

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-051

MEDICAL REVIEW(S)

TEAM LEADER'S MEMORANDUM

Date: March 24, 2007

To: NDA 22-051

From: Sally Seymour, MD
Medical Team Leader, Division of Pulmonary and Allergy Products

Product: Veramyst (fluticasone furoate) Nasal Spray 27.5 mcg

Applicant: GlaxoSmithKline

I. Administrative and Introduction

GlaxoSmithKline submitted a 505(b)(1) new drug application (NDA 22-051) on June 28, 2006, for use of fluticasone furoate nasal spray 27.5 mcg for the once daily treatment of symptoms of seasonal and perennial allergic rhinitis in patients 2 years of age and older. The PDUFA due date for this application is April 29, 2007. GSK has a related product, fluticasone propionate nasal spray (Flonase), on the market approved for the management of the nasal symptoms of seasonal and perennial allergic rhinitis and nonallergic rhinitis in adults and pediatric patients 4 years of age and older. Fluticasone propionate is a different ester of fluticasone. It is important to note that in this fluticasone furoate NDA, GSK seeks to broaden the indication by proposing to treat the symptoms of SAR and PAR, not just the nasal symptoms of PAR and SAR. Based upon the information available at the time of finalization of this review, GSK has submitted the necessary CMC data, pre-clinical data, and clinical data that support approval of this application in patients 2 years of age and older.

II. Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug substance is fluticasone furoate, which is a synthetic fluorinated corticosteroid. Fluticasone furoate is not a new molecular entity, but it is a new ester of fluticasone. Fluticasone is currently marketed as fluticasone propionate. The formulation is a white aqueous suspension of micronized fluticasone furoate, dextrose anhydrous, microcrystalline cellulose, carboxymethylcellulose, polysorbate 80 (), purified water; and edetate disodium and benzalkonium chloride as . The final drug product is the formulation contained in an amber glass bottle, fitted with a metering (50µL) atomizing spray pump. The bottle is contained within a white plastic device with a dose indicator window, a dark blue side-actuated lever and a lid, which contains a stopper (Figure 1). Throughout development, the content of fluticasone furoate in the nasal spray was approximated to be 25mcg; however, the actual dose of fluticasone furoate in each actuation is 27.5mcg in each 50mcL spray. The commercial presentation is a 10.0 gram bottle that provides 120 actuations.

Figure 1 – External View of Delivery System for Fluticasone Furoate Nasal Spray



Source: N22051/2006-06-28/2-3-qos-intro.pdf, pg 2

According to the CMC reviewer, all DMFs associated with this application are acceptable. The drug substance is manufactured at the Glaxo facility in Singapore. Micronization of the drug substance is performed at the Glaxo Ware facility in the UK. The drug product is manufactured at the Glaxo Barnard Castle facility in the UK. The EER status of the manufacturing and testing facilities associated with this drug product is pending at the time of this review.

There were several CMC issues identified by the CMC review team early in the review period. These issues were communicated to GSK in discipline review letters. There is **one major CMC issue worth discussion** – changes to the device during clinical development and after NDA submission. Early versions of the device used during phase 2b and early phase 3 were noted to have a problem with ' _____ version 1) and leakage (version 1.1). GSK modified the device to version 1.2 to address these issues. Version 1.2 was used during later phase 3 studies and the appropriate CMC information to support version 1.2 (and commercial version 1.3) was provided in the original NDA submission. During the course of the NDA review, GSK modified the device to version 1.4. The CMC team reviewed version 1.2 of the product and finds version 1.2 acceptable with respect to the CMC attributes. Analytical comparison of version 1.2 and version 1.4 devices were not submitted until late into the review cycle. The CMC team has not completed the review regarding the acceptability of version 1.4 of the device at the time of finalization of this review.

III. Pharmacology and Toxicology

GSK submitted results from a full preclinical program with this submission. The program included studies where the animals were dosed with the drug product via inhalation as well as intranasal studies to evaluate local toxicity. The toxicology program for fluticasone furoate was reviewed in detail in the PharmTox review by Dr. Hao. The PharmTox team has determined that the submitted pharmacology/toxicology program is adequate and recommends an approval action. I concur with that recommendation. Brief comments on some key preclinical issues are made in the following paragraphs.

The toxicology program showed that toxicities associated with fluticasone furoate are typical of glucocorticoid effects; however, the following toxicology issue warrants further discussion. Intranasal and inhalation dog toxicology studies showed that fluticasone furoate is associated with bile duct epithelial and gall bladder epithelial vacuolation. GSK convened a Pathology Working Group (PWG) to review the gall bladder data from the toxicology studies and control dogs from other studies. GSK submitted the report from the PWG on October 5, 2006. The PWG concluded that the

treatment related increase in bile duct and gallbladder epithelial vacuolation was not cellular toxicity or an adverse effect based upon the following: 1) vacuolation was a common background finding in beagle dogs; 2) the magnitude of the changes was within the limits observed in historical control dogs; 3) there was no morphologic evidence of cell damage or inflammation; and 4) the changes did not progress with time. The pharmacology/toxicology team accepts the PWG conclusion.

Other toxicology issues included increased eosinophilic inclusions in rat bronchiolar epithelium, focal nephropathy in dogs, and chronic stomach inflammation. Intranasal toxicology studies revealed local lymphoid atrophy and nasal goblet cell hypertrophy. The pharmacology/toxicology team determined these findings were not safety concerns or there was an adequate safety margin present for the toxicity.

Studies addressing genotoxicity, carcinogenicity, and reproductive toxicity did not show any unique findings for fluticasone furoate not seen with other corticosteroids. All genotoxicity studies were negative. Two-year carcinogenicity studies conducted in mice and rats with inhalation dosing were negative. Reproductive toxicology studies with fluticasone furoate in rabbits were negative. The pregnancy category for fluticasone furoate was determined to be Class C, which is same category for many other corticosteroids.

IV. Clinical Pharmacology

GSK submitted results from a comprehensive clinical pharmacology program with this application. The program addressed the key pharmacokinetic issues, including in vitro studies to assess protein binding and metabolism, pharmacokinetics after single and multiple doses, in vitro and in vivo metabolism, effect of hepatic impairment, QTc effect, and drug-drug interaction. Studies in renal impaired patients were not conducted since renal excretion of fluticasone furoate is a minor route of elimination. Clinical pharmacology studies included intranasal, inhalation, oral, and IV administration to fully characterize the pharmacokinetics of fluticasone furoate. These studies are reviewed in **Dr. Al-Habet's review and found to be adequate** to support approval. A brief summary of pertinent findings is contained in the following paragraphs.

Fluticasone furoate is a pharmacologically active ester of fluticasone, which is a glucocorticoid. The binding affinity to the glucocorticoid receptor is greater for fluticasone furoate than for fluticasone propionate. Intranasal fluticasone furoate has low systemic bioavailability (0.55%) and data from oral administration suggests low bioavailability and extensive first pass metabolism. Elimination of fluticasone furoate is primarily via metabolism (hydrolysis) with excretion of the metabolites in the feces. The metabolites generally lack glucocorticoid activity. Urinary excretion is a minor route.

Plasma concentrations of fluticasone furoate after nasal administration were measured in three adult allergic rhinitis studies (FFR20001, FFR20002, FFR102123) and three pediatric allergic rhinitis studies (FFR100010, FFR100012, FFR30008). The lower level of quantification of the assay was 10 pg/mL. In these studies, the majority of subjects did

not have quantifiable concentrations of fluticasone furoate, thus systemic exposure to fluticasone furoate was minimal.

GSK conducted a hepatic impairment study since there is extensive first pass effect and in vitro evidence that CYP3A4 is involved in the metabolism of fluticasone furoate. Plasma Cmax and AUC increased in patients with moderate hepatic impairment (42% and 172%, respectively) following inhalation administration of 400mcg of fluticasone furoate. In addition, a decrease in serum cortisol was noted in these patients compared to healthy subjects. It should be noted that this study was conducted with 400mcg fluticasone furoate via inhalation and the systemic exposure from 110mcg delivered intranasal would be expected to be lower; however, the study is a single dose study and the effects of multiple dose exposure to fluticasone furoate are unknown. Therefore caution should be used in patients with severe hepatic impairment, as metabolism of fluticasone would likely be further delayed in these patients.

Since fluticasone furoate is metabolized by CYP3A4, there is potential for increased exposure when co-administered with a CYP3A4 inhibitor. To evaluate this potential effect, GSK conducted a drug-drug interaction study with 110mcg fluticasone furoate intranasal and 200mg of ketoconazole (CYP3A4 inhibitor). The systemic exposure of fluticasone furoate increased (fluticasone detected in 6 out of 20 subjects versus 1 out of 20 subjects) following co-administration with ketoconazole. It is important to note that this study was conducted with 200mg of ketoconazole, not the maximum dose of 400mg. In addition, data from a fluticasone propionate drug interaction study with ritonavir showed an increased exposure with decrease in cortisol AUC with coadministration. Therefore, caution should be used with co-administration of CYP3A4 inhibitors and fluticasone furoate.

GSK conducted a QTc study with 4000mcg of fluticasone furoate administered via inhalation and 400mg moxifloxacin as a positive control. According to Dr. Al-Habet, the results indicate that there was no significant effect of fluticasone furoate on the QTc interval. However, the consult from the QT Interdisciplinary Review Team is pending at the time of finalization of the review.

HPA-axis function was the primary objective in adult clinical study FFR20002 (6 week PAR) and pediatric clinical study FFR100012 (6 week PAR). These studies were adequately designed to assess the effect of fluticasone furoate on HPA axis function. In addition, HPA axis effect was also assessed in Study FFR102123 (one year safety -adult), **Study FFR30008 (12 week PAR – adult)**, and FFR20001 (2 week dose ranging-adult). While these studies and the findings are discussed in detail later in this review, the conclusions are briefly summarized here. Fluticasone furoate 110mcg intranasal showed no effect on serum cortisol in adults or pediatric patients. There was a numerical decrease in mean 24 hour urinary cortisol with fluticasone furoate in pediatric patients. However, no patients had urine cortisol levels below the normal range; therefore, there was no evidence of HPA-axis suppression.

V. Clinical and Statistical

A. Overview of the clinical program

The clinical program for fluticasone furoate nasal spray was typical of a new product being developed for allergic rhinitis. Unique aspects to this application include GSK's proposal to include information about ocular symptoms in the product label and to include information about the RhinoConjunctivitis Quality of Life Questionnaire (RQLQ) in the product label. The pivotal clinical studies submitted to support efficacy and safety of fluticasone furoate nasal spray in adults and adolescent patients 12 years and older with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) included one 2-week dose ranging study in SAR patients (Study FFR20001), three 2-week studies in SAR patients (Studies FFR30003, FFR103184, FFR104861), one 4-week study in PAR patients (Study FFR30002), one 52-week long-term safety study in PAR patients (Study FFR102123), one 6-week HPA axis study (Study FFR20002), and one onset of action allergen chamber study in SAR patients (Study FFR101816). The results of two VMR studies were submitted in the 120 day safety update; however, GSK did not seek a nonallergic rhinitis indication in this application.

Pivotal clinical studies submitted to support efficacy and safety in pediatric patients included one 12-week study in PAR patients 2 to <12 years of age (Study FFR30008), one 2-week study in SAR patients 2 to <12 years of age (Study FFR100010) and one 6-week/HPA axis study in PAR patients 2 to <12 years of age (Study FFR100012). In addition, one 2-week knemometry study in SAR/PAR patients 6 to 11 years of age was conducted to assess the effects of fluticasone furoate on short-term lower leg growth (Study FFR101747).

Detailed review of the clinical program can be found in Dr. Durmowicz's medical review with detailed statistical analysis in Ms. Feng's statistical review. The clinical and statistical teams concluded that the submitted studies support efficacy and safety of fluticasone furoate nasal spray in patients 2 years and older. I concur with that conclusion. The pivotal clinical studies mentioned above, which have direct bearing on the approvability decision of this application are briefly reviewed in the following sections.

B. Design and conduct of the pivotal efficacy and safety studies

1. Dose-ranging study (Study FFR20001)

Study FFR20001 was a double-blind, placebo-controlled, parallel group study conducted in 8 centers in Texas during the mountain cedar allergy season in patients 12 years of age and older with a history of SAR. The study had at least a 5 day screening period, followed by 2-week double blinded treatment period. The treatment arms were fluticasone furoate nasal spray 440 mcg, fluticasone furoate spray 220 mcg, fluticasone furoate nasal spray 110 mcg, fluticasone furoate nasal spray 55 mcg, and placebo nasal spray, once daily in the morning. The primary efficacy variable was reflective patient scoring of four nasal symptoms, rTNSS, (Total Nasal Symptom Score - rhinorrhea, nasal congestion, nasal itching, and sneezing) twice daily (AM and PM) on a four point scale

(0=absent, 1=mild, 2=moderate, and 3=severe). The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily, rTNSS i.e. the average of AM + PM rTNSS averaged over the 2-week treatment period. The study was designed to have 118 patients per treatment arm to give 90% power to detect a 0.85 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05.

A secondary efficacy variable included scoring of three ocular symptoms (Total Ocular Symptom Score - eye itching/burning, eye tearing/watering, and eye redness) twice daily using the same four point scale for the TNSS. Additional efficacy variables included instantaneous TNSS to assess efficacy at the end of dosing interval, individual TNSS symptoms, overall response to therapy, and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). The RQLQ is a 28 item disease specific (allergic rhinitis) quality of life instrument with seven domains (activity limitations, sleep problems, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional function). An overall QOL score is calculated from the mean of all items. A mean change from baseline of 0.5 or more for the RQLQ score is considered beneficial.

Safety assessment included recording of adverse events, vital signs, clinical laboratory measures, ECG, nasal examinations, and 24 hour urinary cortisol measurements. A total of 642 patients were randomized approximately equally to the five treatment arms and 620 patients (97%) completed the study. There were no preferential discontinuations in any treatment arms.

2. Adult & Adolescent Efficacy and Safety Studies

SAR - Studies FFR30003, FFR103184, FFR104861, FFR30002

Studies FFR30003, FFR103184, and FFR104861 were randomized, double-blind, placebo-controlled, parallel group studies in patients with SAR. The studies were identical in design except the patient population differed by allergen: Study FFR30003 - mountain cedar allergy; Study FFR103184 - grass allergy; and Study FFR104861 - ragweed allergy. The studies were conducted in centers in Texas and Europe in patients 12 years of age and older with history of SAR and positive sensitivity to the respective allergen by skin or RAST test. The studies had a 5-21 day screening period, followed by a 2-week double blind treatment period. The treatment arms were fluticasone furoate nasal spray 110 mcg and placebo nasal spray, both dosed in the morning. The intent of the studies was to confirm the efficacy of the 110 mcg dose seen in Study FFR20001.

The primary efficacy variable was the reflective nasal symptom score, rTNSS, (rhinorrhea, nasal congestion, nasal itching, and sneezing) recorded by the patient twice daily (AM and PM) on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). Other efficacy variables included instantaneous patient recording of the same symptoms, iTNSS, on the same scale, three eye symptoms (Total Ocular Symptom Score (TOSS) - eye itching/burning, eye tearing/watering, and eye redness) twice daily using the same four point scale for the TNSS, Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ) assessment at week 2, and an overall response to therapy (7 point scale). The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily rTNSS (i.e. the average of AM + PM rTNSS averaged over the 2 weeks of

treatment). Key secondary endpoints were the mean change from baseline iTNSS and rTOSS over the entire treatment period. To assess the onset of action, iTNSS was measured at 4, 6, 8, 10, and 12 hours post first dose and daily thereafter. The studies were designed to have approximately 144 patients per treatment arms to give 90% power to detect a 1.0 unit mean difference for the primary efficacy endpoint with a two-sided alpha-level of 0.05. Safety assessment included recording of adverse events, vital signs, physical examination specifically looking for nasal findings, clinical laboratory measures, and ECGs. Approximately 300 (285-302) patients were randomized in each of the three studies to the two treatment arms and approximately 95% of patients completed each study.

PAR – Study FFR30002

Study FFR30002 was a randomized, double-blind, placebo-controlled, parallel group study conducted in 47 centers in the United States and Canada in patients 12 years of age and older with history of PAR and positive sensitivity test to relevant allergen by skin test. The study had a 7-14 day screening period, followed by a 4-week double blind treatment period. The treatment arms were fluticasone furoate nasal spray 110 mcg, and placebo nasal spray, both dosed in the morning. The intent of the study was to assess if the efficacy of the 110 mcg dose seen in Study FFR20001 in subjects with SAR also pertained to subjects with PAR. Efficacy and safety variables were similar to the SAR studies described above with the notable difference that the primary efficacy endpoint was assessed over the 4 weeks of treatment. The study was designed to have 144 patients per treatment arms to give 90% power to detect a 1.0 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. A total of 302 patients were randomized approximately equally to the two treatment arms and 279 patients (92%) completed the study. There were no preferential discontinuations in any treatment arms.

3. Pediatric Efficacy and Studies (Studies FFR100010, FFR30008)

Study FFR100010 was a randomized, double-blind, placebo-controlled, parallel group study conducted in 57 centers in the United States in patients 2 to <12 years of age with history of SAR and positive sensitivity to relevant allergen by skin test. The study had a 5-21 day screening period, followed by 2-weeks double blind treatment period. The treatment arms were fluticasone furoate nasal spray 110 mcg, fluticasone furoate nasal spray 55 mcg, and placebo nasal spray dosed once daily in the morning. The primary efficacy variable was reflective patient scoring of four nasal symptoms, rTNSS, either subject or parent/guardian rated. The other efficacy variables assessed included iTNSS, TOSS, and overall response to therapy. The primary efficacy endpoint was the change from baseline in daily rTNSS over the entire treatment period in patients 6 to <12 years. The study was designed to have 192 patients per treatment arms (approximately 48 age 2 to <6 years) to give 90% power to detect a 1.0 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. Safety assessment included recording of adverse events, vital signs, physical examination (including nasal examination), clinical laboratory measures, and ECGs. Pharmacokinetic assessment was done in all patients. A total of 554 patients were randomized approximately equally to the treatment arms and 536 (97%) completed the study. In terms of stratification, 448

patients were 6 to < 12 years of age and 105 patients were 2 to < 6 years of age. There were no preferential discontinuations in any treatment arms.

Study FFR30008 was a randomized, double-blind, placebo-controlled, parallel group study conducted in a 61 study centers in the US, Europe, Mexico, and South America in patients 2 to < 12 years of age with a history of PAR and positive sensitivity to relevant allergen. The study had a 7-14 day screening period, followed by 12-week double blind treatment period. The treatment arms were fluticasone furoate nasal spray 110 mcg, fluticasone furoate nasal spray 55 mcg, and placebo nasal spray dosed once daily in the morning. The primary objective of the study was to establish the efficacy and safety of fluticasone furoate nasal spray in children with PAR. The primary efficacy variable was reflective patient scoring of four nasal symptoms, rTNSS, either subject or parent/guardian rated. The primary efficacy endpoint was the change from baseline in daily rTNSS over the first 4 weeks of the treatment period in patients 6 to <12 years. The other efficacy variables assessed included iTNSS and overall response to therapy over the first 4 weeks of the treatment period. Safety assessment included recording of adverse events, vital signs, physical examination (including nasal examination), clinical laboratory measures, 24-hour urinary cortisol, ECGs, and ophthalmic evaluation (slit-lamp evaluation for cataracts and changes in IOP). Pharmacokinetic assessment was performed in all patients. Compliance was assessed by efficacy data (diary cards) and bottle weights. A total of 558 patients were randomized approximately equally to the treatment arms and 492 (88%) completed the study. In terms of stratification, 434 patients were 6 to < 12 years of age, 120 patients were 2 to < 6 years of age, and 4 patients were ≥ 12 years of age. There were no significant preferential discontinuations in any treatment arms.

