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Study No.: ADA103575
Title: Multicenter, Randomized, Double-Blind, Triple-Dummy, Placebo-Controlled, Parallel Group, Four-Week Study Assessing the Efficacy of Fluticasone Propionate Aqueous Nasal Spray 200mcg QD versus Montelukast 10mg QD in Adolescent and Adult Subjects with Asthma and Seasonal Allergic Rhinitis Who are Receiving ADVAIR DISKUS® 100/50mcg BID or Placebo BID
Rationale: Asthma and allergic rhinitis are often found to be co-morbid conditions. Over 75% of asthma patients have symptoms of allergic rhinitis. These co-morbid conditions continue to be actively studied to ascertain if they are manifestations of one disease entity with concurrent symptoms of the upper and lower airways that can be controlled by targeting treatment to only one compartment. This study was conducted to further evaluate the addition of fluticasone propionate aqueous nasal spray (FPANS) or montelukast (MON) to fluticasone propionate/salmeterol combination product (FSC), FSC alone, and MON alone, in the treatment of asthma and allergic rhinitis in subjects with both of these diseases concurrently.
Phase: IV
Study Period: 07Sep2005 -3 1Oct2007
Study Design: This was a randomized, double-blind, triple-dummy, parallel group, multicenter trial. Subjects who met entry criteria entered a 7- to 14-day run-in period during which time they completed a daily diary card to establish evidence of asthma and symptomatic seasonal allergic rhinitis. Subjects were required to be treated with a short-acting beta-agonist, inhaled corticosteroid, or non-corticosteroid controller for 3 months and on a stable regimen 1 month prior to the screening visit. Subjects who completed the run-in period and qualified for the study by meeting all Visit 2 randomization criteria were assigned to double-blind treatment for 4 weeks. Albuterol inhalation aerosol was provided as rescue medication during the screening and treatment periods to relieve acute asthma symptoms. Total subject participation in the run-in period and double-blind treatment period was 5-6 weeks. Safety measures included adverse events and asthma exacerbations.
Centres: This Phase IV multicenter study, sponsored by GlaxoSmithKline (GSK), was conducted at 79 sites in the United States (US), 6 sites in Canada, 2 sites in Estonia, and 4 sites in Poland. A total of 725 subjects comprised the Intent-To-Treat population randomized into the study. Three hundred fifty-seven (357) of these subjects, from 62 sites in the US, 6 sites in Canada, 1 site in Estonia, and 2 sites in Poland comprised the modified Per Protocol population. The study was initiated on 07 September 2005 and completed on 31 October 2007.
Indication: Asthma and allergic rhinitis
Treatment: At Visit 2, eligible subjects were randomized to receive one of the following double-blind treatments for 4 weeks: <ul style="list-style-type: none"> • FSC BID, plus FPANS QD, plus placebo capsule QD • FSC BID, plus vehicle placebo nasal spray QD, plus MON QD • FSC BID, plus vehicle placebo nasal spray QD, plus placebo capsule QD • Placebo DISKUS BID, plus vehicle placebo nasal spray QD, plus MON QD.
Objectives: The primary objectives of this study were to demonstrate that fluticasone propionate/salmeterol combination product (FSC) 100/50mcg BID (available as ADVAIR DISKUS®) was superior to montelukast (MON) 10mg QD (available as Singulair) as monotherapy for asthma, and that MON administered concurrently with FSC added no additional benefit to FSC alone in improving asthma control in a population of subjects with allergic asthma.
Primary Outcome/Efficacy Variable: The primary efficacy measures were the mean change from baseline at endpoint in AM PEF compared between the FSC 100/50mcg BID and MON 10mg QD treatment groups to assess superiority and compared between the FSC and FSC+MON treatment groups to assess equivalence.

