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Study No.: FFR104861
Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Evaluate the Efficacy and Safety of Once-Daily, Intranasal Administration of GW685698X Aqueous Nasal Spray 100mcg* for 2 Weeks in Adult and Adolescent Subjects ≥ 12 Years of Age with Seasonal Allergic Rhinitis
Rationale: Allergic rhinitis is an immunoglobulin E (IgE)-mediated, inflammatory disorder of the upper airway that occurs following allergen exposure. The focus of this study, seasonal allergic rhinitis, is one type of allergic rhinitis that is triggered by the pollen from trees, grasses, and weeds. Commonly referred to as 'hay fever', SAR is characterized by sneezing, nasal congestion and pruritus, rhinorrhea, and itchy, watery, red eyes. GW685698X (hereafter referred to as fluticasone furoate), is a novel corticosteroid with potent glucocorticoid activity. Because of the efficacy of corticosteroids in the treatment of allergic rhinitis, fluticasone furoate is being developed as a nasal spray for this disease.
Phase: III
Study Period: 14Aug2005 to 27Oct2005
Study Design: Multi-center, 2-week, double-blind, randomized, parallel-group, placebo-controlled trial. There was a 5- to 21-day screening period during which baseline symptoms were collected. A follow-up phone call was made 3 to 5 days after the last visit.
Centres: Seventeen centers in the United States enrolled and randomized subjects. An additional site screened subjects but study enrollment was closed before any subjects were randomized.
Indication: Seasonal allergic rhinitis (SAR)
Treatment: Subjects meeting specified symptom criteria were randomized to 2 weeks' treatment with fluticasone furoate nasal spray 110mcg once daily (QD) or vehicle placebo nasal spray QD. *Note: GW685698X aqueous nasal spray 110mcg (actual); Drug content of Fluticasone Furoate Nasal Spray was approximated at 25mcg/spray in all Phase 3 clinical trial documentation pending confirmation from final batch and stability testing. Final testing and analyses determined one spray to contain 27.5mcg of fluticasone furoate, equating to 110mcg for the recommended adult dose of two sprays administered to each nostril.
Objectives: The objective of this study was to compare the efficacy and safety of fluticasone furoate nasal spray 110mcg QD with vehicle placebo nasal spray QD in adult and adolescent subjects ≥ 12 years of age with SAR.
Primary Outcome/Efficacy Variable: Mean change from baseline over the entire treatment period in daily reflective total nasal symptom scores (rTNSS). The total nasal symptom score (TNSS) was the sum of four individual symptom scores for rhinorrhea, nasal congestion, nasal itching, and sneezing where each symptom was scored on a scale of 0 to 3. The rTNSS was a rating of the severity of symptoms over the previous 12 hours and was performed in the morning (AM rTNSS) and evening (PM rTNSS). The daily rTNSS was the average of the AM rTNSS and PM rTNSS assessments.
Secondary Outcome/Efficacy Variables: Key Secondary <ul style="list-style-type: none"> • Mean change from baseline over the entire treatment period in morning (AM) pre-dose instantaneous total nasal symptom scores (iTNSS). • Mean change from baseline over the entire treatment period in daily reflective total ocular symptom scores (rTOSS). The total ocular symptom score (TOSS) was the sum of three individual symptom scores for itching/burning eyes, tearing/watering eyes, and eye redness where each symptom was scored on a scale of 0 to 3. The rTOSS was a rating of the severity of symptoms over the previous 12 hours and was performed in the AM (AM rTOSS) and PM (PM rTOSS). The daily rTOSS was the average of the AM rTOSS and PM rTOSS assessments. • Overall evaluation of response to therapy. Overall evaluation of response to therapy was assessed at the end of the study at the clinic by the subject using the following 7-point categorical scale: significantly improved, moderately improved, mildly improved, no change, mildly worse, moderately worse, significantly worse. • Mean change from baseline to endpoint in the global score of the rhinoconjunctivitis quality of life questionnaire (RQLQ)
Statistical Methods: A total of 288 subjects were required for this study with 144 subjects in each of the two treatment groups: fluticasone furoate 110mcg nasal spray and vehicle placebo nasal spray. The standard deviation for the mean change from

baseline over the entire treatment period in daily rTNSS was assumed to be 2.6, based on a previous GlaxoSmithKline (GSK) allergic rhinitis study. Using a two-sample t-test with a two-sided significance level of 0.05, the chosen sample size provided 90% power to detect a difference of 1.0 between active treatment and placebo.

