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<b>Study No.:</b> FFR20002
<b>Title:</b> A randomized, double-blind, parallel group, placebo and active (prednisone) controlled, 6-week study of the effect of fluticasone furoate aqueous nasal spray 100mcg* QD on the hypothalamic pituitary adrenocortical (HPA) axis in adolescents and adults 12 to 65 years of age with perennial allergic rhinitis (PAR)
<b>Rationale:</b> Considering the potential for suppression of hypothalamic pituitary adrenocortical (HPA) axis function secondary to systemic exposure with a corticosteroid, a thorough assessment of adrenal function following treatment is required for the development of a corticosteroid by any route, including intranasal.
<b>Phase:</b> III
<b>Study Period:</b> 17Jan2005 - 31May2005
<b>Study Design:</b> Randomized, double-blind, placebo-controlled, active-controlled (prednisone for the last 7 days), parallel group
<b>Centres:</b> One in the US and one in Canada
<b>Indication:</b> Perennial allergic rhinitis
<b>Treatment:</b> Fluticasone furoate aqueous nasal spray 110mcg QD for 42 days plus placebo capsules for the last 7 days, or Vehicle placebo aqueous nasal spray QD for 42 days plus placebo capsules for the last 7 days, or Vehicle placebo aqueous nasal spray QD for 42 days plus prednisone 10mg QD for the last 7 days. *Note: The 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 primary objective of this study was to assess the effects of six weeks treatment with fluticasone furoate aqueous nasal spray 110mcg QD on HPA axis function compared to vehicle placebo aqueous nasal spray in adolescents and adults 12 to 65 years of age with PAR. Prednisone was included, as an active control during the last 7 days of study treatment, to ensure the assay was sufficiently sensitive to detect a drug effect.
<b>Primary Outcome/Efficacy Variable:</b> The primary study endpoint was the pharmacodynamic assessment, change from baseline (expressed as a ratio) in 24-hour serum cortisol weighted mean. Efficacy was not assessed as a primary outcome measurement.
<b>Secondary Outcome/Efficacy Variable(s):</b> Efficacy was not assessed as a secondary outcome measurement. No other secondary outcome variables were defined.
<b>Statistical Methods:</b> The primary endpoint and comparison of interest to assess HPA axis function was change from baseline (expressed as a ratio) in 24-hour serum cortisol weighted mean for fluticasone furoate 110mcg QD versus Placebo following 6-weeks of treatment for the Serum Cortisol Population. The secondary treatment comparison of interest was Prednisone 10mg QD vs. Placebo after 7 days of treatment, used as a positive control to test the sensitivity of the study methodology to detect differences in 24-hour serum cortisol. The serum cortisol weighted mean (0-24h) was determined for each subject at Visit 2 (Baseline) and Visit 6 (Week 6). The weighted mean was calculated by dividing the AUC over the 24 hour period by the sample collection time interval. A statistical analysis was performed on the ratio from baseline of the serum cortisol weighted mean 0-24h. Baseline was defined as the weighted mean 0-24h from Visit 2. The ratio was log transformed prior to analysis. An analysis of covariance (ANCOVA) model was fitted with baseline (loge transformed), center and treatment group as terms in the model. Baseline was fitted as a continuous covariate. Treatment ratios for each comparison were calculated by back-transforming the difference between the least square means. Using the pooled estimate of variance, 95% confidence intervals were calculated for the difference and then back-transformed. Non-inferiority would be demonstrated if the lower limit of the two sided 95% confidence interval for the geometric mean ratio of fluticasone furoate and placebo was greater than 0.80. In addition, the serum cortisol data were displayed in a manner that allowed identification and review of subjects with outlying cortisol values. The primary analysis was conducted on the Serum Cortisol (SC) population that excluded from the intent to treat (ITT) population subjects whose serum samples were considered to have confounding factors that would affect the interpretation of the results. An ITT analysis was also performed.
<b>Study Population:</b> Male and female subjects were eligible for randomization if they were 12 to 65 years of age and had a diagnosis of perennial allergic rhinitis. Additionally, a minimum symptom score of 5 out of 12 for average AM and PM reflective total nasal symptom scores on 4 of the 7 days just prior to domiciling was required as part of the randomization criteria.

