The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: FFR104503
Title: A Randomized, Open Label, Active Controlled (Mometasone Furoate Aqueous Nasal Spray [Nasonex®] 200mcg QD), Parallel Group, Multi-Center, 52-Week Study to Assess the Long Term Safety of GW685698X Aqueous Nasal Spray 100mcg* QD via Nasal Biopsy in Subjects ≥18 Years of Age with Perennial Allergic Rhinitis (PAR)
Rationale: This study was conducted to study the effects of fluticasone furoate nasal spray (FFNS) 110mcg once daily (QD) on the histopathological features of the nasal mucosa in subjects with PAR.
Phase: IIIb
Study Period: 20 September 2005 – 01 February 2007
Study Design: 52-week, randomized, open-label, controlled, parallel, multicenter study
Centres: Three centers in the Netherlands and one center in Belgium
Indication: Perennial Allergic Rhinitis (PAR)
Treatment: Eligible PAR subjects were assigned to receive either FFNS 110mcg or mometasone fuorate nasal spray (MFNS) 200mcg. *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 FF, equating to 110mcg for the recommended adult dose of two sprays administrated to each nostril.
Objectives: The primary objective of this study was to determine effects to the nasal mucosa of PAR subjects after one year of continuous treatment with GW685698X (FFNS) 110mcg QD compared to Nasonex® (MFNS) 200mcg QD reference control group as determined by blinded morphological and immunocytochemical analyses of nasal biopsy specimens. A separate healthy (non-allergic) control (HC) group of approximately 25 subjects did not receive any treatment, but under went a nasal biopsy at baseline and after 12 months to assess biopsy sampling technique artifact and monitor the influence of environmental factors over 12 months. Indigo carmine saccharine transport time (ICST) assessments of mucociliary clearance were also conducted in subjects at one selected investigational site to determine the effects, if any, of treatment on ciliary function.
Primary Outcome Variables: Quantitative and qualitative differences in the morphology and cytology of the nasal mucosa before and after treatment were based on the following parameters: - epithelial thickness based on the ratio of cross sectional area to basement membrane length - percentage of intact ciliated epithelium - abundance of goblet cells - extent of inflammatory cell infiltration (eosinophils, basophils, dendritic cells) in the epithelial tissue and sub-epithelial tissue
Statistical Methods: No formal statistical hypotheses were planned. Summary statistics were provided for all safety and compliance efficacy data. The sample size of 100 completed active treated subjects (1:1 ratio with approximately 50 subjects randomized to FFNS 110mcg QD and approximately 50 subjects randomized to MFNS 200mcg QD) was based on feasibility as the study was not designed or powered to detect any treatment differences. Approximately 25 normal healthy control subjects were planned to complete nasal biopsy assessments at baseline and at 12 months for study reference comparison purposes.

Based on published data for a MFNS nasal biopsy study, the standard deviation was estimated to be about 0.02mm on the epithelial thickness. With 50 completed subjects per active arm, it was anticipated that the width of the 95% confidence interval for the mean treatment difference on the epithelial thickness would be no larger than 0.016mm.
For the nasal biopsy data, the analysis was also performed for the Nasal Biopsy (NB) population (of primary interest), in addition to the intent-to-treat (ITT) population (supportive). The ITT population was defined as all randomized PAR subjects who received at least one dose of study drug. The NB population was defined as all ITT PAR subjects and healthy subjects for whom the nasal biopsy samples (both GMA embedded sample and the frozen sample) at baseline (Visit 2 for PAR subjects and Visit 1 for the healthy control subjects) and at Week 52 were obtained and analyzed. In addition, PAR subjects should not have used any prohibited corticosteroids that may have had any confounding effect on the nasal biopsy results. For all other safety and efficacy data, the analysis was based on the ITT population.

Study Population: Male and female subjects were eligible if they were ≥18 years of age and had a diagnosis and two year history of perennial allergic rhinitis. Additionally, a minimum symptom score of 4 out of 12 for daily rTNSS on any 4 of the 7 days just prior to randomization was required.

