MEDICAL OFFICER REVIEW

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

APPLICATION:	NDA 20-548, (b)(4) 8-018	**TRADE NAME:**	Flovent® Inhalation Aerosol
APPLICANT:	GlaxoSmithKline	**USAN NAME:**	Fluticasone propionate inhalation aerosol (CFC MDI)
MEDICAL OFFICER:	Peter Starke, MD	**CATEGORY:**	Corticosteroid
TEAM LEADER:	Eugene Sullivan, MD	**ROUTE:**	Oral inhalation
PDUFA DATE:	14 June 2003	**REVIEW DATE:**	2 June 2003

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
13 December 2002	16 December 2002	N20-548 (b)(4) 8-018	Supplement with final studies for Pediatric Exclusivity determination. 170-Day Due Date: 4 June 2003
16 January 2003	16 January 2003		(b)(4)
14 February 2003	14 February 2003		Answers to questions regarding Pediatric Exclusivity determination
14 February 2003	19 February 2003		Answers to questions regarding (b)(4) site
22 April 2003	22 April 2003		Answers to questions regarding oropharyngeal and nasal exams and fungal cultures
15 May 2003	15 May 2003		Answers to question regarding Data Quality and Integrity issues
19 May 2003	19 May 2003		Re-plots of growth & HPA axis figures

RELATED APPLICATIONS

26 September 1986	IND (b)(4)	(b)(4)	Original IND (b)(4)
29 December1994	NDA 20-548	Flovent® Inhalation Aerosol	NDA Approved 27 March 1996
26 September1996	NDA 20-770	Flovent® Rotadisk®	Pediatric supplement for ages 4-11y

REVIEW SUMMARY:

This supplement addresses the use of Flovent® CFC MDI when used with a holding chamber with a mask in young children ages 6 to 47 months. Flovent is currently approved for the maintenance treatment of asthma in patients 12 years of age and above, and is not approved for use in children below 12 years of age. Two clinical studies, a (b)(4) study, and a population PK report from the clinical studies were submitted in response to a pediatric Written Request. Since Flovent® Diskus® and Flovent® Rotadisk® are approved down to 4 years of age, studies were not requested for this age group. This submission included the final studies for the Written Request. The Pediatric Exclusivity Board met on February 25, 2003, and exclusivity was granted.

A major Data Quality and Integrity issue was found in the population PK samples, where 13 patients randomized to placebo had detectable levels of FP (LLQ = 10pg/mL). The applicant did not have an adequate explanation for this observation. Of the potential causes, a drug allocation error would have had the effect of minimizing any efficacy or safety signals found in the studies. (b)(4)

OUTSTANDING ISSUES:

None

(b)(4)

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EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1. Recommendation (b) (4)

(b) (4)

1.2. Recommendation on Phase 4 Studies and/or Risk Management Steps

No Phase 4 studies or risk management steps are required.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Background and Administrative Issues

This submission is a (b) (4) supplement for Flovent® Inhalation Aerosol (fluticasone propionate [FP] inhalation aerosol CFC MDI). Flovent Inhalation Aerosol is currently indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. (b) (4) GSK is not seeking an extension of the indicated age range below 12 years of age. The clinical studies were 12-week efficacy and safety studies using 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.

This submission is also the final of three submissions in response to a pediatric Written Request for the fluticasone propionate moiety. 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. Since Flovent® Diskus® and Flovent® Rotadisk® are approved down to 4 years of age, studies were not requested for children 4 years of age and older.

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, and exclusivity was granted.

The dermatology studies for fluticasone propionate have previously submitted and resulted in changes to the label of Cutivate. The pulmonary/allergy portion of the pediatric Written Request also included one clinical hypothalamic-pituitary-adrenocortical (HPA) axis safety study. This study (FNM40183) was a 6-week HPA axis study using Flonase® Nasal Spray in children between ≥2 and <4 years of age with allergic rhinitis, using the highest recommended dose of 200mcg daily. (b) (4)

Study FNM40183 was not reviewed as part of this efficacy supplement, but was reviewed for the Pediatric Exclusivity determination. (b) (4)

2.2. 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 with this application 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 (b) (4) study that sought to characterize the dose delivery from the fluticasone propionate CMC MDI with three different U.S.-marketed spacers/holding chambers. The population PK report is for the pharmacokinetics of fluticasone propionate CMC 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,	Yes	12-week, multicenter, randomized, double-blind, parallel group, placebo-controlled efficacy and safety study in 211 6-23	Flovent CFC MDI 44mcg BID 88mcg BID Placebo	1°: Parent/guardian assessed mean daily asthma symptom scores over last 2 weeks

Study or Report Centers	Conducted for pediatric Written Request?	Design	Dosage	Evaluations
and Chile		month old patients with asthma	Aerochamber with mask	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
RM2002/00318/00	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.
RD2000/02054/00	Yes	In Vitro Study Report: Comparison of the particle size distribution [redacted] 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	[redacted] study

HPA = hypothalamic-pituitary-adrenocortical axis, PK = pharmacokinetic.