4. 52-week safety study (Study FFR102123)

Study FFR102123 was a randomized, double-blind, placebo-controlled, parallel group, safety study conducted in 75 centers in 13 countries in patients 12 years of age and older with PAR. The study had a 7-14 day screening period where eligibility was determined, followed by 12 months of double blind treatment with either fluticasone furoate nasal spray 110 mcg or placebo once daily in the morning. Safety was assessed by recording of adverse events, vital signs, physical examination (including nasal examination), clinical laboratory measures, HPA axis assessment (24 hour urinary cortisol), and eye examination. Eye examinations were performed by an ophthalmologist or optometrist and included visual acuity, slit-lamp, fundoscopic exam, and intraocular pressure evaluation. HPA axis assessment and eye examination were performed at baseline, Week 12, 24, and 52. There were pre-defined criteria for adequacy of the non-domiciled 24 hour urine collections. Pharmacokinetic assessment of fluticasone furoate plasma concentrations was performed. Efficacy was assessed by recording of TNSS for evaluation of compliance. Compliance was also assessed with bottle weights.

5. ACC Onset-of-Action Study (Study FFR101816)

Study FFR101816 was a randomized, double-blind, placebo-controlled, parallel group, allergen challenge study conducted in a single center in Marietta, Georgia in patients 12 years of age and older with SAR with sensitivity to ragweed. Study FFR101816 was

primarily designed to evaluate the onset of action for fluticasone furoate nasal spray. Eligible patients were primed in the allergen chamber twice, and patients who met the eligibility criteria of a predefined minimum nasal symptom score were exposed to the allergen on the test day and administered a single dose fluticasone furoate nasal spray 110 mcg or placebo nasal spray. Efficacy was assessed by hourly patient scoring of four nasal symptoms, iTNSS, (rhinorrhea, nasal congestion, nasal itching, and sneezing) on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe) for 12 hours following study medication administration. A total of 382 patients were randomized and 380 completed the study.

6. HPA-axis safety studies

Adults and Adolescents - Study FFR20002

Study FFR20002 was a 6-week, randomized, double-blind, placebo-controlled, active-controlled, parallel group study conducted in two centers (San Antonio, Texas and Ontario, Canada) in patients 12 years of age and older with PAR. The objective of this study was to evaluate the effect of fluticasone furoate 110mcg nasal spray on the HPA axis. There were 3 treatment groups: fluticasone furoate 110mcg once daily, placebo once daily, and prednisone as the active control (one week). HPA axis function was assessed by plasma cortisol and urinary cortisol assessment by collection of samples over 24 hours (domiciled) at baseline and the end of the treatment periods. Plasma samples were collected for fluticasone furoate on the last treatment day. Efficacy was assessed by patient diaries for the purpose of evaluating compliance. A total of 112 subjects with a mean age of 36 years were randomized in this study as follows: 48 to the fluticasone furoate group; 13 to the prednisone group; and 51 to the placebo group.

Pediatric – Study FFR100012 and FFR30008 (discussed above)

Study FFR100012 was a 6 week, randomized, double-blind, placebo-controlled, parallel design study conducted in ten centers in the United States in patients 2 to < 12 years of age with PAR. The objective of this study was to evaluate the effect of fluticasone furoate 110mcg nasal spray on the HPA axis. There were 2 treatment groups: fluticasone furoate 110mcg once daily and placebo once daily. HPA axis function was assessed by serum cortisol level and urinary cortisol assessment by collection of samples over 24 hours (domiciled) at baseline and the end of the treatment period. Plasma samples were collected for fluticasone furoate on the last treatment day. Efficacy was assessed by patient diaries for the purpose of evaluating compliance. A total of 112 patients with a mean age of 6.3 years were randomized in this study as follows: 57 to the fluticasone furoate group and 55 to the placebo group. One hundred five patients completed the study. The majority of the patients were 6 to < 12 years of age (59%), while approximately 20% of patients were 2 to < 4 years and 4 to < 6 years of age.

C. Efficacy Findings and Conclusions

The submitted studies support the efficacy of fluticasone furoate nasal spray in patients with SAR and PAR ages 2 years and older.

Adults and Adolescents

In the dose ranging study conducted in patients 12 years of age and older (Study FFR20001) a clear dose-related increase in efficacy was not observed, which is not unexpected for a nasal corticosteroid. All doses of fluticasone furoate demonstrated a statistically significant difference from placebo in the change from baseline rTNSS (Table 1). Pre-dose iTNSS is a measure of end-of-dosing interval efficacy that supports the dosing frequency. For change from baseline pre-dose iTNSS, there was a statistically significant difference from placebo for all four treatment groups with the same numerical trend as the primary endpoint (220mcg < 55mcg < 110mcg < 440mcg). Additional secondary endpoints were also supportive of all four fluticasone furoate doses. There were similar safety profiles between the dose groups.

Table 1. Study FFR20001. Mean Baseline and LS Mean Change from Baseline Reflective AM+PM TNSS and AM Instantaneous TNSS						
Reflective AM+PM TNSS over 2 weeks (SAR)						
Treatment	n	Baseline	Change from Baseline	Difference from Placebo		
				LS Mean	95% CI	p-value
Fluticasone Furoate 440 mcg	130	9.6	-4.02	-2.19	-2.75, -1.62	< 0.001
Fluticasone Furoate 220 mcg	129	9.5	-3.19	-1.36	-1.93, -0.79	< 0.001
Fluticasone Furoate 110 mcg	127	9.5	-3.84	-2.01	-2.58, -1.44	< 0.001
Fluticasone Furoate 55 mcg	127	9.6	-3.50	-1.68	-2.25, -1.11	< 0.001
Placebo	128	9.6	-1.83			
Mean Baseline and LS Mean Change from Baseline Instantaneous AM TNSS over 2 weeks (SAR)						
Treatment	n	Baseline	Change from Baseline	Difference from Placebo		
				LS Mean	95% CI	p-value
Fluticasone Furoate 440 mcg	130	9.1	-3.36	-2.22	-2.77, -1.66	< 0.001
Fluticasone Furoate 220 mcg	129	9.2	-2.57	-1.42	-1.98, -0.86	< 0.001
Fluticasone Furoate 110 mcg	127	9.3	-3.03	-1.89	-2.45, -1.32	< 0.001
Fluticasone Furoate 55 mcg	127	9.1	-2.74	-1.59	-2.15, -1.02	< 0.001
Placebo	128	9.2	-1.15			

To understand the rationale for selecting the 110mcg dose group, the following should be noted. For the AM iTNSS, the 55 mcg dose group was not statistically significant. The onset of action was faster in the 110mcg and 440mcg dose groups. Although the 440mcg dose group provided the largest numerical improvement in symptom scores, the difference between the 110mcg and 440mcg group was minimal. Finally, there were a smaller proportion of patients with detectable fluticasone furoate levels in the 110mcg group compared to the 440mcg group. Therefore, GSK selected the 110mcg dose as the appropriate clinical dose.

The 110 mcg once daily dose was further studied to confirm its efficacy in three SAR and one PAR study in patients 12 years of age and older. In all of these studies the 110 mcg dose of fluticasone furoate was statistically superior to placebo in the primary efficacy endpoint of rTNSS, and also for iTNSS (Table 2). The AM iTNSS supports this particular dose and the dosing frequency. Supportive evidence of efficacy was seen in the one-year safety study (Study FFR102123). In that study, over the one-year treatment period, the change from baseline rTNSS was -3.3 in the fluticasone furoate group compared to -2.5 in the placebo group. However, no statistical analyses were performed.

Table 2 Adult SAR and PAR Studies Primary and Key Secondary Endpoints						
Treatment	n	Baseline	Change from Baseline – LS Mean	Difference from Placebo		
				LS Mean	95% CI	p-value
Primary Endpoint - Reflective TNSS, AM+PM Score						
Study FFR30003 (SAR – Mountain Cedar)						
Fluticasone Furoate 110 mcg	152	9.8	-3.03	-0.78	-1.28, -0.27	0.003
Placebo	150	9.7	-2.25			
Study FFR103184 (SAR - Grass)						
Fluticasone Furoate 110 mcg	141	8.3	-4.94	-1.76	-2.28, -1.23	<0.001
Placebo	144	8.4	-3.18			
Study FFR104861 (SAR - Ragweed)						
Fluticasone Furoate 110 mcg	151	9.6	-3.55	-1.47	-2.01, -0.94	<0.001
Placebo	148	9.9	-2.07			
Study FFR30002 (PAR)						
Fluticasone Furoate 110 mcg	149	8.6	-2.78	-0.71	-1.20, -0.21	0.005
Placebo	153	8.7	-2.08			
Secondary Endpoint - Instantaneous TNSS, AM Score						
Study FFR30003 (SAR – Mountain Cedar)						
Fluticasone Furoate 110 mcg	152	9.4	-2.38	-0.90	-1.38, -0.42	<0.001
Placebo	150	9.5	-1.47			
Study FFR103184 (SAR - Grass)						
Fluticasone Furoate 110 mcg	141	8.1	-4.50	-1.90	-2.42, -1.38	<0.001
Placebo	144	8.3	-2.60			
Study FFR104861 (SAR - Ragweed)						
Fluticasone Furoate 110 mcg	151	9.4	-2.90	-1.38	-1.90, -0.85	<0.001
Placebo	148	9.3	-1.53			
Study FFR30002 (PAR)						
Fluticasone Furoate 110 mcg	149	8.2	-2.45	-0.71	-1.20, -0.21	0.006
Placebo	153	8.3	-1.75			

Efficacy of the 110 mcg dose of fluticasone furoate was also supported by secondary endpoints. GSK seeks an indication for symptoms of PAR and SAR, not just nasal symptoms. To support this broader indication, a secondary efficacy variable included scoring of three ocular symptoms (Total Ocular Symptom Score (TOSS) - eye itching/burning, eye tearing/watering, and eye redness) twice daily using the same four point scale for the TNSS. As shown below in Table 3, adult patients treated with fluticasone furoate 110mcg demonstrated a statistically significant improvement in rTOSS compared to placebo in all 3 SAR studies; however, there was no significant improvement in rTOSS in adult patients with PAR. The improvement in rTOSS in the SAR studies supports the effectiveness of fluticasone furoate in treating eye symptoms in patients with SAR, but not PAR. However, the negative results for the PAR study should be included in the label.

An additional efficacy variable was the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). The RQLQ is a 28 item disease specific (allergic rhinitis) quality of life instrument with seven domains (activity limitations, sleep problems, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional function). Initially, the statistical reviewer raised concerns with the amount of missing data (26-

52%) in some of the activity domains of the RQLQ. The statistical reviewer recommended re-analysis of the data for the activity domain if the text entries at baseline and endpoint had the same meaning, even if there was not 100% match (e.g. walk vs. taking a walk). The statistical reviewer confirmed the re-analysis of the RQLQ data and the sensitivity analyses. As shown below in Table 3, adult patients treated with fluticasone furoate 110mcg demonstrated a statistically significant improvement in RQLQ compared to placebo in all 3 SAR studies, but not the PAR study. The treatment group difference in each of the SAR studies was >0.5, which is believed to be the MID.

Table 3 Adult SAR and PAR Studies Key Secondary Endpoints						
Treatment	n	Baseline	Change from Baseline – LS Mean	Difference from Placebo		
				LS Mean	95% CI	p-value
Reflective TOSS, AM+PM Score						
Study FFR30003 (SAR – Mountain Cedar)						
Fluticasone Furoate 110 mcg	152	6.6	-2.15	-0.55	-0.95, -0.14	0.008
Placebo	150	6.5	-1.60			
Study FFR103184 (SAR - Grass)						
Fluticasone Furoate 110 mcg	141	5.4	-3.00	-0.74	-1.14, -0.34	<0.001
Placebo	144	5.3	-2.26			
Study FFR104861 (SAR - Ragweed)						
Fluticasone Furoate 110 mcg	151	6.6	-2.23	-0.60	-1.01, -0.19	0.004
Placebo	148	6.5	-1.63			
Study FFR30002 (PAR)						
Fluticasone Furoate 110 mcg	149	4.8	-1.39	-0.15	-0.52, 0.22	0.428
Placebo	153	5.0	-1.24			
RQLQ (Re-analyzed activities domain included)						
Study FFR30003 (SAR – Mountain Cedar)						
Fluticasone Furoate 110 mcg	149	4.1	-1.66	-0.69	-1.08, -0.30	<0.001
Placebo	149	4.1	-0.97			
Study FFR103184 (SAR - Grass)						
Fluticasone Furoate 110 mcg	137	3.5	-2.23	-0.70	-0.99, -0.41	<0.001
Placebo	140	3.5	-1.53			
Study FFR104861 (SAR - Ragweed)						
Fluticasone Furoate 110 mcg	144	3.9	-1.77	-0.60	-0.93, -0.28	<0.001
Placebo	144	3.9	-1.16			
Study FFR30002 (PAR)						
Fluticasone Furoate 110 mcg	143	3.5	-1.41	-0.23	-0.59, 0.13	0.214
Placebo	151	3.4	-1.18			

Based upon review of the submitted data, the recommended dose of fluticasone furoate nasal spray in adults and adolescents 12 years and older is 110 mcg once daily.

Pediatric

To support efficacy in patients 2 to 11 years of age, results from two studies (Studies FFR100010 and FFR30008) were submitted. The intent of the pediatric program was to demonstrate efficacy in children 6 to 11 years of age, and support efficacy in children 2 to 5 years. Study FFR100010 was conducted in patients with SAR and the primary analysis was performed on children 6 to < 12 years. Study FFR30008 was conducted in

patients with PAR and the primary analysis was performed on children 6 to < 12 years. Additional analyses were performed for the entire 2 to 11 years population to support efficacy in children 2 to 5 years of age.

Although the results of the pediatric studies are not consistent, the results support the effectiveness of fluticasone furoate nasal spray in children 2 to < 12 years of age. As shown in the table below, in Study FFR100010 (SAR), there was a statistically significant difference between the fluticasone furoate 110mcg group versus placebo in terms of the rTNSS and AM iTNSS endpoints. While there was a numerical decrease in the TNSS in the 55mcg group, the difference from placebo was not statistically significant. The results were similar when analyzed for the entire 2 to < 12 year population. In terms of the rTOSS, there was no statistically significant difference in either treatment group compared to placebo.

In Study FFR30008 (PAR), there was a statistically significant difference between the fluticasone furoate 55mcg group versus placebo in terms of the rTNSS endpoint. While there was a numerical decrease in the rTNSS in the 110mcg group, the difference from placebo was not statistically significant. The rTNSS results were significant for both treatment groups when analyzed for the 2 to < 12 year population and post-hoc analysis of the rTNSS for the entire 12 week treatment period; however, the 55mcg group had a greater numerical decline in the rTNSS. In terms of the AM iTNSS endpoint, both treatment groups showed a statistically significant difference compared to placebo.

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Table 4. Pediatric SAR and PAR Studies Primary and Key Secondary Endpoints						
Treatment	n	Baseline	Change from Baseline	Difference from Placebo		
				LS Mean	95% CI	p-value
Primary Endpoint - Reflective TNSS, AM+PM Score						
Study FFR100010 (SAR- Grass and Ragweed) in 6 to < 12 years – 2 weeks						
Fluticasone Furoate 110 mcg	146	8.5	-3.16	-0.62	-1.15, -0.08	0.025
Fluticasone Furoate 55 mcg	152	8.6	-2.71	-0.16	-0.69, 0.37	0.553
Placebo	150	8.4	-2.54			
Study FFR30008 (PAR) in 6 to < 12 years – 4 weeks						
Fluticasone Furoate 110 mcg	140	8.6	-3.86	-0.45	-0.95, 0.04	0.073
Fluticasone Furoate 55 mcg	144	8.5	-4.16	-0.75	-1.24, -0.27	0.003
Placebo	147	8.5	-3.41			
Instantaneous TNSS, AM Score						
Study FFR100010 (SAR- Grass and Ragweed) in 6 to < 12 years						
Fluticasone Furoate 110 mcg	146	8.3	-2.8	-0.67	-1.21, -0.13	0.015
Fluticasone Furoate 55 mcg	152	8.4	-2.4	-0.23	-0.77, 0.30	0.389
Placebo	150	8.4	-2.2			
Study FFR30008 (PAR) in 6 to < 12 years – 4 weeks						
Fluticasone Furoate 110 mcg	140	8.3	-3.52	-0.65	-1.14, -0.16	0.009
Fluticasone Furoate 55 mcg	144	8.3	3.62	-0.75	-1.24, -0.27	0.002
Placebo	147	8.3	-2.87			
Reflective TOSS, AM+PM Score (not key secondary EP)						
Study FFR100010 (SAR- Grass and Ragweed) in 6 to < 12 years						
Fluticasone Furoate 110 mcg	146	4.1	-1.45	-0.15	-0.52, 0.22	0.426
Fluticasone Furoate 55 mcg	152	4.4	-1.26	0.04	-0.33, 0.41	0.826
Placebo	150	3.8	-1.30			

In summary, although 110mcg fluticasone furoate was effective in pediatric patients with SAR, the 55mcg dose did demonstrate a numerical improvement in the rTNSS and the 55mcg dose was effective in pediatric patients with PAR. Together, the results of the pediatric SAR and PAR studies support the effectiveness of fluticasone furoate in this population and support the strategy of initiating therapy with the 55mcg once daily and increasing to 110mcg if improvement does not occur. However, there was no effect of fluticasone furoate on ocular symptoms of allergic rhinitis as measured by the rTOSS in pediatric patients with SAR.

Onset of Action

Results from one allergen chamber study (Study FFR10186) in SAR patients were submitted to support a pharmacodynamic onset of action claim for fluticasone nasal spray 110 mcg once daily. For regulatory purposes, onset of action is defined as the first time point, replicated in two studies, where the difference between the active treatment and placebo in efficacy measure is statistically significant and the difference persists consistently after that time point. It is also expected that the difference would be clinically meaningful. In Study FFR10186, the difference between a single dose of fluticasone furoate nasal spray 110 mcg and placebo nasal spray for iTNSS was not significant at any timepoint. Thus, the onset of action was not demonstrated in this study.

Onset of action was also assessed in the pivotal adult studies. Onset of action was defined as the time when the mean change from baseline in iTNSS in the fluticasone furoate group was significantly greater than placebo and remained significantly greater. In the pivotal studies, the onset of action ranged from 8-24 hours in the SAR studies to day 4 in the PAR study.

D. Safety findings and conclusions

The submitted studies support the safety of fluticasone furoate nasal spray 110 mcg once daily in patients with SAR and PAR ages 2 years and older. The overall safety database for fluticasone nasal spray includes 2618 subject ages 2 years of and older who received any dose of fluticasone furoate nasal spray. In any clinical program, placebo-controlled repeat-dose studies are generally more useful for safety assessment because these studies allow some ascertainment of drug effect. Such studies for the fluticasone furoate nasal spray program included one 2-week dose ranging study in SAR patients (Study FFR20001), three 2-week studies in SAR patients (Studies FFR30003, FFR103184, FFR104861), one 4-week study in PAR patients (Study FFR30002), one 52-week long-term safety study in PAR patients (Study FFR102123), and one 6-week HPA axis study (Study FFR20002). In pediatric patients, pertinent studies included one 12-week study in PAR patients 2 to <12 years of age (Study FFR30008), one 2-week study in SAR patients 2 to <12 years of age (Study FFR100010), one 6-week/HPA axis study in PAR patients 2 to <12 years of age (Study FFR100012) and one 2-week knemometry study in SAR/PAR patients 6 to 11 years of age (Study FFR101747).

In these studies (dose ranging, SAR(3), PAR, HPA axis), a total of 768 patients ages 12 and older received fluticasone furoate nasal spray at the dose of 110 mcg once daily for duration of 2 to 12 weeks. In the one-year study (Study 102123) 605 patients ages 12 and older received fluticasone furoate 110 mcg once-daily. These exposure numbers are reasonable for safety assessment in patients 12 years of age and older.