Secondary Outcome/Efficacy Variable(s): The secondary efficacy measures were:

Rhinitis:

For treatment comparisons between FSC+FPANS and FSC+MON to assess superiority:

- Mean change from baseline in subject-rated daytime, total nasal symptom scores (D-TNSS_{w1-2}: equal to the sum of symptom scores assessing rhinorrhea, nasal congestion, nasal itching, and sneezing) averaged over Weeks 1-2
- Mean change from baseline in subject-rated nighttime total nasal symptom scores (N-TNSS_{w1-2}: the sum of symptom scores assessing AM nasal congestion upon waking, difficulty in going to sleep due to nasal symptoms, and nighttime awakenings due to nasal symptoms) averaged over Weeks 1-2

Asthma:

For treatment comparisons of FSC vs MON to assess superiority and of FSC vs FSC+MON to assess equivalence:

- Mean change from baseline at endpoint in pre-dose AM FEV₁
- Mean change from baseline at endpoint in percentage of asthma symptom-free days
- Mean change from baseline at endpoint in percentage of rescue-free days

Endpoint was defined as the average of the last 7 days' worth of data.

Statistical Methods: A sample size of 133 subjects per treatment was determined sufficient to provide 80% power to show equivalence (within 18 L/min) in the change from baseline at endpoint in morning PEF between the FSC+MON and FSC groups. This estimate is based on two one-sided t-tests and a standard deviation of 45 L/min. In addition, a sample size of 133 subjects per treatment was determined sufficient to provide more than 99% power at a significance level of $\alpha=0.05$ to show superiority of FSC alone compared with MON alone in terms of change in mean morning PEF of at least 28L/min, assuming a standard deviation of 45L/min. This estimate is also based on a two-sided t-test. It was also estimated that the difference between FSC+FPANS and FSC+MON in the change from baseline D-TNSS over the first two weeks of treatment would be between 0.5 and 0.75, and that the standard deviation of D-TNSS would be 2.5. These estimates and a sample size of 133 subjects per treatment suggested that this study would have 69% power to detect a treatment difference of 0.75. These estimates are based on a two-sided t-test and a significance level of $\alpha=0.05$.

Two populations were defined prospectively for the purposes of this study. The Intent-to-Treat (ITT) population was to include all subjects randomized to double-blind treatment, and formed the basis for all summaries of demographic/background and safety data, as well as efficacy analyses supporting the objectives of showing superiority of FSC over MON and of showing superiority of FSC+FPANS over FSC+MON. The Per Protocol population was to form the basis of analyses intended to support the objective of showing equivalence of FSC and FSC+MON, and excluded subjects who violated the protocol. After these prospectively-defined populations were documented, but before the data were unblinded, three additional subjects were excluded from both the ITT and Per Protocol populations. Thus, the modified ITT and modified Per Protocol populations were the bases of all efficacy analyses in this study.

The mean change from baseline at endpoint in morning PEF compared between FSC and MON, in the context of superiority, was summarized by treatment group and compared between treatments using an analysis of covariance (ANCOVA) model that included baseline as a covariate and main effects terms for treatment, investigator, and baseline therapy. The p-value from this test was compared to the nominal $\alpha=0.05$. The mean change from baseline at endpoint in morning PEF compared between FSC and FSC+MON in the context of equivalence, was characterized in terms of a 95% confidence interval using estimates from an ANCOVA model which included baseline as a covariate and main effects terms for treatment, investigator, and baseline asthma therapy. In order to declare FSC and FSC+MON equivalent in terms of the change from baseline at endpoint in morning PEF, this 95% confidence interval had to lie entirely within the equivalence bounds of (-18 L/min, 18 L/min) and had to contain zero.

Study Population: Males and females, 15 years of age and older, with a diagnosis of persistent asthma, as defined by the American Thoracic Society (ATS), for at least 3 months prior to Visit 1 were screened. Subjects were required to have been on an oral short-acting beta₂ agonist (SABA), an approved anticholinergic or cromolyn, or an approved inhaled corticosteroid including dose regimen for 3 months prior to Visit 1 with no change in regimen during the month prior to Visit 1. Asthma severity was required to be an FEV₁ between 65%-95% of predicted at Visit 1 based on NHANES III predicted normal values. A diagnosis of seasonal allergic rhinitis was also required indicating a clinical history of allergic rhinitis during each of the previous 2 allergy seasons and a positive skin test reaction within 2 years prior to or at Visit 1. Subjects were not allowed to be screened who had a current diagnosis of life-threatening asthma or another concurrent respiratory disease, had been hospitalized for asthma within 6 months of Visit 1, or had a respiratory tract infection within 14 days prior to Visit 1. A nasal obstruction was also not allowed, nor was a nasal history of septal perforation or recent surgery. Excluded rhinitis medications included intranasal or ocular corticosteroids, leukotriene modifiers, long-acting or short-acting antihistamines, and decongestants.

