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<b>Study No.:</b> FFR106080
<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 100mcg* for 6 Weeks in Adult and Adolescent Subjects 12 years of Age and Older with Perennial Allergic Rhinitis (PAR)
<b>Rationale:</b> 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.
<b>Phase:</b> III
<b>Study Period:</b> 7 February 2006 to 23 June 2006
<b>Study Design:</b> Multi-center, 6-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.
<b>Centres:</b> A total of 40 investigational sites randomised subjects: 4 in Canada, 7 in Australia, 5 in Lithuania, 3 in Estonia, 4 in Latvia, 7 in the United States (US), 4 in the Russian Federation, 3 in New Zealand and 3 in Germany. One centre each in Germany, Latvia and the US screened subjects only.
<b>Indication:</b> Perennial Allergic Rhinitis (PAR)
<b>Treatment:</b> Subjects meeting specified symptom criteria were randomized to 6 weeks' treatment with once daily fluticasone furoate nasal spray 110mcg or vehicle placebo nasal spray. *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.
<b>Objectives:</b> The objective of this study was to compare the efficacy and safety of fluticasone furoate nasal spray 110mcg once daily with vehicle placebo nasal spray once daily in adult and adolescent subjects $\geq 12$ years of age with PAR.
<b>Primary Outcome/Efficacy Variable:</b> <ul style="list-style-type: none"> <li>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.</li> </ul>
<b>Secondary Outcome/Efficacy Variables:</b> <b>Key Secondary outcomes</b> <ul style="list-style-type: none"> <li>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.</li> <li>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.</li> </ul>
<b>Statistical Methods:</b> The primary analysis method was the comparison of treatment groups (fluticasone furoate nasal spray 110mcg vs. placebo) using analysis of covariance (ANCOVA), adjusting for baseline daily rTNSS, country, age, and gender. The secondary efficacy measures were analysed in a similar manner to the primary efficacy analysis. A total of 288 subjects were required for this study, with 144 subjects in each of the two treatment groups: fluticasone

<p>furoate 110mcg nasal spray and placebo. The randomisation was stratified by country to account for possible country effects on the study outcome due to country-specific medical practices. 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.</p> <p>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.</p>		
<p><b>Study Population:</b> Male and female subjects were eligible for treatment as outpatients if they had a diagnosis of perennial allergic rhinitis and were ≥12 years at Visit 2 for US, Canada, Australia, New Zealand, Latvia, Lithuania, and Estonia; ≥18 years at Visit 2 for Russia; ≥18 years at Visit 1 for Germany. Subjects must have been symptomatic to appropriate perennial allergen including animal dander, house dust mites, cockroach, and mould.</p>		
<b>Number of Subjects (ITT):</b>	<b>Placebo</b>	<b>Fluticasone furoate (FF) 110mcg</b>
Planned, N	144	144
Randomised, N	151	151
Completed, n (%)	120 (79)	121 (80)
Total Number Subjects Withdrawn, N (%)	31 (21)	30 (20)
Withdrawn due to Adverse Events, n (%)	0	2 (1)
Withdrawn due to Lack of Efficacy, n (%)	2 (1)	0
Withdrawn for other reasons, n (%)	29 (20)	28 (19)
<b>Demographics</b>	<b>Placebo</b>	<b>FF 110mcg</b>
N (ITT)	151	151
Females: Males, n	86:65	85:66
Mean Age, years (SD)	37.2	37.1
White, n (%)	140 (93)	135 (89)
Duration of PAR, n (%)		
≥2 to <5 years	25 (17)	29 (19)
≥5 to <10 years	36 (24)	39 (26)
≥10 years	90 (60)	83 (55)
<b>Primary Efficacy Results: Daily rTNSS (ITT)</b>	<b>Placebo N=153</b>	<b>FF 110mcg N=149</b>
LS Mean Change (SE)	-2.69 (0.18)	-3.95 (0.18)
LS Mean Difference		-1.256
95% Confidence Interval		-1.73, -0.78
p-value		<0.001
<b>Secondary Outcome Variables (ITT)</b>		
<b>AM Pre-dose rTNSS</b>		
LS Mean Change (SE)	-2.36 (0.18)	-3.82 (0.18)
LS Mean Difference		-1.459
95% CI		-1.93, -0.99
<b>Overall Response to Therapy, n (%)</b>		
Significantly Improved	21 (14)	56 (37)
Moderately Improved	38 (25)	37 (25)
Mildly Improved	37 (25)	31 (21)
No Change	45 (30)	20 (13)
Mildly Worse	5 (3)	2 (1)
Moderately Worse	3 (2)	3 (2)
Significantly Worse	2 (1)	2 (1)
<b>Health outcomes (Rhinconjunctivitis Quality of Life Questionnaire)</b>	<b>Placebo</b>	<b>FF 110mcg</b>
<b>Overall</b>		
LS Mean Change (SE)	-1.20 (0.09)	-1.85 (0.09)
Difference between treatments		-0.652

95% CI		(-0.90, -0.40)
<b>Safety Results:</b> 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.		
	<b>Placebo N=151</b>	<b>FF 110mcg N=151</b>
<b>Most Frequent Adverse Events – On-Therapy</b>	<b>n (%)</b>	<b>n (%)</b>
Subjects with any AE(s), n(%)	66 (44)	77 (51)
Epistaxis	6 (4)	13 (9)
Pharyngolaryngeal pain	6 (4)	13 (9)
Nasopharyngitis	7 (5)	9 (6)
Diarrhea	2 (1)	3 (2)
Dizziness	1 (<1)	4 (3)
Influenza	2 (1)	3 (2)
Nausea	1 (<1)	4 (3)
Scab	1 (<1)	4 (3)
Nasal septum ulceration	0	4 (3)
Procedural pain	1 (<1)	3 (2)
Viral infection	1 (<1)	3 (2)
<b>Serious Adverse Events – During Treatment</b> <b>n (%) [n considered by the investigator to be related to study medication]</b>		
	<b>Placebo N=153</b>	<b>FF110mcg N=149</b>
Subjects with any SAEs, n (%) [n] -Includes both fatal and non-fatal events	0	1 (<1) [0]
Subjects with Fatal SAEs, n (%) [n]	0	0
<b>Serious Adverse Events – Post-Treatment</b> <b>n (%) [n considered by the investigator to be related to study medication]</b>		
	<b>Placebo N=151</b>	<b>FF 110mcg N=151</b>
Subjects with any SAEs, n (%) [n] -Includes both fatal and non-fatal events	0	0
Subjects with Fatal SAEs, n (%) [n]	0	0
<b>Conclusion:</b> See publications below.		
<b>Publications:</b> Vasar M, Houle P, Douglass J, Meltzer E, Silvey M, Wu W, Caldwell M, Philpot E. A novel enhanced-affinity corticosteroid, once daily fluticasone furoate* nasal spray (FFNS), provides 24-hour relief for the nasal symptoms of perennial allergic rhinitis (PAR). *USAN approved name. Allergy 2007;62(Suppl. 83): 227 (abstract).  Meltzer E, Vasar M, Houle P, Douglass J, Silvey M, Wu W, Philpot E, Caldwell M. Fluticasone furoate nasal spray provides 24-hour relief of perennial allergic rhinitis symptoms. Ann Allergy Asthma Immunol 2008; 100(1) (Supplement 1):A4 (abstract)		

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