BPCA CLINICAL SUMMARY OF NDA 20-548, SE8-018

APPLICATIONS:	NDA 20-548, SE8-018	**TRADE NAME:**	Flovent® Inhalation Aerosol
APPLICANT:	GlaxoSmithKline Research Triangle Park, North Carolina 27709	**USAN NAME:**	Fluticasone propionate inhalation aerosol (CFC MDI)
MEDICAL OFFICER:	Peter Starke, MD	**CATEGORY:**	Corticosteroid
TEAM LEADER:	Eugene Sullivan, MD	**ROUTE:**	Oral inhalation
DUE DATE:	4 June 2003	**REVIEW DATE:**	4 June 2003

1. BACKGROUND AND ADMINISTRATIVE ISSUES

This submission provides the results of two clinical studies and one *in vitro* study, which were performed in response to the Agency's Written Request for pediatric studies of the fluticasone propionate moiety. The clinical studies were 12-week efficacy and safety studies using Flovent® Inhalation Aerosol (fluticasone propionate inhalation aerosol CFC MDI) and a spacer/holding chamber with mask in children with asthma ages 24 to 47 months and 6 months to 23 months. Flovent® Inhalation Aerosol is currently indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. A lowering of the indicated age range was not sought. Since Flovent® Diskus® and Flovent® Rotadisk® are approved down to 4 years of age, studies were not requested for fluticasone propionate in children 4 years of age or older.

The Written Request was issued June 25, 1999, and amended on May 21, 2001, and October 25, 2001. Seven dermatology and pulmonary studies were requested, four for fluticasone propionate topical (Cutivate®) (3 for the 0.05% lotion and 1 for the 0.005% ointment), one for fluticasone propionate nasal spray (Flonase® Nasal Spray), and two for fluticasone propionate inhalation aerosol CFC MDI (Flovent®). Also requested were an *in vitro* CMC study characterizing of the dose delivery from two different U.S.-marketed spacers (GSK evaluated three), and a population PK evaluation of FP levels at the end of 12 weeks of therapy with fluticasone propionate inhalation aerosol CFC MDI in the two requested clinical Flovent studies.

Study reports for the topical and intranasal formulations have previously been submitted. This submission included the final two clinical study reports, the CMC study report, and the population PK report to support Pediatric Exclusivity. On the basis of the completion and submission of the studies requested in the Written Requests, GlaxoSmithKline (GSK) requested a Pediatric Exclusivity determination. The Pediatric Exclusivity Board met on February 25, 2003, determined that Pediatric Exclusivity requirements were met, and granted exclusivity.

2. BRIEF OVERVIEW OF CLINICAL PROGRAM

This submission includes two clinical trials and two other reports, a CMC report and a population PK report. The studies submitted are shown in Table 1.

The two clinical trials were randomized, double-blind, placebo-controlled 12-week efficacy and safety studies using Flovent (CFC) MDI in doses of 44mcg and 88mcg BID in children ages 6 to 23 months and in children ages 24 to 47 months of age. In the older children, both an Aerochamber and an Optichamber valved holding chamber with a facemask were used.

In the younger children, only an Aerochamber with a facemask was used. The CMC report is a cascade impactor study that sought to characterize the dose delivery from the fluticasone propionate MDI with three different U.S.-marketed spacers/holding chambers. The population PK report is for the pharmacokinetics of fluticasone propionate MDI administered with a spacer/holding chamber in the two submitted pediatric clinical studies.

