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Study No.: FFR100652				
Title: Clinical Evaluation of GW685698 for Seasonal Allergic Rhinitis - A Placebo-Controlled Study to Determine the Non-Inferiority of GW685698 over Fluticasone Propionate Using a Double-Blind Manner -				
Rationale: This study was designed to compare once-daily Fluticasone Furoate (FF) 110µg/day to twice-daily Fluticasone Propionate (FP), gold standard of adrenocortical steroid nasal spray, 200µg/day and to evaluate the efficacy and safety of FF in patients with seasonal allergic rhinitis.				
Phase: III				
Study Period: 19 February 2005 to 13 April 2005				
Study Design: A randomized, double-blind, placebo and active controlled, parallel group, multicenter study				
Centres: Seven centres in Japan				
Indication: Seasonal allergic rhinitis				
Treatment: Subjects were randomized to a 2-week treatment with FF 110µg/day once daily, FF placebo once daily, FP 200µg/day twice daily or FP placebo twice daily (FF 110 µg:FF placebo:FP 200 µg:FP placebo=2:1:2:1). (FF nasal spray and FF placebo nasal spray were indistinguishable from each other in appearance, and FP nasal spray and FP placebo nasal spray were indistinguishable from each other in appearance.)				
Objectives: The objectives of this study were to compare once-daily FF 110µg/day to twice-daily FP 200µg/day (non - inferiority) and to evaluate the efficacy and safety of FF in patients with seasonal allergic rhinitis.				
Primary Outcome/Efficacy Variable: Mean change from baseline over the entire treatment period in 3 Total Nasal Symptom Score (3TNSS). (Demonstrate the non-inferiority of once-daily FF 110µg/day to twice-daily FP 200µg/day.) 3 TNSS is the sum (0-9) of three individual symptom scores for sneezing, rhinorrhea and nasal congestion where each symptom is scored on a scale of 0 to 3 in the nasal diary.				
Secondary Outcome/Efficacy Variable(s): Three nasal symptoms <ul style="list-style-type: none"> • Mean changes from baseline over Week 1 and Week 2 in 3TNSS. • Mean percent change from baseline over the entire treatment period in 3TNSS. Four nasal symptoms <ul style="list-style-type: none"> • Mean change from baseline over the entire treatment period, Week 1 and Week 2 in 4 Total Nasal Symptom Score (4TNSS*). • Mean percent change from baseline over the entire treatment period in 4TNSS. Individual nasal symptoms <ul style="list-style-type: none"> • Mean changes from baseline over the entire treatment period, Week 1 and Week 2 in individual nasal symptom (sneezing, rhinorrhea, nasal congestion and nasal itching) scores. *4TNSS is the sum (0-12) of four individual symptom scores for sneezing, rhinorrhea, nasal congestion and nasal itching where each symptom is scored on a scale of 0 to 3 in the nasal diary.				
Statistical Methods: The primary analysis population was the PPS. The primary efficacy analysis method was the calculation of the two-sided 95% confidence interval for the difference between the two active treatment groups in the mean change from baseline over the entire treatment period in 3TNSS using the Analysis of Covariance (ANCOVA) model fitted with study center, baseline, age and gender as covariates.				
Study Population: The patients enrolled in the study were outpatients aged 16 years or older who had clinical history of seasonal allergic rhinitis (cedar pollinosis) diagnosed at least 2 years before, who had positive allergy tests [positive responses to a) skin test or serum IgE antibody assay and to either b) nasal mucosa test or c) nasal discharge eosinophil count test]. The average of 3 Total Nasal Symptom Score (for sneezing, rhinorrhea, and nasal congestion) in the consecutive 4 days just prior to Visit 2 (start date of study medication) must have been 4.0 and more.				
Number of Subjects:	FP Placebo	FP	FF Placebo	FF 110µg
Planned, N	70	140	70	140
Randomised, N	75	148	72	151
Completed, n (%)	71(95)	141(95)	68(94)	144(95)
Total Number Subjects Withdrawn, n (%)	4(5)	7(5)	4(6)	7(5)
Withdrawn due to Adverse Events, n (%)	1(1)	2(1)	2(3)	1(<1)
Withdrawn due to Lack of Efficacy, n (%)	0	0	0	0

