

**Clinical Review**

Anthony G. Durmowicz, M.D.

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mm Hg at more than one treatment visit. Of these 12 subjects, all but one had values of 21 or 22 mm Hg (7 had values of 21 mm Hg and 4 had values of 22 mm Hg). This subject (Subject 1332), whose baseline intraocular pressure measurements had been 12 and 14 mm Hg for the left and right eye, respectively, had a measurement of 24 mm Hg in the left eye and 20 mm Hg in the right eye at Week 52 [Section 7.9.3.1 and Table 36 FFR102123 Study Report, pages 98 and 100].

**Reviewer's Comment:** *While the increases in intraocular pressure for some individual subjects were not much greater than normal, the fact that all 12 increases > 20 mm Hg were in subjects in the FF100 group supports the idea that long-term treatment with FF100 may effect intraocular pressure. While not likely to prevent approval, a Phase 4 eye safety study may be appropriate.*

Fundoscopy cup measurements as a percentage of disc measurements were measured through the 52 week time point in 423 subjects in the FF100 group and in 136 subjects who received placebo. The sponsor-defined threshold limit for cup to disc ratio was > 66%. Baseline mean cup to disc ratios were much the same for the 2 treatment groups, approximately 16.5% for placebo and 17.5% for the FF100 group. The mean cup to disc ratios demonstrated very little change over the course of the study, 0.5% for the left eye and 0.4% for the right eye in subjects who received placebo and -0.9% for the left eye and -0.8% for the right eye in subjects who received FF100 [Table 38 FFR102123 Study Report, page 101].

Three subjects (2 subjects in the FF100 group and 1 subject in the placebo group) had changes in cup to disc ratio to > 66% during the study. The finding of increased cup to disc ratio did not correlate to measurements of increased intraocular pressure as none of the 12 subjects with on-treatment intraocular pressure values > 20 mm Hg had a fundoscopic cup to disc ratio of > 66% at any time during the study.

Slit lamp evaluation of the eye demonstrated corneal abnormalities and pinguecula as the only 2 findings that were present in > 1% of subjects from either treatment group. The incidence of these findings was similar in each treatment group at 1-3%. Cataracts were observed at baseline in 9 subjects in the FF100 group and by 8 subjects in the placebo group, however, long-term follow-up of these subjects is not available as 16 of the 17 subjects were withdrawn prematurely from the study because of a protocol violation. Seven subjects (6 (1%) in the FF100 group and 1 (<1%) in the placebo group) had cataracts identified during the study period that were not present at baseline. A summary of subjects who developed cataracts during the study is presented in the following table.

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**Summary of Subjects Who Developed Cataracts That Were Not Present at Baseline (ITT Population)** [Table 40 FFR102123 Study Report, page 103]

Subject (age/sex)	Visit	Left Eye	Right Eye	AE reported	AE Drug-related	AE led to withdrawal
<b>Placebo (N=201)</b>						
1631 (43/M)	Baseline	No	No			
	Week 12	Posterior subcapsular (trace)	No	Yes	Yes	Yes
	EWV	Posterior subcapsular (trace)	No			
<b>Fluticasone furoate nasal spray 100mcg (N=605)</b>						
17 (15/F)	Baseline	No	No			
	Week 12	No	No			
	Week 24	No	No			
	Week 52	Posterior subcapsular (trace)	No	Yes	Yes	No
1033 (14/M)	Baseline	No	No			
	Week 12	No	No			
	Week 24	No	No			
	Week 52	Posterior subcapsular (definite)	No	Yes	Yes	No
230 (63/F)	Baseline	No	No			
	Week 12	Cortical	Cortical	Yes	Yes	No
	Week 24	Cortical	Cortical			
	Week 52	No	No			
897 (66/M)	Baseline	Cortical	No			
	EWV	Nuclear Sclerotic	Cortical	No	-	-
919 (72/M)	Baseline	No	No			
	Week 12	Nuclear sclerotic	Nuclear Sclerotic	No	-	-
	EWV	No	No			
811 (23/M)	Baseline	No	No			
	Week 12	No	No			
	Week 24	no	No			
	Week 52	Nuclear Sclerotic	Nuclear sclerotic	Yes	Yes	No

Source Data: Table 7.64 and Table 7.15  
 EWV = Early Withdrawal Visit

Posterior subcapsular cataracts were observed in 1 placebo subject who withdrew from the study after Week 12 and for 2 subjects in the FF100 group, both of whom had a

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posterior subcapsular cataract noted in the left eye at the Week 52 visit.

*Reviewer's Comment: These findings, along with the intraocular pressure findings noted above, again support the possibility that long-term (at least a year) use of FF100 may have deleterious effects on the eye, increased intraocular pressure and subcapsular cataracts.*

**Vital Signs and Electrocardiograms**

Mean changes in vital signs were similar and clinically insignificant in the 2 treatment groups. No subjects had an ECG with a clinically significant abnormality at baseline. Two subjects, one in each treatment group had clinically significant changes in ECG during the study. Subject 2205, in the FF100 group had ventricular bigeminy noted on the ECG at Week 52 and Subject 906, in the placebo group, had left bundle branch block. The block had been noted as a finding at screening but at that time it was not considered clinically significant. The abnormal ECG was recorded as an AE but was not considered to be drug-related by the investigator [Sections 7.9.4 and 7.9.5 FFR102123 Study Report, pages 104-105].

**Summary and Discussion**

This was a 52-week, randomized, double blind comparison of the safety of fluticasone furoate 100 mcg daily compared to vehicle placebo in subjects with PAR. The study was conducted at 75 sites in 13 countries throughout Europe. Of the 663 subjects enrolled, 73% completed the trial and compliance with the treatment regimen was > 94%. The large majority of the subjects were Caucasian and between 18 and 64 years of age. All had positive skin tests to one of a variety of perennial antigens, but predominantly dust mite. The primary objective of the study was to evaluate long-term safety.

To meet the requirements for long term exposure, 501 subjects were treated with FF100 for over 6 months and 400 were treated for 12 months. During the year of exposure 77% of the subjects experienced AEs, most of which are consistent with those commonly seen in studies of intranasal corticosteroids used for the treatment of allergic rhinitis. Epistaxis was the one AE that stood out as having a significantly greater incidence, and, possibly greater severity, in the FF100 group than placebo, 20% vs 8%. In addition, 15 subjects withdrew from the FF100 group due to epistaxis, versus none in the placebo group. The incidence of and withdrawals due to epistaxis in subjects treated with FF100 is somewhat greater than that observed for other marketed nasal steroid preparations (see review above). There were no deaths reported, serious adverse events were uncommon and none was likely to be related to drug ingestion. Nasal exams demonstrated slightly more mucosal crusting and bleeding in the FF100 group compared to placebo. The number of ulcerations observed in each treatment group was comparable and there were no septal perforations noted. The results of the ophthalmic examinations showed no significant changes in mean intraocular pressure or fundoscopic cup to disc ratios, however, more subjects in the FF100 group had intraocular pressure measurements above the upper limit of normal (12 subjects vs none in the placebo group) during the course of the study. Three subjects developed posterior subcapsular cataracts during the course of the study, 2 in the FF100 group (both at Week 52) and 1 in the placebo group (at Week

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12). The placebo subject subsequently withdrew from the study. The evaluation of the HPA-axis consisted of measurements of 24-hour urine cortisol excretion and baseline and 3 subsequent time points, Weeks 12, 24, and 52. The subjects were not domiciled for the urine collections, however, criteria were established for adequacy of the collections. There was no evidence of significant effects of FF100 on the HPA-axis. Efficacy was assessed as a secondary objective by daily diary determinations of rTNSS. While no statistical analyses were conducted, the numerically greater decreases in rTNSS for the FF100 group supported compliance with administration of study drug during the course of the study.

In summary, the findings of an incidence of epistaxis higher than other marketed nasal steroid preparations and increased intraocular pressure and posterior subcapsular cataracts occurring predominantly in those subjects treated with FF100 for up to a year suggests that FF100 is a very potent locally-acting corticosteroid. These findings are significant enough to require a Phase 4 commitment to further study the long-term local toxicities of fluticasone furoate.

**10.1.7 STUDY # FFR20002**

**A randomized, double-blind, parallel group, placebo and active (prednisone) controlled, 6-week study of the effect of GW685698X (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)**

**Protocol****Administrative**

Study initiated: January 17, 2005

Study completed: May 31, 2005

Clinical Centers: Two centers, one in the San Antonio, Texas, United States and one in Mississauga, Ontario, Canada

Study report dated: December 2005

Study Sponsor: GlaxoSmithKline (GSK)

Medical Officer: Kathy Rickard, M.D., GSK

**Objective/Rationale**

The primary objective of this study was to assess the effects of six weeks treatment with fluticasone furoate (FF) aqueous nasal spray 100mcg once daily on HPA axis function compared to vehicle nasal spray placebo 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.

**Study Design**

This was a randomized, double-blind, placebo- and active-controlled, parallel group, 6

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week study to assess the effects of fluticasone furoate aqueous nasal spray 100mcg once daily (FF100) on HPA axis function. Subjects were assigned in an approximately 4:4:1 ratio to one of the following three double-blind treatment groups:

- fluticasone furoate 100mcg QD (FF100) for 42 days plus placebo capsules for the last 7 days (48 subjects)
- placebo nasal spray QD for 42 days plus placebo capsules for the last 7 days (51 subjects)
- placebo nasal spray QD for 42 days plus prednisone 10mg QD for the last 7 days (11 subjects)

Subjects who satisfied the entry criteria entered a 7-14 day screening period. During the screening period, subjects scored their allergic rhinitis symptoms on a diary card in order to determine eligibility for randomization. After a minimum of 7 days, subjects who fulfilled the randomization criteria were randomly assigned to one of the 3 treatment groups listed above. Pharmacodynamic measurements of HPA axis function, including both urine and serum cortisol assessments, were conducted during 24-hour domiciled visits at the end of the screening and treatment periods. While efficacy was not studied in this study, a daily symptom diary including TNSS scores and confirmation of taking the daily dose of study medication was maintained. Subjects were seen in the clinic weekly at which time concomitant medications were assessed, diary cards collected, and vital signs and nasal exams performed. Safety assessments included assessments of adverse events (AEs), routine laboratory tests (chemistry and hematology), nasal examinations, vital signs, and 12-lead electrocardiograms.

*Reviewer's Comment: The study followed recommendations for conducting HPA axis evaluations as presented in the FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, 2003.*

## Study Population

### Inclusion Criteria

- Male or female  $\geq 12$  years of age
- Diagnosis of PAR to include:
  - Documented, positive skin test to an appropriate perennial allergen (animal dander, house dust mites, cockroaches and/or mold) or documented, in vitro test results for a specific IgE (RAST, PRIST, etc.) within the 12 months prior to Visit 1. A positive skin test during Visit 1 was also allowed.
  - Two-year medical history and past treatment of PAR.

Subjects who met the above criteria and who also had SAR and/or vasomotor rhinitis were eligible for randomization.

### Exclusion Criteria

Subjects were not eligible for inclusion in this study if any of the following criteria applied:

- Significant concomitant medical conditions. Significant was defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or which would confound the interpretation of

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the study results if the disease/condition exacerbated during the study.

- Asthma, with the exception of mild intermittent asthma [National Asthma Education and Prevention Program (NAEPP) Guidelines, 2002], or very mild asthma (Canada), Adult Asthma Consensus Guidelines Update 2003
- Bacterial or viral infection (e.g., common cold) of the eyes or upper respiratory tract within two weeks of Visit 1 or during the screening period
- Documented evidence of acute or significant chronic sinusitis, as determined by the individual investigator
- Current or history of glaucoma and/or cataracts or ocular herpes simplex
- Clinical evidence of a Candida infection of the nose or oropharynx at Visit 1 or prior to randomization
- History of adrenal insufficiency or history of shingles
- Use of corticosteroids, defined as:
  - Systemic (oral, intramuscular, intravenous) corticosteroids within 6 months prior to Visit 1.
  - Inhaled, ocular, or dermatological corticosteroids within eight weeks prior to Visit 1.
  - Intranasal corticosteroids within four weeks prior to Visit 1.
- Use of other allergy medications within the timeframe indicated relative to Visit 1:
  - Intranasal or ocular cromolyn within 14 days prior to Visit 1
  - Short-acting prescription and OTC antihistamines, including ocular **preparations and antihistamines contained in insomnia and ‘nighttime’** pain formulations taken for insomnia, within 3 days prior to Visit 1
  - Long-acting antihistamines within 10 days prior to Visit 1
  - Oral or intranasal decongestants within 3 days prior to Visit 1
  - Intranasal, oral, or inhaled anticholinergics within 3 days prior to Visit 1
  - Oral antileukotrienes within 3 days prior to Visit 1
  - Subcutaneous omalizumab (Xolair) within 5 months of Visit 1
  - Intranasal antihistamines within 2 weeks prior to Visit 1
- Use of immunosuppressive medications 8 weeks prior to screening and during the study
- Use of any medications that significantly inhibit the cytochrome P450 subfamily enzyme CYP3A4, including ritonavir and ketoconazole
- Immunotherapy (Subjects could be enrolled into the study if the immunotherapy was not initiated within 30 days of Visit 1, if the dose remained fixed over the 30 days prior to Visit 1, and the dose remained fixed for the duration of the study.
- Use of other medications or treatments that could affect the signs and symptoms of allergic rhinitis
- Current tobacco use
- Findings of a clinically significant, abnormal electrocardiogram (ECG)
- Findings of a clinically significant, abnormal clinical laboratory test
- Findings of morning (prior to 10 AM) serum cortisol assessment outside the normal reference range (<2mcg/dL for 12 to 17 years; and, <5mcg/dL for 18 to 65

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(years)

### **Randomization Criteria**

At Visit 2, subjects must have met the following criteria:

- The daily rTNSS on any 4 of the last 7 days prior to Visit 2 must have been  $\geq 5$ .
- The subject must have demonstrated the ability to comply with use of the daily diary card defined as completion of at least 80% of the assessments during the screening period.

### **Withdrawal Criteria**

Subject withdrawal from the study was required and Early Withdrawal procedures must be performed, when a subject:

- was significantly non-compliant with the requirements of the protocol
- had not completed the 6-week treatment period
- became pregnant
- had an adverse event that would, in the investigator's judgment, make continued participation in the study an unacceptable risk
- The treatment blind was broken for a subject (by other than GSK GCSP personnel)
- GlaxoSmithKline discontinued the study.

### **Study Procedures**

#### **Study Treatments**

FF100 or placebo nasal spray was administered for six weeks, while prednisone or placebo capsule was administered only during the last 7 days of the six-week treatment period. To deliver nasal spray medication, 2 sprays were administered into each nostril, alternating one spray in each nostril followed by a second spray in each nostril. To deliver capsule medication, one capsule was taken with food each morning. The first dose of intranasal study medication was self-administered in the clinic at the end of the first domiciled visit prior to discharge. The first dose of capsule study medication was self-administered the morning after the Week 5 visit. The last dose of intranasal and capsule study medication coincided with the planned domiciled visit at Week 6, was self administered in the clinic and was followed by 24-hour urine and timed serum and plasma samples which were collected relative to the time of dosing.

#### **Demographic and Baseline Assessments**

The following demographic and baseline information was obtained: age; sex; race; ethnicity, height, weight, duration of the subject's seasonal allergy, presence of perennial and/or vasomotor rhinitis, and results of skin prick test(s). All subjects also had a physical examination, vital signs assessment, nasal examination, 12-lead ECG, blood hematology and chemistry analyses, pregnancy testing (females). The subjects' self-rated symptom scores over the four days prior to randomization (including the morning of randomization) provided the baseline symptom assessment.

#### **Pharmacokinetic/Pharmacodynamic Assessments**

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Pharmacokinetic blood samples for determination of FF plasma levels were collected at the following times relative to the morning (prior to 10AM) dose given during Visit 6: 0, 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose.

Serum samples for serum cortisol assessments and 24-hour urine collections for urinary free cortisol excretion and 6-beta hydroxycortisol excretion were obtained during domiciled clinic visits (Visit 2/randomization and Visit 6/end-of-treatment). Blood samples to assess serum cortisol were collected at the following time points relative to the 24-hour serial sampling start time (0) which occurred between 8:00AM and 9:00AM at Visit 2: 0, 2, 4, 6, 8, 10, 12, 16, 22, and 24 hours after the start time. At Visit 6, blood samples were collected at the same times relative to the morning (prior to 10 AM) dose.

**Efficacy Evaluation**

Efficacy assessments were completed for the purpose of evaluating compliance with nasal spray study medication only. Throughout the study, subjects rated four nasal symptoms, rhinorrhea, nasal congestion, nasal itching, and sneezing, in a reflective and an instantaneous manner. Reflective symptom scores assessed the subject's symptoms over the preceding 12 hours and were recorded twice daily, once in the AM immediately before dosing and once in the PM 12 hours after dosing. Instantaneous symptom scores assessed the subject's symptoms at that moment and were recorded in the AM immediately before dosing. The Total Nasal Symptom Score (TNSS) was calculated from the diary entries as described for study FFR20001. The AM measurement before the first dose was included in the baseline measurement. The average AM and PM scores were calculated for each of the 42 days of treatment.

**Safety Evaluation**

The primary safety endpoints for the study consisted of the following assessments:

- Frequency and type of clinical adverse events
- Results of clinical laboratory tests (hematology and clinical chemistry)
- Results of gross nasal examinations
- Vital signs (systolic and diastolic blood pressures, heart rate)
- 12-lead electrocardiograms (ECGs)

**Data Analysis****Sample Size**

The sample size calculation was based on the number of subjects needed to demonstrate non-inferiority in serum cortisol weighted mean 0-24h between FF100 and placebo. Non-inferiority was demonstrated if the lower limit of the two-sided 95% confidence interval for the geometric mean ratio of GW685698X and placebo is greater than 0.80.

In previous healthy volunteer and patient studies, the estimated between-subject standard deviation (on the loge scale for 24-hour serum cortisol weighted mean) ranged from 0.18 to 0.31. Assuming a standard deviation of 0.30 with full data available for 40 subjects on FF100 and 40 subjects on placebo, this study will have approximately 90% power to

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demonstrate non-inferiority if there is no true difference between the treatment groups. In addition, with 10 subjects on prednisone, the study would have approximately 90% power to detect a geometric mean decrease in serum cortisol weighted mean of 30% when comparing prednisone to placebo.

### Study Populations

The primary analysis population for the assessment of HPA axis function was the Serum Cortisol (SC) Population. The SC Population was defined as the ITT Population excluding subjects who had any one of the following:

- two or more consecutive missing cortisol concentrations over a twenty-four hour collection period at either Visit 2 or Visit 6
- used a protocol-prohibited systemic (oral, intramuscular, intravenous) corticosteroid within six months prior to the start of any serum sample collection
- used a protocol-prohibited inhaled, ocular, and/or dermatological corticosteroid within eight weeks prior to the start time of any serum sample collection
- used a protocol-prohibited intranasal corticosteroid within 4 weeks prior to the start time of any serum sample collection

The Urinary Cortisol (UC) Population also supported the assessment of HPA axis function. The UC Population was defined as the ITT Population excluding subjects who had any one of the following:

- urine volumes of <600mL for female subjects and <800mL for male subjects, and 24-hour creatinine excretion below the lower limit of threshold range (defined as **mean – 2.5 SD, where the normal range is defined as mean ± 2.0 std**) collection time intervals outside  $24 \pm 2$  hours
- used a protocol-prohibited systemic (oral, intramuscular, intravenous) corticosteroid within six months prior to the start time of any urine sample collection
- used a protocol-prohibited inhaled, ocular, and/or dermatological corticosteroid within eight weeks prior to the start time of any urine sample collection
- used a protocol-prohibited intranasal corticosteroid within 4 weeks prior to the start time of any urine sample collection

The Intent-to-Treat (ITT) population was defined as all randomized subjects who receive at least one dose of study drug. The ITT population was used for all safety analyses.

### Primary and Secondary Analyses

The primary treatment comparison of interest was FF100 QD vs. Placebo. The primary endpoint was change from baseline in 24-hour serum cortisol weighted mean. The secondary treatment comparison of interest was Prednisone 10mg QD vs. Placebo after 7 days of treatment as a positive control to test the sensitivity of the study methodology to detect differences. Supporting pharmacodynamic endpoints included 24-hour urine assessments of HPA axis function.

While the primary analysis was conducted on the SC population an analysis was also

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performed on the ITT population. 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.

## Results

### Study Population

#### Disposition

A total of 183 subjects were screened for this study. One hundred and twelve subjects were randomized into the study (48 to the FF100 group, 13 to the prednisone group, and 51 to Placebo) and comprised the ITT population.

Eighty-nine percent of subjects completed the study. Premature withdrawals occurred for 12 (11%) subjects with 7 withdrawing from the placebo group, 1 from the prednisone group, and 4 from the FF100 group. Two subjects from the placebo group withdrew due to AEs (back pain and sinusitis) [Section 6.1 and Table 4 FFR20002 Study Report, pages 42-43].

Two subjects in the Placebo treatment group did not receive study treatment per the randomization schedule due to a site administrative error and were discontinued. Neither of these subjects was excluded from the SC or UC Populations [Section 6.2 FFR20002 Study Report, page 43].

The following table summarizes the populations analyzed.

#### Summary of Populations Analyzed [Table 5 FFR20002 Study Report, page 44]

	Number (%) of Subjects			
	Placebo	GW685698X 100mcg QD	Prednisone 10mg QD	Total
ITT	51 (100)	48 (100)	13 (100)	112 (100)
Serum Cortisol (SC)	44 (86)	43 (90)	12 (92)	99 (88)
Urine Cortisol (UC)	42 (82)	43 (90)	0	85 (76)
Pharmacokinetic Concentration	NA	44 (92) <sup>a</sup>	NA	44 (39)
Pharmacokinetic Parameter	NA	44 (92) <sup>a</sup>	NA	44 (39)

Source: Table 6.5, Table 6.14 – Table 6.19

a. All 44 subjects who completed the study in the GW685698X 100mcg QD treatment group were included in the PK analyses.

#### Demographics

Demographics were very similar across treatment groups. The mean age range for the ITT population was 36.3 years. The majority of the subjects were White (83%). Males and females were about equally represented at 47 and 53%, respectively. Eighty-five per

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cent of subjects reported having SAR in addition to PAR and 75% of subjects reported a duration of PAR for  $\geq 10$  years. Twenty-six per cent and 25% of subjects in the FF100 and placebo groups, respectively, also reported having perennial allergic rhinitis (PAR). Baseline symptoms were quite similar in the groups. The baseline daily rTNSS and AM iTNSS scores were 7.6 and 7.5, respectively indicating a population that had moderate symptoms during the screening period [Section 6.4 FFR20002 Study Report, page 44].

The nasal spray compliance rate during the treatment period, as determined by diary entry, was 98.4, 98.8, and 99.1% in the placebo, FF100, and prednisone groups, respectively. Regarding compliance with prednisone capsules, according to pill counts, the majority of subjects (8 [67%]) assigned to the prednisone treatment group took the medication correctly during the last 7 days of the study [Table 6 and Section 6.6.4 FFR 20002 Study Report, page 45-47].

