statistically significant improvements on the primary efficacy measure (AM pre-dose FEV<sub>1</sub>), and the secondary measures of 2 hour post-dose FEV<sub>1</sub>, AM pre-dose FVC, 2 hour post-dose FVC, and AM pre-dose IC compared to Tiotropium (Tio). In the FSC + Tio and Tio groups, 100 and 87 subjects, respectively, reported adverse events with the most frequently reported adverse event in both groups being chronic obstructive pulmonary disease. In the FSC + Tio and Tio groups, respectively, 7 and 13 subjects reported a non-fatal SAE with the most frequently reported non-fatal SAE in both groups being chronic obstructive pulmonary disease. There was one fatality in a subject that occurred prior to randomization to double-blind study drug.