There are no published reports of the use of FF nasal spray in the literature. This reviewer searched the MEDLINE database using the **terms "fluticasone furoate" and "fluticasone furoate and allergic rhinitis" on February 6, 2007**. A total of 67 references were found. All the references to fluticasone were for fluticasone propionate, another corticosteroid product indicated for treatment of allergic rhinitis.

7.2.3 Adequacy of Overall Clinical Experience

The study number, design, and duration are sufficient to assess the efficacy and safety of FF 110 mcg nasal spray in adults with SAR and PAR. All of the studies were double blind, randomized, and placebo-controlled. All of the subjects had an appropriate diagnosis for at least 2 years with current evidence of allergy. All were symptomatic at the time or enrollment. The Total Nasal Symptom Score, an accepted instrument for measuring efficacy in allergic rhinitis was used as the primary efficacy variable. The statistical analysis was appropriate. In addition, there were an adequate number of subjects exposed to the drug, and adequate numbers within demographic subsets to allow for an assessment of safety (see Sections 7.2.1.2 and 7.2.1.3).

Given the extent of the adult program, the pediatric studies performed constitute a sufficient database to assess the efficacy and safety of FF 55 and 110 mcg QD with one exception. While the formal pediatric HPA axis study, FFR100012, found no evidence of HPA axis suppression in children 2 < 12 years treated with FF 110 mcg QD for 6 weeks, a dose-dependent decrease in 24 hour urinary cortisol excretion was seen in the longer 12 week study, FFR30008. While no subject in the study had a cortisol excretion level below the normal range, this dose-response relationship strongly suggests that longer term use of FF by children could possibly result in more significant effects on the HPA axis or, possibly, growth. A post-marketing safety study to further assess the effects of FF on the HPA axis and growth of children should be requested.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The drug is a corticosteroid about which the basic mechanism of action and range of toxicities are known. No special animal or in vitro studies were performed. However, while not required for this program, the Applicant conducted a specific QT study to support development of FF for another indication (Study FFR101888). Fluticasone did not affect QTc after single doses of 4000 mcg by inhalation (40 times the intranasal dose) compared to the positive control, moxifloxicin.

7.2.5 Adequacy of Routine Clinical Testing

Adverse events were collected daily and reviewed by the investigators at all clinic visits. Vital signs and nasal exams were collected at all clinic visits and routine laboratory testing and ECGs were performed in all the trials at baseline and at the end of the study other than the single dose allergen chamber study (FFR101816) where studies were performed at baseline only and in the long-term adult safety study when laboratory studies were performed at baseline and weeks 12, 24, and 52. Given that FF is in a class (corticosteroid) about which there is extensive information and the fact that the bioavailability of FF nasal spray is very low, this degree of safety monitoring is sufficient.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Appropriate studies to assess the metabolism, clearance, and possible drug interactions of FF have been conducted for this application (see Tables of Clinical Studies in Section 4.2). Refer to Section 5, Clinical Pharmacology, for details of these assessments.

Fluticasone furoate nasal spray is meant to act locally; it has very limited absorption due to the low dose (110 mcg) and the intranasal administration route. The absorption, distribution, metabolism, and clearance of FF have, however, been extensively studied by the Applicant in support of this NDA application and other planned indications. Studies have been conducted with FF when administered orally, intravenously, applied cutaneously, and by oral inhalation to support the global FF program including studies to assess the effects of CYP 3A4 inhibition, and the effects of moderate hepatic impairment on the metabolism of FF.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Overall, the clinical studies were adequate to assess for both local and systemic corticosteroid-related AEs. Nasal exams were conducted at each study visit in all trials. Specific studies to assess the effects of FF on HPA-axis were conducted for both the adult and pediatric programs (FFR20002 and FFR100012, respectively) and further assessments were made in other clinical studies (FFR20001, FFR102123, and FFR30008). Ophthalmic examinations, including slit lamp evaluation for cataract detection and measurement of intraocular pressure were conducted in the long-term safety studies for adults and children (FFR102123 and FFR30008). While adequate for approval, the possibility of a safety signal for FF as a cause of rare side effects such as cataracts and IOP/glaucoma was raised in the clinical trials and will need to be further evaluated as required Phase 4 commitments.

7.2.8 Assessment of Quality and Completeness of Data

As noted above, the Applicant's safety assessments were adequate to conduct an appropriate safety review.

7.2.9 Additional Submissions, Including Safety Update

A 120-day safety update was submitted by the Applicant that contained new clinical safety data from the time of the cut-off date for the original NDA submission (12/09/05) through 04/09/06. The clinical data are reviewed herein and consist of one clinical pharmacology study and 4 clinical studies that were ongoing at the time of the safety date cutoff date.

- Study FFR101888 was a randomized, placebo-controlled, four period crossover study conducted in 40 healthy male and female volunteers to estimate the effect of a single oral inhaled dose of 4000 mcg of FF on the QTcF interval compared to placebo, as measured by the maximal mean change from baseline and weighted mean change from baseline over the 24-hour postdose time interval. The 4 treatment groups were: inhaled FF with the excipient cellobiose octaacetate (COA), inhaled COA, inhaled placebo (lactose), and moxifloxacin as a positive control. Each subject was to participate in all four study periods, separated by a minimum washout period of at least 7 days.

The mean age of the subjects was 29.1 years. One subject (Subject 39) could not attend Period 2 on 10 May 2005 for personal reasons. Lack of effect on QTcF derived from the manually read ECG data was to be concluded if the upper limit of the two-sided 90% confidence interval for the maximal mean change from baseline was less than or equal to 7.5 msec.

Both the FF 4000 mcg and COA 6.25 mg confidence intervals excluded an effect greater than 7.5 msec, thus demonstrating a lack of effect. The confidence interval for moxifloxacin 400mg included an effect greater than 7.5 msec demonstrating an effect of moxifloxacin as the positive control (See the following table). Analysis of QTcB and uncorrected QT supported these results.

Summary of Statistical Analysis of QTcF Maximal Mean Change from Baseline (FFR101888) *[Table 9 Safety Update, page 40/58]*

Comparison	Treatment Difference (msec)	90% Confidence Interval (msec)
Fluticasone furoate 4000 mcg – Placebo	0.788	(-1.802, 3.378)
Moxifloxacin 400 mg – Placebo	9.929	(7.339, 12.520)
COA 6.25 mg – Placebo	-1.534	(-4.143, 1.076)

Note: N=40 for fluticasone furoate, moxifloxacin and placebo, N=39 for COA
Data Source: FFR101888 Table 10.8

Over the course of the study, AEs were reported for 8-10 subjects in each treatment group (21-25%). The most frequent AEs (reported by two or more subjects within a treatment group) were headache, nasopharyngitis, pharyngolaryngeal pain and nausea. All AEs were of mild or moderate intensity.

- Studies FFR30006 and FFR30007 were 4-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies in approx 350 subjects (in each study) with vasomotor rhinitis (VMR) comparing the efficacy and safety of FF 110 mcg QD nasal spray with placebo nasal spray in adult and adolescent subjects (≥12 years of age).

- Study FFR104503 was a randomized, open label, active controlled (mometasone furoate nasal spray 200 mcg QD), parallel group, multi-center, 52-week study, to assess the long-term safety of FF 110 mcg QD in subjects ≥ 18 years of age with PAR. The clinical study phase is still underway. The primary objective of this study is to determine effects on the nasal mucosa of adult PAR subjects after one year of continuous treatment with FF 110mcg QD compared to a mometasone furoate nasal spray reference control group as determined by morphological and immunocytochemical analyses of nasal biopsy specimens.

- Study FFR106080 is a 6 week randomized, placebo-controlled, parallel group study to compare the efficacy and safety of FF 110 mcg QD nasal spray versus vehicle placebo nasal spray in approx 288 subjects ≥ 12 years of age with PAR. The clinical study phase was still underway as of the safety data cut off date of April 09, 2006.

Adverse event data were not available as of the cut-off date for the safety update, however, during this safety update period, 2 SAEs, both in subjects treated with FF 110 mcg, (one from Study FFR30007 and one from Study FFR104503) have been reported in these 4 studies.

In study FFR30007, a 46 year old male subject developed grade 2 (moderate) nephrotic syndrome for which he was hospitalized and treated. The subject received intranasal FF 110 mcg QD for 10 days (December 02, 2005, to December 12 2005). Medical conditions at the time of the event included diabetes mellitus, elevated cholesterol and peripheral neuropathy. Concomitant medications included glibenclamide, rosiglitazone maleate,

rosuvastatin calcium, amitriptyline and aspirin. On 12 December 2005, 10 days after the start of investigational product, the subject developed grade 2 or moderate nephrotic syndrome. At the time of the update cut-off, the SAE was said to be resolving.

In study FFR104503, a 24 year old female was reported to have spontaneous abortion. The subject received intranasal 110 mcg for 29 days beginning on December 19, 2005. From December 10, 2005, to December 15, 2005 the subject menstruated. She was noted to have a regular cycle (30/5 days). The subject was next due to start menstruating on January 10, 2006; however, her period did not start until January 16, 2006. On 17 January 2006, the subject visited her physician because as she reported the bleeding felt the same as after a previously unsuccessful fertility treatment. The physician was not able to confirm the pregnancy or the miscarriage but felt that it was possible the subject had a spontaneous pregnancy since December 2005. The event was considered serious as it was classified as a congenital anomaly. Treatment with FF was discontinued on January 17, 2006, and the subject was withdrawn from the study. The event was considered resolved on January 17, 2006.

The safety results assessed during this 120-day safety update period do not elicit any new safety signal not observed in the studies comprising the main clinical development program for FF nasal spray. The results of the QT study, after confirmation by the Clinical Pharmacology and Cardiac QT IRT Teams, should be added to the product label.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Adverse events associated with corticosteroid use include adrenal suppression, growth suppression in children, cataracts and glaucoma. In this submission, the HPA-axis was studied in adults and children as young as 2 years of age. In adults there was no evidence of an effect of FF nasal spray on the HPA-axis as measured with plasma and 24-hour urinary cortisol measurements. In children 2 < 12 years of age, plasma and urinary cortisol was not affected when assessed in the 6 week HPA axis study, FFR100012, but there was a small, dose-dependent decrease in urinary cortisol excretion observed in the longer 12 week pediatric study, FFR30008. This finding was observed in children 6 < 12 years of age as urinary cortisol excretion was not assessed in the younger 2 < 6 year population in Study FFR30008. While an effect of FF on the HPA-axis was noted in the longer study, treatment with FF nasal spray did not result in actual HPA-axis suppression as all children tested had 24 hour urinary excretion within normal limits.

No subjects developed glaucoma during the clinical trials reviewed for this FF NDA. However, in the year-long safety study in adults, FFR102123, 12 subjects (2%) treated with FF 110 mcg versus no subjects in the placebo group, had intraocular pressure measurements that were above the threshold limit of 21mmHg, suggesting a small effect

for FF 110 mcg.

Also, in study FFR102123, 7 subjects, 6 (1%) treated with FF110 mcg and 1 (<1%) in the placebo group had cataracts identified during the study period that were not present at baseline. Regardless of the 3:1 difference in number of subjects/group in this study, posterior subcapsular cataracts developing in a 15 year old (#17) and 14 year old (#1033) with three prior visits documenting no cataract is suggestive of a potential for subjects treated with FF to develop cataracts.

In the pediatric program, eye exams were conducted during the 12 week study, FFR30008 which is too short of a period to assess for significant changes in intraocular pressure and for the development of cataracts. That being said, cataracts not present at baseline were observed in 2 subjects in the placebo group, 4 subjects in the FF 55 mcg group but in no subjects in the FF 110 mcg group. Of note is that 2 subjects had trace posterior subcapsular cataracts noted at baseline and at the end of the study. The presence of cataracts at baseline in a generally healthy pediatric population as well as the development of cataracts in so many subjects, including placebo subjects, over a relatively short (12 week) time calls into question the quality of the eye exams performed in the study.

Known AEs associated with local application of corticosteroids to the nasal cavity include epistaxis and nasal mucosal ulcerations. Epistaxis was observed in 6% of adults in the shorter SAR/PAR studies versus 4% in the placebo group, however that difference increased to 20% versus 8% in the year-long safety study. There was little difference in the incidence of nasal ulcerations between those treated with FF 110 mcg or placebo (2% versus <1%, respectively) and there were no nasal septal perforations noted in the clinical program. In children, there were no differences seen in the incidences of AEs associated with epistaxis or nasal ulceration.

In summary, there was no evidence of a systemic effect of FF nasal spray on the HPA-axis in adults; however an effect may be present in children treated with FF for 12 weeks or more. More adults treated with FF 110 mcg for a year also developed cataracts than those treated with placebo. This was not seen in children but the study, FFR30008, was too short to assess for cataracts and several children had cataracts at baseline and throughout the study which would be very unusual for a generally healthy pediatric population and casts doubt on the accuracy of the evaluations. There was also a greater incidence of AEs for epistaxis associated with the longer term use of FF (20% for FF versus 8% for placebo). While there were no new safety signals not seen with other intranasal corticosteroid products found for FF nasal spray, three subjects had AEs of nasal candidiasis, which is rarely seen with nasal steroid products. Also, the possibility of cataract development may be higher for those treated with FF compared to that observed for other marketed intranasal corticosteroid preparations and justifies further evaluation in safety studies post-marketing.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Pooling of data is discussed in the following sections of this review.

7.4.1.1 Pooled data vs. individual study data

To determine appropriateness of pooling data, the study populations, study designs, dosing levels, dosing durations, and administration times for each study were considered. In addition, within the studies, safety measures were reviewed for the appropriateness of pooling. Also, multiple dose studies were analyzed separately from single dose studies.

For the FF clinical development program, AE data for the adult studies were appropriately pooled based on the length of the treatment periods (2-6 weeks) as study designs, population, and dosing levels were otherwise very similar. The data from the long-term safety study was not pooled and gave an assessment of AEs associated with length of exposure to FF and the data for the allergen chamber study was also not pooled as it was a single dose trial. All adverse event data in the pediatric studies were pooled as studies, ranging from 2-12 weeks duration, were similar enough in population, design, and dosing to allow pooling of AEs.

7.4.1.2 Combining data

In general, data for the selected studies were simply combined without the use of any formal weighing method.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Except in 2 of the pediatric trials in which both doses of 55 and 110 mcg were assessed and in the 2 week dose-ranging study in adults with SAR, the only dose tested for efficacy and safety was FF 110 mcg. The dose-ranging study had a limited number of subjects (125-

130) in each treatment group so definitive conclusions cannot be drawn, but there was no evidence of dose dependency for AEs. In the pediatric program, there were no meaningful differences between AEs in subjects dosed with 55 mcg versus 110 mcg FF. However, there appeared to be a dose dependency for the pharmacodynamic effect of FF on the HPA axis (as determined by 24 hour urinary cortisol excretion) of children treated with 55 and 110 mcg doses of FF for 12 weeks.

7.4.2.2 Explorations for time dependency for adverse findings

In general, there were more adverse events reported in the 52-week safety trial than in the shorter efficacy trials. This is not unexpected as longer exposure generally results in more adverse events being reported. When specific AEs were evaluated, the difference in the incidence of epistaxis in the year-long safety study, FFR102123, was higher than in the shorter, 2-6 week, studies with 20% versus 8% and 6% versus 4% for the FF 110 mcg and placebo groups in the year-long safety study and 2-6 week studies, respectively.

7.4.2.3 Explorations for drug-demographic interactions

For the adult program, there were no significant differences in any AEs that were age-related however, the number of subjects > 65 years of age was too small (approximately 50 in the program) to draw any conclusions. Subjects described as Black comprised approximately 10% of the adult study population. There were no apparent differences in the response to FF 110 mcg that could be attributed to Race. There were also no apparent differences in the response of men and woman to FF 110 mcg nasal spray. The Applicant also summarized AEs by region of the world in which they occurred; United States, Europe, or "Other" (Canada only). There were no differences in the incidences of total or any specific AEs between the United States and Europe; however the overall incidence of AEs in Canada (56-57%) was higher than that reported in the United States (27-30%). The AE reported as Headache was notable for being higher in Canada (17-22%) than in the United States (5-8%).

For the pediatric program, there was no significant difference in the overall incidence in AEs in children 2 < 6 years compared to those 6 < 12 years of age. Higher incidences of pyrexia and cough were seen in the younger age groups treated with FF compared with the older 6 < 12 year olds (for pyrexia, 9-13% for FF 110 and 55 mcg treated 2 < 6 year old subjects versus 3% for the older pediatric population and for cough, 6% for FF 110 and 55 mcg treated 2 < 6 year old subjects versus 3% for the older pediatric population. The reason for this difference is unclear but likely related to the greater chance of a fever or cough to be reported as an AE in younger children.

7.4.2.4 Explorations for drug-disease interactions

The population of subjects in the clinical development program for FF was generally healthy other than the presence of allergic rhinitis so no specific drug-disease interactions were assessed. Regarding the effects of FF in the treatment of SAR versus PAR, FF 110 mcg was effective in the treatment of symptoms of both SAR and PAR as determined by changes from baseline in rTNSS compared to placebo. However, while treatment with FF 110 mcg in subjects with SAR also resulted in improvement in eye symptoms determined by changes from baseline in rTOSS compared to placebo and quality of life as measured by the RQLQ, these benefits were not seen in subjects with PAR.

7.4.2.5 Explorations for drug-drug interactions

In the clinical pharmacology study FFR10013, there was some evidence for an increase in systemic exposure on co-administration of FF 110 mcg QD with ketoconazole (a potent CYP3A4 inhibitor), compared to placebo (FF was quantifiable in 6 out of 20 subjects after ketoconazole versus only 1 out of 20 subjects after placebo) however, this effect did not result in any significant change in serum cortisol levels (the geometric mean ratio of 0-24h serum cortisol data was 0.95 with a 90% CI of (0.86 to 1.04). However, the dose of ketoconazole used for the study (200 mg) was one half that recommended (400 mg) (see Clinical Pharmacology review by Sayed Al Habet, Ph.D).

7.4.3 Causality Determination

There were no unusual or rare adverse events that require a causality determination. All of the common adverse events (epistaxis) observed were those commonly seen in this class of drug, in this patient population and in this mode of administration.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimen for FF nasal spray in adolescents and adults 12 years and older is 110 mcg once daily (two activations in each nostril). For children 2 < 12 years of

age, a starting dose of 55 mcg once daily (one activation in each nostril) is recommended with an increase to 110 mcg once daily if not adequately responding to the lower, 55 mcg dose. In the dose-ranging study, FFR20001, all doses tested (55-440 mcg) proved to be efficacious in the treatment of symptoms of SAR as demonstrated by a statistically significant change in rTNSS compared to placebo. The dose ordering for efficacy did not show a dose-response relationship regarding efficacy as the 220 mcg dose proved to be less efficacious than either the FF 55 mcg or 110 mcg groups. This lack of a dose-response relationship for corticosteroids used to treat allergic rhinitis is not unusual and dose selection is then based on secondary endpoints and the safety profile of the different doses tested. The dose of 110 mcg was selected from the dose-ranging study because it appeared to demonstrate a more rapid onset of action than the 55 mcg dose (8 versus 24 hours) without any sign of an increase in side effects. The FF 110 mcg dose was the only dose tested in the adult pivotal trials and proved efficacious for both SAR and PAR as determined by improvement in rTNSS compared to placebo. The once daily dosing regimen was supported by the finding of a significant improvement in iTNSS, again, in both the SAR and PAR trials. In the pediatric trials, the lower dose of 55 mcg was tested as well as the 110 mcg dose used in the adult trials. The lower 55 mcg dose proved efficacious for children with PAR but did not demonstrate a significant improvement in rTNSS in children with SAR, where only FF 110 mcg demonstrated efficacy. However, in light of the inherent imprecision of subjective endpoints such as TNSS, especially when reported by a **child's parent/guardian, the de**monstration that FF 55 mcg was effective in the adult dose-ranging study, and the desire to limit corticosteroid exposure in the pediatric population, it is reasonable to select a starting dose of FF 55 mcg in children and increasing it to 110 mcg once daily if not responding to the lower dose.

In terms of dosing in special populations, dosing modification is not recommended for subjects with renal or mild-moderate hepatic disease.

8.2 Drug-Drug Interactions

In the clinical pharmacology study FFR10013, there was evidence for an increase in systemic exposure on co-administration of FF 110 mcg QD with ketoconazole (a potent CYP3A4 inhibitor), however, this finding had no impact on the HPA-axis as it did not result in any significant change in serum cortisol levels (the geometric mean ratio of 0-24h serum cortisol data was 0.95 with a 90% CI of (0.86 to 1.04). The study was not designed appropriately as the dose of ketoconazole used for the study (200 mg) was one half that recommended (400 mg). While no additional studies with other CYP 3A4 inhibitors have been conducted for this program, based on the results of a drug interaction study with another potent CYP 3A4 inhibitor, ritonavir, performed by the Applicant to support the fluticasone propionate program, co-administration of FF with ritonavir is not recommended because of the risk of systemic side effects (see Section 7.4.2.5 in this review and the Clinical Pharmacology review by Sayed Al Habet, Ph.D).

8.3 Special Populations

Hepatic Insufficiency

Single doses of FF 400 mcg were administered by oral inhalation to 10 male and female patients with moderate hepatic impairment (Child-Pugh B) and 10 matched healthy subjects in study FFA10013 in order to assess the degree, if any, that hepatic impairment would increase exposure of subjects to FF. Results demonstrated that compared to healthy subjects, FF Cmax was increased on average by 42% in subjects with impaired hepatic function (90% CI: 1% decrease to 104% increase). Further, the AUC(0-∞) was increased on average by 172% in subjects with impaired hepatic function compared with healthy subjects (90% CI: 13% decrease to 749% increase). Based on the PK-PD model relating exposure to FF and cortisol suppression this extent of systemic exposure would not be expected to result in detectable suppression of cortisol following repeat dosing of 110 mcg/day intranasally. Therefore, although moderate hepatic impairment may result in an increase in systemic exposure following 110 mcg QD intranasally, it is not expected to require any dose adjustment in this population.

Child-Pugh Classification of Hepatic Dysfunction

	Score		
Risk Factor	**1**	**2**	**3**
Ascites	**Absent**	**Slight**	**Moderate**
Neurological symptoms	**Absent**	**Transient or mild**	**Hepatic coma**
Prothrombin time prolonged from control (sec)	**<4**	**4 to 6**	**>6**
Serum bilirubin (mg/dL)	**<2**	**2 to 3**	**>3**
Serum bilirubin (mg/dL) for subjects with primary biliary cirrhosis	**<4**	**4 to 10**	**>10**
Serum albumin (g/dL)	**>3.5**	**2.8 to 3.5**	**<2.8**

Hepatic dysfunction is considered mild if the Child-Pugh Score was 5 or 6, moderate-to-severe for a score of 7 to 9, and severe for a score of 10 to 12.

