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<b>Study No.:</b> ADC111117
<b>Title:</b> A Randomized, Double-Blind, Double-Dummy, Parallel Group 12-Week Comparison of the Efficacy and Safety of Fluticasone Propionate/Salmeterol Hydrofluoroalkane 134a Metered-Dose-Inhaler 230/42mcg twice-daily with Fluticasone Propionate/Salmeterol DISKUS 250/50mcg twice-daily in Subjects with COPD.
<b>Rationale:</b> Metered-dose-inhalers have been available for nearly 50 years and remain widely used delivery devices for the treatment of COPD [Boyd, 1995]. The availability of the Fluticasone Propionate/Salmeterol (FSC) HFA MDI provides an alternative delivery method for FSC to the DISKUS dry powder inhaler. Although the FSC HFA MDI is not indicated for the treatment of COPD, some patients with COPD may choose the MDI delivery method over the DISKUS. However, the efficacy and safety of the FSC HFA MDI in COPD has not been evaluated. The purpose of this study is to provide information on the efficacy and safety of the FSC HFA MDI in subjects with COPD. The dose of FSC HFA MDI to be evaluated (230/42mcg twice-daily) corresponds to the dose of FSC DISKUS (250/50mcg twice-daily) that is indicated for the treatment of COPD associated with chronic bronchitis and emphysema in the US.
<b>Phase:</b> IV
<b>Study Period:</b> 31 March 2008 – 25 February 2009
<b>Study Design:</b> This was a multicenter, randomized, double-blind, double-dummy, parallel group study.
<b>Centres:</b> This Phase IV study was conducted at 16 sites in the US.
<b>Indication:</b> Chronic Obstructive Pulmonary Disease
<b>Treatment:</b> The treatment arms were FSC HFA 230/42mcg twice-daily or FSC250/50mcg via DISKUS twice-daily. Subjects used a matching placebo for HFA MDI and DISKUS to ensure a double-dummy design. Each subject was instructed to self administer blinded study drug during the double-blind treatment period as follows: Each morning (approximately 6-9AM) take 1 inhalation from the DISKUS followed by 2 inhalations from the MDI Each evening (approximately 6-9PM), approximately 12 hours after morning dosing with blinded study drug, take 1 inhalation from the DISKUS followed by 2 inhalations from the MDI. Subjects were instructed to withhold their morning dose of study drug at study Visits 3, 4 and 5, corresponding to weeks 4, 8, and 12, respectively. The first dose of study drug was administered in the clinic at Visit 2, and the morning dose of study drug was administered in the clinic for all other visits (Visits 3 through 5) following completion of pre-dose pulmonary function tests. Subjects received supplemental albuterol as relief medication. Albuterol had to be withheld for at least 6 hours prior to all visits.
<b>Objectives:</b> The primary study objective was to evaluate the efficacy and safety of FSC HFA MDI 230/42mcg twice-daily in subjects with COPD.
<b>Primary Outcome/Efficacy Variable:</b> The primary efficacy measure was the post-dose FEV1 obtained 2 hours following administration of blinded study drug (i.e., 1 inhalation from the study DISKUS and 2 inhalations from the study MDI). The primary analysis of the 2 hour post-dose FEV1 was at Endpoint, defined as the last scheduled observation for 2 hour post-dose FEV1 during the treatment period.
<b>Secondary Outcome/Efficacy Variable(s):</b> Secondary efficacy measures were AM (morning) pre-dose FEV1 and AM Peak Expiratory Flow (PEF) over weeks 1-12.
<b>Statistical Methods:</b> The sample size for this study was calculated to demonstrate non-inferiority of the FSC HFA treatment response to the FSC DISKUS treatment response for the primary efficacy endpoint of 2-hour post-dose FEV <sub>1</sub> . Using 75mL as the non-inferiority criterion bound and a standard deviation estimate of 185mL, it was estimated that a sample size of 125 subjects per treatment group would provide approximately 90% power to demonstrate non-inferiority of FSC HFA to FSC DISKUS in terms of 2-hour post-dose FEV <sub>1</sub> change from baseline, based on a one-sided significance level of 2.5%. Mean change from baseline values were compared between treatment groups using analysis of covariance (ANCOVA) with terms for treatment, investigator, reversibility stratum and baseline in the model. The analysis population was the Intent-to-Treat population which included all subjects randomized to study drug.
<b>Study Population:</b> Males or females $\geq$ 40 years of age were eligible if they had an established clinical history of COPD (including chronic bronchitis and/or emphysema) in accordance with the following definition by the American Thoracic Society. Subjects were required to demonstrate a post-albuterol FEV <sub>1</sub> /FVC ratio of $\leq$ 0.70 and a post-albuterol FEV <sub>1</sub> $\geq$ 0.70L and $\leq$ 70% of predicted normal OR a post-albuterol FEV <sub>1</sub> of $\leq$ 0.70L and $\geq$ 40% of predicted normal but still $\leq$ 70% of predicted normal based on NHANES III reference values. Subjects also had to be current or previous smokers with a cigarette smoking history of $\geq$ 10 pack-years. Subjects were excluded from the trial if they