The primary population was the Intent-to-Treat (ITT) Population. The ITT Population was defined as all subjects who were randomized and received at least one dose of study drug. Unless otherwise specified, analyses based on the ITT Population included all available data for these subjects. This population was the basis for all efficacy, safety, and health outcomes data.

The primary analysis method was the pairwise comparison of treatment groups (fluticasone furoate 110mcg vs. Placebo) using the analysis of covariance (ANCOVA) with adjustments for baseline daily rTNSS, investigative site, age, and gender. The secondary efficacy measures concerning nasal and non-nasal symptoms were analyzed similarly by pairwise comparisons of the two treatment groups (fluticasone furoate 110mcg vs. Placebo) using ANCOVA, with adjustments for baseline values, investigative site, age, and gender. The key secondary efficacy endpoint of overall evaluation of response to therapy was analyzed using logistic regression adjusting for age, gender, investigative site, and treatment.

Multiplicity adjustments were made for the results from the primary efficacy, key secondary efficacy, and health outcomes endpoints. The primary efficacy endpoint served as a gatekeeper for the interpretation of treatment comparisons for the key secondary efficacy and health outcomes endpoints. To control for multiplicity across the key secondary efficacy and health outcomes endpoints, statistical testing was performed in a sequential order as follows: 1) mean change from baseline over the entire treatment period in AM, pre-dose iTNSS, 2) overall evaluation of response to therapy, and 3) the endpoints of mean change from baseline over the entire treatment period in daily rTOSS and mean change from baseline to endpoint in the global score of the RQLQ were controlled using Hochberg's method.

Study Population: Male and female subjects were eligible for treatment as outpatients if they were ≥ 12 years of age and had a diagnosis of SAR due to Ragweed pollen. Subjects must have resided within a geographical region where exposure to Ragweed pollen was expected to be significant during the entire study period.

Number of Subjects (ITT):	Placebo	Fluticasone furoate (FF) 110mcg
Planned, N	144	144
Randomised, N	148	151
Completed, n (%)	142 (96)	144 (95)
Total Number Subjects Withdrawn, N (%)	6 (4)	7 (5)
Withdrawn due to Adverse Events, n (%)	2 (1)	0
Withdrawn due to Lack of Efficacy, n (%)	2 (1)	0
Withdrawn for other reasons, n (%)	2 (1)	7 (5)
Demographics	Placebo	FF 110mcg
N (ITT)	148	151
Females: Males, n	84:64	96:55
Mean Age, years (SD)	34.5 (14.09)	35.4 (13.85)
White, n (%)	129 (87)	139 (92)
Duration of SAR, n (%)		
≥ 2 to < 5 years	19 (13)	15 (10)
≥ 5 to < 10 years	29 (20)	25 (17)
≥ 10 years	110 (68)	111 (74)
Primary Efficacy Results: Daily rTNSS (ITT)	Placebo N=148	FF 110mcg N=151
LS Mean Change (SE)	-2.07 (0.22)	-3.55 (0.21)
LS Mean Difference	-1.473	
95% Confidence Interval	-2.01, -0.94	
p-value	< 0.001	
Secondary Outcome Variables (ITT)	Placebo N=148	FF 110mcg N=151
AM Pre-dose iTNSS		
LS Mean Change (SE)	-1.53 (0.21)	-2.90 (0.21)
LS Mean Difference	-1.375	