For the pediatric population, a total of 369 and 484 pediatric subjects 2 to < 12 years of age received fluticasone furoate nasal spray at the dose of 55mcg once daily and 110mcg once daily. Of these there were 72 and 104 patients ages 2 to < 6 years of age who received 55mcg and 110mcg fluticasone furoate once daily, respectively. The pivotal safety and efficacy studies in pediatric patients (Studies FFR100010 and FFR30008) included a total of 1112 patients, of which 369 patients received 55mcg and 369 patients received 110mcg fluticasone furoate once daily. These exposure numbers are reasonable for safety assessment in patients 2 years to < 12 years of age.

In the controlled clinical studies, fluticasone furoate nasal spray was generally well tolerated. There were no deaths in any of the studies. Serious adverse events were not common and not of a type that could be ascribed to corticosteroid treatment. Review of vital signs, clinical laboratory tests, and ECG did not show any safety signals of concern. The common adverse events associated with fluticasone furoate were epistaxis, nasopharyngitis, nasal dryness, and nasal septum ulceration. Epistaxis was the most common AE leading to withdrawal in the one year study. These are adverse events not uncommon for nasal corticosteroids. However, nasal examination showed that mucosal

crusting, mucosal bleeding, and ulcers were more common in the fluticasone furoate treatment group. In addition, there was clinical evidence of nasal candidiasis in two patients in the fluticasone furoate group in the one year study, four patients in the fluticasone furoate groups in the 12 week pediatric PAR study (Study FFR30008), and one patient in the dose ranging study (Study 20001). Three of these cases were reported as AEs and 2 led to withdrawal from the study.

HPA Axis Findings

Specific evaluation of HPA-axis in the fluticasone furoate nasal spray program was performed in two clinical studies: Study FFR20002 in adolescents/adults and Study FFR100012 in pediatric patients. These studies were of adequate duration, included pharmacokinetic sampling of fluticasone furoate, and assessed HPA axis by 24 hour urinary cortisol from domiciled patients. Criteria were specified for adequacy of urine sample. Study FFR20002 (adults/adolescents) included a positive control arm, but Study FFR100012 did not (pediatric), which is acceptable. Although fluticasone furoate plasma levels were measured, compliance was supported by bottle weight and efficacy assessments.

In addition, HPA axis assessments were performed in the one year safety study in adults/adolescents (Study FFR102123) and the 12 week PAR study in children (Study FFR30008). Studies FFR102123 and FFR30008 did not include as rigorous assessment of the HPA axis, but they provide some information about the effects of fluticasone furoate nasal spray following longer term use. Overall, HPA axis assessment in the fluticasone furoate nasal spray clinical program was adequate.

Study FFR20002 showed that fluticasone furoate did not have a significant effect on serum cortisol levels in adults/adolescents. The urine cortisol data showed a numerically greater reduction in the fluticasone furoate group compared to placebo as shown in the table below. Two patients in the fluticasone group were outliers with large reductions in urinary cortisol. Both patients had abnormally high urinary cortisol levels at baseline (573 and 651nmol/24 hours) and the levels remained within normal limits or high at the 6 weeks endpoint. Compliance was supported by bottle weights and the efficacy results since the fluticasone furoate treatment group had a numerically greater symptom improvement compared to the placebo group. The active control group showed a decrease in serum cortisol and verifies the internal validity of the study, which is important because 24 hour urinary cortisol data were not available for the prednisone group because of assay interference.

Study FFR100012 showed that fluticasone furoate did not have a significant effect on serum cortisol levels. The mean urine cortisol data showed no significant effect in the fluticasone furoate group as shown in the table below. Two patients in the fluticasone group and one in the placebo group were outliers with large reductions in urinary cortisol; however, all three patients had abnormally high values at baseline that normalized at endpoint. Compliance was supported by weighing the bottles. In addition, efficacy results were supportive of compliance as the fluticasone furoate treatment group had a numerically greater symptom improvement compared to the placebo group.

Table 5- 24 Hour Urinary Cortisol Excretion (nmol/day) Geometric Mean						
Treatment	n	Weeks of Treatment	Baseline	End of Treatment	Change from Baseline	Ratio from Baseline
FFR20002 – 6 week HPA axis study in adults/adolescents						
Fluticasone Furoate 110mcg	43	6	73.13	65.14	-16.68	0.89
Placebo	42	6	54.42	58.40	5.03	1.07
FFR100012 – 6 week HPA axis study in pediatrics						
Fluticasone Furoate 110mcg	43	6	25.06	24.43	-1.47	0.97
Placebo	41	6	22.35	28.20	5.93	1.26
FFR102123 – 52 week long term safety study						
Fluticasone Furoate 110mcg	370	52	57.06	64.80	21.53	1.14
Placebo	120	52	58.27	66.00	14.33	1.13
FFR30008 – 12 week PAR study in pediatrics						
Fluticasone Furoate 55mcg	109	12	34.70	29.03	-6.95	0.97
Fluticasone Furoate 110mcg	103	12	38.91	30.59	-12.67	0.88
Placebo	107	12	39.98	35.81	-2.94	0.91

Study FFR30008 was a 12 week study in PAR patients age 2 to 12 years. HPA axis was evaluated by 24 hour urine cortisol on 6 to < 12 year old patients who met pre-defined criteria (urine cortisol population). Fluticasone furoate was generally not detectable in the plasma of any patients; however, compliance was confirmed by weighing the bottles and the efficacy results support patient compliance. The results of the 24 hour urinary cortisol show that there was a dose related decrease from baseline in the fluticasone furoate groups, which suggests an effect on the HPA axis. However, no patients had a urinary cortisol level below the lower limit of normal; therefore, there is no evidence of HPA axis suppression.

In the one-year safety study in adults and adolescents (Study FFR102123), a total of 810 patients were randomized in a 3:1 ratio to the fluticasone furoate nasal spray (605) and placebo nasal spray (201) treatment arms, respectively and 592 patients (73%) completed the study. The mean age was 32 years. There were no preferential discontinuations in any treatment arms. Pharmacokinetic results showed only 13% of samples with quantifiable levels of fluticasone furoate. However, medication compliance was supported by the efficacy results and bottle weights. HPA axis was evaluated by 24 hour urine cortisol on patients who met pre-defined criteria (urine cortisol population). The proportion of patients who met the criteria was similar between treatment groups. The results show that fluticasone furoate had no significant effect on the HPA axis based upon the urine cortisol data as shown in the table above.

Overall, HPA axis assessment in the fluticasone furoate nasal spray clinical program was adequate. The results of the above studies show that there was no statistically significant effect of fluticasone furoate nasal spray on serum cortisol levels and on urinary cortisol levels in adults. While an effect on the HPA axis was suggested by the urinary cortisol data in the pediatric studies, there were no subjects with urinary cortisol levels outside the normal range. Thus, there was no evidence of HPA axis suppression in pediatric patients.

Ophthalmologic Findings

Ophthalmologic examination was performed in the one-year safety study in adults and adolescents (Study FFR102123). The mean change in intraocular pressure was similar between treatment groups; however, there were more patients in the fluticasone furoate group who had a shift to ≥ 21 mmHg (GSK defined threshold) than in the placebo group. Seven patients (6 fluticasone furoate (1%), 1 placebo (<1%)) were noted to have cataracts in ophthalmic examination during the study that were not present at baseline; three of the cataracts were posterior subcapsular cataracts (2 fluticasone furoate (<1%) and 1 placebo (<1%)). The two patients who developed subcapsular cataracts in the fluticasone furoate treatment group were 14 and 15 years of age. Because of the ophthalmic findings, an ophthalmology consult was requested. Dr. Wiley Chambers reviewed the ophthalmologic findings from Study FFR102123. His review of the optic cup to disk ratio measurement, in his opinion, called into question the quality of the ocular examinations. In addition, Dr. Chambers noted that the development of new cataracts noted at the end of the one-year safety study in 3 healthy young subjects treated with fluticasone furoate was highly suggestive of the cataracts being related to the drug treatment. Also, while no changes in mean IOP were noted, a number of patients, all in the active treatment group had elevations in intraocular pressure. He recommended the labeling reflect these findings.

In addition, ophthalmologic examination was performed in Study FFR30008. Pertinent findings included new cataracts in 4 patients in the fluticasone furoate groups and in 2 patients in the placebo group.

Device Issues

GSK reported device malfunctions from the clinical trials. Clinical trials were performed with both device versions 1.1 and 1.2. Overall, the main device malfunction reported was leakage. There were approximately 12,502 version 1.1 devices used in the clinical trials and approximately 2.9% substantiated reports of device malfunction were noted, with the majority due to leakage. With version 1.2 of the device, there were approximately 2371 devices used in the clinical studies and only 0.2% substantiated reports of device malfunction. For a nasal spray, leakage is likely to be more of an inconvenience than a safety issue and the percent of device malfunction is acceptable.

Data Quality, Integrity, and Financial Disclosure

A DSI audit was not requested because there was no evidence for a treatment by site interaction and investigators with a significant financial interest enrolled few patients. In addition, fluticasone propionate (a different fluticasone ester) is already approved as a nasal spray for the treatment of SAR and PAR, which provides some reassurance regarding the safety and efficacy of fluticasone.

Pediatric Considerations

GSK included children 2 years and older in the studies that were submitted with this application. The lower age bound is typical for a nasal corticosteroid and the Division has not asked that drugs of this class be studied in children younger than 2 years. The Division has historically taken the position that SAR occurs in children 2 years of age

and older and PAR occurs in children 6 months of age and older. Although the lower age cut-off is somewhat arbitrary, there is literature support on the lower age bound (J Allergy Clin Immunol 2000, 106:832). For children younger than 2 years nasal corticosteroids is not an optimum choice because of possible nasal and systemic adverse effects. Such young patients are better treated with drugs of other classes such as **antihistamines**. **Therefore, GSK's lower age cut off for the clinical program is appropriate.**

Linear growth suppression in children is an important marker for systemic effect of corticosteroids including nasal corticosteroids. GSK conducted a randomized, double-blind, placebo-controlled two-week crossover knemometric growth study in 58 pediatric patients 6 to 11 years of age with 110mcg fluticasone furoate nasal spray once-daily and placebo (Study 101747). The mean lower-leg growth rate was 0.40mm/wk in the fluticasone furoate group and 0.42mm/wk for the placebo group. While the results of this study provide some information regarding growth, the issue of fluticasone furoate and potential growth effects has not been adequately addressed; therefore, a one year growth study is recommended as a phase 4 commitment.

Labeling

GSK submitted a label in the new Physician's Labeling Rule format that generally contains information consistent with other products of this class. The label was reviewed by various disciplines of this Division, and on consult by OSE and DDMAC. Various changes to different sections of the label are recommended to reflect the data accurately and truthfully and better communicate the findings to health care providers. The label should clearly reflect the following: the ophthalmologic findings (cataract and increased IOP) in this program; the findings of nasal infection with Candida in the program; the _____ and the negative allergen chamber study. In addition, the carton label has a graphic associated with the tradename (shown below) that should be removed.



Product Name

GSK originally intended to use the tradename _____ for this product. The Division and the OSE found that name unacceptable because of the potential for medication errors with other approved products, such as Alamast, Altamist, Allermed, and Allerest. In addition, at least one of the products with similar name is an ophthalmic solution (Alamast) and confusion of the two products could result in medication error with unacceptable safety risk. This was communicated to GSK within the review period. GSK subsequently proposed the tradenames of Veramyst and _____. These names were reviewed by the OSE and DDMAC and Veramyst was found to be acceptable.

Action

GSK submitted adequate data to support approval of fluticasone furoate nasal spray for the treatment of symptoms associated with SAR and PAR in adults and adolescents 2 years of age and older.

Phase 4 commitment studies:

1. GSK will be asked to submit results from a two year safety study to assess the ophthalmic effects of fluticasone furoate nasal spray in adults and pediatric patients. The study should include examinations by ophthalmologists with specific assessments for cataracts and changes in intra-ocular pressure.
2. GSK will be asked to submit results of a one-year linear growth study in children with fluticasone furoate using a dose that is relevant to the proposed fluticasone furoate nasal spray dose in children. A linear growth study conducted with a formulation other than the nasal formulation may be adequate provided the systemic exposure from that formulation is higher than the systemic exposure from the nasal formulation.

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CLINICAL REVIEW

Application Type: NDA
Submission Number: 22-051
Submission Code: N-000

Letter Date: 2006-06-28
Stamp Date: 2006-06-29
PDUFA Goal Date: 2007-04-29

Reviewer Name: Anthony G. Durmowicz, M.D.
Through: Sally M. Seymour, M.D.
Review Completion Date: 2007-02-27

Established Name: Fluticasone Furoate
(Proposed) Trade Name: Veramyst or _____
Therapeutic Class: Corticosteroid
Applicant: GlaxoSmithKline

Priority Designation: S

Formulation: Aqueous Nasal Spray
Dosing Regimen: 55 or 110 mcg, once daily
Indication: Seasonal and Perennial Allergic Rhinitis (SAR and PAR)
Intended Population: Adults and children 2 years of age and above

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, the data submitted in this NDA provide support for Approval of FF for the treatment 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.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

A Risk Management/Minimization Plan that outlined the known class effects of intranasal and systemic corticosteroid use including, cataracts, glaucoma, suppression of the HPA-

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axis, and decreased growth in children was submitted for review at the time of the Pre-NDA meeting in February, 2006. In it 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 unless unforeseen safety issues developed

1.2.2 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 six of seven subjects who had new-onset cataracts noted during the study had been treated with FF 110 mcg QD and that more subjects treated with FF 110 mcg QD developed increases in intraocular pressure above the normal threshold, thus raising the possibility for the development of glaucoma with long-term use of FF. Additionally, 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 the concerns over possible ocular and growth side effects with long-term use of FF nasal spray, a two year study to assess the effect of long-term treatment with FF nasal spray on the development of cataracts/glaucoma and a one year study to assess the effects of FF nasal on children's growth as determined by stadiometry will be required as Phase 4 commitments.

1.2.3 Other Phase 4 Requests

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

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

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The proposed drug in this application, fluticasone furoate, is a new ester of the synthetic corticosteroid, fluticasone, which is also marketed as fluticasone propionate (Flonase[®]) for the management of nasal symptoms due to SAR, PAR, and non-allergic rhinitis. The **Applicant has submitted the names "Veramyst" and "_____"** as possible trade names. Fluticasone propionate is supplied as an aqueous suspension in a side-actuated nasal spray device that delivers 27.7 mcg of FF per actuation.

The Applicant's proposed indication is for the treatment of symptoms of SAR and PAR in adults and children ≥ 2 years of age. The proposed adult dosing regimen is 110 mcg (2 sprays in each nostril) once daily. For children < 12 years of age, the proposed dosing regimen is to begin treatment with a dose of 55 mcg (1 spray in each nostril) once daily with the option of increasing the dose to 110 mcg if symptoms are not adequately controlled with the lower dose.

For the adult clinical program, the Applicant conducted eight studies, a Phase 2b dose-ranging study, 3 pivotal Phase 3 studies in subjects with SAR, one pivotal study in subjects with PAR, an allergen chamber study to assess onset of action, and HPA-axis and long-term safety studies. Overall, 2,730 adults participated in Phase 2/3 clinical studies with 1,564 (57.3%) being treated with the proposed dose of FF 110 mcg QD. A total of 535 (34%) subjects were exposed to FF 110 mcg for a period ≥ 3 months, 501 (32%) were exposed for a period of ≥ 6 months, and 400 (26%) of the subjects treated with FF were exposed for ≥ 12 months. The pediatric program consisted of pivotal Phase 3 studies in SAR and PAR, an HPA-axis study, and a knemometry study to assess the effects of FF nasal spray on short-term growth. Overall, 1,224 subjects ages $2 < 12$ years participated in placebo-controlled, parallel group design Phase 3 studies of 2-12 weeks duration. There were 83 subjects $2 < 4$ years, 271 from $2 < 6$ years and, 948 from $6 < 12$ years of age in Phase 3 parallel group studies. A total of 125 and 124 pediatric subjects have been exposed to FF 55 mcg and FF 110 mcg QD doses for ≥ 12 weeks duration. Of these, 120 subjects (22%) were ages $2 < 6$ years. Overall, the number of patients and extent of exposure in the adult and pediatric clinical studies were adequate.

In addition to the Phase 2b dose-ranging and HPA-axis studies mentioned above, there were several other pharmacokinetic (PK) and pharmacodynamic (PD) studies in this Application that related to the clinical safety of FF, including a study in subjects with hepatic impairment, a drug interaction study, a high dose cardiac safety (QT) studies, and a mass balance study.

Safety information in this application consisted of integrated safety information from **clinical studies in the applicant's drug development program**. This safety information included adverse events, laboratory studies, physical examinations, nasal and eye examinations, ECGs, and HPA-axis and growth studies.

1.3.2 Efficacy

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The Applicant's data support the efficacy of FF nasal spray for the treatment of symptoms of both SAR and PAR in adults and children ≥ 2 years of age.

The efficacy of FF nasal spray 110 mcg once daily in adults and adolescents age 12 years and above was demonstrated by virtue of achieving the primary endpoint of a statistically significant improvement over the entire treatment period in reflective total nasal symptom score (rTNSS) compared with placebo. Statistical significance was achieved in all 3 pivotal studies in subjects with SAR and the single study in PAR. The effectiveness and the once daily dosing regimen were further supported by the demonstration of statistically significant improvements in the secondary endpoints, mean change from baseline in AM, pre-dose instantaneous TNSS (iTNSS) and overall response to therapy.

In the adult subjects with SAR but not PAR, the effectiveness of FF 110 mcg in treating eye symptoms associated with SAR was shown by the demonstration of statistically significant improvements from baseline in reflective total ocular symptom score (rTOSS) compared to placebo for subjects in all 3 SAR studies. Similarly, in subjects with SAR but not PAR, treatment with FF 110 mcg once daily significantly improved quality of life as determined by meeting the Minimally Important Difference (MID) in overall improvement in the Rhinoconjunctivitis Quality of Life Questionnaire score (RQLQ). Onset of action was not demonstrated within 12 hours in the placebo-controlled allergen chamber study but was demonstrated to occur at approximately 24 hours during the pivotal SAR studies.

For children, 2 doses of FF were evaluated for effectiveness, 110 mcg once daily and a lower, 55 mcg dose. While demonstrating effectiveness by achieving the primary endpoint of showing a statistically significant difference in mean change from baseline in rTNSS compared to placebo in children ages $6 < 12$ years, the doses which proved effective were different in children with SAR compared to those with PAR. For SAR, the 110 mcg but not the 55 mcg dose demonstrated a statistically improvement in rTNSS. In PAR, however, the opposite occurred with the 55 mcg but not the 110 mcg dose proving to be effective. Results for children ages $2 < 6$ years of age in both the SAR and PAR studies also demonstrated numerical changes in rTNSS in favor of treatment with both the 55 or 110 mcg FF doses, thus supporting extrapolation of efficacy to the younger pediatric population. Taking the pediatric program as a whole, given that the 55 mcg dose was shown to be 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.

1.3.3 Safety

The overall exposure in the FF nasal spray clinical development program meets ICH and FDA guidelines and is sufficient to allow for assessment of safety. The exposure, duration of exposure, and the proposed doses of FF nasal spray (110 mcg for adolescents and adults and 55 mcg as a starting dose for children $\geq 2 < 12$ years of age) are also sufficient to allow

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for assessment of safety. The demographics of patients in the clinical program and exposure of subpopulations to FF nasal spray are adequate to provide an assessment of safety.

The safety of FF nasal spray for the treatment of symptoms associated with allergic rhinitis is supported by the Applicant's clinical studies. Known adverse events 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% (FF) versus 8% (placebo) in the year-long safety study, which may be somewhat higher when compared to the incidence of epistaxis reported in the labels of corticosteroid products currently marketed. There was, however, little difference in the incidence of nasal ulcerations between those treated with FF 110 mcg or placebo (2% versus <1%, respectively) and no subjects in the clinical program had nasal septal perforations. In children, there were no differences seen in the incidences of adverse events associated with epistaxis or nasal ulceration.

