

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

<b>Study No.:</b> ADA103578
<b>Title:</b> 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
<b>Rationale:</b> 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), montelukast (MON), or placebo to fluticasone propionate/salmeterol combination product (FSC), or MON alone, in the treatment of asthma and allergic rhinitis in subjects with both of these diseases concurrently.
<b>Phase:</b> IV
<b>Study Period:</b> 07Sep2005 – 16Jul2007
<b>Study Design:</b> 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 for the run-in period and double-blind treatment period was 5-6 weeks. Safety measures included adverse events and asthma exacerbations.
<b>Centres:</b> This Phase IV multicenter study, sponsored by GlaxoSmithKline (GSK), was conducted at 71 sites in the United States (US). A total of 660 subjects comprised the Intent-To-Treat population randomized into the study. Sixty three (63) sites randomized a total of 396 subjects into a Per Protocol population (see Table 1 and Table 2.) The study was initiated on 07 September 2005 and completed on 16 July 2007.
<b>Indication:</b> Asthma and allergic rhinitis
<b>Treatment:</b> 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"> <li>• FSC BID, plus FPANS QD, plus placebo capsule QD</li> <li>• FSC BID, plus vehicle placebo nasal spray QD, plus MON QD</li> <li>• FSC BID, plus vehicle placebo nasal spray QD, plus placebo capsule QD</li> <li>• Placebo DISKUS BID, plus vehicle placebo nasal spray QD, plus MON QD.</li> </ul>
<b>Objectives:</b> 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.
<b>Primary Outcome/Efficacy Variable:</b> 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.
<b>Secondary Outcome/Efficacy Variable(s):</b> The secondary efficacy measures were: <u>Rhinitis:</u>

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

- Mean change from baseline in subject-rated daytime, total nasal symptom scores (D-TNSS<sub>w1-2</sub>: 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<sub>w1-2</sub>: 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 FEV<sub>1</sub>
- 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 mean data over 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 for the purposes of this study. The Intent-to-Treat (ITT) population included 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 formed the basis of analyses intended to support the objective of showing equivalence of FSC and FSC+MON.

There were three families of secondary efficacy measures, each of which corresponded to one of the study objectives:

Asthma Superiority: Changes from baseline at endpoint in morning pre-dose FEV<sub>1</sub>, the percentage of symptom-free days, and the percentage of rescue-free days, compared between FSC and MON to demonstrate superiority in the treatment of asthma;

Asthma equivalence: Changes from baseline at endpoint in morning pre-dose FEV<sub>1</sub>, the proportion of symptom-free days, and the proportion of rescue-free days, compared between FSC and FSC+MON to demonstrate equivalence in the treatment of asthma;

Rhinitis: Changes from baseline over Weeks 1-2 in D-TNSS and in N-TNSS, compared between FSC+FPANS and FSC+MON to demonstrate superiority in the treatment of rhinitis.

Within each of these families, results of hypothesis tests were adjusted using Hochberg's method.

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. 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.

Secondary efficacy measures, including mean change from baseline in D-TNSS<sub>W1-2</sub> and N-TNSS<sub>W1-2</sub>, mean change from baseline at endpoint in morning pre-dose FEV<sub>1</sub>, and the proportions of asthma symptom-free and rescue-free days, were analyzed as described above.

Similarly, in order to declare equivalence between FSC and FSC+MON in terms of change from baseline at endpoint in the three asthma secondary efficacy measures, the resulting confidence intervals, which were adjusted for multiplicity using Hochberg's method, had to contain zero and had to lie within the following equivalence bounds: morning pre-dose FEV<sub>1</sub>:  $\pm 0.2$  L; proportion of symptom-free days:  $\pm 15.7$  percentage points; proportion of rescue-free days:  $\pm 19.5$  percentage points