8.4 Pediatrics

The treatment of children 2 to 12 years of age is covered in the body of the application. The applicant requested and has been granted a waiver for studies in children < 2 years of age due to safety concerns with the use of corticosteroids via nasal inhalation in children < 2 years of age together with the fact that there are other treatments available for the treatment of symptoms of allergic rhinitis in this younger population.

8.5 Advisory Committee Meeting

A Pulmonary Allergy Advisory Committee meeting was not held for this NDA.

8.6 Literature Review

There are no published reports of the use of FF nasal spray in the literature. This reviewer searched the MEDLINE database using the **terms "fluticasone furoate" and "fluticasone furoate and allergic rhinitis" on February 6, 2007**. A total of 67 references were found. All the references to fluticasone were for fluticasone propionate, another corticosteroid product indicated for treatment of allergic rhinitis.

8.7 Postmarketing Risk Management Plan

The Applicant submitted their Risk Management/Minimization Plan to DPAP for review with the Pre-NDA meeting package. The Plan outlined the known class effects of intranasal and systemic corticosteroid use including the development of cataracts, glaucoma, suppression of the HPA-axis, and decreased growth in children. The Applicant proposed to use standard pharmacovigilance activities to monitor adverse events reported post-marketing with a focus on long-term corticosteroid side effects such as ocular disorders and growth suppression. At the Pre-NDA meeting on February 13, 2006, DPAP informed the Applicant that the plan was appropriate for an intranasal steroid, a drug class with a well-known safety profile, and would be acceptable, pending review of the NDA. As no safety signals other than the known class effects of corticosteroids were observed for FF in this NDA review, the proposed Plan is acceptable.

8.8 Other Relevant Materials

A product quality microbiology review conducted by Bryan S. Riley, Ph.D. concluded that NDA 22-051 is recommended for approval on the basis of microbiological product quality. An Ophthalmology consult was obtained to help assess the significance of intraocular pressure data and cataract findings in the clinical trials (see Section 7.1.7.5 and the consult by Wiley Chambers, M.D., dated February 7, 2007).

9. OVERALL ASSESSMENT

9.1 Conclusions

The data submitted in this Application provide support, from a clinical perspective, for approval of FF nasal spray for the treatment of symptoms of both SAR and PAR in adults and children > 2 years of age at a dose of 110 mcg once daily for adolescents and adults and at starting dose of 55 mcg for children 2 < 12 years of age with dose escalation to 110 mcg once daily if symptoms are not adequately controlled.

Data for the primary endpoint of Phase 2b/3 studies provided convincing evidence of efficacy in four, 2-week studies in adults with SAR (including a dose-ranging study) and one 4-week study of adults with PAR. The pediatric efficacy studies, single studies in children with SAR and PAR, also provided evidence of the efficacy of FF nasal spray at a dose of 55 mcg in children with PAR and a dose of 110 mcg in those with SAR. Efficacy was established by the demonstration of a statistically significant improvement over placebo in rTNSS over the course of 2 week and 4 week treatment periods for SAR and PAR, respectively. Secondary efficacy analyses, including iTNSS, individual nasal symptom scores, and overall response to therapy for both SAR and PAR, and, for adults with SAR, improvements in ocular symptoms as measured by rTOSS and quality of life as determined by the RQLQ, supported the primary endpoint analysis.

The Applicant's claim for onset of action as early as 8 hours is not supported by the allergen chamber study or by the overall results from the clinical trials. Onset of action was not observed within the 12 hour post-dose monitoring period in the allergen chamber study and the onset of action in adult subjects with SAR was at 24 hours in 2 of 3 pivotal SAR studies and at 4 days in the pivotal adult PAR study.

In terms of dosing in special populations, dosing modification is not recommended for subjects with renal or mild-moderate hepatic impairment.

The extent of patient exposure to FF nasal spray during the development program was adequate for both the adult and pediatric programs. The safety profile of FF nasal spray at a dose of 110 mcg once daily is acceptable. In the clinical studies conducted for this application, FF was well-tolerated. Adverse events attributable to the drug, such as epistaxis, were generally consistent with those observed for other intranasal corticosteroid products although may be more frequent with long-term use. At the recommended dose and regimen, FF nasal spray did not suppress the HPA-axis. More adult subjects treated with FF 110 mcg once daily for one year had cataracts noted during the treatment period than those that received placebo. This finding will be further evaluated post-marketing by requiring a 2-year Phase 4 study to study the effects of FF on the eye.

9.2 Recommendation on Regulatory Action

From a clinical perspective, the data submitted in this NDA provide support Approval of FF for the treatment of symptoms of SAR and PAR in both adults and in the pediatric population ≥ 2 years of age. The adequate and well-controlled clinical studies demonstrated that the proposed dose of 110 mcg of fluticasone furoate (FF) nasal spray once daily

provided a statistically significant improvement in reflective total nasal symptom score (rTNSS) compared to placebo for both seasonal and perennial allergic rhinitis (SAR and PAR). The rTNSS is a commonly used and accepted clinical endpoint in studies used to assess the effectiveness of therapies for allergic rhinitis. A dose of FF 55 mcg once daily was also effective in the treatment of children 2 < 12 years of age with PAR. Given that the 55 mcg dose was also efficacious in the adult dose-ranging study and the desire to minimize the exposure of children to corticosteroids, it is reasonable to start treatment of children with FF 55 mcg once daily and increasing the dose to 110 mcg once daily only if symptoms are not adequately controlled.

Given its documented clinical efficacy, the safety profile of FF nasal spray is acceptable. In the clinical studies conducted for this application, FF was well-tolerated. Adverse events attributable to the drug, such as epistaxis, were generally consistent with those observed for other intranasal corticosteroid products although may be more frequent with long-term use. At the recommended dose and regimen, FF nasal spray did not suppress the HPA-axis. More adult subjects treated with FF 110 mcg once daily for one year had cataracts noted during the treatment period than those that received placebo. This finding will be further evaluated post-marketing by requiring a 2-year Phase 4 study to study the effects of FF on the eye.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The Applicant submitted their Risk Management/Minimization Plan to DPAP for review with the Pre-NDA meeting package. The Plan outlined the known class effects of intranasal and systemic corticosteroid use including the development of cataracts, glaucoma, suppression of the HPA-axis, and decreased growth in children. The Applicant proposed to use standard pharmacovigilance activities to monitor adverse events reported post-marketing with a focus on long-term corticosteroid side effects such as ocular disorders and growth suppression. At the Pre-NDA meeting on February 13, 2006, DPAP informed the Applicant that the plan was appropriate for an intranasal steroid, a drug class with a well-known safety profile, and would be acceptable, pending review of the NDA. As no safety signals other than the known class effects of corticosteroids were observed for FF in this NDA review, the proposed Plan is acceptable.

9.3.2 Required Phase 4 Commitments

Risks associated with the long-term use of intranasal corticosteroids include the development of cataracts, glaucoma, suppression of the HPA-axis, and decreased growth in children. During the clinical review of this NDA it was noted during the year-long safety study in adults with PAR that seven subjects had cataracts noted that were not present at baseline and that six of the seven had been treated with FF 110 mcg QD, the proposed market dose for FF nasal spray. This is a relatively high number of cataracts for an otherwise healthy, relatively young, study population and suggests that either the eye exams conducted during the study were not reliable or that FF nasal spray may have a greater potential to cause cataracts than other nasal steroid preparations used to treat allergic rhinitis. There is a similar concern for the development of glaucoma as, compared to placebo, more subjects treated with FF 110 mcg QD in the adult safety study developed increases in intraocular pressure above the normal threshold. Additionally, the indication for FF nasal spray for the treatment of SAR and PAR will include its use in children as young as 2 years of age. Because of the potential negative effects of corticosteroids on growth, a required element of a pediatric clinical development program for nasal steroids is to assess the effects of the steroid nasal spray on growth in children (Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products (04/2000).

As a result of these concerns, a one year study to assess the effects of FF nasal on children's growth as determined by stadiometry and a two year study to assess the effect of long-term treatment with FF nasal spray on the development of cataracts/glaucoma will be required as Phase 4 commitments.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests for the FF nasal spray program.

9.4 Labeling Review

The proposed product label was reviewed in detail. The following are general comments regarding the proposed product label.

Section 1: Indications and Usage

- The indication for FF will be for the treatment of symptoms of SAR and PAR...

Section 5: Warnings and Precautions

- List the number of subjects in each treatment group that had intraocular pressure measurements that increased above the normal range in the adult and pediatric safety studies (
- List the number of cataracts not detected at baseline that were observed in the adult

and pediatric long-term safety studies (Seven subjects (6 (1%) in the FF 110 group and 1 (<1%) in the placebo group had cataracts identified during the study period that were not present at baseline. [redacted]

- Note that [redacted] subjects had evidence of a nasal infection with Candida sp. in the FF clinical development program and that, subjects using FF nasal spray for several months should be periodically assessed for Candida infection [redacted]
- Note that FF should be not be co-administered with drugs that inhibit CYP3A4, including ritonavir. State that the recommendation is based on data with fluticasone propionate [redacted]

Section 6: Adverse Reactions

- State that epistaxis and nasal ulcerations were more common in subjects treated with FF compared to placebo
- Revise Table 1 to include all AEs >1% incidence and greater in the FF groups. It appears that only those felt drug related are included.
- Include the severity of epistaxis in subjects treated with placebo

Section 7: Drug Interactions

- Delete reference to the [redacted]

Section 11: Description

- **Remove the word '**[redacted]**' in the des**cription of FF (inappropriate to describe something that is not there).

Section 12: Clinical Pharmacology

- [redacted]

Section 14: Clinical Studies

- [redacted]
- Add rTOSS data to the table of results for the PAR study (Table 2).
- Onset of action should be stated as being observed generally within the first 24 hours.
- [redacted]

DDMAC reviewed the proposed draft labeling and provided comments [Michelle Safarik, DDMAC Reviewer, January 22, 2007]. DPAP reviewed the comments and incorporated many of the suggestions into the revised product label including the removal of language considered promotional.

DMETS reviewed the proposed TRADENAME, container labels, carton, and package insert for arformoterol tartrate and had the following comments [Jinhee L. Jahng, Pharm.D., DMETS Review, November 08, 2006].

Tradename

- DMETS has found the proposed Tradename, " ——— ', **unacceptable as there are** at least 8 proprietary names of other drugs that were thought to have the potential **for confusion with " ———'. Reviews** of the alternate proposed Tradenames, **"Veramyst" and "——— are in progress.**

General Comments

- Ensure that the proprietary and established names are the most prominent information on the label and that the established name is at least ½ the size of the proprietary name.
- Revise the labels and labeling so that th**e strength is presented as "27.5 mcg per spray".**
- Revise the labels and label**ing so that the symbol "—' is replaced with —".**

The Patient Instructions for Use for FF were reviewed by DSRCS and substantial revisions were suggested [Sharon R. Mills, BSN, RN, CCRP., DSRCS Review, February 08, 2007]. Following is a brief summary of the changes suggested.

Comments and Recommendations

- The Patient Information/Patient Instructions for Use have been reorganized into a more patient-friendly question and answer-type format as described in 21 CFR 208.20 for Medication Guides.
- **The section "What you should know about allergic rhinitis" has been moved to the** end of the Patient Information section as it is not the most important information for patients to know.
- A list of active and inactive ingredients in TRADE NAME was added in the Patient Information section.

9.5 Comments to Applicant

There are no comments to convey to the Applicant.

10. APPENDICES

10.1 Review of Individual Study Reports

10.1.1 STUDY # FFR20001

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Study to Evaluate the Efficacy and Safety of Once Daily, Intranasal Administration of Fluticasone furoate (GW685698X) Aqueous Nasal Spray 50 mcg, 100 mcg, 200 mcg, or 400 mcg for 14 days in Adult and Adolescent Subjects with Seasonal Allergic Rhinitis

Protocol

Administrative

Study initiated: December 07, 2003
Study completed: February 02, 2004
Clinical Centers: 8 study sites in south central Texas during the 2003-2004 mountain cedar allergy season
Study report dated: July 31, 2004
Study Sponsor: GlaxoSmithKline (GSK)
Medical Officer: Kathy Rickard, M.D., GSK

Objective/Rationale

The primary objectives of this study were to compare the safety and efficacy of four different doses of fluticasone furoate (FF), also referred to as GW685698X, aqueous nasal spray (50, 100, 200, and 400 mcg) with vehicle placebo nasal spray and characterize the systemic exposure to GW685698X within this dose range in adults and adolescent subjects with SAR. Data from this study were used to determine the optimal dose to move forward in the development program of FF for adults.

Study Design

This study is a randomized, double-blind, placebo-controlled, parallel group, five-arm, multicenter, study of the efficacy and safety of FF aqueous nasal spray 50, 100, 200, and 400 mcg for 14 days in 641 adult and adolescent patients with seasonal allergic rhinitis (SAR) due to mountain cedar pollen. This trial was conducted at 8 study sites in south central Texas during the 2003-2004 mountain cedar allergy season. To document the presence of the allergen, daily pollen counts and rainfall measurements were recorded on a pollen/rainfall log provided by GSK. Four clinic visits were scheduled to occur at the following intervals: Screening, Day 1 (Randomization), Day 8, and Day 15 or early withdrawal. Subjects who met the entrance criteria at Visit 1 entered a 5- to 21-day screening period to determine the severity and frequency of their SAR symptoms. After at least 5 days in the screening period, symptomatic subjects who met the randomization

criteria were randomly assigned to one of the following five intranasal, double-blind treatment groups: FF aqueous nasal spray 50, 100, 200 or 400 mcg once daily (QD) or vehicle placebo nasal spray QD. The primary efficacy outcome was the reflective Total Nasal Symptom Score (r-TNSS) which was calculated from the diary recordings of the 12-hour AM and 12-hour PM r-TNSS scores. Safety was assessed with adverse events, vital signs, collection of urine for cortisol determinations, and routine safety laboratory tests. Subject compliance was assessed with the diary and by inspection of the medication bottles. All the participating subjects were outpatients.

The protocol was amended once during the study. It allowed 3 additional days (up to 5 days total) for collection of the urine sample required for Visit 2. It essentially allowed subjects with Friday visit dates to collect urine samples on the weekend prior to their scheduled visit, thereby, fulfilling the randomization requirement and preventing the need for urine collection during the weekday at their jobs.

Study Population

Inclusion Criteria

1. Subject had provided an appropriately signed and dated informed consent or one had **been obtained from the subject's parent or** guardian if the child was under 18 years of age.
2. Subject was treatable on an outpatient basis.
3. Age ≥ 12 years at Visit 2
4. Male or Eligible Female

   To be eligible for entry into the study, females of childbearing potential must have committed to consistent and correct use of an acceptable method of birth control.
5. Diagnosis of SAR

   SAR was defined as follows:
   - Clinical history of SAR (written or verbal confirmation) with seasonal onset and offset of nasal allergy symptoms during each of the last two mountain cedar allergy seasons, and
   - A positive skin test (by prick method) to mountain cedar allergen within 12 months prior to Visit 1.

A positive skin test was defined as a wheal ≥3mm larger than the diluent control for prick testing. In vitro tests for specific IgE (such as RAST, PRIST) were not allowed as a diagnosis of SAR.

6. Adequate exposure to mountain cedar
   - Subject resided within a geographical region where exposure to mountain cedar allergen was expected to be significant during the entire study period.
   - Subject did not plan to travel outside the geographical region where exposure to mountain cedar allergen was expected to be significant for more than 48 hours of the study period.
7. Ability to comply with study procedures

8. Subject must have been able to read, comprehend, and record information in English.

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 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. history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol) or other conditions that would have limited the validity of informed consent or that would have confounded the interpretation of the study results

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
- Intranasal anticholinergics within 72 hours prior to Visit 1
- Oral antileukotrienes within 72 hours of Visit 1
- **Subcutaneous omalizumab (Xolair†)** within 5 months of 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)

5. Use of immunosuppressive medications 8 weeks prior to screening and during the study
6. Use of any medications that significantly inhibit the cytochrome P450 subfamily enzyme CYP3A4, including ritonavir and ketoconazole
7. Known hypersensitivity to corticosteroids or any excipients in the product
8. Had recent exposure to an investigational study drug within 30 days of Visit 1
9. Positive pregnancy test
10. Affiliation with investigational site
    - Subject was a participating investigator, sub-investigator, study coordinator, or employee of a participating investigator, or was an immediate family member of the aforementioned
11. Current tobacco use
12. Findings of an abnormal ECG
13. Findings of a clinically significant laboratory abnormality

Randomization Criteria
At Visit 2, the subject must have met the following criteria:
1. Clinically symptomatic on the morning of Visit 2 with an instantaneous Total Nasal Symptoms Score (iTNSS) ≥6 and an instantaneous nasal symptom score for nasal congestion of at least 2
2. 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 ≥6. This included the AM assessment on the morning of the randomization visit.
3. 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 ≥2. This included the AM assessment on the morning of the randomization visit.
4. Must have had a 24-hour urine cortisol collection
5. A subject must have completed 80% of assessments on the screening symptom diary cards

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 released 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 traveled outside the geographical region where exposure to mountain cedar allergen was expected to have been significant for more than 48 hours of the study period
- a subject had become pregnant
- 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. Following is a list of medications prohibited at any time during the study and their corresponding exclusion period, if required, prior to Visit 1:

- Intranasal or ocular cromolyn within 14 days prior to Visit 1
- Oral or intranasal short-acting antihistamines within 3 days prior to screening visit
- Long acting (second generation) antihistamines within 10 days prior to Visit 1. These include loratadine, desloratadine, fexofenadine, and cetirizine.
- Corticosteroids
    - Subjects must not have received intranasal corticosteroids within 4 weeks prior to Visit 1
    - Subjects must not have received any inhaled, intravenous, intramuscular, ocular or systemic corticosteroids within 8 weeks prior to Visit 1
    - With the exception of topical hydrocortisone (1% or less), subjects must not have used any dermatological corticosteroids during the study.
- Oral or intranasal decongestants within 72 hours prior to Visit 1
- Long-acting beta-agonists
- Intranasal anticholinergics within 72 hours prior to Visit 1
- Oral antileukotrienes (i.e., montelukast) within 72 hours of Visit 1
- Ophthalmic allergy preparations
    - Subjects must not have used any ocular antihistamines, artificial tears, eyewashes, homeopathic preparations, irrigation solutions, lubricants, sympathomimetic preparations, or vasoconstrictors. No exclusion period prior to Visit 1.
- Immunotherapy
    - Immunotherapy patients may have been enrolled in the study 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 was to remain fixed for the duration of the study.

- CYP3A4 inhibitors
  - Subjects must not have used any medications that significantly inhibit this cytochrome P450 subfamily enzyme, including ritonavir and ketoconazole.
- Subcutaneous omalizumab within 5 months of Visit 1

Study Procedures

Treatments

Schedule of Study Events

Activity	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4 Exit
	Clinic	Clinic	Clinic	Clinic
	Day –5 to -21	Day 1	Day 8±2	Day 15±1 or discontinuation
Informed consent	X			
Subject number assignment				
Inclusion/exclusion criteria verification	X			
Medical history	X			
Concomitant medication assessment	X	X	X	X
Skin test (if not done < 12 months of Visit 1)	X			
Clinical Laboratory studies/serum pregnancy test if female	X			X
12-Lead electrocardiogram	X			X
Issue screening diary card	X			
Dispense 24 hr urine collection kit	X		X	
Obtain 24 hr urine collection		X		X
Collect/Review diary cards		X	X	X
Randomization number assignment		X		
Issue onset diary card		X		
Issue treatment diary cards		X		
Dispense study drug to eligible subjects		X		
Nasal spray technique demonstration		X		
Nasal exam	X	X	X	X
Physical exam	X			X
Adverse events assessment		X	X	X
Vital signs	X			X
Dispense diary card	X	X		
NRQLQ		X	X	X
RQLQ		X	X	X
Contact subject to remind to hold dose AM Visit 4			X	
Pharmacokinetic plasma sampling			X	X
Pharmacogenetic sampling				X
Collect study drug				X
Compliance assessment				X
Subject-rated overall evaluation of response to therapy				X
Follow-up phone call to subject to assess for post-treatment AEs				X

Fluticasone furoate was manufactured as a ——— aqueous suspension containing ——————— of micronized FF corresponding to — ncg, — mcg or = mcg of FF per actuation respectively. The ——————— consisted of — % w/w benzalkonium chloride ——— % disodium edetate. 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, 110, 220, and 440 mcg of FF.

The dose of study drug was administered via a side-actuated nasal spray device filled with a sufficient volume of study drug to deliver a minimum of 120 actuations. 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.

Demographic and Baseline Assessments

Demographic assessments included age, gender, ethnic origin, height, and weight. Baseline assessments included allergy history, current medical conditions, rhinitis symptom assessments, and concurrent medications administered during the screening period. Nasal symptoms and ocular symptoms at baseline were evaluated via reflective and instantaneous assessments as described below. Pollen counts and rainfall totals were recorded by the sites at least 5 days per week.

Pharmacogenetic Assessment

Subject participation in pharmacogenetic research was voluntary and refusal to participate did not indicate withdrawal from the clinical study. Refusal to participate involved no penalty or loss of benefits to which the subject would have been otherwise entitled.

In addition to any blood samples taken for the clinical study, a whole blood sample of approximately 10ml was collected at Visit 4 for pharmacogenetic research using a tube containing EDTA.

The sample was labeled with a study specific number that could be traced or linked back to the subject by the investigator or site staff. Coded samples did not carry personal identifiers.

Efficacy Evaluations

All primary and secondary efficacy assessments were based on subject ratings. The primary and secondary nasal endpoints for evaluation of efficacy were calculated from daily subject-rated nasal scores. The 4 individual nasal symptoms that each subject assessed throughout the study were:

- Nasal congestion
- 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).

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 Total Nasal Symptom Score (rTNSS) was defined as the average of the AM and PM rTNSS. The baseline score was defined as the average of the daily rTNSS over the 4 consecutive 24-hour periods prior to randomization, including the assessment the morning of randomization.

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)
- 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.

Health Outcome Assessments

The Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire (NRQLQ)

The NRQLQ is a 16-item, self-administered, disease-specific (allergic rhinitis), quality of life instrument to measure the functional problems that are most troublesome to patients with nocturnal allergy symptoms over a one-week interval. Each question is scored from 0 to 6 with higher scores indicating more nocturnal impairment. Items are grouped into four domains: Sleep problems (4 items), Sleep time problems (5 items), Symptoms on waking in the morning (4 items) and Practical problems (3 items). An overall score can be calculated from the mean score of all items. The questionnaire was administered during the initial assessment at Visit 2 and again during Visits 3 and 4/Early Discontinuation Visit.