	Placebo	Fluticasone Furoate (FF) 110mcg QD	Prednisone 10mg QD
Number of Subjects:			
Planned, N	50	50	10
Randomized, N	51	48	13
Completed, n (%)	44 (86)	44 (92)	12 (92)
Total Number Subjects Withdrawn, n (%)	7 (14)	4 (8)	1 (8)
Withdrawn due to Adverse Events n (%)	2 (4)	0	0
Withdrawn due to Withdrawal of Consent n (%)	1 (2)	3 (6)	1 (8)
Withdrawn for other reasons n (%)	4 (8)	1 (2)	0
<b>Demographics</b>			
N (ITT)	51	48	13
Females: Males	29:22	23:25	7:6
Mean Age, years (SD)	34.9 (11.90)	38.2 (13.63)	34.7 (13.06)
White, n	40	42	11
<b>Primary Efficacy Results:</b> Efficacy was not assessed as an outcome measure in this study. Pharmacodynamic results for the primary endpoint for the Serum Cortisol Population are presented.			
Summary of Derived Serum Cortisol Weighted Mean (0-24h) (mcg/dL)	<b>Placebo</b> N=44	<b>FF</b> 110mcg QD N=43	<b>Prednisone</b> 10mg QD N=12
<b>Baseline</b>			
N	44	43	12
Geometric Mean	8.63	9.01	8.60
Median	8.39	8.78	8.37
Min - Max	5.73-17.70	5.52-28.16	6.70-11.74
<b>Week 6</b>			
N	44	42	12
Geometric Mean	8.58	8.56	4.20
Median	8.08	8.28	4.71
Min - Max	2.85-23.96	5.24-20.50	2.54-5.61
<b>Ratio from Baseline</b>			
N	44	42	12
Geometric Mean	0.99	0.97	0.49
Median	1.00	1.01	0.50
Min - Max	0.49 - 2.06	0.61 - 1.49	0.34 - 0.67
<b>Treatment Comparison</b>	<b>Least Square Means</b>		<b>Treatment Ratio</b>
	<b>Active</b>	<b>Placebo</b>	<b>95% CI</b>
Fluticasone Furoate 110mcg QD vs. Placebo	0.97	0.99	0.98 (0.89,1.07)
Prednisone vs. Placebo	0.49	0.99	0.49 (0.43,0.57)
<b>Safety Results:</b> Adverse events during the treatment period (on-therapy) 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.			
	<b>Placebo</b>	<b>FF</b> 110mcg QD	<b>Prednisone</b> 10mg QD
<b>Most Frequent Adverse Events – On-Therapy</b>	<b>n (%)</b>		<b>n (%)</b>
Subjects with any AE(s), n(%)	27 (53)	30 (63)	3 (23)
Headache	8 (16)	8 (17)	0
Upper Respiratory Tract Infection	5 (10)	4 (8)	0
Epistaxis	2 (4)	7 (15)	1 (8)
Sinusitis	3 (6)	3 (6)	0
Nasopharyngitis	0	3 (6)	1 (8)
Cough	2 (4)	0	0
<b>Serious Adverse Events :</b> No fatal or non-fatal SAEs were reported during the study.]			

**Conclusion:** See publications below.

**Publications:**

Patel D, Ratner P, Clements D, Wu W, Faris M, Philpot E. Lack of effect on hypothalamic-pituitary-adrenal (HPA) axis function by once-daily fluticasone furoate\* nasal spray (FFNS) 110 mcg in adolescents and adults with perennial allergic rhinitis (PAR). \*USAN approved name. J Allergy Clin Immunol. 2007;119(1): S305 (abstract).

Patel P, Ratner P, Clements D, Wu W, Philpot E. Twenty-four hour serum and urine cortisol data support hypothalamic-pituitaryadrenocortical axis safety of once-daily fluticasone furoate\* nasal spray 110mcg in adolescents and adults with perennial allergic rhinitis.\*USAN approved name. Allergy 2007;62(Suppl. 83): 226 (abstract).

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