Withdrawn for other reasons, n (%)	3(4)	5(3)	2(3)	6(4)
Demographics				
N (PPS/FAS/SP)	72/74/74	144/147/148	70/71/72	147/149/149
Females: Males	37:35	78:66	34:36	76:71
Mean Age, years (SD)	30.6(10.22)	32.1(10.27)	32.5(11.48)	32.4(10.98)
East/Southeast Asians, n (%)	72(100)	144(100)	70(100)	147(100)
Primary Efficacy Results: Mean change from baseline over the entire treatment period in 3TNSS (PPS)				
		FP (N=144)	FF 110µg (N=147)	
Mean (SD)		-1.3(1.70)	-1.4(1.70)	
Adjusted mean (SE)		-1.06(0.142)	-1.23(0.140)	
Adjusted mean difference from FP		-	-0.173	
95% confidence interval (two-sided)		-	-0.51, 0.17	
Secondary Outcome Variable(s):				
Mean change from baseline in 3TNSS (FF placebo vs FF 110 µg)		FF Placebo	FF 110µg	
Entire treatment period	n (PPS)	70	147	
	Adjusted mean (SE)	0.42(0.201)	-1.27(0.151)	
	Adjusted mean difference from FF placebo	-	-1.689	
	95% confidence interval (two-sided)	-	-2.13, -1.25	
Mean change from baseline in 3TNSS (FP placebo vs FP)		FP Placebo	FP	
Entire treatment period	n (PPS)	72	144	
	Adjusted mean (SE)	0.45(0.180)	-1.05(0.138)	
	Adjusted mean difference from FP placebo	-	-1.501	
	95% confidence interval (two-sided)	-	-1.89, -1.11	
Mean change from baseline in 3TNSS (FP vs FF 110 µg)		FP	FF 110µg	
Week 1	n (PPS)	144	147	
	Adjusted mean (SE)	-1.17 (0.147)	-1.31 (0.145)	
	Adjusted mean difference from FP	-	-0.139	
	95% confidence interval (two-sided)	-	-0.49, 0.21	
Week 2	n (PPS)	142	146	
	Adjusted mean (SE)	-0.95 (0.171)	-1.17 (0.169)	
	Adjusted mean difference from FP	-	-0.226	
	95% confidence interval (two-sided)	-	-0.63, 0.18	
Mean percent change from baseline in 3TNSS (FP vs FF 110 µg)		FP	FF 110µg	
Entire treatment period	n (PPS)	144	147	
	Adjusted mean (SE)	-15.68 (2.597)	-20.17 (2.562)	
	Adjusted mean difference from FP	-	-4.490	
	95% confidence interval (two-sided)	-	-10.74, 1.76	
Mean change from baseline in 4TNSS (FP vs FF 110 µg)		FP	FF 110µg	
Entire treatment period	n (PPS)	144	147	
	Adjusted mean (SE)	-1.34 (0.191)	-1.59 (0.188)	
	Adjusted mean difference from FP	-	-0.249	
	95% confidence interval (two-sided)	-	-0.71, 0.21	
Week 1	n (PPS)	144	147	
	Adjusted mean (SE)	-1.44 (0.195)	-1.68 (0.192)	
	Adjusted mean difference from FP	-	-0.245	
	95% confidence interval (two-sided)	-	-0.71, 0.22	
Week 2	n (PPS)	142	146	
	Adjusted mean (SE)	-1.24 (0.230)	-1.52 (0.226)	
	Adjusted mean difference from FP	-	-0.279	
	95% confidence interval (two-sided)	-	-0.82, 0.27	
Mean percent change from baseline in 4TNSS (FP vs FF 110 µg)		FP	FF 110µg	
Entire treatment period	n (PPS)	144	147	
	Adjusted mean (SE)	-14.34 (2.710)	-19.07 (2.660)	
	Adjusted mean difference from FP	-	-4.722	

	95% confidence interval (two-sided)	-	-11.22, 1.77
Mean changes from baseline in individual nasal symptom: sneezing (FP vs FF 110 µg)		FP	FF 110µg
Entire treatment period	n (PPS)	144	147
	Adjusted mean (SE)	-0.37 (0.051)	-0.42 (0.050)
	Adjusted mean difference from FP	-	-0.057
	95% confidence interval (two-sided)	-	-0.18, 0.07
Week 1	n (PPS)	144	147
	Adjusted mean (SE)	-0.41 (0.053)	-0.45 (0.052)
	Adjusted mean difference from FP	-	-0.039
	95% confidence interval (two-sided)	-	-0.17, 0.09
Week 2	n (PPS)	142	146
	Adjusted mean (SE)	-0.33 (0.062)	-0.40 (0.061)
	Adjusted mean difference from FP	-	-0.071
	95% confidence interval (two-sided)	-	-0.22, 0.08
Mean changes from baseline in individual nasal symptom: rhinorrhea (FP vs FF 110 µg)		FP	FF 110µg
Entire treatment period	n (PPS)	144	147
	Adjusted mean (SE)	-0.34 (0.052)	-0.37 (0.051)
	Adjusted mean difference from FP	-	-0.032
	95% confidence interval (two-sided)	-	-0.16, 0.09
Week 1	n (PPS)	144	147
	Adjusted mean (SE)	-0.38 (0.056)	-0.39 (0.055)
	Adjusted mean difference from FP	-	-0.012
	95% confidence interval (two-sided)	-	-0.15, 0.12
Week 2	n (PPS)	142	146
	Adjusted mean (SE)	-0.30 (0.061)	-0.36 (0.060)
	Adjusted mean difference from FP	-	-0.062
	95% confidence interval (two-sided)	-	-0.21, 0.08
Mean changes from baseline in individual nasal symptom: nasal congestion (FP vs FF 110 µg)		FP	FF 110µg
Entire treatment period	n (PPS)	144	147
	Adjusted mean (SE)	-0.35 (0.057)	-0.44 (0.056)
	Adjusted mean difference from FP	-	-0.088
	95% confidence interval (two-sided)	-	-0.22, 0.05
Week 1	n (PPS)	144	147
	Adjusted mean (SE)	-0.39 (0.058)	-0.48 (0.057)
	Adjusted mean difference from FP	-	-0.091
	95% confidence interval (two-sided)	-	-0.23, 0.05
Week 2	n (PPS)	142	146
	Adjusted mean (SE)	-0.31 (0.069)	-0.40 (0.068)
	Adjusted mean difference from FP	-	-0.098
	95% confidence interval (two-sided)	-	-0.26, 0.07
Mean changes from baseline in individual nasal symptom: nasal itching (FP vs FF 110 µg)		FP	FF 110µg
Entire treatment period	n (PPS)	144	147
	Adjusted mean (SE)	-0.29 (0.060)	-0.35 (0.057)
	Adjusted mean difference from FP	-	-0.065
	95% confidence interval (two-sided)	-	-0.21, 0.08
Week 1	n (PPS)	144	147
	Adjusted mean (SE)	-0.28 (0.063)	-0.37 (0.060)
	Adjusted mean difference from FP	-	-0.095
	95% confidence interval (two-sided)	-	-0.24, 0.05
Week 2	n (PPS)	142	146
	Adjusted mean (SE)	-0.31 (0.070)	-0.35 (0.068)