2.3. *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 Studies 1 and 2" (i.e. the two clinical studies using Flovent CFC MDI plus spacer device in children 6 to 23 months and 24 to 47 months of age). In response, GSK performed one *in vitro* study to satisfy the Written Request, which compared the particle size distribution [redacted] for Flovent CFC MDI with and without the use of the Aerochamber, the Aerochamber Plus and the Optichamber.

This study was a highly limited study. The study evaluated the particle size distribution of the dose delivered [redacted]

[redacted]

(b) (4)

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. In addition, extractables coming from the holding chamber were not measured. Therefore the Division assessed that, while the (b) (4) 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.

(b) (4)

2.4. 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 following study drug administration. This included -1.0 to 00 (pre-dose), 0.25 to 2.5, 3 to 8, or 9 to 11 hours post-dose. Many samples could not be used for various different reasons including missing information in the CRF, 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: The applicant 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. Ethnicity was also found to be a covariate. No PK-PD relationship was found for either efficacy or safety endpoints. These relationships were not explored in depth because of the unexplained PK results for the 13 patients on placebo treatment.

2.5. Data Quality and Integrity

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." [HPBio, PK Study, page 36; pkpopulation.pdf]

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. This raised the concern of a major Data Quality and Integrity issue in these studies.

Because of this concern, the Division asked the applicant 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. This information was not sufficient to resolve the concerns over Data Quality and Integrity.

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. It is also conceivable that patients randomized to active drug received placebo. 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, making a risk/benefit assessment impossible.

(b) (4)

2.6. Efficacy

(b) (4)

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. The applicant 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. Lack of ability to quantify exposure potentially blunted the efficacy findings from both studies. As a result, it is impossible to ascertain whether the studies derived an accurate assessment of efficacy. In addition, statistical comparisons were made without adjustment for multiplicity in the primary (and secondary) endpoints. Therefore, the Division judged that meaningful interpretation of the results of these studies is impossible.

The efficacy results are presented below, but must be judged based on the possibility of an allocation problem that may have minimized any efficacy findings.

2.6.1. Summary of the Studies

Efficacy for this application was derived from two clinical trials 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 (CFC MDI), which is currently approved for adolescents and adults 12 years of age and older. This application did not seek to lower the indicated age range.

The trials 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 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 in older children, two holding chambers were used, the Aerochamber and the Optichamber. In study FMS30059 in younger children 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). Male and female 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 5 of the last 7 days of the 14 to 28 day screening period, and use of albuterol on at least 2 occasions during the 5 symptomatic screening days. Blinding between the different dosages and placebo was maintained by administration of one puff from each of two inhalers.

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 comparisons of each dose versus placebo was made without adjustment for multiplicity.

In study FMS30058, 80 outpatient centers were planned, 87 centers participated, and 77 centers enrolled patients (range 1 to 21 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 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.

2.6.2. Summary of Efficacy Results

In study FMS30058, FP88 demonstrated statistically significant reduction in mean daily asthma symptoms at endpoint, albuterol use, and nighttime asthma symptoms when compared with subjects treated with placebo. For FP88, there were also significantly more symptom-free days and symptom free and albuterol free days, and a significantly lower probability of treatment failure compared to subjects treated with placebo. For FP88, the improvement in daytime asthma symptoms was numerically but not significantly greater than placebo. Sub-group analyses showed that the treatment effect for FP88 was numerically greater in children 36 to 47 months than in children 24 to 35 months of age. While the FP44 dose showed greater numerical improvements in all efficacy parameters compared to placebo except daytime asthma symptoms, the differences in improvement were not significant. While patients using the Aerochamber device appeared to have a greater numerical reduction in asthma symptoms at endpoint than patients using the Optichamber, differences in baselines for the two sub-groups precludes any interpretation of the results by holding chamber sub-group.

