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<b>Study No.:</b> FFR100010
<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* and 100mcg* for 2 Weeks in Pediatric Subjects Ages 2 to <12 Years with Seasonal Allergic Rhinitis (SAR)
<b>Rationale:</b> GW685698X (fluticasone furoate) is a novel corticosteroid with potent glucocorticoid activity. Because of the well-established efficacy and tolerability of corticosteroids in the treatment of allergic rhinitis, fluticasone furoate is being developed as a nasal spray for seasonal allergic rhinitis.
<b>Phase:</b> III
<b>Study Period:</b> 18 March 2005 to 01 November 2005
<b>Study Design:</b> Multicenter, 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.
<b>Centres:</b> A total of 57 centers in the United States enrolled subjects for this study.
<b>Indication:</b> Seasonal allergic rhinitis
<b>Treatment:</b> Subjects were randomized to a 2-week treatment with once-daily (QD) fluticasone furoate nasal spray 55mcg, fluticasone furoate nasal spray 110mcg, or vehicle placebo nasal spray. *Note: GW685698X aqueous nasal spray 110mcg (actual), 55mcg (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 55mcg for the recommended pediatric starting dose of one spray administered to each nostril and if needed increasing to 110mcg given two sprays administered to each nostril.
<b>Objectives:</b> The objectives of this study were to: <ul style="list-style-type: none"> <li>• Compare the efficacy and safety of fluticasone furoate nasal spray 55mcg and 110mcg QD with vehicle placebo nasal spray over a period of 2 weeks and to determine the optimal dose in pediatric subjects (ages 2 to &lt;12 years) with SAR.</li> <li>• Characterize the systemic exposure to fluticasone furoate within the doses under study in pediatric subjects' ages 2 to &lt;12 years with SAR over a period of 2 weeks.</li> </ul>
<b>Primary Outcome/Efficacy Variable:</b> Mean change from baseline over the entire treatment period in daily reflective total nasal symptom scores (rTNSS) in the subset of subjects ages 6 to <12 years. The total nasal symptom score (TNSS) was the sum of the 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.
<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) in subjects ages 6 to &lt;12 years. The iTNSS was a rating of the severity of symptoms immediately prior to taking the daily dose.</li> <li>• Overall evaluation of response to therapy in subjects ages 6 to &lt;12 years. The Overall Evaluation of Response to Therapy was based on a 7-point categorical scale where the subjects (and/or subject's parent/guardian) rated their perception of the change or lack of change in their allergic symptoms after 2 weeks of treatment. The seven categories were: significantly improved, moderately improved, mildly improved, no change, mildly worse, moderately worse, and significantly worse.</li> </ul>
<b>Statistical Methods:</b> The primary analysis method was the pairwise comparison of treatment groups (each dose of fluticasone furoate vs. placebo) using the analysis of covariance (ANCOVA) with adjustments for baseline rTNSS, region, age, gender, and season. Analysis of efficacy data was performed for the Intent-to-treat (ITT) subgroup of subjects 6 to <12 years of age. The key secondary efficacy endpoint of mean change from baseline over the entire treatment period in AM pre-dose iTNSS was also analyzed by pairwise comparisons of the three treatment groups (fluticasone furoate 110mcg and 55mcg vs. placebo) using ANCOVA with adjustments for baseline iTNSS, region, age, gender, and season. The key secondary efficacy endpoint of overall evaluation of response to therapy was analyzed using logistic regression adjusting for age, gender, season, region, and treatment.

The multiple comparisons between each of the two active doses and placebo for the primary efficacy endpoint were performed in sequence (fluticasone furoate 110mcg vs. placebo, and then fluticasone furoate 55mcg vs. placebo) to control the overall significance level of 0.05 on the primary efficacy endpoint. No multiplicity adjustments were made on key secondary efficacy endpoints; any p-value  $\leq 0.05$  was identified as (nominally) significant without regard to any issues of multiplicity.

A total of 576 subjects were required for this study, with 192 subjects (approximately 48 [25%] subjects 2 to <6 years of age and 144 [75%] subjects 6 to <12 years of age) in each of the three treatment groups. 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 ITT Population was defined as all subjects who were randomized and received at least one dose of study drug. The population of primary interest for analysis of efficacy data was the subgroup of subjects in the ITT Population who were 6 to <12 years of age at randomization (ITT: 6 to <12 years).

**Study Population:** Male and female subjects 2 to <12 years of age with a diagnosis of SAR residing within a geographical region where exposure to pollen was expected to be significant during the entire study period.