	FSC+FPA NS	FSC+MON	FSC	MON
Number of Subjects:				
Planned, N	133	133	133	133
Randomised, N	182	182	180	181
Completed, n (%)	140 (77)	129 (71)	137 (76)	138 (76)
Total Number Subjects Withdrawn, N (%)	42 (23)	53 (29)	43 (24)	43 (24)
Withdrawn due to Adverse Events n (%)	1 (<1)	3 (2)	1 (<1)	4 (2)
Withdrawn due to Asthma Exacerbation n (%)	0 (0)	0 (0)	0 (0)	4 (2)
Withdrawn for other reasons n (%)	41 (23)	50 (27)	42 (23)	35 (19)
Demographics	FSC+FPA NS	FSC+MON	FSC	MON
N	182	182	180	181
Females: Males	120:62	115:67	102:78	112:69
Mean Age, years (SD)	34.9 (12.62)	33.0 (13.54)	34.5 (14.64)	34.5 (12.47)
Race, n (%)				
White	143 (79)	138 (76)	138 (77)	145 (80)
Other	38 (21)	44 (24)	42 (23)	36 (20)
Primary Efficacy Results:				
Superiority AM PEF, Modified ITT Population			FSC	MON
Baseline, n			179	181
Mean (SE)			394.2 (8.20)	387.7 (7.02)
Change from baseline at Endpoint, n			174	175
Mean (SE)			26.4 (4.10)	3.6 (3.28)
Statistical Comparisons				
Estimated treatment difference (SE)			23.2 (5.41)	
95% Confidence Interval			(12.5, 33.8)	
p-value			<0.001	
Equivalence AM PEF, Modified Per Protocol Population			FSC+MON	FSC
Baseline, n			83	88
Mean (SE)			377.9 (9.67)	386.0 (10.99)
Change from baseline at Endpoint, n			83	88
Mean (SE)			30.9 (4.92)	35.2 (6.41)

Statistical Comparisons		
Estimated treatment difference (SE)		-8.9 (8.00)
95% Confidence Interval		(-24.6, 6.9)
p-value		0.127
Secondary Outcome Variables		
The secondary efficacy measures for rhinitis and asthma were as follows:		
Rhinitis		
Daytime total nasal symptom scores (D-TNNS), Modified ITT Population	FSC+FPANS	FSC+MON
Baseline, n	181	181
Mean (SE)	8.1 (0.14)	8.3 (0.14)
Change from baseline over Weeks 1-2, n	178	175
Mean (SE)	-3.0 (0.18)	-2.3 (0.16)
Nighttime total nasal symptom scores (N-TNSS), Modified ITT Population	FSC+FPANS	FSC+MON
Baseline, n	181	181
Mean (SE)	5.1 (0.15)	5.1 (0.15)
Change from baseline over Weeks 1-2, n	178	174
Mean (SE)	-2.0 (0.13)	-1.7 (0.13)
Asthma		
Superiority Pre-dose AM FEV₁ (L/sec), Modified ITT Population	FSC	MON
Baseline, n	178	180
Mean (SE)	2.86 (0.05)	2.76 (0.05)
Change from baseline at Endpoint, n	162	166
Mean (SE)	0.15 (0.02)	0.04 (0.03)
Equivalence Pre-dose AM FEV₁ (L/sec) Per Protocol Population	FSC+MON	FSC
Baseline, n	83	88
Mean (SE)	2.72 (0.07)	2.83 (0.06)
Change from baseline at Endpoint, n	79	85
Mean (SE)	0.27 (0.04)	0.13 (0.04)
Superiority Percentage of Asthma Symptom-free Days, Modified ITT Population	FSC	MON
Baseline, n	179	181
Mean (SE)	5.2 (1.04)	2.7 (0.64)
Change from baseline at Endpoint, n	175	175
Mean (SE)	34.8 (2.94)	26.1 (2.83)
Equivalence Percentage of Asthma Symptom-free Days, Modified Per Protocol Population	FSC+MON	FSC
Baseline, n	83	88
Mean (SE)	4.3 (1.35)	4.3 (1.26)
Change from baseline at Endpoint, n	83	88
Mean (SE)	34.8 (4.32)	37.1 (4.23)
Superiority Percentage of Albuterol-free Days, Modified ITT Population	FSC	MON
Baseline, n	179	181
Mean (SE)	11.7 (1.56)	13.2 (2.01)