	FFNS 110mcg	**MFNS 200mcg**	**HC**
Number of Subjects:			
Planned, N	50	50	25
Randomised, N	56	60	30
Completed, n (%)	46 (82)	50 (83)	28 (93)
Total Number Subjects Withdrawn, N (%)	10 (18)	10 (17)	2 (7)
Withdrawn due to Adverse Events n (%)	4 (7)	2 (3)	0
Withdrawn due to Lack of Efficacy n (%)	0	0	0
Withdrawn for other reasons n (%)	4 (7)	3 (5)	2 (7)
Demographics	**FFNS 110mcg**	**MFNS 200mcg**	**HC**
N (ITT/Nasal Biopsy)	56/37	60/42	30/17
Females: Males	35:21	43:17	19:11
Mean Age, years (SD)	30.4 (10.91)	32.3 (14.74)	25.5 (7.45)
White, n (%)	49 (88)	54 (90)	30 (100)

Primary Results:

	FFNS 110mcg (N=37)	**MFNS 200mcg (N=42)**	**HC (N=17)**
Epithelial thickness (mm)			
Baseline, n	31	40	13
Mean (SD)	0.0885 (0.01724)	0.0864 (0.01410)	0.0914 (0.02455)
Week 52, n	33	35	16
Mean (SD)	0.0830 (0.01441)	0.0804 (0.01235)	0.0824 (0.01064)
Change from baseline, n	29	33	13
Mean (SD)	-0.0083 (0.01901)	-0.0057 (0.01826)	-0.0077 (0.02620)
Analysis of mean change, n	29	33	N/A
LS Mean(SE)	-0.0045 (0.00318)	-0.0053 (0.00319)	
95% CI	-0.0109, 0.0018	-0.0117, 0.0010	

LS Mean Difference (SE) **95% CI**	- -	-0.0008 (0.00333) -0.0075, 0.0058	N/A
Epithelial histology			
% Basement Membrane (BM only)			
Baseline mean (SD)	3.691 (5.3114)	4.925 (11.9471)	4.232 (7.2604)
Week 52 Mean (SD)	3.028 (3.5300)	6.851 (10.6597)	7.276 (15.1416)
Change from baseline mean (SD)	-0.662 (4.5452)	1.926 (16.1207)	3.552 (16.7847)
% BM plus Basal Cells			
Baseline mean (SD)	17.272 (20.8985)	10.571 (10.7656)	27.398 (29.4031)
Week 52 Mean (SD)	12.532 (19.5257)	18.390 (25.1974)	15.566 (21.6063)
Change from baseline mean (SD)	-4.740 (23.1371)	7.819 (27.0430)	-8.067 (29.7128)
% BM plus Basal Cells plus Dissociated Columnar Cells			
Baseline mean (SD)	27.683 (23.0213)	23.924 (18.8264)	17.731 (15.0007)
Week 52 Mean (SD)	18.157 (17.3830)	19.441 (17.9033)	28.062 (21.5657)
Change from baseline mean (SD)	-9.526 (32.1618)	-4.483 (26.7036)	9.223 (24.7627)
% BM plus Basal Cells plus Intact Columnar Cells			
Baseline mean (SD)	28.890 (27.7516)	38.523 (23.6993)	30.197 (26.4951)
Week 52 Mean (SD)	34.633 (31.9952)	30.384 (25.6873)	30.300 (23.5290)
Change from baseline mean (SD)	5.743 (43.6147)	-8.140 (32.9546)	-1.784 (42.9389)
% Intact Ciliated Cells			
Baseline mean (SD)	22.464 (30.3536)	22.057 (26.2751)	20.443 (22.4167)
Week 52 Mean (SD)	31.648 (32.0263)	24.935 (28.0555)	18.796 (29.9776)
Change from baseline mean (SD)	9.183 (42.3472)	2.878 (40.8399)	-2.925 (25.9679)
Goblet cells (%) (number of goblet cells/number of epithelial cells x100)			
Baseline mean (SD)	14.4 (6.76)	14.6 (8.32)	17.4 (7.69)
Week 52 Mean (SD)	12.6 (8.93)	15.9 (8.91)	14.4 (5.09)
Change from baseline mean (SD)	-2.1 (10.44)	0.7 (10.63)	-3.4 (10.33)
Inflammatory cells in epithelial tissue (number of cells per mm)			
Eosinophils			
Baseline mean (SD)	0.69 (1.37)	0.66 (1.23)	0.21 (0.77)
Week 52 Mean (SD)	0.09 (0.26)	0.10 (0.26)	0.23 (0.81)
Change from baseline mean (SD)	-0.59 (1.40)	-0.55 (1.30)	0.26 (0.88)
Basophils			