In study FMS30059, (b) (4)

Treatment with Flovent did not demonstrate superior efficacy compared to placebo for either the primary or secondary endpoints. Improvements from baseline were observed for all efficacy parameters across all three treatment groups. Both of the FP88 and placebo treatment groups improved more than the FP44 group, which improved to about the same endpoint score as the other groups, but started with a lower baseline score. None of the differences between groups were significant.

2.6.3. Efficacy Conclusions

The efficacy findings must be judged in light of the potential misallocation of active drug product in both studies, making the actual extent exposure to patients impossible to quantify. Lack of ability to quantify exposure might be expected to blunt any efficacy findings. As a result, it is impossible to ascertain whether the studies derived an accurate assessment of efficacy. In addition, statistical comparisons were made without adjustment for multiplicity. Therefore, the Division judged that meaningful interpretation of the results of these studies is impossible.

2.7. Safety

The safety data in this application 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. Detectable FP levels were found in 13 patients who were on placebo treatment, with levels ranging from 11.2 to 135 pg/mL. The applicant 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. Therefore, the actual extent of exposure is impossible to determine. Lack of ability to quantify exposure potentially blunted any safety signals found in either study, and minimized the true extent of the safety risk. The safety results are presented below, but must be judged based on the possibility of an allocation problem that may have minimized any safety findings.

(b) (4)

(b) (4)

A Growth population was 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. In study FMS30059, growth velocity estimates (change in body length as measured by an infantometer) for the Growth population showed no safety signals. Growth velocities were 28.5 mm/12 weeks for placebo, 33.4 mm/12 weeks for FP44, and 29.9 mm/12 weeks for FP88. Patients on FP44 grew more than patients on placebo, while patients on FP88 grew slightly less. None of the differences in growth velocity between active drug and placebo groups were statistically significant. However, the estimates for the growth velocity (change in standing height as measured by stadiometry) for the Growth population in study FMS30058 showed a dose-dependent reduction in growth velocity for both FP44 and FP88 compared to placebo (Figure 2). Growth velocities were 20.8 mm/12 weeks for placebo, 19.1 mm/12 weeks for FP44, and 18.4 mm/12 weeks for FP88. The reduction in growth velocity compared to placebo was 1.680 mm/12 weeks ($p = 0.246$) and 2.388 mm/12 weeks ($p = 0.095$) for FP44 and FP88, respectively. Surprisingly, this effect began within one week of the start of the study and continued throughout, making the results somewhat unusual, since in most growth studies with orally inhaled corticosteroids the effects on growth may not be seen for a period of time. While the actual effect on longer-term growth was not evaluated and is unknown,

the growth estimates based on 12 weeks of data may translate to clinically relevant effects on longer-term growth.

A Urine Cortisol population was defined for each study. 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. The numbers of patients for whom urinary cortisol analyses were available in study FMS30059 were too few to have meaningful results. However, in study FMS30058, changes in 12-hour overnight urinary cortisol excretion showed a non-dose-dependent reduction in urinary cortisol for both FP44 and FP88 compared to placebo. Change from baseline for 12-hour overnight urinary cortisol was +0.6 (SD 2.54; range -3.4 – 6.6), -0.8 (SD 2.08; range -6.5 – 3.2), and -0.8 (SD 1.85; range -4.2 – 2.6) for the placebo, FP44, and FP88 groups, respectively. While this effect was predominantly noted in the 36-47 month sub-group, the numbers of patients in the younger sub-group were too few to have meaningful results.

Measurement of overnight (8PM to 8AM) urine cortisol in this population has several associated problems. First, it is difficult to collect accurate urine samples in successively younger age ranges. Second, it is known that the overnight timing may not pick up the early morning rise in serum cortisol that may be reflected in the urine during the mid-morning hours after the urine collection is completed. In addition, growth effects have been noted in growth studies with other inhaled corticosteroids despite a lack of effect on HPA axis, implying that growth may be the more sensitive indicator of systemic effects of corticosteroids. While there is some question as to whether measurement of overnight urine cortisol may not be relied upon to accurately assess safety, previous HPA axis studies in adults using positive controls (oral corticosteroids) have shown effects on urinary cortisol when measured by 12-hour overnight urine sampling. (b) (4)

In study FMS30058, there was also a trend toward higher incidence of pharyngitis/throat infection in both the FP44 and FP88 groups, and a trend to higher incidence of candidiasis of the mouth/throat or nose, presumably secondary to local effects of the active drug. All five cases of candidiasis of the mouth/throat were noted in the FP88 younger age group (24-35 months). No specific adverse event trends were noted in study FMS30059, except that patients on FP44 had higher incidences of upper respiratory infections.

