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<b>Study No.:</b> FFR100650			
<b>Title:</b> Clinical Evaluation of GW685698 for Perennial Allergic Rhinitis - Dose-Finding Study by Double-Blind Comparative Method -			
<b>Rationale:</b> Fluticasone furoate (FF) is a novel corticosteroid with potent glucocorticoid activity. Although well-established efficacy and tolerability of intranasal corticosteroids in the treatment of allergic rhinitis are reported, there are no once daily products in Japan under existing circumstances. Therefore, FF is being developed as a first once daily nasal spray for allergic rhinitis in Japan.			
<b>Phase:</b> II			
<b>Study Period:</b> 16 September 2004 to 11 December 2004			
<b>Study Design:</b> A randomized, double-blind, placebo-controlled, parallel group, multicenter study.			
<b>Centres:</b> Three centres in Japan			
<b>Indication:</b> Perennial allergic rhinitis			
<b>Treatment:</b> Subjects were randomized to a 2-week treatment with once-daily (QD) FF nasal spray 110µg, FF nasal spray 220µg, or vehicle placebo nasal spray.			
<b>Objectives:</b> The purpose of this study was to evaluate the efficacy and safety of FF in comparison with placebo when the investigational drug (110µg or 220µg) was sprayed into the nostril once daily for 2 weeks in patients with perennial allergic rhinitis, and to find the recommended dose for allergic rhinitis.			
<b>Primary Outcome/Efficacy Variable:</b> Mean change from baseline over the entire treatment period in 3 Total Nasal Symptom Score (3TNSS). 3TNSS is the sum (0 to 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 allergy diary.			
<b>Secondary Outcome/Efficacy Variable(s):</b>			
<ul style="list-style-type: none"> <li>• Mean change from baseline over Week1 and Week 2, and mean percent change from baseline over the entire treatment period in 3TNSS.</li> <li>• Mean change from baseline over the entire treatment period, Week 1 and Week 2, and mean percent change from baseline over the entire treatment period in 4 total nasal symptom score (4TNSS*).</li> <li>• Mean change from baseline over the entire treatment period, Week 1 and Week 2 in individual nasal symptom scores (sneezing, rhinorrhea, nasal congestion and nasal itching).</li> <li>• Time (number of days) to the onset of treatment effect in terms of the change from baseline in 3TNSS.</li> <li>• Time (number of days) to maximal treatment effect relative to placebo in terms of the change from baseline in 3TNSS.</li> <li>• Mean change from baseline over the entire treatment period, Week 1 and Week 2 in disturbance to daily life score.</li> </ul> <p>* 4TNSS is the sum (0 to 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 allergy diary.</p>			
<b>Statistical Methods:</b> The Full Analysis Set (FAS) was the primary population for efficacy analyses. The primary efficacy measure was the mean change from baseline over the entire treatment period in 3TNSS. The primary analysis method was the analysis of covariance adjusting for study site, baseline, age and gender. The multiple comparisons between each of the two active doses and placebo were controlled at 0.05 significance level using Dunnett's method. Adjusted mean changes from baseline were summarized for all treatment groups and compared to that in placebo group. The 95% simultaneous confidence interval for the mean difference (active vs. placebo) was also reported.			
<b>Study Population:</b> Patients with perennial allergic rhinitis who were positive in a) skin test or serum IgE antibody quantitation, and positive either in b) nasal challenge test or c) test for eosinophil count in rhinorrhea. The patients should have been outpatients at age 16 years and older with 3 total nasal symptom score (sneezing, rhinorrhea and nasal congestion) of 4.0 and more during the 4 consecutive days just prior to Visit 2 (start date of study medication).			
<b>Number of Subjects:</b>	<b>FF Placebo</b>	<b>FF 110µg</b>	<b>FF 220µg</b>
Planned, N	80	80	80
Randomised, N	79	80	81
Completed, n (%)	72(91)	79(99)	78(96)
Total Number Subjects Withdrawn, n (%)	7(9)	1(1)	3(4)
Withdrawn due to Adverse Events, n (%)	3(4)	1(1)	2(2)
Withdrawn due to Lack of Efficacy, n (%)	0	0	0