The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)

The RQLQ is a 28-item, self-administered, disease-specific (allergic rhinitis) quality of life instrument, which assesses quality of life over a one-week interval. Each question is scored from 0 to 6, with higher scores indicating more impairment on quality of life. Items are grouped into seven domains: Activity limitations (3 items), Sleep problems (3 items), Non-nose/eye symptoms (7 items), Practical problems (3 items), Nasal symptoms (4 items), Eye symptoms (4 items) and Emotional function (4 items). An overall quality of life score can be calculated from the mean score of all items. As part of this study, subjects were asked during their initial assessment at Visit 2 to identify their three most important daily activities (in which they were likely to engage in during the study period) which are limited by their nose/eye symptoms. These same activities were used as references and were evaluated on subsequent questionnaires completed during Visits 3 and 4/Early Discontinuation Visit.

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)
- 24-hour urinary cortisol assessment
- Results of gross nasal examinations
- Vital signs (systolic and diastolic blood pressures, heart rate)
- 12-lead electrocardiograms (ECGs)

Data Analysis

Sample Size

The study randomization was planned for equal allocation of subjects among five treatment groups and stratified among the eight investigational sites to account for possible site-to-site variability.

A total of 590 evaluable subjects were required for this study, with 118 subjects in each of the five treatment groups: vehicle placebo nasal spray, GW685698X aqueous nasal

spray 50 mcg QD, 100 mcg QD, 200 mcg QD, and 400 mcg QD.
This sample size provided 90% power to detect a difference of 0.85 between active treatment and placebo in mean change from baseline over the entire treatment period in daily rTNSS, assuming a standard deviation of 2.00. This calculation was based on a two-sample t-test with a 0.05 two-sided significance level.

It was projected that an estimated 620 subjects should be randomized into the study to ensure 118 subjects per treatment group, assuming an approximately 5% drop out rate.

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 all efficacy, safety, and health outcomes analyses.

The Urine Cortisol (UC) population was defined to exclude subjects from the ITT population whose urine samples were considered to have confounding factors that would have affected the interpretation of the results. Specifically, the UC population was defined as the ITT population excluding subjects who had any one of the following:

1. urine volumes of <600 mL for female subjects and <800 mL for male subjects, and 24-hour creatinine excretion below the lower limit of threshold range (defined **as mean – 2.5 std, where the normal range** was defined as the mean ± 2.0 std)
2. collection time intervals outside 24 ± 4 hours
3. used protocol-prohibited systemic (oral or injectable) and inhaled corticosteroids within 8 weeks prior to any start time of urine collection
4. used protocol-prohibited intranasal and topical (except 1% hydrocortisone cream/ointment) within 4 weeks prior to any start time of urine collection
5. had been off study drug for more than 1 day at the start time of the post-baseline urine collection.

The pharmacokinetic (PK) population included all subjects who provided plasma samples for measurement of FF concentration, i.e. all subjects excluding those in the placebo group.

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, investigative site, age, and gender, in addition to treatment effect.

Mean change from baseline in daily rTNSS over the entire treatment period was analyzed. The least squares mean changes from baseline is summarized for all treatment groups and compared to that in placebo group. The 95% confidence interval (CI) for the

mean difference (active vs. placebo) is also reported, as well as the p-values corresponding to the test of significance for the mean difference (active vs. placebo).

The secondary efficacy measures on nasal symptoms, ocular symptoms, and combined nasal and ocular symptoms were analyzed similarly to the primary analysis. The analysis method was the pairwise comparisons of treatment groups (active vs. placebo) using an analysis of covariance (ANCOVA) and adjusting for baseline value, investigative site, age, and gender, in addition to treatment effect.

Onset of Action/Time to Maximal Effect

The onset of action was defined as the first time point after initiation of treatment when the drug demonstrated a significantly greater change (from baseline) than the placebo treatment in the nasal symptoms. Onset of action was assessed by the mean change from baseline in iTNSS (at 4, 8 and 12 hours after the first dose, and daily thereafter) and the mean change from baseline in daily rTNSS (days 1 - 14), and supported by the mean change from baseline in AM and PM rTNSS. Statistical summary and analysis, as well as the graphical presentation were performed similarly to the primary analysis.

The time to maximal effect was defined as the earliest time that the primary efficacy endpoint demonstrated the greatest numerical difference from the placebo in change from baseline. Time to maximal treatment effect was evaluated by the mean change from baseline in daily rTNSS over days 1-14 during the treatment period.

Health Outcome Analyses

Rhinoconjunctivitis Quality of Life Questionnaire

The primary analysis of the RQLQ was the mean change from baseline in the global score compared between the active treatment groups and placebo at endpoint. Baseline was defined from the Visit 2 questionnaire. The endpoint was defined from the last available questionnaire completed at least 1 week after the baseline questionnaire. An analysis of covariance model including terms for treatment, investigator, treatment-by-investigator interaction, and baseline was used to test statistical differences in treatment group mean changes from baseline and endpoint. A mean change from baseline of 0.5 or more for the RQLQ scores is considered to be the minimally important difference (MID) that should be met in order for an intervention to be considered to have a positive impact quality of life[1,2,3].

For each domain, the mean score for any patient at any time point was calculated only if at least 75% of the questions included in that domain were answered. If fewer than 75% of the questions in a domain were answered, then the mean for that domain and time point was set to missing for that patient. An overall score for any patient at any time point was calculated only if at least 75% of all questions were answered. If fewer than 75% of all questions were answered, then the mean for the overall score at that time point was set to missing for that patient.

Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire

The primary analysis of the NRQLQ is the mean change from baseline in the global score compared between the active treatment groups and placebo at endpoint. The overall quality of life score is the mean score of all items and each domain score is the mean score of all domain items.

Baseline was defined from the Visit 2 questionnaire. The endpoint was defined from the last available questionnaire completed at least 1 week after the baseline questionnaire. An analysis of covariance model including terms for treatment, investigator, treatment-by-investigator interaction, and baseline was used to test statistical differences in treatment group mean changes from baseline and endpoint.

Results

Study Population

Disposition

A total of 879 subjects were screened for this study at the eight investigative sites. Six hundred forty-two subjects were randomized, however, one subject did not receive any study drug after randomization; therefore, the ITT population consisted of 641 subjects. Enrollment ranged from 47 (7%) to 112 (17%) subjects at each of the 8 investigational sites. Ninety-seven percent of subjects completed the study. Premature withdrawals occurred for 21 subjects (3%) and ranged from 2 (2%) in the FF 100 mcg group to 6 (5%) in the FF 50 mcg group. A total of 593 subjects (93% of the randomized population) comprised the UC population. The following table shows the subject disposition as of the end of the study. Reasons for exclusion from the UC population included insufficient urine collection, collections performed outside the 24 ± 4-hour window, subjects off study drug for more than a day, and missing data.
Reviewer's Comment: The numbers of subjects *in each treatment group and reasons for exclusion were reviewed and the number of exclusions and reasons for exclusion are similar across treatment groups.*

Study FFR20001: Subject Disposition *[Table 4 FFR20001 Study Report, page 69]*

	Placebo (N=128)	GW685698X 50 mcg (N=127)	GW685698X 100 mcg (N=127)	GW685698X 200 mcg (N=129)	GW685698X 400 mcg (N=130)	Total (N = 641)
Completion Status						
Completed	124 (97%)	121 (95%)	125 (98%)	124 (96%)	126 (97%)	620 (97%)
Prematurely Withdrawn	4 (3%)	6 (5%)	2 (2%)	5 (4%)	4 (3%)	21 (3%)
Primary Reason for Withdrawal (n)						
Adverse Event	1 (<1%)	2 (2%)	1 (<1%)	4 (3%)	1 (<1%)	9 (1%)
Lost to Follow-Up	0	2 (2%)	0	0	1 (<1%)	3 (<1%)
Protocol Violation	0	1 (<1%)	0	0	1 (<1%)	2 (<1%)
Subject decided to withdraw	0	1 (<1%)	0	0	1 (<1%)	2 (<1%)
Lack of efficacy	0	0	0	1 (<1%)	0	1 (<1%)
Other	3 (2%)	0	1 (<1%)	0	0	4 (<1%)

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

Demographics

Demographics were similar across treatment groups. The mean age range was 38.3–40.6 years among treatment groups with a range of 12-80 years. Most subjects in each treatment group were in the 18-64 years of age subgroup (88-94%). The majority of the subjects were White (57-61%) or American Hispanic (33–38%). Females were more prevalent across all groups (64–68%). Ninety to ninety-five percent of subjects receiving treatment reported having SAR for ≥5 years. Approximately two-thirds of subjects also reported having perennial allergic rhinitis (PAR). Baseline demographics are listed in the following table.

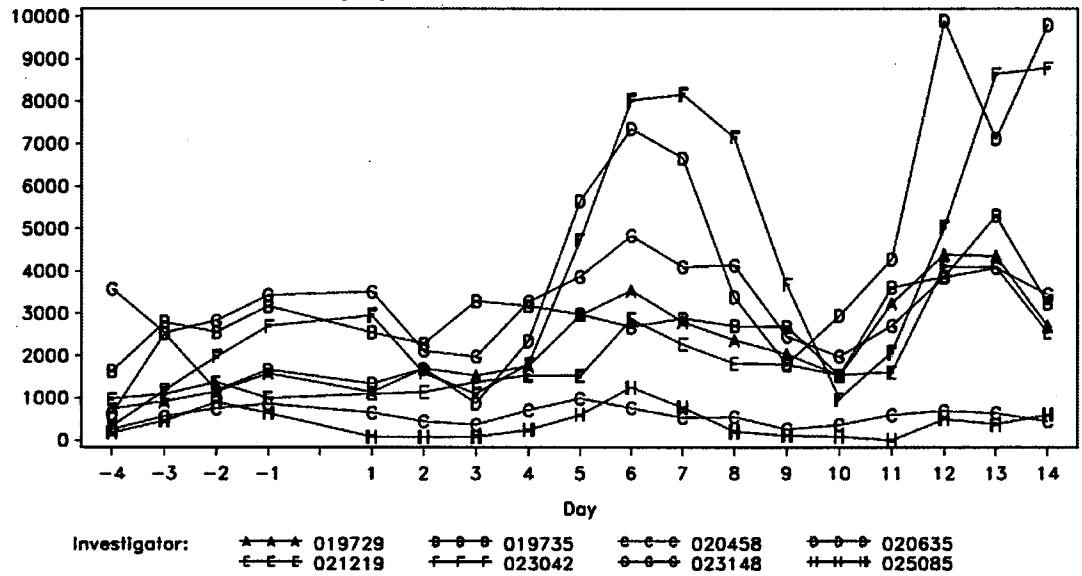
Study FFR20001: Demographics and Baseline Characteristics *[Table 6 FFR20001 Study Report, page 69]*

	Placebo n (%) (N=128)	GW685698X 50 mcg n (%) (N=127)	GW685698X 100 mcg n (%) (N=127)	GW685698X 200 mcg n (%) (N=129)	GW685698X 400 mcg n (%) (N=130)	Total N (%) (N= 641)
Age (years)						
Mean, SD	38.6, 13.99	38.3, 14.45	40.6, 13.62	39.4, 13.10	39.6, 13.91	39.3, 13.8
Range (min-max)	12 - 75	12 – 80	13 – 70	12 – 71	13 - 71	12 – 80
Age Groups						
<18	11 (9)	10 (8)	6 (5)	5 (4)	11 (8)	43 (7)
≥18 – 64	112 (88)	111 (87)	116 (91)	121 (94)	115 (88)	575 (90)
≥65 – 74	4 (3)	5 (4)	5 (4)	3 (2)	4 (3)	21 (3)
≥75	1 (<1)	1 (<1)	0	0	0	2 (<1)
Gender						
Female	85 (66)	81 (64)	86 (68)	83 (64)	86 (66)	421 (66)
Male	43 (34)	46 (36)	41 (32)	46 (36)	44 (34)	220 (34)
Ethnic Origin						
White	76 (59)	73 (57)	75 (59)	76 (59)	79 (61)	379 (59)
American Hispanic	46 (36)	42 (33)	47 (37)	49 (38)	48 (37)	232 (36)
Black	6 (5)	9 (7)	4 (3)	3 (2)	3 (2)	25 (4)
Asian[a]	0	2 (<1%)	1 (<1)	0	0	3 (<1)
Other	0	1 (<1)	0	1 (<1)	0	2 (<1)
Duration of SAR						
≥2 - <5 yrs	6 (5%)	10 (8%)	10 (8%)	8 (6%)	13 (10%)	47 (7)
5- <10 yrs	30 (23%)	34 (27%)	28 (22%)	26 (20%)	32 (25%)	150 (23)
≥ 10 yrs	92 (72%)	83 (65%)	89 (70%)	95 (74%)	85 (65%)	444 (69)

***Reviewer's Comment: All subjects were allergic** to Mountain Cedar. Baseline wheals from allergy tests were very similar across treatment groups ranging from 8.2-8.6 mm. Wheals from diluent ranged from 01.-0.3 mm [Table 15.16 FFR20001 Study Report, page 262].*

Measurements of mountain cedar pollen were recorded on a daily basis throughout the study from seven of the sites. Pollen counts varied widely from day to day and between the 3 Texas cities. Mountain cedar pollen counts were highest in the San Antonio and New Braunfels areas and lowest in the Austin area. The following table shows mean exposure to Mountain Cedar pollen during the course of the study.

Mean Exposure to Mountain Cedar Allergen over the Baseline and Treatment Periods *[Figure 15.1 FFR20001 Study Report, page 136]*



***Reviewer's Comment: Pollen counts were much** higher at some sites than others with sites C and H having relatively low pollen counts (<1000 particles/cubic meter). However, stratification for site would tend to negate any differences in pollen counts at the different sites.*

Efficacy Results

Primary Efficacy Outcome

The primary efficacy endpoint was the mean change from baseline in the reflective TNSS over the entire treatment period. 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 2-week treatment period.

Daily rTNSS (ITT Population) *[Table 12 FFR20001 Study Report, page 76]*

	Placebo (N=128)	GW685698X 50 mcg (N=127)	GW685698X 100 mcg (N=127)	GW685698X 200 mcg (N=129)	GW685698X 400 mcg (N=130)
Baseline (n)	128	127	127	129	130
Mean (SE)	9.6 (0.15)	9.6 (0.13)	9.5 (0.13)	9.5 (0.14)	9.6 (0.15)
Weeks 1-2[a] (n)	128	125	127	129	130
Mean (SE)	7.9 (0.19)	6.2 (0.22)	5.8 (0.23)	6.5 (0.23)	5.7 (0.24)
Change from Baseline					
Week 1					
Mean Change (SE)	-1.6 (0.19)	-3.1 (0.21)	-3.4 (0.25)	-2.7 (0.21)	-3.6 (0.22)
Week 2					
Mean Change (SE)	-1.7 (0.21)	-3.6 (0.25)	-3.9 (0.27)	-3.3 (0.25)	-4.1 (0.25)
Weeks 1-2[a]					
Mean Change (SE)	-1.7 (0.18)	-3.4 (0.22)	-3.6 (0.24)	-3.0 (0.22)	-3.9 (0.22)
LS mean Chg (SE)	-1.83 (0.21)	-3.50 (0.21)	-3.84 (0.21)	-3.19 (0.21)	-4.02 (0.21)
Δ LS mean Chg		-1.675[b]	-2.012[b]	-1.359[b]	-2.188[b]
95% CI	---	-2.25,-1.10	-2.58,-1.44	-1.93,-0.79	-2.75,-1.62

Source Data: Table 16.1, Table 16.2, Table 16.3
a = entire treatment period; b = p< 0.001 for all active treatment groups vs. placebo
SE = Standard error; Chg = change; LS = Least square; CI = Confidence Interval
Δ LS mean Chg = LS mean Chg in active – LS mean Chg in placebo

Baseline mean daily rTNSS values were very similar across all treatment groups ranging from 9.5-9.6 out of a possible 12. The least square (LS) mean changes for the five treatments over the entire treatment period were: placebo (-1.83); 50 mcg (-3.50); 100 mcg (-3.84); 200 mcg (-3.19); and 400 mcg (-4.02). Statistically significantly greater reductions ($p < 0.001$) occurred for all active treatment groups compared to placebo. The treatment effect, as measured by the LS mean difference between FF (GW685698X) and placebo in mean change from baseline in daily rTNSS, occurred in the order of: 200 mcg (-1.36) < 50 mcg (-1.68) < 100 mcg (-2.01) < 400 mcg (-2.18).

Change from baseline in daily rTNSS was assessed for subjects ≥ 65 years of age. The mean changes over the 2-week treatment period were: placebo (-1.4); 50 mcg (-5.0); 100 mcg (-2.3); 200 mcg (-1.0); and 400 mcg (-1.0).
***Reviewer's Comment: The sample size** for this age group was very small (3-6 subjects/treatment group) and precludes making any meaningful judgment regarding lack of efficacy in this population.*

Secondary Efficacy Outcomes

Pre-dose AM iTNSS was a key secondary endpoint that was used to assess the duration of action of the different FF doses. Mean AM, pre-dose, iTNSS were similar at baseline across all treatment groups and ranged from 9.1 to 9.3 out of a possible of 12. The LS mean changes in iTNSS over the 2-week period were: placebo (-1.15); 50 mcg (-2.74); 100 mcg (-3.03); 200 mcg (-2.57); and 400 mcg (-3.36) *[Table 13 FFR20001 Study Report, page 79]*. Differences between placebo and all treatment groups were statistically significant ($p < 0.001$). The treatment effect, as measured by the LS mean difference between active and placebo in mean change from baseline in AM, pre-dose, iTNSS, was the same as for the primary endpoint rTNSS (group order: 200 mcg < 50 mcg < 100 mcg

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. Using logistic regression analysis, the pairwise comparisons between all four doses of FF showed a significantly better response ($p < 0.0001$) to the active treatments. Significant improvement was reported in 16%, 28%, 23%, and 26%, of patients treated with FF 50, 100, 200, and 400 mcg respectively, compared to 8% of patients treated with placebo. ***Reviewer's Comment: It is interesting*** *to note that once again, the 200 mcg group performed less well than the 100 mcg group, albeit for this endpoint there is little separation between the 100, 200, and 400 mcg treatment groups.*

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
  - am rTNSS
  - pm rTNSS
- 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
- rating by the primary investigator

In all these endpoints save one, all treatment groups demonstrated statistically significant improvements compared to placebo [Section 7.3 FFR20001 Study Report, pages 82-100]. The lone endpoint that did not show a statistical difference from placebo was mean change from baseline in am iTOSS for the 50 mcg dosing group only [Section 7.3.5.2 FFR20001 Study Report, page 91].
Reviewer's Comment: Virtually all the secondary *endpoints were either a subset of the primary endpoint or would be expected to have outcomes similar to the primary endpoint. Interestingly, again, the 200 mcg dosing group performed worse than the 50, 100, and 400 mcg dosing groups for most of the endpoints. The lack of significance in the 50 mcg group in the am iTOSS endpoint supports selecting 100 mcg as an appropriate clinical dose.*

Onset of Action

The onset of effect by FF was evaluated by mean changes in AM, pre-dose iTNSS at 4 hours, 8 hours, and 12 hours post-first dose on Day 1, then daily in the AM, pre-dose thereafter. There were no significant differences between the active treatments and placebo on change from baseline in AM, pre-dose iTNSS at 4 hours post-dose on day 1, however, at 8 hours post-dose both the 100-mcg and 400-mcg doses achieved significantly greater reductions in iTNSS compared to placebo. The LS mean difference for these two treatment groups compared to **placebo was –0.710 (p =0.03) for the 100 mcg dose and –0.815 (p =0.013) for the 400 mcg dose. This significant treatment** difference between FF 100 mcg/400 mcg and placebo was maintained at 12 hours through Day 14. Both the 50-mcg dose and the 200-mcg dose achieved a significantly greater mean reduction than placebo in AM, pre-dose iTNSS at 24 hours post-dose *[Table 29 FFR20001 Study Report, page 97]*.

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 reduction in mean change from baseline occurred at Day 9 for all active groups. The maximal effect (LS mean difference on the primary efficacy measure) for the active treatment groups compared to placebo was: -2.146, **-2.462, -1.811, and –2.570 for FF 50mcg, 100mcg,** 200mcg, and 400mcg, respectively [Section 7.3.7 FFR20001 Study Report, page 98].

Health Related Outcomes

A summary of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores and analysis of mean change in these scores is provided in the following table.