(b) (4)

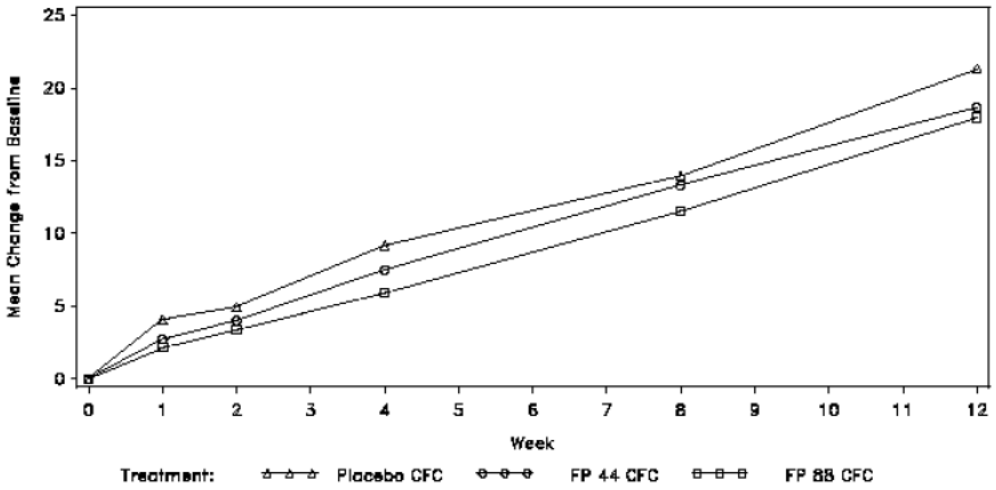

Figure 2. Study FMS30058, Mean change in height over time, Growth population

Source; Clinical, Study FMS30058, Figure 15.1, page 1333; fms30058.pdf

2.8. Dosing

Flovent® Inhalation Aerosol is currently approved for the maintenance treatment of asthma in patients 12 years of age and above, and is not approved for use in children below 12 years of age. (b) (4)

The reader is cautioned that the results do not support or imply that either the FP44 or the FP88 dose is the appropriate dose for use in children in this age range. In this age range, these dosages may (or may not) be efficacious, and may (or may not) be associated with potential for systemic effects. If a clinician chooses to use this drug off-label in children below 12 years of age, the dose should be titrated to the lowest dose that appears to provide efficacy for that child, and the child should be monitored for signs and symptoms of systemic corticosteroid effects.

2.9. Special Populations

(b) (4)

CLINICAL REVIEW

1. INTRODUCTION AND BACKGROUND

This submission is a (b) (4) supplement for Flovent® Inhalation Aerosol (fluticasone propionate [FP] inhalation aerosol CFC MDI). Flovent® Inhalation Aerosol is currently indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. (b) (4) GSK is not seeking an extension of the indicated age range below 12 years of age. The clinical studies were 12-week efficacy and safety studies using 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.

This submission is also the final of three submissions in response to a pediatric Written Request for the fluticasone propionate moiety. On the basis of the completion and submission of the studies requested in the Written Requests, GlaxoSmithKline (GSK) requested a Pediatric Exclusivity determination.

1.1. Pediatric Written Request History

Note: The reader will find the full text of the Pulmonary Section of the Pediatric Written Request, as Amended, in Appendix A of this review.

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 evaluating 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. Since Flovent® Diskus® and Flovent® Rotadisk® are approved down to 4 years of age, studies were not requested for children 4 years of age and older.

This submission included the final two clinical study reports, the CMC study report, and the population PK study report to support Pediatric Exclusivity. GSK chose to submit study reports in a rolling fashion. The dermatology studies for fluticasone propionate have previously submitted and resulted in changes to the label of Cutivate. The pulmonary/allergy portion of the pediatric Written Request also included one clinical hypothalamic-pituitary-adrenocortical (HPA) axis safety study. This study (FNM40183) was a 6-week HPA axis study using Flonase® Nasal Spray in children between ≥2 and <4 years of age with allergic rhinitis, using the highest recommended dose of 200mcg daily. (b) (4)

[redacted] Study FNM40183 was not reviewed as part of this efficacy supplement, but was reviewed for the Pediatric Exclusivity determination. [redacted]

The Pediatric Exclusivity Board met on February 25, 2003, and exclusivity was granted.