**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 beta  $\alpha$ -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 FEV<sub>1</sub> 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	MON	FSC+MON	FSC+FPAN S
Number of Subjects:				
Planned, N	166	166	166	166
Randomised, N	157	170	165	168
Completed, n (%)	125 (80)	134 (79)	139 (84)	139 (83)
Total Number Subjects Withdrawn, N (%)	32 (20)	36 (21)	26 (16)	29 (17)
Withdrawn due to Adverse Events n (%)	3 (2)	2 (1)	2 (1)	5 (3)
Withdrawn due to Asthma Exacerbation n (%)	2 (1)	5 (3)	1 (<1)	1 (<1)
Withdrawn for other reasons n (%)	27 (17)	29 (17)	23 (14)	23 (14)
<b>Demographics</b>	<b>FSC</b>	<b>MON</b>	<b>FSC+MON</b>	<b>FSC+FPAN S</b>
N	157	170	165	168
Females: Males	108:49	108:62	120:45	116:52
Mean Age, years (SD)	37.4 (13.85)	36.7 (13.90)	36.6 (12.47)	36.2 (13.12)
Race, n (%)				
White	129 (82)	144 (85)	131 (79)	140 (84)
Other	28 (18)	26 (15)	34 (21)	27 (16)
<b>Primary Efficacy Results:</b>				
<b>Superiority</b>				
<b>AM PEF ITT Population</b>	<b>FSC</b>		<b>MON</b>	

Baseline, n Mean (SE)	N=157 364.7 (7.48)	N=170 384.7 (7.39)
Change from baseline at Endpoint, n Mean (SE)	N=154 28.9 (3.99)	N=162 -2.2 (3.50)
<b>Statistical Comparisons</b>		
Estimated treatment difference (SE) 95% Confidence Interval p-value	29.7 (4.92) (20.1, 39.4) <0.001	
<b>Equivalence</b> <b>AM PEF Per Protocol Population</b>	<b>FSC</b>	<b>FSC+MON</b>
Baseline, n Mean (SE)	N=78 355.5 (9.62)	N=115 380.8 (9.56)
Change from baseline at Endpoint, n Mean (SE)	N=78 37.0 (6.75)	N=115 32.4 (3.66)
Statistical Comparisons Estimated treatment difference (SE) 95% Confidence Interval p-value	0.4 (7.02) (-13.4, 14.2) 0.006	
<b>Secondary Outcome Variables</b>		
The secondary efficacy measures for rhinitis and asthma were as follows:		
<b><u>Rhinitis</u></b>		
<b>Daytime total nasal symptom scores (D-TNNS) ITT Population</b>	<b>FSC+FPANS</b>	<b>FSC+MON</b>
Baseline, n Mean (SE)	168 7.9 (0.14)	165 8.2 (0.14)
Change from baseline over Weeks 1-2, n Mean (SE)	167 -3.3 (0.18)	162 -2.5 (0.16)
Statistical Comparisons LS means difference (SE) Hochberg corrected CI	-0.9 (0.22) (-1.4, -0.4)	
<b>Nighttime total nasal symptom scores (N-TNSS) ITT Population</b>	<b>FSC+FPANS</b>	<b>FSC+MON</b>
Baseline, n Mean (SE)	168 4.9 (0.15)	165 5.1 (0.14)
Change from baseline over Weeks 1-2, n Mean (SE)	167 -2.1 (0.13)	161 -1.8 (0.12)
Statistical Comparisons LS means difference (SE) Hochberg corrected CI	-0.4 (0.15) (-0.7, -0.1)	
<b><u>Asthma</u></b>		
<b>Superiority</b> <b>Pre-dose AM FEV<sub>1</sub> (L/sec) ITT Population</b>	<b>FSC</b>	<b>MON</b>
Baseline, n Mean (SE)	156 2.61 (0.05)	170 2.73 (0.05)
Change from baseline at Endpoint, n Mean (SE)	143 0.21 (0.03)	153 0.06 (0.03)
Statistical Comparisons LS means difference (SE) Hochberg corrected CI	0.131 (0.04) (0.06, 0.21)	
<b>Equivalence</b> <b>Pre-dose AM FEV<sub>1</sub> (L/sec) Per Protocol Population</b>	<b>FSC+MON</b>	<b>FSC</b>