Table 1. Summary of Studies and Reports

Study or Report Centers	Conducted for pediatric Written Request?	Design	Dosage	Evaluations
FMS30058 77 centers in US	Yes	12-week, multicenter, randomized, double-blind, parallel group, placebo-controlled efficacy and safety study in 332 24-47 month old patients with asthma	Flovent CFC MDI 44mcg BID 88mcg BID Placebo Aerochamber and Optichamber with mask	1°: Parent/guardian assessed mean daily asthma symptom scores over last 2 weeks 2°: % symptom-free days, % albuterol-free days, day and night asthma symptom scores, time to treatment failure, daily rescue albuterol use, daily albuterol use, daily AM PEF, subgroup analyses
FMS30059 54 centers in the US, Puerto Rico, and Chile	Yes	12-week, multicenter, randomized, double-blind, parallel group, placebo-controlled efficacy and safety study in 211 6-23 month old patients with asthma	Flovent CFC MDI 44mcg BID 88mcg BID Placebo Aerochamber with mask	1°: Parent/guardian assessed mean daily asthma symptom scores over last 2 weeks 2°: % symptom-free days, % albuterol-free days, day and night asthma symptom scores, time to treatment failure, daily rescue albuterol use, daily albuterol use, subgroup analyses
RM2002/00 318/00	Yes	Pharmacokinetic Report for studies FMS30058 and FMS30059: Population PK analysis of FP CFC MDI plus a valved holding chamber (Aerochamber or Optichamber) & facemask in young children with asthma		Pop PK approach used. Only 7 patients with evaluable PK results.
RD2000/02 054/00	Yes	In Vitro Study Report: Comparison of the particle size distribution by cascade impaction for FP CFC MDI with and without the use of the Aerochamber, the Aerochamber Plus, and the Optichamber	Flovent CFC MDI Aerochamber Aerochamber Plus Optichamber	Cascade impaction study
HPA = hypothalamic-pituitary-adrenocortical axis, PK = pharmacokinetic.				

3. *IN VITRO* CMC STUDY

The Written Request of June 25, 1999 stated that before starting the clinical program with the inhalation aerosol, GSK should "characterize the dose delivery from the inhaler with two different U.S.-marketed spacers in *in vitro* studies to determine the optimum doses" for the clinical studies. In response, GSK performed an *in vitro* study that compared the particle size distribution by cascade impaction for Flovent Metered Dose Inhaler (44mcg) with and without the use of the Aerochamber, the Aerochamber Plus and the Optichamber.

The study evaluated the particle size distribution of the dose delivered into a cascade impactor from 10 puffs (actuations) from each of the MDI/holding chamber combinations and the MDI alone. The study was performed with a 5-second inversion/shaking and 30-second delay between puffs at a constant flow rate of 28.3 L/minute. In order to attach the holding chambers to the cascade impactor, the facemasks were removed. On the basis of this study, GSK states that the fine particle mass (FPM) for the Aerochamber is virtually the same as for the MDI alone. Although there was a slight decrease in FPM for the Optichamber and a slight increase for the Aerochamber Plus when compared to the MDI alone, they state that the differences were not significant.

The results of this study appear to indicate that the *in vitro* respirable particle content is quite similar when the MDI is studied alone, or with either of the three spacers. A comparable amount of drug to the amount that is typically deposited in the throat of the cascade impactor (which clinically relates to the patient's throat) when using the MDI alone appears to be deposited in the holding chamber with the addition of the holding chamber. The respirable dose (CI stages 3-5) remains relatively similar. However, this study failed to evaluate a number of factors that might affect the outcomes of such testing and that might be important *in vivo* in the clinical setting. These include evaluation of the variability in fine particle mass that might be introduced based on variations in total air volume, flow rate, the delay between actuation and in-flow, how long the mask is held over the nose and mouth, and spacer cleaning technique. 'Extractables' coming from the holding chamber were not measured. Therefore the Division assessed that, while the cascade impactor study did to some extent characterize dose delivery from the inhaler with several holding chambers (thus satisfying the Written Request), the study could not be used to establish the emitted or the inspired dose when a spacer/holding chamber is used clinically in conjunction with an MDI.

