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Study No.: FFR100012:		
Title: A randomized, double-blind, parallel group, placebo controlled, 6-week study of the effect of fluticasone furoate aqueous nasal spray 100mcg* QD on the hypothalamic pituitary adrenocortical (HPA) axis in children 2 to <12 years of age with perennial allergic rhinitis (PAR)		
Rationale: 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.		
Phase: III		
Study Period: 04Feb2005 – 30Jun2005		
Study Design: Randomized, double-blind, placebo-controlled, parallel group		
Centers: ten in the US		
Indication: Perennial allergic rhinitis		
Treatment: Fluticasone furoate aqueous nasal spray 110mcg QD for 42 days, or Vehicle placebo aqueous nasal spray QD for 42 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 highest recommended dose of two sprays administered to each nostril as was utilized in this study.		
Objectives: 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 children 2 to <12 years of age with PAR.		
Primary Outcome/Efficacy Variable: The primary study endpoint was the change from baseline (expressed as a ratio) in 24-hour serum cortisol weighted mean. Efficacy was not assessed as a primary outcome measurement.		
Secondary Outcome/Efficacy Variable(s): Efficacy was not assessed as a secondary outcome measurement.		
Statistical Methods: The primary analysis was the comparison of fluticasone furoate 110mcg QD versus Placebo on change from baseline (expressed as a ratio) in 24-hour serum cortisol weighted mean following 6-weeks of treatment. The serum cortisol weighted mean (0-24h) was determined for each subject at Visit 2 (baseline) and Visit 5 (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 (log _e 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 derived serum cortisol ratio 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 who had more than 1 consecutive missing cortisol sample over a twenty four hour collection period at either Visit 2 (baseline) or Visit 5 (end of study) or subjects who received any protocol-prohibited medications (e.g. systemic or inhaled corticosteroids) that may have confounding effects on the interpretation of the results.		
Study Population: Male and female subjects were eligible for randomization if they were 2 to <12 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
Number of Subjects:		
Planned, N	50	50
Randomized, N	55	57
Completed, n (%)	52 (95)	53 (93)

Total Number Subjects Withdrawn, n (%)	3 (5)	4 (7)	
Withdrawn due to Adverse Events n (%)	1 (2)	1 (2)	
Withdrawn due to Protocol Violation n (%)	0	2 (4)	
Withdrawn for other reasons n (%)	2 (4)	1 (2)	
Demographics			
N (ITT)	55	57	
Females: Males	24:31	32:25	
Mean Age, years (SD)	6.4 (2.83)	6.1 (2.58)	
White, n	40	33	
Primary Efficacy Results: 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)	Placebo N=49	FF 110mcg QD N=52	
Baseline			
N	48	50	
Geometric Mean	6.71	6.88	
Median	6.41	7.02	
Min - Max	3.76-14.81	3.90-12.58	
Week 6			
N	48	50	
Geometric Mean	6.58	6.58	
Median	6.59	6.21	
Min - Max	3.66-15.02	3.77-17.88	
Ratio from Baseline			
N	47	48	
Geometric Mean	0.979	0.935	
Median	0.972	0.989	
Min - Max	0.52 - 1.66	0.56 - 1.86	
Treatment Comparison	Least Square Means	Treatment Ratio	95% CI
	Active	Placebo	
Fluticasone Furoate 110mcg QD vs. Placebo	0.94	0.97	0.97 (0.88,1.07)
	Placebo	FF 110mcg QD	
Most Frequent Adverse Events – On-Treatment	n (%)	n (%)	
Subjects with any AE(s)	9 (16)	10 (18)	
Pyrexia	0	2 (4)	
Serious Adverse Events - On-Therapy (n - considered by the investigator to be related to study medication)			
	Placebo	FF 110mcg QD	
	n (related)	n (related)	
Subjects with non-fatal SAEs, n	1 (0)	0	
Subjects with fatal SAEs, n	0	0	
Conclusion: See publications below			
Publications:			
Tripathy I, Sterling R, 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 children with perennial allergic rhinitis (PAR). *USAN approved name. J Allergy Clin Immunol. 2007;119(1): S232 (abstract).			
Clements D, Wu W, Philpot E. Videophone technology, a novel measure of true treatment compliance in a 6-week pediatric safety study of fluticasone furoate* nasal spray. *USAN approved name. J Allergy Clin Immunol. 2007;119(1): S306 (abstract).			
Ratner P, Tripathy I, Sterling R, Clements D, Faris M, Philpot E. Hypothalamic-pituitary-adrenocortical axis safety of once-daily fluticasone furoate nasal spray 110mcg in children with perennial allergic rhinitis supported by observed dosing via videophone. Allergy 2007;62(Suppl. 83): 130 (abstract).			

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