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<b>Study No.:</b> FFR20001
<b>Title:</b> 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 50mcg*, 100mcg*, 200mcg*, or 400mcg* for 14 days in Adult and Adolescent Subjects with Seasonal Allergic Rhinitis.
<b>Rationale:</b> Fluticasone furoate has been developed as an intranasal, aqueous nasal spray for the treatment of allergic rhinitis. Data from this dose ranging study were used to determine the optimal dose to move forward in the clinical development program for adolescents and adults and to provide direction for dosing in the pediatric clinical development program.
<b>Phase:</b> IIB
<b>Study Period:</b> 7 Dec 2003 - 02 Feb 2004
<b>Study Design:</b> Randomized, double-blind, placebo-controlled, parallel-group, multicenter, study in adult and adolescent subjects with seasonal allergic rhinitis.
<b>Centres:</b> 8 centers in the United States.
<b>Indication:</b> Seasonal Allergic Rhinitis (SAR)
<b>Treatment:</b> Fluticasone furoate aqueous nasal spray 55 (administered as 1 spray of the 27.5mcg/actuation strength to each nostril), 110 (administered as 2 sprays of the 27.5mcg/actuation strength to each nostril), 220 (administered as 2 spray of the 55mcg/actuation strength to each nostril) or 440mcg (administered as 2 sprays of the 110mcg/actuation strength to each nostril) once daily (QD) or vehicle placebo nasal spray QD each morning.
* Note: GW685698X aqueous nasal spray 55mcg (actual), 110mcg (actual), 220mcg (actual), and 440mcg (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. This 27.5mcg/actuation strength was used for the 55 and 110mcg doses in this Phase IIB dose-ranging study and in all Phase III studies. The 220 and 440mcg doses in this study had actuation strengths of 55mcg/actuation and 110mcg/actuation, respectively.
<b>Objectives:</b> The primary objectives of this study were to compare the safety and efficacy of once-daily fluticasone furoate aqueous nasal spray 55, 110, 220, and 440mcg with vehicle placebo nasal spray and characterize the systemic exposure to fluticasone furoate within this dose range in adult and adolescent subjects ( $\geq 12$ years) with SAR.
<b>Primary Outcome/Efficacy Variable:</b> 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 the 4 individual symptom scores for rhinorrhea, nasal congestion, nasal itching and sneezing, where each symptom was scored on a scale of 0 to 3. (The maximum sum for a TNSS is 12.) The daily reflective Total Nasal Symptom Score (rTNSS) was defined as the average of the AM and PM rTNSS. The baseline score was defined as the average of the daily rTNSS over the 4 consecutive 24-hour periods prior to randomization.
<b>Secondary Outcome/Efficacy Variable(s):</b> <b>Key Secondary</b> <ul style="list-style-type: none"> <li>• Mean change from baseline over the entire treatment period in AM, pre-dose, instantaneous total nasal symptom scores (iTNSS)</li> <li>• Subject-rated overall evaluation of response to therapy (evaluated on a 7-point categorical scale)</li> </ul>
<b>Statistical Methods:</b> The study randomization was planned for equal allocation of subjects among five treatment groups. The randomization was stratified by investigative site to account for possible site-to-site variability. A total of 590 subjects were required for this study, with 118 subjects in each of the five treatment groups. The proposed sample size was to provide 90% power to detect a difference of 0.85 between active treatment and placebo in mean change from baseline over the entire treatment period in daily rTNSS, assuming a standard deviation of 2.00. This calculation was based on a two-sample t-test with a 0.05 two-sided significance level. The Intent-to-Treat (ITT) population (641 subjects) was used for all efficacy, safety, and health outcomes analyses. The ITT population was defined as all randomized subjects who received at least one dose of study drug. The pairwise comparison between each of the fluticasone furoate treatment groups and placebo on the mean change from baseline over the entire treatment period in daily rTNSS was performed using the analysis of covariance (ANCOVA), adjusting for baseline value, investigative site, age, and gender.