Change from baseline at Endpoint, n Mean (SE)	175 37.5 (2.84)	175 26.7 (2.92)
Equivalence Percentage of Albuterol-free Days, Modified Per Protocol Population	FSC+MON	FSC
Baseline, n Mean (SE)	83 12.0 (2.44)	88 9.1 (1.84)
Change from baseline at Endpoint, n Mean (SE)	83 41.2 (3.97)	88 42.9 (4.20)

	FSC+ FPANS	FSC+ MON	FSC	MON
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)	n (%)	n (%)
Subjects with any AE(s)	32 (18)	33 (18)	43 (24)	41 (23)
Headache	7 (4)	7 (4)	8 (4)	8 (4)
Upper respiratory tract infection	1 (<1)	1 (<1)	3 (2)	4 (2)
Nasopharyngitis	1 (<1)	3 (2)	4 (2)	0
Sinusitis	3 (2)	0	4 (2)	1 (<1)
Epistaxis	0	1 (<1)	4 (2)	3 (2)
Pharyngolaryngeal pain	1 (<1)	1 (<1)	2 (1)	4 (2)
Back pain	2 (1)	1 (<1)	3 (2)	1 (<1)
Sinus headache	0	2 (1)	3 (2)	1 (<1)
Myalgia	1 (<1)	2 (1)	1 (<1)	1 (<1)
Diarrhoea	2 (1)	0	0	3 (2)
Nausea	2 (1)	1 (<1)	0	1 (<1)
Vomiting	0	0	0	3 (2)
Gastroenteritis	2 (1)	0	0	0
Lower respiratory tract infection	0	2 (1)	0	0
Musculoskeletal stiffness	2 (1)	0	0	0
Eye pruritus	2 (1)	0	0	0
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]				
	FSC+ FPAN S	FSC+ MON	FSC	MON
Subjects with non-fatal SAEs, n (%) [related]	0	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Gastrooesophageal reflux disease	0	0	1 (<1)	0
Appendicitis	0	0	0	1 (<1)
Spinal fracture	0	1 (<1)	0	0
Subjects with fatal SAEs, n (%) [related]	0	0	0	0

Conclusions:**Efficacy:**

- Asthma control was superior in subjects with persistent asthma and seasonal rhinitis when treated with FSC 100/50mcg BID compared to MON 10mg QD, as demonstrated by the mean change from baseline at endpoint in AM PEF.
- Asthma control, as demonstrated by the mean change from baseline at endpoint in AM PEF, was clinically similar in subjects with persistent asthma and seasonal allergic rhinitis when treated with FSC compared to FSC+MON. The confidence interval for the difference in mean change from baseline at endpoint in AM PEF contained zero; however, the two treatments were not statistically equivalent as the treatment difference in mean AM PEF did not fall

entirely within the pre-specified equivalence bounds.

Safety:

- A total of 32 (18%) subjects in the FSC+FPANS group, 33 (18%) in the FSC+MON group, 43 (24%) in the FSC group, and 41 (23%) in the MON group reported adverse events.
- The most common adverse event was headache (FSC+FPANS, 7 (4%); FSC+MON, 7 (4%); FSC, 8 (4%); MON, 8 (4%).
- Headache was also considered by the investigators to be the most common drug-related adverse event, occurring in 3 (2%) subjects treated with FSC+FPANS, 2 (1%) subjects treated with FSC+MON, 2 (1%) subjects treated with FSC, and 0 subjects treated with MON.
- No serious adverse events (n=2 during double-blind period and n=1 following study completion) were considered related to study medications, and withdrawals (n=8) due to adverse events ($\leq 2\%$ of subjects across the treatment groups) were infrequent. There were no deaths during the study

Publications: No Publications

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