*Reviewer's Comment: The fact that serum cortisol data unequivocally demonstrated the effects of prednisone after 7 days of treatment was also supportive of adequate compliance in this group.*

## Efficacy Results

### Primary Efficacy Outcome

No inferential statistical testing was planned or performed for TNSS recorded in subject diaries. However, the mean changes of -0.5, -1.4, and -0.7 in rTNSS over the entire 6-week treatment period for the placebo, FF100, and prednisone groups, respectively, supports adequate compliance in the FF100 group [Table 8 FFR20002 Study Report, page 47].

## Safety

The safety findings from this study are included in and will be fully reviewed in the Integrated Review of Safety in Section 7 of the main NDA review. This review will focus primarily on the effects of FF100 on suppression of the HPA axis.

### Extent of Exposure

Per protocol, subjects were to be dosed for 42 days. Eighty-six, 96, and 92% of subjects in the placebo, FF100, and prednisone groups, respectively, were exposed to between 41-45 days of nasal spray study drug and 92% (12 subjects) were exposed to prednisone 10mg QD for 5-9 days [Tables 9 and 10 FFR20002 Study Report, page 48].

### Adverse Events

Headache and epistaxis were the most frequently reported AEs during the study. The incidence of headache was similar between placebo and FF100 groups while epistaxis was seen more frequently in the FF100 group (7 subjects (15%) vs 2 subjects (4%) for placebo). The following table shows all AEs reported in  $\geq 2$  subjects during the treatment period.

### Adverse Events reported in $\geq 2$ subjects during the treatment period (ITT population)

[Table 11 FFR20002 Study Report, page 49]

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	Number (%) of Subjects		
	Placebo N=51	GW685698X 100mcg QD N=48	Prednisone 10mg QD N=13
<b>All AEs</b>			
<b>Any Event</b>	27 (53)	30 (63)	3 (23)
Headache	8 (16)	8 (17)	0
Epistaxis	2 (4)	7 (15)	1 (8)
Nasopharyngitis (cold syndrome)	0	3 (6)	1 (8)
<b>Drug-Related AEs</b>			
<b>Any Event</b>	2 (4)	4 (8)	1 (8)
Epistaxis	0	3 (6)	0

Source: Table 8.3, Table 8.5, and Table 8.10

#### Deaths, Serious Adverse Events, and Events Leading to Withdrawal

No deaths or SAEs were reported during the study.

Two subjects, both in the placebo group withdrew due to AEs, back pain and sinusitis.

#### Pregnancy

No subjects became pregnant during the study.

#### Laboratory Results

The majority of subjects in each treatment group had either no change in hematology or chemistry parameters or a shift into the normal range. Shifts to low for hemoglobin occurred to a greater degree in the FF100 and the prednisone groups, 6 (13%) and 3 (23%) subjects, respectively compared to 2 (4%) placebo subjects. There were 4 instances of abnormal chemistry laboratory values that were reported as AEs during the study, 2 instances of elevated glucose (1 FF100 group, 1 placebo), 1 instance of mildly elevated AST (FF100 group), and a mildly decreased WBC in a subject who experienced a herpes simplex infection (FF100 group). Otherwise, there were isolated laboratory test values outside the normal ranges for several subjects as assessed by shift table, no others were remarkable and no meaningful differences were seen between treatment groups

[Sections 8.7.2, 8.7.3 FFR20002 Study Report, pages 51-53].

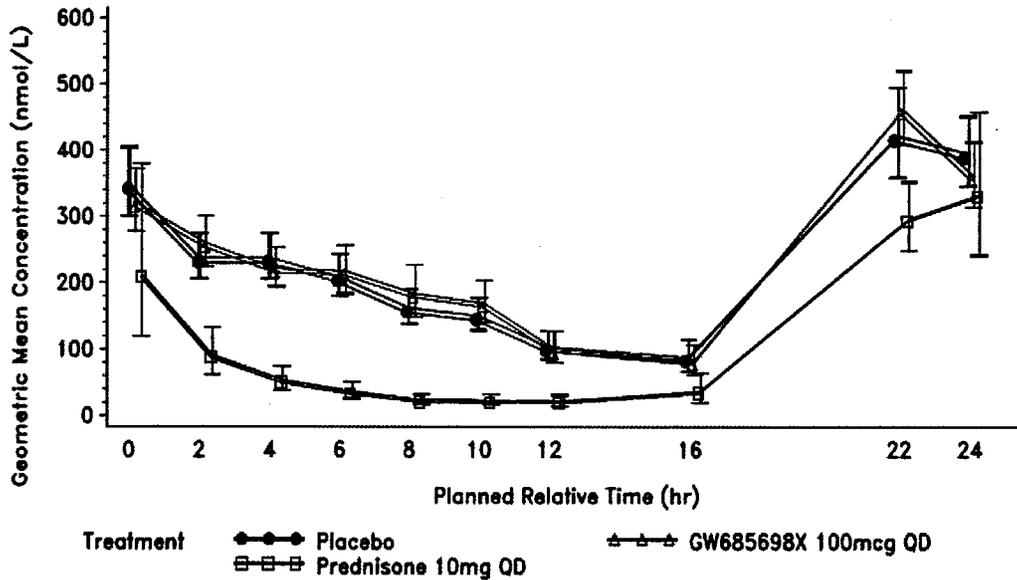
#### Nasal Exams, Vital Signs, and Electrocardiograms

Over the treatment period, there were no significant differences in the observance of or in worsening of nasal mucosal bleeding or ulceration in any of the treatment groups. No subjects had evidence of nasal candidiasis. There were no clinically meaningful adverse changes from baseline in vital signs. One subject in the FF100 group had what was felt to be a clinically relevant change from baseline in ECG, a second-degree atrioventricular block that was judged mild and resolved on the same day. This change from baseline was reported as an AE [Sections 8.8.1-8.8.3 FFR20002 Study Report, page 53-55].

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**Pharmacodynamic (HPA axis) Results**

At Week 6 mean serum cortisol concentrations were similar for the FF100 and placebo groups but showed a marked reduction in the prednisone group (see figure below).

**Geometric Mean Serum Cortisol Concentration-Time Profile by Treatment Group at Week 6 (SC Population)** [Figure 1 FFR20002 Study Report, page 57]



The primary endpoint of the study was change from baseline (expressed as a ratio) in 24-hour serum cortisol weighted mean for the FF100 group compared with placebo using the SC Population. The following table shows a summary of serum cortisol weighted means for the SC population.

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**Summary of Derived Serum Cortisol Weighted Means (0-24h) (nmol/L) (SC Population)** [Table 16 FFR20002 Study Report, page 58]

	<b>Placebo N=44</b>	<b>GW685698X 100mcg QD N=43</b>	<b>Prednisone 10mg QD N=12</b>
<b>Baseline</b>			
n	44	43	12
Geometric Mean	238.21	248.70	237.36
95% CI for Geometric Mean	220.57, 257.27	223.59, 276.62	213.27, 264.18
Median	231.43	242.29	231.02
Min - Max	158.0 - 488.5	152.4 - 777.0	184.9 - 324.0
<b>Week 6</b>			
n	44	42	12
Geometric Mean	236.85	236.26	115.93
95% CI for Geometric Mean	214.35, 261.71	215.35, 259.20	97.13, 138.37
Median	222.97	228.35	129.87
Min - Max	78.7 - 661.0	144.5 - 565.5	70.0 - 154.9
<b>Ratio from Baseline</b>			
n <sup>a</sup>	44	42 <sup>a</sup>	12
Geometric Mean	0.99	0.97	0.49
95% CI for Geometric Mean	0.92, 1.07	0.90, 1.04	0.42, 0.56
Median	1.00	1.01	0.50
Min - Max	0.49 - 2.06	0.61 - 1.49	0.34 - 0.67

Source: Table 10.4

a. Ratios were not calculated if the first (0 hr) or last (24 hr) samples were missing.

Geometric mean ratios from baseline at Week 6 were similar for the FF100 (GW685698X 100mcg QD) and placebo treatment groups. Adjusting for baseline weighted mean and center, FF100 was non-inferior to placebo with respect to the ratio from baseline in serum cortisol weighted mean. The treatment ratio of FF100 vs placebo was 0.98 (0.89, 1.07) while the treatment ratio of the prednisone group vs placebo was 0.49 (0.43, 0.57). The non-inferiority margin of the confidence interval was 0.80. Results for the ITT Population were consistent with the primary SC analysis [Table 17 FFR20002 Study Report, page 58].

Urinary cortisol data obtained from domiciled 24 hour urine collections supported the primary endpoint. Two subjects (1 FF100 and 1 placebo) had 24 hour cortisol levels below the normal range at the 6 collection. Neither subject used any exogenous corticosteroid nor had any significant laboratory abnormalities or safety issues. [Tables 18, 19, 20 FFR2002 Study Report, pages 60-62]. The 6-beta hydroxycortisol excretion results were similar to those for 24-hour urinary free cortisol.

**Reviewer's Comment:** *Due to assay interference, no 24-hour urinary cortisol data were available for subjects in the prednisone treatment group, however, the effect of prednisone in decreasing serum cortisol levels in the primary analysis was unequivocal and acted as an adequate positive control.*

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**Summary and Discussion**

Fluticasone furoate at a dose of 100 mcg intranasally once daily had a similar effect as placebo (non-inferior to placebo) in its effect on the HPA axis as determined by assessing both serum and urinary cortisol levels after 6 weeks of treatment in adolescents and adults with PAR. The study was conducted with appropriate controls including an active prednisone control that was shown to reduce serum cortisol excretion compared to placebo after 7 days of treatment. While no formal efficacy analyses were conducted, changes in TNSS in the FF100 group gave supporting evidence of compliance for the treatment groups. No unanticipated safety signal was observed. Epistaxis, which is typically seen with the use of intranasal corticosteroids and was observed more in the FF100 group than placebo (7 subjects vs 2 subjects).

**10.1.8 STUDY # FFR101816**

**A Randomized, Double Blind, Placebo-Controlled, Single-Dose, Parallel-Group Study to Evaluate the Onset of Action of a Single Dose of Intranasal GW685698X (fluticasone furoate) Aqueous Nasal Spray 100mcg in Adolescent and Adult Subjects ( $\geq 12$  years of age) with Seasonal Allergic Rhinitis Exposed to Ragweed Pollen in an Allergen Challenge Chamber**

**Protocol****Administrative**

Study initiated: April 4, 2005

Study completed: July 30, 2005

Clinical Centers: One center, Allergen Response Research Center, Marietta, GA, Robert Berkowitz, M.D., Principal Investigator

Study report dated: December 2005

Study Sponsor: GlaxoSmithKline (GSK)

Medical Officer: Kathy Rickard, M.D., GSK

**Objective/Rationale**

The objective of this study was to evaluate the onset of action of fluticasone furoate 100mcg aqueous nasal spray (FF100), also known as GW685698X, compared to vehicle placebo nasal spray following a single dose in subjects  $\geq 12$  years of age with seasonal allergic rhinitis (SAR) exposed to controlled pollen concentrations in an allergen challenge chamber (ACC).

**Study Summary**

This was a randomized, double-blind, single-dose, parallel group, single center study that was conducted in an ACC in order to evaluate the onset of action of FF100. Male and

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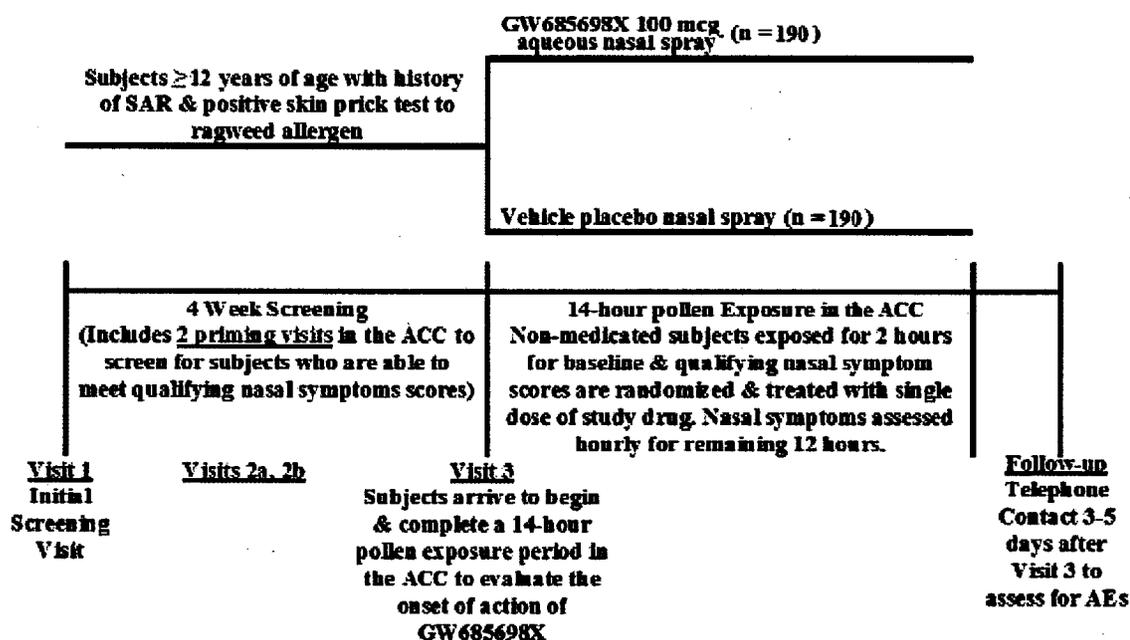
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female subjects were eligible for participation in the study if they were  $\geq 12$  years of age and had been diagnosed as having SAR as determined by a positive skin test to ragweed allergen and a moderate level of nasal symptoms (mean instantaneous total nasal symptom score [iTNSS] of  $\geq 6$  and a mean instantaneous nasal congestion scores of  $\geq 2$ ) during two priming visits. Subjects completed a screening visit, two priming visits, and a randomization visit. The screening visit occurred within 53 days of the randomization visit (Visit 3) when the onset of action of FF100 was assessed. The priming visits (Visits 2a and 2b) could occur anytime after the screening visit but were separated by at least 1 day. The last priming visit (Visit 2b) occurred within 14 days of the randomization visit. See the following figure for a schematic of the study design.

### Study Design Schematic



Three hundred eighty-two subjects who met the above criteria were exposed to controlled pollen concentrations ( $3500 \pm 500$  grains/ $m^3$ ), randomized 1:1 to receive a single dose of either FF100 or vehicle placebo nasal spray and subsequently complete a 12-hour postdose exposure period.

The criteria for evaluation were based on the subjects' seasonal allergy symptoms of rhinorrhea, nasal congestion, nasal itching, and sneezing. Symptoms experienced during the chamber visits were scored on diary cards using a four-point scale (0 to 3). The four symptom scores were summed giving a maximum possible instantaneous Total Nasal Symptom Score (iTNSS) of 12 for any one time point. Symptoms were assessed at 30, 60 and 90 minutes during the priming visits and prior to randomization (Visit 3). Subjects who qualified for randomization assessed symptoms hourly in the ACC following administration of a single dose of treatment. The primary efficacy measure was the mean

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change from baseline in subject-rated iTNSS, assessed hourly during the 12-hour, post-dose exposure period in the ACC. The primary analysis method was the comparison of treatment groups at each time point (active vs. placebo) using a repeated measures model with an unstructured covariance, adjusting for baseline TNSS, age, gender, session, treatment, time, and treatment by time interaction. The secondary efficacy endpoint was the mean change from baseline in the individual instantaneous nasal symptom scores for rhinorrhea, nasal congestion, nasal itching and sneezing, as assessed hourly during the 12-hour, post-dose exposure period in the ACC. The secondary efficacy measures for the four nasal symptoms were analyzed similarly to the primary analysis.

Demographics of the treatment groups were similar. The mean ages of subjects were 33.7 years and 33.1 years for the placebo and FF100 groups, respectively. Females comprised 70% of study subjects, 80% of subjects were Black, and 20% Caucasian [Table 5 FFR101816 Study Report, page 43].

**Reviewer's Comment:** *It is notable that in this negative study the racial demographics were very different from the SAR/PAR pivotal studies. In the present study 80% of subjects were listed as Black (which is reflective of the population in the Atlanta, GA metropolitan area) while in the pivotal studies Caucasians comprised  $\geq 90\%$  of the study population.*

For the primary endpoint, the LS mean difference between the two treatments for iTNSS was not statistically significant at any time point ( $p \geq 0.167$ ), thus, the onset of effect was not seen. For the secondary endpoint analyses an onset of effect was also not seen for any of the four individual nasal symptoms [Table 7 FFR101816 Study Report, pages 47-49].

**Reviewer's Comment:** *Careful review of the study inclusion/exclusion criteria and design failed to demonstrate any design or procedural reasons that could account for the failure of the study to meet the primary endpoint.*

Safety was assessed by monitoring adverse events (AEs) reported following treatment. There were 12 subjects (6%) in the placebo group and 9 (5%) in the FF100 group who experienced AEs following treatment. The most common AEs were headache and pharyngolaryngeal pain, experienced by 1 and 5 and 1 and 1 subjects in the placebo and FF100 groups, respectively. Single AEs in the FF100 group were reported for diarrhea, dyspepsia, conjunctivitis, eye irritation, and ocular hyperemia [Table 8 FFR101816 Study Report, page 53]. One subject in the FF100 group withdrew due to headache and one subject in the placebo group withdrew due to chest discomfort and wheezing. There were no deaths or non-fatal SAEs.

In summary, for this allergen chamber study, FF100 failed to demonstrate an onset of action, as determined by a statistical difference in iTNSS between FF100 and placebo, within 12 hours of treatment. It is notable that the study population differed significantly from that of the pivotal trials, 80% Black vs < 10% Black. No significant safety issues were observed in this short 1 day study.

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10.1.9 STUDY # FFR101747

**A Randomized, Double-Blind, Placebo-Controlled, Two-Week Crossover, Knemometric Assessment of the Effect of Fluticasone Furoate Nasal Spray 100mcg Once Daily on Short-Term Growth in Children Aged 6 to 11 Years with Seasonal and/or Perennial Allergic Rhinitis****Protocol****Administrative**

Study initiated: April 11, 2005  
Study completed: November 16, 2005  
Clinical Centers: One center in Denmark, Ole D. Wolthers, M.D., Principal Investigator  
Study report dated: March 2006  
Study Sponsor: GlaxoSmithKline (GSK)  
Medical Officer: Katharine Knobil, M.D., GSK

**Objective/Rationale**

The primary objective of this study was to evaluate for any potential effect on lower-leg growth rate from treatment with fluticasone furoate nasal spray 100mcg (FF100) once daily versus placebo nasal spray in children aged 6 to 11 years with seasonal allergic rhinitis (SAR) and/or perennial allergic rhinitis (PAR).

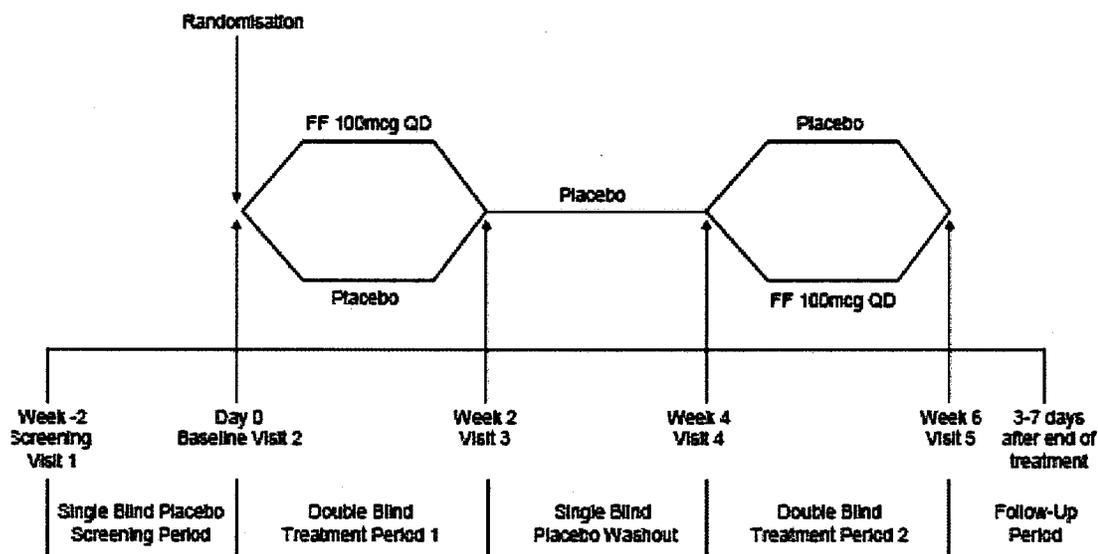
**Study Summary**

This was a two-week, double-blind, randomized, placebo-controlled, crossover study of 58 children aged 6 to 11 years with SAR and/or PAR in order to evaluate the effect of 2 weeks treatment with FF100 on short-term lower-leg growth as determined by knemometry. Eligible subjects were premenarchal females 6 to <11 years of age or male subjects 6 to <12 years of age, in Tanner Stage 1 and with a documented clinical history of SAR and/or PAR for at least one year prior to study entry. Additionally, subjects had to have normal growth at the time of screening, as reflected by a height between the 5th and 95th percentile of normal for age and gender, as determined by stadiometry and Danish growth charts.

Following a two-week, single-blind, placebo run-in period, 58 subjects were randomly allocated in a 1:1 ratio to a double-blind treatment sequence of either FF100 followed by placebo nasal spray QD, or placebo nasal spray followed by FF100 QD. Each double-blind treatment in the sequence was administered for 2 weeks. The 2 double-blind treatment periods were separated by a 2-week, washout period, during which single-blind, placebo nasal spray was again administered. A follow-up phone call was made 3 to 7 days after completing the last treatment to assess for adverse events (AEs).

The study consisted of five visits and four treatment periods: Run-in (Screening), Treatment Period 1, Washout, and Treatment Period 2. Knemometric assessments of lower leg length were made at each study visit. See the following figure for a schematic of the study design.

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 Study Design Schematic



The main safety objective of the study was to assess the effects of 2 weeks treatment with FF100 QD on bone growth based on knemometry assessments carried out at every visit. A knemometer was used to measure the distance between the top of the knee and the bottom of the heel of a seated subject. The length of the lower-leg was electronically calculated based on the maximum distance detected between a footplate and a knee-level measuring board. Four measurements were taken of the right leg at each visit and the final three measurements were recorded. The three recorded measurements were averaged. The difference between the average at the start of the period and the end of the period was divided by the period length (weeks) to obtain the lower-leg growth rate in millimeters per week for each period. Measurements for each subject were taken by the same study investigator/technician at each visit. The primary safety endpoint was mean growth rate (mm/wk) in lower-leg length, as determined by knemometry, over a two week treatment period with FF100 QD vs placebo nasal spray QD. The primary analysis was the non-inferiority comparison of the treatment groups (FF100 vs. placebo) using analysis of covariance (ANCOVA), adjusting for baseline lower-leg growth rate measured by knemometry, age, and gender. FF100 was considered to be non-inferior to placebo with respect to lower-leg growth rate if the lower limit of the two-sided 95% confidence interval for the treatment difference (FF100 minus placebo) was  $\geq -0.20\text{mm/wk}$  (approximately 40-50% of the expected placebo growth rate). The primary analysis was conducted on the Growth Population. This population excluded from the intent to treat (ITT) population subjects who did not have sufficient or reliable lower-leg growth data in order to provide estimates for either 2-week treatment periods or subjects who received any protocol-prohibited medications that may have affected short term growth. An ITT analysis of the primary safety endpoint was also performed.