Baseline, n	115	78
Mean (SE)	2.67 (0.06)	2.55 (0.07)
Change from baseline at Endpoint, n	113	77
Mean (SE)	0.22 (0.03)	0.22 (0.38)
Statistical Comparisons		
LS means difference (SE)	0.053 (0.04)	
Hochberg corrected CI	(-0.05, 0.16)	
<b>Superiority</b>		<b>MON</b>
<b>Percentage of Asthma Symptom-free Days ITT Population</b>	<b>FSC</b>	
Baseline, n	157	170
Mean (SE)	3.0 (0.72)	4.7 (1.05)
Change from baseline at Endpoint, n	155	161
Mean (SE)	32.1 (2.99)	13.9 (2.43)
Statistical Comparisons		
LS means difference (SE)	18.5 (4.09)	
Hochberg corrected CI	(8.7, 28.3)	
<b>Equivalence</b>		
<b>Percentage of Asthma Symptom-free Days Per Protocol Population</b>	<b>FSC+MON</b>	<b>FSC</b>
Baseline, n	115	78
Mean (SE)	2.9 (1.07)	3.4 (1.19)
Change from baseline at Endpoint, n	115	78
Mean (SE)	37.3 (3.72)	35.7 (4.18)
Statistical Comparisons		
LS means difference (SE)	3.6 (5.69)	
Hochberg corrected CI	(-7.6, 14.8)	
<b>Superiority</b>		<b>MON</b>
<b>Percentage of Albuterol-free Days ITT Population</b>	<b>FSC</b>	
Baseline, n	157	170
Mean (SE)	12.0 (1.81)	11.0 (1.64)
Change from baseline at Endpoint, n	155	161
Mean (SE)	37.0 (3.18)	21.4 (2.83)
Statistical Comparisons		
LS means difference (SE)	15.8 (4.22)	
Hochberg corrected CI	(7.5, 24.1)	
<b>Equivalence</b>		
<b>Percentage of Albuterol-free Days Per Protocol Population</b>	<b>FSC+MON</b>	<b>FSC</b>
Baseline, n	115	78
Mean (SE)	9.6 (2.18)	8.3 (1.88)
Change from baseline at Endpoint, n	115	78
Mean (SE)	39.1 (3.73)	43.4 (4.54)
Statistical Comparisons		
LS means difference (SE)	-3.4 (5.95)	
Hochberg corrected CI	(-16.8, 10.0)	

<b>Safety Results:</b>	<b>FSC</b>	<b>MON</b>	<b>FSC + MON</b>	<b>FSC + FPAN S</b>
<b>Most Frequent Adverse Events – On-Therapy</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
Subjects with any AE(s)	44 (28)	40 (24)	28 (17)	39 (23)
Headache	7 (4)	17 (10)	8 (5)	13 (8)