Withdrawn for other reasons, n (%)		4(5)	0	1(1)
<b>Demographics</b>		<b>FF Placebo</b>	<b>FF 110µg</b>	<b>FF 220µg</b>
N (FAS/PPS/SP)		79/77/79	80/80/80	81/80/81
Females: Males		23:56	23:57	32:49
Mean Age, years (SD)		29.7(9.28)	31.0(10.42)	29.3(9.36)
East/Southeast Asians, n (%)		79(100)	80(100)	81(100)
<b>Primary Efficacy Results: Mean Change from baseline over the entire treatment period in 3TNSS (FAS)</b>				
		<b>FF Placebo (N=79)</b>	<b>FF 110µg (N=80)</b>	<b>FF 220µg (N=81)</b>
Mean (SD)		-1.3(1.47)	-2.0(1.56)	-1.9(1.46)
Adjusted mean (SE)		-1.16(0.165)	-1.95(0.163)	-2.14(0.160)
Adjusted mean difference from placebo		-	-0.791	-0.985
95% Simultaneous confidence interval		-	-1.29, -0.30	-1.50, -0.47
p-value (using Dunnett's method)		-	<0.001	<0.001
<b>Secondary Outcome Variable(s): FAS</b>				
		<b>FF Placebo</b>	<b>FF 110µg</b>	<b>FF 220µg</b>
Mean change from baseline in 3TNSS				
Week 1	n	79	80	81
	Adjusted mean (SE)	-0.99(0.162)	-1.76(0.160)	-1.92(0.157)
	Adjusted mean difference from placebo	-	-0.769	-0.930
	95% Simultaneous confidence interval	-	-1.26, -0.28	-1.43, -0.43
Week 2	n	75	79	79
	Adjusted mean (SE)	-1.34(0.192)	-2.13(0.186)	-2.37(0.183)
	Adjusted mean difference from placebo	-	-0.787	-1.030
	95% Simultaneous confidence interval	-	-1.36, -0.21	-1.62, -0.44
Mean percent change from baseline in 3TNSS				
Entire treatment period	n	79	80	81
	Adjusted mean (SE)	-18.05(2.676)	-30.13(2.642)	-34.25(2.591)
	Adjusted mean difference from placebo	-	-12.081	-16.199
	95% Simultaneous confidence interval	-	-20.12, -4.04	-24.50, -7.89
Mean change from baseline in 4TNSS				
Week 1	n	79	80	81
	Adjusted mean (SE)	-1.30(0.211)	-2.34(0.208)	-2.39(0.202)
	Adjusted mean difference from placebo	-	-1.045	-1.090
	95% Simultaneous confidence interval	-	-1.68, -0.41	-1.74, -0.44
Week 2	n	75	79	79
	Adjusted mean (SE)	-1.71(0.245)	-2.83(0.239)	-2.99(0.233)
	Adjusted mean difference from placebo	-	-1.119	-1.283
	95% Simultaneous confidence interval	-	-1.85, -0.39	-2.03, -0.53
Entire treatment period	n	79	80	81
	Adjusted mean (SE)	-1.50(0.215)	-2.59(0.212)	-2.69(0.206)
	Adjusted mean difference from placebo	-	-1.090	-1.183
	95% Simultaneous confidence interval	-	-1.74, -0.45	-1.85, -0.52
Mean percent change from baseline in 4TNSS				
Entire treatment period	n	79	80	81
	Adjusted mean (SE)	-19.10(2.749)	-32.15(2.713)	-33.97(2.640)
	Adjusted mean difference from placebo	-	-13.058	-14.873
	95% Simultaneous confidence interval	-	-21.31, -4.80	-23.34, -6.41
Mean change from baseline in individual nasal symptom scores: sneezing				
Week 1	n	79	80	81
	Adjusted mean (SE)	-0.24(0.058)	-0.57(0.058)	-0.55(0.056)
	Adjusted mean difference from placebo	-	-0.337	-0.311
	95% Simultaneous confidence interval	-	-0.51, -0.16	-0.49, -0.13
Week 2	n	75	79	79