**Reviewer's Comment:** *The Applicant supplied published literature that supported both the sensitivity of knemometry as a means to assess the effect of corticosteroids on growth*

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*and the choice of the non-inferiority margin. For instance, it has been reported that the mean lower-leg growth rate for placebo-treated subjects is 0.40mm/wk to 0.50mm/wk and that a 50% or greater reduction in lower-leg growth rate would be considered a clinically significant effect (Wolthers OD, Pedersen S., Arch Dis Child, 1993b;68:673-6; Skoner DP, et al., Ann Allergy Asthma Immunol 2003;90:56-62).*

Secondary safety endpoints included the frequency and type of clinical AEs, nasal examinations, and assessment of vital signs. There were no efficacy determinations made in the study.

Fifty-eight subjects were randomized into the study and 57 subjects (98%) completed both treatment arms. One subject withdrew at the end of the first treatment period after taking a prohibited medication (inhaled budesonide) for asthma. Five subjects (8.6%) violated criteria for inclusion into the Growth Population. These subjects either took a prohibited medication during the course of the study or did not have knemometry growth assessments at the planned time points.

Demographics of the treatment groups were similar. The mean age of subjects was 9.1 years. Males comprised 67% of study subjects and 97% of the subjects were Caucasian. Fifty-five per cent of subjects reported having allergic rhinitis for  $\geq 3$  years [Table 6 FFR101747 Study Report, page 45]. Treatment compliance, based on subjects' diary record, was  $\geq 96\%$  for both treatment groups in both treatment sequences. All but one subject was exposed to  $\geq 11$  days of study medication in each treatment period (Run-in, Period 1, Washout and Period 2). That one subject was exposed to placebo for 10 days during Treatment Period 2.

The primary safety endpoint was the mean growth rate (mm/wk) in lower-leg length, as determined by knemometry, over a 2-week treatment period with FF100 QD versus a two-week treatment period with placebo. Baseline mean lower-leg growth rates were similar between the two treatment sequences (0.40mm/wk for FF100/placebo treatment sequence and 0.38mm/wk for placebo/FF100treatment sequence.

Over the course of the study, mean lower-leg growth rate was 0.40mm/wk for the FF100 group and 0.42mm/wk for the placebo group with a difference in growth rates between the groups of -0.016mm/wk (95% CI: [-0.13, 0.10]). Since the lower limit of the 95% CI (-0.13mm/wk) was greater than the non-inferiority margin of -0.20mm/wk, FF100 was judged as non-inferior to placebo in terms of an effect on lower-leg growth rate [Table 10 FFR101747 Study Report, page 55]. An analysis of the primary safety endpoint in the ITT population was supportive of that observed in the Growth Population (Treatment difference:-0.013mm/wk; 95% CI [-0.12, 0.10]) [Table 11 FFR101747 Study Report, page 59].

Safety was also assessed by monitoring adverse events (AEs), conducting nasal examinations, and monitoring vital signs. During the treatment periods, a total of 10 subjects in each treatment group (17%) experienced at least 1 AE. The most common AE was nasopharyngitis occurring in 4 and 1 subjects in the placebo and FF100 groups,

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respectively. Epistaxis was the only AE reported more frequently in the FF100 group (3 subjects vs 0 in the placebo group) [Table 12 FFR101747 Study Report, page 63]. There were no fatalities, SAEs, or AEs causing early withdrawal reported in the study. Regarding nasal exams, there was no difference between the groups in the incidence of mucosal bleeding and no subject had nasal ulcers during the study. There were no differences in vital signs between subjects in the two treatment sequences at any time point.

In summary, for this knemometry study in children ages 6-11 years, FF100 QD, at the adult proposed dose, was shown to be non-inferior to placebo nasal spray based on the lower bound of the 95% CI being above the pre-specified non-inferiority margin of -0.20mm/wk in lower-leg growth rate for the Growth Population. Results in the ITT Population were similar and supportive of those in the Growth Population. There were no safety issues in the study population in terms of AEs, nasal exams, or vital signs. While this study is supportive that there is little effect of FF on short-term long bone growth, the longer term effects of FF on growth in children still need to be evaluated.

### 10.1.10 STUDY # FFR100012

**A randomized, double-blind, parallel group, placebo controlled, 6-week study of the effect of GW685698X (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)**

## **Protocol**

### **Administrative**

Study initiated: February 4, 2005

Study completed: June 30, 2005

Clinical Centers: Ten centers in the United States

Study report dated: December 2005

Study Sponsor: GlaxoSmithKline (GSK)

Medical Officer: Kathy Rickard, M.D., GSK

### **Objective/Rationale**

The primary objective of this study was to assess the effects of six weeks treatment with fluticasone furoate (FF) aqueous nasal spray 100mcg once daily on HPA axis function compared to vehicle nasal spray placebo in pediatric subjects 2 to < 12 years of age with PAR.

### **Study Design**

This was a randomized, double-blind, placebo-controlled, parallel group, 6 week study to assess the effects of fluticasone furoate aqueous nasal spray 100mcg once daily (FF100) on HPA axis function. Subjects were assigned in a 1:1 ratio to one of the following two double-blind treatment groups:

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- fluticasone furoate 100mcg QD (FF100)
- placebo nasal spray QD

Subjects who satisfied the entry criteria entered a 7-14 day screening period. During the screening period, subjects or parents/guardians **rated the subject's allergic rhinitis** symptoms on a diary card in order to determine eligibility for randomization. After a minimum of 7 days, subjects who fulfilled the randomization criteria were randomly assigned to one of the 2 treatment groups listed above. Pharmacodynamic measurements of HPA axis function, including both urine and serum cortisol assessments, were conducted during 24-hour domiciled visits at the end of the screening and treatment periods. While efficacy was not studied in this study, a daily symptom diary including TNSS scores and confirmation of taking the daily dose of study medication was maintained. Subjects were seen in the clinic weekly at which time concomitant medications were assessed, diary cards collected, and vital signs and nasal exams performed. Safety assessments included assessments of adverse events (AEs), routine laboratory tests (chemistry and hematology), nasal examinations, vital signs, and 12-lead electrocardiograms.

*Reviewer's Comment: The study generally followed recommendations for conducting HPA axis evaluations as presented in the FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, 2003. Because the study was performed in young pediatric subjects, an active control such as systemic prednisone was not included.*

## Study Population

Approximately 100 subjects, 2 to <12 years of age with a diagnosis of PAR and who met the inclusion and randomization criteria, were required for randomization to complete at least 80 subjects (approximately 40 subjects in each group). Approximately 20% of the randomized subjects were planned for the 2 to <4 year old population, 20% were planned for the 4 to <6 year old population, and 60% were planned for the 6 to <12 year old population.

### Inclusion Criteria

- Male or female age 2 to < 12 years
- Informed consent of parent/guardian and assent, when appropriate, from the child
- Diagnosis of PAR to include:
  - Documented, positive skin test to an appropriate perennial allergen (animal dander, house dust mites, cockroaches and/or mold) or documented, in vitro test results for a specific IgE (RAST, PRIST, etc.) within the 12 months prior to Visit 1. A positive skin test during Visit 1 was also allowed.
  - One year clinical history and treatment of PAR for 4 to < 12 year olds; or, a six month clinical history and treatment of PAR for 2 to < 4 year olds.

Subjects who met the above criteria and who also had SAR and/or vasomotor rhinitis were eligible for randomization.

### Exclusion Criteria

Subjects were not eligible for inclusion in this study if any of the following criteria

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applied:

- Significant concomitant medical conditions. Significant was defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or which would confound the interpretation of the study results if the disease/condition exacerbated during the study.
- Asthma, with the exception of mild intermittent asthma [National Asthma Education and Prevention Program (NAEPP) Guidelines, 2002]
- Bacterial or viral infection (e.g., common cold) of the eyes or upper respiratory tract within two weeks of Visit 1 or during the screening period
- Documented evidence of acute or significant chronic sinusitis, as determined by the individual investigator
- Current or history of glaucoma and/or cataracts or ocular herpes simplex
- Clinical evidence of a Candida infection of the nose or oropharynx at Visit 1 or prior to randomization
- History of adrenal insufficiency or history of shingles
- Use of corticosteroids, defined as:
  - Systemic (oral, intramuscular, intravenous) corticosteroids within 6 months prior to Visit 1.
  - Inhaled, ocular, or dermatological corticosteroids within eight weeks prior to Visit 1.
  - Intranasal corticosteroids within four weeks prior to Visit 1.
- Use of other allergy medications within the timeframe indicated relative to Visit 1:
  - Intranasal or ocular cromolyn within 14 days prior to Visit 1
  - Short-acting prescription and OTC antihistamines, including ocular **preparations and antihistamines contained in insomnia and 'nighttime' pain formulations taken for insomnia**, within 3 days prior to Visit 1
  - Long-acting antihistamines within 10 days prior to Visit 1
  - Oral or intranasal decongestants within 3 days prior to Visit 1
  - Intranasal, oral, or inhaled anticholinergics within 3 days prior to Visit 1
  - Oral antileukotrienes within 3 days prior to Visit 1
  - Subcutaneous omalizumab (Xolair) within 5 months of Visit 1
  - Intranasal antihistamines within 2 weeks prior to Visit 1
- Use of immunosuppressive medications 8 weeks prior to screening and during the study
- Use of any medications that significantly inhibit the cytochrome P450 subfamily enzyme CYP3A4, including ritonavir and ketoconazole
- Immunotherapy (Subjects could be enrolled into the study if the immunotherapy was not initiated within 30 days of Visit 1, if the dose remained fixed over the 30 days prior to Visit 1, and the dose remained fixed for the duration of the study.
- Use of other medications or treatments that could affect the signs and symptoms of allergic rhinitis
- Findings of a clinically significant, abnormal electrocardiogram (ECG)
- Findings of a clinically significant, abnormal clinical laboratory test
- Findings of morning (prior to 10 AM) serum cortisol assessment outside the normal reference range (<2mcg/dL)

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### **Randomization Criteria**

At Visit 2, subjects must have met the following criteria:

- The daily rTNSS on any 4 of the last 7 days prior to Visit 2 must have been  $\geq 5$ .
- The subject or parent/guardian must have demonstrated the ability to comply with use of the daily diary card defined as completion of at least 80% of the assessments during the screening period.

### **Withdrawal Criteria**

Subject withdrawal from the study was required and Early Withdrawal procedures must be performed, when a subject:

- was significantly non-compliant with the requirements of the protocol
- had not completed the 6-week treatment period
- subject began menses
- had an adverse event that would, in the investigator's judgment, make continued participation in the study an unacceptable risk
- The treatment blind was broken for a subject (by other than GSK GCSP personnel)
- GlaxoSmithKline discontinued the study.

### **Study Procedures**

#### **Study Treatments**

FF100 or placebo nasal spray was administered for six weeks. To deliver nasal spray medication, 2 sprays were administered into each nostril by the subject or parent/guardian, alternating one spray in each nostril followed by a second spray in each nostril. The first dose of intranasal study medication was administered in the clinic at the end of the first domiciled visit prior to discharge. The last dose of intranasal study medication coincided with the planned domiciled visit at Week 6, was administered in the clinic and was followed by 24-hour urine and timed serum and plasma samples which were collected relative to the time of dosing.

#### **Demographic and Baseline Assessments**

The following demographic and baseline information was obtained: age; sex; race; ethnicity, height, weight, duration of the subject's **seasonal allergy**, presence of perennial and/or vasomotor rhinitis, and results of skin prick test(s). All subjects also had a physical examination, vital signs assessment, nasal examination, 12-lead ECG, blood hematology and chemistry analyses, pregnancy testing (**females**). **The subjects' self/parent/guardian-rated symptom scores over the four days prior to randomization (including the morning of randomization) provided the baseline symptom assessment.**

#### **Pharmacokinetic/Pharmacodynamic Assessments**

Pharmacokinetic blood samples for determination of FF plasma levels were collected at the following times relative to the morning (prior to 10AM) dose given during Visit 5: pre-dose and at 0.5, 1, 2, and 4, hours post-dose.

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Serum samples for serum cortisol assessments and 24-hour urine collections for urinary free cortisol excretion and 6-beta hydroxycortisol excretion were obtained during domiciled clinic visits (Visit 2/randomization and Visit 5/end-of-treatment). Blood samples to assess serum cortisol were collected at the following time points relative to the 24-hour serial sampling start time (0) which occurred prior to 10:00 AM at Visit 2: 0, 2, 4, 8, 12, 16, and 24 hours after the start time. At Visit 5, blood samples were collected at the same times relative to the morning (prior to 10 AM) dose.

**Efficacy Evaluation**

Efficacy assessments were completed for the purpose of evaluating compliance with nasal spray study medication only. Throughout the study, subjects or parents/guardian rated four nasal symptoms, rhinorrhea, nasal congestion, nasal itching, and sneezing, in a reflective and an instantaneous manner. **Reflective symptom scores assessed the subject's symptoms over the preceding 12 hours and were recorded twice daily, once in the AM immediately before dosing and once in the PM 12 hours after dosing.** **Instantaneous symptom scores assessed the subject's symptoms at that moment and were recorded in the AM immediately before dosing.** The Total Nasal Symptom Score (TNSS) was calculated from the diary entries as described for study FFR20001. The sums of the 4 individual AM and PM reflective scores were averaged giving a daily rTNSS with a maximum score of 12. The sum of the 4 individual AM instantaneous scores gave an AM instantaneous total nasal symptom score (iTNSS), which also had a maximum score of 12.

**Safety Evaluation**

The primary safety endpoints for the study consisted of the following assessments:

- Frequency and type of clinical adverse events
- Results of clinical laboratory tests (hematology and clinical chemistry)
- Results of gross nasal examinations
- Vital signs (systolic and diastolic blood pressures, heart rate)
- 12-lead electrocardiograms (ECGs)

**Data Analysis****Sample Size**

The sample size calculation was based on the number of subjects needed to demonstrate non-inferiority in serum cortisol weighted mean 0-24h between FF100 and placebo. Non-inferiority was demonstrated if the lower limit of the two-sided 95% confidence interval for the geometric mean ratio of GW685698X and placebo is greater than 0.80.

In previous healthy volunteer and patient studies, the estimated between-subject standard deviation (on the loge scale for 24-hour serum cortisol weighted mean) ranged from 0.18 to 0.31. Assuming a standard deviation of 0.30 with full data available for 40 subjects on FF100 and 40 subjects on placebo, this study will have approximately 90% power to demonstrate non-inferiority if there is no true difference between the treatment groups.

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**Study Populations**

The primary analysis population for the assessment of HPA axis function was the Serum Cortisol (SC) Population. The SC Population was defined as the ITT Population excluding subjects who had any one of the following:

- More than 1 consecutive missing cortisol concentrations over a twenty-four hour collection period at either Visit 2 or Visit 5
- used a protocol-prohibited systemic (oral, intramuscular, intravenous) corticosteroid within six months prior to the start of any serum sample collection
- used a protocol-prohibited inhaled, ocular, and/or dermatological corticosteroid within eight weeks prior to the start time of any serum sample collection
- used a protocol-prohibited intranasal corticosteroid within 4 weeks prior to the start time of any serum sample collection

The Urinary Cortisol (UC) Population also supported the assessment of HPA axis function. The UC Population was defined as the ITT Population excluding subjects who had any one of the following:

- urine volumes of < 160mLs for 2 to <4 years, <300mLs for 4 to <6 years, <400mLs for 6 to < 12 years; and, 24-hour creatinine excretion below the lower limit of normal range (defined as 8mg/kg/24hrs)
- collection time intervals outside  $24 \pm 2$  hours
- used a protocol-prohibited systemic (oral, intramuscular, intravenous) corticosteroid within six months prior to the start time of any urine sample collection
- used a protocol-prohibited inhaled, ocular, and/or dermatological corticosteroid within eight weeks prior to the start time of any urine sample collection
- used a protocol-prohibited intranasal corticosteroid within 4 weeks prior to the start time of any urine sample collection

The Intent-to-Treat (ITT) population was defined as all randomized subjects who receive at least one dose of study drug. The ITT population was used for all safety analyses.

**Primary and Secondary Analyses**

The primary treatment comparison of interest was FF100 QD vs. Placebo. The primary endpoint was change from baseline in 24-hour serum cortisol weighted mean. Supporting pharmacodynamic endpoints included 24-hour urine assessments of HPA axis function.

While the primary analysis was conducted on the SC population an analysis was also performed on the ITT population. 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.

**Results****Study Population**

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### Disposition

A total of 158 subjects were screened for this study. One hundred and thirteen subjects were randomized into the study, however, one subject was erroneously randomized and did not receive any study treatment. Thus, 112 subjects (57 in the FF100 group and 55 in the Placebo group) comprised the ITT population.

Ninety-four percent of subjects completed the study. Premature withdrawals occurred for 7 (6%) subjects with 3 withdrawing from the placebo group and 4 from the FF100 group. One subject from each treatment group withdrew due to an AE [Section 6.1 and Table 4 FFR100012 Study Report, page 41].

The following table summarizes the populations analyzed.

### Summary of Populations Analyzed [Table 5 FFR100012 Study Report, page 42]

	Number (%) of Subjects		
	Placebo	GW685698X 100mcg QD	Total
ITT	55 (100)	57 (100)	112 (100)
Serum Cortisol (SC)	49 (89)	52 (91)	101 (90)
Urine Cortisol (UC)	41 (75)	43 (75)	84 (75)
Pharmacokinetic Concentration	NA	53 (93) <sup>a</sup>	53 (47)
Pharmacokinetic Parameter	NA	53 (93) <sup>a</sup>	53 (47)

Source: Table 6.5, Table 6.14 – Table 6.19

a. All 53 subjects who completed the study in the GW685698X 100mcg QD treatment group were included in the PK analyses.

### Demographics

Demographics were very similar across treatment groups. The mean age range for the ITT population was 6.3 years. Subjects aged 2 to <4 years comprised 19%, 4 to <6 years comprised 22%, and 6 to <12 years comprised 59% of the ITT Population. The majority of the subjects were White (65%). Males and females were equally represented. Eighty-four per cent of subjects reported having SAR in addition to PAR. Most subjects were allergic to dust mites (79%), molds (65%), animal danders (65%), and cockroaches (53%). The baseline daily rTNSS and AM iTNSS scores were 7.6 and 7.5, respectively, indicating a population that had moderate symptoms [Section 6.4 and Table 6.20 FFR100012 Study Report, pages 43, 106-107].

Greater than >96% of subjects had greater than or equal to 90% compliance with study treatment across both treatment groups for the ITT and SC populations.

### Efficacy Results

#### Primary Efficacy Outcome

No inferential statistical testing was planned or performed for TNSS recorded in subject diaries. However, the mean changes of -1.6 and -2.5 in rTNSS over the entire 6-week treatment period for the placebo, and FF100 groups, respectively, supports adequate

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compliance in the FF100 group [Table 8 FFR100012 Study Report, page 46].

**Safety**

The safety findings from this study are included in and will be fully reviewed in the Integrated Review of Safety in Section 7 of the main NDA review. This review will focus primarily on the effects of FF100 on suppression of the HPA axis.

**Extent of Exposure**

Per protocol, subjects were to be dosed for 42 days. Eighty-nine per cent of all subjects were dosed for 41-45 days with the mean length of exposure 40.7 and 41.1 days for the placebo and FF100 groups, respectively [Table 9 FFR100012 Study Report, page 48].

**Adverse Events**

Nine subjects (16%) in the placebo group and 10 subjects (18%) in the FF100 group experienced at least one adverse event during the treatment period. The most common adverse event was pyrexia reported by 2 subjects (4%) in the FF100 group. The following table shows all AEs reported in  $\geq 2$  subjects during the treatment period.

**Adverse Events reported in  $\geq 2$  subjects during the treatment period and more common in the FF100 (GW685698X) group (ITT population)** [Table 10 FFR100012 Study Report, page 49]

	Number (%) of Subjects	
	Placebo N=51	GW685698X 100mcg QD N=48
<b>All AEs</b>		
<b>Any Event</b>	9 (16)	10 (18)
Pyrexia	0	2 (4)
<b>Drug-Related AEs</b>		
<b>Any Event</b>	1 (2)	1 (2)
Pruritis and urticaria	1 (2)	0
Nasal discomfort	0	1 (2)

Source and Associated Subject Listings: Table 8.3, Table 8.5, Table 8.7 – Table 8.11

**Deaths, Serious Adverse Events, and Events Leading to Withdrawal**

No deaths were reported during the study. One SAE occurred during the study. An 11-year-old male subject (103) fell while roller skating and experienced a displaced fracture of the ulna and radius.

Two subjects, one in each treatment group withdrew due to AEs, ear infection (placebo) and pneumonia (FF100).

**Pregnancy**

No subjects became pregnant during the study.

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**Laboratory Results**

The majority of subjects in each treatment group ( $\geq 90\%$ ) had either no change in hematology or chemistry parameters or a shift into the normal range. Subject 380 had an abnormally high alkaline phosphatase at screening (1365 IU/L) which normalized to 270 IU/L at Week 6. The investigator did not consider the abnormal baseline value to be clinically significant. Otherwise, there were isolated laboratory test values outside the normal ranges for several subjects as assessed by shift table, no others were remarkable and no meaningful differences were seen between treatment groups [Section 8.6.1 and 8.6.2 FFR100012 Study Report, pages 50-52].

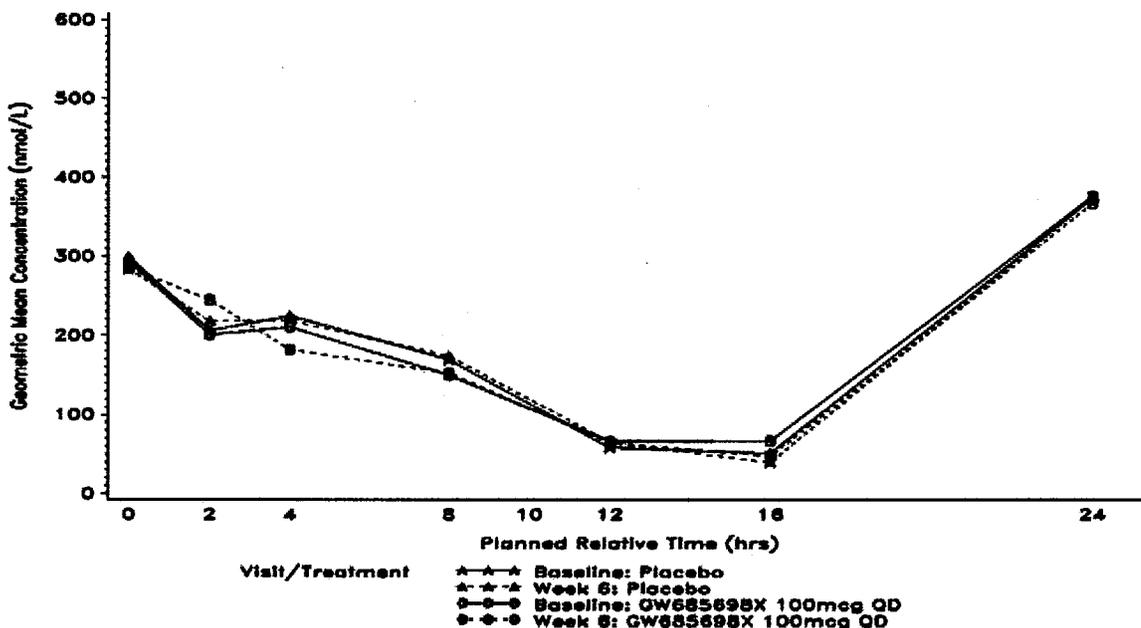
**Nasal Exams, Vital Signs, and Electrocardiograms**

Over the treatment period, there were no significant differences in the observance of or in worsening of nasal mucosal bleeding or ulceration in any of the treatment groups. Two subjects, both in the placebo group, had nasal ulcers at Week 1 only and 2 subjects in the Placebo group and 3 subjects in the FF100 group had mucosal bleeding post-baseline. No subjects had evidence of nasal candidiasis. There were no clinically meaningful adverse changes from baseline in vital signs and no clinically significant changes in ECG compared to baseline [Sections 8.7.1-8.7.3 FFR100012 Study Report, page 52-55].