Baseline mean (SD)	1.41 (2.97)	1.87 (3.67)	0.19 (0.37)
Week 52 Mean (SD)	0.39 (1.13)	0.22 (0.43)	0.80 (1.39)
Change from baseline mean (SD)	-1.01 (2.63)	-1.68 (3.72)	0.45 (0.98)
Dendritic cells			
Baseline mean (SD)	0.79 (1.90)	1.88 (2.62)	1.42 (1.83)
Week 52 Mean (SD)	0.88 (2.74)	0.61 (0.95)	2.91 (2.87)
Change from baseline mean (SD)	0.10 (3.25)	-1.26 (2.86)	1.52 (3.62)
Inflammatory cells in sub-epithelial tissue (number of cells per mm^2)			
Eosinophils			
Baseline mean (SD)	40.00 (74.54)	33.53 (35.52)	10.59 (29.20)
Week 52 Mean (SD)	18.48 (41.81)	31.50 (66.57)	28.33 (42.10)
Change from baseline mean (SD)	-21.12 (89.66)	-1.51 (70.48)	26.75 (43.08)
Basophils			
Baseline mean (SD)	62.13 (43.14)	65.74 (43.05)	69.13 (59.53)
Week 52 Mean (SD)	12.79 (22.87)	27.94 (39.10)	78.94 (45.01)
Change from baseline mean (SD)	-44.98 (46.50)	-35.87 (56.25)	14.07 (49.08)
Dendritic cells			
Baseline mean (SD)	78.97 (54.13)	66.33 (35.98)	80.57 (54.84)
Week 52 Mean (SD)	71.83 (49.51)	71.80 (50.49)	70.79 (38.01)
Change from baseline mean (SD)	-7.14 (71.01)	5.47 (64.82)	-9.78 (64.14)

Safety Results: All adverse events (AEs) related to study participation were collected from Visit 1 through to the post-treatment Follow-up Visit. On therapy AEs were defined as those occurring between treatment initiation and end of treatment/early withdrawal. In addition, a follow-up visit occurred 14 +/- 2 days after study completion (Final Study Visit) to assess for post-treatment adverse events. On therapy SAEs were those defined as those occurring between treatment initiation and the follow-up contact.

Most Frequent Adverse Events – On-Therapy	**FFNS 110mcg (N=56)**	**MFNS 200mcg (N=60)**
Subjects with any AE(s), n(%)	50 (89)	54 (90)
Pharyngolaryngeal pain	25 (45)	15 (25)
Epistaxis	21 (38)	18 (30)
Nasopharyngitis	20 (36)	26 (43)
Headache	17 (30)	24 (40)
Influenza	11 (20)	9 (15)
Influenza like illness	8 (14)	8 (13)
Cough	10 (18)	4 (7)
Upper respiratory tract infection	9 (16)	5 (8)
Diarrhoea	5 (9)	3 (5)
Nausea	2 (4)	5 (8)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]		
	FFNS 110mcg	**MFNS 200mcg**
Subjects with non-fatal SAEs, n (%)		
Spontaneous abortion	1 (2)	0
Crohn's dis ease	0	1 (2)
Subjects with fatal SAEs, n (%)	0	0

Conclusion:
See publication below

Publications:
Fokkens W, Hellings P, Blom H, Jansen A, van Drunen K, Clements D, Wu W, Caldwell M,

Philpot E. A comparison of the effects of fluticasone furoate and mometasone furoate nasal sprays on the nasal mucosa. Ann Allergy Asthma Immunol 2008; 100(1) (Supplement 1):A12 (abstract)

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