APPEARS THIS WAY
ON ORIGINAL

Change from Baseline in RQLQ Scores over the Entire Treatment Period *[Table 48 FFR20001 Study Report, pages 127-128]*

	Placebo	GW685698X 50 mcg	GW685698X 100 mcg	GW685698X 200mcg	GW685698X 400 mcg
Overall					
Baseline (n)	127	124	127	129	130
Mean (SD)	3.9 (0.99)	4.0 (0.95)	3.9 (1.01)	4.1 (0.95)	3.9 (0.99)
Endpoint (n)	126	121	126	128	129
LS Mean Chg (SE)	-0.97 (0.12)	-1.79 (0.13)	-1.97 (0.13)	-1.83 (0.12)	-1.97 (0.12)
Δ LS mean Chg		-0.816	-1.000	-0.851	-0.996
Activities					
Baseline (n)	74	85	71	80	92
Mean (SD)	4.4 (1.34)	4.5 (1.20)	4.7 (1.26)	4.7 (1.05)	4.5 (1.18)
Endpoint (n)	74	85	71	80	92
LS Mean Chg (SE)	-1.18 (0.23)	-2.51 (0.20)	-2.24 (0.24)	-2.12 (0.20)	-2.40 (0.19)
Δ LS mean Chg		-1.323	-1.058[a]	-0.934[b]	-1.220
Sleep					
Baseline (n)	128	125	127	129	130
Mean (SD)	3.7 (1.22)	3.8 (1.37)	3.5 (1.34)	3.8(1.31)	3.8 (1.25)
Endpoint (n)	127	123	126	128	129
LS Mean Chg (SE)	-0.87 (0.14)	-1.57 (0.14)	-1.83 (0.14)	-1.71 (0.14)	-1.91 (0.14)
Δ LS mean Chg		-0.700	-0.953	-0.841	-1.042
Non-Hayfever Symptoms					
Baseline (n)	128	125	127	129	130
Mean (SD)	3.6 (1.10)	3.7 (1.17)	3.6 (1.15)	3.7 (1.18)	3.7 (1.13)
Endpoint (n)	127	123	126	128	128
LS Mean Chg (SE)	-0.96 (0.12)	-1.55 (0.13)	-1.84 (0.13)	-1.69 (0.12)	-1.79 (0.12)
Δ LS mean Chg		-0.593	-0.882	-0.726	-0.828
Practical Problems					
Baseline (n)	126	124	127	128	129
Mean (SD)	4.2 (1.21)	4.3 (1.10)	4.4 (1.25)	4.5 (1.13)	4.2 (1.12)
Endpoint (n)	125	121	125	127	128
LS Mean Chg (SE)	-0.97 (0.14)	-2.00 (0.14)	-2.16 (0.14)	-1.97 (0.14)	-2.18 (0.14)
Δ LS mean Chg		-1.032	-1.183	-0.999	-1.204
Nasal Symptoms					
Baseline (n)	127	124	127	129	130
Mean (SD)	4.4 (1.00)	4.4 (1.01)	4.5 (1.05)	4.5 (1.02)	4.3 (0.97)
Endpoint (n)	126	121	126	128	129
LS Mean Chg (SE)	-0.91 (0.13)	-2.03 (0.14)	-2.24 (0.13)	-2.02 (0.13)	-2.21 (0.13)
Δ LS mean Chg		-1.118	-1.325	-1.103	-1.298
Eye Symptoms					
Baseline (n)	127	124	127	129	130
Mean (SD)	3.8 (1.37)	4.0 (1.24)	4.0 (1.37)	4.1 (1.40)	3.9 (1.38)
Endpoint (n)	126	121	126	128	129
LS Mean Chg (SE)	-1.07 (0.14)	-1.64 (0.15)	-1.77 (0.14)	-1.62 (0.14)	-1.76 (0.14)
Δ LS mean Chg		-0.568[c]	-0.697	-0.551[c]	-0.689

	Placebo	GW585698 50QD	GW585698 100QD	GW585698 200QD	GW585698 400QD
Emotional Problems					
Baseline (n)	127	120	125	125	128
Mean (SD)	3.5 (1.27)	3.7 (1.25)	3.6 (1.32)	3.6 (1.29)	3.5 (1.27)
Endpoint (n)	126	118	125	124	127
LS Mean Chg (SE)	-0.99 (0.13)	-1.67 (0.14)	-1.91 (0.13)	-1.74 (0.13)	-1.93 (0.13)
Δ LS mean Chg		-0.676	-0.921	-0.749	-0.934

Source Data: Table 20.1, Table 20.2
P<0.001 for LS mean difference over placebo for all except where identified
a. P=0.002 for LS mean difference over placebo, b. P=0.003, c. P=0.006, Chg = Change

When LS mean change scores from baseline to endpoint are compared, all active treatments and placebo experienced statistically significant and clinically meaningful improvements (greater improvement of at least -0.5 from baseline) in overall RQLQ scores, and in each of the seven individual domains: activities, sleep, non-hay fever system, practical problems, nasal symptoms, eye symptoms, and emotional problems. In addition, when comparing LS mean change from placebo, all active treatments experienced statistically significant and clinically meaningful improvements (greater improvement of at least -0.5 over placebo) in overall RQLQ scores, and in each of the seven individual domains.
***Reviewer's Comment: There was a significant** placebo effect regarding the RQLQ. However, even when this is taken into account, the improvements in RQLQ were both statistically significant and probably clinically meaningful as the improvements occurred in each category and were greater than what is felt to be the minimally important difference (0.5 improvement).*

Safety

***Reviewer's Comment: The primary safety review** will be conducted in the body of the NDA review on the safety population as defined in the Integrated Summary of Safety (ISS). Since the 100 mcg dose was selected as the dose for additional Phase 3 studies, safety data from the 50, 200, and 400 mcg are not included in the ISS. This safety summary will, therefore, concentrate on eliciting any dose-related safety signals that may exist.*

Extent of Exposure

Per protocol, subjects were to be dosed for 15 days. The mean number of days of exposure for all subjects by group was 15 days (range, 14.8 to 15.1 days) *[Section 8.1 FFR20001 Study Report, page 103].*

Adverse Events

In total, 173 subjects (27%) experienced at least one adverse event (AE) during the treatment period: placebo (35 subjects, 27%), 50 mcg (35 subjects, 28%), 100 mcg (37 subjects 29%), 200 mcg (35 subjects, 27%), and 400 mcg (31 subjects, 24%). Most adverse events were reported by ≤2% of subjects, except for epistaxis and headache, the

most frequently reported events. Epistaxis had incidence rates of 4% (placebo), 3% (50 mcg), 8% (100 mcg), 9% (200 mcg), and 7% (400 mcg).
***Reviewer's Comment: There appears to be a** higher rate of epistaxis in the 100, 200, and 400 mcg groups than in the placebo and 50 mcg groups, however the rate remains constant in the higher dose groups. With the exception of epistaxis, there were no trends suggesting a dose-related increase in the incidence of any of these adverse events.*

All events of epistaxis observed during the treatment period were rated as mild in intensity. Headache had incidence rates of 5% (placebo), 6% (50 mcg), 6% (100 mcg), 2% (200 mcg), and 3% (400 mcg). Back pain, the only other event with a group incidence greater than 2%, had a 3% occurrence in the 100-mcg treatment group, 2% in the 400-mcg group and ≤1% in the other groups (including placebo). No notable AEs were seen when subgroup analyses were performed for age and gender *[Sections 8.2.2-8.2.4 FFR Study Report, pages 104-106]*.

Deaths, Serious Adverse Events, and Events Leading to Withdrawal
No deaths or serious adverse events (SAEs) were reported during the study.

A total of 9 subjects (1%) withdrew from the study because of an AE. The following events were cited as the reason for withdrawal: 1 event of tendon rupture in the placebo group, 1 event of pruritus and 1 event of sinusitis in the 50 mcg group, 1 event of bronchitis in the 100 mcg group, 1 event each of bronchitis, nasal candidiasis, sinusitis, and elevated urine cortisol in the 200 mcg group, and 1 event of asthma in the 400 mcg group.
***Reviewer's Comment: Despite the increase** number of events in the 200 mcg group, there does not appear to be a dose-related increase in AEs leading to withdrawal as the 400 mcg group had only one withdrawal.*

Pregnancy
There was one female in the 50 mcg dosing group that was found to be pregnant subsequent to starting treatment. She was exposed to the investigational product until two weeks gestation. The pregnancy resulted in a normal delivery.

Laboratory Results
The majority of subjects in each treatment group (>90%) 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, none were remarkable and no dose-related changes were noted for active treatment versus placebo. There were no changes in any laboratory value in the active treatment groups that were clinically significantly from baseline or from the placebo group for the ITT population. There was no notable difference in the percentage of subjects who shifted from normal at baseline to significantly abnormal after treatment for any parameter *[Section 8.7.2 FFR20001 Study Report, pages 110-112]*.

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 any active treatment group compared to placebo *[Section 8.8 FFR20001 Study Report, pages 117-122]*.

Urine Cortisol
Urine cortisol was examined using data collected at baseline (Visit 2) and Week 2 (Visit 4), and analyzed for the Urine Cortisol (UC) population (of primary interest) and the ITT population (supportive). The UC population was defined to exclude subjects from the ITT population whose urine samples were considered to have confounding factors that would have affected the interpretation of the results. The normal range for urine cortisol excretion, as determined by Quest Laboratories, **was 2.1 – 38 mcg/24hr for subjects 12 to 16 years of age and 2 – 42.4 mcg/24hr for subjects > 16 years of age.**

Mean 24-hour urinary cortisol excretion at baseline was similar across all treatment groups and ranged from 20.0 to 22.4 mcg/24 hr. After two weeks treatment, mean changes in 24-hour urinary cortisol excretion (mcg/24hr) were small for both the active and placebo groups: 0.9 (placebo), 2.0 (50 mcg), -0.5 (100 mcg), -1.2 (200 mcg), and 0.6 (400 mcg). Changes in mean cortisol levels were not dose-related.

Six subjects, two subjects (2%) in the 100-mcg group and 1 subject in each of the other groups (1%), had shifts in cortisol levels to below the normal range while 45 subjects had shifts above the upper limit of normal: 8% (placebo), 9% (50 mcg), 4% (100 mcg), 11% (200 mcg) and 6% (400 mcg). Again, no dose-related trend for an effect on urinary cortisol was evident *[Table 41 FFR20001 Study Report, page 113]*.
Reviewer's Comment: Twenty-four hour urine *cortisol levels were essentially unchanged from baseline in all active treatment groups, however, one must say that 24 hour urinary cortisol determination is a rather insensitive measurement of pituitary-adrenal axis suppression The above conclusions are unchanged when urine cortisol levels are evaluated for the ITT population.*

Summary and Discussion

All doses of FF (50, 100, 200, and 400 mcg) once daily demonstrated statistically significantly greater reductions ($p<0.001$) in SAR symptoms versus placebo for the primary endpoint of mean change from baseline over the entire treatment period in rTNSS and most secondary endpoints as well. All doses demonstrated efficacy at 24-hours post-dose, as assessed by AM, pre-dose iTNSS, thus supporting a once daily dosing regimen. The group order of the treatment effect seen for the primary endpoint (200 mcg < 50 mcg < 100 mcg < 400 mcg) was repeatedly found in the analysis of the secondary efficacy endpoints. This study also supported the efficacy of FF in reducing the ocular symptoms of allergic rhinitis (watering, redness, and itching).

A statistically significant onset of effect compared to vehicle placebo for FF was evident at 8 hours for both the 100-mcg and 400-mcg doses based on the mean change from

baseline in AM, pre-dose iTNSS. This effect on nasal symptoms was maintained throughout the remainder of the trial.

Regarding quality of life endpoints, all active treatments experienced statistically significant and clinically meaningful improvements over placebo in overall RQLQ scores, and in each of the seven individual domains: activities, sleep, non-hay fever symptoms, practical problems, nasal symptoms, eye symptoms, and emotional problems. No significant safety signals were detected at any dose level. Epistaxis was the most common AE with incidence rates slightly higher in the higher dose treatment groups, 4% (placebo), 3% (50 mcg), 8% (100 mcg), 9% (200 mcg), and 7% (400 mcg).

Considering that the safety profiles were similar across treatment groups, the differences in efficacy rested on the fact that the 50-mcg dose failed to reach significance on AM, predose iTOSS while all other doses demonstrated statistically significant efficacy compared with placebo for nearly all efficacy endpoints. While the 400 mcg dose provided the greater numerical improvement in symptom scores, the difference in efficacy between the 100 mcg and 400 mcg doses was small and the four-fold increase in dose was not felt to merit the minimal additional efficacy of the 400-mcg dose over the 100 mcg dose.
***Reviewer's Comment: Taking into account the** similar safety profiles among the four doses, the 100 mcg once daily was a reasonable clinical dose to take into Phase 3 studies.*

10.1.2 STUDY # FFR30003

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Study to Evaluate the Efficacy and Safety of Once Daily, Intranasal Administration of Fluticasone furoate (GW685698X) Aqueous Nasal Spray 100 mcg for 14 days in Adult and Adolescent Subjects with Seasonal Allergic Rhinitis

Protocol

Administrative
Study initiated: December 10, 2004
Study completed: January 19, 2005
Clinical Centers: 7 study sites in south central Texas during the 2004-2005 mountain cedar allergy season
Study report dated: November 2005
Study Sponsor: GlaxoSmithKline (GSK)
Medical Officer: Kathy Rickard, M.D., GSK

Objective/Rationale
The primary objective of this study was to compare the safety and efficacy of fluticasone furoate (FF), also referred to as GW685698X, aqueous nasal spray 100 mcg once daily

Study Design

This study is a randomized, double-blind, placebo-controlled, parallel group, multicenter study of the efficacy and safety of FF aqueous nasal spray 100 mcg once daily for 14 days in approximately 288 adult and adolescent (≥ 12 yrs.) patients with seasonal allergic rhinitis (SAR) due to mountain cedar pollen. This trial was conducted at 7 study sites in south central Texas during the 2004-2005 mountain cedar allergy season. Its design complied with that suggested in the Allergic Rhinitis: Clinical Development Programs for Drug Products Draft Guidance for Industry, April, 2000. The primary efficacy outcome was the reflective Total Nasal Symptom Score (r-TNSS) which was calculated from diary recordings of the 12-hour AM and 12-hour PM r-TNSS scores. Safety was assessed with adverse events, vital signs, and routine safety laboratory tests. Subject compliance was assessed by diary entries and by inspection of the medication bottles.

This study was performed under a protocol that was virtually identical to the protocol for Study FFR20001, the dose-ranging study, with the following minor exceptions:

- 24 hr urinary cortisol levels were not assessed in this study
- The secondary endpoint of mean change from baseline over the entire treatment period in daily reflective total ocular symptom scores (rTOSS) in Study FFR20001 was now listed as a key secondary endpoint.

The reader is referred to the description of the protocol FFR20001 discussed as Study #1 above for a detailed description of the protocol.

Results

Study Population

Disposition

A total of 575 subjects were screened for this study at the seven investigative sites. Three hundred three subjects were randomized into the study. One subject had scores that did not meet the randomization criteria and was inappropriately randomized. The error was discovered prior to the subject being dosed. Thus, 302 subjects (150 placebo and 152 FF100) received at least one dose of study medication and comprised the ITT population.

Enrollment ranged from 8 (3%) to 60 (20%) subjects at each of the 7 investigational sites. Ninety-four percent of subjects completed the study. Premature withdrawals occurred for 19 subjects (6%) with 12 (8%) withdrawing from the placebo group and 7 (5%) from the FF100 group. No subject in the FF100 group withdrew due to an adverse event (AE). Two subjects in the placebo group and 3 in the FF100 group withdrew due to lack of efficacy *[Table 4 FFR30003 Study Report, page 50].*
***Reviewer's Comment: Very few** subjects withdrew from the study and those that did were fairly equally distributed across all treatment groups.*

There were few protocol deviations with most due to use of a prohibited medication during the treatment period (5 subjects in the FF100 group and 8 in the placebo group). There was one incident of an inclusion/exclusion deviation when a subject with a history of ocular herpes (viewed as a significant concomitant medical condition, Exclusion Criterion 1) was randomized to the FF100 group *[Section 6.2 FFR30003 Study Report, page 50]*.

Demographics

Demographics were very similar across treatment groups. The mean age range was 37.0–38.1 years among treatment groups with a range of 12-75 years. Most subjects in each treatment group were in the 18-64 years of age subgroup (88%). The majority of the subjects were White (72-75%), 4% were listed **as Black, and 21-24% listed as "Other"** (primarily Hispanic). Females were more prevalent across all groups **(61–66%). Eighty-**four to 89% of subjects receiving treatment reported having SAR for ≥5 years. Fifty-five and 56% of subjects in the FF100 and placebo groups, respectively, also reported having perennial allergic rhinitis (PAR). Baseline demographics are listed in the following table.

Study FFR30003: Demographics and Baseline Characteristics *[Table 6 FFR30003 Study Report, page 52]*

APPEARS THIS WAY
ON ORIGINAL

	Placebo (N=150)	GW685698X 100mcg (N=152)	Total (N= 302)
Age (years)			
Mean, SD	38.1, 13.60	37.0, 13.9	37.6, 13.74
Min-Max	13 - 67	12 – 75	12 – 75
Age Groups, n(%)			
<18	11 (7)	16 (11)	27 (9)
≥18 – 64	132 (88)	133 (88)	265 (88)
≥65 – 74	7 (5)	2 (1)	9 (3)
≥75	0	1 (<1)	1 (<1)
Gender, n(%)			
Female	99 (66)	92 (61)	191 (63)
Male	51 (34)	60 (39)	111 (37)
Race, n(%)			
White[a]	113 (75)	110 (72)	223 (74)
Black[b]	6 (4)	6 (4)	12 (4)
Other[c]	31 (21)	36 (24)	67 (22)
Ethnicity, n(%)			
Hispanic/Latino	78 (52)	73 (48)	151 (50)
Not Hispanic/Latino	72 (48)	79 (52)	151 (50)
Height (cm)			
Mean, SD	165.7, 8.92	166.3, 10.13	166.0, 9.54
Min-Max	147-196	138-193	138-196
Weight (kg)			
Mean, SD	81.3, 21.52	80.5, 20.59	80.9, 21.02
Min-Max	45-190	42-136	42-190
Duration of SAR, n(%)			
≥2 to <5 years	16 (11)	24 (16)	40 (13%)
≥5 to <10 years	37 (25)	32 (21)	69 (23%)
≥10 years	97 (65)	96 (63)	193 (64%)

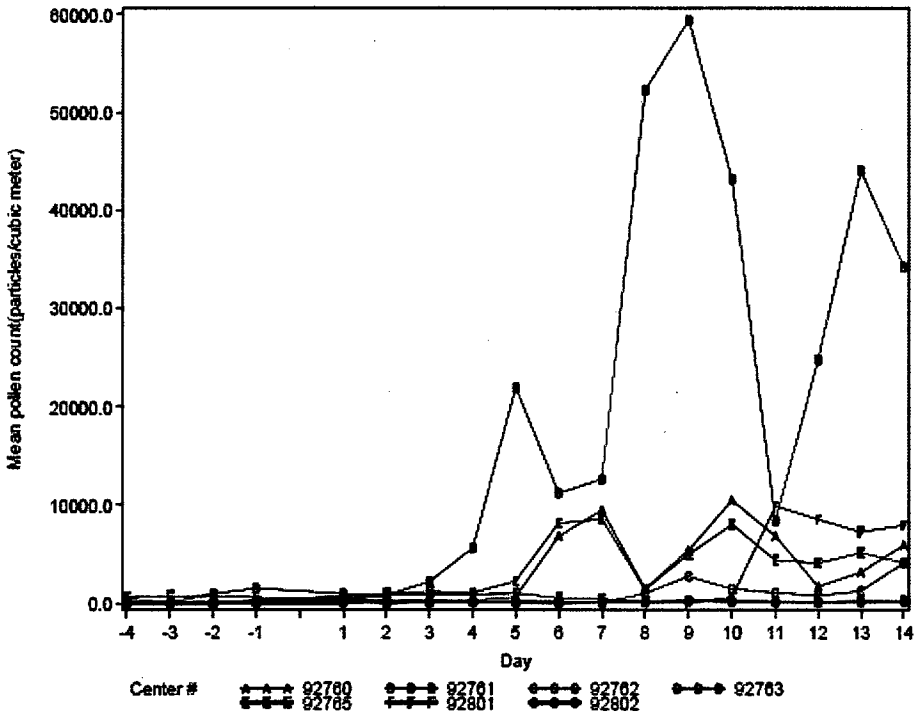
Source: Table 6.14, Table 6.19

a. White is defined as those subjects who chose only the White (Arabic/North African Heritage) and/or White (White/Caucasian/European Heritage) categories;
b. Black is defined as those subjects who chose only the African American/African Heritage category;
c. Other is defined as those subjects who chose all other races on the CRF

***Reviewer's Comment: All subjects were allergic to Mountain Cedar. Baseline wheals from allergy tests were very similar across the 2 treatment groups ranging from 7.1-7.3 mm. Wheals from diluent ranged from 0.1 mm** [Table 6.19 FFR30003 Study Report, page 211].*

Measurements of mountain cedar pollen were recorded at least 5 out of 7 days each week. Pollen counts varied widely from day to day and between the 2 Texas cities, San Antonio and Austin with higher counts typically reported in San Antonio. The following table shows mean exposure to Mountain Cedar pollen during the course of the study.

Mean Exposure to Mountain Cedar Allergen over the Baseline and Treatment Periods *[Figure 6.1 FFR30003 Study Report, page 108]*



***Reviewer's Comment: Pollen counts were much** higher at some sites than others with sites C and D having relatively low pollen counts (<1000 particles/cubic meter at all measurement points). However, stratification for site would tend to negate any differences in pollen counts at the different sites.*

During the treatment period of the study, all sites but one reported less than an inch of rainfall. One site in San Antonio reported 1.4 inches for the period *[Section 6.8.2 Study FFR30003 Study Report, page 57].*

Efficacy Results

Primary Efficacy Outcome

The primary efficacy endpoint was the mean change from baseline in the reflective TNSS over the entire treatment period. 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 2-week treatment period.

Daily rTNSS (ITT Population) *[Table 10 FFR30003 Study Report, page 59]*

	Placebo (N=150)	GW685698X 100mcg (N=152)
Baseline (n)	150	152
Mean (SE)	9.7 (0.11)	9.8 (0.11)
Weeks 1-2[a] (n)	150	152
Mean (SE)	7.4 (0.20)	6.7 (0.20)
Change from Baseline		
Week 1		
Mean Change (SE)	-2.3 (0.19)	-2.7 (0.20)
Week 2		
Mean Change (SE)	-2.4 (0.22)	-3.6 (0.22)
Weeks 1-2[a]		
Mean Change (SE)	-2.3 (0.19)	-3.1 (0.20)
LS Mean Change (SE)[b]	-2.25 (0.21)	-3.03 (0.21)
LS Mean Difference [b]		-0.777
p-value[b]		0.003
95% CI[b]	---	-1.28,-0.27

Source Data: Table 7.1, Table 7.2,
a = entire treatment period; b = based on ANCOVA adjusting for baseline daily rTNSS, investigative site, age, gender, and treatment
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 both groups ranging from 9.7-9.8 out of a possible 12. The least square (LS) mean changes for the two treatments over the entire treatment period were: placebo (-2.25) and FF100 mcg (-3.03). Compared to placebo, there was a statistically significant greater reduction in rTNSS in the FF100 group ($p = 0.003$).