**Pharmacodynamic (HPA axis) Results**

Baseline and Week 6 mean serum cortisol concentrations were similar for the FF100 and placebo groups (see figure below).

**Geometric Mean (95% CI) Serum Cortisol Concentration-Time Profile by Treatment Group (SC Population)** [Figure 2 FFR100012 Study Report, page 58]



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The primary endpoint of the study was change from baseline (expressed as a ratio) in 24-hour serum cortisol weighted mean for the FF100 group compared with placebo using the SC Population. The following table shows a summary of serum cortisol weighted means for the SC population.

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**Summary of Derived Serum Cortisol Weighted Means (0-24h) (nmol/L) (SC Population)** [Table 15 FFR100012 Study Report, page 58]

	<b>Placebo N=49</b>	<b>GW685698X 100mcg N=52</b>
<b>Baseline</b>		
n	48	50
Geometric Mean	185.04	189.88
95% CI for Geometric Mean	171.06, 200.17	175.06, 205.96
Median	176.79	193.76
Min - Max	103.8 – 408.5	107.7 – 346.9
<b>Week 6</b>		
n	48	50
Geometric Mean	181.58	181.55
95% CI for Geometric Mean	168.50, 195.68	166.88, 197.50
Median	181.70	171.27
Min - Max	101.0 – 414.5	104.0 – 493.3
<b>Ratio from Baseline</b>		
n <sup>a</sup>	47 <sup>a</sup>	48 <sup>a</sup>
Geometric Mean	0.979	0.935
95% CI for Geometric Mean	0.912, 1.052	0.860, 1.017
Median	0.972	0.989
Min - Max	0.52 – 1.66	0.56 – 1.86

Source: Table 10.4, 10.7

a. Ratios were not calculated if the first (0 hr) or last (24 hr) samples were missing.

Geometric mean ratios from baseline at Week 6 were similar for the FF100 (GW685698X 100mcg QD) and placebo treatment groups. Adjusting for baseline weighted mean and center, FF100 was non-inferior to placebo with respect to the ratio from baseline in serum cortisol weighted mean. The treatment ratio of FF100 vs placebo was 0.97 (0.88, 1.07). The non-inferiority margin of the confidence interval was 0.80. Results for the ITT Population were consistent with the primary SC analysis [Table 16 FFR100012 Study Report, page 59].

Urinary cortisol data obtained from domiciled 24 hour urine collections supported the primary endpoint. No subjects had 24-hour urinary cortisol excretion below the normal range at Week 6 [Tables 17 and 18 FFR100012 Study Report, pages 60-61]. The 6-beta hydroxycortisol excretion results were similar to those for 24-hour urinary free cortisol.

### Summary and Discussion

Fluticasone furoate at a dose of 100 mcg intranasally once daily had a similar effect as placebo (non-inferior to placebo) in its effect on the HPA-axis as determined by assessing both serum and urinary cortisol levels after 6 weeks of treatment in children 2 < 12 years of age with PAR. The study was conducted without an active control group due to ethical concerns over inducing HPA-axis impairment in young children. While no formal

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efficacy analyses were conducted, changes in TNSS in the FF100 group gave supporting evidence of compliance for the treatment groups. No unanticipated safety signals were observed.

**10.1.11 STUDY # FFR100010**

**A Randomized, Double-Blind, Placebo-Controlled, Parallel- Group, Multicenter Study to Evaluate the Efficacy and Safety of Once-Daily, Intranasal Administration of GW685698X (fluticasone furoate) Aqueous Nasal Spray 50mcg and 100mcg for 2 Weeks in Pediatric Subjects Ages 2 to <12 Years with Seasonal Allergic Rhinitis (SAR)**

**Protocol****Administrative**

Study initiated: March 18, 2005

Study completed: November 01, 2005

Clinical Centers: 57 study sites in the United States during the Spring and Fall allergy seasons

Study report dated: March 29, 2006

Study Sponsor: GlaxoSmithKline (GSK)

Medical Officer: Kathy Rickard, M.D., GSK

**Objective/Rationale**

The primary objectives of this study were to compare the efficacy and safety of GW685698X (fluticasone furoate) nasal spray 50mcg and 100mcg once daily (QD) with vehicle placebo nasal spray over a period of two weeks and to determine the optimal dose in pediatric subjects (ages 2 to <12 years) with SAR.

**Study Design**

This study is a randomized, double-blind, placebo-controlled, parallel group, three-arm, multicenter, study of the efficacy and safety of fluticasone furoate (FF) aqueous nasal spray 50 and 100mcg for 14 days in 554 pediatric subjects ages 2 < 12 years with SAR. After a 5-21 day screening period, subjects who met the specified symptom criteria were randomized to 2 weeks treatment with FF 50mcg (FF50), FF100mcg (FF100), or vehicle placebo with subjects returning to the study site for mid-treatment and final safety evaluations. Treatments were either self-administered or administered with the help of a parent/guardian once daily in the AM. The use of loratadine, not to exceed 5mg/day was allowed on an as-needed basis as a rescue allergy medication for subjects 2 < 6 years of age only. The primary efficacy measure for the study was the mean change from baseline over the entire treatment period in daily reflective, total nasal symptom scores (rTNSS), which were entered daily into a study diary. Key secondary measures were the mean change from baseline over the entire treatment period in AM, pre-dose, instantaneous, total nasal symptom scores (iTNSS) and an overall evaluation of response to therapy. All

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efficacy measures were based on subject or **the subject's parent/guardian assessments**. Subject compliance was assessed with the diary and by inspection of the medication bottles. Safety measures included adverse events, routine laboratory tests (hematology and clinical chemistry), physical examinations, nasal examinations, vital signs, and electrocardiograms.

The protocol was amended once, dated May 31, 2005, in order to add the Fall allergy season, remove of documentation of seasonal onset and offset of nasal allergy symptoms from the inclusion criteria, and revise the secondary endpoints for Total Ocular Symptom Scores (TOSS) from mean percent change from baseline to mean change from baseline for the daily reflective (rTOSS) and AM, predose instantaneous Total Ocular Symptom Scores (iTOSS).

*Reviewer's Comment: While, theoretically, the removal of documented seasonal onset and offset of nasal allergy symptoms may allow subjects without SAR into the study, the inclusion criteria, including positive allergy testing for seasonal allergens, and randomization criteria which required a specified degree of nasal symptoms in order to be randomized, makes it unlikely that subjects without allergic rhinitis would be enrolled.*

#### **Study Population**

A total of 554 subjects were enrolled in the study, 184 in each of the FF50 and FF100 groups and 186 in the placebo group. While enrollment for the 2 < 6 years of age group was planned to comprise approximately 25% of the study population, a total of 105 (19%) of subjects enrolled were 2 < 6 years of age.

##### **Main Inclusion Criteria**

1. Male or females ages 2 < 6 years
2. Diagnosis of SAR

SAR was defined as follows:

- Clinical history of SAR with seasonal allergy symptoms during the last allergy season
- A positive skin test (by prick method) or in vitro tests (RAST/PRIST) to seasonal allergens prevalent in the geographic area within 12 months prior to Visit 1.

A positive skin test was defined as a wheal  $\geq 3$ mm larger than the diluent control for prick testing.

Subjects who met the above criteria and who may also have had perennial allergic rhinitis were eligible for randomization.

3. Adequate exposure to seasonal (spring/summer/fall) allergen prevalent to the geographic area.

##### **Main Exclusion Criteria**

1. Significant concomitant medical conditions, defined as:

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- a. a historical or current evidence of clinically significant uncontrolled disease of any body system (e.g., tuberculosis, psychological disorders).
- b. a severe physical obstruction of the nose (e.g., deviated septum or nasal polyp) that could have affected the deposition of double-blind intranasal study drug
- c. recent nasal septal surgery or nasal septal perforation
- d. asthma, with the exception of mild intermittent asthma
- e. rhinitis medicamentosa
- f. bacterial or viral infection (e.g., common cold) of the upper respiratory tract within two weeks of Visit 1 or during the screening period
- g. documented evidence of acute or significant chronic sinusitis, as determined by the individual investigator
- h. glaucoma and/or cataracts or ocular herpes simplex
- i. physical impairment that would have affected **subject's ability** to participate safely and fully in the study
- j. clinical evidence of a Candida infection of the nose or oropharynx
- k. If the subject or his/her parent or legal guardian had a condition that limited the validity of informed consent or that would confound the interpretation of the study results
- l. A subject was not eligible if he/she currently had chickenpox or measles, or had been exposed to chickenpox or measles during the last three weeks prior to the study and was non-immune.

2. Use of corticosteroids, defined as:

- Intranasal corticosteroid within four weeks prior to Visit 1.
- Inhaled, oral, intramuscular, intravenous, and/or dermatological corticosteroid (with the exception of hydrocortisone cream/ointment, 1% or less) within eight weeks prior to Visit 1.

3. Use of other allergy medications within the timeframe indicated relative to Visit 1

- Intranasal or ocular cromolyn within 14 days prior to Visit 1
- Short-acting prescription and OTC antihistamines within 3 days prior to screening visit
- Long-acting antihistamines within 10 days prior to Visit 1: loratadine, desloratadine, fexofenadine, cetirizine
- Oral or intranasal decongestants within 72 hours prior to Visit 1
- Intranasal anticholinergics within 72 hours prior to Visit 1
- Oral antileukotrienes within 72 hours of Visit 1
- **Subcutaneous omalizumab (Xolair<sup>®</sup>)** within 5 months of Visit 1
- Intranasal antihistamines within 2 weeks prior to Visit 1

Note: Subjects were not permitted to use any ocular antihistamines, artificial tears, eyewashes, homeopathic preparations, irrigation solutions, lubricants, sympathomimetic preparations, vasoconstrictors and combinations during the screening and treatment periods. No exclusion period prior to Visit 1 was required for these treatments.

4. Use of other medications that may have affected allergic rhinitis

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- Chronic use of concomitant medications, such as tricyclic antidepressants, that would have affected assessment of the effectiveness of the study drug.
  - Chronic use of long-acting beta-agonists (e.g., salmeterol) or other intranasal medications
5. Use of immunosuppressive medications 8 weeks prior to screening and during the study
  6. Immunotherapy as long as the immunotherapy was not initiated within 30 days of Visit 1 and if the dose had remained fixed over the 30 days prior to Visit 1, and the dose remained fixed for the duration of the study.
  7. Use of any medications that significantly inhibit the cytochrome P450 subfamily enzyme CYP3A4, including ritonavir and ketoconazole
  8. Known hypersensitivity to corticosteroids or any excipients in the product
  9. Known clinical trial/experimental medication experience
  10. Affiliation with investigational site
  11. Findings of an abnormal ECG
  12. Findings of a clinically significant laboratory abnormality

### **Randomization Criteria**

At Visit 2 (randomization visit), the subject must have met the following criteria:

1. Average of the last 8 reflective Total Nasal Symptoms Scores (rTNSS) assessments, comprised of 4 morning (AM) assessments, 4 evening (PM) assessments, over the four 24-hour periods prior to randomization must have been  $\geq 6$ . This included the AM assessment on the morning of the randomization visit.
2. Average of the last 8 reflective nasal symptom assessments for congestion, comprised of 4 AM assessments and 4 PM assessments, over the four 24-hour periods prior to randomization must have been  $\geq 2$ . This included the AM assessment on the morning of the randomization visit.
3. A subject must have completed 80% of assessments on the screening symptom diary.

### **Withdrawal Criteria**

Premature discontinuation of the study drug was defined as discontinuation of the study drug for more than 2 consecutive days before the end of the study period. Subjects who discontinued administration of study drug prematurely were withdrawn from the study.

Subject withdrawal from the study was required and discontinuation procedures must have been performed, when:

- a subject had been significantly non-compliant with the requirements of the protocol
- a subject had not completed the 2-week treatment period
- a subject had an adverse event that would have, in the investigator's judgment, made continued participation in the study an unacceptable risk
- the treatment blind had been broken for a subject, or
- GSK discontinued the study

A subject may have voluntarily discontinued participation in this study at any time.

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The investigator may have also, at his or her discretion, discontinued the subject from participating in this study at any time.

**Prohibited Medications**

Concomitant use of any prescription or over-the-counter medications that may have affected the duration/severity of rhinitis was not allowed during the study. These are listed in the exclusion criteria.

**Study Procedures**

The schedule of study procedures is summarized in the table below.

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Schedule of Study Events [Table 1 FFR100010 Study Report, pages 25-26]

	Visit Number					
	1	2	3	4	EW <sup>a</sup>	Phone Call <sup>b</sup>
	Study Day					
	-21 to -5	1	8	15		
	Permitted Visit Window (# of days)					
			±2	±1		
<b>ACTIVITY</b>						
Informed Consent	X					
Subject number assignment	X					
Medical history	X					
Concomitant medication assessment	X	X	X	X	X	
Verification of inclusion/exclusion criteria	X					
Vital Signs	X			X	X	
Physical examination	X			X	X	
Nasal examination	X	X	X	X	X	
Skin testing (if not done within 12 months of Visit 1)	X					
Clinical laboratory tests	X			X	X	
12-lead electrocardiograms (ECGs)	X			X	X	
Issue screening diary	X					
Collect/Review diary		X	X	X	X	
Adverse event assessment		X	X	X	X	X
Randomization number assignment		X				
Nasal spray technique demonstration		X				
Dispense rescue medication <sup>c</sup>		X	X			
Dispense double-blind study drug to eligible subjects		X				
Issue treatment diary		X	X			
Pharmacogenetic sampling <sup>d</sup>				X	X	
Pharmacokinetic sampling <sup>e</sup>				X	X	
Collect study drug				X	X	
Compliance assessment		X	X	X	X	
Product Characteristic Questionnaire <sup>f</sup>				X	X	
Subject-rated, overall evaluation of response to therapy				X	X	

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### Fluticasone Furoate Nasal Spray

Fluticasone furoate was manufactured as a \_\_\_\_\_, aqueous suspension containing \_\_\_\_\_ of micronized FF. The \_\_\_\_\_ consisted of \_\_\_\_\_ benzalkonium chloride plus \_\_\_\_\_ disodium edetate. Each nasal spray device contained a volume of suspension sufficient to deliver a minimum of 120 actuations. Each spray of the suspension contained approximately 25mcg of fluticasone furoate. The placebo nasal spray was comprised of the FF vehicle.

*Reviewer's Comment: Later analyses demonstrated that 27.5 mcg of study drug was emitted with each spray. Thus, doses actually received were 55 and 110mcg of FF.*

All randomized subjects received two aqueous nasal sprays, Nasal Spray A and Nasal Spray B. The subjects were instructed to administer one spray to each nostril from each nasal spray, beginning with Nasal Spray A, each morning. The contents on Nasal Spray A and B were different (FF or placebo) for each dosing group such that each subject would administer the proper dose of study medication for that group.

### Dose Rationale

The doses selected for this study, 50mcg and 100mcg QD, were based on the results GSK study FFR20001, which compared the safety and efficacy of 50mcg, 100mcg, 200mcg, and 400mcg QD doses of FF in adults and adolescents ( $\geq 12$  years of age) with SAR. All doses of fluticasone furoate evaluated in that dose-ranging study demonstrated statistically significantly greater reductions in SAR symptoms versus vehicle placebo. A final comparison of the efficacy, safety, and onset findings supported the proposed choice of 100mcg QD as the adult dose for further study in Phase III clinical trials. In addition to the proposed adult Phase III dose of 100mcg, half of the adult dose (50mcg) was evaluated in this pediatric study to provide dose-ranging information and determine the optimal dose in subjects ages 2 to <12 years.

### Demographic and Baseline Assessments

Demographic assessments included age, gender, ethnic origin, height, weight, and rhinitis history. All subjects also had a physical examination, vital signs assessment, nasal examination, 12-lead ECG, and blood hematology and chemistry analyses. The subjects' (and/or subject's parent/guardian) rated symptom scores over the four days prior to randomization (including the morning of randomization) provided the baseline symptom assessment.

### Efficacy Evaluations

All primary and secondary efficacy assessments were based on subject ratings. Because of the difficulty in assessing subjective symptoms in children, particularly in those very young subjects, the primary efficacy analyses and sample size calculation for the pediatric program was based on children ages 6 to < 12 years.

The primary and secondary nasal endpoints for evaluation of efficacy were calculated from daily subject (and/or subject's parent/guardian) -rated nasal scores. The 4 individual nasal symptoms that each subject assessed throughout the study were:

- Nasal congestion

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- Nasal itching
- Rhinorrhea
- Sneezing

The ocular secondary endpoints for evaluating efficacy were calculated using the subject-rated ocular symptoms recorded on the diary card. The three individual ocular symptoms that each subject assessed throughout the study were:

- Eye itching and burning
- Eye tearing and watering
- Eye redness

Subjects used the following scale to assess the severity of each of the 4 nasal and 3 ocular symptoms:

0 = none (symptom is not present)

1 = mild (sign/symptom is clearly present but minimal awareness; easily tolerated)

2 = moderate (definite awareness of sign/symptom that is bothersome but tolerable)

3 = severe (sign/symptom is hard to tolerate; causes interference with activities of daily living and/or sleeping)

Using this 0 to 3 scale, subjects were instructed to score and document their nasal and ocular symptoms twice daily in a reflective manner and once daily in an instantaneous manner on a diary card.

**Primary Efficacy Endpoint**

The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily, reflective total nasal symptom scores (rTNSS) in subjects ages 6 to < 12 years.

The total nasal symptom score (TNSS) was the sum of the 4 individual symptom scores for rhinorrhea, nasal congestion, nasal itching and sneezing, where each symptom was scored on a scale of 0 to 3. (The maximum sum for a TNSS is 12.) The daily reflective rTNSS was defined as the average of the AM and PM rTNSS.

**Secondary Efficacy Endpoints**

Key secondary endpoints for the study were:

- Mean change from baseline over the entire treatment period in AM, pre-dose, instantaneous total nasal symptom scores (iTNSS) in subjects ages 6 < 12 years.
- Overall evaluation of response to therapy (evaluated on a 7-point categorical scale)

Other secondary endpoints included total nasal symptoms, individual nasal symptoms, total ocular symptoms, a composite nasal and ocular symptom score, and time to onset/time to maximal effects assessment.

**Safety Evaluation**

The primary safety endpoints for the study consisted of the following assessments:

- Frequency and type of clinical adverse events
- Results of clinical laboratory tests (hematology and clinical chemistry)

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- Results of nasal examinations
- Vital signs (systolic and diastolic blood pressures, heart rate)
- 12-lead electrocardiograms (ECGs)

**Data Analysis****Sample Size**

The planned sample size was based on the primary efficacy endpoint, the mean change from baseline in daily rTNSS over the entire treatment period in subjects ages 6 to <12 years.

A total of 576 subjects were required for this study, with 192 subjects (approximately 48 (25%) subjects ages 2 to <6 years and 144 (75%) subjects ages 6 to <12 years) in each of the three treatment groups: FF50, FF100, and placebo. Data from the FF dose-ranging study (GSK FFR20001) suggested that a reasonable assumption for the standard deviation of the mean change from baseline over the entire treatment period in daily rTNSS was 2.6. Using a two-sample t-test with a two-sided significance level of 0.05, the proposed sample size should provide 90% power to detect a difference of 1.0 between active treatment and placebo.

**Study Populations**

The Intent-to-Treat (ITT) population was defined as all randomized subjects who receive at least one dose of study drug. The ITT population was used for study population and safety analyses. A subset of the ITT population, the ITT population who were 6 to < 12 years of age, was the population of interest for analysis of efficacy data. The primary and key secondary efficacy endpoints were also analyzed for the entire ITT Population as supportive data.

The pharmacokinetic (PK) population included all subjects who provided plasma samples for measurement of FF concentration.

**Primary and Secondary Efficacy Analyses**

The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily reflective TNSS (rhinorrhea, nasal congestion, nasal itching and sneezing), as evaluated on a 4-point categorical scale.

The primary analysis method was the pairwise comparisons of treatment groups (active vs. placebo) using analysis of covariance (ANCOVA) adjusting for baseline reflective TNSS, region, age, gender, and season.

Multiplicity adjustments were made for the results from the primary efficacy analyses. The multiple comparisons between each of the two active doses and placebo for the primary efficacy endpoint were performed in the following sequence to control the Type I error rate at 0.05:

- The comparison of FF100 vs. vehicle placebo nasal spray
- The comparison of FF50 vs. vehicle placebo nasal spray.

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Any p-values  $\leq 0.05$  were identified as nominally significant. The secondary efficacy measures on nasal symptoms, ocular symptoms, and combined nasal and ocular symptoms were analyzed similarly to the primary analysis. However, no multiplicity adjustments were made on any secondary efficacy endpoints.

### Onset of Action/Time to Maximal Effect

The onset of action was assessed by the mean change from baseline in AM pre-dose iTNSS and the mean change from baseline in daily rTNSS (Days 1 to 14) and supported by the mean changes from baseline in AM and PM rTNSS.

The time to maximum effect was defined as the earliest day that the mean change from baseline in daily rTNSS demonstrated the greatest reduction as compared with placebo.

## Results

### Study Population

#### Disposition

A total of 821 subjects were screened for this study at the 57 investigative sites. Five hundred fifty-four subjects were randomized and received at least one dose of study drug and comprised the ITT population. Subject enrollment was stratified by region (based on sites' geographic location) and age group; 448 subjects were 6 to <12 years of age and 105 subjects were 2 to <6 years of age. The number of subjects enrolled at each site ranged between 1 (<1%) and 21 (4%). Ninety-seven percent of subjects completed the study. Premature withdrawals occurred for 18 subjects (3%) and ranged from 3 (2%) in the FF 100 group to 9 (5%) in the FF 50 group. Six subjects (3%) in the placebo group withdrew prematurely. The most common reason for subject withdrawal was an adverse event (10 subjects, 2%). The placebo and FF50 groups each had 4 subjects (2%) withdrawn due to an AE, while the FF100 group had 2 subjects (1%) withdraw due to an AE [Table 4 FFR100010 Study Report, page 53]

*Reviewer's Comment: Very few subjects withdrew from the study and those that did were fairly equally distributed across all treatment groups.*

There was one notable problem with randomization of subjects which was responsible for incorrect randomization for 13-14% of subjects. Prior to April 22, 2005, age group stratification was not being performed by the automated randomization system resulting in all subjects randomized prior to that date being assigned a treatment from the randomization schedule for the 2 < 6 years of age strata. Additional subjects were added to the 6 to <12 years of age strata to ensure adequate enrollment in this population and after study completion and unblinding, subjects who had been incorrectly stratified to the 2 to <6 years of age group were included in their correct age group for analyses.