	Adjusted mean (SE)	-0.35(0.066)	-0.69(0.065)	-0.72(0.063)
	Adjusted mean difference from placebo	-	-0.339	-0.363
	95% Simultaneous confidence interval	-	-0.54, -0.14	-0.57, -0.16
Entire treatment period	n	79	80	81
	Adjusted mean (SE)	-0.29(0.057)	-0.64(0.056)	-0.63(0.055)
	Adjusted mean difference from placebo	-	-0.347	-0.343
	95% Simultaneous confidence interval	-	-0.52, -0.18	-0.52, -0.17
Mean change from baseline in individual nasal symptom scores: rhinorrhea				
Week 1	n	79	80	81
	Adjusted mean (SE)	-0.35(0.059)	-0.62(0.058)	-0.72(0.057)
	Adjusted mean difference from placebo	-	-0.271	-0.363
	95% Simultaneous confidence interval	-	-0.45, -0.09	-0.54, -0.18
Week 2	n	75	79	79
	Adjusted mean (SE)	-0.48(0.072)	-0.79(0.070)	-0.89(0.068)
	Adjusted mean difference from placebo	-	-0.316	-0.414
	95% Simultaneous confidence interval	-	-0.53, -0.10	-0.63, -0.20
Entire treatment period	n	79	80	81
	Adjusted mean (SE)	-0.42(0.059)	-0.71(0.059)	-0.80(0.057)
	Adjusted mean difference from placebo	-	-0.290	-0.384
	95% Simultaneous confidence interval	-	-0.47, -0.11	-0.57, -0.20
Mean change from baseline in individual nasal symptom scores: nasal congestion				
Week 1	n	79	80	81
	Adjusted mean (SE)	-0.42(0.069)	-0.57(0.069)	-0.62(0.067)
	Adjusted mean difference from placebo	-	-0.149	-0.198
	95% Simultaneous confidence interval	-	-0.36, 0.06	-0.41, 0.02
Week 2	n	75	79	79
	Adjusted mean (SE)	-0.52(0.079)	-0.66(0.078)	-0.74(0.076)
	Adjusted mean difference from placebo	-	-0.138	-0.220
	95% Simultaneous confidence interval	-	-0.38, 0.10	-0.46, 0.02
Entire treatment period	n	79	80	81
	Adjusted mean (SE)	-0.47(0.069)	-0.62(0.069)	-0.68(0.067)
	Adjusted mean difference from placebo	-	-0.147	-0.209
	95% Simultaneous confidence interval	-	-0.36, 0.06	-0.42, 0.00
Mean change from baseline in individual nasal symptom scores: nasal itching				
Week 1	n	79	80	81
	Adjusted mean (SE)	-0.30(0.064)	-0.58(0.064)	-0.48(0.061)
	Adjusted mean difference from placebo	-	-0.280	-0.181
	95% Simultaneous confidence interval	-	-0.47, -0.09	-0.37, 0.01
Week 2	n	75	79	79
	Adjusted mean (SE)	-0.35(0.070)	-0.69(0.068)	-0.64(0.066)
	Adjusted mean difference from placebo	-	-0.343	-0.293
	95% Simultaneous confidence interval	-	-0.55, -0.13	-0.50, -0.08
Entire treatment period	n	79	80	81
	Adjusted mean (SE)	-0.33(0.062)	-0.64(0.062)	-0.56(0.059)
	Adjusted mean difference from placebo	-	-0.308	-0.227
	95% Simultaneous confidence interval	-	-0.50, -0.12	-0.42, -0.04
Time (number of days) to the onset of treatment effect in terms of the change from baseline in 3TNSS				
	n	-	80	81
	days	-	3	2
Time (number of days) to maximal treatment effect relative to placebo in terms of the change from baseline in 3TNSS				
	n	-	80	81
	days	-	7	7
Mean change from baseline in disturbance to daily life score				
Week 1	n	79	80	81