Adverse events associated with systemic 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. In children 2 < 12 years of age, plasma and urinary cortisol were not affected when assessed in the 6 week HPA axis study, FFR100012, but there was a small but dose-dependent decrease in urinary cortisol excretion observed in the longer 12 week pediatric 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 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 21 mmHg, 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 with two teenage subjects treated with FF developing posterior subcapsular cataracts. The occurrence of posterior subcapsular cataracts (a type known to be caused by corticosteroids) at the one year study visit in 2 young subjects who had had three prior visits documenting no cataract is suggestive of a potential for FF to cause 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

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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.

In summary, FF nasal spray, at the 55 and 110 mcg doses administered in these studies, was generally safe. Adverse events were, for the most part, mild and infrequent and similar to those seen with the administration of other nasal corticosteroids. There was, however, a greater incidence of adverse events for epistaxis associated with the long term (one year) use of FF (20% for FF versus 8% for placebo). There was no evidence of a systemic effect of FF nasal spray on the HPA-axis in adults and, while FF had a detectable effect on the HPA-axis of children treated with for 12 weeks, actual HPA-axis suppression did not occur. More subjects treated with FF nasal spray had cataracts noted on eye exams during the long-term studies. This finding could be the result of a greater propensity for FF nasal spray to cause cataracts or to differences in the quality of the eye exams conducted in the studies and justifies further evaluation in safety studies conducted post-marketing.

1.3.4 Dosing Regimen and Administration

A dose of 110 mcg once daily (two activations in each nostril) is recommended for adolescents and adults 12 years and older. 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.

1.3.5 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) but this effect did not result in any significant change in serum cortisol levels. However, the study was not designed appropriately as the dose of ketoconazole used for the study (200 mg) was one half that recommended (400 mg). No additional studies with other CYP 3A4 inhibitors have been conducted for this program but, based on the results of a drug interaction study with another potent CYP 3A4 inhibitor, ritonavir, with the related drug, fluticasone propionate, 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).

1.3.6 Special Populations

Special dosing is not recommended for FF nasal spray based upon gender, race, renal, or

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hepatic disease. Clinical trials did not include sufficient numbers of subjects aged 65 years or older to determine if they respond differently to FF nasal spray than younger subjects. Subjects with moderate hepatic insufficiency have increased systemic exposure to FF but not to levels that would be expected to result in cortisol suppression. Therefore, no dosage adjustment is needed for patients with mild-moderate hepatic impairment. No data are available for patients with severe hepatic impairment.

Fluticasone furoate has not been studied in pregnant women; therefore, it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Similarly, it is not known if FF is excreted in human milk, however, other corticosteroids have been detected in human milk. Therefore, caution should be exercised when FF nasal spray is administered to nursing mothers.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

The Applicant, GlaxoSmithKline, submitted NDA 22-051 on June 28, 2006, for an intranasal corticosteroid suspension containing the active ingredient, fluticasone furoate, a new ester of the base product, fluticasone (currently available on the market as fluticasone propionate), for the treatment of symptoms associated with SAR and PAR in adults and children ≥ 2 years of age. Fluticasone furoate is a synthetic, water insoluble, fluorinated corticosteroid that exists as a white powder with a molecular weight of 538.6 with the empirical formula, $C_{27}H_{29}F_3O_6S$. The drug product is supplied as an alcohol free, preserved aqueous suspension of micronized fluticasone furoate for intranasal administration by means of a metering (50 mcg/L), atomizing spray pump. Fluticasone furoate nasal spray also contains 0.015% w/w benzalkonium chloride, dextrose anhydrous, edetate disodium, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 80, and purified water. It has a pH of approximately 6.

The suspension used in the phase 2b/3 trials and in the to-be marketed product contains 27.5 mcg/ 50 mL actuation. The 110 mcg adult dose is administered as two activations in **each nostril once daily while the children's** recommended dose of 55 mcg is delivered as one activation in each nostril once daily.

The Applicant initially proposed the trade name "~~_____~~", however, this name was judged unacceptable because it too closely resembled the names of other drug products. Subsequently, the Applicant submitted the names Veramyst and ~~_____~~ for review. The trade name review is ongoing at the time of this clinical review.

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2.2 Currently Available Treatment for Indications

There are currently 7 corticosteroid preparations formulated for intranasal administration indicated for the treatment of both seasonal and perennial rhinitis:

- Nasacort[®] AQ (triamcinolone) nasal spray and HFA aerosol
- Beconase[®] AQ (beclomethasone) nasal spray
- Flonase[®] (fluticasone propionate) nasal spray
- Nasonex[®] (mometasone) nasal spray
- Rhinocort[®] Aqua (budesonide) nasal spray
- Nasarel[®] (flunisolide) metered nasal aerosol
- Omnaris[®] (ciclesonide) nasal spray

They are all approved for patients 6 years of age or older with the exceptions that Flonase[®] is approved for children as young as 4 years, Nasonex[®] for children as young as 2 years, and that Omnaris[®] is not approved for patients < 12 years of age.

2.3 Availability of Proposed Active Ingredient in the United States

Fluticasone furoate nasal spray is not marketed in the United States or any foreign country. A related corticosteroid nasal spray, fluticasone propionate, is marketed in the United States as Flonase[®].

2.4 Important Issues With Pharmacologically Related Products

Because of limited systemic absorption when delivered intranasally and extensive first-pass metabolism, fluticasone furoate nasal spray has low systemic bioavailability. However, as a potent corticosteroid it has the potential to produce the adverse events associated with corticosteroid administration. These adverse effects include adrenal suppression, the development of cataracts and glaucoma, and decreased growth in children.

2.5 Presubmission Regulatory Activity

The following are pertinent regulatory milestones for the development of FF nasal spray including pertinent DPAP clinical comments:

Pre-IND Meeting

On August 8, 2003, the Applicant (GSK) discussed development plans and a new IND submission for FF nasal spray. Comments included:

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- The non-clinical toxicology studies would permit clinical studies up to 14 days in duration.
- The carcinogenicity study protocol previously submitted was under review.
- Juvenile animal studies would not be required if the pediatric population is equal to or older than 2 years of age.
- DPAP recommended that the dose ranging study should also include a suboptimal dose and that a full dose-response curve should be demonstrated.
- Regarding indications, DPAP would accept one study each for SAR and PAR; however, in order to obtain an indication for two adequate and well-controlled studies would be required
- In addition to the proposed Phase 3 studies for pediatrics, FDA recommended either a growth or knemometry study, as well as an HPA axis study, be completed pre-approval.

IND # 48,647 was submitted on October 30, 2003.

End-of-Phase 2 Meeting

On July 19, 2004, an End-of-Phase 2 meeting was held to discuss the proposed Phase 3 development program. Comments included:

- FDA was in acceptance of the overall clinical development plan. There was acceptance of dose selection for adults (110mcg) and for the pediatric population (55mcg and 110mcg). DPAP recommended studying a lower dose in children (27.5mcg) if possible.
-
- The long-term safety study protocol design was considered acceptable. DPAP requested an increase in patient numbers for the safety database, beyond 300 patients at 6 months and 100 patients at 1 year and to use the Flonase safety database as a reference.
- GSK would get an indication for the treatment of symptoms of allergic rhinitis. A specific ocular indication would not be possible. If improvement was shown on ocular symptoms in the Phase 3 studies, and if the data were replicated with no safety concerns and with some possible evidence of the mechanism of action for ocular symptom relief, then the data could be described in the Clinical Trials Section of the label.
- DPAP was concerned with potential ocular safety with FF and stated that careful and complete assessment of ocular safety in the long-term safety study would be important.
- Onset of action could be included in the label provided the data were replicated. If different duration is seen in different studies, then the higher number/hours would

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need to be replicated. Phase 2 dose ranging study data could be used to support onset of action along with the Phase 3 data.

- Studying RQLQ for health outcomes was acceptable. There would need to be an adjustment for multiplicity for the global score.
- It was considered important that GSK demonstrate that there is no HPA axis suppression in children treated with FF. GSK could do either a separate HPA axis study in children (domicile study) or consider including an active (positive control) arm in the planned 12-week PAR study to look for HPA axis suppression.

General Correspondence

On December 9, 2004, GSK submitted toxicology data from a 6 month intranasal dog study.

- Intranasal administration of supra-therapeutic levels of FF (up to 20-fold the dose and 4-fold the concentration to be used clinically) was well tolerated with no evidence of local nasal toxicity. The 6-month toxicology data from the intranasal dog study supported continued dosing in the ongoing Phase 3 long-term safety study.

General Correspondence (Fax)

On March 29, 2005, DPAP provided comments on the pediatric HPA axis study, FFR100012, and reminded GSK of the importance of including an approved intranasal corticosteroid as an active comparator for assay sensitivity.

General Correspondence (Fax)

On July 26, 2005, DPAP provided comments on the non-clinical data submitted to the IND and asked GSK to explain the following findings in the preclinical studies submitted to the intranasal IND during the period of October 2003 through March 2005: bile duct epithelial vacuolation, gall bladder vacuolation, heart Purkinje fiber vacuolation, and nephropathy seen in the 6-month dog intranasal study. Also, explain increased eosinophilic inclusion of bronchiolar epithelium in the 6-month rat inhalation study. DPAP noted that if the above toxicology findings were considered significant and not monitorable, GSK was to conduct additional toxicology studies to define NOAELs and include a fluticasone propionate group.

Pre-NDA Meeting

A Pre-NDA meeting with the DPAP was held on February 13, 2006. Comments and agreements included:

- DPAP stated they would need to consider all the clinical data during the review regarding onset of action. In addition to statistical significance, the review would also include an assessment of clinical judgment.
- Regarding dose individualization, DPAP agreed that the goal of Dose Individualization/Maintenance was to minimize exposure to corticosteroids; however, regarding a maintenance dose for FF, while DPAP acknowledged the efficacy and safety at 55mcg in the phase 2b study they also pointed out that this

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was the only study in the clinical development that examined the lower dose of 55mcg. DPAP stated that they were leaving the door open on this issue and wanted GSK to provide a strong argument in the NDA to support 55mcg individualization of dose and provide a rationale for why the 110mcg dose from the dose-ranging study was selected for Phase 3 development when 55mcg dose was significantly efficacious. The Division acknowledged that titration or maintenance studies were not conducted to support similar claims for other nasal steroids.

- DPAP was in agreement that a definitive QTc study was not needed in the original NDA for safety assessment based on the low systemic exposure and pharmacological class. DPADP agreed that for completeness and full disclosure purposes, GSK could submit the QTc study CSR in the 120-day Safety Update.

- After consultation with the Division of Pediatric Drug Development, DPAP determined that it would not issue a Written Request outlining the pediatric studies that had already been performed. DPAP had not yet determined the safety and efficacy of the drug in adults and adolescents, and had not concluded that the pediatric studies utilized the most appropriate dose. Therefore, there was insufficient evidence that the pediatric studies would provide public health benefit.

2.6 Other Relevant Background Information

Fluticasone furoate nasal spray has not been marketed in any other country and there have not been any foreign regulatory actions on fluticasone furoate.

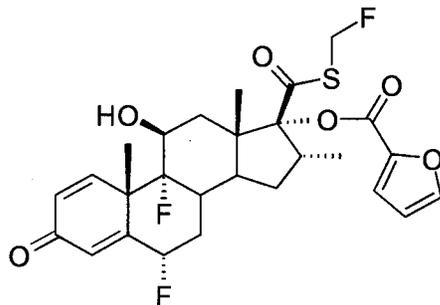
3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The drug substance, fluticasone furoate, is a new ester form of fluticasone. It is a white solid and possesses _____ and _____ configuration. The drug substance is practically insoluble in water (< 1 mcg/mL at 20°C) and has no _____.

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The Chemical Structure of Fluticasone Furoate



The drug product consists of a white suspension containing _____ mg of FF, _____ mg of anhydrous dextrose, _____ mg of microcrystalline cellulose with _____ carboxymethylcellulose sodium (_____), _____ mg of polysorbate 80 (_____), _____ benzalkonium chloride _____, mg edetate disodium (_____) and _____ mg of purified water per _____. It has a pH between 5 and 7.

The product is contained within an amber glass bottle, fitted with a metering (50 mL) spray pump. The bottle and pump are incorporated in an off white plastic device with a view window and dark blue side-actuated lever and dark blue detachable cap covering the applicator tip. Each spray of the suspension delivers 27.5 mcg of micronized fluticasone furoate as an ex-device dose. The fill weight of 10.0 g delivers at the minimum 120 sprays after priming (commercial pack), and the fill weight of _____).

The Applicant has modified the drug product spray device at least twice during Phase 2/3 clinical trials to correct deficiencies; f _____

_____. The Applicant has notified DPAP that, despite version 1.2 being the device currently under active review, _____

At the present time the application is considered to be approvable from a CMC perspective **pending the Applicant's response to information** requests for revised drug substance specifications, stability protocols including adequate evaluation of drug substance crystal form, additional stability data, and an explanation for what device characteristics are responsible for what has been noted to be a _____

_____. For a more complete analysis of CMC issues, see the CMC review of NDA 21-051 by Eugenia M. Nashed, Ph.D.

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3.2 Animal Pharmacology/Toxicology

General Toxicology

During the non-clinical evaluation of the toxicology of FF, repeated inhalation administration of fluticasone furoate in mice, rats and dogs at doses up to 76.9, 20.3 and 59.6 mcg/kg/day for durations up to 3, 6 and 9 months, respectively, resulted in findings typically associated with glucocorticoid excess including suppressed weight gain, development of Cushingoid syndrome with chronic treatment, lymphocytopenia, reduced adrenal weight/cortical atrophy, decreased cellularity of lymphoid tissues, hypocellularity/prominent adipocytes in bone marrow, reduced plasma cortisol, increased liver weight and increased hepatic glycogen.

In rats, alveolar histiocytosis/ aggregations of foamy macrophages around terminal bronchioles was noted in both treated and control rats, along with mild irritation of the larynx in the mouse and rat.

In dogs, FF produced an increased incidence of bile duct and gall bladder vacuolation and, in the 9 month study, focal nephropathy.

In intranasal toxicity studies, fluticasone furoate was well tolerated following administration for 14 days to male rats at doses of up to 160 mcg/day and for 1 month to dogs at doses of up to 1200 mcg/day. Mild laryngeal irritation was noted in some rats. In a 6 month intranasal study in the dog at 1200 mcg once or twice a day, local effects consisted of increased numbers of goblet cells in the nasal epithelium. There was no evidence of inflammatory changes or other indications of a nasal irritant response, i.e. no loss or damage to cilia and no evidence of cellular degeneration. Additionally, an increased incidence of biliary tract epithelial vacuolation, Purkinje fiber vacuolation and focal nephropathy was noted.

Over the course of the FF development program, as a result of not being able to define a NOAEL for many of the toxicology findings not typically associated with administration of high doses of corticosteroids, many discussions occurred surrounding the severity and relevancy of the findings of alveolar histiocytosis/ aggregations of foamy macrophages in rats, and an increased incidence of Purkinje fiber, bile duct and gall bladder vacuolation and focal nephropathy in dogs. After repeated evaluation of these findings, including convening an expert panel, it was concluded that the above findings were seen in historical controls at similar levels or were a non-adverse pharmacologically mediated exacerbation of a common background finding, which is within the range normally observed.

Carcinogenicity

In a 2 year carcinogenicity study, there were no treatment-related increases in the incidence of tumors in when FF was administered by the inhaled route to rats and mice at doses of up to 8.6 and 18.8 mcg/kg/day, respectively.

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Mutagenicity

Fluticasone furoate did not cause gene mutation in a bacterial mutagenicity test or chromosomal damage in a mammalian in vitro assay. There was no evidence of genotoxicity in two in vivo micronucleus tests in which rats received FF at very high multiples of clinical exposure (two IV doses of up to 4 mg/kg administered 24 hours apart).

Reproductive and Developmental Toxicity

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled doses of up to 24 and 91 mcg/kg/day, respectively (approximately equivalent to 2 and 8 times, respectively, the maximum recommended daily intranasal dose in adults on a mcg/m² basis). Also, in a pre- and post-natal development study (doses up to 27.2 mcg/kg/day) in rats, there were no adverse effects on mating performance, precoital interval, or male and female fertility, nor evidence of major skeletal, visceral or developmental abnormalities in the F1 or F2 offspring.

In an embryo-fetal development (EFD) study in rats, inhalation administration of FF at a dose of 91 mcg/kg/day was associated with reductions in maternal body weight and an increased incidence of fetuses with incompletely ossified sternebrae. The no-observed-adverse-effect-level (NOAEL) for EFD in the rat was 23 mcg/kg/day. Administration of fluticasone furoate in rabbits was associated with fetal abortion at doses of 46.6 mcg/kg/day. The NOAEL for EFD in the rabbit was 8 mcg/kg/day.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data submitted in support of this NDA are derived from the studies performed **as part of the Applicant's** clinical development program. The application does not rely on reports in the medical literature or other sources of data. The review of efficacy was based exclusively on the reports of the clinical trials submitted with the original NDA application. The review of safety was based on the clinical trials and the 120-Day safety update.