*Reviewer's Comment: While unfortunate, the error in randomization was dealt with appropriately and would not affect the primary analysis.*

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**Demographics**

Demographics were similar across treatment groups. The mean age was 8.1 years and was similar between treatment groups. Most subjects in each treatment group were in the 6 < 12 years of age subgroup (79-83%). The majority of the subjects were White (80%) with 14% being Black. Males comprised approximately 60% of the population. Most subjects reported having SAR for either  $\geq 2$  years to <5 years (40% to 51%) or  $\geq 5$  years to <10 years (30% to 38%). In the placebo, FF50, and FF100 groups, 75%, 71%, and 71%, and of subjects, respectively, reported having PAR. Baseline demographics are listed in the following table.

**Demographics and Baseline Characteristics** [Table 6 FFR100010 Study Report, page 56]

Demographic	Placebo N=186	Fluticasone furoate 50mcg N=184	Fluticasone furoate 100mcg N=184	Total N=554
<b>Age (years)</b>				
Mean (SD)	8.0 (2.55)	8.2 (2.43)	8.0 (2.54)	8.1 (2.50)
Min-Max	2-12	2-11	2-11	2-12
<b>Age Group, n (%)</b>				
2 to <6 yr	35 (19)	32 (17)	38 (21)	105 (19)
6 to <12 yr	150 (81)	152 (83)	146 (79)	448 (81)
$\geq 12$	1 (<1)	0	0	1 (<1)
<b>Gender, n (%)</b>				
Female	78 (42)	80 (43)	73 (40)	231 (42)
Male	108 (58)	104 (57)	111 (60)	323 (58)
<b>Race<sup>2</sup>, n (%)</b>				
White	148 (80)	156 (85)	140 (76)	444 (80)
Black	30 (16)	22 (12)	26 (14)	78 (14)
Other	8 (4)	6 (3)	18 (10)	32 (6)
<b>Ethnicity, n (%)</b>				
Hispanic/Latino	33 (18)	25 (14)	41 (22)	99 (18)
Non-Hisp/Latino	153 (82)	159 (86)	143 (78)	455 (82)
<b>Height (cm)</b>				
Mean (SD)	132.4 (17.32)	132.8 (15.66)	131.2 (16.68)	132.1 (16.55)
Min-Max	86-171	91-165	76-168	76-171
<b>Weight (kg)</b>				
Mean (SD)	34.3 (14.79)	32.9 (12.31)	33.2 (12.77)	33.4 (13.33)
Min-Max	11-82	13-87	13-77	11-87
<b>Duration of SAR, n (%)</b>				
$\geq 6$ months to <1 year	7 (4)	2 (1)	11 (6)	20 (4)
$\geq 1$ to <2 years	25 (13)	22 (12)	28 (15)	75 (14)
$\geq 2$ to <5 years	94 (51)	85 (46)	74 (40)	253 (46)
$\geq 5$ to <10 years	55 (30)	70 (38)	65 (35)	190 (34)
$\geq 10$ years	5 (3)	4 (2)	5 (3)	14 (3)

Source Data: Table 6.22 and Table 6.33

*Reviewer's Comment: Approximately 66% of the ITT population had positive skin tests to grass and tree pollens and 18 and 15% had positive skin tests to mold and animal*

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*dander, respectively [Table 6.33 FFR100010 Study Report, page 290].*

Baseline TNSS symptom scores were very similar across treatment groups with rTNSS scores of 8.4, 8.7, and 8.6 for the placebo, FF50, and FF100 groups, respectively [Table 8 FFR100010 Study Report, page 59].

Treatment compliance was assessed by asking the subject or parent/guardian to note in the subject diary that a dose was given that day. Compliance was very similar across treatment groups with 82-85% of subjects in all treatment groups had compliance at  $\geq 80\%$ . Nasal spray malfunctions were reported by a total of 5 out of the 554 subjects in the study.

*Reviewer's Comment: This incidence is even lower because each subject received and used 2 sprayers to administer doses of study medication.*

Pollen measurements were recorded on at least 5 out of 7 days each week during the study by the investigative sites. During the treatment period, maximum exposure to pollen occurred at baseline or during Week 1 in all regions except the Northeast which had maximum exposure occurring during Week 2. Exposure to pollen was less in the Western region than in the other regions. A summary of mean weekly and mean total pollen exposure for the 2-week treatment period by region is provided in the following table.

**Summary of Pollen Counts (particle per cubic meter) (ITT Population)** [Table 10 FFR100010 Study Report, page 62]

Region	Midwest	Northeast	Southcentral	Southeast	West
Number of Sites	19	8	5	15	10
Number of Subjects (n)	206	43	66	112	82
Baseline Mean	221.3	195.4	282.4	214.8	35.6
SD	(247.46)	(242.59)	(217.39)	(443.83)	(54.54)
n	207	42	67	118	81
Week 1 Mean	367.3	281.8	258.6	194.6	31.9
SD	(650.51)	(334.05)	(235.47)	(488.17)	(49.06)
n	204	41	67	113	76
Week 2 Mean	318.5	398.6	238.3	85.2	30.0
SD	(536.80)	(431.56)	(169.13)	(152.3)	(38.65)
n	209	42	67	118	82
Weeks 1- 2 Mean	346.1	329.5	247.8	142.9	32.5
SD	(488.13)	(319.20)	(186.95)	(285.27)	(48.84)

Source Data: Table 6.61

## Efficacy Results

### Primary Efficacy Outcome

The primary efficacy endpoint was the mean change from baseline in the reflective TNSS over the entire treatment period in subjects ages 6 to < 12 years. The reflective TNSS is defined as the average of the AM and PM reflective severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all

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days. The following table summarizes the mean daily rTNSS at baseline and over the 2-week treatment period.

**Mean Change from Baseline in Daily rTNSS (ITT Population)** [Table 11 FFR100010

Study Report, page 65]

<b>Daily rTNSS</b>	<b>Placebo N=150</b>	<b>Fluticasone furoate 50mcg N=152</b>	<b>Fluticasone furoate 100mcg N=146</b>
<b>Baseline, n</b>	150	151	146
<b>Mean (SE)</b>	8.4 (0.14)	8.6 (0.15)	8.5 (0.14)
<b>Weeks 1-2<sup>a</sup>, n</b>	149	152	146
<b>Mean (SE)</b>	5.9 (0.22)	5.9 (0.21)	5.4 (0.22)
<b>Chg from Baseline</b>			
<b>Week 1, n</b>	149	151	146
<b>Mean chg (SE)</b>	-2.2 (0.19)	-2.3 (0.20)	-2.7 (0.18)
<b>Week 2, n</b>	146	149	142
<b>Mean chg (SE)</b>	-2.8 (0.23)	-3.2 (0.24)	-3.7 (0.23)
<b>Weeks 1-2<sup>a</sup>, n</b>	149	151	146
<b>Mean change (SE)</b>	-2.5 (0.20)	-2.7 (0.21)	-3.1 (0.19)
<b>LS mean chg (SE)<sup>b</sup></b>	-2.54 (0.21)	-2.71 (0.20)	-3.16 (0.21)
<b>LS mean difference<sup>b</sup></b>	—	-0.161	-0.616
<b>p-value vs. placebo<sup>b</sup></b>	—	0.553	0.025
<b>95% CI<sup>b</sup></b>	—	(-0.69, 0.37)	-1.15, -0.08

Source Data: Table 7.1 and Table 7.2

a. Entire treatment period;

b. Based on ANCOVA adjusting for baseline daily rTNSS, region, age, gender, and season.

SE = Standard error; LS = Least square; CI = Confidence Interval;

LS mean Difference = LS mean Change in active – LS mean Change in placebo

Baseline mean daily rTNSS values were very similar across all treatment groups ranging from 8.4-8.6 out of a possible 12. The LS mean change from baseline over the entire treatment period in daily rTNSS was greater for FF100 (-3.16) compared with placebo (-2.54) with the LS mean difference between FF100 and placebo (-0.616) being statistically significant (p=0.025). While the LS mean change in daily rTNSS was numerically greater for FF50 (-2.71) compared with placebo (-2.54) the LS mean difference was not statistically significant (LS mean difference: -0.161, p=0.553).

**Reviewer's Comment:** *Since the FF50 dose was shown to be efficacious in the adult dose-ranging study, the lack of efficacy in this pediatric SAR study is likely due to an even greater degree of variation in subjective symptom scoring in children compared to adults. The FF50 treatment group decrease in rTNSS was going in the right direction, however.*

For the ITT Population, significant differences in LS mean changes from baseline in daily rTNSS in favor of FF100 compared with placebo were observed over the entire treatment period (-0.609, p=0.012). Differences for the FF50 group, again, were not significant.

**Secondary Efficacy Outcomes**

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Pre-dose AM iTNSS was identified as a key secondary endpoint. The LS mean change from baseline over the entire treatment in AM pre-dose iTNSS was numerically greater for both FF100 (-2.80) and FF50 (-2.37) compared with placebo (-2.13), however, the LS mean difference, as it was for the primary endpoint, was significant only for the FF100 group (-0.668,  $p=0.015$ ) [Table 13 FFR100010 Study Report, page 68].

Another key secondary endpoint was the overall response to therapy over the entire treatment period using a 7-point categorical scale in which subjects rated their response to therapy as Significantly Improved, Moderately Improved, Mildly Improved, No Change, Mildly Worse, Moderately Worse, or Significantly Worse. Subject assessment of their overall response to therapy was rated as “**significantly improved**” by a greater number of subjects in the FF100 group (28%) and FF50 group (20%) as compared with placebo (13%). Consistent with the results of the primary endpoint, the treatment difference in the overall response to therapy was significant for FF100 compared with placebo ( $p<0.001$ ) but not significant for FF50 ( $p=0.083$ ).

There were many other secondary endpoints for the study including:

- mean change from baseline in am rTNSS
- mean change from baseline in pm rTNSS
- mean % change from baseline in
  - daily rTNSS
  - am iTNSS
- mean change from baseline daily rTNSS, am rTNSS, and pm rTNSS individual symptom scores of rhinorrhea, nasal congestion, nasal itching, and sneezing
- mean change from baseline in reflective total ocular symptom score (rTOSS)
- mean change from baseline in am iTOSS
- mean change from baseline in total symptom scores [(TSS) TNSS + TOSS]
  - daily rTSS
  - am iTSS
  - am TSS
  - pm TSS

For the majority of the nasal symptom-derived endpoints, consistent with the primary and key secondary endpoints, there was a significant difference between the FF100 treatment group and placebo but no with the FF50 group.

For ocular symptoms scores, neither the FF100 nor FF50 group showed a statistical difference in symptom scores compared to placebo.

### Onset of Action

The onset of effect was assessed for subjects ages 6 to <12 years by the mean change from baseline in AM pre-dose iTNSS and the mean change from baseline in daily rTNSS. A significant treatment difference in mean change from baseline for AM pre-dose iTNSS was first observed on Day 6 ( $p=0.035$ ) for FF100 and significance was maintained over

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the treatment period, except for Day 14 ( $p=0.184$ ). For the FF50 group, a significant treatment difference in mean change from baseline for AM pre-dose iTNSS was only observed on Day 12 ( $p=0.040$ ). For rTNSS, a significant treatment difference in mean change from baseline for daily rTNSS was first observed on Day 4 ( $p=0.046$ ) for FF100. Significance was maintained ( $p\leq 0.046$ ) over the treatment period, except for Days 5, 9, 10, and 14. Similar to the iTNSS, for the FF50 group, a significant treatment difference in mean change from baseline for daily rTNSS for was only observed on Day 12 ( $p=0.044$ ) [Section 7.3.5 FFR100010 Study Report, pages 87-88].

The time to maximal effect was defined per protocol as the earliest day during the treatment period that the mean change from baseline in daily rTNSS demonstrated the greatest reduction for the FF treatments as compared to placebo. The greatest LS mean difference between the both FF100 and FF50 compared with the placebo group (maximum effect) occurred on Day 12 ( $-1.207$ ,  $p<0.001$  for FF100 and  $-0.701$ ,  $p=0.044$  for FF50) [Section 7.3.6 FFR100010 Study Report, page 88].

**Safety**

*Reviewer's Comment: The safety findings from this study, along with the safety data from the other placebo-controlled studies, will be reviewed in depth in the Integrated Review of Safety section of this review. Brief observations are described below.*

**Extent of Exposure**

Per protocol, subjects were to be dosed for 15 days. The mean number of days of exposure for subjects in the placebo, FF50, and FF100 groups was 15.0, 15.1, and 15.3 days, respectively [Section 8.1 FFR100010 Study Report, page 90].

**Adverse Events**

Thirty-seven subjects (20%) in the placebo group, 55 subjects (30%) in the FF50 group, and 55 subjects (30%) in the FF100 group experienced at least one AE during the treatment period. The most common AE was headache which was the only event that occurred at a greater than 3% incidence and was more common in the FF groups than in the placebo group. One (<1%) subject in the placebo group, 3 (2%) subjects in the FF50 group, and 5 (3%) subjects in the FF100 group reported nasopharyngitis (common cold) during the treatment period. Epistaxis was reported in 4 (2%) subjects in the placebo group, 5 (3%) subjects in the FF50 group, and in 4 (2%) of subjects in the FF100 group. The following table summarizes AEs with a greater than 1% incidence and more common in the FF groups.

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 Adverse Events with Incidence Greater than or Equal to 1% in Either Fluticasone Furoate Group and More Common than Placebo (ITT Population) [Table 29  
 FFR100010 Study Report, page 92]

Adverse Event (Preferred Term)	Number (%) of Subjects		
	Placebo N=186	Fluticasone furoate 50mcg N=184	Fluticasone furoate 100mcg N=184
Subjects with any Adverse Event	37 (20)	55 (30)	55 (30)
Headache	7 (4)	8 (4)	11 (6)
Nasopharyngitis	1 (<1)	3 (2)	5 (3)
Pyrexia	0	4 (2)	5 (3)
Abdominal pain upper	2 (1)	0	5 (3)
Cough	1 (<1)	4 (2)	2 (1)
Asthma	1 (<1)	4 (2)	1 (<1)
Pharyngolaryngeal pain	1 (<1)	3 (2)	2 (1)
Gastroenteritis viral	1 (<1)	1 (<1)	3 (2)
Upper respiratory tract infection	1 (<1)	3 (2)	1 (<1)
Ear infection	0	4 (2)	0
Vomiting	0	4 (2)	0
Conjunctivitis allergic	0	2 (1)	1 (<1)
Excoriation	1 (<1)	2 (1)	0

Source Data: Table 8.7, Table 8.8, and Table 8.9

#### Deaths, Serious Adverse Events, and Events Leading to Withdrawal

No deaths were reported during the study. There was one SAE reported in a subject in the placebo group for diabetes mellitus on Study Day 3.

A total of 10 subjects (1%) withdrew from the study because of an AE, 4 (2%) subjects from the placebo group, 4 (2%) from the FF50 group, and 2 (1%) from the FF100 group. AEs leading to withdrawal in the placebo group were epistaxis, headache, and nasal congestion, diabetes mellitus, asthma with acute sinusitis, and rhinitis. For the FF50 group, AEs leading to withdrawal were listed as drug hypersensitivity, conjunctivitis, asthma, nasopharyngitis and ear infection, conjunctivitis, nasopharyngitis, asthma, and vomiting, and cough with post-nasal drip. For the FF100 group, AEs leading to withdrawal included asthma and allergic conjunctivitis [Section 8.4 FFR100010 Study Report, pages 94-97.

#### Laboratory Results

The majority of subjects in each treatment group ( $\geq 84\%$  for hematology and  $\geq 90\%$  for chemistry) had either no change in hematology or chemistry parameters or a shift into the normal range. Although there were isolated laboratory test values outside the normal ranges for several subjects as assessed by shift table, no treatment-related changes were noted for active treatment versus placebo. One subject (Subject 122) receiving placebo

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was discontinued due to the onset of diabetes mellitus insulin dependent. The subject had a normal glucose value (5.3mmol/L) at baseline, however, the Early Withdrawal visit glucose was above the normal range (27.5mmol/L) [Sections 8.6.2.1 and 8.6.2.2 FFR100010 Study Report, pages 98-101].

### **Nasal Exams, Vital Signs, and Electrocardiograms**

There were no dose-related clinically meaningful adverse changes from baseline in findings on nasal exam (edema, crusting, bleeding, secretions, ulceration, and polyps) vital signs or ECGs in either active treatment group compared to placebo. Specifically, the incidence of mucosal bleeding declined from 5% at randomization to 3% at Week 2 for placebo subjects and from 5% at randomization to 2% at Week 2 for FF50 subjects. An increase from 4% to 5% was seen in the FF100 subjects [Sections 8.7 and 8.8 FFR100010 Study Report, pages 102-105].

### **Summary and Discussion**

In pediatric subjects aged 6 < 12 years, FF100 but not FF50 once daily demonstrated statistically significantly greater reductions ( $p=0.025$ ) in SAR symptoms versus placebo for the primary endpoint of mean change from baseline over the entire treatment period in rTNSS although the FF50 group did demonstrate a numerical beneficial treatment effect. These results were consistent for all nasal-symptom based secondary endpoints as well. Neither the FF100 nor FF50 doses on fluticasone furoate showed a statistical benefit in reducing the ocular symptoms of allergic rhinitis (watering, redness, and itching). In this pediatric SAR trial the onset of action for the FF100 group was on Day 6 and the maximal effect was reached on Day 12.

No significant safety signals were detected at any dose level. Headache was the most common AE and the incidence of epistaxis, an AE associated with use of inhaled corticosteroid use, was low and not greater in the treatment groups than in placebo.

*Reviewer's Comment: Unlike the adult dose-ranging study in which FF50 demonstrated efficacy for the primary and virtually all secondary endpoints, the benefit of FF50 in this trial, while in the right direction, did not meet statistical significance nor did either dose of FF benefit ocular symptoms.*

### 10.1.12 STUDY # FFR30008

**A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Safety and Efficacy of Once-Daily, Intranasal Administration of GW685698X (fluticasone furoate) Aqueous Nasal Spray 50mcg and 100mcg for 12 Weeks in Pediatric Subjects Ages 2 to <12 Years with Perennial Allergic Rhinitis (PAR)**

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**Protocol****Administrative**

Study initiated: February 23, 2005  
Study completed: November 23, 2005  
Clinical Centers: 61 study sites: 39 in the United States, 5 in Argentina, 5 in Italy, 4 in Slovakia, 3 in Mexico, 3 in Finland, and 2 in Chile.  
Study report dated: April 2006  
Study Sponsor: GlaxoSmithKline (GSK)  
Medical Officer: Kathy Rickard, M.D., GSK

**Objective/Rationale**

The primary objectives of this study were to compare the efficacy and safety of GW685698X (fluticasone furoate) nasal spray 50mcg and 100mcg once daily (QD) with vehicle placebo nasal spray over a period of 12 weeks and to determine the optimal dose in pediatric subjects (ages 2 to <12 years) with PAR.

**Study Design**

This study is a randomized, double-blind, placebo-controlled, parallel group, three-arm, multicenter, study of the efficacy and safety of fluticasone furoate (FF) aqueous nasal spray 50 and 100mcg for 12 weeks in 558 pediatric subjects ages 2 < 12 years with PAR. After a 7-14 day screening period, subjects who met the specified symptom criteria were randomized to 12 weeks treatment with FF 50mcg (FF50), FF100mcg (FF100), or vehicle placebo. Subjects were seen in the clinic weekly for the first 2 weeks, then every 2 weeks thereafter. Treatments were either self-administered or administered with the help of a parent/guardian once daily in the AM. The use of loratadine was allowed on an as-needed basis as a rescue allergy medication for subjects 2 < 6 years of age throughout the study period and for subjects 6 < 12 years of age after the 4-week study period. The primary efficacy measure for the study was the mean change from baseline over the entire treatment period in daily reflective, total nasal symptom scores (rTNSS), which were entered daily into a study diary. Key secondary measures were the mean change from baseline over the entire treatment period in AM, pre-dose, instantaneous, total nasal symptom scores (iTNSS) and an overall evaluation of response to therapy. All efficacy measures were based on subject or the **subject's parent/guardian** assessments. Subject compliance was assessed with the diary and by inspection of the medication bottles. Safety measures included AEs, routine laboratory tests (hematology and clinical chemistry), physical examinations, nasal examinations, vital signs, ECGs, 24-hour urinary cortisol (6 to < 12 year olds only), and ophthalmic examinations (slit-lamp evaluation for cataracts, and changes in intraocular pressure). Pharmacokinetic assessments of FF were also conducted.

**Study Population**

A total of 558 subjects were enrolled in the study, 185 in each of the FF50 and FF100 groups and 188 in the placebo group. Enrollment for the 2 < 6 years of age group was

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planned to comprise approximately 25% of the study population.

**Main Inclusion Criteria**

1. Male or premenarchal females ages 2 < 12 years except in Bulgaria (4 to <12 years) and Argentina (6 to <12 years)
2. Diagnosis of PAR
  - PAR was defined as follows:
    - Medical history and past treatment of PAR. PAR symptoms included nasal congestion, rhinorrhea, sneezing, and nasal itching. For subjects 4 to <12 years of age, 1 year clinical history and treatment of PAR was necessary and for subjects 2 to <4 years of age, a 6-month clinical history and treatment of PAR was required.
    - A positive skin test (by prick method) or in vitro tests (RAST/PRIST) to an appropriate perennial allergen (animal dander, house dust mites, cockroach, mold) within last 12 months prior to screening). A positive skin test was defined as a wheal  $\geq 3$ mm larger than the diluent control for prick testing.

Subjects who met the above criteria for PAR and who also had a history of allergy to a seasonal pollen that would be present in their geographic area during study participation were NOT eligible for randomization.

**Main Exclusion Criteria**

1. Significant concomitant medical conditions, defined as:
  - a. a historical or current evidence of clinically significant uncontrolled disease of any body system (e.g., tuberculosis, psychological disorders).
  - b. a severe physical obstruction of the nose (e.g., deviated septum or nasal polyp) that could have affected the deposition of double-blind intranasal study drug
  - c. recent nasal septal surgery or nasal septal perforation
  - d. asthma, with the exception of mild intermittent asthma
  - e. rhinitis medicamentosa
  - f. bacterial or viral infection (e.g., common cold) of the upper respiratory tract within one week of Visit 1 or during the screening period
  - g. documented evidence of acute or significant chronic sinusitis, as determined by the individual investigator
  - h. glaucoma and/or cataracts or ocular herpes simplex
  - i. physical impairment that would have affected **subject's ability** to participate safely and fully in the study
  - j. clinical evidence of a Candida infection of the nose or oropharynx
  - k. If the subject or his/her parent or legal guardian had a condition that limited the validity of informed consent or that would confound the interpretation of the study results
  - l. A subject was not eligible if he/she currently had chickenpox or measles, or had been exposed to chickenpox or measles during the last three weeks prior to the study and was non-immune.
2. Use of corticosteroids, defined as:
  - Intranasal corticosteroid within four weeks prior to Visit 1.

