GSK Medicine: Fluticasone propionate

Study Number: RH01619

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Assess the Efficacy of Once-Daily Fluticasone Propionate Aqueous Nasal Spray 200mcg for 14 Days on Ocular Symptoms Associated with Seasonal Allergic Rhinitis (SAR)

Rationale: Although current Fluticasone propionate indication is limited to the treatment of nasal symptoms, several large scale studies have indicated that it also maintained adequate control of ocular symptoms. This study evaluated the efficacy of FP on ocular symptoms.

Phase: III

Study Period: 04 December 2012 - 16 February 2013

Study Design: Randomized, double-blind, placebo-controlled, parallel-group, multi-center study

Centres: 6 US sites

Indication: Seasonal Allergic Rhinitis

Treatment:

- Test Product: Fluticasone propionate aqueous nasal spray (50 mcg/spray) two sprays in each nostril (200 mcg total) once per day
- Reference Product: Placebo nasal spray two sprays in each nostril

Objectives: The primary objective of this study was to demonstrate that a 14-day course of Fluticasone propionate (200 mcg QD) is superior to placebo in relieving ocular symptoms associated with AR as determined by mean change from baseline in subject-rated reflective total ocular symptom scores (rTOSS)

Primary Outcome/Efficacy Variable: Mean change from baseline in rTOSS for a 14-day course

Secondary Outcome/Efficacy Variable(s):

- Mean change from baseline in both the AM rTOSS and PM rTOSS
- Mean change from baseline in both the individual AM reflective and PM reflective ocular symptom scores for each symptom of itching/burning, tearing/watering, redness
- Mean change from baseline in AM pre-dose Instantaneous Total Ocular Symptom Scores (iTOSS)
- End-of-treatment assessment of response to therapy for ocular symptoms
- Impact of rhinitis on activities of daily living and overall well-being using the Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) variables, overall scores, and individual domains
- Mean change from baseline in daily Reflective Nasal Congestion Symptom Score (rNCSS)
- Objective assessment of conjunctival redness

Statistical Methods: Subjects who were randomized and received at least one dose of study product were included in the safety and intent-to-treat (ITT) population. All safety analyses were conducted on safety population. All efficacy analyses were conducted on ITT population. Mean change from baseline in all efficacy parameters (except the end of treatment analysis) for a 14-day course was analyzed using an ANCOVA model using a linear fixed effects model. For end of treatment assessment, subjects' scores for the assessment of effectiveness of treatment were analyzed using a Cochran-Mantel-Haenszel test. Fluticasone propionate treatment was compared with placebo using the LS means from the ANCOVA model. This was two-sided test and was conducted at a significance level of α=0.05.

Study Population: The participants (both genders included) were ≥ 12 years of age with a diagnosis of SAR and AR symptoms of at least moderate severity. Females of child bearing potential practised a reliable method of contraception

	Fluticasone propionate	**Placebo**
Number of Subjects:	314	312
Planned, N	610	
Randomised, N	314	312
Completed, n (%)	310 (98.7)	304 (97.4)
Total Number Subjects Withdrawn, N (%)	4 (1.3)	8 (2.6)
Withdrawn due to Adverse Events n (%)	0	2 (0.6)
Withdrawn due to Lack of Efficacy n (%)	0	0
Withdrawal due to Lost to follow up	0	1(0.3)
Withdrawal due to Protocol Violation	2 (0.6)	1(0.3)
Withdrawal due to Withdrawal of Consent	1(0.3)	3 (1.0)
Withdrawal due to Other Reasons	1(0.3)	1(0.3)
Demographics	**Fluticasone propionate**	**Placebo**
N (Safety Population)	314	312
Females: Males	212:102	201:111
Mean Age, years (SD)	40.4 (14.55)	40.5 (16.36)

Race, n (%) • American Indian or Alaska Native • Asian • White • Black or African American • Native Hawaiian or Other Pacific Islander • Multiple	 1 (0.3) 1 (0.3) 272 (86.6) 36 (11.5) 1 (0.3) 3 (1.0)	 0 2 (0.6) 270 (86.5) 38 (12.2) 1 (0.3) 1 (0.3)
Children/adolescents (included in Total Safety Population) Age Group 12-17 n (%)	 28 (8.9)	 47 (15.1)

