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Study No.: FFR30002
Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Study to Evaluate the Efficacy and Safety of Once-Daily, Intranasal Administration of GW685698X Aqueous Nasal Spray 100mcg* for 4 Weeks in Adult and Adolescent Subjects (≥ 12 years of age) with Perennial Allergic Rhinitis (PAR)
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, perennial allergic rhinitis (PAR), is one type of allergic rhinitis that is triggered by allergens year round. The allergens that cause PAR are part of most household environments including animal dander from household pets, house dust mites, cockroach, and mold spores. PAR is characterized by nasal congestion, rhinorrhea, nasal itching, sneezing and, often times, 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: 15 January 2005 to 04 May 2005
Study Design: Multi-center, 4-week, double-blind, randomized, parallel-group, placebo-controlled trial. There was a 7- to 14-day screening period during which time baseline symptoms were collected on subject-completed daily diaries. A follow-up phone call was made to the subjects 3 to 5 days after the last clinic visit.
Centres: This was a multi-center study conducted by forty-two investigators in the United States (US) and five investigators in Canada. Forty-one US investigators and four Canadian investigators randomized subjects.
Indication: Perennial allergic rhinitis (PAR)
Treatment: Subjects meeting specified symptom criteria were randomized to 4 weeks' treatment with once daily fluticasone furoate nasal spray (FFNS) 110mcg or vehicle placebo nasal spray. *NOTE: GW685698X aqueous nasal spray 110mcg (actual); Drug content of FFNS 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 FFNS 110mcg once daily with vehicle placebo nasal spray once daily in adult and adolescent subjects ≥ 12 years of age with PAR.
Primary Outcome/Efficacy Variable: <ul style="list-style-type: none"> • 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). • The AM, pre-dose iTNSS is the sum of the 4 individual nasal symptom score assessments for rhinorrhea, nasal congestion, nasal itching, and sneezing performed at the moment immediately prior to taking the daily dose, where each symptom is scored on a scale of 0 to 3. • 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.
Statistical Methods: The primary analysis method was the comparison of treatment groups (FFNS vs. vehicle placebo nasal spray) using the analysis of covariance (ANCOVA) with adjustments for baseline rTNSS, country, age, and gender. The secondary efficacy measures were analyzed in a similar manner. A total of 288 subjects were required for this study with 144 subjects in each of the two treatment groups: FFNS 110mcg QD and vehicle placebo nasal spray. The proposed sample size should provide 90% power to detect a

difference of 1.0 between active treatment and placebo in mean change from baseline over the entire treatment period in daily rTNSS, assuming a standard deviation of 2.6 based on data from a previous study of fluticasone furoate (GSK study FFR20001). This calculation was based on a two-sample t-test (two-sided) with a 0.05 significance level. Efficacy and safety data were analyzed based on the Intent-to-Treat (ITT) Population, defined as all subjects who were randomized and received at least one dose of study drug.

Study Population: Male and female subjects were eligible for treatment as outpatients if they were ≥ 12 years of age (≥ 18 years of age in Canada) at randomization and had a diagnosis of PAR. Subjects must have been symptomatic to appropriate perennial allergen including animal dander, house dust mites, cockroach, mold.

Number of Subjects (ITT):	Placebo	Fluticasone furoate (FF) 110mcg
Planned, N	144	144
Randomised, N	153	149
Completed, n (%)	142 (93)	137 (92)
Total Number Subjects Withdrawn, N (%)	11 (7)	12 (8)
Withdrawn due to Adverse Events, n (%)	4 (3)	4 (3)
Withdrawn due to Lack of Efficacy, n (%)	1 (<1)	3 (2)
Withdrawn for other reasons, n (%)	6 (4)	5 (3)
Demographics	Placebo	FF 110mcg
N (ITT)	153	149
Females: Males, n	84: 69	105 : 44
Mean Age, years (SD)	35.8	37.7
White, n (%)	126 (82)	127 (85)
Duration of PAR, n (%)		
≥ 2 to <5 years	33 (22)	26 (17)
≥ 5 to <10 years	46 (30)	36 (24)
≥ 10 years	74 (48)	87 (58)
Primary Efficacy Results: Daily rTNSS (ITT)	Placebo N=153	FF 110mcg N=149
LS Mean Change (SE)	-2.08 (0.21)	-2.78 (0.21)
LS Mean Difference		-0.706
95% Confidence Interval		-1.20, -0.21
p-value		0.005
Secondary Outcome Variables (ITT)		
AM Pre-dose iTNSS		
LS Mean Change (SE)	-1.75 (0.21)	-2.45 (0.22)
LS Mean Difference		-0.705
95% CI		-1.20, -0.21
Overall Response to Therapy, n (%)		
Significantly Improved	20 (13)	30 (20)
Moderately Improved	30 (20)	36 (24)
Mildly Improved	38 (25)	43 (29)
No Change	47 (31)	30 (20)
Mildly Worse	9 (6)	8 (5)
Moderately Worse	3 (2)	0
Significantly Worse	5 (3)	2 (1)
Health outcomes (Rhinconjunctivitis Quality of Life Questionnaire)	Placebo	FF 110mcg
Overall		
LS Mean Change (SE)	-1.18 (0.13)	-1.41 (0.13)
Difference between treatments		-0.227
95% CI		(-0.59, 0.13)

Safety Results:		
All adverse events (AEs) occurring between Visit 1 (Screening) and Visit 6/Early Withdrawal were collected. On-therapy AEs were defined as events with an onset date the same as or after the treatment start date but prior to or the same as the treatment stop date + 1. In addition, a follow-up contact was made to all subjects 3 to 5 days after study completion (Visit 6) to assess post-treatment AEs.		
	Placebo N=153	FF 110mcg N=149
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n (%)	63 (41)	69 (46)
Headache	17 (11)	17 (11)
Epistaxis	9 (6)	12 (8)
Pharyngolaryngeal pain	5 (3)	8 (5)
Nasal septum ulceration	2 (1)	6 (4)
Nasal ulcer	2 (1)	3 (2)
Blood glucose increase	2 (1)	2 (1)
Nausea	2 (1)	2 (1)
Abdominal pain	1 (<1)	2 (1)
Cough	1 (<1)	2 (1)
Dizziness	1 (<1)	2 (1)
Dry throat	1 (<1)	2 (1)
Nasal dryness	1 (<1)	2 (1)
Abdominal pain upper	0	2 (1)
Influenza-like illness	0	2 (1)
Muscle spasms	0	2 (1)
Urinary tract infection	0	2 (1)
Serious Adverse Events – During Treatment		
n (%) [n considered by the investigator to be related to study medication]		
	Placebo N=153	FF110mcg N=149
Subjects with any SAEs, n (%) [n -Includes both fatal and non-fatal events]	1 (<1) [0]	1 (<1) [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=153	FF 110mcg N=149
Subjects with any SAEs, n (%) [n -Includes both fatal and non-fatal events]	0	0
Subjects with Fatal SAEs, n (%) [n]	0	0
Conclusion: See publication below.		
Publications: Nathan R, Berger W, Yang W, Cheema A, Silvey MJ, Wu W, Faris M, Philpot E. Once daily fluticasone furoate* nasal spray (FFNS), a novel enhanced affinity steroid, provides 24-hour relief for the nasal symptoms of perennial allergic rhinitis (PAR) J Allergy Clin Immunol. 2007;119(1): S65 (abstract)		

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