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- Inhaled, oral, intramuscular, intravenous, and/or dermatological corticosteroid (with the exception of hydrocortisone cream/ointment, 1% or less) within eight weeks prior to Visit 1.
3. Use of other allergy medications within the timeframe indicated relative to Visit 1
    - Intranasal or ocular cromolyn within 14 days prior to Visit 1
    - Short-acting prescription and OTC antihistamines within 3 days prior to screening visit
    - Long-acting antihistamines within 10 days prior to Visit 1: loratadine, desloratadine, fexofenadine, cetirizine
    - Oral or intranasal decongestants within 3 days prior to Visit 1
    - Intranasal anticholinergics within 3 days prior to Visit 1
    - Oral antileukotrienes within 3 days of Visit 1
    - **Subcutaneous omalizumab (Xolair<sup>†</sup>)** within 5 months of Visit 1
    - Intranasal antihistamines within 2 weeks prior to Visit 1

Note: Subjects were not permitted to use any ocular antihistamines, artificial tears, eyewashes, homeopathic preparations, irrigation solutions, lubricants, sympathomimetic preparations, vasoconstrictors and combinations during the screening and treatment periods. No exclusion period prior to Visit 1 was required for these treatments.

4. Use of other medications that may have affected allergic rhinitis
  - Chronic use of concomitant medications, such as tricyclic antidepressants, that would have affected assessment of the effectiveness of the study drug.
  - Chronic use of long-acting beta-agonists (e.g., salmeterol) or other intranasal medications
5. Use of immunosuppressive medications 8 weeks prior to screening and during the study
6. Immunotherapy as long as the immunotherapy was not initiated within 30 days of Visit 1 and if the dose had remained fixed over the 30 days prior to Visit 1, and the dose remained fixed for the duration of the study.
7. Use of any medications that significantly inhibit the cytochrome P450 subfamily enzyme CYP3A4, including ritonavir and ketoconazole
8. Known hypersensitivity to corticosteroids or any excipients in the product
9. Known clinical trial/experimental medication experience within 30 days of Visit 1
10. Affiliation with investigational site
11. Findings of an abnormal ECG
12. Findings of a clinically significant laboratory abnormality

**Randomization Criteria**

At Visit 2 (randomization visit), the subject must have met the following criteria:

1. Average of the last 8 reflective Total Nasal Symptoms Scores (rTNSS) assessments, comprised of 4 morning (AM) assessments, 4 evening (PM) assessments, over the four 24-hour periods prior to randomization must have been  $\geq 6$ . This included the AM assessment on the morning of the randomization visit.
2. Average of the last 8 reflective nasal symptom assessments for congestion, comprised

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of 4 AM assessments and 4 PM assessments, over the four 24-hour periods prior to randomization must have been  $\geq 2$ . This included the AM assessment on the morning of the randomization visit.

3. A subject must have completed 80% of assessments on the screening symptom diary.

4. Subjects completed slit lamp and fundoscopic examinations, including evaluation of cataract formation performed by a licensed ophthalmologist or optometrist and results were within normal limits.

5. Subjects completed an evaluation for glaucoma and changes in intraocular pressure performed by a licensed ophthalmologist or optometrist and results were within normal limits for subjects ages 6 to <12 years, and if completed, for subjects ages 2 to <6 years.

**Withdrawal Criteria**

Premature discontinuation of the study drug was defined as discontinuation of the study drug for more than 2 consecutive days before the end of the study period. Subjects who discontinued administration of study drug prematurely were withdrawn from the study.

Subject withdrawal from the study was required and discontinuation procedures must have been performed, when:

- a subject had been significantly non-compliant with the requirements of the protocol
- a subject had not completed the 12-week treatment period
- a subject had an adverse event that would have, in the **investigator's judgment**, made continued participation in the study an unacceptable risk
- the treatment blind had been broken for a subject, or
- GSK discontinued the study

A subject may have voluntarily discontinued participation in this study at any time. The investigator may have also, at his or her discretion, discontinued the subject from participating in this study at any time.

**Prohibited Medications**

Concomitant use of any prescription or over-the-counter medications that may have affected the duration/severity of rhinitis was not allowed during the study. These are listed in the exclusion criteria.

**Study Procedures**

The following table summarizes the study schedule of evaluations.

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**Schedule of Study Events**

Visit Number	1	2	3	4	5	6	7	8	9	EW <sup>1</sup>	Contact <sup>2</sup>
Days	-14 to -7	0	1	8	15	29	43	57	71	85	
<b>ACTIVITY</b>											
Informed Consent	X										
Subject number assignment	X										
Medical history	X										
Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	
Verification of inclusion/exclusion criteria	X	X									
Vital Signs	X								X	X	
Physical examination	X								X	X	
Nasal examination	X	X	X	X	X	X	X	X	X	X	
Schedule ophthalmic examination	X							X			
Review ophthalmic examination results	X	X							X	X	
Skin testing (if not done within 12 months of Visit 1)	X								X	X	
Clinical laboratory tests	X										
Dispense a 24-hour urine collection kit <sup>4</sup>	X							X			
Obtain the 24-hour urine collection kit		X							X	X	
12-lead electrocardiograms (ECGs)	X								X	X	
Pharmacokinetic sampling <sup>5</sup>						X					
Issue screening diary card	X										
Collect/Review diary cards		X	X	X	X	X	X	X	X	X	
Adverse event assessment		X	X	X	X	X	X	X	X	X	X
Randomization number assignment		X									
Nasal spray technique demonstration		X									
Dispense rescue medication (as needed) <sup>6</sup>		X	X	X	X	X	X	X	X		
Dispense double-blind study drug to eligible subjects		X									
Issue treatment diary cards		X	X	X	X	X	X	X	X		
Pharmacogenetic sampling <sup>7</sup>						X				X	X
Collect study drug and allergy rescue medications			X	X	X	X	X	X	X	X	X

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## Study Treatments

Fluticasone furoate was manufactured as a \_\_\_\_\_ aqueous suspension containing \_\_\_\_\_% (w/w) of micronized FF. The \_\_\_\_\_ consisted of \_\_\_\_\_% w/w benzalkonium chloride plus \_\_\_\_\_% disodium edetate. Each nasal spray device contained a volume of suspension sufficient to deliver a minimum of 120 actuations. Each spray of the suspension contained approximately 25mcg of fluticasone furoate. The placebo nasal spray was comprised of the FF vehicle.

*Reviewer's Comment: Later analyses demonstrated that 27.5 mcg of study drug was emitted with each spray. Thus, doses actually received were 55 and 110mcg of FF.*

All randomized subjects received two aqueous nasal sprays, Nasal Spray A and Nasal Spray B. The subjects were instructed to administer one spray to each nostril from each nasal spray, beginning with Nasal Spray A, each morning. The contents on Nasal Spray A and B were different (FF or placebo) for each dosing group such that each subject would administer the proper dose of study medication for that group.

## Dose Rationale

The doses selected for this study, 50mcg and 100mcg QD, were based on the results of GSK study FFR20001, which compared the safety and efficacy of 50mcg, 100mcg, 200mcg, and 400mcg QD doses of FF in adults and adolescents ( $\geq 12$  years of age) with SAR. All doses of fluticasone furoate evaluated in that dose-ranging study demonstrated statistically significantly greater reductions in SAR symptoms versus vehicle placebo. A final comparison of the efficacy, safety, and onset findings supported the proposed choice of 100mcg QD as the adult dose for further study in Phase III clinical trials. In addition to the proposed adult Phase III dose of 100mcg, half of the adult dose (50mcg) was evaluated in this pediatric study to provide dose-ranging information and determine the optimal dose in subjects ages 2 to <12 years.

## Demographic and Baseline Assessments

Demographic assessments included age, gender, ethnic origin, height, weight, and rhinitis history. All subjects also had a physical examination, vital signs assessment, nasal examination, 12-lead ECG, and blood hematology and chemistry analyses. The subjects' (and/or subject's parent/guardian) rated symptom scores over the four days prior to randomization (including the morning of randomization) provided the baseline symptom assessment.

## Efficacy Evaluations

All primary and secondary efficacy assessments were based on subject ratings. Because of the difficulty in assessing subjective symptoms in children, particularly in those very young subjects, the primary efficacy analyses and sample size calculation for the pediatric program was based on children ages 6 to < 12 years.

The primary and secondary nasal endpoints for evaluation of efficacy were calculated from daily subject (and/or subject's parent/guardian) -rated nasal scores. The 4 individual nasal symptoms that each subject assessed throughout the study were:

- Nasal congestion

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- Nasal itching
- Rhinorrhea
- Sneezing

The ocular secondary endpoints for evaluating efficacy were calculated using the subject-rated ocular symptoms recorded on the diary card. The three individual ocular symptoms that each subject assessed throughout the study were:

- Eye itching and burning
- Eye tearing and watering
- Eye redness

Subjects used the following scale to assess the severity of each of the 4 nasal and 3 ocular symptoms:

0 = none (symptom is not present)

1 = mild (sign/symptom is clearly present but minimal awareness; easily tolerated)

2 = moderate (definite awareness of sign/symptom that is bothersome but tolerable)

3 = severe (sign/symptom is hard to tolerate; causes interference with activities of daily living and/or sleeping)

Using this 0 to 3 scale, subjects were instructed to score and document their nasal and ocular symptoms twice daily in a reflective manner and once daily in an instantaneous manner on a diary card.

### **Primary Efficacy Endpoint**

The primary efficacy endpoint was the mean change from baseline over the first 4 weeks of the treatment period in daily, reflective total nasal symptom scores (rTNSS) in subjects **ages 6 to < 12 years. The subjects' (and/or subject's parent/guardian) rated symptom scores** over the four days prior to randomization (including the morning of randomization) provided the baseline symptom assessment.

The total nasal symptom score (TNSS) was the sum of the 4 individual symptom scores for rhinorrhea, nasal congestion, nasal itching and sneezing, where each symptom was scored on a scale of 0 to 3. (The maximum sum for a TNSS is 12.) The daily reflective rTNSS was defined as the average of the AM and PM rTNSS.

### **Secondary Efficacy Endpoints**

Key secondary endpoints for the study were:

- Mean change from baseline over the first 4 weeks of the treatment period in AM, pre-dose, instantaneous total nasal symptom scores (iTNSS) in subjects ages 6 < 12 years.
  - Overall evaluation of response to therapy (evaluated on a 7-point categorical scale)
- Other secondary endpoints included total nasal symptom and individual nasal symptom scores

### **Safety Evaluation**

The primary safety endpoints for the study consisted of the following assessments:

- Frequency and type of clinical adverse events
- Results of clinical laboratory tests (hematology and clinical chemistry)

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- 24-hour urinary cortisol (subjects ages 6 to <12 years only)
- Results of nasal examinations
- Ophthalmic examinations (slit-lamp evaluation for cataracts, changes in intraocular pressure);
- Vital signs (systolic and diastolic blood pressures, heart rate)
- 12-lead electrocardiograms (ECGs)

**Data Analysis****Sample Size**

The planned sample size was based on the primary efficacy endpoint, the mean change from baseline in daily rTNSS over the first 4 weeks of the treatment period in subjects ages 6 to <12 years.

A total of 432 subjects ages 6 to <12 years were needed for this study, with 144 subjects in each of the three treatment groups: FF50, FF100, and placebo. The study also planned to enroll 144 subjects ages 2 to <6 years (48 per treatment group), approximately 25% of the total randomized subjects, to provide sufficient safety data and supportive efficacy data in this young age group. The standard deviation for the mean change from baseline in daily rTNSS over the first 4-week treatment period was assumed to be 2.6, based on a previous GSK allergy rhinitis study. The proposed sample size would provide 90% power to detect a difference of 1.0 between active treatment and placebo in mean change from baseline over the first 4-week treatment period in daily rTNSS in children ages 6 to <12 years, using a two-sample t-test with a 0.05 two-sided significance level.

**Study Populations**

The Intent-to-Treat (ITT) population was defined as all randomized subjects who receive at least one dose of study drug. The ITT population was used for study population and safety analyses.

For the purposes of efficacy analyses, a decision was made by GSK after study treatment unblinding to establish a Reduced ITT (RITT) population. The RITT Population (N=431) excluded the 8 subjects (2 FF50, 4 FF100, and 2 in the placebo group) enrolled at Dr. Rooklin's site (Inv. No. 018742) because of study conduct irregularities based on the standard GSK monitoring and auditing practices. A subset of the RITT population, the RITT population who were 6 to < 12 years of age, was the population of interest for analysis of efficacy data.

The 24-hour urinary cortisol (UC) data were collected for subjects who were at least 6 years old at randomization. The 24-hour urinary cortisol excretion was summarized for the UC Population. The UC Population excluded subjects from the ITT Population whose urine samples (from either collection visit) were considered to have confounding factors that could affect the interpretation of the results. These include:

- urine volumes of <400mLs for 6 to < 12 years; and, 24-hour creatinine excretion below the lower limit of normal range (defined as 8mg/kg/24hrs)
- collection time intervals outside 24 ± 2 hours

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- used a protocol-prohibited systemic (oral, intramuscular, intravenous) corticosteroid within six months prior to the start time of any urine sample collection
- used a protocol-prohibited inhaled, ocular, and/or dermatological corticosteroid within eight weeks prior to the start time of any urine sample collection
- used a protocol-prohibited intranasal corticosteroid within 4 weeks prior to the start time of any urine sample collection

The pharmacokinetic (PK) population included all subjects who provided plasma samples for measurement of FF concentration.

**Primary and Secondary Efficacy Analyses**

The primary efficacy endpoint was the mean change from baseline over the first 4 weeks of the treatment period in daily reflective TNSS (rhinorrhea, nasal congestion, nasal itching and sneezing), as evaluated on a 4-point categorical scale.

The primary analysis method was the pairwise comparisons of treatment groups (active vs. placebo) using analysis of covariance (ANCOVA) adjusting for baseline reflective TNSS, region, age, gender, and season.

Multiplicity adjustments were made for the results from the primary efficacy analyses. The multiple comparisons between each of the two active doses and placebo for the primary efficacy endpoint were performed in the following sequence to control the Type I error rate at 0.05:

- The comparison of FF100 vs. vehicle placebo nasal spray
- The comparison of FF50 vs. vehicle placebo nasal spray.

Any p-values  $\leq 0.05$  were identified as nominally significant. The secondary efficacy measures were analyzed similarly to the primary analysis. However, no multiplicity adjustments were made on any secondary efficacy endpoints.

**Onset of Action/Time to Maximal Effect**

The onset of action was assessed by the mean change from baseline in AM pre-dose iTNSS and the mean change from baseline in daily rTNSS (Days 1 to 28) and supported by the mean changes from baseline in AM and PM rTNSS.

The time to maximum effect was defined as the earliest day that the mean change from baseline in daily rTNSS demonstrated the greatest reduction as compared with placebo.

**Results****Study Population****Disposition**

A total of 808 subjects were screened for this study at the 61 investigative sites. Five hundred fifty-eight subjects were randomized and received at least one dose of study drug and comprised the ITT population. The RITT Population (N=431) excluded the 8 subjects

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(2 in the placebo group, 2 FF50 group, and 4 in the FF100 group) enrolled at Dr. Rooklin's site in the US (Inv. No. 018742, Site No. 011546) (because of study conduct irregularities). The UC Population (subjects 6 to <12 year of age only) consisted of 319 subjects balanced across treatment groups. The primary reason for subject exclusion from the UC population was that the 24-hour urine cortisol excretion could not be determined (106 subjects). This would include subjects who had either a missing baseline or endpoint cortisol assessment, those with a low urine volume (<400 mL), or the collection time was outside the required time interval of 24±2 hrs. The number of subjects enrolled at each site ranged between 1 (<1%) and 70 (13%). Eighty-eight percent of subjects completed the study. Premature withdrawals occurred in 27 (14%) of subjects in the placebo group compared with 22 (12%) and 17 (9%) in the FF50 and FF100 groups, respectively. The most common reason for subject withdrawal was an adverse event (16 subjects, 3%) and protocol violation (15 subjects 3%). The FF50 group had 6 subjects (3%) withdraw due to an AE while the FF100 group and placebo group had 2 (1%) and 8 (4%) subjects withdraw due to a AEs, respectively. [Table 3 FFR30008 Study Report, page 57]

### Protocol Deviations

The definition of protocol deviation included failure to meet inclusion, exclusion, or randomization criteria, use of prohibited medications, and any other deviations deemed to have the potential for notably influencing study results. At least one inclusion/exclusion/randomization criteria deviation was reported for 14 subjects, comprising 2% to 4% of each treatment group. These reported deviations included not meeting the nasal congestion symptom score requirement (5 subjects), subject did not meet age criteria at randomization (4 subjects), no diagnosis of PAR (2 subjects), not meeting minimum rTNSS requirement (2 subjects), subject had a clinically significant ECG (1 subject), a history of allergy to a seasonal pollen present in the geographic area (1 subject), and did not complete slit lamp and fundoscopic examinations or results not within normal limits (1 subject). The most common deviation during the treatment period, other than the use of prohibited medications, was incorrect randomization of age stratum, which occurred in 2% to 4% of subjects in each treatment group [Table 4 FFR30008 Study Report, page 58].

**Reviewer's Comment:** *In addition to the deviations described above, 3 subjects in the FF50 group and 2 subjects in the FF100 group had cataracts in at least one eye at the Visit 2 ophthalmic exam that were not noted as protocol deviations when they should have been. This error could have the potential to make the eye exam for cataracts difficult to interpret since the incidence of cataracts would be expected to be very low.*

### Demographics

Demographics were similar across treatment groups. The mean age was 7.7 years and was similar between treatment groups. Most subjects in each treatment group were in the 6 < 12 years of age subgroup (77-78%). The majority of the subjects were White (73%) with 4% being Black. The Hispanic/Latino ethnic group comprised 61% of the study population. Males comprised 56% of the population. Most subjects reported having PAR for either ≥2 years to <5 years (54% to 56%) or ≥5 years to <10 years (28% to 31%). In the Placebo, FF50, and FF100 groups, 7%, 5%, and 6% of subjects, respectively, reported also having SAR. Baseline demographics are listed in the following table.

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**Demographics and Baseline Characteristics (ITT Population)** [Table 6 FFR30008 Study Report, page 60]

Demographic	Placebo N=188	Fluticasone furoate 50mcg N=185	Fluticasone furoate 100mcg N=185	Total N=558
<b>Age (years)</b>				
Mean (SD)	7.9 (2.47)	7.7 (2.59)	7.4 (2.50)	7.7 (2.52)
Min-Max	3-12	2-11	2-12	2-12
<b>Age Group, n (%)</b>				
2 to <6 yr	38 (20)	40 (22)	42 (23)	120 (22)
6 to <12 yr	147 (78)	145 (78)	142 (77)	434 (78)
≥12	3 (2)	0	1 (<1)	4 (<1)
<b>Gender, n (%)</b>				
Female	81 (43)	84 (45)	83 (45)	248 (44)
Male	107 (57)	101 (55)	102 (55)	310 (56)
<b>Race<sup>a</sup>, n (%)</b>				
White	141 (75)	136 (74)	131 (71)	408 (73)
Black	6 (3)	8 (4)	9 (5)	23 (4)
Other	41 (22)	41 (22)	45 (24)	127 (23)
<b>Ethnicity, n (%)</b>				
Hispanic/Latino	115 (61)	111 (60)	112 (61)	338 (61)
Non-Hisp/Latino	73 (39)	74 (40)	73 (39)	220 (39)
<b>Height (cm)</b>				
Mean (SD)	130.4 (15.97)	128.6 (17.01)	127.5 (16.31)	128.8 (16.45)
Min-Max	95-169	82-168	86-172	82-172
<b>Weight (kg)</b>				
Mean (SD)	31.3 (10.91)	31.1 (13.01)	30.0 (11.34)	30.8 (11.78)
Min-Max	15-68	11-84	12-65	11-84
<b>Duration of PAR, n (%)</b>				
≥6 months to <1 year	1 (<1)	4 (2)	3 (2)	8 (1)
≥1 to <2 years	23 (12)	22 (12)	22 (12)	67 (12)
≥2 to <5 years	101 (54)	99 (54)	104 (56)	304 (54)
≥5 to <10 years	58 (31)	58 (31)	52 (28)	168 (30)
≥10 years	5 (3)	2 (1)	4 (2)	11 (2)

Source Data: Table 6.37 and Table 6.49

a. White = Arabic/North African heritage or White/Caucasian/European heritage; Black = African/African American heritage only; Other = all other races indicated on CRF

Baseline TNSS symptom scores were very similar across treatment groups with rTNSS scores of 8.5 for all 3 treatment groups [Table 8 FFR30008 Study Report, page 63].

Treatment compliance was assessed by asking the subject or parent/guardian to note in the subject diary that a dose was given that day. Compliance was very similar across treatment groups with 95-97% of subjects in all treatment groups had compliance at ≥ 80%.

Nasal spray malfunctions were reported by a total of 32 out of the 558 subjects in the study. *Reviewer's Comment: The actual incidence of malfunction is lower because each subject received and used 2 sprayers to administer doses of study medication.*

## Efficacy Results

**Primary Efficacy Outcome**

The primary efficacy endpoint was the mean change from baseline in the reflective TNSS over the first 4 weeks of the treatment period in subjects ages 6 to < 12 years in the RITT Population. The reflective TNSS is defined as the average of the AM and PM reflective severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days. The following table summarizes the mean daily rTNSS at baseline and over the 4-week treatment period.

**Mean Change from Baseline in Daily rTNSS (RITT Population)** [Table 10 FFR30008 Study Report, page 67]

Daily rTNSS Ages 6 to <12	Placebo N=147	Fluticasone furoate 50mcg N=144	Fluticasone furoate 100mcg N=140
<b>Baseline, n</b>	147	144	140
Mean (SE)	8.5 (0.13)	8.5 (0.14)	8.6 (0.13)
<b>Weeks 1-4, n</b>	145	144	140
Mean (SE)	5.5 (0.20)	4.8 (0.21)	5.0 (0.23)
<b>Chg from Baseline</b>			
<b>Week 1, n</b>	145	144	140
Mean chg (SE)	-2.2 (0.18)	-2.5 (0.22)	-2.6 (0.21)
<b>Week 2, n</b>	144	143	139
Mean chg (SE)	-3.1 (0.21)	-3.8 (0.24)	-3.5 (0.22)
<b>Week 3, n</b>	144	142	138
Mean chg (SE)	-3.4 (0.21)	-4.2 (0.23)	-4.0 (0.24)
<b>Week 4, n</b>	139	137	135
Mean chg (SE)	-3.6 (0.23)	-4.8 (0.23)	-4.3 (0.23)
<b>Weeks 1-4, n</b>	145	144	140
Mean chg (SE)	-3.0 (0.19)	-3.8 (0.21)	-3.6 (0.21)
LS mean chg (SE) <sup>a</sup>	-3.41 (0.24)	-4.16 (0.24)	-3.86 (0.24)
LS mean difference <sup>a</sup>	—	-0.754	-0.452
p-value vs. placebo <sup>a</sup>	—	0.003	0.073
95% CI <sup>a</sup>	—	-1.24, -0.27	-0.95, 0.04

Source: Table 7.1 and Table 7.2

a. Based on ANCOVA adjusting for baseline daily rTNSS, country, age, and gender;

SE = Standard error; LS = Least square; CI = Confidence Interval;

LS mean Difference = LS mean Change in active – LS mean Change in placebo

Baseline mean daily rTNSS values were very similar across all treatment (8.5-8.6 out of a possible 12). While the LS mean change from baseline over the first 4 week treatment period in daily rTNSS was numerically greater for FF100 (-3.60) compared with placebo (-3.00), the LS mean difference between FF100 and placebo (-0.452) was not statistically significant (p=0.073). The LS mean change in daily rTNSS was also numerically greater for FF50 (-3.80) compared with placebo (-3.00), however, in contrast to the higher FF100 dose, the LS mean difference was statistically significant (LS mean difference: -0.754, p=0.003).