95% CI	-1.90, -0.85	
Daily rTOSS		
LS Mean Change (SE)	-1.63 (0.17)	-2.23 (0.16)
LS Mean Difference	-0.600	
95% CI	-1.01, -0.19	
Overall Response to Therapy, n (%)		
Significantly Improved	11 (7)	30 (20)
Moderately Improved	20 (14)	33 (22)
Mildly Improved	45 (31)	46 (31)
No Change	45 (31)	32 (21)
Mildly Worse	9 (6)	4 (3)
Moderately Worse	8 (5)	2 (1)
Significantly Worse	9 (6)	2 (1)
Health Outcomes (Rhinconjunctivitis Quality of Life Questionnaire)		
Overall		
LS Mean Change (SE)	-1.16 (0.12)	-1.77 (0.11)
LS Mean Difference	-0.606	
95% CI	(-0.93,-0.28)	
Safety Results:		
All adverse events (AEs) occurring between Visit 1 (Screening) and Visit 4/Early Withdrawal were collected. On-therapy AEs were defined as those occurring between randomization and Visit 4/Early Withdrawal. In addition, a follow-up contact was made to all subjects 3 to 5 days after study completion (Visit 4) to assess post-treatment AEs. On-therapy SAEs were defined as those occurring between randomization and the follow-up contact.		
	Placebo N=148	FF 110mcg N=151
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n (%)	18 (12)	31 (21)
Headache	4 (3)	12 (8)
Epistaxis	1 (<1)	3 (2)
Musculoskeletal stiffness	1 (<1)	2 (1)
Toothache	1 (<1)	2 (1)
Hypersensitivity	0	2 (1)
Dizziness	0	1 (<1)
Sinus headache	0	1 (<1)
Pain in jaw	1 (<1)	1 (<1)
Back pain	0	1 (<1)
Dyspepsia	0	1 (<1)
Bronchitis	0	1 (<1)
Otitis externa	0	1 (<1)
Back injury	0	1 (<1)
Fall	0	1 (<1)
Joint injury	0	1 (<1)
Joint sprain	0	1 (<1)
Muscle strain	0	1 (<1)
Post-traumatic pain	0	1 (<1)
Road traffic accident	0	1 (<1)
Nasal discomfort	0	1 (<1)
Pain	0	1 (<1)
Vessel puncture site bruise	0	1 (<1)
Dermatitis contact	0	1 (<1)
Eye pain	0	1 (<1)
Crying	0	1 (<1)
Dysmenorrhea	0	1 (<1)
Arthralgia	1 (<1)	0
Myalgia	1 (<1)	0

Pain in extremity	1 (<1)	0
Abdominal pain	1 (<1)	0
Rectal hemorrhage	1 (<1)	0
Infectious mononucleosis	1 (<1)	0
Nasopharyngitis	1 (<1)	0
Sinusitis	1 (<1)	0
Contusion	1 (<1)	0
Allergy to arthropod sting	1 (<1)	0
Urticaria	1 (<1)	0
Ventricular extrasystoles	1 (<1)	0
Ear pain	1 (<1)	0
Blood alkaline phosphatase increased	1 (<1)	0
Serious Adverse Events – During Treatment n (%) [n considered by the investigator to be related to study medication]		
	Placebo N=148	FF 110mcg N=151
Subjects with any SAEs, n (%) [n] -Includes both fatal and non-fatal events	0	0
Subjects with Fatal SAEs, n (%) [n]	0	0
Serious Adverse Events – Post-Treatment n (%) [n considered by the investigator to be related to study medication]		
	Placebo N=148	FF 110mcg N=151
Subjects with any SAEs, n (%) [n] -Includes both fatal and non-fatal events	0	1 (<1) [0]
Cholelithiasis	0	1 (<1) [0]
Subjects with Fatal SAEs, n (%) [n]	0	0
Conclusion: See publications below.		
Publications: Kaiser HB, Naclerio RM, Given J, Toler T, Ellsworth A, Philpot EE. Fluticasone furoate nasal spray: A single treatment option for the symptoms of seasonal allergic rhinitis. J Allergy Clin Immunol 2007;119:1430-1437. Kaiser HB, Naclerio RM, Given J, Philpot E, Toler T, Ellsworth A. Once-daily fluticasone furoate* nasal spray (FFNS) is effective for the treatment of seasonal allergic rhinitis (SAR) caused by ragweed. *USAN-approved name. J Allergy Clin Immunol. 2007;119(1): S232 (abstract). Lumry WR, Cohen SH, Levy A, Philpot E, Toler T, Ellsworth A. Ocular efficacy of a novel, enhanced affinity corticosteroid, fluticasone furoate* nasal spray, in ragweed-sensitive patients. *USAN-approved name. J Allergy Clin Immunol. 2007;119(1): S231 (abstract). Naclerio R, Kaiser H, Lumry W, Philpot E, Toler T, Ellsworth A. Fluticasone furoate nasal spray provided 24-hr relief of nasal and ocular symptoms of seasonal allergic rhinitis (SAR) caused by ragweed. Allergy 2007;62(Suppl. 83): 134 (abstract).		

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