had a current diagnosis of asthma and/or any clinically significant and uncontrolled disease that in the opinion of the investigator would put the safety of the subject at risk through study participation or would affect the efficacy analysis if the disease/condition exacerbated during the study.		
Number of Subjects:		
	<b>HFA MDI</b>	<b>DISKUS</b>
Planned Randomised, N	125	125
Actual Randomised, N	121	126
Completed, N (%)	106 (88)	103 (82)
Total Number Subjects Withdrawn, N (%)	15 (12)	23 (18)
Primary Reason for Withdrawal		
Adverse Event N (%)	5 (4)	9 (7)
Lack of Efficacy	0	2 (2)
Protocol Deviation	3 (2)	7 (6)
Lost to Follow-up	2 (2)	2 (2)
Investigator discretion	2 (2)	0
Withdrew Consent	3 (2)	3 (2)
<b>Demographics</b>		
	<b>HFA MDI</b>	<b>DISKUS</b>
N (ITT)	121	126
Males, N (%)	66 (55)	66 (52)
Mean Age, years (range)	61.6 (40-84)	63.4 (45-86)
Race, n (%)		
African American/African Heritage	10 (8)	9 (7)
White - White/Caucasian/European Heritage	109 (90)	117 (93)
<b>Primary Efficacy Results: Summary of 2 hour post-dose FEV1 [ITT Population]</b>		
2 hour post-dose FEV1		
	<b>HFA MDI</b>	<b>DISKUS</b>
Baseline		
N	121	126
Mean, mL (SE)	1289 (44.0)	1228 (38.6)
Endpoint		
N	116	115
Mean, mL (SE)	1446 (49.2)	1372 (43.8)
Mean change from baseline, mL (SE)	155 (23.4)	150 (21.9)
LSM difference, mL (SE)	-2 (31.2)	
95% Confidence Interval	(-64, 59)	
<b>Secondary Outcome Variable(s):</b> The secondary efficacy endpoints were AM pre-dose FEV1 and AM Peak Expiratory Flow.		
AM pre-dose FEV1 (mL)		
	<b>HFA MDI</b>	<b>DISKUS</b>
Baseline		
N	121	126
Mean (SE)	1289 (44)	1228 (38.6)
Endpoint		
N	116	115
Mean (SE)	1365 (47.3)	1299 (42.9)
Mean change from baseline (SE)	74 (20.6)	77 (20.5)
LSM difference (SE)	-8 (28.9)	
95% Confidence Interval	(-65, 49)	
Peak Expiratory Flow (L/min)		
	<b>HFA MDI</b>	<b>DISKUS</b>
Baseline		
N	121	119
Baseline Mean (SE)	200.6 (7.14)	201.0 (6.20)
At Weeks 1-12		
N	119	116
At Weeks 1-12	222.7 (8.10)	218.0 (6.85)
Mean change from baseline (SE)	21.8 (2.66)	18.7 (2.48)
LSM difference (SE)	2.3 (3.55)	

95% Confidence Interval	(-4.7, 9.3)	
<b>Safety Results:</b> Adverse events (AE) were summarized for the ITT population.		
Adverse Events Occurring in Greater Than 2 Percent of Subjects in Any Group During Treatment [ITT Population]		
	<b>HFA MDI</b>	<b>DISKUS</b>
Subjects with any AE(s), n (%)		
Any event, n (%)	54 (45)	59 (47)
Headache	10 (8)	8 (6)
Nasopharyngitis	5 (4)	8 (6)
Cough	4 (3)	5 (4)
Sinusitis	3 (2)	6 (5)
Oropharyngeal pain	5 (4)	2 (2)
<b>Serious Adverse Events - On-Therapy n (%)</b> [n considered by the investigator to be related to study medication]		
	<b>HFA MDI</b>	<b>DISKUS</b>
Subjects with non-fatal SAEs, n (%)	6 (5)	3 (2)
COPD Exacerbation	3 (2)	2 (2) [1]
Urinary Tract Infection	2 (2)	0
Pneumonia	0	1 (<1) [1]
Appendicitis	1	1 (<1)
Gastritis	1 (<1)	0
Contusion	1 (<1)	0
Hypoglycaemia	1 (<1)	0
Lumbar Spinal Stenosis	1 (<1)	0
Subjects with fatal SAEs, n (%)	0	0

**Conclusion:**

The HFA MDI demonstrated similar efficacy to the DISKUS in subjects with COPD.  
The safety profiles were similar between treatments.

**Publications:** None