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4.2 Tables of Clinical Studies

Summary of Clinical Phase 2b/3 Studies in NDA 22-051

Study #	Design	Treatments Fluticasone Furoate QD	# of Subjects	Duration	Population	Study Objectives	Relevance to Review
FFR20001	Dose-ranging R, DB, PC, PG Ages ≥ 12 yrs	55 mcg 110 mcg 220 mcg 440 mcg placebo	127 127 129 130 128	2 weeks	SAR US, Mountain Cedar	Safety and efficacy (TNSS)	Dose Ranging Safety
FFR30003	R, DB, PC, PG Ages ≥ 12 yrs	110 mcg placebo	152 150	2 weeks ¹	SAR US, Mountain Cedar	Safety and efficacy (TNSS)	Pivotal SAR study
FFR103184	R, DB, PC, PG Ages ≥ 12 yrs	110 mcg placebo	141 144	2 weeks	SAR Europe Grass	Safety and efficacy (TNSS)	Pivotal SAR study
FFR104861	R, DB, PC, PG Ages ≥ 12 yrs	110 mcg placebo	151 148	2 weeks	SAR US Ragweed	Safety and efficacy (TNSS)	Pivotal SAR study
FFR30002	R, DB, PC, PG Ages ≥ 12 yrs	110 mcg placebo	149 153	4 weeks	PAR US/Canada	Safety and efficacy (TNSS)	Pivotal PAR study
FFR102123	R, DB, PC, PG Ages ≥ 12 yrs	110 mcg placebo	605 201	52 weeks	PAR Europe, South America, Australasia	Long-term safety	Long-term exposure to drug
FFR20002	R, DB, PC, AC, PG	110 mcg Placebo Placebo/ prednisone	48 51 13	6 weeks	PAR US/Canada	Safety/HPA axis	Adult HPA axis study
FFR101816	R, DB, PC, PG	110 mcg placebo	191 191	One day (single dose)	SAR US/Canada	Onset of action	Allergen Chamber Study
FFR100010	R, DB, PC, PG	55 mcg 110 mcg placebo	184 184 186	2 weeks	SAR US Multiple allergens	Safety and efficacy	Pivotal pediatric SAR study
FFR30008	R, DB, PC, PG	55 mcg 110 mcg placebo	185 185 188	12 weeks	PAR US, South America, Europe	Safety and efficacy	Pivotal pediatric PAR study with safety extension
FFR100012	R, DB, PC, PG	110 mcg placebo	57 55	6 weeks	PAR US	Safety/HPA axis	Pediatric HPA axis study
FFR101747	R, DB, PC, 2-week Crossover	110 mcg placebo	58	2 week treatment periods	PAR/SAR Denmark	Safety/assess for effects on growth	Pediatric knemometry study

Summary of Other Clinical Studies Performed to Support the Intranasal Administration of Fluticasone Furoate*

Study No. Report No.	Description of Study	Total No. Subjects	Country	Relevance to Review

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FFR10001	Tolerability and pharmacokinetics of single and multiple increasing doses of FF suspension in normal volunteers (50-8,000 mcg)	24-healthy	Germany	Safety/PK/PD
FFR10002	Tolerability and pharmacokinetics of single increasing doses of FF solution in normal volunteers (5-80 mcg).	24-healthy	UK	Safety/PK/PD
FFR10003	Tolerability and pharmacokinetics of single and multiple increasing doses of FF suspension in normal volunteers (50-8,000 mcg)	24-healthy	UK	Safety/PK/PD
FFR10005	Tolerability and pharmacokinetics of single and multiple increasing doses of FF suspension in normal volunteers (110-440 mcg)	12-healthy	Japan	Safety/PK/PD
FFR10006	Pharmacodynamic study after a single 440 mcg dose in healthy subjects (nasal biopsies performed)	20-healthy	UK	PD
FFR10007	Efficacy of 220 mcg FF X 8 days on TNSS in an environmental chamber study	59-allergic rhinitis	Austria	Efficacy
FFR10008	Metabolic study of 2,000mcg orally-administered C-14 labeled FF in healthy volunteers.	5- healthy	UK	Metabolism
FFR10010	Bioavailability study of FF 880 mcg q 8 hrs X 10 doses versus 250 mcg administered IV	16-healthy	UK	Bioavailability
FFR10013	Drug interaction study of FF 110 mcg QD and ketoconazole 200 mg QD	20-healthy	UK	Safety, Drug interaction with CYP 3A4 inhibitor
FFA10013	Pharmacokinetics of a single 440 mcg dose of FF administered by inhalation to subjects with hepatic impairment.	10-moderate hepatic impairment	Germany	PK in subjects with hepatic impairment

* All studies used intranasal dosing except FFR10008 (oral), FFR10010 (IV and nasal), and FFA10013 (inhalation)

4.3 Review Strategy

The Applicant identified eight clinical studies in adults and four in children as those that comprised the clinical development program for FF nasal spray (see table in Section 4.2, Table of Clinical Studies). The adult program consisted of four, 2-week SAR studies (the dose-ranging study and pivotal studies in subjects with allergies to Mountain Cedar, Grasses, and Ragweed), a 4-week pivotal PAR study, an allergen chamber study to assess onset of action, a 6-week HPA axis study, and a year-long safety study in adults with PAR. The pediatric program consisted of a 2-week pivotal study in SAR, a 12-week pivotal safety and efficacy study in PAR with efficacy determined at the 4-week time point, a 6-week HPA-axis study, and a 2-week knemometry growth study. All twelve of these studies are reviewed in depth in the Appendix to this review and form the primary basis for the assessments of safety and efficacy of FF nasal spray. Clinical pharmacology studies that dealt with specific clinical safety issues such as dosing in subjects with hepatic impairment, drug-drug interaction, and QT prolongation were also summarized within the body of this review.

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the results of these studies.

5. CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

At the clinically relevant intranasal dose, 110 mcg once daily, systemic concentrations of FF were generally below the limit of quantitation (10pg/mL). The low systemic bioavailability of intranasal FF is considered to be due to a combination of poor aqueous solubility, mucosal contact time in the nose and extensive first pass metabolism of the swallowed fraction of the dose. The table below summarizes the systemic exposure of subjects enrolled in the dose-ranging study (FFR20001) and demonstrates the low systemic bioavailability of FF with only 8 of 367 blood samples from subjects who had received the FF 110 mcg dose having quantifiable FF plasma measurements. The mean plasma values for those 8 samples from subjects receiving FF 110 mcg intranasally was 17.2 pg/mL.

Summary of Systemic Exposure to Fluticasone Furoate*

Dose	Samples			Subjects		
	With quantifiable value	Total	Percentage	With at least one quantifiable value	Total	Percentage
50mcg	4	363	1.1%	4	124	3.2%
100mcg	8	367	2.2%	8	126	6.4%
200mcg	9	375	2.4%	9	126	7.1%
400mcg	57	371	15.4%	38	126	30.2%
Overall	78	1476	5.3%	59	502	11.8%

* Upon further testing it was determined that the actual dose of FF delivered was 27.5 mcg/spray not 25.0 mcg/spray. Thus, the actual doses delivered were 55, 110, 220, and 440 mcg.

Absorption

As blood levels of FF are generally below the limit of quantification when dosed intranasally and because when dosed intranasally, any systemic absorption would be via the GI tract, the absorption, distribution, metabolism and excretion of FF were evaluated after administration of [¹⁴C]-fluticasone furoate by both oral and intravenous routes (study FFR10008).

Comparison of radioactivity AUC(0-t) values following oral and intravenous dosing

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indicated that at least 30% of the dose was absorbed following oral administration of [¹⁴C] FF. Oral bioavailability was low, on average 1.26%, indicative of extensive first pass metabolism of absorbed drug following oral dosing. The absolute bioavailability for FF dosed intranasally, as an aqueous suspension, at 800mcg TID was also very low averaging 0.55%.

Distribution

Following intravenous dosing, FF was extensively distributed with an average volume of distribution at steady-state was 608L. The terminal phase elimination half-life of FF following intravenous dosing was, on average, 15.12 hours.

Metabolism

The main route of in vitro metabolism in human hepatocytes was loss of the S-fluoromethyl carbothioate function to form the carboxylic acid metabolite (M1). The metabolite M1 was measurable in plasma following oral dosing at levels about 5 times lower than FF. The M1 metabolite has negligible pharmacological activity compared with parent FF (6,000 times less active).

Elimination

Studies using radiolabeled FF to evaluate the metabolism of FF demonstrated that elimination occurred almost entirely via the fecal route with total radioactivity in the feces accounting for approximately 90-100% of the administered dose. The majority of the drug was metabolized with little unchanged FF being observed in fecal samples (up to 7% of dose). Urinary excretion was a minor route of elimination accounting for on average only 1-2% of administered doses.

Special Populations

The pharmacokinetic profile of FF was assessed in 10 subjects with moderate hepatic impairment and compared to 10 matched healthy subjects. The systemic exposure (C_{max} and AUC) of FF increased 42% and 172% in subjects with hepatic impairment compared to 10 healthy control subjects. This increase in exposure is not felt to be clinically relevant as it should not lead to HPA-axis suppression.

5.2 Pharmacodynamics

The Applicant conducted one dose-ranging study, FFR20001 which is reviewed individually in the Appendix of this NDA review. This study found that, similar to other nasal corticosteroid products used to treat SAR and PAR, there was no consistent dose-response relationship between relative to efficacy. All doses studied (55, 110, 220, and 440

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mcg once daily) proved to be efficacious in the following dose order; 220 < 55 < 110 < 440 mcg.

The effect of FF nasal spray on the HPA axis was specifically assessed in 2 clinical studies, FFR20002 in adolescents and adults and FFR100012 in children ages. These studies assessed both serum cortisol levels and 24 hour urine cortisol excretion at baseline and at the end of the 6 week treatment periods. Subjects were domiciled for the serum/urine collections. HPA axis assessments (24 hour cortisol excretion only) were also conducted in adult studies FFR20001 and FFR102123 and in study FFR30008 in children. While these studies lacked the rigor of the specific HPA axis studies, they supply information on longer-term (12-52 week) use of FF (FFR 102123 and FFR30008) or the use of FF at higher doses for a 2 week period (FFR20001). The results of these studies demonstrated that doses of FF 110 mcg once daily had no significant effect on HPA-axis of adults. In the pediatric population, while there was no effect of FF 110 mcg on the HPA-axis in the 6 week study (FFR20002), a dose-related effect was observed in the 12 week pediatric study (FFR30008), however, all children tested had normal 24 hour urinary excretion. A more in depth discussion of the results of HPA-axis assessments can be found in Section 7.1.12, Special Safety Studies and in the reviews of individual studies in the Appendix to this review.

At the Pre-NDA meeting, an agreement was made that there was no requirement for a specific QT study for the FF nasal spray program. The Applicant has, however, conducted a thorough QT study and submitted it with the 120-Day Safety Update, (reviewed in Section 7.2.9). 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. A lack of effect of FF 4000 mcg by inhalation on QTcF was demonstrated when defined as the upper limit of the two-sided 90% confidence interval for the maximal mean change from baseline in QTcF being less than or equal to 7.5 msec. The QT study remains under review by the QT IRT group at the time of this review.

5.3 Exposure-Response Relationships

Exposure-Response relationships were not formally addressed in this application as systemic exposure to FF and the M1 metabolite is generally negligible after intranasal dosing of FF nasal spray.

6. INTEGRATED REVIEW OF EFFICACY

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6.1 Indication

Fluticasone furoate nasal spray is indicated for the treatment of the symptoms of seasonal and perennial rhinitis in adults and children 2 years of age and older.

Reviewer's Comment: This indication can be viewed as somewhat broader than that usually given for nasally-delivered products for SAR and PAR in which the indication is for treatment of "nasal symptoms" only. This change reflects the beneficial effect of FF nasal spray on adult subject-reported eye symptoms associated with SAR.

6.1.1 Methods

Efficacy was assessed with randomized, placebo-controlled, double-blind clinical trials.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint for the dose-ranging and pivotal efficacy and safety studies for both SAR and PAR in both adult and pediatric studies (FFR20001, 30003, 103184, 104861, 30002, 100010, and 30008) was the mean change from baseline in the reflective total nasal symptom score (rTNSS). The rTNSS was defined as the average of the AM and PM reflective severity scores **for the patients' assessments of** four components (runny nose, stuffy nose, itchy nose, and sneezing), which were graded on a 4-point scale (absent, mild, moderate, and severe) with a maximum score of 12. For the analysis in the pivotal trials, averaged baseline measurements were compared to the averaged rTNSS measurements made over the course of the study using a repeated measures ANCOVA statistical analysis. To assess onset of action, the environmental chamber study, FFR101816, utilized instantaneous TNSS, recorded hourly during a 12-hour post-dose exposure period as the primary efficacy endpoint. Safety studies, FFR102123, 20002, and 100012, did not have efficacy assessments as the primary endpoint; however, rTNSS was determined from subject diary recordings as a measure of drug compliance. It should be noted that the primary efficacy endpoint in pediatric studies for children ages 2 < 12 years was the rTNSS for the subset of children ages 6 < 12 years. In addition, for pediatric trials, TNSS determinations could be reported by either the subject or by the parent/guardian. This difference could introduce a level of subjectivity and inconsistency in endpoint analyses not present in adult studies.

Key secondary efficacy endpoints prospectively identified by the Applicant included:

- The mean change from baseline in the AM instantaneous TNSS (iTNSS), defined as the morning instantaneous severity scores **for the patients' assessments of** runny nose, stuffy nose, itchy nose, and sneezing

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- Changes in ocular symptoms of allergic rhinitis as determined by the mean change from baseline over the entire treatment period in daily reflective total ocular symptom score (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)
- 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
- Overall change from baseline of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) variables, overall scores, and individual domains. The RQLQ is a validated instrument for assessing the impact of rhinitis on activities of daily living and overall well-being^{1,2,3}. It is a 28-item, disease-specific instrument designed to measure the seven domains of functional impairment that are most important to patients with SAR: sleep impairment, non-nasal symptoms (e.g., headache and fatigue), practical problems, nasal symptoms, eye symptoms, activity limitations, and emotional function. There is also an overall quality of life score for the RQLQ that is expressed as the mean of the seven individual domains. Patients are asked to consider their experiences over the previous seven days and to score their degree of impairment on a seven-point scale (0 = not bothered, 6 = extremely bothered). The questionnaire has been shown to be reliable, responsive, and to have construct validity. A minimally important difference (MID) in the RQLQ is considered to be the smallest difference in score that is considered to be of clinical significance. The MID for the RQLQ has been determined to be 0.5⁴.

It should be noted that the key secondary endpoints of mean change from baseline in rTOSS and change from baseline in RQLQ were identified for the adult SAR studies only although both were evaluated as lesser secondary endpoints in the adult PAR study (FFR30002). Other secondary efficacy endpoints in these studies will not be discussed because they were of lesser importance and generally were a component of the primary or key secondary endpoints.

6.1.3 Study Design

All of the trials in this submission were randomized, double-blind, and placebo controlled. All subjects had diagnoses of SAR or PAR. In all of the trials conducted in subjects ≥ 12 years of age, the minimum duration of symptoms for SAR was for at least the last 2 allergy seasons and for at least 2 years for PAR. In the children $2 < 12$ years with SAR, the minimum duration of symptoms was for at least 1 past allergy season. For children ages $2 < 4$ years with PAR, symptoms requiring treatment were required for a minimum of 6 months and for the subjects $4 < 12$ years, symptoms were required for a minimum of 1 year. All of the subjects in the efficacy trials were symptomatic and all of the subjects had evidence of allergies [positive skin tests or RAST (in pediatric trials and in the adult SAR study

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conducted in Europe)] to appropriate antigens. SAR studies were conducted in subjects allergic to 3 different types of pollen. The adult dose-ranging and a separate efficacy trial were performed in Central Texas in subjects allergic to Mountain Cedar pollen. Two other SAR efficacy studies were conducted in subjects allergic to Ragweed (throughout the USA) and Grasses (throughout Europe including Eastern Europe). Ambient pollen counts were made throughout the study. The PAR subjects were allergic to a wide variety of antigens with the majority were allergic to mites or animal dander. The efficacy trials were adequately powered to assess efficacy in the subjects age 6 and above. All studies enrolled approximately 140-180 subjects in each treatment group and the follow-up and compliance were good. Efficacy data in children 2 < 6 years of age were not included in analyses of the primary endpoints of the pediatric trials but, in general, was supportive of results observed in the older children.

Reviewer's Comment: Throughout development the spray content of fluticasone furoate nasal spray had been approximated as 25mcg/actuation in the clinical trial documentation pending final confirmation of the spray content, thus the doses documented in the study reports of clinical trials were 50mcg, 100mcg, 200mcg, and 400mcg. Since the proposed label dose for the commercial product is the overall mean of the spray content database for clinical batches at release and long term stability, it was subsequently determined that the actual dose delivered from the product is 27.5mcg/actuation. Based on this spray content assessment, the doses examined in the clinical program were actually 55mcg, 110mcg, 220mcg, and 440mcg.

The duration of the trials was adequate to demonstrate efficacy; two weeks for SAR and 4 weeks for PAR. Some of the trials were carried out over longer periods of time in subjects with PAR, but the primary efficacy evaluation was performed at the 4 week time point with the additional dosing period used to collect safety data.

The onset of action was demonstrated in the pivotal trials by assessing iTNSS frequently over the first 12 hours after the initial dose of study medication was administered as well as by conducting an environmental exposure chamber study. For the chamber study, subjects allergic to ragweed were primed prior to the test exposure. On the test day, the subjects were exposed continuously to a standard dose of ragweed pollen for two hours. At the two hour time point, they were treated with 110 mcg of fluticasone furoate and the iTNSS was recorded hourly for the subsequent 12 hours.

6.1.4 Efficacy Findings

6.1.4.1 Adults and Adolescents

6.1.4.1.1 Dose-Ranging

In the Phase 2b dose-finding study (FFR20001), adults and adolescents ≥ 12 years of age with SAR were treated with 55, 110, 220, or 440 mcg of FF nasal spray once daily for 2

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weeks. The primary efficacy variable was the mean change from baseline compared to placebo in rTNSS over the entire 2 week treatment period. All doses achieved the primary endpoint of a statistically significant difference from baseline in mean rTNSS over the entire treatment period with a treatment difference in the order of 220 mcg < 55 mcg < 110 mcg < 440 mcg. See the following table.

Dose-Ranging Study: FFR20001, Primary Endpoint Analysis: Mean Change from Baseline in rTNSS after 2 Weeks Treatment with Fluticasone Furoate Nasal Spray

	Difference from vehicle placebo in mean change in rTNSS			
Dose of fluticasone	55 mcg N=121	110 mcg N=125	220 mcg N=124	440 mcg N=126
Difference from placebo*, LS mean change from baseline * placebo = -1.83	-1.675	-2.012	-1.359	-2.188
p value	< 0.001	< 0.001	<0.001	<0.001

While all doses met the primary endpoint, the 55 mcg dose did not show a difference in the secondary endpoint of mean change from baseline in AM iTOSS and the onset of action of the 55 mcg dose was slightly longer than the 110 and 440 mcg doses. Thus 110 mcg was determined to be the lowest effective dose in subsequent Phase 3 trials. In children < 12 years of age the 55 mcg dose was administered in addition to the 110 mcg dose.

There were 3 pivotal trials in SAR subjects ≥ 12 years of age, one in subjects allergic to Mountain Cedar (FFR30003), one in those allergic to Grass pollens (FFR103184) and one in those allergic to Ragweed (FFR104861). All 3 studies demonstrated a statistically significant greater decrease (improvement) in the primary endpoint of LS mean change from baseline in rTNSS compared to placebo over the entire 2 week treatment periods.

There was one pivotal study (FFR30002) in subjects ≥ 12 years of age with PAR, again with the primary endpoint of mean change from baseline in rTNSS over the entire treatment period (4 weeks for PAR studies) for subjects treated with FF 110 mcg once daily. This study also met the primary endpoint, the LS mean change from baseline for FF 110 mcg was -2.78 compared to -2.08 for placebo resulting in a treatment difference of -0.706 (p = 0.005).

See the following table for a summary of the results for the primary endpoint for both SAR and PAR.

Pivotal SAR/PAR Studies in Adults and Adolescents: Primary Endpoint: Mean Change from Baseline in rTNSS after Treatment with Fluticasone Furoate Nasal Spray (SAR = 2 Weeks, PAR = 4 Weeks)

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Fluticasone Furoate 110 mcg Once Daily				
	Study FFR30002 (PAR) N=149	Study FFR30003 (SAR) N=145	Study FFR103184 (SAR) N=138	Study FFR104861 (SAR) N=144
Change from baseline: Placebo	-2.08	-2.25	-3.18	-2.07
Change from baseline: FF 110 mcg	-2.78	-3.03	-4.94	-3.55
Difference from placebo, LS mean change from baseline	-0.706	-0.777	-1.757	-1.473
p value	0.005	0.003	< 0.001	< 0.001

Key secondary endpoints designated by the Applicant in the pivotal SAR and PAR studies included mean change from baseline over the entire treatment period in AM, pre-dose iTNSS and overall response to therapy as evaluated on a 7-point categorical scale. For the SAR studies but not the PAR study, the mean change from baseline in rTOSS over the entire 2 week treatment period was also designated a key secondary endpoint.

Reviewer's Comment: *It should be noted that if the difference between FF 110 mcg and placebo on the primary efficacy endpoint was statistically significant, the subsequent inferential analysis results for only the key secondary efficacy endpoints and the global score on RQLQ (reviewed below) were adjusted for multiplicity and not the other secondary endpoints (reviewed in the individual study reviews located in the Appendix).*

For the key secondary endpoint of change from baseline in AM iTNSS, all 4 pivotal studies in SAR/PAR, FF 110 mcg once daily demonstrated a statistically significant improvement in iTNSS compared to placebo (see the following table). These results adequately support the once daily dosing interval.

Mean Change from Baseline in AM iTNSS Over the Entire Treatment Period

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Fluticasone Furoate 110 mcg Once Daily				
	Study FFR30002 (PAR) N=149	Study FFR30003 (SAR) N=145	Study FFR103184 (SAR) N=138	Study FFR104861 (SAR) N=144
Change from baseline: Placebo	-1.75	-1.47	-2.60	-1.53
Change from baseline: FF 110 mcg	-2.45	-2.38	-4.50	-2.90
Difference from placebo, LS mean change from baseline	-0.705	-0.902	-1.898	-1.375
p value	0.006	< 0.001	< 0.001	< 0.001

For the key secondary endpoint designated in only the 3 pivotal SAR studies of mean change from baseline in rTOSS as a specific assessment of improvement of eye symptoms, FF 110 mcg once daily resulted in a statistically significant improvement in rTOSS in all 3 SAR studies as demonstrated in the following table.