Primary Efficacy Results:
Mean Change from Baseline in Daily rTOSS Over the Treatment Period (ITT Population)

	Fluticasone propionate (N=314)	**Placebo (N=312)**
Mean Baseline (SD)	6.75 (1.364)	6.98 (1.365)
Mean Change from Baseline (SD)	-0.91 (1.625)	-0.63 (1.525)
Least Square (LS) Mean (SE)[1]	-0.97 (0.083)	-0.61 (0.084)
LS Mean Difference between treatments[1]	-0.36	
95% Confidence Interval[1]	(-0.59, -0.13)	
p-value[1]	0.0024	

[1]From ANCOVA model: Treatment and site as fixed factors and baseline score as covariate. LS mean difference is Fluticasone propionate *minus* placebo.

Secondary Outcome Results:

1. Mean Change from Baseline in AM rTOSS and PM rTOSS Over the Treatment Period (ITT Population)

	AM rTOSS		**PM rTOSS**	
	Fluticasone propionate (N=314)	**Placebo (N=312)**	**Fluticasone propionate (N=314)**	**Placebo (N=312)**
Mean Baseline (SD)	6.88 (1.358)	7.01 (1.391)	6.63 (1.497)	6.95 (1.434)
Mean Change from Baseline (SD)	-0.96 (1.627)	-0.68 (1.573)	-0.87 (1.735)	-0.60 (1.577)
LS Mean (SE)[1]	-1.00 (0.084)	-0.67 (0.085)	-0.96 (0.087)	-0.55 (0.087)
LS Mean Difference between treatments[1]	-0.33		-0.41	
95% Confidence Interval[1]	(-0.56, -0.10)		(-0.65, -0.17)	
p-value[1]	0.0057		0.0009	

[1]From ANCOVA model: Treatment and site as fixed factors and baseline score as covariate. LS mean difference is Fluticasone propionate *minus* placebo.

2. Mean change from baseline in both the individual AM reflective and PM reflective ocular symptom scores

2a. Mean Change from Baseline in AM and PM Reflective Symptom Scores for Eye Itching/Burning (ITT Population)

	AM Scores		**PM Scores**	
	Fluticasone propionate (N=314)	**Placebo (N=312)**	**Fluticasone propionate (N=314)**	**Placebo (N=312)**
Mean Baseline (SD)	2.41 (0.468)	2.47 (0.450)	2.34 (0.512)	2.45 (0.451)
Mean Change from Baseline (SD)	-0.35 (0.581)	-0.28 (0.553)	-0.33 (0.626)	-0.24 (0.554)
LS Mean (SE)[1]	-0.37 (0.029)	-0.27 (0.029)	-0.37 (0.030)	-0.22 (0.030)
LS Mean Difference between treatments[1]	-0.10		-0.15	
95% Confidence Interval[1]	(-0.19, -0.02)		(-0.23, -0.06)	
p-value[1]	0.0117		0.0005	

[1]From ANCOVA model: Treatment and site as fixed factors and baseline score as covariate. LS mean difference is Fluticasone propionate *minus* placebo.

2b. Mean Change from Baseline in AM and PM Reflective Symptom Scores for Eye Tearing/Watering (ITT Population)

	AM Scores		**PM Scores**	
	Fluticasone propionate (N=314)	**Placebo (N=312)**	**Fluticasone propionate (N=314)**	**Placebo (N=312)**
Mean Baseline (SD)	2.28 (0.544)	2.34 (0.532)	2.19 (0.599)	2.29 (0.570)
Mean Change from Baseline (SD)	-0.35 (0.596)	-0.24 (0.589)	-0.32 (0.653)	-0.19 (0.586)
LS Mean (SE)[1]	-0.36 (0.031)	-0.23 (0.031)	-0.35 (0.031)	-0.17 (0.032)