**Reviewer's Comment:** One would normally think it unusual that the FF50 dose would be more effective than the FF100 dose. However, the dose-response curve of nasal steroid

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*products for SAR/PAR is generally quite flat. Also, in this study, because the placebo effect was quite large (a mean LS difference for the placebo group of -3.0), there was less separation in the active treatment groups than otherwise would have occurred. In addition, the FF50 dose was effective in the adult dose-ranging study so it being effective in children with PAR is not that much of a surprise.*

For the entire RITT Population (included the younger 2 < 6 year old population), significant differences in LS mean changes from baseline in daily rTNSS were observed over the first 4 week treatment period for both the FF100 and FF50 treatment groups, although more highly significant for the FF50 group (-0.475, p=0.031 for the FF100 group and -0.812, p<0.001 for the FF50 group) [Table 11 FFR30008 Study Report, page 69].

### Secondary Efficacy Outcomes

Pre-dose AM iTNSS was identified as a key secondary endpoint. The LS mean changes from baseline over the first 4 weeks of the treatment period for RITT subjects 6 < 12 years of age in AM pre-dose iTNSS were significantly greater for both the FF100 (-3.52) and FF50 (-3.62) groups compared with placebo (-2.87) with the LS mean differences between FF100 and placebo (-0.651) and FF50 and placebo (-0.751) both being statistically significant (p=0.009 and p=0.002, respectively) [Table 14 FFR3008 Study Report, page 73].

Another key secondary endpoint was the overall response to therapy over the entire treatment period using a 7-point categorical scale in which subjects rated their response to therapy as Significantly Improved, Moderately Improved, Mildly Improved, No Change, Mildly Worse, Moderately Worse, or Significantly Worse. For RITT subjects 6 to <12 years of age, while a greater percentage of subjects (or subject/guardians) treated with FF100 rated overall response to **therapy as “significantly improved” compared with placebo (26% compared with 20%)**, the treatment difference for overall response to therapy was not statistically significant (p=0.414). However, consistent with the results of the primary endpoint, the treatment difference for overall response to therapy for FF50 compared with placebo was statistically significant (p=0.024) [Table 16 FFR30008 Study Report, Page 76].

Other secondary endpoints for the study included:

- mean change from baseline in am rTNSS
- mean change from baseline in pm rTNSS
- mean % change from baseline in
  - daily rTNSS
  - am iTNSS
- mean change from baseline daily rTNSS, am rTNSS, and pm rTNSS individual symptom scores of rhinorrhea, nasal congestion, nasal itching, and sneezing

For the nasal symptom-derived secondary endpoints listed above, consistent with the results of the primary endpoint, there were significant differences between the FF50 group alone and placebo or for both the FF50 and FF100 doses [Section 7.3 FFR30008 Study Report, pages 73-86].

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### **Onset of Action**

The onset of effect was assessed for subjects ages 6 to <12 years in the RITT population by the mean change from baseline in AM pre-dose iTNSS and the mean change from baseline in daily rTNSS. For the FF100 group, a significant treatment difference in mean change from baseline for AM pre-dose iTNSS was first observed on Day 3 ( $p=0.024$ ) and then on Days 7, 8, 10, and 16-28 with the exception of Day 27. For the FF50 group, a significant treatment difference in mean change from baseline for AM pre-dose iTNSS was first observed on Day 5 ( $p=0.037$ ) and then on Days 10, 11, and 16-28. For rTNSS, a significant treatment difference in mean change from baseline for daily rTNSS was first observed on Day 18 ( $p=0.015$ ) for FF100. Significance was maintained ( $p\leq 0.046$ ) over the treatment period, except for Days 5, 9, 10, and 14. For the FF50 group, a significant treatment difference in mean change from baseline for daily rTNSS was first observed on Day 6 ( $p=0.022$ ) [Section 7.3.3.1 FFR30008 Study Report, pages 86-87].

The time to maximal effect was defined per protocol as the earliest day during the first 4 week of the treatment period that the mean change from baseline in daily rTNSS demonstrated the greatest reduction for the FF treatments as compared to placebo. The greatest LS mean difference between the FF100 group compared with the placebo group occurred on Day 18 ( $-0.804$ ,  $p=0.015$ ) while the maximal effect for the FF50 group occurred on Day 23 ( $-1.529$ ,  $p<0.001$ ) [Section 7.3.3.2 FFR30008 Study Report, page 87].

### **Safety**

*Reviewer's Comment: The safety findings from this study, along with the safety data from the other placebo-controlled studies, will be reviewed in depth in the Integrated Review of Safety section of this review. This section will focus on potential long-term effects of nasal corticosteroids including suppression of the HPA axis and increased intraocular pressure/cataract development.*

### **Extent of Exposure**

The mean number of days of exposure for subjects in the placebo, FF50, and FF100 groups was very similar at 80.0, 79.8, and 81.5 days, respectively [Section 8.1 FFR30008 Study Report, page 89].

### **Adverse Events**

One hundred and eleven subjects (59%) in the placebo group, 103 subjects (56%) in the FF50 group, and 109 subjects (59%) in the FF100 group experienced at least one AE during the treatment period. The most common AE was headache which was reported in 11-12% of subjects in each treatment group. Nasopharyngitis (common cold) was also reported fairly frequently (9-11%) across treatment groups. Epistaxis was reported equally (6%) across all treatment groups. The following table summarizes AEs with a greater than 3% incidence and more common in the FF groups.

**Adverse Events with Incidence >3% in Either Fluticasone Furoate Group and More Common than Placebo (ITT Population)** [Table 26 FFR30008 Study Report, page 92]

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Adverse Event	Number (%) of Subjects		
	Placebo N=188	Fluticasone furoate 50mcg N=185	Fluticasone furoate 100mcg N=185
Subjects with any adverse event	111 (59)	103 (56)	109 (59)
Pharyngolaryngeal pain	13 (7)	13 (7)	10 (5)
Epistaxis	11 (6)	11 (6)	12 (6)
Pyrexia	7 (4)	13 (7)	12 (6)
Cough	10 (5)	8 (4)	13 (7)
Bronchitis	11 (6)	11 (6)	8 (4)
Pharyngitis	4 (2)	4 (2)	7 (4)
Sinusitis	5 (3)	6 (3)	4 (2)
Upper respiratory tract infection	4 (2)	3 (2)	6 (3)
Vomiting	3 (2)	3 (2)	7 (4)

Source Data: Table 8.8

Nasal ulcers were reported as an AE in 2 (1%) subjects in the FF100 group and in no subjects in either the placebo or FF50 groups.

#### Deaths, Serious Adverse Events, and Events Leading to Withdrawal

No deaths were reported during the study. There was one SAE reported in each of the FF50 and FF100 groups during the treatment period and none reported in the placebo group. The subject in the FF50 group was an 11 year old male with a reported term of peritonitis (appendicular) on Study Day 59 and the subject in the FF100 group was an 11 year old female with a reported term of appendicitis on Study Day 21. Dosing was not altered in either subject and both recovered within 4-5 days.

Eight (4%) subjects from the placebo group, 6 (3%) from the FF50 group, and 2 (1%) from the FF100 group withdrew from the study because of an AE. AEs leading to withdrawal in the placebo group were URI, sinusitis, cataract (subcapsular), headache, epistaxis, varicella (2), and asthma.

AEs leading to withdrawal in the FF50 group included URI, asthma (2), varicella, contact dermatitis, and nasal candidiasis and those leading to withdrawal in the FF100 group included fungal skin infection and ear infection [Section 14.2 FFR30008 Study Report, pages 127-132].

*Reviewer's Comment: It is quite unusual that a 7 year old white female in the placebo group would develop a subcapsular cataract (trace) during the course of the study. There were no reports of corticosteroid usage for this child during the treatment period.*

#### Laboratory Results

The majority of subjects in each treatment group ( $\geq 81\%$  for hematology and  $\geq 89\%$  for chemistry) had either no change in hematology or chemistry parameters or a shift into the normal range. Although there were isolated laboratory test values outside the normal ranges for several subjects as assessed by shift table, no treatment-related changes were noted for active treatment versus placebo. One subject (Subject 2199) in the FF50 group had hypoglycemia (2.8 mmol/L) reported as an AE but this was 19 days post-treatment [Sections 8.6.2.1 and 8.6.2.2 FFR30008 Study Report, pages 97-99].

**24-Hour Urine Cortisol excretion**

Urinary cortisol data were analyzed for subjects 6 to <12 years of age in the UC Population. Baseline UC excretion was similar across treatment groups with values of 49.15, 44.3, and 52.43nmol/24 hours in the placebo, FF50, and FF100 groups, respectively. Mean changes from baseline to endpoint in 24-hour UC excretion values were -2.94 (SD=67.5) for placebo, -6.95 (SD=47.43) for the FF50 group, and -12.67 (SD=45.48) for the FF100 group. The geometric means for the ratio of Week 12 to Baseline were 0.90 for placebo, 0.84 for FF50, and 0.79 for the FF100 group. For the UC Population, no subjects in either active group or in the placebo group had 24-hour UC excretion below the normal range at baseline or at endpoint. Urine cortisol excretion data are summarized for the UC population in the following table.

**24-hour Urinary Cortisol Excretion (UC population)** [Table 31 FFR30008 Study Report, page 100]

<b>Cortisol Concentration (nmol/24 hr)</b>	<b>Placebo N=107</b>	<b>Fluticasone furoate 50mcg N=109</b>	<b>Fluticasone furoate 100mcg N=103</b>
<b>Baseline, n</b>	107	109	103
Mean (SD)	49.15 (34.717)	44.33 (36.569)	52.43 (63.947)
Median	40.60	34.80	38.20
Geometric mean	39.98	34.70	38.91
Min-Max	9.7 – 195.0	3.9 – 231.7	4.1 – 568.1
<b>Week 12, n</b>	107	109	103
Mean (SD)	46.21 (37.565)	37.37 (32.064)	39.76 (29.061)
Median	34.20	30.70	30.60
Geometric mean	35.81	29.03	30.59
Min-Max	5.3 - 249.8	3.3 - 253.4	3.0 - 182.4
<b>Change from Baseline, n</b>	107	109	103
Mean (SD)	-2.94 (47.430)	-6.95 (45.481)	-12.67 (67.476)
Median	-2.80	-0.60	-5.00
Min-Max	-161.4 – 204.3	-214.5 – 222.5	-546.0 – 154.6
<b>Ratio of Week 12 to Baseline, n</b>	107	109	103
Median	0.91	0.97	0.88
Geometric mean	0.90	0.84	0.79

Source Data: Table 8.38  
 SD = Standard Deviation

The lower limit of normal for 24-hour urine cortisol excretion used in the study was defined as 8mg/kg/24hrs.

*Reviewer's Comment: While no subject receiving FF had urinary cortisol excretion below the normal level at baseline or at the end of the 12 week treatment period, despite the large standard deviations, there is a definite dose-response effect for the active treatment groups in reducing urine cortisol excretion, both in mean changes from baseline and in the ratio of Week 12 values to baseline values.*

**Nasal Exams**

## Clinical Review

Anthony G. Durmowicz, M.D.

NDA 22-051

Fluticasone Furoate Nasal Spray

Nasal exams were conducted at all study visits. From randomization to Week 12, the incidence of mucosal bleeding declined from 5% to 3% for placebo subjects, from 4% to 1% for FF50 subjects, and from 5% to <1% for FF100 subjects. When summarized by shifts from baseline, there were no meaningful differences between either FF group compared to placebo in the incidence of subjects who had a worsening of mucosal bleeding or septal ulcerations over the course of the study. Of the 3% of placebo subjects, 1% of FF50 subjects, and 2% of FF100 subjects had nasal ulcers noted at randomization, by Week 12, there was no evidence of ulcers in any subject in any of the 3 groups. During the treatment period, 2 subjects in each of the FF groups had evidence of nasal candidiasis as opposed to no subjects in the placebo group. One subject in the FF50 group was withdrawn from the study due to nasal candidiasis [Section 8.8 and Table 34 FFR30008 Study Report, pages 103-106].

### Ophthalmic Examinations

Ophthalmic examinations, including slit lamp and fundoscopic examinations primarily for the detection of cataracts, and measurements of intraocular pressure, were performed at baseline and at the end of the study (Week 12) or at Early Discontinuation.

Intraocular pressure was measured through the 12 week time point in 156, 155, and 154 subjects in the placebo, FF50, and FF100 groups, respectively. The mean values demonstrated very little change over the course of the study, -0.1 and 0.3mm Hg, 0.2 and 0.0mm Hg, and 0.3 and 0.4mm Hg for the left and right eyes of subjects in the placebo, FF50, and FF100 groups, respectively [Table 35 FFR30008 Study Report, page 107].

**Reviewer's Comment:** *While the differences are very small and likely considered to be clinically insignificant, when looking at the mean values, there is a dose-response for increased intraocular pressure in the active treatment groups compared to placebo.*

At the end of the study a total of 8 subjects had an intraocular pressure increase from baseline to endpoint to > 20 mm Hg, the pressure considered to be the upper limit of normal, in at least one eye. Of these 8 subjects, 7 were receiving active treatment (4 in the FF50 group and 3 in the FF100 group) and one was in the placebo group. No glaucoma was reported in the study [Section 8.9.1 and Table 36 FFR30008 Study Report, pages 107-108].

**Reviewer's Comment:** *Consistent with the adult long-term safety study (FFR102123), the large majority of increases in intraocular pressure to > 20mm Hg reported were in subjects in the active groups (7 of 8). This data again supports the notion that treatment with either FF50 or FF100 in children may increase intraocular pressure.*

Fundoscopy cup measurements as a percentage of disc measurements were measured through the 12 week time point in 161, 161, and 165 subjects in the placebo, FF50, and FF100 groups, respectively. The sponsor-defined threshold limit for cup to disc ratio was > 66%. Baseline mean cup to disc ratios were much the same for the 3 treatment groups ranging from 17.7 to 18.4%. From baseline to endpoint, no subjects in any treatment group had a shift to >66% or <66% in fundoscopic cup to disc ratio measurements [Table 37 FFR30008 Study Report, page 111].

**Reviewer's Comment:** *My impression is that a change in the fundoscopic disk ratio, while clinically important, is less sensitive than increases in intraocular pressure measurements*

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*(increases in which may not be clinically significant).*

Fundoscopic and slit lamp evaluations of the eye demonstrated the development of macular abnormalities in 3 subjects receiving active treatment (2 FF50 and 1 FF100) and 1 subject receiving FF50 developed abnormal retinal vessels. Cataracts not present at baseline were observed in 2 subjects in the placebo group and in 4 subjects in the FF50 group. While no subjects in the FF100 group developed new cataracts during the treatment period, 2 subjects had trace posterior subcapsular cataracts noted at baseline and at the end of the study [Section 8.9.3 and Tables 38 and 39, pages 112-114].

**Reviewer's Comment:** *While no dose-relationship was found for the development of cataracts, there were more cataracts that developed in the FF50 group than in the placebo group.*

### Vital Signs and Electrocardiograms

There were no dose-related clinically meaningful adverse changes from baseline in findings in vital signs or ECGs in either active treatment group compared to placebo [Section 8.10 and Table 40 FFR30008 Study Report, pages 114-115].

### Summary and Discussion

In pediatric subjects aged 6 < 12 years, FF50 but not FF100 once daily demonstrated statistically significantly greater reductions ( $p=0.025$ ) in PAR symptoms versus placebo for the primary endpoint of mean change from baseline in rTNSS over the first 4 weeks of the treatment period in this 12-Week study. The FF100 group did demonstrate a numerical, but not statistically significant, beneficial treatment effect as well. These results were consistent for all nasal-symptom based secondary endpoints as well. In this pediatric PAR trial the onset of action for both FF50 and FF100 was generally within the first week of treatment and the maximal effect was reached between 2 and 3 weeks of treatment.

Headache and nasopharyngitis were the most common AEs and did not substantially differ between active treatment groups and placebo. The incidence of epistaxis, an AE associated with use of inhaled corticosteroid use, was not greater in the treatment groups than in placebo.

Although no urinary cortisol measurement fell below the lower limit of normal, there were dose-related decreases in both 24 hour urinary cortisol excretion and in the 12 week to baseline ratio of urinary cortisol excretion in the FF50 and FF100 treatment groups compared to placebo.

Increases in mean intraocular pressure over the course of the treatment period were small but there was a dose response for the active treatment groups compared to placebo. In addition, 7 of 8 subjects who developed intraocular pressures greater than the upper limit of normal were in the active treatment groups. Four subjects in the FF50 group developed cataract(s) over the course of the treatment period compared to 2 subjects in the placebo group. It is difficult to attribute the development of cataracts directly to FF as it would be highly unusual to develop cataracts within a 12 week period and no cataracts were seen in

**Clinical Review**

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Fluticasone Furoate Nasal Spray

the higher dose, FF 100 mcg group.

In summary, fluticasone furoate, at a dose of 50mcg once daily demonstrated statistically significantly greater reductions in allergic rhinitis symptoms in pediatric subjects < 12 years of age with PAR. Both the FF50 and FF100 doses had an effect on the HPA-axis, however HPA-axis suppression did not occur as no subject had urine cortisol excretion below the normal value. Similar to the adult long-term safety study, there is evidence that fluticasone furoate may be associated with increases in intraocular pressure and, possibly, the development of cataracts. These potential significant adverse side effects should be evaluated further in post-approval clinical studies.

**10.2 Line-by-Line Labeling Review**

A line-by-line labeling review has not been performed. At the time of this review, labeling negotiations have not begun with the Applicant.

**Other Pertinent Information**

**APPEARS THIS WAY  
ON ORIGINAL**

**Clinical Review**

Anthony G. Durmowicz, M.D.

NDA 22-051

Fluticasone Furoate Nasal Spray

**REFERENCES**

1. Juniper EF, Guyatt GH. *Clin Exp Allergy*. 21(1):77-83, 1991
2. Juniper EF, et. al. *J Clin Epidemiol*. 47(1):81-87, 1994
3. Juniper EF, et. al. *CMAJ*. 156(8):1123-1131, 1997
4. Juniper EF, et al. *J Allergy Clin Immunol*. 98(4):843-845, 1996

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Anthony Durmowicz  
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Sally Seymour  
2/28/2007 08:20:40 AM  
MEDICAL OFFICER

Medical Officer's Consultative Review of ND 22-051  
Ophthalmology Consult

Submission date: June 28, 2006

Review date: February 8, 2007

Sponsor: GlaxoSmithKline  
PO Box 13398  
Five Moore Drive  
Research Triangle Park, NC 27709

Drug: Fluticasone Furoate Nasal Spray

Route of Administration: Nasal Spray

Proposed Indication: Symptoms of allergic rhinitis

Consult Request: Ophthalmology Review of Ophthalmic Findings

**Reviewer's Comments:** *Comments are limited to areas of ophthalmologic concern. This review is divided into a discussion of the qualifications of the investigators, cataract development, elevation of IOP and efficacy with respect to the treatment of ocular symptoms of allergic rhinitis.*

**Qualification of Investigators:**

*Ocular safety examinations were to be conducted by either ophthalmologists or optometrists. The training of these two groups is markedly different. Training for optometrists focuses on optics, while the training of ophthalmologists focuses on the diagnosis, medical, and surgical management of ocular disease. In light of a number of the findings in the data listings, particularly the cup to disc ratios, the investigators performing many of the ophthalmic examinations were not qualified to conduct that examinations requested of them.*

*This raises concerns for all ophthalmic evaluations.*

**Summary of Subjects Who Developed Cataracts During the Study That Were Not Present at Baseline (ITT Population –FFR102123)**

<b>Subject</b>	<b>(age/gender) Visit</b>	<b>Left</b>	<b>Right</b>
<b>Placebo (N=201)</b>			
1631 (43/M)	Baseline	No	No
	Week 12	Posterior subcapsular (trace)	No
	EWV	Posterior subcapsular (trace)	No
<b>Fluticasone furoate nasal spray 100mcg (N=605)</b>			
17 (15/F)	Baseline	No	No
	Week 12	No	No
	Week 24	No	No
	Week 52	Posterior subcapsular (trace)	No
1033 (14/M)	Baseline	No	No
	Week 12	No	No
	Week 24	No	No
	Week 52	Posterior subcapsular (definite)	No
230 (63/F)	Baseline	No	No
	Week 12	Cortical	Cortical
	Week 24	Cortical	Cortical
	Week 52	No	No
897 (66/M)	Baseline	Cortical	No
	EWV	Nuclear sclerotic	Cortical
919 (72/M)	Baseline	No	No
	Week 12	Nuclear sclerotic	Nuclear sclerotic
	EWV	No	No
811 (23/M)	Baseline	No	No
	Week 12	No	No
	Week 24	No	No
	Week 52	Nuclear sclerotic	Nuclear sclerotic

**Reviewer's Comments:** *The development of cataracts in the presence of a corticosteroid is well known and has been recently better studied. The 40% of cataracts that will develop in eyes continually bathed in corticosteroids are not noticeable until the second year of treatment.*

*Recognizing that there is a 3 to 1 imbalance in the number of patients studied, a one to six difference would not be striking except that there are creditability concerns raised about the patient in the placebo group and three of the fluticasone group patients.*

*Posterior subcapsular cataracts developing in a 15 year old (#17) and 14 year old (#1033) with three prior visits documenting no cataract is highly suggestive of a potential to develop*

*cataracts. Patient #811, a twenty-three year old male developing cataracts after 52 weeks and having 3 prior evaluations which were negative for cataracts is also highly suggestive of the potential for cataract development.*

## **IOP**

*As noted by the sponsor:*

Few subjects had intraocular pressure measurements that were  $\geq 21$ mmHg (the sponsor defined threshold limit) at any examination. The majority of subjects ( $\geq 98\%$ ) had no shift from baseline in intraocular pressure at any time in the study. A summary of the number of subjects with shifts to above the threshold limit during the study is presented below.

There were nine subjects (five,  $<1\%$  subsequently treated with fluticasone furoate nasal spray 100mcg and four,  $2\%$  subsequently treated with placebo nasal spray) with intraocular pressure  $\geq 21$ mmHg at baseline. The five subjects randomized to the fluticasone furoate nasal spray group did not show further increases in intraocular pressure during treatment. Of these subjects, one subject had no further measurements, one had an intraocular pressure measurement  $\geq 21$ mmHg at a subsequent visit but values were lower than at baseline, and the remaining three subjects all had values below 21mmHg at all on-treatment visits.

Twelve subjects ( $2\%$ ), all treated with fluticasone furoate nasal spray 100mcg, had IOPs of at least 21mmHg during the study. No subject had a value above 21mmHg at more than one on-treatment visit. Of these 12 subjects, all but one had values of 21 or 22mmHg (7 subjects had values of 21mmHg and 4 subjects had values of 22mmHg). One subject (Subject 1332) had a measurement of 24mmHg in the left eye at Week 52 (right eye 20mmHg). This subject, whose baseline intraocular pressure measurements had been 12 and 14mmHg for the left and right eye respectively, had increased intraocular pressure reported as an AE. Two of the 12 subjects (Subject 160 and Subject 1852) had raised values at Week 12 which were  $<21$ mmHg at subsequent visits at Week 24 and Week 52.

Increased intraocular pressure was reported as an AE for three subjects (Subject 894, Subject 910 and Subject 1334), in addition to Subject 1332. All were considered to be of mild intensity. These three subjects had intraocular pressure measurements  $\geq 21$ mmHg at Week 52 which were below this value at all previous visits. Events in all subjects were considered by the investigator to be related to study treatment.