Mean Change from Baseline in rTOSS over the Entire 2 Week Treatment Period in the 3 Studies of Subjects with SAR

Fluticasone Furoate 110 mcg Once Daily			
	Study FFR30003 N=145	Study FFR103184 N=138	Study FFR104861 N=144
Change from baseline: Placebo	-1.60	-2.26	-1.63
Change from baseline: FF 110 mcg	-2.15	-3.00	-2.23
Difference from placebo, LS mean change from baseline	-0.546	-0741	-0.600
p value	0.008	< 0.001	0.004

Reviewer's Comment: The Division has had several discussions with the Applicant regarding the mechanism of action for the effect of intranasal FF on ocular symptoms. Since little of intranasally delivered FF reaches the systemic circulation and the bioavailability of that which does is extremely low (about 0.5%), it is most likely that the beneficial effect of FF nasal spray on ocular symptoms is a local effect. This possibility is further justification for the requirement to conduct a Phase 4 eye safety study. Nevertheless, the rTOSS data reported above supports the efficacy of FF in the alleviation of eye symptoms associated with SAR. This is not true for PAR as the benefit for PAR was

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not statistically significant and the inferential analysis for the rTOSS endpoint in the PAR study was not adjusted for multiplicity as it was in the analysis of rTOSS endpoint in the SAR studies.

The overall response to therapy was another key secondary endpoint designated by the Applicant for the pivotal SAR/PAR studies. This assessment used 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. The pairwise comparisons between FF 110 mcg and placebo-treated subjects showed a significantly better response for the FF 110 mcg treated group in all 4 of the studies ($p < 0.001$ for all 3 SAR studies and $p = 0.005$ for study FFR30002 in PAR).

Reviewer's Comment: *Despite its designation as a key secondary endpoint, this is a subjective, nonspecific global assessment of response to therapy that is not a validated instrument to assess efficacy in allergic rhinitis trials and is not appropriate for a label claim.*

For the one-year safety (FFR102123) and HPA axis (20002) studies in adults with PAR, efficacy was assessed only as a means to evaluate treatment compliance. The results were supportive to the program as mean and median changes from baseline over the entire treatment periods showed numerically greater symptom improvement in the FF 110 mcg group versus placebo (see efficacy assessments in the individual study reports in the Appendix).

Onset of Action

To assess onset of action, an environmental chamber study, FFR101816, utilized iTNSS, recorded hourly during a 12-hour post-dose exposure period as the primary efficacy endpoint. The onset of action was also assessed in the pivotal trials by assessing iTNSS frequently over the first 12 hours after the initial dose of study medication then again at 24 hours post-dose. For the chamber study, subjects allergic to ragweed were primed prior to the test exposure. On the test day, the subjects were exposed continuously to a standard dose of ragweed pollen for two hours. At the two hour time point, they were treated with 110 mcg of fluticasone furoate and the iTNSS was recorded hourly for the subsequent 12 hours. Three hundred eighty-two subjects were exposed to controlled pollen concentrations (3500 ± 500 grains/m³) and then randomized 1:1 to receive a single dose of either FF 110 mcg or placebo nasal spray and subsequently complete a 12-hour postdose exposure period. For the primary endpoint, the LS mean difference between the two treatments for iTNSS, there was no statistically significant difference at any time point ($p \geq 0.167$), thus, the onset of effect was not seen. In the pivotal clinical trials, an onset of action, defined as when the mean change from baseline in iTNSS in the FF 110 mcg group was significantly greater than placebo and remained significantly greater, the following results were seen:

- FFR104861 (SAR): significant at 8, 10, and 24 hours (12 hours not significant)
- FFR30003 (SAR): significant at 24 hours (not significant on days 3 and 5)
- FFR103184 (SAR): significant at 24 hours
- FFR30002 (PAR); significant at day 4

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Time to maximal effect was defined as when the daily rTNSS in the FF 110 mcg group demonstrated the greatest numerical reduction (improvement) compared with placebo. Maximal effect was observed on days 12, 4, and 9 for SAR studies FFR30003, FFR103184, and FFR104861, respectively and on day 20 for PAR study FFR30002.

Reviewer's Comment: *Onset of action and time to maximal effect will be a significant labeling issue. It appears that onset of action occurs within the first 24 hours for SAR and within several days for PAR while maximal effect is achieved within the first 2 weeks for SAR and 3 weeks for PAR.*

Rhinoconjunctivitis Quality of Life Questionnaire

The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) assesses the impact of rhinitis on activities of daily living and overall well-being. A minimally important difference (MID) in the RQLQ is considered to be the smallest difference in score of clinical significance. The MID for the RQLQ has been determined to be 0.5. To support labeling claims, the Division requires that the MID for the active treatment be demonstrated in replicate for change from baseline compared to vehicle placebo. The change from baseline of the RQLQ overall scores in the 3 pivotal SAR efficacy and safety studies is summarized in the following table.

Change in RQLQ Overall Score over the 2 Week Treatment Period for the Pivotal SAR Studies

	Study 30003 MTN Cedar USA Placebo 149 110 FF 149	Study 103184 Grass EU Placebo 140 110 FF 137	Study 104861 Ragweed USA Placebo 144 110 FF 144
Baseline (placebo/110 FF)	4.1/4.1	3.5/3.5	3.9/3.9
LS Mean Change from baseline (placebo/110 FF)	- 0.97/- 1.66	- 1.53/- 2.23	- 1.16/- 1.77
LS Mean Difference (p value)	-0.690 <0.001	-0.701 <0.001	-0.604 <0.001
95% CI	-1.08, -0.30	-0.99, -0.41	-0.93, -0.28
Comments on individual activity domains	< -0.50 in 7/7	< -0.50 in 6/7 Non-hay fever -0.420	< -0.50 in 6/7 Eye Sx -0.254

The MID of 0.5 compared to placebo in change from baseline in overall RQLQ score was demonstrated in each of the 3 pivotal SAR studies in subjects allergic to 3 different types of pollen. In addition, the MID was achieved in all 7 activity domains in study FFR30003 and in 6 of 7 activity domains in studies FFR103184 and FFR104861.

For the pivotal adult PAR study, FFR30002, while the LS mean difference in overall RQLQ was in favor of the FF 110 mcg group (- 0.227), the benefit was neither statistically significant nor met the MID of 0.5.

Reviewer's Comment: *This RQLQ quality of life claim would be a significant addition to*

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the label as I believe it would be the only nasal steroid for SAR/PAR to have such a claim. The initial submission of the data set for the RQLQ appeared to have a large percentage of missing data points (> 25%) in the activity domains. The statistical team requested an explanation for the missing data points, many of which were due to the analysis approach that the activity domain scores at endpoint were set as missing if texts entries did not match 100% at baseline and final visit. The Applicant was asked to re-analyze the RQLQ data while including the activity domain scores where the text entries have the same meaning at baseline and endpoint even if they do not match 100% (e.g. walk, walking, gone walking have different text but have the same meaning). The Applicant also conducted 2 sensitivity analyses where imputation was employed for the missing activity scores at endpoint using the prorating method based on the other non-missing activity scores specified in the RAP for the overall score. The above RQLQ data are from the re-analysis of RQLQ data submitted in response to the above-mentioned request made on 11/20/2006, and are very similar to the results of the analyses of the original data set with no difference in any outcome parameter. For a more complete description of the statistical analyses, please see the statistical review by Feng Zhou, Ph.D. It is my opinion that, since the RQLQ data are robust and have been replicated twice in subjects with SAR, a quality of life labeling claim is justified in SAR. The complicated issue is that in PAR, the RQLQ data did not reach statistical or clinical significance and that any labeling claim would need to address the difference from SAR.

Children Less than 12 Years of Age

There were 2 pivotal trials to assess the efficacy and safety of fluticasone furoate in pediatric subjects with allergic rhinitis 2 < 12 years of age, FFR100010 in subjects with SAR and FFR30008 in subjects with PAR. Two doses of fluticasone furoate were evaluated in the trials, 110 mcg, the dose identified in the adult dose-ranging study that was used in the pivotal adult trials, and a lower dose, 55 mcg, using the rationale that the lower dose would result in less steroid exposure in children but also was a dose that proved efficacious in the adult dose-ranging study, FFR20001. For these studies the primary endpoint was the same as for the adult studies, mean change from baseline in rTNSS over the 2 week treatment period for SAR and over the first 4 weeks of the treatment period for the PAR study, with the exceptions that the symptom scores could be recorded in the subject diaries by the parent/guardian and that the population of children ages 6 < 12 years of age was used in the analysis of the primary endpoint. Study FFR30008 continued for a total of 12 weeks to gather safety data in young children. Key secondary endpoints identified by the Applicant, again, similar to the adult program, were mean change from baseline in AM pre-dose iTNSS and overall response to therapy. Unlike the adult program ocular symptoms and quality of life were not identified as key secondary endpoints. The studies were stratified by age with the goal of having approximately 25% of subjects between 2 < 6 years of age. Both studies demonstrated a statistically significant greater decrease (improvement) in the primary endpoint of LS mean change from baseline in rTNSS compared to placebo over their respective 2 week and 4 week treatment periods, however, the results were discordant with respect to the doses which proved efficacious. In SAR study FFR100010, children aged 6 to < 12 years treated with FF 110 mcg demonstrated statistically significant greater decreases in mean daily rTNSS than placebo

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subjects but not for the 55 mcg dose. On the contrary, in PAR study FFR30008, children aged 6 to < 12 years treated FF 110 mcg failed to show statistically greater decreases in mean daily rTNSS compared with placebo, however, the lower 55 mcg dose demonstrated a reduction in mean rTNSS that was significant compared to placebo. The following table summarizes the results for the primary endpoint in the pivotal pediatric studies.

Pivotal SAR and PAR Studies in Children: Primary Endpoint: Mean Change from Baseline in rTNSS in Children 6 < 12 Years of Age

	Study FFR100010 SAR		Study FFR30008 PAR	
	55 mcg N=152	110 mcg N=146	55 mcg N=144	110 mcg N=140
Change from baseline: placebo	-2.54	-2.54	-3.41	-3.41
Change from baseline: FF	-2.71	-3.16	-4.16	-3.86
Difference from placebo, LS mean change from baseline	-0.161	-0.616	-0.754	-0.452
p value	0.553	0.025	0.003	0.073

For both studies, analysis of the rTNSS endpoint for children ages 2 < 6 years of age supported the findings of the primary endpoint in the older children ages 6 < 12 years. In addition to achieving the primary endpoint with the 55 mcg dose, for study FFR30008, analysis of the entire ITT population, which included all children 2 < 12 years of age, resulted in a statistically significant decrease in rTNSS compared to baseline from placebo for the 110 mcg dose group (LS mean difference -0.475, p=0.031) as well.

The results of the key secondary endpoints of change from baseline in AM pre-dose iTNSS compared to placebo and overall response to therapy for the SAR study (FFR100010) were consistent with that seen for the primary endpoint. Regarding the iTNSS endpoint, the 55 mcg dose failed to show a significant difference compared to placebo (LS mean difference -0.234, p=0.389) while the 110 mcg dose was showed a statistically significant improvement (decrease) in iTNSS (LS mean difference -0.668, p=0.015). The overall response to therapy was also significant for the 110 mcg dose (p<0.001) but not the 55 mcg dose (p=0.083).

For study FFR30008 in subjects with PAR, in contrast to the results seen for the primary endpoint when the 55 mcg dose was statistically significantly different from placebo but not the 110 mcg dose, both doses demonstrated a statistically significant improvement in AM pre-dose iTNSS compared to baseline versus placebo with an LS mean difference of -0.751 (p=0.002) and -0.651 (p=0.009) for the 55 and 110 mcg doses, respectively. The

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overall response to therapy endpoint, however, showed statistically significant improvement for the 55 mcg dose only ($p=0.024$ versus 0.414 for the 110 mcg dose).

In the pediatric pivotal trials, there were 71 and 78 children ages 2 < 6 years treated with FF 55 and 110 mcg doses, respectively which accounted for between 20-25% of subjects enrolled in each treatment group. Results of the analyses of TNSS scores in children 2 < 6 years of age were consistent with those observed for the older age group.

Reviewer's Comment: Results of the pediatric trials are somewhat confounding, especially in the finding of efficacy for the 55 mcg dose but not the 110 mcg dose for the primary endpoint of the PAR study (FFR30008). However, a similar secondary endpoint (AM Pre-dose iTNSS) showed a significant result for both doses and post-hoc analyses of the data over a more prolonged treatment period of 6 and 12 weeks also supported the efficacy of both the 55 and 110 mcg doses. When taken as a whole, I believe the pediatric program supports the effectiveness of fluticasone furoate in the pediatric age group down to the age of 2 years, including the dosing strategy of beginning with a dose of 55 mcg once daily and increasing to 110 mcg if improvement does not occur.

6.1.5 Clinical Microbiology

No microbiology was submitted as this drug product is not an antimicrobial.

6.1.6 Efficacy Conclusions

Fluticasone furoate 110 mcg once daily demonstrated effectiveness in the treatment of the symptoms of SAR and PAR in adults and adolescents age 12 years and above by virtue of achieving the primary endpoint of a statistically significant mean change from baseline over the entire treatment period in rTNSS compared with placebo. Statistical significance was achieved in all 3 studies in subjects with SAR as well as the study in PAR. The effectiveness and the once daily dosing regimen were further supported by the demonstration of statistically significant improvements in the secondary endpoints, mean change from baseline in AM, pre-dose iTNSS and overall response to therapy.

In the adult subjects with SAR but not PAR, the effectiveness of FF 110 mcg in treating specific eye symptoms was shown by the demonstration of statistically significant reductions in mean changes from baseline in rTOSS compared to placebo for subjects in all 3 SAR studies. Similarly, in subjects with SAR but not PAR, treatment with FF 110 mcg once daily significantly improved quality of life as determined by the RQLQ. The MID of 0.5 compared to placebo in change from baseline in overall RQLQ score was demonstrated in each of the 3 pivotal SAR studies in subjects allergic to 3 different types of pollen. In addition, the MID was achieved in all 7 activity domains in study FFR30003 and in 6 of 7 activity domains in studies FFR103184 and FFR104861. Onset of action was not demonstrated within 12 hours in the placebo-controlled allergen chamber study but was

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demonstrated to occur at approximately 24 hours during the pivotal SAR studies and at Day 4 in the PAR study. Maximal effect was demonstrated from between 4-12 days in the SAR studies and on Day 20 in PAR.

For children, 2 doses of FF were evaluated for effectiveness, 110 mcg once daily, which was the same dose evaluated in the adult trials, and a lower 55 mcg dose, which was shown to also be an effective dose in the adult dose-ranging study. While demonstrating effectiveness by achieving the primary endpoint of showing a statistically significant difference in mean change from baseline in rTNSS compared to placebo in children ages 6 < 12 years, the doses which proved effective were different in children with SAR compared to those with PAR. For SAR, children treated with FF 110 mcg demonstrated statistically significant greater decreases in rTNSS than placebo subjects but not for those treated with the 55 mcg dose. On the contrary, in PAR, children treated with FF 110 mcg failed to show statistically greater decreases rTNSS compared with placebo, however, the lower 55 mcg dose demonstrated a reduction in rTNSS that was significant compared to placebo. In contrast, a similar secondary endpoint, mean change in AM, pre-dose iTNSS, did demonstrate significant improvement for both the 55 and 110 mcg doses in children with PAR. Results for children ages 2 < 6 years of age in both the SAR and PAR studies also demonstrated numerical changes in rTNSS in favor of treatment with both the 55 or 110 mcg FF doses thus supporting extrapolation of efficacy to the younger population. To summarize, when taken as a whole, I believe the pediatric program supports the effectiveness of fluticasone furoate in the pediatric age group down to the age of 2 years, including the dosing strategy of beginning with a dose of 55 mcg once daily and increasing to 110 mcg if improvement does not occur.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The global clinical development program for intranasal FF consisted of 12 studies (1 Phase 2b dose-ranging study, 10 repeat-dose Phase 3 safety and efficacy studies and 1 single-dose allergen challenge chamber study) to support the safety and efficacy of once daily administration of FF nasal spray. The safety and efficacy of all 12 of these studies are reviewed individually in the Appendix of this NDA review. The adult program consisted of four, 2-week safety and efficacy studies in subjects with SAR (FFR20001, 30003, 103184, and 104861), one, 4-week study in subjects with PAR (FFR30002), a 6-week safety study to assess the effects of FF on the HPA axis in subjects with PAR (FFR20002), a single-dose, allergen chamber study in subjects with SAR (FFR101816), and a year-long safety study in subjects with PAR (FFR102123). All studies utilized 1 dose of FF (110 mcg) in

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the clinical trials except study FFR20001, the dose-ranging study where doses of 55, 110, 220, and 440 mcg FF were evaluated in subjects with SAR. Safety data for the adult clinical program were integrated from all studies except for the year-long safety study and the allergen chamber study which, because of differences in dosing period, are presented separately. Safety data for the doses other than the 110 mcg dose of FF that were evaluated in the dose-ranging study (55, 220, and 440 mcg) were also presented separately.

The pediatric program clinical program evaluated the safety and efficacy of 55 and 110 mcg doses of FF in children ages 2 < 12 years and consisted of one, 2-week study in subjects with SAR (FFR100010), one, 12-week study in children with PAR which included additional safety assessments (FFR30008), a 6-week HPA-axis safety study in children with PAR (FFR100012), and a knemometry study to assess the effects of FF on short-term lower leg growth (FFR101747). All safety data except for that of the knemometry are integrated in this summary of safety.

In addition to adverse events, nasal examinations, vital signs, ECG, and laboratory examinations (clinical chemistry and hematology) were performed on all subjects. Studies FFR102123, 20002, 30008, and 100012 also evaluated HPA-axis suppression by assessment of plasma cortisol and/or 24-hour urine cortisol excretion (reviewed in Section 7.1.12). Individual safety reviews of non-integrated studies FFR101816 (allergen chamber study) and FFR101747 (knemometry growth study) are located in the Appendix of this clinical NDA review. General safety findings for those studies will be referred to in this review if those findings add additional important safety information not observed in the integrated studies. The effects of FF on short-term bone growth in children (study FFR101747) will be summarized in Section 7.1.12.

7.1.1 Deaths

There were no deaths in any of the studies reviewed for this NDA.

7.1.2 Other Serious Adverse Events

In the adult program, 5 subjects reported SAEs in the integrated SAR/PAR studies while 24 additional SAEs were reported in the year-long safety study. None was likely to have been related to drug treatment. Of the 5 subjects in the SAR/PAR studies, 2 were experienced during the screening period (diabetes mellitus and gastroenteritis) and one in the post-treatment period (cholelithiasis in the FF 110 mcg group). The 2 SAEs during the treatment period included an SAE of breast cancer (FF 110 mcg) and one of abdominal pain/nephrolithiasis (placebo). In the long-term safety study, subjects were randomized 1:3 to receive placebo or FF 110 mcg. Twenty subjects (3%) and 4 subjects (2%) in the FF 110 mcg and placebo groups, respectively, reported SAEs. No individual SAE was reported by

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more than one subject in either treatment group. The most severe SAEs included malignant melanoma, uterine hemorrhage, cervical vertebral fracture (all in the FF 110 mcg group), and interstitial lung disease (placebo group).