Change from baseline in daily rTNSS was assessed for age subgroups 12-17 years, 18-64 years, and ≥ 65 years. Subjects 18-64 years of age comprised 92% of the ITT population. There was essentially no mean difference from placebo in daily rTNSS over the 2-week treatment period for the 12-17 and ≥ 65 year groups *[Table 28 FFR30003 Study Report, page 83].*

***Reviewer's Comment: The sample sizes for** the younger and older age groups was very small (3-16 subjects/treatment group) and precludes making any meaningful judgment regarding lack of efficacy in these populations.*

Secondary Efficacy Outcomes

Pre-dose AM iTNSS was a key secondary endpoint that was used to assess the duration of action of FF. Mean AM, pre-dose iTNSS were very similar at baseline (9.5 for placebo and 9.4 for FF100). The LS mean changes in iTNSS over the 2-week period were -1.47 for placebo and -2.38 for FF100 with the difference of -0.902 being statistically significant ($p < 0.001$) *[Table 11 FFR30003 Study Report, page 61].*

A key secondary efficacy endpoint identified by the Applicant that specifically assessed ocular symptoms was the mean change from baseline over the entire treatment period in daily rTOSS. The daily rTOSS was the average of the AM and PM rTOSS assessments. Each rTOSS assessment was comprised of the sum of the three eye symptom scores for itching/burning, tearing/ watering, and eye redness where each symptom was scored on a scale of 0 to 3 (maximum score 9). At baseline, the mean daily rTOSS were very similar for both treatment groups (6.5 for placebo and 6.6 for FF100). The LS mean change from baseline over the entire treatment period in daily rTOSS was greater for the FF100 group (-2.15) compared with placebo (-1.60) with the LS mean difference between the two treatments of -0.546 being significant (p =0.008) *[Table 12 FFR30003 Study Report, page 63].*

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. Using logistic regression analysis, the pairwise comparison between placebo and FF100 showed a significantly better response ($p < 0.001$) with the FF100 treatment. Twenty-one percent and 27% of subjects receiving FF100 reported significant and moderate improvement, respectively, in their overall evaluation of response to therapy compared with 11% and 20%, respectively, of those subjects receiving placebo *[Table 13 FFR30003 Study Report, page 65].*

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 and am iTNSS individual symptom scores of rhinorrhea, nasal congestion, nasal itching, and sneezing
- mean change from baseline in am iTOSS
- mean change from baseline in am rTOSS
- mean change from baseline in pm rTOSS
- mean % change from baseline in daily rTOSS
- mean % change from baseline in am pre-dose iTOSS
- mean change in daily reflective individual ocular scores

For all these endpoints save one, the individual daily reflective nasal symptom score of nasal itchiness (p=0.063), FF100 demonstrated statistically significant improvements compared to placebo *[Section 7.3 FFR30003 Study Report, pages 66-78].*

Throat/Palatal itching was an exploratory endpoint for which there was no significant difference between FF100 and placebo *[Section 7.3.5 FFR30003 Study Report, page 78].*

Onset of Action

The onset of effect by FF was evaluated by mean changes in AM, pre-dose iTNSS at 4, 6, 8, 10, and 12 hours post-first dose on Day 1, then daily thereafter. The LS mean difference between the two treatments was not significant until 24 hours after the first dose ($p \leq 0.045$). A significant treatment difference in favor of FF100 ($p \leq 0.045$) continued daily throughout the remaining 2-week treatment period except on Day 3 ($p = 0.162$) and Day 5 ($p = 0.061$) *[Table 26 FFR30003 Study Report, page 80].*

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 reduction in mean change from baseline occurred at Day 12 *[Section 7.3.7 FFR30003 Study Report, page 82].*

Health Related Outcomes

A summary of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores and analysis of mean change in these scores is provided in the following table.

Change from Baseline in RQLQ Scores over the Entire Treatment Period *[Table 37 HLQOL amended data report for Study FFR30003, pages 5-6]*

	Placebo	GW685698X 100mcg
Overall		
Baseline (n)	150	151
Mean (SE)	4.1 (0.9)	4.1 (0.9)
Endpoint (n)	149	150
Mean (SE)	3.1 (1.5)	2.4 (1.4)
LS Mean Chg (SE)	-0.98 (0.14)	-1.67 (0.14)
Δ LS mean		-0.688
Activities		
Baseline (n)	139	141
Mean (SE)	4.5 (1.1)	4.4 (1.0)
Endpoint (n)	102	101
Mean (SE)	3.4 (1.7)	2.7(1.6)
LS Mean Chg (SE)	-1.15 (0.20)	-1.79 (0.23)
Δ LS mean		-0.644[a]
Sleep		
Baseline (n)	149	152
Mean (SE)	4.0 (1.2)	3.8(1.3)
Endpoint (n)	149	151
Mean (SE)	2.9 (1.8)	2.3 (1.6)
LS Mean Chg (SE)	-1.00 (0.16)	-1.50 (0.16)
Δ LS mean		-0.508[b]

Non-Hay fever Symptoms		
Baseline (n)	150	152
Mean (SE)	3.8 (1.1)	3.7 (1.1)
Endpoint (n)	149	151
Mean (SE)	2.8 (1.6)	2.2 (1.5)
LS Mean Chg (SE)	-0.92 (0.15)	-1.49 (0.15)
Δ LS mean		-0.574[c]
Practical Problems		
Baseline (n)	150	151
Mean (SE)	4.4 (1.2)	4.5 (1.2)
Endpoint (n)	149	151
Mean (SE)	3.2 (1.6)	2.4 (1.6)
LS Mean Chg (SE)	-1.05 (0.16)	-1.97 (0.16)
Δ LS mean		-0.919
Nasal Symptoms		
Baseline (n)	150	151
Mean (SE)	4.6 (0.9)	4.7 (1.0)
Endpoint (n)	149	151
Mean (SE)	3.5 (1.7)	2.7 (1.6)
LS Mean Chg (SE)	-1.05 (0.16)	-1.99 (0.16)
Δ LS mean		-0.943
Eye Symptoms		
Baseline (n)	150	150
Mean (SE)	4.1 (1.2)	4.1 (1.1)
Endpoint (n)	149	150
Mean (SE)	3.2 (1.7)	2.5 (1.7)
LS Mean Chg (SE)	-0.88 (0.16)	-1.62 (0.16)
Δ LS mean		-0.743[d]
Emotional Problems		
Baseline (n)	150	151
Mean (SE)	3.7 (1.3)	3.6 (1.3)
Endpoint (n)	149	150
Mean (SE)	2.7 (1.7)	2.0 (1.5)
LS Mean Chg (SE)	-0.97 (0.15)	-1.51 (0.15)
Δ LS mean		-0.544[e]

Source Data: Table 10.1 and 10.2
p<0.001 for LS mean difference over placebo for all except where identified
a. p=0.034, b. p=0.023, c. p=0.006, d. p=0.001, e. p=0.013
Chg = Change

When LS mean change scores from baseline to endpoint were compared, the FF100 treatment group demonstrated a statistically significant and what has generally been agreed to as clinically meaningful improvement (greater improvement of at least -0.5 from baseline) in overall RQLQ scores, and in each of the seven individual domains: activities, sleep, non-hay fever system, practical problems, nasal symptoms, eye

symptoms, and emotional problems.
***Reviewer's Comment: There was a significant** placebo effect regarding the RQLQ. However, even when this is taken into account, the improvements in RQLQ were both statistically significant and probably clinically meaningful as the improvements occurred in each category and were greater than what is felt to be the minimally important difference (0.5 improvement).*

Safety

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 the FF100 and placebo subject groups was 14.9 and 14.8 days, respectively. *[Section 8.1 FFR30003 Study Report, page 87].*

Adverse Events

In all, 34 subjects (22%) in the FF100 group and 43 subjects in the placebo group (29%) experienced at least one AE during the treatment period. The most common AE was headache occurring in 4% of placebo subjects and 5% of those who received FF100. Epistaxis occurred in 3% (5 subjects) in both the placebo and FF100 groups. *[Tables 31 and 32 FFR 30003 Study Report, pages 88-89]*

Deaths, Serious Adverse Events, and Events Leading to Withdrawal

No deaths or serious adverse events (SAEs) were reported during the study.

A total of 2 subjects, both from the placebo group withdrew from the study due to an AE, one for sinusitis and another for pharyngitis.

Pregnancy

There was one female in the placebo group that became pregnant during the course despite the use of oral contraceptives. She received study drug from 12/21/2004 until 01/5/2005. The pregnancy resulted in the birth of a normal infant.

Laboratory Results

The majority of subjects in each treatment group (92%) 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, none were remarkable and no meaningful differences were seen between the FF100 group and placebo. *[Section 8.7.2 FFR30003 Study Report, pages 91-93].*

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 any active treatment group compared to placebo. Changes in vital signs and ECGs from baseline were rare, not related to treatment group and, clinically not significant. *[Section 8.8.1-8.8.3 FFR 30003 Study Report, pages 94-96].*

Summary and Discussion

Fluticasone furoate at a dose of 100 mcg once daily demonstrated statistically significantly greater reductions (p = 0.003) in SAR symptoms versus placebo for the primary endpoint of mean change from baseline over the entire treatment period in rTNSS and most secondary endpoints as well. It demonstrated efficacy at 24-hours post-dose, as assessed by AM, pre-dose iTNSS, thus supporting a once daily dosing regimen as well as the efficacy of FF100 in reducing the ocular symptoms of allergic rhinitis (watering, redness, and itching) as measured by rTOSS (p = 0.008).

A statistically significant onset of effect compared to vehicle placebo for FF100 was evident at 24 hours based on the mean change from baseline in AM, pre-dose iTNSS.

Regarding quality of life endpoints, subjects treated with FF100 experienced statistically significant and clinically meaningful improvements over placebo in overall RQLQ scores, and in each of the seven individual domains: activities, sleep, non-hay fever symptoms, practical problems, nasal symptoms, eye symptoms, and emotional problems. No significant safety signals were detected. Headache was the most common AE with incidence rates of 4 and 5% in the placebo and FF100 groups, respectively. Epistaxis occurred with the same frequency (3%) in both groups.

10.1.3 STUDY # FFR104861

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Study to Evaluate the Efficacy and Safety of Once Daily, Intranasal Administration of Fluticasone furoate (GW685698X) Aqueous Nasal Spray 100 mcg for 2 Weeks in Adult and Adolescent Subjects ≥ 12 Years of Age with Seasonal Allergic Rhinitis

Protocol

Administrative

Study initiated: August 14, 2005
Study completed: October 27, 2005
Clinical Centers: 17 study sites in the United States during the 2005 Fall Ragweed season
Study report dated: March 2006
Study Sponsor: GlaxoSmithKline (GSK)
Medical Officer: Kathy Rickard, M.D., GSK

Objective/Rationale

The primary objective of this study was to compare the safety and efficacy of fluticasone furoate (FF), also referred to as GW685698X, aqueous nasal spray 100 mcg once daily (QD) with vehicle placebo nasal spray in adult and adolescent subjects ≥12 years of age with seasonal allergic rhinitis (SAR).

Study Design

This study is a randomized, double-blind, placebo-controlled, parallel group, multicenter study of the efficacy and safety of FF aqueous nasal spray 100 mcg once daily for 2 weeks in approximately 288 adult and adolescent (≥ 12 yrs.) subjects with SAR due to mountain cedar pollen. This trial was conducted at 17 study sites in the United States during the 2005 Fall Ragweed season. Its design complied with that suggested in the Allergic Rhinitis: Clinical Development Programs for Drug Products Draft Guidance for Industry, April, 2000. The primary efficacy outcome was the reflective Total Nasal Symptom Score (r-TNSS) which was calculated from diary recordings of the 12-hour AM and 12-hour PM r-TNSS scores. Safety was assessed with adverse events, vital signs, and routine safety laboratory tests. Subject compliance was assessed by diary entries and by inspection of the medication bottles.

This study was performed under a protocol that was virtually identical to the protocol for Study FFR20001, the dose-ranging study, with the following minor exceptions:

- The study was conducted in subjects with SAR due to Ragweed rather than Mountain Cedar
- 24 hr urinary cortisol levels were not assessed in this study
- The secondary endpoint of mean change from baseline over the entire treatment period in daily reflective total ocular symptom scores (rTOSS) in Study FFR20001 was now listed as a key secondary endpoint.

The reader is referred to the description of the protocol FFR20001 discussed as Study #1 above for a detailed description of the protocol.

Results

Study Population

Disposition

A total of 428 subjects were screened for this study. Two hundred ninety-nine subjects were randomized into the study and comprised the ITT population.

Enrollment ranged from 3 (1%) to 33 (11%) subjects at each of the 17 investigational sites. Ninety-six percent of subjects completed the study. Premature withdrawals occurred for 13 subjects (4%) with 6 (4%) withdrawing from the placebo group and 7 (5%) from the FF100 group. No subject in the FF100 group withdrew due to an adverse event (AE). Two subjects in the placebo group withdrew due to lack of efficacy and 2 due to AEs *[Table 4 FFR104861 Study Report, page 51].*

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

There were few protocol deviations with most due to use of a prohibited medication during the treatment period (2 subjects in the FF100 group and 6 in the placebo group). One subject randomized to the FF100 group received an incorrect nasal spray container, however, after study unblinding, the nasal spray was confirmed to be fluticasone furoate 100mcg. *[Section 6.2 FFR104861 Study Report, page 51-52].*

Demographics

Demographics were very similar across treatment groups. The mean age range was 34.5–35.4 years among treatment groups with a range of 12-74 years. Most subjects in each treatment group were in the 18-64 years of age subgroup (83%). The majority of the subjects were White (90%), 9% were listed as **Black, and 2% listed as "Other". Females** were more prevalent across all groups **(57–64%). Sixty-eight to 74% of subjects** receiving reported having SAR for ≥5 years. Sixty and 57% of subjects in the FF100 and placebo groups, respectively, also reported having perennial allergic rhinitis (PAR).
***Reviewer's Comment: Baseline wheals from** allergy tests were very similar across the 2 treatment groups, 10.4 and 10.8 mm for the FF100 and placebo groups, respectively. Wheals from diluent were 0.5 mm for both groups. [Table 6.19 FFR104861 Study Report, page 195].*

Collection of Ragweed pollen was performed at all sites between July 8, 2005 and October 28, 2005. During the treatment period, maximum exposure to pollen occurred at baseline or during Week 1 at the majority of study sites, with lower counts occurring during Week 2. The following table summarizes Ragweed pollen counts at the various study sites.

Summary of Ragweed Pollen Counts *[Table 9 FFR104861 Study Report, page 59]*

APPEARS THIS WAY
ON ORIGINAL

Center	Baseline Pollen Count Mean (SD)	Week 1 Pollen Count Mean (SD)	Week 2 Pollen Count Mean (SD)	Weeks 1- 2 Pollen Count Mean (SD)
017471 (Spartanburg, SC)	86.3 (112.19)	3.3 (1.93)	4.8 (1.58)	4.0 (0.71)
017472 (Papillion, NE)	21.8 (9.82)	24.1 (8.64)	23.4 (14.73)	23.7 (9.19)
017479 (Canton, OH)	7.3 (2.34)	5.8 (3.00)	3.4 (1.47)	4.6 (2.15)
017480 (Louisville, KY)	13.8 (4.10)	11.1 (4.85)	5.6 (3.46)	8.5 (4.25)
017482 (Indianapolis, IN)	13.8 (6.45)	14.1 (9.69)	6.9 (5.25)	10.3 (6.95)
017484 (Sylvania, OH)	8.5 (4.57)	5.8 (2.82)	3.9 (1.46)	4.9 (2.03)
017485 (Minneapolis, MN)	68.0 (19.50)	105.7 (7.17)	76.3 (17.25)	93.3 (9.94)
017486 (West Allis, WI)	29.5 (10.88)	26.7 (5.92)	17.1 (5.22)	22.4 (6.90)
017487 (Novi, MI)	64.9 (21.93)	59.7 (10.98)	34.3 (9.19)	47.3 (9.57)
017488 (Chicago, IL)	25.7 (8.95)	19.6 (10.69)	15.5 (13.35)	17.5 (11.01)
017489 (Lincoln, NE)	45.9 (10.30)	32.5 (9.99)	12.4 (5.39)	23.4 (7.92)
017490 (Dallas, TX)	11.7 (2.21)	17.5 (1.10)	30.6 (2.20)	24.1 (1.65)
017793 (Dallas, TX)	22.6 (13.96)	37.4 (13.26)	42.8 (10.27)	40.1 (8.49)
017796 (Greenfield, WI)	69.7 (34.62)	41.1 (17.52)	23.1 (10.37)	33.5 (14.88)
017797 (Rolla, MO)	29.0 (7.26)	24.4 (3.68)	12.9 (6.05)	18.6 (4.05)
017798 (Columbia, MO)	16.9 (7.56)	21.1 (4.49)	9.5 (4.35)	16.1 (3.21)
017799 (St. Louis, MO)	14.9 (9.80)	6.4 (2.28)	5.7 (2.45)	6.0 (1.60)

In general, mean pollen counts were consistently above 20 grains/m3 (range 21.5 to 64.7), with the exception of Days 7, 12, 13, and 14 where counts ranged between 10.6 and 18.5 grains/m3. *[Section 6.81 Study FFR104861 Study Report, page 60].*

During the period of August 15, 2005 to October 28, 2005, the total amount of rainfall ranged from 6.8 cm (Novi, MI) to 37.6 cm (Rolla, MO). *[Section 6.8.2 Study FFR104861 Study Report, page 60].*

Efficacy Results

Primary Efficacy Outcome

The primary efficacy endpoint was the mean change from baseline in the reflective TNSS over the entire treatment period. 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 2-week treatment period.

Daily rTNSS (ITT Population) *[Table 10 FFR104861 Study Report, page 62]*

	Placebo (N=148)	Fluticasone furoate 100mcg (N=151)
Baseline (n)	148	151
Mean (SE)	9.9 (0.11)	9.6 (0.13)
Weeks 1-2[a] (n)	147	151
Mean (SE)	7.8 (0.22)	6.1 (0.22)
Change from Baseline		
Week 1		
Mean Change (SE)	-1.9 (0.18)	-3.1 (0.22)
Week 2 (n)	142	149
Mean Change (SE)	-2.3 (0.20)	-3.9 (0.24)
Weeks 1-2[a]		
Mean Change (SE)	-2.1 (0.18)	-3.5 (0.22)
LS Mean Change (SE)[b]	-2.07 (0.22)	-3.55 (0.21)
LS Mean Difference[b]		-1.473
p-value[b]		<0.001
95% CI[b]	---	-2.01, -0.94

Source Data: Table 7.1, Table 7.2
a. Entire treatment period;
b. Based on ANCOVA adjusting for baseline daily rTNSS, investigative site, age, gender, and treatment;
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 both groups ranging from 9.6-9.9 out of a possible 12. The least square (LS) mean changes for the two treatments over the entire treatment period were: placebo (-2.07) and FF100 mcg (-3.55). Compared to placebo, there was a statistically significant greater reduction in rTNSS in the FF100 group ($p < 0.001$).

Change from baseline in daily rTNSS was assessed for age subgroups 12-17 years, 18-64 years, and ≥ 65 years. There was essentially no mean difference from placebo in daily rTNSS over the 2-week treatment period for the ≥ 65 year groups *[Table 27 FFR104861 Study Report, page 85].*
***Reviewer's Comment: The sample sizes for** the older age groups was very small (1-2 subjects/treatment group) and precludes making any meaningful judgment regarding lack of efficacy in this population.*

Secondary Efficacy Outcomes

Pre-dose AM iTNSS was a key secondary endpoint that was used to assess the duration of action of FF. Mean am pre-dose iTNSS were very similar at baseline (9.3 for placebo and 9.4 for FF100). The LS mean changes in iTNSS over the 2-week period were -1.53 for placebo and -2.90 for FF100 with the difference of -1.375 being statistically significant ($p < 0.001$) *[Table 11 FFR104861 Study Report, page 64].*

A key secondary efficacy endpoint identified by the Applicant that specifically assessed ocular symptoms was the mean change from baseline over the entire treatment period in daily rTOSS. The daily rTOSS was the average of the AM and PM rTOSS assessments. Each rTOSS assessment was comprised of the sum of the three eye symptom scores for itching/burning, tearing/ watering, and eye redness where each symptom was scored on a scale of 0 to 3 (maximum score 9). At baseline, the mean daily rTOSS were very similar for both treatment groups (6.5 for placebo and 6.6 for FF100). The LS mean change from baseline over the entire treatment period in daily rTOSS was greater for the FF100 group (-2.23) compared with placebo (-1.63) with the LS mean difference between the two treatments of -0.600 being significant (p =0.004) *[Table 12 FFR104861 Study Report, page 66].*

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. Using logistic regression analysis, the pairwise comparison between placebo and FF100 showed a significantly better response ($p < 0.001$) with the FF100 treatment. Twenty and 27% of subjects receiving FF100 reported significant and moderate improvement, respectively, in their overall evaluation of response to therapy compared with 7 and 14%, respectively, of those subjects receiving placebo *[Table 13 FFR104861 Study Report, page 68].*

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 and am iTNSS individual symptom scores of rhinorrhea, nasal congestion, nasal itching, and sneezing
- mean change from baseline in am iTOSS
- mean change from baseline in am rTOSS
- mean change from baseline in pm rTOSS
- mean % change from baseline in daily rTOSS
- mean % change from baseline in am pre-dose iTOSS
- mean change in daily reflective individual ocular scores

For all these endpoints FF100 demonstrated statistically significant improvements compared to placebo *[Section 7.3 FFR104861 Study Report, pages 69-81].*

Throat/Palatal itching was an exploratory endpoint for which there was a significant difference between FF100 and placebo (p=0.001) *[Section 7.3.5 FFR104861 Study Report, page 81].*

Onset of Action

The onset of effect by FF100 was evaluated by mean changes in AM, pre-dose iTNSS at 4, 6, 8, 10, and 12 hours post-first dose on Day 1, then daily thereafter. The LS mean difference between the two treatments was significant at 8, 10 and 24 hours post first dose and was then maintained throughout the study. The Day 1 12-hour LS mean change from baseline iTNSS was not significantly different from placebo *[Table 26 FFR104861 Study Report, page 83]*.

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 reduction in mean change from baseline occurred at Day 9 *[Section 7.3.7 FFR104861 Study Report, page 84]*.

Health Related Outcomes

A summary of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores and analysis of mean change in these scores is provided in the following table.