	Shift	Number (%) of Subjects	
		Placebo (N=201)	FF 100mcg (N=605)
<b>Week 12</b>	n	168	531 <sup>1</sup>
	Left eye to $\geq 21$ mmHg	0	1 (<1)
	Right eye to $\geq 21$ mmHg	0	2 (<1)
	Both to $\geq 21$ mmHg	0	1 (<1)
<b>Week 24</b>	n	156	500 <sup>2</sup>
	Left eye to $\geq 21$ mmHg	0	0
	Right eye to $\geq 21$ mmHg	0	0
	Both to $\geq 21$ mmHg	0	0
<b>Week 52</b>	n	142	445 <sup>3</sup>
	Left eye to $\geq 21$ mmHg	0	6 (1)
	Right eye to $\geq 21$ mmHg	0	4 (<1)
	Both to $\geq 21$ mmHg	0	1 (<1)
<b>Source Data: FFR102123 Table 7.56</b>			
1. n= 532 for left eye			
2. n=501 for left eye			
3. n=446 for left eye			

**Reviewer's Comments:** *As noted by the applicant, all elevations in IOP occurred in patients treated with fluticasone. This is a known corticosteroid response which at this level of corticosteroid exposure occurs only in patients with a genetic predisposition to have the elevated pressure. These individuals are typically called "steroid responders." The mean IOP is not expected to significantly rise because only a small portion of the patients will be steroid responders.*

**Efficacy for ocular symptoms**

*It is well known that nasal stimulation can produce tearing and other ocular symptoms. Products which decrease nasal irritation would therefore be expected to demonstrate the same effect on the ocular symptoms caused by nasal stimulation. This should, however, be distinguished from allergic conjunctivitis in which there is a direct allergic response in the eye.*

*Allergic conjunctivitis is evaluated by evaluating the effect of an ocular stimulus. Ocular signs and symptoms, most notably ocular itching and ocular redness are evaluated using carefully anchored scales which include pictures of different degrees of ocular redness.*

*Ocular allergic responses have not been evaluated in this new drug application. It is therefore recommended that if secondary labeling indications are granted for an ocular component of the nasal irritation, that the labeling distinguish this from the direct effects of ocular allergen stimulus.*

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**Summary:**

1. Some of the investigators involved in the ocular evaluations of this NDA do not appear to have had sufficient training to permit them to adequately evaluate portions of the eye.
2. There are at least 3 cases of cataract development which appear to be directly attributable to treatment with fluticasone furoate. In light of the known class effect of corticosteroids causing cataract development and the cases presented, it is recommended that the labeling identify fluticasone furoate as a potential cause for cataract development.
3. A number of patients have had elevations in their ocular pressure following treatment with fluticasone furoate. In light of the known class effect of corticosteroids causing elevations in intraocular pressure in steroid responsive patients and the cases presented, it is recommended that the labeling identify fluticasone furoate as a potential cause for elevated intraocular pressure, potentially leading to glaucoma in steroid response patients.
4. A reduction in some ocular symptoms resulting from a decrease nasal irritation may have been demonstrated in this new drug application. Ocular allergic responses have not been evaluated in this application. It is therefore recommended that if secondary labeling indications are granted for an ocular component of the nasal irritation, that the labeling distinguish this from the direct effects of an ocular allergen stimulus.

Wiley A. Chambers, M.D.  
Supervisory Medical Officer, Ophthalmology

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Wiley Chambers  
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**MEDICAL OFFICER REVIEW**

**Division Of Pulmonary and Allergy Drug Products (HFD-570)**

<b>APPLICATION #:</b> 22-051	<b>APPLICATION TYPE:</b> NDA
<b>SPONSOR:</b> GlaxoSmithKline	<b>PROPRIETARY NAME:</b> _____ (proposed)
<b>INVESTIGATOR:</b> Multiple	<b>USAN NAME:</b> Fluticasone furoate
<b>CATEGORY:</b> corticosteroid	<b>ROUTE:</b> Nasal spray
<b>MEDICAL OFFICER:</b> Anthony Durmowicz, MD	<b>REVIEW DATE:</b> August 23, 2006

**SUBMISSIONS REVIEWED IN THIS DOCUMENT -**

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission Type</u>	<u>Comments</u>
June 28, 2006	June 29, 2006	NDA	

**RELATED APPLICATIONS**

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>
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**REVIEW SUMMARY:**

This is a 45-day Filing Review of NDA 22-051. This NDA is submitted in support of the use of the corticosteroid, fluticasone furoate (GW685698X), as a nasal spray, for the treatment of the symptoms of seasonal and perennial allergic rhinitis (SAR and PAR, respectively) in patients 2 years of age and older. The proposed doses of fluticasone furoate are 110 mcg intranasally QD for adolescents and adults  $\geq 12$  years and 55-110 mcg intranasally QD for children  $2 < 12$  years. Fluticasone furoate is the second fluticasone-based product developed by the Applicant to treat SAR and PAR. Fluticasone propionate (Flonase) was approved for use to treat the nasal symptoms of SAR and PAR in October 1997.

The Applicant has completed clinical development programs for both adult and pediatric SAR/PAR indications. For the adult program the application consists of a total of eight clinical studies, 3 pivotal trials for SAR, one pivotal trial for PAR with dose-ranging and long-term safety trials acting as supportive studies. An HPA axis study and allergen chamber study were also conducted. For the pediatric indication, the Applicant has identified two pivotal clinical trials, one for SAR and one for PAR. In addition, pediatric HPA axis and knemometry studies were also conducted. The development program in general complied with the FDA Guidance For Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products (Draft Guidance April 2000). The submission appears complete enough to allow for a further more complete review, and is therefore considered "fileable." The Division does not plan to present this NDA to the Pulmonary-Allergy Drugs Advisory Committee. An audit by the Division of Scientific Investigations will not be requested.

**OUTSTANDING ISSUES:**

None.

**RECOMMENDED REGULATORY ACTION**

\_\_\_\_\_ **X** **FILEABLE** \_\_\_\_\_ **NOT FILEABLE**

**REVIEWERS**

**Medical Reviewer:** Anthony G. Durmowicz, MD  
**Acting Team Leader:** Sally Seymour, MD

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**I. General Information**

Drug Substance

Trade Name:	_____ (proposed)
US Adopted Name:	fluticasone furoate
International Non-proprietary Name:	fluticasone furoate
Molecular Formula:	_____
Molecular Weight:	_____
Manufacturer:	GlaxoSmithKline

This NDA is submitted in support of the use of the corticosteroid, fluticasone furoate nasal spray for the treatment of the symptoms of SAR and PAR in patients 2 years of age and older. The proposed doses of fluticasone furoate are 110 mcg intranasally QD for adolescents and adults  $\geq 12$  years and 55-110 mcg intranasally QD for children  $2 < 12$  years. Fluticasone furoate is the second fluticasone-based product developed by the Applicant to treat SAR and PAR. Fluticasone propionate (Flonase<sup>®</sup>) was approved for use to treat the nasal symptoms of SAR and PAR in October 1997.

The clinical program for fluticasone furoate consists of a total of 34 completed clinical trials. There are 22 clinical pharmacology studies in healthy volunteers and subjects with allergic rhinitis or asthma, and 12 Phase 2b/3 studies in adults, adolescents and children with SAR or PAR. For the adult program, 3 pivotal trials for SAR and one pivotal trial for PAR have been identified; a dose-ranging trial and a long-term safety trial act as supportive studies. HPA axis and allergen chamber studies were also conducted. For the pediatric indication,

the Applicant has identified two pivotal clinical trials, one for SAR and one for PAR. In addition, pediatric HPA axis and knemometry studies were also conducted.

## **II. Background and Rationale**

Fluticasone furoate (GW685698X) is a new fluticasone-based corticosteroid developed by GSK as an aqueous nasal spray suspension delivered via a side actuated spray device as a once daily treatment for the symptoms of allergic rhinitis. Similar to the product presently marketed by the Applicant for SAR/PAR, fluticasone propionate (Flonase<sup>®</sup>) fluticasone

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## **III. Regulatory and Foreign Marketing History**

### **A. Regulatory History**

An initial IND (48,647) for fluticasone furoate nasal spray was submitted on October 30, 2003. The Phase 2b/3 program for fluticasone furoate nasal spray was designed taking into consideration the FDA Guidance For Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products (Draft Guidance April 2000) as well as with consultation with DPAP during End-of-Phase-2 and Pre-NDA meetings on July 19, 2004, and February 13, 2006, respectively. No previous NDAs have been submitted for fluticasone furoate nasal spray.

### **B. Foreign Marketing History**

As of August 2006, fluticasone furoate nasal spray is not marketed in any country. This NDA is the first global regulatory submission for fluticasone furoate. The Applicant intends to submit applications for SAR and PAR indications to other regulatory bodies, including those of the European Union and Japan.

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#### IV. Items Required for Filing and Reviewer Comments

##### A. Necessary Elements (21 CFR 314.50)

The table below lists the necessary elements for an NDA and their location within the electronic submission.

<b>Necessary Elements</b>		
Type	Status	Location (Item #: Folder from Main Table of Contents)
Application Form (FDA 356h):	Present	Module 1.1.2 356h.pdf
Investigator Debarment Certification:	Present	Module 1.3.3 other\debar.pdf
Financial Disclosure:	Present	Module 1.3.4 other\financial.pdf
Statements of Good Clinical Practice:	Present	Individual study reports
Environmental Assessment:	Present	Module 1.12.14 other\environ-anal.pdf
Proposed label:	Present	Module 1.14 labeling\labeltoc.pdf
Integrated Summary of Efficacy	Present	Module 5.3.5.3 clinstat\ise\ise.pdf
Integrated Summary of Safety:	Present	Module 5.3.5.3 clinstat\iss\iss.pdf
Integrated Summary of Benefits and Risks:	Present	Module 2.5 summary\clinical-overview.pdf
Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures:	Present	Individual study reports
Statistical Analyses:	Present	Module 2.7.3 summary\summary-clin- efficacy.pdf (addendum)
Pediatric Use Section:	Present	Pediatric indication
Case Report Tabulations:	Present	Module 5.3.7 crf\crftoc.pdf
Case Report Forms (for patients who died or did not complete study):	Present	Module 5.3.7 crf\crftoc.pdf

### Necessary Elements

Type	Status	Location (Item #: Folder from Main Table of Contents)
Patent Information:	Present	Module 1.3.5.1 other\pat-info.pdf

### B. Decision

The submission appears adequate from a clinical standpoint to allow for further review, and is therefore fileable.

### V. Preliminary Review of Package Insert

Draft labeling in the new structured product label format is included in the electronic submission. The Clinical Studies section of the proposed label includes data on reduction of ocular symptom scores in addition to the primary endpoint of reduction in reflective total nasal symptom scores (rTNSS). Similarly, disease-specific quality of life data appears in the clinical trials section as well. QOL was evaluated through use of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). The RQLQ assesses the impact of allergic rhinitis treatment on 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional) on a 7-point scale where 0 = no impairment and 6 = maximum impairment.

*Reviewer's Comments: The Applicant had previously intended to try to get a specific product indication for the treatment of nasal and ocular symptoms of SAR and PAR (see EOP-2 meeting minutes), however has since backed off. As an alternative, GSK has included data from the adult SAR clinical trials in which the ocular symptom score was pre-specified as a key secondary endpoint and appropriate correction for multiple comparisons was made during the statistical evaluation of the results. This Reviewer's expectation is that GSK would like this information in the label so they could use it in marketing the product. Regarding the inclusion of RQLQ data in the clinical trials section, the Applicant would also be able to use the information presented for marketing. This is significant because, if the data are correct, this would be the first time a nasal steroid product has been able to demonstrate a clinically meaningful improvement in RQLQ.*

### VI. Clinical Studies

The clinical program includes 22 Clinical Pharmacology studies in healthy volunteers and subjects with allergic rhinitis or asthma, and 12 Phase 2b/3 studies in adults, adolescents and children with SAR or PAR.

The efficacy evaluation in the adult and adolescent population consists of three pivotal SAR studies (30003, 103184, 104861), and one pivotal PAR study (30002). There was also one SAR dose-ranging study (20001) and two PAR safety studies in which efficacy assessments were also made, an HPA axis study (20002) and a one year long-term safety study (102123). In addition, there was a single dose allergen challenge chamber study (101816) in subjects with SAR which was used to determine the time to onset of drug activity. Table 1 in the Appendix outlines the primary clinical studies in adults used to support safety and efficacy of fluticasone furoate.

For efficacy evaluation in pediatric subjects, two pivotal, repeat dose efficacy and safety studies were conducted; one SAR study (100010) and one PAR study (30008). There was also an HPA axis study in children with PAR (100012). In this study efficacy assessments were used to assess compliance with study medication. A knemometry study, which was conducted to assess for steroid-related decreases in growth (101747), did not assess efficacy. Table 2 in the Appendix lists the pediatric clinical studies used to support the safety and efficacy of fluticasone furoate in children.

***Reviewer's Comment:** The clinical development program for the SAR/PAR indications was conducted in accordance with the FDA guidance for development of drugs for allergic rhinitis and in consultation with DPAP at EOP-2 and Pre-NDA meetings.*

Throughout development the spray content of fluticasone furoate nasal spray had been approximated as 25mcg/actuation. The actual dose delivered from the product is 27.5mcg/actuation, which is proposed as the label claim. Based on this spray content assessment, the doses examined in the clinical program were actually 55mcg, 110mcg, 220mcg, and 440mcg rather than the 50mcg, 100mcg, 200mcg, and 400mcg doses indicated in the clinical documentation of this dossier. The proposed starting dosage for adults and adolescents 12 years of age and older is therefore 110mcg once daily (administered as two sprays in each nostril). When the maximum benefit has been achieved and symptoms have been controlled, reducing the dose to 55mcg (one spray in each nostril) once daily may be effective in maintaining control of symptoms. In children, the proposed starting dosage is 55mcg once daily with the option to increase the dosage to 110mcg once daily in children not adequately responding to the lower dose.

#### **A. Pivotal Studies**

For the adult clinical program, the SAR and PAR pivotal clinical studies have essentially the same design. After a run-in period, adults allergic to the appropriate SAR or PAR antigens for the study were randomized to receive either 110 mcg fluticasone furoate QD (delivered as two, 27.5 mcg sprays in each nostril every morning) or a placebo spray delivered in a similar manner. The duration of treatment was 2 weeks for the SAR studies and 4 weeks for the PAR study.

The inclusion criteria for SAR studies included adolescents and adults  $\geq 12$  years with a diagnosis of SAR triggered by the allergen specified for the study (see Table 1). The subject also had to reside, without intent to travel outside during the study, within the specific geographic area the study was conducted. Subjects with a history of asthma (other than mild intermittent), recent viral or bacterial infection, physical obstruction of the nose, or those receiving steroid, antihistamine, or other allergy medications were excluded.

The primary endpoint was the mean change from baseline over the entire treatment period in daily reflective total nasal symptom scores (rTNSS). Secondary endpoints included the mean change from baseline over the entire treatment period in morning predose instantaneous total nasal symptom scores (iTNSS), mean change from baseline over the entire treatment period in daily reflective total ocular symptom scores (rTOSS), overall evaluation of response to therapy, total and individual nasal and ocular symptom scores and quality of life.

The pivotal pediatric SAR and PAR studies were essentially the same as the adult studies with differences mainly to account for the younger, less verbal population. Parents/guardians were allowed to fill in the symptom scores for young children. While the primary endpoint, rTNSS, was the same, for statistical purposes, the primary endpoint was determined for children ages 6-11 years. Reflective TNSS scores from younger children were used as supportive data and were not included in the primary endpoint analysis. The treatment period for the pediatric PAR study was 12 weeks in length, longer than the typical 4-6 week PAR study. This was in order to accumulate additional safety data in the pediatric population. The efficacy determination, however, was made after 4 weeks of treatment, the same treatment time as for the adult PAR pivotal study.

#### **B. Other Studies**

In addition to those studies that comprise the Applicant's adult and pediatric programs, 22 clinical pharmacology studies have been conducted with fluticasone furoate. These include:

- 6 intranasal, 6 inhalational and 4 intravenously dosed studies in healthy subjects
- 1 intranasally dosed study in allergic rhinitis subjects
- 5 inhalation studies in subjects with asthma
- 1 inhalation study in subjects with hepatic impairment

An overview of these clinical pharmacology studies is included in Table 3 of the Appendix to this Review.

#### **VII. Advisory Committee Meeting**

There are no issues at present that would require input from the Pulmonary Allergy Drugs Advisory Committee.

#### **VIII. DSI Review / Audit**

Preliminary review of the data from the pivotal studies by the Biometrics reviewer (Dr. Feng Zhou) shows there is no for evidence of treatment-by-site interaction. Also, investigators that had a significant financial interest in the Applicant enrolled relatively few subjects in the trials. This would preclude them from having the ability to alter the outcomes of the pivotal studies. For these reasons, and because the molecular entity, fluticasone is already approved for the treatment of SAR and PAR and the efficacy data are as would be expected for the product, there are no plans to otherwise request audits by the Division of Scientific Investigation.

## IX. Summary

This NDA is submitted in support of the use of the corticosteroid, fluticasone furoate (GW685698X) for the treatment of the symptoms of seasonal and perennial allergic rhinitis (SAR and PAR, respectively) in patients 2 years of age and older. The proposed doses of fluticasone furoate are 110 mcg intranasally QD for adolescents and adults  $\geq 12$  years and 55-110 mcg intranasally QD for children  $2 < 12$  years. The Applicant has completed clinical development programs for both adult and pediatric SAR/PAR indications. For the adult program the application consists of a total of eight clinical studies, 3 pivotal trials for SAR and one pivotal trial for PAR with dose-ranging and long-term safety trials acting as supportive studies. An HPA axis study and allergen chamber study were also conducted. For the pediatric indication, the Applicant has identified two pivotal clinical trials, one for SAR and one for PAR. In addition, pediatric HPA axis and knemometry studies were also conducted. The development program in general complied with the FDA Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products (Draft Guidance April 2000). The submission appears complete enough to allow for a further more complete review, and is therefore considered "fileable." The Division does not plan to present this NDA to the Pulmonary-Allergy Drugs Advisory Committee. An audit by the Division of Scientific Investigations will not be requested.

## X. Timeline for Review

Timeline for Review

Milestone	Target Date for Completion
Adult Clinical Studies: 20001, 30003, 103184, 104861, 30002, 102123, 20002, 101816 Pediatric Clinical Studies: 100010, 30008, 100012, 101747	10/31/06
ISE	11/30/06
ISS	01/12/07
Other Sections	02/14/07
Draft Review	02/14/07
PADAC Meeting	NA
Label Review	8/11/06
GRMP Goal Date	02/28/07
PDUFA Due Date	04/29/07

## XI. Comments for the Applicant

No clinical comments will be conveyed to the Applicant at this time.

Reviewed by:  
Anthony G. Durmowicz, MD  
Medical Officer, DPAP

Sally Seymour, MD  
Acting Team Leader, DPAP

## XII. Appendix: Clinical Trials

**Table 1: Applicant's Adult and Adolescent SAR/PAR Studies**

Study No.	Phase	Study Type	Doses	No. of Subjects <sup>a</sup>	Treatment Duration
<b>Repeat Dose Efficacy and Safety Studies</b>					
FFR20001	2b	SAR/Dose-ranging (US, Mountain Cedar Season)	FF 50mcg QD FF 100mcg QD FF 200mcg QD FF 400mcg QD Placebo	127 127 129 130 128	2 weeks
FFR30003	3	SAR (US, Mountain Cedar Season)	FF 100mcg QD Placebo	152 150	2 weeks
FFR103184	3	SAR (Europe, Grass Season)	FF 100mcg QD Placebo	141 144	2 weeks
FFR104801	3	SAR (US, Ragweed Season)	FF 100mcg QD Placebo	151 148	2 weeks
FFR30002	3	PAR (US/Canada)	FF 100mcg QD Placebo	149 153	4 weeks
<b>Safety Studies with Efficacy Assessments</b>					
FFR102123	3	PAR/Long term safety (Europe, South America, Australasia)	FF 100mcg QD Placebo	605 201	52 weeks
FFR20002	3	PAR/HPA axis safety (US/Canada)	FF 100mcg QD Placebo Placebo/Prednisone	48 51 13	6 weeks
<b>Single Dose Allergen Challenge Chamber Study</b>					
FFR101816	3	SAR/ACC (US, Ragweed Pollen)	FF 100mcg QD Placebo	191 191	Single dose

SAR = seasonal allergic rhinitis; PAR = perennial allergic rhinitis; FF = fluticasone furoate; QD = once daily;  
 HPA = hypothalamic pituitary adrenocortical; ACC = allergen challenge chamber  
 a = subjects who were randomised and received at least one dose of study medication

**Table 2: Applicant's Pediatric SAR/PAR Studies**

Study No.	Phase	Study Type	Doses	No. of Subjects <sup>a</sup>	Treatment Duration
<b>Repeat Dose Efficacy and Safety Studies</b>					
FFR100010	3	SAR (US)	FF 50mcg QD FF 100mcg QD Placebo	184 184 186	2 weeks
FFR30008	3	PAR (North America, South America, Europe)	FF 50mcg QD FF 100mcg QD Placebo	185 185 188	12 weeks
<b>Safety Studies with Efficacy Assessments</b>					
FFR100012	3	PAR/HPA axis safety (US)	FF 100mcg QD Placebo	57 55	6 weeks

SAR = seasonal allergic rhinitis; PAR = perennial allergic rhinitis; FF = fluticasone furoate; QD = once daily;  
 HPA = hypothalamic pituitary adrenocortical  
 a = subjects who were randomised and received at least one dose of study medication

**Table 3: Overview of Completed Clinical Pharmacology Studies by Route and Population**

Study	Route					Subjects	
	IN	IH	O (S)	CS	IV	Type	Dosed/ Completed
FFR10001	X					Healthy	24 /21
FFR10002 <sup>1</sup>	X					Healthy	24 /23
FFR10003 <sup>2</sup>	X					Healthy	24 /22
FFR10005	X					Healthy Japanese	12 /11
FFR10006	X					Healthy	20 /20
FFR10007	X					Allergic Rhinitis	59 /55
FFR10008			X		X	Healthy	5 /5
FFR10010	X				X	Healthy	16 /16
FFR10013	X					Healthy	20 /20
FFA10001		X				Healthy	20 /19
FFA10002		X				Healthy	36 /35
FFA10003		X			X	Healthy	24 /23
FFA10004				X		Healthy	24 /24
<hr/>							
FFA10009		X				Healthy	24 /24
FFA10013		X				Moderate hepatic impairment & Healthy	10 /10 10 /10
FFA10022		X				Asthmatic	40 /38
<hr/>							
FFA10028		X				Asthmatic	28 /27
FFA103096		X				Healthy	44 /40
						Total	533 /494 (92.7%)
Route: IN                      Intranasal (Nasally Inhaled) IH                      Orally Inhaled O (S)                    Oral (Swallowed) CS                      Cutaneous IV                        Intravenous All of the nasal inhalation studies used a suspension formulation except for 1. FFR10002 (solution) and 2. FFR10003 (microfluidized suspension). 3. These studies did not provide relevant pharmacokinetic, pharmacodynamic or safety data for consideration of this intranasal product and are not discussed further in m2.7.2, Summary of Clinical Pharmacology. Clinical study reports for these studies are, however, available in Module 5. 4. Study _____ was discontinued for _____							

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/s/

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I concur