LS Mean Difference between treatments[1]	-0.13		-0.18	
95% Confidence Interval[1]	(-0.22, -0.05)		(-0.26, -0.09)	
p-value[1]	0.0023		<.0001	
[1]From ANCOVA model: Treatment and site as fixed factors and baseline score as covariate. LS mean difference is Fluticasone propionate *minus* placebo.				
2c. Mean Change from Baseline in Daily Reflective Symptom Scores for Eye Redness				
	AM Scores		**PM Scores**	
	Fluticasone propionate (N=314)	**Placebo (N=312)**	**Fluticasone propionate (N=314)**	**Placebo (N=312)**
Mean Baseline (SD)	2.19 (0.570)	2.20 (0.617)	2.10 (0.611)	2.21 (0.619)
Mean Change from Baseline (SD)	-0.26 (0.597)	-0.17 (0.613)	-0.22 (0.628)	-0.17 (0.635)
LS Mean (SE)[1]	-0.26 (0.031)	-0.17 (0.031)	-0.25 (0.032)	-0.15 (0.032)
LS Mean Difference between treatments[1]	-0.10		-0.10	
95% Confidence Interval[1]	(-0.18, -0.01)		(-0.19, -0.01)	
p-value[1]	0.0304		0.0361	
[1]From ANCOVA model: Treatment and site as fixed factors and baseline score as covariate. LS mean difference is Fluticasone propionate *minus* placebo.				
3. Mean Change from Baseline in AM Pre-Dose iTOSS (ITT Population)				
	Fluticasone propionate (N=314)		**Placebo (N=312)**	
Mean Baseline (SD)	6.81 (1.399)		6.89 (1.360)	
Mean Change from Baseline (SD)	-0.80 (1.443)		-0.55 (1.531)	
LS Mean (SE)[1]	-0.83 (0.079)		-0.55 (0.080)	
LS Mean Difference between treatments[1]	-0.28			
95% Confidence Interval[1]	(-0.50, -0.06)			
p-value[1]	0.0129			
[1]From ANCOVA model: Treatment and site as fixed factors and baseline score as covariate. LS mean difference is Fluticasone propionate *minus* placebo.				
4. End-of-Treatment Assessment of Response to Therapy for Ocular Symptoms				
Response	**Fluticasone propionate (N=314)**		**Placebo (N=312)**	
No Response Provided (n)	1		3	
Response Provided (n)	313		309	
Significantly Improved	22 (7.0)		16 (5.2)	
Moderately Improved	76 (24.3)		59 (19.1)	
Mildly Improved	79 (25.2)		71 (23.0)	
No Change	81 (25.9)		97 (31.4)	
Mildly Worse	21 (6.7)		20 (6.5)	
Moderately Worse	24 (7.7)		24 (7.8)	
Significantly Worse	10 (3.2)		22 (7.1)	
Between Treatment p-value*	0.0118			
*Using Cochran-Mantel-Haenszel test controlling for investigative site.				
5. Mean Change from Baseline in MiniRQLQ Scores (ITT Population)				
	Fluticasone propionate		**Placebo**	
N	314		311	
Mean Baseline (SD)	4.30 (0.981)		4.24 (1.038)	
Mean Change from Baseline (SD)	-0.98 (1.311)		-0.49 (1.091)	
LS Mean (SE)[1]	-0.98 (0.065)		-0.51 (0.065)	
LS Mean Difference between treatments[1]	-0.47*			
ACTIVITIES				
N	314		311	
Mean Baseline (SD)	4.17 (1.134)		4.03 (1.253)	
Mean Change from Baseline (SD)	-0.93 (1.384)		-0.39 (1.269)	
LS Mean (SE)[1]	-0.91 (0.069)		-0.42 (0.070)	
LS Mean Difference between treatments[1]	-0.49*			
Practical Problems				