	Adjusted mean difference from FP	-	-0.042	
	95% confidence interval (two-sided)	-	-0.21, 0.12	
Safety Results: Safety population (SP).				
AEs occurred after the start of treatment (treatment period + post-treatment period).				
AE(s)	FP Placebo (N=74)	FP (N=148)	FF Placebo (N=72)	FF 110µg (N=149)
	Subject with any AE(s), n (%)			
Total	14(19)	27(18)	15(21)	25(17)
Headache	1(1)	4(3)	3(4)	5(3)
Nasopharyngitis	2(3)	4(3)	1(1)	5(3)
Alanine aminotransferase increased	2(3)	2(1)	1(1)	2(1)
Toothache	1(1)	2(1)	0	2(1)
Aspartate aminotransferase increased	1(1)	1(<1)	0	2(1)
Cough	1(1)	1(<1)	2(3)	2(1)
Pharyngolaryngeal pain	0	1(<1)	1(1)	2(1)
White blood cell count increased	0	1(<1)	1(1)	2(1)
Blood alkaline phosphatase increased	1(1)	1(<1)	1(1)	1(<1)
Blood cortisol decreased	0	0	1(1)	1(<1)
Neutrophil count increased	0	0	0	1(<1)
Productive cough	1(1)	0	0	1(<1)
Nasal discomfort	0	0	1(1)	1(<1)
Pharynx discomfort	0	0	0	1(<1)
Dizziness	0	0	1(1)	1(<1)
Nausea	1(1)	0	1(1)	1(<1)
Stomatitis	0	0	0	1(<1)
Eye pain	0	0	0	1(<1)
Flank pain	0	0	0	1(<1)
Epistaxis	3(4)	3(2)	1(1)	0
Limb injury	0	3(2)	0	0
Pyrexia	0	2(1)	1(1)	0
Rash	0	2(1)	0	0
Platelet count decreased	0	1(<1)	0	0
Influenza	1(1)	1(<1)	0	0
Thirst	0	1(<1)	0	0
Eczema	1(1)	1(<1)	0	0
Drug eruption	0	1(<1)	0	0
Palpitations	0	1(<1)	0	0
Eosinophil count increased	1(1)	0	1(1)	0
Somnolence	0	0	1(1)	0
Dizziness postural	0	0	1(1)	0
Vomiting	0	0	1(1)	0
Chest discomfort	0	0	1(1)	0
Conjunctival oedema	0	0	1(1)	0
γ-glutamyltransferase increased	1(1)	0	0	0
Blood bilirubin increased	1(1)	0	0	0
Acute sinusitis	1(1)	0	0	0
Diarrhoea	1(1)	0	0	0
Ear pain	1(1)	0	0	0
Calculus ureteric	1(1)	0	0	0
Serious Adverse Events - On-Therapy				
n (%) [n considered by the investigator to be related to study medication]				
	FP Placebo (N=74)	FP (N=148)	FF Placebo (N=72)	FF 110µg (N=149)

Subjects with non-fatal SAE(s), n (%)	0	0	0	0
Subjects with fatal SAE(s), n (%)	0	0	0	0

Conclusion:

- This study demonstrated non-inferiority of FF aqueous nasal spray (110µg/day, once daily) to FP aqueous nasal spray (200µg/day, twice daily) in the primary endpoint “mean change from baseline over the entire treatment period in 3TNSS.” Although no statistical analysis was performed, FF 110µg and FP were comparable in the secondary endpoints, suggesting that the two active treatments are comparable in treatment effect.
- A comparison between the FF 110µg and FF placebo groups demonstrated superiority of FF 110µg over FF placebo in the secondary efficacy endpoint “mean change from baseline in 3TNSS.” The FF 110µg group showed statistically significant improvements in all other secondary endpoints compared with the placebo group.
- There were no AEs that were specific to FF 110µg group or clinically significant.

Publications: No publication

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