Number of Subjects:	Placebo	Fluticasone furoate (FF) 55mcg	Fluticasone furoate (FF) 110mcg
Planned, N	192	192	192
Ages 6 to <12 years	144	144	144
Ages 2 to <6 years	48	48	48
Randomised, N	186	184	184
Ages 6 to <12 years	150	152	146
Ages 2 to <6 years	35	32	38
Ages $\geq 12$ years	1	0	0
Completed, n (%)	180 (97)	175 (95)	181 (98)
Total Number Subjects Withdrawn, N (%)	6 (3)	9 (5)	3 (2)
Withdrawn due to Adverse Events n (%)	4 (2)	4 (2)	2 (1)
Withdrawn due to Lack of Efficacy n (%)	0	0	0
Withdrawn for Other Reasons n (%)	2 (1)	5 (3)	1 (<1)
Demographics:	Placebo	FF 55mcg	FF 110mcg
N (ITT)	186	184	184
Females: Males	78:108	80:104	73:111
Mean Age, years (SD)	8.0 (2.55)	8.2 (2.43)	8.0 (2.54)
White, n (%)	148 (80)	156 (85)	140 (76)
Primary Efficacy Results: Daily rTNSS: ITT: 6 to <12 years			
	Placebo N=150	FF 55mcg N=152	FF 110mcg N=146
Baseline, n	150	151	146
Mean (SE)	8.4 (0.14)	8.6 (0.15)	8.5 (0.14)
Weeks 1-2, n	149	151	146
LS mean change (SE)	-2.54 (0.21)	-2.71 (0.20)	-3.16 (0.21)
LS mean difference vs Placebo	--	-0.161	-0.616
95% CI vs Placebo	--	-0.69, 0.37	-1.15, -0.08
p-value vs Placebo	--	0.553	0.025
Key Secondary Outcome Variables: ITT: 6 to <12 years			
AM Pre-dose iTNSS			
Baseline,	150	151	146
Mean (SE)	8.4 (0.17)	8.4 (0.17)	8.3 (0.15)
Weeks 1-2, n	149	151	146
LS mean change (SE)	-2.13 (0.21)	-2.37 (0.20)	-2.80 (0.21)
LS mean difference vs Placebo	---	-0.234	-0.668
95% CI vs Placebo	---	-0.77, 0.30	-1.21, -0.13

Response to Therapy, n (%)	150	150	144
Significantly improved	19 (13)	30 (20)	41 (28)
Moderately improved	45 (30)	39 (26)	49 (34)
Mildly improved	35 (23)	47 (31)	38 (26)
No change	41 (27)	26 (17)	14 (10)
Mildly worse	5 (3)	2 (1)	0
Moderately worse	2 (1)	5 (3)	0
Significantly worse	3 (2)	1 (<1)	2 (1)
Safety Results (ITT Population): All 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/Early Withdrawal) to assess post-treatment AEs. On-therapy SAEs were defined as those occurring between randomization and the follow-up contact.			
Most Frequent Adverse Events – On-Therapy	Placebo N=186	FF 55mcg N=184	FF 110mcg N=184
Subjects with any AE(s), n (%)	37 (20)	55 (30)	55 (30)
Headache	7 (4)	8 (4)	11 (6)
Epistaxis	8 (4)	6 (3)	5 (3)
Nasopharyngitis	1 (<1)	3 (2)	5 (3)
Pyrexia	0	4 (2)	5 (3)
Abdominal pain upper	2 (1)	0	5 (3)
Cough	1 (<1)	4 (2)	2 (1)
Asthma	1 (<1)	4 (2)	1 (<1)
Pharyngolaryngeal pain	1 (<1)	3 (2)	2 (1)
Gastroenteritis viral	1 (<1)	1 (<1)	3 (2)
Upper respiratory tract infection	1 (<1)	3 (2)	1 (<1)
Ear infection	0	4 (2)	0
Vomiting	0	4 (2)	0
Conjunctivitis allergic	0	2 (1)	1 (<1)
Excoriation	1 (<1)	2 (1)	0
Scab	2 (1)	1 (<1)	0
Diabetes Mellitus	2 (1)	0	0
Nasal ulcer	1 (<1)	0	1 (<1)
Nasal congestion	1 (<1)	0	0
Rhinitis seasonal	1 (<1)	0	0
Rhinorrhea	1 (<1)	0	0
Otitis media	1 (<1)	1 (<1)	0
Viral infection	1 (<1)	0	0
Acute sinusitis	1 (<1)	0	0
Bronchitis acute	1 (<1)	0	0
Skin candida	1 (<1)	0	0
Psychomotor hyperactivity	1 (<1)	0	0
Tension headache	1 (<1)	0	0
Abdominal pain	1 (<1)	0	0
Skin laceration	1 (<1)	1 (<1)	1 (<1)
Arthropod bite	1 (<1)	1 (<1)	0
Arthropod sting	1 (<1)	1 (<1)	0
Local swelling	1 (<1)	0	0
Dermatitis contact	1 (<1)	1 (<1)	0
Rash	1 (<1)	0	1 (<1)
Urticaria	1 (<1)	0	1 (<1)
Arthralgia	1 (<1)	1 (<1)	1 (<1)
Conjunctivitis	1 (<1)	0	0
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]			
	Placebo	FF 55mcg	FF 110mcg

	N=186	N=184	N=184
Subjects with any SAEs, n (%) -Includes both fatal and non-fatal events	1 (<1) [0]	0	0
Diabetes mellitus insulin-dependent	1 (<1) [0]	0	0
Subjects with fatal SAEs, n (%)	0	0	0

<b>Conclusion:</b>			
See publications below			
Publications: Meltzer EO, Tripathy I, Lee J, Lim J, Ellsworth A, Philpot E. Once-daily fluticasone furoate nasal spray (FF) provides 24-hour relief of the nasal symptoms of seasonal allergic rhinitis (SAR) in children ages 2-11 years. J Allergy Clin Immunol. 2007;119(1): S305 (abstract).			
Meltzer E, Lee J, Tripathy I, Lim J, Ellsworth A, Philpot E. Study to assess the efficacy and safety of two doses of fluticasone furoate nasal spray in children with seasonal allergic rhinitis. Allergy 2007;62(Suppl. 83): 130 (abstract).			

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