In the pediatric program, 4 SAEs were reported; diabetes mellitus and radial/ulnar fracture in subjects in the placebo group and appendicitis and peritonitis (appendicular) in subjects who received FF 110 mcg and 55 mcg, respectively. Again, none were likely related to treatment with FF.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In the adult integrated studies, the incidence of withdrawals was low with 94 % (1451/1542) of subjects finishing the studies. AEs, lack of efficacy, and “other”, were the most frequently cited reasons for withdrawal accounting for 1-2% each with more withdrawals in the placebo group than in the FF 110 mcg group. Withdrawal due to protocol violations was infrequent ($\leq 1\%$) and distributed equally across groups. There were more withdrawals in the long-term safety study likely due to its much greater length than the efficacy trials with 73% of subjects completing the study. Protocol violations and subjects deciding to withdraw accounted for the majority of withdrawals with incidences of 8-10% and 7-8%, respectively. AEs accounted for 6% and 3% of withdrawals in the FF 100 mcg and placebo groups, respectively.

In the pediatric trials, 93% of subjects completed the studies. AEs and subject deciding to withdraw were the most common reasons for discontinuation and were equally distributed across the placebo and FF 55 and 110 mcg treatment groups (approximately 2% each).

7.1.3.2 Adverse events associated with dropouts

Overall, for the integrated trials the incidence of withdrawals due to AEs was higher in the placebo group than active treatment groups. In the adult integrated studies, 12/774 subjects (2%) of from the placebo group and 6/768 (<1%) from the FF 110 mcg group were withdrawn from the 6 integrated adult studies due to AEs with the majority of withdrawals due to infections common to those with SAR/PAR, viral infection, nasopharyngitis, URI, and sinusitis. One subject, a 62 year-old male in the FF 110 mcg group withdrew from study FFR30002 in PAR on Day 9 of treatment due to an AE of increased intraocular pressure diagnosed during a routine ophthalmologic exam. There was a history of

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glaucoma in the subject's family.

Reviewer's Comment: *While a significant finding due to the association of corticosteroid use and glaucoma, it appears unlikely that the finding was due to fluticasone since it was seen after only 9 days of treatment with FF 110 mcg once daily.*

In the pediatric trials 13/429 subjects (3%) in the placebo group and 15/795 subjects (2%), 10/369 and 5/426 in the FF 55 and FF 110 mcg groups, respectively withdrew due to AEs. The majority of AEs, like in the adult trials, were due to infections such as ear infections, varicella, and nasopharyngitis with no difference in incidence in any one treatment group. There was one report of nasal candidiasis in a 10 year old female 8 days after beginning treatment with FF 55 mcg. Nine days later treatment was discontinued and the subject was withdrawn from the study. The event resolved 18 days after onset.

Contrary to the shorter integrated studies, in the long-term safety study there was a higher incidence of withdrawal due to AEs (38 subjects (6%) in the FF 110 group and 7 subjects (3%) in the placebo group). The AE epistaxis was the most common AE in the FF 110 mcg group that lead to study withdrawal with 15 subjects (2%) versus 0 subjects in the placebo group. Nasal ulceration/nasal ulcers were reported in 3/605 subjects ($\leq 1\%$) in the FF 110 mcg group versus 0/201 subjects who received placebo.

In the dose-ranging study (FFR20001), 1 subject who received FF 220 mcg, a higher dose than the proposed clinical dose, withdrew due to nasal candidiasis and elevated urine cortisol.

Reviewer's Comment: *Adverse events associated with drop-outs were generally those seen in subjects with SAR/PAR such as sinusitis and nasopharyngitis and not more common with placebo versus the FF groups with some notable exceptions. The incidence of withdrawals in the long-term safety study due to epistaxis was greater in the FF 110 group than in placebo. This AE, which is associated with the use of nasal steroids, was not a cause of withdrawal in the shorter 2-4 week studies in SAR/PAR but became noted with longer-term use. In addition, there were 2 cases of nasal candidiasis noted, one of which was in a higher (220 mcg) than proposed dose (110 mcg) of FF and one subject discontinued as a result of increased intraocular pressure, albeit unlikely due to FF as it had only been administered for 9 days.*

7.1.3.3 Other significant adverse events

No other significant adverse events were described in the application.

7.1.4 Other Search Strategies

No other search strategy was employed.

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7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the fluticasone furoate nasal spray clinical development program, an AE was **appropriately defined as “any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product”**. **During the trials AEs were elicited by several methods.** At every visit (weekly in all studies except the long-term safety study where subjects were seen every 4 weeks) after the subject had an opportunity to spontaneously mention any problems, the Investigator inquired about AEs by asking the following standard questions:

- **“Have you had any (other) medical problems or worsening of any medical problems since your last visit/assessment?”**
- **“Have you taken any new medicines, other than those given to you in this study, since your last visit/assessment?”**

Diary cards were also reviewed at each visit and if the subject did not mention an event that was recorded, he/she was questioned for further information in order to determine if an AE had occurred. The Investigator was responsible for determining what constituted an AE, including any clinical laboratory finding that was abnormal.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The CRF text for AEs was coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events were summarized and grouped by primary System Organ Class (SOC) and by AE (i.e., Preferred Term) within a primary SOC. Results were displayed in the order of decreasing frequency, both across primary SOC and within primary SOC. For the purposes of labeling only, several similar AE event terms were combined to arrive at an overall incidence for an adverse event (see the following table).

Applicant Grouping of Reported Terms for Labeling Purposes (*ISS.pdf, page 132 of 1692*)

Preferred Term	Terms Grouped Under Preferred Term
Sinusitis	Sinusitis, acute sinusitis, sinus bacterial
Tonsillitis	Tonsillitis, acute tonsillitis, pharyngotonsillitis
Bronchitis acute	bronchitis acute, bronchitis acute viral, bronchitis bacterial, tracheobronchitis
Headache	Headache, tension headache, migraine, migraine with aura, sinus headache
Nasal Ulcer	Nasal ulcer, nasal septum ulceration
Abdominal pain	Abdominal pain, abdominal pain upper

7.1.5.3 Incidence of common adverse events

In the adult clinical trials, AEs were reported in 27 and 29% of subjects in the placebo and FF 110 mcg groups, respectively, who took part in short clinical trials of 2-6 weeks duration. As would be expected, the incidence of AEs reported was greater in the longer one-year safety study with 71 and 77% of subjects in the placebo and FF 110 mcg groups, respectively, reporting AEs. Overall, headache was the most common AE, the incidence of which differed little between the FF 110 mcg group and placebo. Adverse events that occurred more commonly in the FF 110 mcg group than in the placebo group in the shorter, integrated adult studies (by 1-2% only) were headache, epistaxis, pharyngolaryngeal pain, back pain, and nasal septum ulceration. For these studies, there was no difference in the severity of any AEs in the FF 110 mcg treatment group compared to placebo. For the long-term safety study, again, nasopharyngitis was the most common AE reported with the incidence about equal (25-26%) among the FF 110 mcg and placebo groups. Epistaxis was the most notable AE that had an increased incidence in the FF 110 mcg group compared to placebo at 20% (123/605 subjects) versus 8% (17/201 subjects). In addition, more instances of epistaxis were reported as being moderate or severe for subjects receiving FF 110 mcg (40/605) compared to placebo (0/17). For nasal septal ulceration, similar to the short-term studies, the incidence was higher in the FF 110 mcg group (2%, 12/605) than in placebo (< 1%, 2/201) and more were reported to be of moderate severity (4/12) in the FF 110 mcg group than in the placebo group where both AEs of nasal septal ulceration were reported as mild.

Reviewer's Comment: The long-term safety study elicited that incidence and severity of the AE of epistaxis was dependent on the duration of treatment. A questionable safety signal regarding a higher degree of the severity of nasal septal ulcerations may also exist for the FF 110 mcg group. A limited amount of dose-related safety information is available since only one dose of FF was studied in the Phase 3 adult clinical trials and the dose-ranging

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study was of short duration and in a limited number of subjects (2 weeks in SAR with 127-130 subjects/arm). That being said, there was no apparent dose relationship for epistaxis or nasal ulceration elicited in that trial.

In the pediatric trials the incidence of AEs reported was very similar with 37, 43, and 41% of subjects reporting AEs in the placebo, FF 55 mcg and FF 110 mcg groups, respectively. Headache, again, was the most common AE reported (7-8%/group) while pyrexia was the most common AE reported that was greater in the FF treated groups than placebo (4-5% for FF 55 and 110 mcg) versus 2% for placebo). Of note was that there was no difference in the incidence of epistaxis between any of the treatment groups (4-5%). The majority of the adverse events reported in the pediatric population were events that are commonly reported in the general population overall and are events seen commonly in pediatric subjects.

7.1.5.4 Common adverse event tables

Summary of AEs from the Adult Integrated Studies with an Incidence \geq 1% during Treatment (ITT Population, Studies FFR20001, 20002, 30002, 30003, 103184, 104861)
 [Table 26 ISS.pdf, page 82/1692]

Adverse Event	Number (%) of Subjects	
	Placebo N=774	FF 100mcg QD N=768
Any Event	209 (27)	225 (29)
Headache	50 (6)	64 (8)
Epistaxis	32 (4)	45 (6)
Pharyngolaryngeal pain	8 (1)	15 (2)
Nasal septum ulceration	2 (<1)	9 (1)
Nasopharyngitis	11 (1)	9 (1)
Sinusitis	13 (2)	6 (<1)
Back pain	7 (<1)	9 (1)
Ear pain	8 (1)	4 (<1)

Source Data: Table 14.20

Reviewer's Comment: A variation of this table modified to include only those AEs that had a higher incidence in the FF 110 mcg group, should be used for the label. If the table proposed by the Applicant is used (AEs with an incidence of 3% or greater), nasal septal ulceration, an important AE known to be associated with nasal corticosteroids would be dropped.

7.1.5.5 Identifying common and drug-related adverse events

The relatively common (\geq 1%) AEs that could be considered drug related are those of epistaxis and nasal ulcerations. Both are noted to be class-related AEs associated with

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intranasal steroid spray use. The incidence of epistaxis was slightly greater in the FF 110 mcg group during the course of the short-term adult studies, however, during the year-long safety study in adult subjects with PAR, the incidence and severity of epistaxis was greater in the FF 110 mcg group compared to placebo. For nasal ulceration, the incidence was slightly greater (1-2%) in the FF 110 mcg groups than in placebo, however, more subjects were reported to have ulcerations of moderate severity in the FF 110 mcg group (see Section 7.1.5.3 above). Nasal candidiasis was a less common AE that could be considered to be drug related and occurred in 3 subjects in the FF clinical program (see Section 7.1.6).

7.1.5.6 Additional analyses and explorations

As noted in Section 7.1.5.3, the AE of epistaxis in the adult clinical trials was related to the duration of treatment.

7.1.6 Less Common Adverse Events

The uncommon AEs that are pertinent to this review are those related to local corticosteroid effects on the nose and eyes such as nasal candidiasis and elevation of intraocular pressure and formation of cataracts, especially those that are subcapsular. There were 3 subjects in the FF clinical program, one each in studies FFR30008, FFR20001, and FFR102123, that had AEs reported for nasal candidiasis, all in a FF active treatment group. One child receiving FF 55 mcg in study FFR30008 and one adult who received FF 220 mcg in study FFR20001 withdrew prematurely. The effects of FF on the eyes were evaluated in studies FFR102123 and FFR30008 and will be presented in Section 7.1.12, Special Studies.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine safety hematology and chemistry blood tests were performed at baseline and at the end of the study/early withdrawal in all of the integrated adult and pediatric pivotal trials other than the long-term safety study (FFR102123) when studies were performed at baseline and at Weeks 12, 24, and 52/early withdrawal and FFR 101816, the allergen chamber onset of action study when studies were performed at screening only. The HPA-axis was evaluated in studies FFR20001, FFR20002 FFR102123, FFR30008, and

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FFR100012 and intra-ocular pressure was measured in studies FFR102123 and FFR30008.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

All laboratory results were reviewed for each of the 12 randomized, placebo-controlled adult and pediatric studies which comprised the clinical development program.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

There were no clinically meaningful changes in the mean values of any of the routine laboratory values. Laboratory values were reported rarely as AEs and the incidence was no higher in subjects who received FF compared to placebo.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

All clinical trials also compared the numbers of subjects with shifts in hematology and clinical chemistry values from baseline to endpoint. Shifts were categorized as “to low”, “to normal/no change”, or “to high”. Outliers were designated as any value greater or less than the reference range, regardless of amount. Overall, there were no clinically relevant differences between FF and placebo groups for either adults or children in the incidence of subjects who shifted from normal at baseline to any abnormal value after treatment for any hematology or chemistry parameter.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

The only significant marked outlier for any laboratory value occurred in a child (Subject 122) in the placebo group of study FFR100010 in SAR who was discontinued due to the onset of insulin dependent diabetes mellitus. While the subject had a normal glucose value of 5.3mmol/L (about 100 mg/dL at baseline), the glucose level at withdrawal was quite high at 27.5mmol/L (about 500 mg/dL).

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7.1.7.4 Additional analyses and explorations

There was no indication for further analyses.

7.1.7.5 Special assessments

Nasal Examinations

An ENT examination that included protocol specified evaluation of nostrils, septum, and mucosa for edema, bleeding, secretions, etc. was performed at all of the clinic visits in all clinical studies except the short allergen chamber study. Most of the subjects showed evidence of active rhinitis throughout the studies. In the 6 short-term (2-6 week) adult studies there was no difference in the detection of mucosal bleeding between placebo and FF 110 mcg treated groups. After 4 weeks of treatment, 2% of subjects in the placebo group and 3% in the FF 110 mcg group were noted to have septal/turbinate ulcers, all mild. In the one-year adult safety study, mucosal bleeding was seen in a higher proportion of subjects in the FF 110 mcg group at the 12 and 24 week time points (4% and < 1% for placebo versus 7% and 5% for FF 110 mcg, respectively) however the proportion of subjects with mucosal bleeding did not increase with longer term treatment as 1% and 2% of subjects in the placebo and FF 110 mcg group were reported to have mucosal bleeding present. At week 52, there were a higher proportion of subjects with nasal ulcers detected in the FF 110 mcg group than placebo (3% in the FF 110 mcg group versus 1% in the placebo group).

In the pediatric program (FFR100010, FFR30008, and FFR101747), detection of mucosal bleeding was 5% at baseline for all 3 treatment groups (FF 55 and 110 mcg and placebo) and remained at 1-3% over the course of the studies (up to 12 weeks). No subjects in any of the treatment groups had findings of nasal ulcers in the turbinates at the study endpoints.

Over the course of the clinical development program, 4 subjects (2 in the pediatric 12 week study, FFR30008, and 2 in the adult year-long study, FFR102123), all treated with FF, had evidence of nasal candidiasis on exam.

Reviewer's Comment: The evidence of nasal candidiasis and the increased finding of mucosal bleeding/epistaxis in the long-term study will need to be addressed in the product label.

Ophthalmic Exams

Intraocular pressure measurements and slit lamp examinations were conducted in adult study FFR102123 (one year) and pediatric study FFR30008 (12 weeks). For all ophthalmic examinations, the sponsor defined a threshold limit for intraocular pressure (IOP) evaluations as any value ≥ 21 mmHg, and the sponsor-defined threshold for fundoscopic cup to disc percentage was >66%. In study FFR102123, there was no meaningful difference in mean changes in IOP for either eye between treatment groups. Twelve subjects (2%), all

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treated with FF 110 mcg, had IOPs that were above the threshold limit of 21mmHg during the study. No subject had a value above 21mmHg at more than one on-treatment visit. Of these 12 subjects, all but one had values of 21 or 22mmHg (7 subjects had values of 21mmHg and 4 subjects had values of 22mmHg). One subject (Subject 1332) had a measurement of 24mmHg in the left eye at Week 52.

Seven subjects (6 (1%) in the FF110 group and 1 (<1%) in the placebo group, had cataracts identified during the study period that were not present at baseline (see table below). Regardless of the 3:1 difference in the number of subjects/group, posterior subcapsular cataracts developing in a 15 year old (#17) and 14 year old (#1033) with three prior visits documenting no cataract is highly suggestive of a potential to develop cataracts. Subject #811, a twenty-three year old male who developed nuclear sclerotic cataracts after 52 weeks and having 3 prior evaluations which were negative for cataracts is also highly suggestive of cataract development.

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

Subject	(age/gender)	Visit	Left	Right
Placebo (N=201)				
1631		Baseline	No	No
(43/M)		Week 12	Posterior subcapsular (trace)	No
		EWV	Posterior subcapsular (trace)	No
Fluticasone furoate nasal spray 110mcg (N=605)				
17		Baseline	No	No
(15/F)		Week 12	No	No
		Week 24	No	No
		Week 52	Posterior subcapsular (trace)	No
1033		Baseline	No	No
(14/M)		Week 12	No	No
		Week 24	No	No
		Week 52	Posterior subcapsular (definite)	No
230		Baseline	No	No
(63/F)		Week 12	Cortical	Cortical
		Week 24	Cortical	Cortical
		Week 52	No	No
897		Baseline	Cortical	No
(66/M)		EWV	Nuclear sclerotic	Cortical
919		Baseline	No	No
(72/M)		Week 12	Nuclear sclerotic	Nuclear sclerotic
		EWV	No	No

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811	Baseline	No	No
(23/M)	Week 12	No	No
	Week 24	No	No
	Week 52	Nuclear sclerotic	Nuclear sclerotic

In the pediatric 12 week study, FFR30008, mean changes in IOP, again, were not meaningfully different between FF 55, 110, or placebo groups. There were 3 children, all receiving active treatment, (2 in the FF 55 and 1 in the FF110 mcg groups) who developed IOPs ≥ 21 mmHg at the end of the study. Cataracts not present at baseline were observed in 2 subjects in the placebo group and in 4 subjects in the FF 55 mcg group. While no subjects in the FF110 group developed new cataracts during the treatment period, 2 subjects had trace posterior subcapsular cataracts noted at baseline and at the end of the study. 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.

Reviewer's Comment: An ophthalmology consult by Wiley Chambers, M.D. was obtained in order to obtain a more expert opinion as to the meaning of the eye findings described above. Dr. Chambers felt that the development of cataracts, especially the posterior subcapsular type, in two young healthy individuals who had had three prior negative evaluations, was suggestive for drug-related cataract development. In addition, it appeared that FF increased IOP in the subset of individuals with a genetic susceptibility to have elevated IOP with steroid usage (See Ophthalmology Consult by Wiley Chambers, M.D. dated February 7, 2007).

There were no subjects in the adult or pediatric clinical programs that developed an abnormal fundoscopic cup to disk ratio during the trials.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were assessed at baseline and at the study endpoint for all studies in the clinical development program except for the allergen chamber study when vital signs were assessed at baseline/screening only and in the year-long adult safety study, FFR102123, when vital signs were assessed at every monthly treatment visit.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

All of the 12 clinical studies were reviewed for overall FF/placebo comparisons.

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7.1.8.3 Standard analyses and explorations of vital signs data

There was no evidence of a clinically meaningful effect of FF nasal spray on any vital sign.

7.1.8.4 Additional analyses and explorations

No additional analyses were performed

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiograms were performed at baseline and at study endpoint/early withdrawal in all studies in the clinical program except in the allergen chamber study when ECGs were obtained at baseline/screening only and in the pediatric knemometry study when no ECG studies were performed. Digital, centrally-read, 12-lead ECGs were performed in the adult long term safety study (FFR102123), the 12-week pediatric study (FFR30008), and the Phase 2b dose-ranging study (FFR20001), while investigator-read ECGs were evaluated in the remaining Phase 3 repeat-dose studies.

In addition to standard ECG assessments made in the clinical program, the Applicant has submitted a thorough QT clinical pharmacology study as part of the 120-day safety update. This was not viewed as a requirement for this clinical program as the systemic availability of FF when administered intranasally is quite low, however, the Applicant apparently conducted the study to support another FF indication as the study was conducted with FF administered by oral inhalation and therefore submitted the QT study to this NDA for completeness and full disclosure. The results show that FF did not have any clinically meaningful affect on QTc. A brief notation of the study design and results can be found in Section 7.2.9, Safety Update. At the time of this review, the QT study is still under review by the QT Interdisciplinary Review Team (IRT).