N	314	311
Mean Baseline (SD)	4.76 (1.035)	4.69 (1.033)
Mean Change from Baseline (SD)	-1.04 (1.476)	-0.57 (1.258)
LS Mean (SE)[1]	-1.03 (0.073)	-0.59 (0.073)
LS Mean Difference between treatments[1]	-0.44*	
Nose Symptoms		
N	313	310
Mean Baseline (SD)	4.48 (1.093)	4.32 (1.078)
Mean Change from Baseline (SD)	-1.09 (1.456)	-0.50 (1.257)
LS Mean (SE)[1]	-1.07 (0.071)	-0.54 (0.072)
LS Mean Difference between treatments[1]	-0.53*	
Eye Symptoms		
N	313	310
Mean Baseline (SD)	4.41 (1.118)	4.43 (1.206)
Mean Change from Baseline (SD)	-0.98 (1.512)	-0.55 (1.284)
LS Mean (SE)[1]	-1.00 (0.074)	-0.56 (0.074)
LS Mean Difference between treatments[1]	-0.44*	
Other Symptoms		
N	313	310
Mean Baseline (SD)	3.85 (1.379)	3.87 (1.434)
Mean Change from Baseline (SD)	-0.89 (1.607)	-0.48 (1.294)
LS Mean (SE)[1]	-0.91 (0.076)	-0.49 (0.077)
LS Mean Difference between treatments[1]	-0.42*	
*LS mean difference over placebo for all domains and overall score was statistically significant (p<0.0001). [1]From ANCOVA model: Treatment and site as fixed factors and baseline score as covariate. LS mean difference is Fluticasone propionate *minus* placebo.		

6. Mean Change from Baseline in Daily rNCSS Over the Treatment Period (ITT Population)

	Fluticasone propionate (N=314)	**Placebo (N=312)**
Mean Baseline (SD)	2.54 (0.381)	2.56 (0.363)
Mean Change from Baseline (SD)	-0.34 (0.547)	-0.20 (0.443)
LS Mean (SE)[1]	-0.35 (0.027)	-0.21 (0.027)
LS Mean Difference between treatments[1]	-0.14	
95% Confidence Interval[1]	(-0.22, -0.07)	
p-value[1]	0.0002	
[1]From ANCOVA model: Treatment and site as fixed factors and baseline score as covariate. LS mean difference is Fluticasone propionate *minus* placebo.		

7. Mean Change from Baseline in Objective Assessment of Conjunctival Redness (ITT Population)

	Fluticasone propionate (N=314)	**Placebo (N=312)**
Mean Baseline (SD)	1.77 (0.723)	1.71 (0.696)
Mean Change from Baseline (SD)	-0.20 (0.815)	-0.15 (0.736)
LS Mean (SE)[1]	-0.20 (0.038)	-0.19 (0.039)
LS Mean Difference between treatments[1]	-0.01	
95% Confidence Interval	(-0.12, 0.10)	
p-value	0.8586	
[1]From ANCOVA model: Treatment and site as fixed factors and baseline score as covariate. LS mean difference is Fluticasone propionate *minus* placebo.		

Safety Results: AEs were regarded as treatment emergent if they occurred on or after the onset date and time of first randomized treatment dose at Visit 3 (Baseline). All other AEs data prior to this were termed as pre-treatment.

Adverse Events – On-Therapy (By System Organ Class and Preferred Term)	**Fluticasone propionate (N=314)**	**Placebo (N=312)**
Subjects with any AE(s), n(%)	8 (2.5)	8 (2.6)
General Disorders And Administration Site Conditions		
Pain	0	1 (0.3)
Pyrexia	1 (0.3)	2 (0.6)
Thirst	1 (0.3)	0

Infections and Infestations		
Bronchitis	0	2 (0.6)
Gastroenteritis Viral	1 (0.3)	0
Influenza	0	1 (0.3)
Nervous System Disorders		
Headache	2 (0.6)	0
Migraine	0	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	0	1 (0.3)
Respiratory Tract Congestion	0	1 (0.3)
Throat Irritation	1 (0.3)	0
Cardiac Disorders		
Palpitations	1 (0.3)	0
Immune System Disorders		
Hypersensitivity	0	1 (0.3)
Injury, Poisoning And Procedural Complications		
Laceration	1 (0.3)	0
Skin and Subcutaneous Tissue Disorders		
Dermatitis	0	1 (0.3)
Vascular Disorders		
Hypertension	1 (0.3)	0
Serious Adverse Events - On-Therapy		
Subjects with non-fatal SAEs, n (%)	0	0
Subjects with fatal SAEs, n (%)	0	0