	Adjusted mean (SE)	-0.31(0.060)	-0.54(0.061)	-0.52(0.059)
	Adjusted mean difference from placebo	-	-0.222	-0.205
	95% Simultaneous confidence interval	-	-0.41, -0.04	-0.39, -0.02
Week 2	n	75	79	79
	Adjusted mean (SE)	-0.33(0.069)	-0.68(0.068)	-0.66(0.066)
	Adjusted mean difference from placebo	-	-0.347	-0.333
	95% Simultaneous confidence interval	-	-0.56, -0.14	-0.55, -0.12
Entire treatment period	n	79	80	81
	Adjusted mean (SE)	-0.33(0.060)	-0.61(0.060)	-0.59(0.058)
	Adjusted mean difference from placebo	-	-0.286	-0.265
	95% Simultaneous confidence interval	-	-0.47, -0.10	-0.45, -0.08

**Safety Results:** Safety population (SP).

AEs occurred after the start of treatment (treatment period + post-treatment period).

AE(s)	FF Placebo (N=79)	FF 110µg (N=80)	FF 220µg (N=81)
	Subject with any AE(s), n (%)		
Total	32(41)	20(25)	18(22)
Nasopharyngitis	11(14)	9(11)	5(6)
Headache	5(6)	1(1)	4(5)
Epistaxis	3(4)	1(1)	0
Blood cortisol decreased	2(3)	2(3)	0
White blood cell count increased	2(3)	1(1)	0
Pharyngolaryngeal pain	1(1)	1(1)	2(2)
Abdominal pain upper	0	0	2(2)
Back pain	1(1)	0	1(1)
Malaise	0	1(1)	1(1)
Gastroenteritis viral	0	0	1(1)
Acute tonsillitis	0	0	1(1)
Herpes simplex	0	0	1(1)
Nasal abscess	0	0	1(1)
Feeling hot	0	0	1(1)
Constipation	0	0	1(1)
Neck pain	0	0	1(1)
Hyperlipidaemia	0	0	1(1)
Vaginal candidiasis	0	1(1)	0
Lymphocyte count decreased	0	1(1)	0
Neutrophil count increased	0	1(1)	0
Pharynx discomfort	0	1(1)	0
Rhinalgia	0	1(1)	0
Feeling abnormal	0	1(1)	0
Venipuncture site haemorrhage	0	1(1)	0
Asthenia	0	1(1)	0
Joint sprain	0	1(1)	0
Pharyngitis	1(1)	0	0
Aspartate aminotransferase increased	1(1)	0	0
Alanine aminotransferase increased	1(1)	0	0
Liver function test abnormal	1(1)	0	0
Blood bilirubin increased	1(1)	0	0
Blood chloride increased	1(1)	0	0
Eosinophil count increased	1(1)	0	0
Dry throat	1(1)	0	0
Chest discomfort	1(1)	0	0
Pyrexia	1(1)	0	0
Stomach discomfort	1(1)	0	0
Asthenopia	1(1)	0	0

Anaemia	1(1)	0	0
Eczema	1(1)	0	0
<b>Serious Adverse Events - On-Therapy</b>			
<b>n (%) [n considered by the investigator to be related to study medication]</b>			
	<b>FF Placebo (N=79)</b>	<b>FF 110µg (N=80)</b>	<b>FF 220µg (N=81)</b>
Subjects with non-fatal SAE(s), n (%)	0	0	0
Subjects with fatal SAE(s), n (%)	0	0	0

**Conclusion:**

- Two doses of FF (110µg and 220µg) demonstrated statistically significantly greater reductions over placebo for the primary efficacy endpoint of "mean change from baseline in 3TNSS over the entire treatment period", suggesting the improvement of perennial allergic rhinitis symptoms.
- Mean change in 3TNSS over the entire treatment period in 220µg showed a slightly higher dose-response effect compared to 110µg; however, mean change in 4TNSS over the entire treatment period and other secondary endpoints suggested nearly similar efficacy in 110µg and 220µg.
- None of the adverse events and the incidence rates reported in FF 110µg and 220µg treatment groups were deemed clinically significant.

**Publications:** No publication

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