Change from Baseline in RQLQ Scores over the Entire Treatment Period *[Table 35 HLQOL amended data report for Study FFR104861, pages 6-7]*

APPEARS THIS WAY
ON ORIGINAL

	Placebo	Fluticasone furoate 100mcg
Overall		
Baseline Mean (SD)	3.9 (0.9) (n=147)	3.9 (0.9) (n=149)
Endpoint Mean (SD)	2.8 (1.4) (n=145)	2.2 (1.3) (n=146)
LS Mean (SE)	-1.18 (0.12) (n=144)	-1.78 (0.11) (n=144)
LS mean difference		-0.599
Activities		
Baseline Mean (SD)	4.6 (1.0) (n=135)	4.5 (1.1) (n=136)
Endpoint Mean (SD)	3.3 (1.6) (n=72)	2.6 (1.6) (n=71)
LS Mean (SE)	-1.35 (0.23) (n=67)	-1.93 (0.24) (n=64)
LS mean difference		-0.588 [a]
Sleep		
Baseline Mean (SD)	3.6 (1.2) (n=148)	3.7(1.2) (n=151)
Endpoint Mean (SD)	2.6 (1.6) (n=145)	2.0 (1.6) (n=147)
LS Mean (SE)	-1.08 (0.15) (n=145)	-1.81 (0.13) (n=147)
LS mean difference		-0.724
Non-Nose/Eye Symptoms		
Baseline Mean (SD)	3.5 (1.1) (n=147)	3.6 (1.2) (n=150)
Endpoint Mean (SD)	2.6 (1.4) (n=146)	2.1 (1.4) (n=147)
LS Mean (SE)	-1.10 (0.13) (n=145)	-1.63 (0.12) (n=146)
LS mean difference		-0.538 [b]
Practical Problems		
Baseline Mean (SD)	4.3 (1.2) (n=146)	4.2 (1.2) (n=150)
Endpoint Mean (SD)	3.0 (1.6) (n=146)	2.2 (1.4) (n=147)
LS Mean (SE)	-1.22 (0.15) (n=144)	-1.99 (0.13) (n=146)
LS mean difference		-0.773
Nasal Symptoms		
Baseline Mean (SD)	4.5 (1.1) (n=146)	4.4 (1.1) (n=150)
Endpoint Mean (SD)	3.3 (1.6) (n=146)	2.4 (1.4) (n=147)
LS Mean (SE)	-1.16 (0.14) (n=144)	-2.03 (0.13) (n=146)
LS mean difference		-0.873
Eye Symptoms		
Baseline Mean (SD)	3.9 (1.3) (n=147)	3.9 (1.3) (n=149)
Endpoint Mean (SD)	2.8 (1.7) (n=145)	2.5 (1.7) (n=146)
LS Mean (SE)	-1.22 (0.14) (n=144)	-1.47 (0.12) (n=144)
LS mean difference		-0.254 [c]

Emotional Problems		
Baseline Mean (SD)	3.5 (1.2) (n=146)	3.4 (1.2) (n=149)
Endpoint Mean (SD)	2.5 (1.6) (n=145)	1.8 (1.4) (n=146)
LS Mean (SE)	-1.11 (0.14) (n=143)	-1.70 (0.13) (n=144)
LS mean difference		-0.590 [d]

Source Data: Table 10.1 and 10.2
p<0.001 for LS mean difference over placebo for all except where identified
a. p=0.027 for LS mean difference over placebo
b. p=0.003 for LS mean difference over placebo
c. p=0.168 for LS mean difference over placebo
d. p=0.002 for LS mean difference over placebo

At the study endpoint, the LS mean difference of -0.599 (p<0.001) in overall RQLQ score between the FF100 treatment group and placebo was statistically significant. In addition, the improvements in overall RQLQ score and in 6 of the 7 individual domains: activities, sleep, non-hay fever system, practical problems, nasal symptoms, and emotional problems were what has generally been agreed to as clinically meaningful (greater improvement of at least -0.5 from baseline). The difference for Eye Symptoms of -0.254 was not statistically significant (p=0.168).
***Reviewer's Comment: There was a significant** placebo effect regarding the RQLQ. However, even when this is taken into account, the improvements in RQLQ were both statistically significant and probably clinically meaningful as the improvements occurred in 6 of the 7 categories and were greater than what is felt to be the minimally important difference (0.5 improvement). It is interesting to note, however, that improvement in the **individual symptom of "Eye Symptoms" was not** statistically significant in the RQLQ but the outcome for the secondary endpoint, rTOSS, demonstrated a significant difference in favor of the FF100 group.*

Safety

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 the FF100 and placebo subject groups was 15.0 and 14.8 days, respectively. *[Table 28 FFR104861 Study Report, page 87].*

Adverse Events

In all, 31 subjects (21%) in the FF100 group and 18 subjects in the placebo group (12%) experienced at least one AE during the treatment period. The most common AE was headache occurring in 3% of placebo subjects and 12% of those who received FF100. Epistaxis occurred in <1% (1 subject) in the placebo group and in 2% (3 subjects) in the FF100 group. *[Section 8.2.2 FFR104861 Study Report, pages 88-89]*

Deaths, Serious Adverse Events, and Events Leading to Withdrawal

No deaths or serious adverse events (SAEs) were reported during the treatment period.

Two subjects (31 and 16 year-old females) from the placebo group withdrew from the study due to AEs, nasopharyngitis and asthma exacerbation, respectively.

Pregnancy

No subjects became pregnant during the study.

Laboratory Results

The majority of subjects in each treatment group (88-92%) 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, none were remarkable and no meaningful differences were seen between the FF100 group and placebo. *[Section 8.7.2 FFR104861 Study Report, pages 91-94].*

Nasal Exams, Vital Signs, and Electrocardiograms

Over the treatment period, the incidence of nasal bleeding increased from 3% (4 subjects) at randomization to 5% (seven subjects) at Week 2 for FF100 subjects and declined from 3% (five subjects) to <1% (1 subject) for Placebo subjects. No subject developed ulcers of the nasal septa or turbinates during the study. No subjects had evidence of nasal candidiasis. There were no clinically meaningful adverse changes from baseline in vital signs. One subject in the Placebo group who had an abnormal/not clinically significant ECG at baseline had an ECG at Visit 4 that showed ventricular extrasystoles of mild intensity which was reported as an abnormal, clinically significant ECG event. *[Sections 8.8.1-8.8.3 FFR104861 Study Report, pages 95-97].*

Summary and Discussion

Fluticasone furoate at a dose of 100 mcg once daily demonstrated statistically significantly greater reductions ($p < 0.001$) in SAR symptoms versus placebo for the primary endpoint of mean change from baseline over the entire treatment period in rTNSS and most secondary endpoints as well. It demonstrated efficacy at 24-hours post-dose, as assessed by AM, pre-dose iTNSS, thus supporting a once daily dosing regimen as well as the efficacy of FF100 in reducing the ocular symptoms of allergic rhinitis (watering, redness, and itching) as measured by rTOSS ($p = 0.004$).

A statistically significant onset of effect compared to vehicle placebo for FF100 was evident at 8 hours based on the mean change from baseline in AM, pre-dose iTNSS.

Regarding quality of life endpoints, subjects treated with FF100 experienced statistically significant and clinically meaningful improvements over placebo in overall RQLQ scores, and in six of seven individual domains: activities, sleep, non-hay fever symptoms,

practical problems, nasal symptoms, and emotional problems. Improvement in Eye Symptoms did not reach statistical significance (p = 0.168).

No unforeseen safety signals were detected. Headache was the most common AE with incidence rates of 3 and 12% in the placebo and FF100 groups, respectively.
Reviewer's Comment: The large difference (8%) *in incidence of headache was not seen in the other adult SAR studies.*

Epistaxis occurred in <1% and 2% in the Placebo and FF100 groups, respectively.

10.1.4 STUDY # FFR103184

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Two Week Study to Evaluate the Efficacy and Safety of Once-Daily, Intranasal Administration of GW685698X (fluticasone furoate) Aqueous Nasal Spray 100mcg in Adult and Adolescent Subjects with Seasonal Allergic Rhinitis in Europe

Protocol

Administrative
Study initiated: May 14, 2005
Study completed: August 22, 2005
Clinical Centers: 17 study sites in the United States during the 2005 Fall Ragweed season
Study report dated: January 2006
Study Sponsor: GlaxoSmithKline (GSK)
Medical Officer: Katharine Knobil, M.D., GSK

Objective/Rationale
The primary objective of this study was to compare the safety and efficacy of fluticasone furoate (FF), also referred to as GW685698X, aqueous nasal spray 100 mcg once daily (QD) with vehicle placebo nasal spray in adult and adolescent subjects ≥12 years of age with seasonal allergic rhinitis (SAR).

Study Design
This study is a randomized, double-blind, placebo-controlled, parallel group, multicenter study of the efficacy and safety of FF aqueous nasal spray 100 mcg once daily for 2 weeks in approximately 285 adult and adolescent (≥ 12 yrs.) subjects with SAR due to an allergy to spring grasses. This trial was conducted at 23 study sites in 6 European countries (Estonia, Latvia, Lithuania, Netherlands, Russia, and Sweden) during the 2005 spring grass allergy season. Its design complied with that suggested in the Allergic Rhinitis: Clinical Development Programs for Drug Products Draft Guidance for Industry, April, 2000. The primary efficacy outcome was the reflective Total Nasal Symptom

Score (r-TNSS) which was calculated from diary recordings of the 12-hour AM and 12-hour PM r-TNSS scores. Safety was assessed with adverse events, vital signs, and routine safety laboratory tests. Subject compliance was assessed by diary entries and by inspection of the medication bottles.

This study was performed under a protocol that was virtually identical to the protocol for Study FFR20001, the dose-ranging study, with the following minor exceptions:

- The study was conducted in subjects with SAR due to an allergy to spring grasses
- RAST testing was accepted in lieu of skin-testing as proof of allergy to spring grasses
- 24 hr urinary cortisol levels were not assessed in this study
- The secondary endpoint of mean change from baseline over the entire treatment period in daily reflective total ocular symptom scores (rTOSS) in Study FFR20001 was now listed as a key secondary endpoint.

The reader is referred to the description of the protocol FFR20001 discussed as Study #1 above for a detailed description of the protocol.

Results

Study Population

Disposition

A total of 425 subjects were screened for this study. Two hundred eighty-five subjects were randomized into the study (141 to the FF100 group and 144 to Placebo) and comprised the ITT population.

Enrollment ranged from 3 (1%) to 33 (12%) subjects at each of the 23 investigational sites. The number of subjects enrolled in each country ranged from 19 in Sweden to 70 in Russia. Ninety-six percent of subjects completed the study. Premature withdrawals occurred for 19 subjects (7%) with 16 (11%) withdrawing from the placebo group and 3 (2%) from the FF100 group. No subject in the FF100 group and 2 subjects in the placebo group withdrew due to adverse AEs *[Section 6.1 and Table 4 FFR103184 Study Report, pages 56-57].*

There were few protocol deviations with most due to use of a prohibited medication during the treatment period (1subject in the FF100 group and 6 in the placebo group) *[Section 6.2 FFR103184 Study Report, page 57-58].*

Demographics

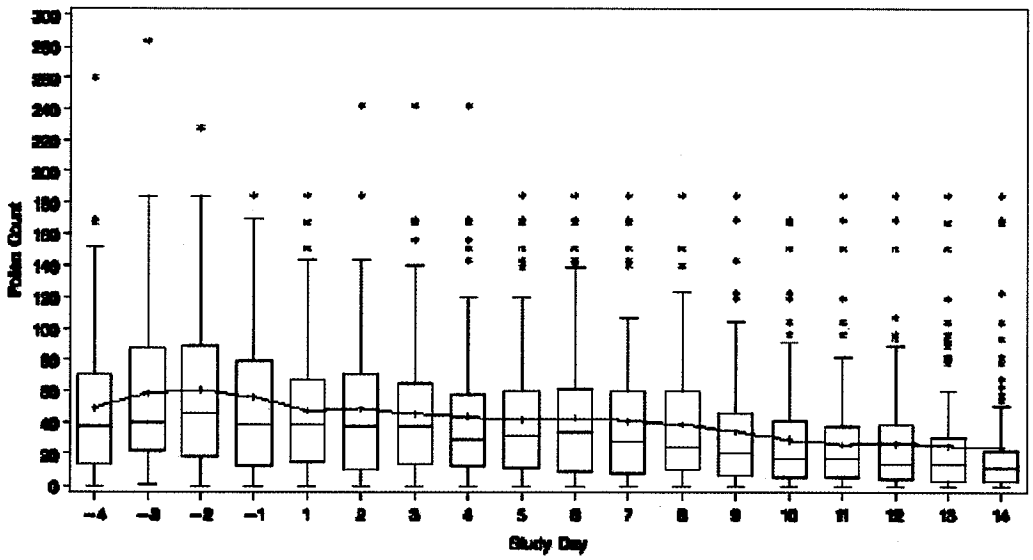
Demographics were very similar across treatment groups. The mean age range was 29.4 years fro the placebo group and 30.7 for the FF100 group with a range of 12-65 years. Most subjects in each treatment group were in the 18-64 years of age subgroup (91%). The majority of the subjects were White (95%), 4% were listed as Black, and 1% listed as **"Other". Females were more prevalent in** the study (53%). Seventy-eight and 75% of

subjects in the placebo and FF100 groups, respectively, reported having SAR for ≥5 years. Thirty-five and 46% of subjects in the FF100 and placebo groups, respectively, also reported having perennial allergic rhinitis (PAR).
Reviewer's Comment: Baseline wheals from allergy tests were very similar across the 2 treatment groups, 7.2 and 7.5 mm for the FF100 and placebo groups, respectively. Wheals from diluent were 0.1 mm for both groups *[Table 6.19 FFR103184 Study Report, page 217].*

Pollen counts were classified as (pollen grains/m3 of air): low (<30), moderate (30 to 49), high (50 to 149) and very high (≥150). The figure of 30 grains of grass pollen/m^3 was set as the threshold of the start of the peak of the grass pollen allergy season; at this time randomization for the study was begun.

In Estonia, sites 12705 and 12706 received pollen counts from the same pollen counter, as did sites 12691, 12693 and 12694 in Latvia, sites 12711, 12713 and 12714 in Lithuania, all six sites in the Netherlands, and all three sites in Sweden. The following figure summarizes exposure to grass pollen over the course of the study.

Mean Exposure to Grass Pollen Allergen over the Study Period *[Figure 1 FFR103184 Study Report, page 65]*



Source Data: Figure 6.1
Description of box plot: the bottom and top edges of the box represent the sample 25th and 75th percentiles. The horizontal line represents the sample median and the "plus" sign (+) represents the sample mean. The central vertical lines or "whiskers", extend from the box as far as the data extend, to a distance of at most 1.5 inter-quartile ranges (an inter-quartile range being the distance between the 25th and the 75th sample percentiles). Any value more extreme than this was marked with a zero if it was within three inter-quartile ranges of the box, or with an asterisk (*) for more extreme values.

Subjects were exposed to a mean range of 47 to 63 pollen grains/m^3 during screening, 39 to 53 pollen grains/m^3 during Week 1 and 24 to 39 pollen grains/m^3 during Week 2 of the

study *[Section 6.81 Study FFR103184 Study Report, pages 63-65].*

During the spring/summer season (April 4, 2005, to August 31, 2005), most sites reported long spells with little rainfall interrupted by short periods of heavy rainfall, reaching maximums of (mm/day): 24 in Estonia, 49 in Latvia, 85 in Lithuania, 57 in the Netherlands, 39 in Russia and 16 in Sweden *[Section 6.8.2 Study FFR103184 Study Report, page 65].*

Efficacy Results

Primary Efficacy Outcome

The primary efficacy endpoint was the mean change from baseline in the reflective TNSS over the entire treatment period. 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 2-week treatment period.

Daily rTNSS (ITT Population) *[Table 10 FFR103184 Study Report, page 67]*

	Placebo (N= 144)	GW685698X 100mcg (N= 141)
Baseline (n)	143	140
Mean (SE)	8.4 (0.11)	8.3 (0.12)
Weeks 1-2[a] (n)	143	140
Mean (SE)	5.3 (0.21)	3.5 (0.18)
Change from Baseline		
Week 1		
Mean Change (SE)	-2.7 (0.20)	-4.3 (0.20)
Week 2		
Mean Change (SE)	-3.7 (0.24)	-5.4 (0.21)
Weeks 1-2[a]		
Mean Change (SE)	-3.1 (0.21)	-4.8 (0.20)
LS Mean Change (SE)[b]	-3.18 (0.20)	-4.94 (0.20)
LS Mean Difference [b]	-	-1.757
p-value[b]	-	<0.001
95% CI[b]	-	-2.28, -1.23

Source Data: Table 7.1, Table 7.2,
a = entire treatment period; b = 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 GW685698X – LS mean Change in Placebo

Baseline mean daily rTNSS values were very similar across both groups ranging from 8.3-8.4 out of a possible 12. The least square (LS) mean changes for the two treatments over the entire treatment period were: placebo (-3.18) and FF100 (-4.94). Compared to

placebo, there was a statistically significant greater reduction in rTNSS in the FF100 group ($p < 0.001$).

The Primary Endpoint was also summarized by country. At baseline, the mean daily rTNSS range was 7.9 to 8.8 for the FF100 groups and 7.8 to 8.9 for the Placebo groups across all six countries. The mean change in daily rTNSS in the FF100 group was numerically greater than Placebo in all countries. The mean change varied among countries and ranged between -3.9 to -6.4 for FF100 and -2.6 to -3.8 for the Placebo group *[Table 28 FFR103184 Study Report, page 91]*.
Reviewer's Comment: Review of the results from individual countries showed that results were consistent and in favor of FF100 in all countries. No single country stood out due to having results grossly different than others.

Change from baseline in daily rTNSS was assessed for age subgroups 12-17 years, 18-64 years, and ≥ 65 years. The mean change from baseline in daily rTNSS over the 2-week treatment period was greater for the FF100 group than vehicle Placebo for all three age groups *[Table 27 FFR103184 Study Report, page 90]*.
Reviewer's Comment: The sample sizes for the younger and older age groups was very small (1-14 subjects/treatment group) and precludes making any meaningful judgment regarding efficacy in this population.

Secondary Efficacy Outcomes

Pre-dose AM iTNSS was a key secondary endpoint that was used to assess the duration of action of FF. Mean AM, pre-dose iTNSS were very similar at baseline (8.3 for placebo and 8.1 for FF100). The LS mean changes in iTNSS over the 2-week period were -2.60 for placebo and -4.50 for FF100 with the difference of -1.898 being statistically significant ($p < 0.001$) *[Table 11 FFR103184 Study Report, page 69]*.

A key secondary efficacy endpoint identified by the Applicant that specifically assessed ocular symptoms was the mean change from baseline over the entire treatment period in daily rTOSS. The daily rTOSS was the average of the AM and PM rTOSS assessments. Each rTOSS assessment was comprised of the sum of the three eye symptom scores for itching/burning, tearing/ watering, and eye redness where each symptom was scored on a scale of 0 to 3 (maximum score 9). At baseline, the mean daily rTOSS was very similar for both treatment groups (5.3 for placebo and 5.4 for FF100). The LS mean change from baseline over the entire treatment period in daily rTOSS was greater for the FF100 group (-3.00) compared with placebo (-2.26) with the LS mean difference between the two treatments of -0.741 being significant ($p < 0.001$) *[Table 12 FFR103184 Study Report, page 71]*.

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. Using logistic regression analysis, the pairwise comparison between placebo and FF100 showed a significantly better response ($p < 0.001$) with the FF100 treatment. Sixty-seven per cent

of subjects receiving FF100 reported significant and moderate improvement in their overall evaluation of response to therapy compared with 39% of subjects receiving placebo *[Table 13 FFR103184 Study Report, page 73].*

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 and am iTNSS individual symptom scores of rhinorrhea, nasal congestion, nasal itching, and sneezing
- mean change from baseline in am iTOSS
- mean change from baseline in am rTOSS
- mean change from baseline in pm rTOSS
- mean % change from baseline in daily rTOSS
- mean % change from baseline in am pre-dose iTOSS
- mean change in daily reflective individual ocular scores

For all these endpoints FF100 demonstrated statistically significant improvements compared to placebo *[Section 7.3 FFR103184 Study Report, pages 74-86].*

Throat/Palatal itching was an exploratory endpoint for which there was a significant difference between FF100 and placebo ($p < 0.001$) *[Table 25 FFR103184 Study Report, page 86].*

Onset of Action

The onset of effect by FF100 was evaluated by mean changes in AM, pre-dose iTNSS at 4, 6, 8, 10, and 12 hours post-first dose on Day 1, then daily thereafter. The LS mean difference between the two treatments was significant at 24 hours post first dose and was then maintained throughout the study. The Day 1 12-hour LS mean change from baseline iTNSS was not significantly different from placebo *[Table 26 FFR103184 Study Report, page 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 treatment as compared to placebo. The greatest reduction in mean change from baseline occurred at Day 4 *[Section 7.3.7.1 FFR103184 Study Report, page 89].*

Health Related Outcomes

A summary of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores and analysis of mean change in these scores is provided in the following table.

Change from Baseline in RQLQ Scores over the Entire Treatment Period *[Table 36 HLQOL amended data report for Study FFR103184, pages 5-6]*

	Placebo (N= 144)	GW685698X 100mcg (N= 141)
Overall		
Baseline (n)	144	141
Mean (SD)	3.5 (0.9)	3.5 (1.0)
Endpoint (n)	140	137
Mean (SD)	2.0 (1.2)	1.3 (1.1)
LS Mean Change (SE)	-1.53 (0.10)	-2.23 (0.11)
Δ LS mean		-0.700
Activities		
Baseline (n)	134	128
Mean (SD)	4.3 (1.0)	4.4 (1.1)
Endpoint (n)	95	97
Mean (SD)	2.6 (1.5)	1.7 (1.4)
LS Mean Change (SE)	-1.75 (0.16)	-2.65 (0.17)
Δ LS mean		-0.902
Sleep		
Baseline (n)	144	141
Mean (SD)	3.1 (1.5)	3.0 (1.6)
Endpoint (n)	139	138
Mean (SD)	1.7 (1.4)	1.0 (1.2)
LS Mean Change (SE)	-1.35 (0.11)	-2.06 (0.12)
Δ LS mean		-0.710

APPEARS THIS WAY
ON ORIGINAL

Change from Baseline in RQLQ Scores over the Entire Treatment Period Continued *[Table 36 HLQOL amended data report for Study FFR103184, pages 5-6]*

Non-Nose/Eye Symptoms[c]		
Baseline (n)	144	141
Mean (SD)	2.9 (1.2)	3.0 (1.3)
Endpoint (n)	140	138
Mean (SD)	1.6 (1.2)	1.2 (1.2)
LS Mean Change (SE)	-1.37 (0.10)	-1.79 (0.10)
Δ LS mean		-0.420[a]
Practical Problems		
Baseline (n)	144	141
Mean (SD)	4.2 (1.2)	4.2 (1.3)
Endpoint (n)	140	136
Mean (SD)	2.4 (1.6)	1.5 (1.4)
LS Mean Change (SE)	-1.84 (0.13)	-2.74 (0.13)
Δ LS mean		-0.903
Nasal Symptoms		
Baseline (n)	143	141
Mean (SE)	4.0 (1.1)	4.1 (1.1)
Endpoint (n)	139	138
Mean (SE)	2.4 (1.4)	1.5 (1.2)
LS Mean Change (SE)	-1.64 (0.12)	-2.65 (0.12)
Δ LS mean		-1.008
Eye Symptoms		
Baseline (n)	144	141
Mean (SD)	3.4 (1.2)	3.5 (1.4)
Endpoint (n)	140	137
Mean (SD)	1.9 (1.4)	1.5 (1.4)
LS Mean Change (SE)	-1.54 (0.12)	-2.06 (0.12)
Δ LS mean		-0.520[b]
Emotional Problems		
Baseline (n)	144	141
Mean (SE)	3.1 (1.2)	3.1 (1.3)
Endpoint (n)	140	137
Mean (SE)	1.8 (1.4)	1.1 (1.2)
LS Mean Change (SE)	-1.40 (0.11)	-2.11 (0.12)
Δ LS mean		-0.710

Source Data: Table 10.1 and 10.2
p<0.001 for LS mean difference over Placebo for all except where identified
a. p=0.004 for LS mean difference over Placebo
b. p=0.003
c. Non-nose/eye Symptoms= Non-hay fever symptoms

At the study endpoint, the LS mean difference of -0.700 (p<0.001) in overall RQLQ score between the FF100 treatment group and placebo was statistically significant. In

addition, the improvements in overall RQLQ score and in 6 of the 7 individual domains: activities, sleep, non-hay fever system, practical problems, nasal symptoms, and emotional problems were what has generally been agreed to as clinically meaningful (greater improvement of at least -0.5 from baseline). The difference for Non-Nose/Eye Symptoms of -0.420, while statistically significant (p = 0.004) failed to meet the clinically meaningful level.
***Reviewer's Comment: There was a significant** placebo effect regarding the RQLQ. However, even when this is taken into account, the improvement in overall RQLQ was both statistically significant and probably clinically meaningful as the improvements occurred in all 7 categories and were greater than what is felt to be the minimally important difference (0.5 improvement) in 6 of 7 categories.*

Safety

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 the FF100 and placebo subject groups was 15.1 and 14.4 days, respectively. *[Table 29 FFR103184 Study Report, page 93].*

Adverse Events

In all, 24 subjects (17%) in the FF100 group and 23 subjects (16%) in the placebo group experienced at least one AE during the treatment period. The most common AE was headache occurring in 6% of placebo subjects and 9% of those who received FF100. Epistaxis occurred in 1% (2 subjects) in the placebo group and in 3% (4 subjects) in the FF100 group. *[Section 8.2.2 FFR103184 Study Report, page 94]*

Deaths, Serious Adverse Events, and Events Leading to Withdrawal

No deaths or serious adverse events (SAEs) were reported during the treatment period.

