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Study No.: ADA109057
Title: A 52-week, Randomized, Double-Blind, Parallel-Group Study of Fluticasone Propionate/Salmeterol DISKUS™ Combination Product (FSC) 250/50mcg BID and Fluticasone Propionate (FP) DISKUS 250 mcg BID in Treatment of Subjects with Asthma
Rationale: This study was conducted to provide information on the efficacy and safety of the long-acting beta agonist (LABA) component of a commonly prescribed asthma treatment regimen. This study evaluated the efficacy of the regular use of FSC DISKUS 250/50 twice daily (BID) compared with FP DISKUS 250 BID in a 52-week study using measures of pulmonary function and asthma control.
Phase: IV
Study Period: 04 May 2007- 29 April 2009
Study Design: Randomized, double-blind, parallel-group, multicenter study
Centers: A total of 76 centers randomized subjects to treatment: 54 in the United States, 8 in Argentina, 4 in Brazil, 8 in Canada and 2 in the Philippines.
Indication: Asthma
Treatment: FSC DISKUS 250/50 mcg BID or FP DISKUS 250 mcg BID for 52 weeks
Objectives: The primary objective of this study was to demonstrate that FSC DISKUS 250/50 BID is superior to FP DISKUS 250 BID at increasing pulmonary function as measured by forced expiratory volume in one second (FEV ₁) over a 52-week treatment period. Secondary objectives were to compare the efficacy of the two treatment groups with respect to the following parameters: morning (AM) peak expiratory flow (PEF), percent of symptom-free days, and the incidence of asthma attacks. The criteria for worsening asthma that were considered to represent an asthma attack during the double-blind treatment period of the study were defined as follows: 1. PEF Stability Criteria: A $\geq 20\%$ decrease in AM PEF (from baseline or below the AM PEF Stability Limit) on any 2 consecutive days. The AM PEF Stability Limit was defined as 80% of the baseline AM PEF. Baseline AM PEF was defined as the average of the last 7 days prior to randomization. 2. Albuterol Use Criteria: A $\geq 70\%$ increase in albuterol use (from baseline) on any 2 consecutive days (with a minimum of 2 puffs increase). Baseline was defined as the average of the last 7 days prior to randomization. 3. Asthma Exacerbation Criteria: Occurrence of an asthma exacerbation, defined as the requirement of treatment with an oral or parenteral corticosteroid OR an unscheduled urgent care (e.g., unscheduled clinic visit, MD office visit, emergency room visit, hospitalization) for acute asthma symptoms requiring intervention.
Primary Outcome/Efficacy Variable: Mean change from baseline in pre-dose FEV ₁ over Weeks 1-52
Secondary Outcome/Efficacy Variable(s): Mean change from baseline in AM PEF, mean change from baseline in the percentage of symptom-free days, and rate of asthma attacks per subject per year.
Statistical Methods: It was estimated that 289 subjects per treatment group would provide approximately 90% power for detection of a significant difference of 0.10 L in trough, pre-dose FEV ₁ change from baseline over the 52-week treatment period at a significance level of 0.05 based on a two-sample two-sided t-test with a standard deviation estimate of 0.37L. The analysis

population for this study was the Intent-to-Treat (ITT) Population which included all subjects randomized to study drug.

The primary efficacy measure (change from baseline in pre-dose FEV₁ over the 52-week treatment period) and secondary measures of AM PEF and percentage of symptom-free days were compared between treatment groups using analysis of covariance (ANCOVA). The analysis of asthma attacks compared the rate of asthma attacks per subject per year between treatment groups using a generalized linear model (assuming the Negative Binomial distribution).

The proportion of subjects reporting adverse events (AEs) was summarized for each treatment group using the Medical Dictionary for Regulatory Activities (MedDRA) primary System Organ Class and preferred term.

Study Population: Male and female subjects ≥ 12 years old with a documented diagnosis of persistent asthma for at least 6 months. Subjects were required to be using a low-to-medium dose of an inhaled corticosteroid (ICS) or a combination of controller medications containing a low (total daily) dose ICS for at least 4 weeks preceding Screening. Subjects had to have a pre-albuterol/salbutamol FEV₁ of $\geq 50\%$ and $\leq 85\%$ of predicted normal value at Screening (Visit 1) after withholding asthma medications and demonstrate an increase in FEV₁ of $\geq 12\%$ over the pre-albuterol/salbutamol FEV₁ within 30 minutes after the inhalation of 2-4 puffs of albuterol/salbutamol. In addition, each subject must have experienced asthma symptoms requiring albuterol/salbutamol use within the 4 weeks preceding Screening. Subjects could not have any current clinically significant condition which would put the safety of the subject at risk through study participation. To be randomized to treatment, subjects were required to meet the asthma symptom (score ≥ 1 on \geq any 2 days during the 7 consecutive days immediately prior to the randomization visit) and albuterol use (use on \geq any 2 days during the 7 consecutive days immediately prior to the randomization visit) criteria while taking FP DISKUS 100 BID during the 14-21 day run-in period.