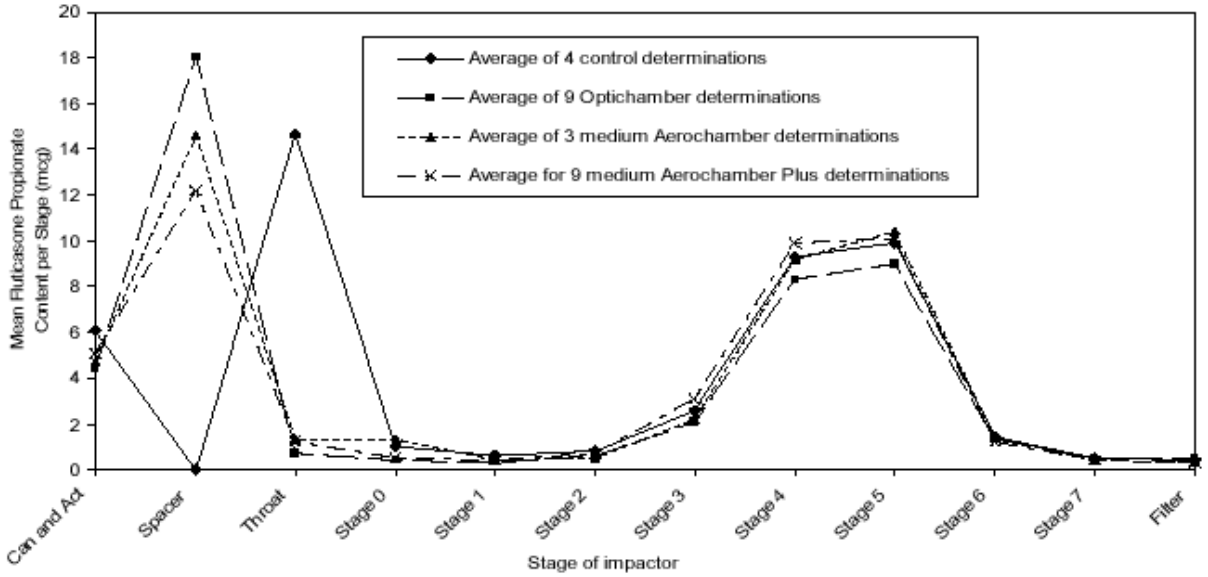

Figure 1. Comparison of the particle size distribution for the Flovent control with that produced when using the Optichamber, the medium Aerochamber and medium Aerochamber Plus

4. POPULATION PK REPORT

The population PK study combined sparse-sampling PK data from studies FMS30058 and FMS30059. One blood sample was taken from each patient on the last day of treatment (Visit 7 at 12 weeks). Samples were taken at one of four time intervals: -1.0 hour to 00 (pre-dose), 0.25 to 2.5 hours, 3 to 8 hours, or 9 to 11 hours post-dose. Many samples could not be used for various reasons including missing information in the case report form, insufficient sample for assay, problems with the analysis, samples stored longer than 15 months, and samples below the limits of quantification (BLQ). Lower limit of quantification (LLQ) was 10 pg/mL.

The results of the PK sampling may be briefly summarized as follows: 49% of the FP44 group and 31% of the FP88 group had levels BLQ (<10 pg/mL). Detectable FP levels were found in 13 patients who were on placebo treatment, with levels ranging from 11.2 to 135 pg/mL, from PK samples drawn at all timepoints. (*Note: GlaxoSmithKline was not able to provide an adequate explanation of this observation. Please refer to the next section for further details*.) There was high variability of plasma concentrations. The highest plasma concentrations were found to be during the first 2.5 hours. FP exposure increased with dose, with an average of 54.4 pg/mL for the FP88 and 35.8 pg/mL for the FP44 groups. FP exposure was found to increase with height. No PK-PD relationship was found for either efficacy or safety endpoints. These data were not explored in depth because of the unexplained PK results for the 13 patients on placebo treatment.

5. DATA QUALITY

A significant data quality concern was raised during the review process. The PK report stated the following:

> "Plasma samples from all subjects were measured for FP prior to unblinding. Samples from subjects who received placebo were BQL (<10pg/mL) in 94 of 107 subjects. The remaining 13 samples in the placebo group (10 samples from FMS30058 and 3 samples from FMS30059) had measurable FP concentrations. Concentrations ranged between 11.2 to 135pg/mL with the mean concentration of 40.5pg/mL. These unexpected drug levels in placebo samples could not be explained."

Because of these unusual results, the Division evaluated the PK data from these patients. The placebo group with detectable plasma FP levels included ten patients from ten different sites in study FMS30058 and three patients from two different sites in study FMS30059. The range of FP levels and timing of the positive samples for the placebo group were quite comparable to the range of FP levels and timing of the positive samples found in patients assigned to active drug treatment. Because of this concern, the Division asked GlaxoSmithKline to submit information regarding what steps were taken to evaluate the cause of the detectable FP levels in patients randomized to placebo, to summarize those results, and to comment on any further steps that could be taken to clarify these issues. GSK responded that they looked into several possibilities, but were unable to find the cause of the detectable FP levels in the 13 out of 107 placebo patients for whom FP measurements were performed. These 13 patients had no record of receiving FP during the study, and were not exposed to FP on the day of PK testing. While there are a number of possible explanations for the observed results, one possible explanation was a drug allocation error. Therefore, the Division judged that it was impossible to evaluate the actual patient exposure in the two clinical studies submitted. It is conceivable that patients randomized to placebo received active drug in error. It is also conceivable that patients randomized to active drug received placebo in error. Since many patients on active treatment did not have detectable FP levels, the problem may have been larger than stated. Misallocation of study drug would have the effect of blunting both the efficacy and safety findings from the studies, thereby making a risk/benefit assessment impossible.