Two subjects from the placebo group and 1 subject from the FF100 group withdrew from the study due to AEs. Both subjects in the placebo group withdrew due to severe seasonal allergy symptoms while the subject from the FF100 group withdrew due to nasopharyngitis.

Pregnancy

No subjects became pregnant during the study.

Laboratory Results

The majority of subjects in each treatment group (88-90%) 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, none were remarkable and no meaningful differences were seen between the FF100 group and placebo *[Section 8.7.2 FFR103184 Study Report, pages 98-101]*.

Nasal Exams, Vital Signs, and Electrocardiograms

Over the treatment period, the incidence of nasal mucosal bleeding worsened in 1 (< 1 %) subject in the placebo group and in 2 subjects (1%) in the FF100 group.

Two subjects (1%) in the FF100 group and three subjects (2%) in the Placebo group had nasal ulcers at baseline. At Week 2, five subjects (4%) in the FF100 group and none in the Placebo group had nasal ulcers. No subjects had evidence of nasal candidiasis. There were no clinically meaningful adverse changes from baseline in vital signs or ECGs in the study *[Sections 8.8.1-8.8.3 FFR103184 Study Report, page3 102-104]*.

Summary and Discussion

Fluticasone furoate at a dose of 100 mcg once daily demonstrated statistically significantly greater reductions ($p < 0.001$) in SAR symptoms versus placebo for the primary endpoint of mean change from baseline over the entire treatment period in rTNSS and most secondary endpoints as well. It demonstrated efficacy at 24-hours post-dose, as assessed by AM, pre-dose iTNSS, thus supporting a once daily dosing regimen as well as the efficacy of FF100 in reducing the ocular symptoms of allergic rhinitis (watering, redness, and itching) as measured by rTOSS ($p = 0.004$).

A statistically significant onset of effect compared to vehicle placebo for FF100 was evident at 24 hours based on the mean change from baseline in AM, pre-dose iTNSS.

Regarding quality of life endpoints, subjects treated with FF100 experienced statistically significant and clinically meaningful improvements over placebo in overall RQLQ scores, and in six of seven individual domains: activities, sleep, practical problems, nasal symptoms, eye symptoms, and emotional problems. Improvements in Non Hay Fever Symptoms were statistically significant ($p = 0.004$) but did not reach the level felt to correlate with clinical significance (0.5 difference).

No unforeseen safety signals were detected. Headache was the most common AE with incidence rates of 6 and 9% in the placebo and FF100 groups, respectively.

Epistaxis occurred in 1% and 3% in the Placebo and FF100 groups, respectively and while 2 subjects (1%) in the FF100 group and 3 subjects (2%) in the Placebo group had nasal ulcers at baseline, five subjects (4%) in the FF100 group and none in the Placebo group had nasal ulcers at the conclusion of the study.
***Reviewer's Comment: The numbers of subjects** with nasal ulcerations was small overall but more frequent in the FF100 group. If a safety signal exists for nasal ulcerations it should be more apparent in the longer-term PAR and safety studies.*

10.1.5 STUDY # FFR30002

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 100mcg for 4 Weeks in Adult and Adolescent Subjects (≥ 12 years of age) with Perennial Allergic Rhinitis (PAR)

Protocol

Administrative

Study initiated: January 05, 2005
Study completed: May 04, 2005
Clinical Centers: 42 study sites in the United States and 5 sites in Canada
Study report dated: November 2005
Study Sponsor: GlaxoSmithKline (GSK)
Medical Officer: Kathy Rickard, M.D., GSK

Objective/Rationale

The primary objective of this study was to compare the efficacy and safety of 100mcg QD GW685698X (fluticasone furoate) aqueous nasal spray with vehicle placebo nasal spray in adult and adolescent subjects (≥ 12 years of age) with PAR.

Study Design

This randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluated the efficacy and safety of once-daily, intranasal administration of fluticasone furoate 100mcg (FF100) aqueous nasal spray administered for 4 weeks in 302 adult and adolescent subjects (12 years of age and older) with perennial allergic rhinitis. 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 in a 1:1 ratio to receive either FF100 or placebo nasal spray in a blinded fashion self-administered for 4 Weeks. The first dose of study drug was self-administered in the clinic prior to noon at Visit 2 by randomized subjects; thereafter, subjects were instructed to administer two sprays per nostril each morning. Subjects returned to the clinic each week for four weeks (Visits 3 to 6) during the treatment period. Subject clinic visits were to be scheduled to occur every week for four weeks based on the date of Visit 2 (Randomization). Subjects were instructed not to take any anti-allergy/anti-rhinitis medication during the screening or treatment study periods. No allergy rescue medication was allowed throughout the entire study period. During the 4-week treatment period, subjects rated their nasal and non-nasal symptoms of allergic rhinitis and recorded them on a symptom diary card. Subjects also documented study drug administration/compliance, medical conditions experienced and

concomitant medications taken. At the final visit (Visit 6/Early Withdrawal) subjects rated their overall improvement and completed Health Outcomes (Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ]) and Product Characteristic Questionnaires. A follow-up telephone contact was made to the subject 3 to 5 days after Visit 6/Early Withdrawal Visit to assess for any post-treatment adverse events. Blood and urine for safety hematology and chemistry as well as ECGs were obtained at baseline and end of study. No ophthalmology exam was performed. Subject compliance was assessed with the diary and by visual inspection of the medication bottle.

Study Population

Inclusion Criteria

- Male or female ≥ 12 years (United States) or ≥ 18 years (Canada)
- Diagnosis of PAR to include:
  - A positive skin test (by prick method) response to appropriate perennial allergen (animal dander, house dust mites, cockroach, mold) within last 12 months prior to Visit 1 or at Visit 1. In vitro tests for specific IgE (such as RAST, PRIST) were not allowed for the diagnosis of PAR.
  - Two-year medical history and past treatment of PAR
  - • **Subject must have been symptomatic** to appropriate perennial allergen (animal dander, house dust mites, cockroach, mold) and willing to maintain same environment throughout the study (e.g., exposure to animal dander should not change during the study).

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 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
- Diagnosed with seasonal allergic rhinitis (SAR) and had a positive skin test (by prick method) response to a seasonal allergen (other than a fall seasonal allergen [weeds]) within the last 12 months prior to Visit 1 or at Visit 1.
- Use of corticosteroids, defined as:
  - Intranasal corticosteroid within four weeks prior to Visit 1.

- Inhaled, oral, intramuscular, intravenous, ocular, and/or dermatological corticosteroid (with the exception of hydrocortisone cream/ointment, 1% or less) within eight 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.

Randomization Criteria

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

1. Average of the last 8 rTNSS assessments (4 AM assessments, 4 PM assessments) over the four 24-hour periods prior to randomization must have been ≥6.
2. Average of the last 8 reflective nasal symptom assessments for congestion (4 AM assessments, 4 PM assessments) over the four 24-hour periods prior to randomization must have been ≥2.
3. A subject must have completed 80% of assessments on the screening symptom diary cards.

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 4-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

Demographic and Baseline Assessments
The following demographic and baseline information was obtained: age; sex; race; ethnicity, height, weight, duration of the subject's perennial allergic rhinitis, presence of seasonal 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, serum pregnancy test (females) urine pregnancy test (females at randomization [Visit 2 and Visit 4]). The subjects' self-rated symptom scores over the four days prior to randomization (including the morning of randomization) provided the baseline symptom assessment.

Efficacy Evaluation
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 28 days of treatment. The adult and adolescent Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was administered as in study FFR20001. The onset of action was also calculated as in study FFR20001, however, the instantaneous TNSS (iTNSS) was recorded only once during the first day of treatment.

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).

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

Data Analysis

Sample Size

The study randomization was planned for equal allocation of subjects among two treatment groups. A total of 288 subjects were required for this study, with 144 subjects in each of the two treatment groups: FF100 and Placebo. The randomization was stratified by country (USA and Canada) to account for possible country effects on the study outcome due to country-specific medical practices.
Data from a previous study of Study FFR20001 (Study #1 in this Appendix) suggested that a reasonable assumption for the standard deviation of 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 all efficacy, safety, and health outcomes analyses.

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 (FF100 vs. placebo) using analysis of covariance (ANCOVA) adjusting for baseline reflective TNSS, investigative site, age, and gender, in addition to treatment effect.

Mean change from baseline in daily rTNSS over the entire treatment period was analyzed. The least squares mean changes from baseline is summarized for all treatment groups and compared to that in placebo group. The 95% confidence interval (CI) for the mean difference (active vs. placebo) is also reported, as well as the p-values corresponding to the test of significance for the mean difference (active vs. placebo).

The secondary efficacy measures on nasal symptoms, ocular symptoms, and combined nasal and ocular symptoms were analyzed similarly to the primary analysis. The analysis method was the pairwise comparisons of treatment groups (FF100 vs. placebo) using an analysis of covariance (ANCOVA) and adjusting for baseline value, investigative site, age, and gender, in addition to treatment effect.

Results

Study Population

Disposition

A total of 511 subjects were screened for this study. Three hundred and two subjects were randomized into the study (149 to the FF100 group and 153 to Placebo) and comprised the ITT population.

Enrollment ranged from 1 (< 1%) to 17 (6%) subjects at each of the 42 investigational sites. Ninety-two percent of subjects completed the study. Premature withdrawals occurred for 23 subjects (7%) with 1 (7%) withdrawing from the placebo group and 12 (8%) from the FF100 group. Four subjects in each group withdrew due to adverse an AE *[Section 6.1 and Table 4 FFR30002 Study Report, pages 51-52].*

There were no protocol deviations in the FF100 group and 3 (all for use of a prohibited medication) in the placebo group *[Section 6.2 FFR30002 Study Report, page 54].*

Demographics

Demographics were very similar across treatment groups. The mean age range was 35.8 years for the placebo group and 37.7 for the FF100 group with a range of 12-76 years. Most subjects in each treatment group were in the 18-64 years of age subgroup (86%). The majority of the subjects were White (84%), 11% were listed as Black, and 6% listed as "Other". Females were more prevalent in the study (63%). Seventy-eight and 82% of subjects in the placebo and FF100 groups, respectively, reported having SAR for ≥5 years. Twenty-six per cent and 25% of subjects in the FF100 and placebo groups, respectively, also reported having perennial allergic rhinitis (PAR).

Thirty-four per cent, 49%, and 81% of subjects were skin test positive to mold, animal danders, and dust mites, respectively. These subjects were distributed evenly across the 2 treatment groups *[Table 6.19 FFR30002 Study Report, page 210].*

Baseline symptoms were quite similar between the FF100 and placebo groups with the AM rTNSS 8.6 and 8.7 in the placebo and FF100 groups, respectively. Nasal congestion scores were also similar with the AM reflective score 2.6 for both treatment groups *[Table 7 FFR30002 Study Report, page 58].*

The compliance rate during the treatment period, as determined by diary entry, was 94.9% and 95.2% in the placebo and FF100 groups, respectively.

Efficacy Results

Primary Efficacy Outcome

The primary efficacy endpoint was the mean change from baseline in the reflective TNSS over the entire treatment period. 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.

Daily rTNSS (ITT Population) *[Table 9 FFR30002 Study Report, page 61]*

	Placebo (N=153)	GW685698X 100mcg (N=149)
Baseline (n)	153	149
Mean (SE)	8.7 (0.14)	8.6 (0.13)
Weeks 1-4[a] (n)	153	149
Mean (SE)	6.4 (0.20)	5.6 (0.19)
Change from Baseline		
Week 1		
Mean Change (SE)	-1.6 (0.17)	-2.1 (0.17)
Week 2		
Mean Change (SE)	-2.3 (0.20)	-3.0 (0.19)
Week 3		
Mean Change (SE)	-2.5 (0.21)	-3.5 (0.21)
Week 4		
Mean Change (SE)	-2.8 (0.23)	-3.6 (0.22)
Weeks 1-4[a]		
Mean Change (SE)	-2.3 (0.18)	-3.0 (0.18)
LS Mean Change (SE)[b]	-2.08 (0.21)	-2.78 (0.21)
LS Mean Difference[b]		-0.706
p-value[b]		0.005
95% CI[b]	---	-1.20, -0.21

Source Data: Table 7.1, Table 7.2,
a = entire treatment period; b = based on ANCOVA adjusting for baseline daily rTNSS, country, age, gender, and treatment
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 both groups ranging from 8.6-8.7 out of a possible 12. The least square (LS) mean changes for the two treatments over the entire 4-wee treatment period were: placebo (-2.08) and FF100 (-2.78). Compared to placebo, there was a statistically significant greater reduction in rTNSS in the FF100 group (p = 0.005). The treatment difference between groups was also significant for each of the study weeks.

The Primary Endpoint was also summarized by country. There were no meaningful differences in baseline rTNSS or treatment effect in subjects from the United States compared to those from Canada *[Table 24 FFR30002 Study Report, page 81]*.

Change from baseline in daily rTNSS was assessed for age subgroups 12-17 years, 18-64 years, and ≥ 65 years. The mean change from baseline in daily rTNSS over the 2-week treatment period was greater for the FF100 group than vehicle Placebo for all three age groups *[Table 23 FFR30002 Study Report, page 80]*.
***Reviewer's Comment: The sample sizes for** the younger and older age groups was very small (2-20 subjects/treatment group) and precludes making any meaningful judgment regarding efficacy in these populations.*

Secondary Efficacy Outcomes

Pre-dose AM iTNSS was a key secondary endpoint that was used to assess the duration of action of FF. Mean AM, pre-dose iTNSS were very similar at baseline (8.3 for placebo and 8.1 for FF100). The LS mean changes in iTNSS over the 4-week period were -1.75 for placebo and -2.45 for FF100 with the difference of -0.705 being statistically significant (p = 0.006) *[Table 10 FFR30002 Study Report, page 63].*

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. Using logistic regression analysis, the pairwise comparison between placebo and FF100 showed a significantly better response (p = 0.005) with the FF100 treatment. Forty-four per cent of subjects receiving FF100 reported significant and moderate improvement in their overall evaluation of response to therapy compared with 33% of subjects receiving placebo *[Table 11 FFR30002 Study Report, page 65].*

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 and am iTNSS individual symptom scores of rhinorrhea, nasal congestion, nasal itching, and sneezing
- mean change from baseline in daily rTOSS
- mean change from baseline in am iTOSS
- mean change from baseline in am rTOSS
- mean change from baseline in pm rTOSS
- mean % change from baseline in daily rTOSS
- mean % change from baseline in am pre-dose iTOSS
- mean change in daily reflective individual ocular scores

For these endpoints, in general, subjects in the FF100 treatment group demonstrated statistically significant improvements compared to placebo in secondary endpoints that assessed nasal symptoms (TNSS) but not those that assessed ocular symptoms (TOSS) *[Section 7.3 FFR30002 Study Report, pages 66-76].*

Throat/Palatal itching was an exploratory endpoint for which there was no significant difference between FF100 and placebo (p = 0.808) *[Table 22 FFR30002 Study Report, page 77].*

Onset of Action

The onset of effect by FF100 was evaluated by primarily by mean changes from baseline

in AM, pre-dose iTNSS and mean change in rTNSS on Days 1-28. A significant treatment difference (LS mean difference from baseline for AM pre-dose iTNSS) was first observed on Day 4 (p = 0.028) which was maintained except for study days 7, 16, 24, 25, and 26. Regarding the rTNSS, a significant treatment difference was also first observed on Day 4 (p = 0.014) which was maintained throughout the treatment period, except for study days 7, 8, 10, and 25 *[Section 7.3.6.1 FFR30002 Study Report, page 78].*

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 treatment as compared to placebo. The greatest reduction in mean change from baseline occurred at Day 20 *[Section 7.3.6.2 FFR30002 Study Report, page 78].*

Health Related Outcomes

No differences were observed at baseline between subjects in the FF100 or placebo groups for any of the domain scores or the overall scores of the RQLQ. There were no statistical or clinically meaningful (improvement of at least -0.5 over vehicle placebo) differences between FF100 and placebo in overall RQLQ scores, or in 6 of 7 individual domains: Activities, Sleep, Non-hay fever symptoms, Practical problems, Eye symptoms, and Emotional problems. However, the seventh domain, Nasal Symptoms, achieved statistical significance and minimally important difference *[Section 10 FFR30002 Study Report, pages 96-99].*

Reviewer's Comment: These findings are in contrast to those of the SAR studies in which the improvement in overall RQLQ was both statistically significant and probably clinically meaningful as the improvements occurred in at least 6 of 7 categories.

Safety

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 28 days. The mean number of days of exposure for both the FF100 and placebo subject groups was 28.2 days *[Table 25 FFR30002 Study Report, page 82].*

Adverse Events

In all, 69 subjects (46%) in the FF100 group and 63 subjects (41%) in the placebo group experienced at least one AE during the treatment period. The most common AE was headache occurring in 11% of subjects in both groups. Epistaxis occurred in 6% (9 subjects) in the placebo group and in 8% (12 subjects) in the FF100 group. Nasal septal ulceration/nasal ulcer (combined) was reported in 2% (4 subjects) in the placebo group and in 6% (9 subjects) in FF100 treated subjects. All nasal ulcerations were noted to be either mild or moderate in intensity with large ulcers (≥ 2 mm) reported for 1 subject in the FF100 group and 2 subjects in the placebo group. Three subjects in the FF100 group

and one subject in the placebo group had ulcerations that were ongoing at the end of treatment *[Section 8.2.2 FFR30002 Study Report, pages 83-84].*
When summarized by shifts from baseline, 3 and 4 subjects in the placebo and FF100 groups, respectively, had improvement in ulcerations while 5 subjects in each group were reported to have worsened ulcerations at the end of the study *[Table 30 FFR30002 Study Report, page94].*

Deaths, Serious Adverse Events, and Events Leading to Withdrawal

No deaths were reported during the treatment period. An SAE of breast cancer was reported by Subject 439 (FF100 group) on Day 11. The subject stopped taking study medication and the investigator scheduled an Early Withdrawal visit. Two SAEs were reported for a subject in the placebo group during the treatment and post-treatment periods. The subject reported severe abdominal pain on Day 15 of treatment, was hospitalized, and withdrawn from the study as a result of the event. On Day 18 (post-treatment) a serious adverse event of nephrolithiasis was reported *[Section 8.3 FFR30002 Study Report, pages 86-87].*

Four subjects (3%) in each treatment group withdrew from the study due to an AE. In the FF100 group the withdrawals were due to viral gastroenteritis, viral infection, hypersensitivity (allergic reaction), and increased intraocular pressure. In the placebo group, withdrawals were due to viral gastroenteritis, upper respiratory tract infection, abdominal pain/nephrolithiasis, and epistaxis *[Section 8.4 FFR30002 Study Report, pages 86-87].*
Reviewer's Comment: Review of the narrative for the AE of intraocular pressure revealed it was reported in a 62 year-old male in the FF100 group on Day 9 of treatment. The increase was diagnosed during a routine ophthalmologic exam. There was a history of glaucoma in the subject's family.

Pregnancy

No subjects became pregnant during the study.

Laboratory Results

The majority of subjects in each treatment group (91-92%) had either no change in hematology or chemistry parameters or a shift into the normal range. There were 5 instances of abnormal glucose levels, 4 increased, 1 decreased, that were reported as AEs (all mild). Three of the reports (2 increased, 1 decreased) were in the FF100 group and 2 (both increased) were in placebo subjects. 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 the FF100 group and placebo *[Section 8.7.2, 8.7.3 FFR30002 Study Report, pages 88-92].*

Nasal Exams, Vital Signs, and Electrocardiograms

Over the treatment period, the incidence of nasal mucosal bleeding increased from 7% to 13% for FF100 subjects but remained the same (4%) for placebo subjects. Five subjects

(3%) in the FF100 group and 4 subjects (3%) in the placebo group had nasal ulcers (turbinates/septum) at Visit 2 (Day 1). At the end of the treatment period (Week 4), 6 subjects (4%) in the GW685698X 100mcg group and 4 subjects (3%) in the vehicle Placebo group had nasal ulcers. When summarized by shifts from baseline (Table 30, page 94), 3 and 4 subjects in the placebo and FF100 groups, respectively, had improvement in ulcerations while 5 subjects in each group were reported to have worsened ulcerations at the end of the study. No subjects had evidence of nasal candidiasis. There were no clinically meaningful adverse changes from baseline in vital signs or ECGs in the study *[Sections 8.8.1-8.8.3 FFR30002 Study Report, page 92-95]*.

Summary and Discussion

Fluticasone furoate at a dose of 100 mcg once daily demonstrated statistically significantly greater reductions ($p = 0.005$) in PAR symptoms versus placebo for the primary endpoint of mean change from baseline over the entire treatment period in rTNSS. It also won on most TNSS-derived secondary endpoints. It maintained efficacy at 24-hours post-dose, as assessed by AM, pre-dose iTNSS, thus supporting a once daily dosing regimen. Treatment with FF100 failed to demonstrate efficacy in reducing the ocular symptoms of allergic rhinitis (watering, redness, and itching) as measured by rTOSS or in improving quality of life as measured by the RQLQ.

A statistically significant onset of effect compared to vehicle placebo for FF100 was evident at 4 days based on the mean change from baseline in AM, pre-dose iTNSS and rTNSS.