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

All studies in the clinical development program in which ECGs were obtained at baseline and study endpoint were reviewed to assess ECG results with particular attention paid to the digital, centrally-read studies which would not be subject to inter-investigator variation.

7.1.9.3 Standard analyses and explorations of ECG data

Adverse changes from baseline in ECGs obtained on subjects in the clinical program were rare and none likely related to the use of FF nasal spray. For the integrated adult studies, approximately 25% of subjects in each treatment group had abnormal/not clinically significant ECG findings at both baseline and at the end of the treatment period. Over the course of these 6 studies, 3 subjects, 1 who received placebo and 2 who received FF 110 mcg had what was determined to be a clinically significant abnormal change from baseline. The placebo subject was noted to have ventricular extrasystoles of mild intensity and the 2 subjects who received FF 110 mcg had mild AV-block that resolved on the day it was detected and mild intensity non-specific T-wave changes, respectively.

In the long-term safety study in which ECGs were performed digitally and centrally read, 7% of subjects had abnormal/not clinically significant ECG findings at baseline. There were 2 subjects, 1 placebo and 1 in the FF 110 mcg group that had significant abnormal changes in ECG over the course of the study; the placebo subject had left bundle branch block while the subject in the FF 110 mcg group had ectopic ventricular beats noted at the week 52 visit.

ECG findings for the dose-ranging study revealed no clinically significant changes in ECG from baseline to study endpoint.

In the pediatric program 1 subject in each of the placebo and FF 55 mcg groups had abnormal changes from baseline at the end of the studies, both of which were termed mild prolongation of QTc noted on the last day of treatment (Week 12) of study FFR30008.

7.1.9.4 Additional analyses and explorations

No additional analyses were performed as corticosteroids have a low potential to effect cardiac rhythm or function.

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7.1.10 Immunogenicity

Immunogenicity was not assessed in clinical studies as FF is not a therapeutic protein.

7.1.11 Human Carcinogenicity

Carcinogenicity was not formally assessed in the clinical development program. Two subjects in clinical trials who received FF 110 mcg were diagnosed with cancer during the treatment period; breast cancer in a subject enrolled in study FFR30002 in PAR and malignant melanoma in a subject enrolled in the long-term safety study, FFR102123. There is no reason to believe these cancers are related to treatment with FF.

7.1.12 Special Safety Studies

The effect of FF nasal spray on the HPA axis was specifically assessed in 2 clinical studies, FFR20002 in adolescents and adults and FFR100012 in children ages 2 < 12 years. These studies assessed both serum cortisol levels and 24 hour urine cortisol excretion at baseline and at the end of the 6 week treatment periods. Additionally, subjects were domiciled for the serum/urine collections which ensured both complete collections of urine and controlled for fluid intake and use of concomitant medications. HPA axis assessments (24 hour cortisol excretion only) were also conducted in adult studies FFR20001 and FFR102123 and in study FFR30008 in children. While these studies lacked the rigor of the specific HPA axis studies, they supply information on longer-term (12-52 week) use of FF (FFR 102123 and FFR30008) or the use of FF at higher doses for a 2 week period (FFR20001).

Overall, the studies show little to no apparent effect of FF 110 mcg on the HPA axis of adult subjects who received treatment for up to one year. The pediatric data are not as clean, however. While FF 110 mcg did not appear to effect the HPA axis of children in the 6 week pediatric HPA axis study, there did appear to be a dose-response relationship for a decrease in 24 hour urinary cortisol excretion compared to placebo in the 12 week pediatric study (FFR30008). Results of the studies are outlined in more depth below and each study is reviewed separately in the Appendix of this NDA review.

For the adult HPA axis study, FFR20002, in addition to placebo and FF 110 mcg groups, a group which received prednisone 10 mg QD for the last 10 days of the treatment period was also studied as a positive control. The primary endpoint of the study was change from baseline, expressed as a ratio, in 24 hour serum cortisol weighted mean for the FF 110 mcg group versus placebo. There was little difference in the changes from baseline for either the

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placebo or FF 110 mcg groups with ratios of weighted mean values of 0.99 and 0.97, respectively, indicating little or no suppression of cortisol levels. In contrast, the active control prednisone group ratio of the weighted means from baseline and endpoint was 0.49. Regarding 24 hour urinary excretion, mean changes from baseline for the placebo and FF 100 mcg groups was 5.03 mcg and -16.68 mcg, respectively, with the ratios of the means from baseline being 1.07 and 0.89 for the placebo and FF 110 mcg groups, respectively.

Results of 24 hour urinary determinations for urinary cortisol excretion for the Adult studies FFR20001 and FFR102123 also showed little effect of FF on the HPA axis. Specifically, for study FFR20001, there was no dose-response relationship with doses of FF ranging from 55-440 mcg/day for 2 weeks and for study FFR102123, there was no evidence of a decrease in urinary cortisol excretion in adults treated with FF 110 mcg for one year.

Results of the pediatric HPA axis study, FFR100012, were similar to those of the adult HPA axis study. There was very little change in mean serum cortisol levels from baseline in the placebo or FF 110 mcg groups and the ratios from baseline in serum cortisol weighted means were also very similar (0.97 and 0.94 for the placebo and FF 110 mcg groups, respectively). For urinary 24 hour cortisol excretion, no subject was noted to have 24 hour urinary cortisol excretion levels below the normal range at the 6 week study endpoint and the geometric mean ratio from baseline for the FF 110 mcg group was 0.97, implying little effects on the HPA axis. The geometric mean ratio from baseline for the placebo group was rather high at 1.26.

In the 12 week pediatric PAR study with a safety extension, decreases from baseline were observed in 24 hour urine cortisol excretion for both the FF 55 and 110 mcg active treatment groups compared with placebo. A dose response relationship exists with mean changes in 24 hour urinary cortisol excretion of -2.94 mcg, -6.95 mcg, and -12.67 mcg for the placebo, 55 mcg, and 110 mcg treatment groups, respectively. These decreases corresponded to geometric means for the ratio of week 12 to baseline of 0.90 for placebo, 0.84 for FF 55 mcg, and 0.79 for FF 110 mcg. Despite these findings, no subjects in the study had lower than normal 24 hour urine cortisol excretion at baseline or endpoint.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There was no evidence of drug abuse or dependence in these studies. No evidence of withdrawal phenomena or rebound was described during the post-treatment period.

7.1.14 Human Reproduction and Pregnancy Data

During the clinical development program 5 subjects became pregnant. For the 3 subjects who received FF, one pregnancy resulted in a normal term delivery and 2 subjects were lost

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to follow-up. For the 2 subjects who received placebo, both pregnancies resulted in term deliveries.

7.1.15 Assessment of Effect on Growth

Since a class effect of corticosteroids is to decrease longitudinal growth in children, a formal 6 week, randomized, placebo-controlled cross-over knemometry growth study was conducted in 58 pre-pubertal children ages 6 < 11 (females) and 6 < 12 (males) with SAR/PAR (FFR101747). The study was conducted using standard and accepted knemometric techniques with lower leg measurements obtained at baseline and at the end of 2 week treatment periods separated by a 2week washout period. The endpoint was to determine if treatment with FF 110 mcg nasal spray was non-inferior to placebo with respect to lower leg growth over 2 week treatment periods. The mean lower-leg growth rate was 0.40mm/wk for the FF100 mcg group and 0.42mm/wk for the placebo group with a difference in growth rates between the groups of -0.016mm/wk (95% CI: [-0.13, 0.10]). Since the lower limit of the 95% CI (-0.13mm/wk) was greater than the non-inferiority margin of -0.20mm/wk, FF110 was judged as non-inferior to placebo in terms of an effect on lower-leg growth rate. Study FFR101747 is reviewed in detail in the Appendix of this NDA review.

Reviewer's Comment: Per the Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products, a short-term growth study such as a knemometry study, while helpful, is not adequate to assess growth over the long term. The Applicant is aware that a year long study to assess growth via stadiometry will be a Phase 4 commitment.

7.1.16 Overdose Experience

No overdose was reported in the clinical program. However, single- and repeat-dose studies with **inhaled** FF doses of 50mcg to 4,000 mcg have shown decreased mean serum cortisol at doses of 500 mcg or higher [ISS.pdf, page 237/1692]

7.1.17 Postmarketing Experience

Fluticasone furoate nasal spray is not marketed anywhere in the world.

7.2 Adequacy of Patient Exposure and Safety Assessments

The designs of the studies in this application, patient demographics, exposure of

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subpopulations, and duration of exposure to FF nasal spray are sufficient to allow for assessment of safety. Adequacy of patient exposure and safety assessments are reviewed in depth below.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety**7.2.1.1 Study type and design/patient enumeration**

The tables of clinical studies provided in Section 4.2 provides a summary of the Phase 2b/3 studies that comprise the clinical development program as well as other clinical studies in this application including descriptive information on study type, treatment groups, design, patient population, subject numbers, dosing schedule, and indication.

7.2.1.2 Demographics

The demographics of patients in the adult short-term (2-6 weeks) clinical studies in the FF nasal spray drug development program are summarized the following table. Ninety seven per cent of subjects in the clinical studies ranged between 12-64 years of age. There were more females than males in the studies in the drug development program. The racial distribution was heavily skewed towards those listed as White (81%) with 7% of subjects reported as Black. Hispanic/Latino was listed as an ethnicity as opposed to a Race and comprised 21% of the study population. The majority of subjects were from the United States (75%).

Demographic Characteristics of Adults Enrolled Studies 2-6 Weeks of Duration (ITT Population-FFR20001/FFR20002/FFR30002/FFR30003/FFR103184/FFR104861)

[Table 20 ISS.pdf, page 73]

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	Placebo (N=774)	FF 100mcg QD (N=768)	Total (N=1542)
Age (years)			
Mean, SD	35.2, 13.79	36.3, 13.96	35.8, 13.88
Median	35.0	36.0	35.0
Min-Max	12 - 75	12 - 76	12 - 76
Age Groups, n (%)			
12 to <18 years	85 (11)	75 (10)	160 (10)
18 to <65	672 (87)	675 (88)	1347 (87)
65 to <75	16 (2)	16 (2)	32 (2)
≥75	1 (<1)	2 (<1)	3 (<1)
Gender, n (%)			
Female	461 (60)	473 (62)	934 (61)
Male	313 (40)	295 (38)	608 (39)
Race, n (%)			
White ^a	620 (80)	628 (82)	1248 (81)
Black ^b	60 (8)	41 (5)	101 (7)
Other ^c	94 (12)	99 (13)	193 (13)
Ethnicity, n (%)			
Hispanic/Latino	162 (21)	162 (21)	324 (21)
Not Hispanic/Latino	612 (79)	606 (79)	1218 (79)
Height (cm)			
Mean, SD	168.7, 9.98	168.4, 9.95	168.6, 9.96
Median	168.0	168.0	168.0
Min-Max	140-198	130-203	130-203
Weight (kg)			
Mean, SD	78.7, 19.92	79.5, 20.54	79.1, 20.23
Median	76.0	76.0	76.0
Min-Max	30-190	40-208	30-208
Region, n (%)			
United States	581 (75)	579 (75)	1160 (75)
Europe	144 (19)	141 (18)	285 (18)
Rest of World ^d	49 (6)	48 (6)	97 (6)

Source Data: Table 14.18

The demographics of subjects in the long-term safety study, FFR102123, were very similar to that of subjects in the shorter, pivotal studies. The proportion of those listed as White was slightly higher (87%) likely due to the study being performed in Europe and South America.

The demographics of patients in the pediatric (2-12 weeks) clinical studies in the FF nasal spray drug development program are summarized the table below. The mean age of children in the studies was 7.7 years with children ages 2 < 6 years accounting for 22% of the pediatric study population (261 subjects) and children 2 < 4 years accounting for 7% (83 subjects). There were slightly more males enrolled in the studies than females. Those

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listed as White accounted for 76% of the study population with 11% listed as being Black. Again, Hispanic/Latino was listed as an ethnicity as opposed to a Race and comprised 37% of the study population. The majority of subjects were from the United States (70%).

Demographic Characteristics in Pediatric Studies (ITT Population - FFR100010/FFR30008/FFR100012) [Table 23 ISS.pdf, page 77]

	Placebo (N=429)	FF 50mcg (N=369)	FF 100mcg (N=426)	Total (N=1224)
Age (years)				
Mean (SD)	7.7 (2.6)	8.0 (2.52)	7.5 (2.59)	7.7 (2.58)
Median	8.0	9.0	8.0	8.0
Min-Max	2 to 12	2 to 11	2 to 12	2 to 12
Age Groups, n (%)				
2 to <4 years	29 (7)	20 (5)	34 (8)	83 (7)
4 to <6 years	66 (15)	52 (14)	70 (16)	188 (15)
6 to <12 years	330 (77)	297 (80)	321 (75)	948 (77)
≥12 years	4 (<1)	0	1 (<1)	5 (<1)
Gender, n (%)				
Female	183 (43)	164 (44)	188 (44)	535 (44)
Male	246 (57)	205 (56)	238 (56)	689 (56)
Race, n (%)				
White ^a	329 (77)	292 (79)	304 (71)	925 (76)
Black ^b	51 (12)	30 (8)	58 (14)	139 (11)
Other ^c	49 (11)	47 (13)	64 (15)	160 (13)
Ethnicity, n (%)				
Hispanic/Latino	157 (37)	136 (37)	163 (38)	456 (37)
Not Hispanic/Latino	272 (63)	233 (63)	263 (62)	768 (63)
Height (cm)				
Mean (SD)	130.1 (17.15)	130.7 (16.46)	128.0 (17.07)	129.6 (16.94)
Median	132.0	134.0	131.0	132.0
Min-Max	86 to 171	82 to 168	70 to 172	70 to 172
Weight (kg)				
Mean (SD)	31.9 (12.83)	32.0 (12.68)	30.9 (12.19)	31.6 (12.57)
Median	29.9	30.0	28.5	29.5
Min-Max	11 to 82	11 to 87	12 to 77	11 to 87
Region, n (%)				
United States	304 (71)	247 (67)	303 (71)	854 (70)
Europe	20 (5)	19 (5)	20 (5)	59 (5)
Rest of World	105 (24)	103 (28)	103 (24)	311 (25)

Source Data: Table 14.19

The demographics of patients in the clinical program and exposure of subpopulations to FF nasal spray are adequate to provide an assessment of safety.

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7.2.1.3 Extent of exposure (dose/duration)

Overall, 3954 adult, adolescent, and pediatric subjects have participated in the Phase 2 and Phase 3 clinical studies, with approximately 60% of these subjects (2359) treated with FF 55 or 110 mcg doses QD. Of these 3954 subjects in the database, 547 (27%) were exposed to FF110 mcg for a period ≥ 3 months, 501 (25%) for a period of ≥ 6 months, 473 (24%) exposed for a period of ≥ 9 months, and 400 (20%) of the subjects treated with FF were exposed for ≥ 12 months. Overall, the numbers of subjects exposed to fluticasone furoate met or exceeded the International Conference on Harmonization (ICH) Guidance E1 for extent of population exposure to assess clinical safety, where total population exposure is recommended to be 500 to 1500 subjects, with 300 to 600 subjects exposed for 6 months and 100 subjects exposed to investigational drug for a minimum of one year.

The extent of exposure in all adult and pediatric Phase 2/3 clinical programs is summarized in the tables below.

For the adult population, 2730 subjects participated in Phase 2/3 clinical studies with 1564 (57.3%) being treated with the proposed dose of FF 110 mcg QD. A total of 535 (34%) subjects were exposed to FF 110 mcg for a period ≥ 3 months, 501 (32%) were exposed for a period of ≥ 6 months, 473 (30%) were exposed for a period of ≥ 9 months, and 400 (26%) of the subjects treated with fluticasone furoate were exposed for ≥ 12 months.

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Summary of Extent of Exposure of Adolescents and Adults to Study Medication (ITT Population of Adult and Adolescent Clinical Studies) [Table 4 ISS.pdf, page 51/1692]

	Placebo (N=1166)	FF 100mcg QD (N=1564)	Total (N=2730)
Number of Subjects, n (%)			
1 day	193 (17)	192 (12)	385 (14)
2 days - 4 weeks	617 (53)	632 (40)	1249 (46)
4 - 8 weeks	177 (15)	171 (11)	348 (13)
8 - 12 weeks	5 (<1)	18 (1)	23 (<1)
12 - 16 weeks	6 (<1)	13 (<1)	19 (<1)
16 - 20 weeks	2 (<1)	10 (<1)	12 (<1)
20 - 24 weeks	2 (<1)	14 (<1)	16 (<1)
24 - 28 weeks	4 (<1)	5 (<1)	9 (<1)
28 - 32 weeks	1 (<1)	17 (1)	18 (<1)
32 - 36 weeks	2 (<1)	4 (<1)	6 (<1)
36 - 40 weeks	2 (<1)	8 (<1)	10 (<1)
40 - 44 weeks	2 (<1)	5 (<1)	7 (<1)
44 - 48 weeks	2 (<1)	13 (<1)	15 (<1)
48 - 52 weeks	46 (4)	112 (7)	158 (6)
365 - 370 days	94 (8)	330 (21)	424 (16)
>370 days	7 (<1)	11 (<1)	18 (<1)
Treatment Duration¹, n (%)			
≥3 months ²	166 (14)	535 (34)	701 (26)
≥6 months ³	157 (13)	501 (32)	658 (24)
≥9 months ⁴	152 (13)	473 (30)	625 (23)
≥12 months ⁵	125 (11)	400 (26)	525 (19)
Exposure, days			
n	1162	1555	2717
Mean	63.5	128.9	101.0
SD	118.21	158.57	146.31
Median	15.0	23.0	16.0
Min-Max	1 - 387	1 - 376	1 - 387

Source Data: Table 14.13

Adult and adolescent studies included FFR20001, FFR20002, FFR30002, FFR30003, FFR103184, FFR104861, FFR102123, FFR101816

In the pediatric program, 1224 subjects ages 2 < 12 years participated in placebo-controlled, parallel group design Phase 3 studies of 2-12 weeks duration. There were 83 subjects 2 < 4 years, 271 from 2 < 6 years and, 948 from 6 < 12 years of age in Phase 3 parallel group studies. A total of 125 and 124 pediatric subjects have been exposed to FF 55 mcg and FF 110 mcg QD doses for ≥ 12 weeks duration. Of these, 120 subjects (22%) were ages 2 < 6 years. An additional 58 subjects participated in the knemometry growth study, FFR101747 which was of crossover design with 2 week treatment periods of FF 110 mcg versus placebo.

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Summary of Extent of Exposure of Children < 12 years of Age to Study Medication (ITT Population-FFR100010/FFR30008/FFR100012) [Table 8 ISS.pdf, page 55/1692]

	Placebo (N=429)	FF 50mcg QD (N=369)	FF 100mcg QD (N=426)	Total (N=1224)
Number of Subjects, n (%)				
0 - 2 weeks	38 (9)	36 (10)	36 (9)	110 (9)
2 - 4 weeks	161 (38)	157 (43)	161 (38)	479 (39)
4 - 6 weeks	37 (9)	3 (<1)	32 (8)	72 (6)
6 - 8 weeks	21 (5)	4 (1)	23 (5)	48 (4)
8 - 10 weeks	3 (<1)	2 (<1)	1 (<1)	6 (<1)
10 - 12 weeks	41 (10)	40 (11)	45 (11)	126 (10)
>12 weeks	123 (29)	125 (34)	124 (29)	372 (31)
Exposure, days¹				
n	424	367	422	1213
Mean	46.4	47.6	47.2	47.0
SD	32.77	34.75	32.87	33.39
Median	41.5	18.0	41.5	41.0
Min-Max	1 - 99	6 - 95	1 - 98	1 - 99

Source Data: Table 14.15

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

All pertinent studies performed for the fluticasone furoate are provided in this NDA application.

7.2.2.2 Postmarketing experience

Fluticasone furoate nasal spray is not marketed in any country.

7.2.2.3 Literature