<b>Study Population:</b> Male and female subjects were eligible for treatment as outpatients if they were $\geq 12$ years of age and had a diagnosis of SAR due to mountain cedar pollen. Subjects must have resided within a geographical region where exposure to mountain cedar pollen was expected to be significant during the entire study period.					
<b>Number of Subjects:</b>	<b>Placebo</b>	<b>Fluticasone Furoate (FF) 55mcg</b>	<b>Fluticasone Furoate (FF) 110mcg</b>	<b>Fluticasone Furoate (FF) 220mcg</b>	<b>Fluticasone Furoate (FF) 440mcg</b>
Planned, N	118	118	118	118	118
Randomized, N	128	127	127	129	130
Completed, n (%)	124 (97%)	121 (95%)	125 (98%)	124 (96%)	126 (97%)
Total Number Subjects Withdrawn, N (%)	4 (3%)	6 (5%)	2 (2%)	5 (4%)	4 (3%)
Withdrawn due to Adverse Events n (%)	1 (<1%)	2 (2%)	1 (<1%)	4 (3%)	1 (<1%)
Withdrawn due to Lack of Efficacy n (%)	0	0	0	1 (<1%)	0
Withdrawn for other reasons n (%)	3 (2%)	4 (3%)	1 (<1%)	0	3 (2%)
<b>Demographics</b>	<b>Placebo (N=128)</b>	<b>FF 55mcg (N=127)</b>	<b>FF 110mcg (N=127)</b>	<b>FF 220mcg (N=129)</b>	<b>FF 440mcg (N=130)</b>
N (ITT)	128	127	127	129	130
Females: Males	85:43	81:46	86:41	83:46	86:44
Mean Age, years (SD)	38.6 (13.99)	38.3 (14.45)	40.6 (13.62)	39.4 (13.10)	39.6 (13.91)
White, n (%)	76 (59)	73 (57)	75 (59)	76 (59)	79 (61)