No unforeseen safety signals were detected. Headache, as in most of the other studies was the most common AE and epistaxis was slightly increased (reported in 6% of placebo subjects versus 8% of those in the FF100 group). Nasal ulcerations occurred in both treatment groups; an increased incidence/severity in the FF100 group was not apparent.

10.1.6 STUDY # FFR102123

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter, Long-Term Study to Evaluate the Safety of Once-Daily, Intranasal Administration of GW685698X (fluticasone furoate) Aqueous Nasal Spray 100mcg for 52 weeks in Adult and Adolescent Subjects with Perennial Allergic Rhinitis (PAR)

Protocol

Administrative

Study initiated: September 14, 2004
Study completed: December 09, 2005
Clinical Centers: 75 study sites in 13 countries ((Australia, Chile, Estonia, Germany, Italy, Latvia, Lithuania, Netherlands, New Zealand, Romania, Russia,

Spain, and Sweden).
Study report dated: April 19, 2006
Study Sponsor: GlaxoSmithKline (GSK)
Medical Officer: Katharine Knobil, M.D., GSK

Objective/Rationale

The primary objective of this study was to assess the safety and tolerability of 12 months of treatment with fluticasone furoate aqueous nasal spray 100 mcg once daily in adult and adolescent subjects (≥ 12 years of age) with PAR.

Study Design

This was a 12 month randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted internationally in 75 investigative sites in 13 countries. The study was stratified by country. Subjects who satisfied the entry criteria entered a 7 to 14 day screening period. During the screening period subjects scored their symptoms on a diary card in order to determine eligibility for randomization. At Visit 2, subjects who had completed the screening period and fulfilled the randomization criteria were randomized in a 3:1 ratio to receive either fluticasone furoate 100mcg or placebo, respectively, intranasally for 52 weeks. Subjects were instructed not to take any anti-allergy/anti-rhinitis medications during the screening or treatment study periods. GSK provided loratadine 10mg tablets, as allergy rescue medication for subjects to use during the double-blind treatment period of the study on an as needed basis. Subjects returned to the clinic every four weeks (Visit 3 to Visit 15) during the treatment period. Pharmacokinetic sampling was performed at Visits 3, 5, 8, 11, and 15. At the end of the treatment period (Visit 15), the subjects returned for a post-treatment follow-up visit (Visit 16). Throughout the study, subjects rated their nasal symptoms daily in a reflective manner each morning before dosing with study medication. These ratings of drug efficacy were used as a measure of drug administration compliance. Subjects also documented on the diary card their study medication administration/compliance, their daily use of allergy rescue medication, any medical conditions experienced, and any concomitant medications taken. Long-term safety endpoints included 24-hour urinary cortisol assessments, slit-lamp, fundoscopic, and evaluation for changes in intraocular pressure, all performed by an ophthalmologist or optometrist at baseline and at Visits 5, 8, and 15. Safety was also assessed by reporting of AEs, laboratory tests (hematology, chemistry, and urinalyses), ECGs, vital signs, and nasal examinations.

Study Population

Inclusion Criteria

- Male or female ≥ 12 years
- Diagnosis of PAR to include:
  - A positive skin test (by prick method) response to appropriate perennial allergen (animal dander, house dust mites, cockroach, mold) within last 12 months prior to Visit 1 or at Visit 1. In vitro tests for specific IgE (such as RAST, PRIST) were not allowed for the diagnosis of PAR.

- Two-year medical history and past treatment of PAR
- • **Subject must have been symptomatic** to appropriate perennial allergen (animal dander, house dust mites, cockroach, or mold)

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 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
- Use of corticosteroids, defined as:
  - Intranasal corticosteroid within four weeks prior to Visit 1.
  - Inhaled, oral, intramuscular, intravenous, ocular, and/or dermatological corticosteroid (with the exception of hydrocortisone cream/ointment, 1% or less) within 6 months prior to Visit 1.
- Use of other allergy medications within the timeframe indicated relative to Visit 1
  - Intranasal 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 5 days prior to Visit 1
  - Intranasal calcitonin within 3 days of 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 (immunotherapy patients could be enrolled in the study as long as 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 would remain fixed for the duration of the study).

Randomization Criteria

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

- Reflective total nasal symptom scores (rTNSS) ≥4 during 4 of the last 7 days prior to Visit 2
- Completed 80% of assessments on the screening symptom diary cards
- Completed a 24-hour urine cortisol collection (minimum urine volumes were 600mL for females and 800mL for males)
- Completed slit lamp and fundoscopic examinations, including evaluation of cataract formation, performed by a licensed ophthalmologist or optometrist and results were within normal limits
- Completed an evaluation for glaucoma and changes in intraocular pressure performed by a licensed ophthalmologist or optometrist and results were within normal limits

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 52-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
- GlaxoSmithKline discontinued the study.

Study Procedures

Treatment
Concomitant use of any prescription or over-the-counter medications listed in the exclusion was not allowed during the study. Loratadine 10mg tablets, not exceeding 1/day, were allowed as allergy rescue medication. Oral decongestants use for not more than 3 consecutive days was also allowed.

Efficacy Evaluation
As this was primarily a safety study, no primary efficacy endpoint was defined. Efficacy was assessed as a means to determine compliance with drug administration. The Total Nasal Symptom Score (TNSS) was. Daily reflective total nasal symptom scores (rTNSS) calculated from the diary entries as described for study FFR20001 were recorded on the diary card each day. Subjects rated four nasal symptoms, rhinorrhea, nasal congestion, nasal itching, and sneezing. The sum of the four individual reflective scores gave the daily rTNSS which had a maximum score of 12.

Safety Evaluation
Assessment of safety was the primary objective of this study. Safety was assessed by:

- Frequency and type of clinical adverse events
- Vital signs and nasal examinations at all study visits

- Results of clinical laboratory tests (hematology and chemistry, and urinalysis), 12-lead ECGs, 24-hour urinary cortisol assessments, slit lamp and fundoscopic examinations, and evaluation for glaucoma and changes in intraocular pressure performed at baseline and at Visits 5, 8, and 15.

Data Analysis

Sample Size

The proposed sample size was to provide a minimum of 300 subjects treated with active drug for 6 months and 100 subjects treated for 12 months, in accordance with ICH guidelines. A total of 700 subjects (525 randomized to FF100 and 175 to placebo) were projected to be required for the study. The proposed sample size allowed more than 350 subjects to be treated with the active drug for 6 months, assuming a drop out rate of 25%-30% over the first 6-month treatment period, and also allowed for approximately 100 placebo-treated subjects to complete the 12-month study assuming a drop out rate of 40% over the 12-month treatment period.

Study Populations

There were 3 main 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 all efficacy and safety analyses. The Urine Cortisol (UC) population was based on the ITT Population but excluded subjects whose urine samples were considered to have confounding factors that would affect the interpretation of the results of 24-hour urine cortisol excretion. It was the primary population for analysis of 24-hour urine cortisol excretion. In addition, the Pharmacokinetic (PK) population included all subjects who provided plasma samples for measurement of fluticasone furoate concentrations.
Reviewer's Comment: There were criteria specified prospectively that were used to determine what defined an evaluable 24-hour urine cortisol sample *[Section 5.8.3 FFR 102123 Study Report, page 50].*

Results

Study Population

Disposition

A total of 984 subjects were screened for this study. Eight hundred and ten subjects were randomized into the study (605 to the FF100 group and 201 to Placebo) and comprised the ITT population. The UC population consisted of 490 subjects (61% of the ITT Population). The proportion of subjects in the UC population in each group was 370 subjects (61%) received FF100 and 120 (60%) received placebo. The main reasons for the large number of subjects excluded from the UC population was because of collection time intervals outside the 24±2 hour collection time window (10% of FF100 and 10% of placebo populations) and because 24-hour urine cortisol excretion could not be determined (30% FF100 and 31% placebo) *[Table 6 FFR102123 Study Report, page 56].*

***Reviewer's Comment: The reasons 24-hour** urine cortisol excretion could not be determined was either because the sample was not collected by subject or the sample was collected but the test could not be performed by the laboratory (e.g., insufficient quantity, leaking in transit, sample not frozen properly upon receiving at the laboratory, laboratory error, or interference of other substance).*

Enrollment ranged from 1 (< 1%) to 73 (9%) subjects at each of the 75 investigational sites and from 164 (20%) in Russia to 20 (2%) in Sweden. Seventy-three percent of subjects completed the 12 month study. The early withdrawal rate was 26% for the FF100 group and 28% for placebo. Thirty-eight subjects (6%) in the FF100 group and 7 in the placebo group withdrew due to adverse an AE *[Section 6.1 and Table 4 FFR102123 Study Report, pages 53-54].*

There were 35 (17%) protocol deviations in the placebo group and 109 (18%) in the FF100 group. The great majority, 17 and 16%, respectively, were due to taking a prohibited medication during the treatment period *[Table 5 FFR102123 Study Report, page 55].*

Demographics

Demographics were very similar across treatment groups. The mean age range was 31.6 years for the placebo group and 32.7 for the FF100 group with a range of 12-77 years. Most subjects in each treatment group were in the 18-64 years of age subgroup (80%). The majority of the subjects were White (87%), < 1% were listed as Black, 11% were listed as American Hispanic, and 2% listed as **"Other". Females and males were about** equally represented (51% female, 49% male). Forty-five and 46% of subjects in the placebo and FF100 groups, respectively, reported having PAR for ≥10 years. Forty-six and 50% of subjects in the FF100 and placebo groups, respectively, also reported having Seasonal allergic rhinitis (SAR) *[Section 6.4.1 and Table 7 FFR102123 Study Report, page 56-57].*

Eighty-four and 83% of subjects in the placebo and FF100 groups, respectively, were skin test positive to dust mites *[Table 8 FFR102123 Study Report, page 58].*

Baseline symptoms were quite similar between the FF100 and placebo groups with the daily rTNSS 6.3 and 6.1 in the placebo and FF100 groups, respectively *[Table 9 FFR102123 Study Report, page 58].*

The compliance rate during the treatment period, as determined by diary entry, was 94.2% and 94.8% in the placebo and FF100 groups, respectively.

Efficacy Results

Primary Efficacy Outcome

No inferential statistical testing was planned or performed for TNSS recorded in subject diaries. However, mean changes in daily rTNSS over each 4-week time point through the study and ranging from -2.4 to -3.9 for FF100 group compared with -1.4 to -3.4 for placebo group 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 43 FFR102123 Study Report, page 109].*

Baseline mean daily rTNSS values were very similar across both groups ranging from 8.6-8.7 out of a possible 12. The least square (LS) mean changes for the two treatments over the entire 4-wee treatment period were: placebo (-2.08) and FF100 (-2.78). Compared to placebo, there was a statistically significant greater reduction in rTNSS in the FF100 group ($p = 0.005$). The treatment difference between groups was also significant for each of the study weeks.

The Primary Endpoint was also summarized by country. There were no meaningful differences in baseline rTNSS or treatment effect in subjects from the United States compared to those from Canada *[Table 24 FFR30002 Study Report, page 81].*

Change from baseline in daily rTNSS was assessed for age subgroups 12-17 years, 18-64 years, and ≥ 65 years. The mean change from baseline in daily rTNSS over the 2-week treatment period was greater for the FF100 group than vehicle Placebo for all three age groups *[Table 23 FFR30002 Study Report, page 80].*

Safety

Extent of Exposure

The mean number of days of exposure was 310.3 days for the FF100 group and 298.8 days for the placebo group. Specifically, 501 and 400 subjects were treated with FF100 for ≥ 6 months and ≥ 12 months, respectively. When broken down into age groups, 70 subjects aged 12 to <18 years, 322 subjects aged 18 to <65 years and 8 subjects aged ≥65 years were treated with FF100 for at least 12 months *[Section 7.1 and Tables 13 and 14 FFR102123 Study Report, page 63-65].*
***Reviewer's Comment: These numbers exceed the** ICH guidelines for long-term exposure to the study drug.*

Adverse Events

In all, 464 subjects (77%) in the FF100 group and 142 subjects (71%) in the placebo group experienced at least one AE during the treatment period. The most common AE was headache occurring in 31% of subjects in the FF100 group and 34% in the placebo group. Epistaxis occurred more frequently in the FF100 group (123 (20%) vs 17 (8%) subjects in the placebo group). For the FF100 group, 83 subjects (14%) reported epistaxis of mild intensity, 39 subjects (6%) of moderate intensity, and one subject reported 2 episodes considered to be severe. In the placebo nasal spray group, all episodes of epistaxis were of mild intensity. Nasal septal ulceration was reported as an AE 2 (< 1%) subjects in the placebo group and in 12 (2%) subjects in the FF100 group. No septal perforations were reported. The following table summarizes AEs that occurred at an incidence of ≥ 1% and were more common in the FF100 group.

Adverse Events that Occurred at ≥ 1% Incidence and More Common than Placebo (ITT Population) *[Table 16 FFR102123 Study Report, page 68]*

	Number (%) of Subjects	
Adverse Event	**Placebo (N=201)**	**FF 100mcg (N=605)**
Subjects with any Adverse Event	142 (71%)	464 (77%)
Nasopharyngitis	51 (25%)	157 (26%)
Epistaxis	17 (8%)	123 (20%)
Back pain	12 (6%)	39 (6%)
Cough	7 (3%)	29 (5%)
Toothache	5 (2%)	29 (5%)
Nausea	6 (3%)	20 (3%)
Pharyngitis	5 (2%)	18 (3%)
Diarrhoea	5 (2%)	17 (3%)
Bronchitis	4 (2%)	17 (3%)
Conjunctivitis	3 (1%)	18 (3%)
Nasal dryness	1 (<1%)	17 (3%)
Eye pruritus	2 (<1%)	15 (2%)
Rhinitis	3 (1%)	14 (2%)
Abdominal pain	2 (<1%)	14 (2%)
Dizziness	2 (<1%)	13 (2%)
Gastroenteritis	1 (<1%)	14 (2%)
Viral infection	3 (1%)	12 (2%)
Nasal septum ulceration	2 (<1%)	12 (2%)
Dyspepsia	2 (<1%)	11 (2%)
Acute tonsillitis	2 (<1%)	9 (1%)
Urinary tract infection	2 (<1%)	9 (1%)
Urticaria	2 (<1%)	9 (1%)
Pruritus	1 (<1%)	9 (1%)
Bronchitis acute	1 (<1%)	8 (1%)
Dyspnoea	2 (<1%)	7 (1%)
Hypertension	2 (<1%)	7 (1%)
Pain in extremity	2 (<1%)	7 (1%)
Tonsillitis	0	9 (1%)
Herpes simplex	0	8 (1%)

Source Data: Table 7.9, Table 7.10

The cumulative incidence of AEs was similar throughout the treatment period for active and placebo treatment for all AEs except epistaxis *[Table 18 FFR102123 Study Report, page 73]*.

Deaths, Serious Adverse Events, and Events Leading to Withdrawal

No deaths were reported during the treatment period. During the study period, 20 subjects (3%) in the FF100 group and 4 subjects (2%) in the placebo group experienced SAEs. Not more than 1 subject was reported to have any one particular SAE in either the FF100 or placebo group. No SAEs were considered to be related to study drug. Four subjects, all

in the FF100 group were withdrawn prematurely from the study due to SAEs: Subject 1258 had a glandular polyp of the endometrium and uterine bleeding, Subject 1638 had worsening hemorrhoids, Subject 1351 had herpes zoster of the face and neck, and Subject 62 had a cervical vertebral fracture *[Section 7.3.2 and Table 20 FFR102123 Study Report, pages 75-76]*.

In addition to the subjects withdrawn due to SAEs, 38 (6%) subjects in the FF100 group and 7 (3%) subjects in the placebo group were discontinued from the study prematurely due to AEs. Fifteen subjects (2%) in the FF100 group withdrew due to epistaxis compared to no subjects in the placebo group. There were no other differences between the FF100 and placebo group in the number or per cent of subjects withdrawing from the study for a particular event *[Table 21 FFR102123 Study Report, page 77]*.
***Reviewer's Comment: Regarding AEs and withdrawals** due to epistaxis, while epistaxis is a known side effect of nasal steroid administration, the incidence of epistaxis and withdrawals due to epistaxis in this long-term safety study in the FF100 group appear higher than other nasal steroid preparations. For example, epistaxis lead to withdrawal in 15/605 subjects treated with FF100 in this study but in 2/441 subjects treated with ciclesonide 200mcg in the 52-week safety study for that intranasal steroid. Also, epistaxis was reported as an AE in 10.0 and 7.2% of subjects receiving ciclesonide 200mcg and placebo, respectively in that study compared to 17 and 7% in those who received FF100 and placebo in this study. These findings support the notion that fluticasone furoate is a more potent locally-acting nasal steroid [Source: NDA 22004 Medical Officer Clinical Review Study #146/2005 Tables 44 and 45, pages 108-109]*.

Pregnancy

Three subjects, two treated with FF100 and one with placebo, became pregnant during the study. In the FF100 group, Subject 1756 had an estimated delivery date of October 1, 2005, and Subject 1780 had an estimated delivery date in April 2006. Both women were said to be lost to follow-up. In the placebo group, Subject 745 had an estimated delivery date of August 20, 2006 with the delivery resulting in the birth of a normal, term infant.

Laboratory Results

The majority of subjects in each treatment group (≥88%) had either no change in hematology or chemistry parameters or a shift into the normal range. Less than 1% of subjects reported a shift to high AST or ALT in the FF100 group compared to 1-2% in the placebo group. Shifts to a high serum glucose (21 subjects (5%) in the FF100 group and 3 subjects (2%) in the placebo group) and to high calcium (1 subject (3%) in the FF100 group and 2 subjects (1%) in the placebo group) were the only parameters where the FF100 group had more shifts to abnormal values. There was also no evidence for trends in any laboratory data, including urinalyses over time in this study. Few laboratory abnormalities were reported as AEs in the study. There were no differences in number or severity of laboratory AEs in the FF100 group compared to placebo *[Table 31 FFR102123 Study Report, page 90]*.

24-Hour Urine Cortisol excretion

Twenty-four hour urine cortisol excretion was assessed at baseline and at Weeks 12 (Visit 5), 24 (Visit 8), and 52 (Visit 15) during the study. When assessed by looking at both mean cortisol excretion values and ratio to baseline in the UC population, there was no evidence for any decrease in 24-hour urinary cortisol excretion at any time point. In both treatment groups, 24-hour urinary cortisol excretion was higher at Week 52 than at baseline (geometric mean ratio to baseline was 1.14 for the FF100 group and 1.13 for placebo). Urine cortisol excretion data are summarized for the UC population in the following table.

24-hour Urinary Cortisol Excretion (UC population) *[Table 32 FFR102123 Study Report, page 91]*

	Placebo (N=120)	FF 100mcg (N=370)
Baseline		
Geometric mean	58.27	57.06
Mean (SD)	75.56 (60.460)	70.58 (55.161)
Median	60.00	57.00
Min - Max	3.6 - 441.7	5.0 - 572.1
Change from Baseline		
Week 12		
Mean (SD)	-1.37 (74.744)	3.39 (70.095)
Median	-4.15	1.35
Min - Max	-330.3 - 456.2	-435.8 - 601.0
Week 24 (n)		
Mean (SD)	0.10 (76.909)	6.54 (72.784)
Median	-0.95	2.45
Min - Max	-341.2 - 428.5	-505.8 - 434.7
Week 52 (n)		
Mean (SD)	14.33 (94.613)	21.53 (111.020)
Median	4.90	5.75
Min - Max	-370.9 - 573.7	-483.7 - 1160.2
Ratio to Baseline		
Week 12 (n)		
Geometric mean	0.99	1.01
Median	0.94	1.03
Week 24 (n)		
Geometric mean	0.96	1.05
Median	0.98	1.06
Week 52 (n)		
Geometric mean	1.13	1.14
Median	1.08	1.12

The normal ranges for 24-hour urine cortisol excretion used in the study were 5.8 to 104.9nmol/24 hours for subjects aged 12 to 16 years, and 5.5 to 117nmol/24 hours for subjects aged ≥17 years. Only 3 subjects, 1 in the FF100 group and 2 in the placebo group, had 24-hour urinary cortisol excretion below the normal range or a shift to below

normal from baseline at any time during the study. As for the subject in the FF100 group, Subject 559 had 24-hour urine cortisol excretion values within the normal range at baseline (38.2nmol), Week 12 (49.5nmol), and Week 24 (44.1nmol), but a value below the normal range at Week 52 (5.2nmol). Results were similar when urine cortisol excretion was assessed using the ITT population *[Section 7.9.1.1 FFR102123 Study Report, page 92]*.

***Reviewer's Comment: It is interesting to** note that in both the placebo and FF100 groups, there were a large proportion of subjects who had 24-hour urinary cortisol levels that were actually above the normal range at baseline as well as during the treatment period. There is no good explanation for this observance, however, the incidence of subjects with high urinary cortisol levels after baseline was similar for both groups (38% in each group) and it is noteworthy that the ratio of urine cortisol excretion to baseline was actually increased at the 52 week time point for both groups.*

Nasal Exams

Nasal exams were conducted at all study visits. Overall, mucosal crusting and mucosal bleeding were seen in a higher proportion of subjects in the FF100 group than in the placebo group, 9% vs 3% and 2% vs 1%, respectively. However, it should be noted that within the FF100 group, the incidence of mucosal crusting remained about the same from baseline to week 52, 8% vs 9% of subjects, respectively, and the incidence of mucosal bleeding observed at week 52 was actually decreased from that seen at baseline, 2% vs 4%, respectively *[Table 34 FFR102123 Study Report, page 95]*.

When summarized by shifts from baseline, there was no meaningful difference between the FF100 and placebo groups in the incidence of subjects who had a worsening of mucosal bleeding or septal ulcerations over the course of the study. 3 and 4 subjects in the placebo and FF100 groups, respectively, had improvement in ulcerations while 5 subjects in each group were reported to have worsened ulcerations at the end of the study. During the treatment period, 2 subjects, both in the FF100 group, had evidence of nasal candidiasis *[Section 7.9.2 and Table 35 FFR102123 Study Report, pages 96-97]*.

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 Weeks 12, 24, and 52. Any diagnosis was to be recorded as an AE.

Intraocular pressure was measured through the 52 week time point in 446 subjects in the FF100 group and in 142 subjects who received placebo. The mean values demonstrated very little change over the course of the study, 0.1 mm Hg for each eye for subjects in the placebo group and 0.1 mm Hg for the left eye and 0.2 mm Hg for the right eye for subjects who received FF100.

At the end of the study a total of 12 subjects (2%), all in the FF100 group, had intraocular pressure measurement changes to > 20 mm Hg, the pressure considered to be the upper limit of normal, at some time during the study. None of these subjects had a value > 20