	FSC DISKUS 250/50	FP DISKUS 250
Number of Subjects:		
Planned, N	289	289
Randomised, N	310	318
Completed, n (%)	231 (75)	234 (74)
Total Number Subjects Withdrawn, N (%)	79 (25)	84 (26)
Withdrawn due to Adverse Events n (%)	6 (2)	9 (3)
Withdrawn due to Lack of Efficacy n (%)	2 (<1)	4 (1)
Withdrawn for other reasons n (%)	71 (23)	71 (22)
Demographics	FSC DISKUS 250/50	FP DISKUS 250
N (ITT)	310	318
Females: Males	186:124	181:137
Mean Age, years (SD)	40.9 (15.71)	39.6 (16.56)
Race, White, n (%)	254 (82)	262 (82)
Primary Efficacy Results:		
Pre-dose FEV₁ (L)	FSC DISKUS 250/50 N=310	FP DISKUS 250 N=318
Mean Baseline (SE)	2.37 (0.042)	2.41 (0.043)
n analyzed	303	304
Mean change from Baseline over Weeks 1-52 (SE)	0.16 (0.017)	0.12 (0.020)
LS mean difference vs. FP DISKUS 250	0.04	
95% CI	-0.01, 0.09	

p-value	0.09	
Secondary Outcome Variables:		
AM PEF (L/min)	FSC DISKUS 250/50 N=310	FP DISKUS 250 N=318
Mean Baseline (SE)	355.8 (6.56)	360.4 (6.28)
n analyzed	305	310
Mean change from Baseline over Weeks 1-52 (SE)	27.7 (2.85)	14.6 (2.49)
LS mean difference vs. FP DISKUS 250	12.8 (3.74)	
95% CI	5.5, 20.2	
Percentage of Symptom-free Days (%)		
Mean Baseline (SE)	19.7 (1.47)	20.7 (1.45)
n analyzed	305	310
Mean change from Baseline over Weeks 1-52	37.4 (2.03)	28.9 (1.82)
LS mean difference vs. FP DISKUS 250	8.0 (2.54)	
95% CI	3.0, 13.0	
Asthma Attack Rate over 52 Weeks		
n analyzed	310	318
Mean asthma attack rate	2.63	2.73
Treatment comparison (FSC/FP) ratio	0.963	
95% CI	0.778, 1.193	
Safety Results:		
Most Frequent Adverse Events – On-Therapy (start of double-blind treatment through end of double-blind treatment)	FSC DISKUS 250/50 N=310 n (%)	FP DISKUS 250 N=318 n (%)
Subjects with any AE(s), n (%)	242 (78)	260 (82)
Nasopharyngitis	54 (17)	70 (22)
Headache	51 (16)	60 (19)
Upper respiratory tract infection	45 (15)	55 (17)
Sinusitis	33 (11)	40 (13)
Bronchitis	34 (11)	38 (12)
Back pain	23 (7)	24 (8)
Oropharyngeal pain	23 (7)	19 (6)
Rhinitis	23 (7)	18 (6)
Cough	19 (6)	18 (6)
Influenza	15 (5)	21 (7)
Serious Adverse Events - On-Therapy (start of double-blind treatment through end of follow-up period) n (%) [n considered by the investigator to be related to study medication]		

	FSC DISKUS 250/50 N=310 n (%) [related]	FP DISKUS 250 N=318 n (%) [related]
Subjects with non-fatal SAEs, n (%)	6 (2) [1]	8 (3) [1]
Chest pain	0	1 (<1) [1]
Cholelithiasis	0	2 (<1) [0]
Cholecystitis	0	1 (<1) [0]
Appendicitis	0	1 (<1) [0]
Cellulitis	0	1 (<1) [0]
Ankle fracture	1 (<1) [0]	0
Foot fracture	0	1 (<1) [0]
Humerus fracture	0	1 (<1) [0]
Tibia fracture	0	1 (<1) [0]
Anaemia	1 (<1) [0]	0
Atrial fibrillation	1 (<1) [0]	0
Large intestine perforation	0	1 (<1) [0]
Syncope	0	1 (<1) [1]
Spontaneous abortion	0	1 (<1) [0]
Ovarian cyst	1 (<1) [0]	0
Breast cancer	1 (<1) [0]	0
Asthma (exacerbation)	1 (<1) [1]	0
Subjects with fatal SAEs, n (%)	1 (<1) [0]	1 (<1) [0]
Breast cancer	0	1 (<1)[0]
Cardiac disease	1 (<1)[0]	0

Conclusion: FSC DISKUS 250/50 was not statistically significantly superior to FP DISKUS 250 at increasing pulmonary function as measured by the change from baseline in pre-dose FEV₁ over a 52-week treatment period.

Nominally statistically significant differences were seen in favor of FSC DISKUS 250/50 compared with FP DISKUS 250 in mean change from baseline AM PEF, percentage of symptom free days but not for the asthma attack rate.

Both treatments were well-tolerated during the 52-week course of the study with a comparable incidence of AEs occurring between the treatment groups. Nasopharyngitis was the most commonly reported AE. Headache, upper respiratory tract infection, sinusitis and bronchitis were the next most frequently reported AEs. Two deaths occurred during the study; neither was considered related to study treatment.

Publications: None at the time of this report.