Primary Efficacy Results: Daily rTNSS (ITT)					
Daily rTNSS	Placebo (N=128)	FF 55mcg (N=127)	FF 110mcg (N=127)	FF 220mcg (N=129)	FF 440mcg (N=130)
Mean Change (SE)	-1.7 (0.18)	-3.4 (0.22)	-3.6 (0.24)	-3.0 (0.22)	-3.9 (0.22)
LS mean Chg (SE)	-1.83 (0.21)	-3.50 (0.21)	-3.84 (0.21)	-3.19 (0.21)	-4.02 (0.21)
Δ LS mean Chg		-1.675	-2.012	-1.359	-2.188
95% CI	---	-2.25,-1.10	-2.58,-1.44	-1.93,-0.79	-2.75,-1.62
P value	---	<0.001	<0.001	<0.001	<0.001
Secondary Outcome Variables (ITT):					
AM, pre-dose iTNSS	Placebo (N=128)	FF 55mcg (N=127)	FF 110mcg (N=127)	FF 220mcg (N=129)	FF 440mcg (N=130)
Mean Change (SE)	-1.0 (0.18)	-2.5 (0.22)	-2.9 (0.23)	-2.5 (0.21)	-3.2 (0.22)
LS mean Chg (SE)	-1.15 (0.21)	-2.74 (0.21)	-3.03 (0.21)	-2.57 (0.20)	-3.36 (0.20)
Δ LS mean Chg		-1.587	-1.885	-1.422	-2.215
95% CI	---	-2.15,-1.02	-2.45,-1.32	-1.98,-0.86	-2.77,-1.66
Overall evaluation of response to therapy					
Significantly Improved	10 (8%)	20 (16%)	36 (28%)	30 (23%)	33 (26%)
Moderately Improved	25 (20%)	46 (37%)	30 (24%)	33 (26%)	43 (33%)
Mildly Improved	39 (30%)	32 (26%)	37 (29%)	33 (26%)	30 (23%)
No Change	31 (24%)	21 (17%)	14 (11%)	19 (15%)	14 (11%)
Mildly Worse	6 (5%)	0	1 (<1%)	9 (7%)	3 (2%)
Moderately Worse	8 (6%)	2 (2%)	6 (5%)	4 (3%)	4 (3%)
Significantly Worse	9 (7%)	4 (3%)	3 (2%)	1 (<1%)	2 (2%)
Health outcomes (Rhinoconjunctivitis Quality of Life Questionnaire)	Placebo (N=128)	FF 55mcg (N=127)	FF 110mcg (N=127)	FF 220mcg (N=129)	FF 440mcg (N=130)
Overall					
LS Mean Change (SE)	-0.97 (0.12)	-1.79 (0.13)	-1.97 (0.13)	-1.83 (0.12)	-1.97 (0.12)
Difference between treatments		-0.816	-1.000	-0.851	-0.996
95% CI		(-1.17, -0.46)	(-1.35, -0.65)	(-1.20, -0.51)	(-1.34, -0.65)
Safety Results:					
The time period for collecting AEs/SAEs was from Visit 1 (Screening) through Visit 4/ Early Withdrawal. In addition, a phone call must have been placed to subjects 3 to 5 days after study completion to assess for adverse events.					
	Placebo (N=128)	FF 55mcg (N=127)	FF 110mcg (N=127)	FF 220mcg (N=129)	FF 440mcg (N=130)
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any AE(s), n (%)	35 (27)	35 (28)	37 (29)	35 (27)	31 (24)
Epistaxis	5 (4)	4 (3)	10 (8)	11 (9)	9 (7)
Nasal passage irritation	1 (<1)	3 (2)	0	1 (<1)	2 (2)
Pharyngo-laryngeal pain	2 (2)	1 (<1)	2 (2)	0	2 (2)
Rhinorrhea	2 (2)	2 (2)	2 (2)	0	0
Nasal dryness	0	2 (2)	0	0	1 (<1)
Nasal septum ulceration	0	0	2 (2%)	0	0
Headache	6 (5)	7(6)	7 (6)	2 (2)	4 (3)
Dizziness	0	3 (2)	0	0	1 (<1)
Dyspepsia	1 (<1)	2 (2)	2 (2)	1 (<1)	1 (<1)
Toothache	2 (2)	1 (<1)	2 (2)	0	0
Dry mouth	0	2 (2)	1 (<1)	0	1 (<1)
Back pain	1 (<1)	1 (<1)	4 (3)	1 (<1)	2 (2)
Myalgia	0	0	0	2 (2)	2 (2)

Ear pain	1 (<1)	1 (<1)	2 (2)	0	0
Sinusitis	0	2 (2)	0	2 (2)	0
Pain	0	1 (<1)	2 (2)	0	0
Insomnia	1 (<1)	0	2 (2)	0	0
Dysmenorrhea	0	0	3 (2)	0	0

Subjects with any SAEs: No fatal or non-fatal SAEs were reported during the study.

Conclusion: See publications below

**Publications:**

Martin BG, Ratner PH, Hampel FC, Andrews CP, Toler T, Wu W, Faris MA, Philpot EE.

Optimal dose selection of fluticasone furoate nasal spray for the treatment of seasonal allergic rhinitis in adults and adolescents. *Allergy Asthma Proc* 2007;28: 216-225.

Nathan RA, Martin BG, Ratner PH, Hampel FC, Andrews CP, Toler T, Wu W, Faris MA, Philpot EE.

Fluticasone furoate nasal spray provides 24-hour relief of nasal and ocular symptoms of seasonal allergic rhinitis with once-daily dosing. *Allergy Asthma Proc* 2007;28: 244 (abstract).

Stanford R, Philpot E, Faris M, Toler T, Wu W. Fluticasone furoate nasal spray once-daily improves quality of life in subjects with seasonal allergic rhinitis (SAR). *Ann Allergy Asthma Immunol* 2007;98(1) (Suppl 1): A90 (abstract).

Stanford R, Philpot E, Faris M, Toler T, Wu W. Fluticasone furoate nasal spray once-daily improves nocturnal quality of life in subjects with seasonal allergic rhinitis (SAR). *Ann Allergy Asthma Immunol* 2007;98(1) (Suppl 1): A88 (abstract).

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