In conclusion, while the cause of the detectable FP levels in 13 placebo-treated patients was not determined, due to the issues stated above the studies could not be meaningfully interpreted, and no conclusions may be drawn regarding either efficacy or safety from the clinical studies.

6. SUMMARY OF THE CLINICAL STUDIES

Two clinical studies were performed in young children spanning 6-47 months of age. Both were specifically designed to satisfy the requirements of the pediatric Written Request. Both used Flovent Inhalation Aerosol 44mcg (CFC MDI), which is currently approved for adolescents and adults 12 years of age and older.

The studies were identical 12-week, randomized, double-blind, parallel group, placebo-controlled multicenter efficacy and safety studies using Flovent Inhalation Aerosol (CFC MDI) administered via a spacer/holding chamber with facemask in male and female patients

with asthma. The studies compared Flovent dosages of 44mcg (1 puff of FP44, 1 puff placebo) BID and 88mcg (2 puffs of FP44) BID with placebo (2 puffs) BID. Study FMS30058 was conducted in children ages 24 to 47 months, and study FMS30059 was conducted in children 6 months to 23 months. In study FMS30058, two holding chambers were used, the Aerochamber and the Optichamber. In study FMS30059, only one holding chamber was used, the Aerochamber. Information regarding care or handling of the holding chambers was not reported. There were only minor differences in study design, all related to minor differences in the pediatric Written Request.

The studies were conducted in two periods: a 2- to 4-week screening period, and a 12-week treatment period. Patients attended clinic visits at treatment weeks 1, 2, 4, 8, and 12 (Weeks 6 and 10 were phone contacts only). For entry into the study, patients were required to have a documented history of symptomatic asthma and to have experienced at least 2 episodes of increased symptoms of asthma requiring medical attention and asthma pharmacotherapy within the preceding 12 months. Patients also had to require therapy with a maintenance asthma medication other than systemic corticosteroids on a regular basis for the preceding 6 weeks and/or require therapy with a short-acting beta-agonist for the relief of respiratory symptoms at least twice per week over the preceding 3 weeks prior to Visit 1. To be eligible for randomization, patients had to have documented asthma symptoms during 5 of the last 7 days of the screening period, and use of albuterol on at least 2 occasions during the 5 symptomatic screening days.

The primary efficacy variable for both studies was the parent/guardian rating of the patient's daytime and nighttime asthma symptoms. The daily asthma symptom score was the average of daytime and nighttime asthma symptom scores scored on a 0-3 scale and recorded on the daily diary record by the parent/guardian. Each assessment was a single score that evaluated a composite of symptoms including wheeze, cough and shortness of breath. The primary efficacy endpoint was the average change from baseline in daily (daytime and nighttime) asthma symptom scores to Endpoint (the last two weeks of diary data prior to end of study, asthma exacerbation, or study withdrawal). Secondary efficacy endpoints included the percentage of symptom-free 24-hour days, percentage of symptom-free and albuterol-free 24-hour days, change from baseline to endpoint in daytime asthma symptom scores, change from baseline to endpoint in nighttime asthma symptom scores, time to treatment failure, and change from baseline in albuterol use. Other efficacy endpoints included the diary AM peak expiratory flow rate (PEF) (study FMS30058 only), the frequency of treatment failure, and patient discontinuations.