Migraine	2 (1)	1 (<1)	0	0
Nasopharyngitis	2 (1)	4 (2)	2 (1)	1 (<1)
Upper respiratory tract infection	4 (3)	4 (2)	1 (<1)	0
Sinusitis	1 (<1)	0	0	3(2)
Influenza	3 (2)	0	0	0
Pharyngolaryngeal pain	2 (1)	2 (1)	1 (<1)	3 (2)
Oral candidiasis	1 (<1)	0	1 (<1)	1 (<1)
Acute sinusitis	0	1 (<1)	1 (<1)	0
Bronchitis	0	1 (<1)	1 (<1)	0
Dysphonia	1 (<1)	0	1 (<1)	2 (1)
Epistaxis	1 (<1)	1 (<1)	0	2 (1)
Rhinitis seasonal	2 (1)	1 (<1)	1 (<1)	0
Cough	0	0	0	3 (2)
Rhinitis allergic	2 (1)	0	1 (<1)	0
Nasal congestion	2 (1)	0	0	0
Nasal oedema	0	0	1 (<1)	0
Abdominal pain upper	1 (<1)	2 (1)	2 (1)	2 (1)
Diarrhoea	1 (<1)	2 (1)	1 (<1)	0
Dyspepsia	2 (1)	0	0	0
Stomach discomfort	1 (<1)	0	1 (<1)	0
Dry mouth	0	0	1 (<1)	0
Food poisoning	0	0	1 (<1)	0
Back pain	3 (2)	1 (<1)	4 (2)	2 (1)
Myalgia	1 (<1)	2 (1)	0	0
Neck pain	0	2 (1)	1 (<1)	0
Arthralgia	1 (<1)	0	1 (<1)	0
Pain in extremity	0	2 (1)	0	0
Joint pain	1 (<1)	0	1 (<1)	0
Hand fracture	0	0	1 (<1)	0
Angioedema	0	0	1 (<1)	0
Pyrexia	0	0	1 (<1)	0
Ear pain	0	1 (<1)	0	2 (1)
Hypersensitivity	0	0	1 (<1)	0
Lymphadenopathy	0	0	1 (<1)	0
Serious Adverse Events - On-Therapy				
n (%) [n considered by the investigator to be related to study medication]				
	<b>FSC</b>	<b>MON</b>	<b>FSC + MON</b>	<b>FSC + FPAN S</b>
Subjects with non-fatal SAEs, n (%) [related]	0	2 (1) [0]	0	0
Breast cancer	0	1 (<1)	0	0
Pelvic fracture	0	1 (<1)	0	0
Subjects with fatal SAEs, n (%) [related]	0	0	0	0

**Conclusions:****Efficacy**

Asthma control was determined to be superior in subjects with persistent asthma and seasonal rhinitis when treated with FSC 100/50mcg BID treatment compared to MON 10mg BID, as demonstrated by clinical and statistical significance in the mean change at endpoint for AM PEF. Treatment comparisons between FSC+FPANS and FSC+MON, in subjects with seasonal rhinitis (and persistent asthma), also demonstrated clinical and statistical superiority for FSC+FPANS in daily total nasal symptom scores, as well as nighttime total nasal symptom scores. Secondary measures for asthma control (mean change at endpoint in pre-dose FEV<sub>1</sub>, percentage

of asthma symptom free days, and asthma rescue free days) were all clinically and statistically significant, supporting the superiority of asthma control with FSC compared to MON. Likewise, these secondary measures demonstrated clinical and statistical equivalence of control in subjects with persistent asthma and seasonal rhinitis when treated with FSC compared to treatment with FSC+MON.

**Safety**

A total of 39 (23%) subjects in the FSC+FPANS group, 28 (17%) in the FSC+MON group, 44 (28%) in the FSC group, and 40 (24%) in the MON group reported adverse events.

The most common adverse event was headache (FSC+FPANS, 13 (8%); FSC+MON, 8 (5%); FSC, 7 (4%); MON, 17(10%).

Headache was also considered by the investigators to be the most common drug related adverse event, occurring in 3 (2%) of subjects treated with FSC+FPANS, 2 (1%) of subjects treated with FSC+MON, 0 subjects treated with FSC, and 1 (<1%) of subjects treated with MON.

Serious adverse events (n=2 during double-blind period) were considered by the investigators to be unrelated to study medications, and withdrawals (n=12) due to adverse events ( $\leq 3\%$  of subjects across the treatment groups) were infrequent. There were no deaths during the study. The occurrence of asthma exacerbations (n=9) was low and similar across all treatment groups ( $\leq 3\%$  of subjects in any treatment group).

**Publications:** No publication

Date updated: 24-Apr-2008