For each study, a Reduced Intent to Treat (RITT) population was defined prior to breaking the study blind. The RITT population excluded from the Intent to Treat (ITT) population a total of four patients because of study conduct irregularities at one study site, and any patients for whom study blind was broken (the most common cause was "flaking" of the blinding cover). In both studies, statistical comparison of each dose versus placebo was made without adjustment for multiplicity. In addition, a Growth population and a Urine Cortisol population were defined for each study. The Growth population excluded patients who did not have sufficient or reliable growth data to provide an estimate for the 12-week growth velocity. Specifically, the Growth population excluded patients who did not have three growth assessments including measurements at both baseline (Visit 2) and Week 12 (Visit 7), had a decrease in height over time, or received oral, injectable, or medium-dose

inhaled corticosteroids within 8 weeks of a measurement. The Urine Cortisol population was defined to exclude patients from the ITT population whose urine samples were considered to have confounding factors that would affect interpretation of the results. Specifically, the urine cortisol population excluded patients who did not have a sufficient urine volume or creatinine, had a collection interval >12 ± 2 hours, received oral, injectable, or medium-dose inhaled corticosteroids within 8 weeks of a collection, received intranasal or topical corticosteroids >1% potency within 30 days of a collection, or had been off study drug for more than one full day at the time of the post-baseline collection.

In study FMS30058, 80 outpatient centers were planned, 87 centers participated, and 77 centers enrolled patients (range 1 to 21 patients per center). Approximately 390 patients were planned, 493 enrolled, and 332 were randomized. The ITT population included 113 placebo, 111 FP44, and 108 FP88 patients. The RITT population included 111 placebo, 108 FP44, and 105 FP88 patients. The demographics, patient and family history of asthma and allergies, incidence of other medical conditions, use of non-asthma concurrent medications, and use of asthma medications other than corticosteroids were comparable among groups at baseline. The FP44 group had a slightly lower baseline use of corticosteroids for control of asthma symptoms.

In study FMS30059, 80 outpatient centers were planned, 71 centers participated, and 54 centers enrolled patients (range 1 to 17 patients per center). Approximately 390 patients were planned, 337 enrolled, and 211 were randomized. The ITT population included 69 placebo, 73 FP44, and 69 FP88 patients. The RITT population included 69 placebo, 71 FP44, and 69 FP88 patients. About 1/3 of the randomized patients were between 6 and 12 months of age (randomization was stratified by age). The demographics, patient and family history of asthma and allergies, incidence of other medical conditions, use of non-asthma concurrent medications, and use of asthma medications other than corticosteroids were comparable among groups at baseline. While the history of smoking exposure was comparable between the placebo group and the active treatment groups (23% placebo, 21% FP44, 23% FP88), the placebo group included children with less pet exposure (32% placebo, 42% FP44, 43% FP88) and more likelihood of attending day care (41% placebo, 32% FP44, 29% FP88). The placebo group also had a slightly higher baseline use of corticosteroids (both oral and inhaled) within the six months of study onset.

7. EFFICACY

A meaningful interpretation of the efficacy results from these studies cannot be made because of detectable plasma levels of fluticasone seen in placebo treated patients. Therefore, efficacy data from the studies are not presented in this summary.

The Division judged that it was impossible to evaluate the actual patient exposure in the two clinical studies submitted. Detectable FP levels were found in 13 patients who were on placebo treatment, with levels ranging from 11.2 to 135 pg/mL. GlaxoSmithKline was not able to explain this observation. While there are a number of possible explanations for the observed results, one possible explanation was a drug allocation error. Since many patients on active treatment did not have detectable FP levels, the possibility is raised that the problem may have been larger than stated. Additional placebo patients may have received active treatment and yet had undetectable FP levels. In addition, active treatment patients

with undetectable FP levels may in fact have received placebo. The actual extent of exposure is impossible to determine. Misallocation of study drug would have the effect of blunting the efficacy findings from both studies. As a result, it is impossible to ascertain whether the studies derived an accurate assessment of efficacy.

8. SAFETY

The safety data in this submission are considered uninterpretable as to the true extent of the safety risk. The Division judged that it was impossible to evaluate the actual patient exposure in the two clinical studies submitted. Misallocation of study drug would have the effect of blunting any safety signals found, and minimizing the true extent of the safety risk. Since it is impossible to ascertain whether the studies derived an accurate assessment of safety, the Division judged that meaningful interpretation of the safety results of these studies is impossible. Therefore, safety data from the studies are not presented in this summary.

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Marianne Mann
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Signing for Dr. Sullivan, acting team leader, in his absence.