1.2. Important Milestones in Product Development

IND [redacted] was submitted on September 26, 1986. NDA 20-548 for Flovent® Inhalation Aerosol 44mcg, 110mcg, and 220mcg for the maintenance treatment of asthma as a prophylactic therapy in patients 12 years and above was submitted on December 29, 1994, and approved on March 27, 1996.

1.3. Current Indications [redacted]

Flovent® Inhalation Aerosol is currently indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. Flovent® Inhalation Aerosol is available in three formulations: 44mcg, 110mcg, and 220mcg.

[redacted]

(b) (4)

[redacted]

1.5. State of Armamentarium for Indication(s)

Flovent® Inhalation Aerosol is currently approved for the maintenance treatment of asthma in patients 12 years of age and above. Other forms of orally inhaled fluticasone propionate, marketed as Flovent® Diskus® and Flovent® Rotadisk®, are currently approved for use in children 4 years of age and older.

1.6. Other Relevant Information

All relevant information is stated in the other sections of this review.

1.7. Important Issues with Pharmacologically Related Agents

Orally inhaled corticosteroids have the potential to cause a number of systemic effects, which may include (but are not limited to) hypercorticism, adrenal suppression, and suppression of linear growth. Suppression of growth, which may be clinically relevant by itself, is also considered to be one of the most sensitive measures of systemic effect of

topical corticosteroids. In previous studies with other inhaled corticosteroids, growth suppression has been found even when no evidence of HPA axis suppression was noted. Therefore, growth is felt to be the most sensitive indicator of any potential systemic effects from corticosteroids. This supplement includes safety data relating to both HPA axis and growth from children 6 to 47 months of age exposed to Flovent CFC MDI administered with a holding chamber with mask. Unfortunately, the growth evaluation in these studies was limited to the 12-week study period, and 12 weeks of growth data is likely not sufficient to provide adequate information to assess long-term growth. Therefore, the safety information regarding systemic effects of FP provided in these studies is somewhat limited.

The labels for both Flovent Rotadisk and Flovent Diskus contain information regarding the potential for growth and other systemic effects. The current label for Flovent Diskus contains the following information, including class-labeling regarding growth, in the PRECAUTIONS: Pediatric Use section:

> Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm/year (range, 0.3 to 1.8 cm/year) and appears to depend upon the dose and duration of exposure. The specific growth effects of inhaled fluticasone propionate have also been studied in a controlled clinical trial (see data below). This effect was observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The growth of children and adolescents receiving orally inhaled corticosteroids, including FLOVENT DISKUS, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including FLOVENT DISKUS, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.
>
> A 52-week, placebo-controlled study to assess the potential growth effects of fluticasone propionate inhalation powder at 50 and 100 mcg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females) 4 to 11 years of age. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and 5.66 cm/year in the 100-mcg group(n = 89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the 100-mcg group(n = 79). The clinical significance of these growth data is not certain. In children 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is: boys--3 rd percentile = 3.8 cm/year, 50 th percentile = 5.4 cm/year, and 97 th percentile = 7.0 cm/year; girls--3 rd percentile = 4.2 cm/year, 50 th percentile = 5.7 cm/year, and 97 th percentile = 7.3 cm/year.

The current label for Flovent Rotadisk contains the following information, including modified class-labeling regarding growth: in the PRECAUTIONS section:

> A reduction of growth velocity in children or adolescents may occur as a result of poorly controlled asthma or from the therapeutic use of corticosteroids, including inhaled corticosteroids. A 52-week placebo-controlled study to assess the potential growth effects of [redacted] (b) (4) at 50 and 100 mcg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females) 4 to 11 years of age. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and 5.66 cm/year in the 100-mcg group (n = 89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the 100-mcg group (n = 79). The clinical significance of these growth data is not certain. In children 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is: boys - 3 rd percentile = 3.8 cm/year, 50 th percentile = 5.4 cm/year, and 97 th percentile = 7.0 cm/year; girls - 3 rd percentile = 4.2 cm/year, 50 th percentile = 5.7 cm/year, and 97 th percentile = 7.3 cm/year. The effects of long-term treatment of children with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route, and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if growth appears slowed. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.
>
> **Pediatric Use:** Two hundred fourteen (214) patients 4 to 11 years of age and 142 patients 12 to 16 years of age were treated with fluticasone propionate inhalation powder in US clinical trials. The safety and effectiveness of FLOVENT ROTADISK Inhalation Powder in children below 4 years of age have not been established.
>
> Inhaled corticosteroids, including fluticasone propionate, may cause a reduction in growth in children and adolescents (see PRECAUTIONS). If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.

2. CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

2.1. Chemistry, Manufacturing and Controls: (b) (4) 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 Studies 1 and 2" (i.e. the two clinical studies using Flovent CFC MDI plus spacer device in children 6 to 23 months and 24 to 47 months of age). In response, GSK performed one *in vitro* study to satisfy the Written Request, which compared the particle size distribution (b) (4) for Flovent CFC MDI with and without the use of the Aerochamber, the Aerochamber Plus and the Optichamber. (b) (4)

Comment: Please note that, within the application, the results of this study are presented in Section 5, the Nonclinical Pharmacology and Toxicology Section, rather than in Section 4, the Chemistry Section. This was clearly an oversight on the part of the applicant.

(b) (4)

3 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

(b) (4)

In summary, GSK made an effort to gain information regarding the delivered particle size and dose (b) (4) 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. In addition, extractables coming from the holding chamber were not measured. Finally, GSK failed to describe how patients were instructed to use the devices during the clinical studies. Therefore, use of the spacers in the clinical setting may have varied widely, both on an intra- and inter-patient basis. Since GSK failed to evaluate for these differences in the CMC study, the question of whether any differences in use in the clinical setting might have results in significant differences in the delivered dose was not adequately addressed or answered.

The Division assessed that the (b) (4) study did satisfy the specific wording of the Written Request to characterize dose delivery from the inhaler with several holding chambers. However, 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.

2.2. Animal Pharmacology and Toxicology

No new preclinical pharmacology or toxicology studies were conducted in support of this application.

2.3. Microbiology

No new microbiological studies were conducted in support of this application.

2.4. Statistics

Because of the other problems with this application, an in-depth statistical review was not performed. However, the results of the clinical studies were reviewed with the Division's statistician and several problems were identified. First, the applicant did not make a multiplicity adjustment for the two primary efficacy comparisons against placebo, one for each dose of FP44 and FP88. Second, it was noted that the applicant used raw means for a number of efficacy and safety tables, but LS means for inferential comparisons. This changed some of the results, e.g. changes in height over the duration of the study vs estimation of growth velocity in study FMS30059.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1. Pharmacokinetics

Basic pharmacokinetic properties of FP are discussed in the product label and in the original NDA review, and will not be addressed in this review.

However, the application included a population PK report combining 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 following study drug administration. This included -1.0 to 00 (pre-dose), 0.25 to 2.5, 3 to 8, or 9 to 11 hours post-dose. Many samples could not be used for various different reasons including missing information in the CRF, insufficient sample for assay, problems with the analysis, samples stored longer than 15 months, and samples below the limits of quantification. The number of patients who were included in the PK analysis, including a breakdown by study population, are shown in Table 3.

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: The applicant was not able to provide an adequate explanation of this observation. Before reading this review, the reader is strongly advised to read Section 5.3 (Data Quality and Integrity) on page 27 for an in-depth discussion of this topic and the implications for interpretation of the data in these studies.)* 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. Ethnicity was also found to be a covariate. No PK-PD relationship was found for either efficacy or safety endpoints. These relationships were not explored in depth because of the unexplained PK results for the 13 patients on placebo treatment.

Table 3. Distribution of PK subjects by study population

Distribution of PK Subjects by Types of Study Population									
	FMS30058			FMS30059			Total		
	44	88	Total	44	88	Total	44	88	Total
Subjects included in the final pop PK analysis	31	44	75	19	22	41	50	66	116
RITT[a] population	31	43	74	19	22	41	50	65	115
Not in RITT population	---	1	1	---	---	---	---	1	1
Growth population	25	35	60	16	19	35	41	54	95
Not in growth population	6	9	15	3	3	6	9	12	21
Urine cortisol population	9	13	22	2	3	5	11	16	27
Not in urine cortisol population	22	31	53	17	19	37	39	50	89
[a] Reduced Intent-to-treat									

3.2. Pharmacodynamics

No pharmacodynamic studies were conducted in support of this application. Basic pharmacokinetic properties of Flovent Inhalation Aerosol are discussed in the product label and in the original NDA review.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Sources of Clinical Data

This submission included two pivotal clinical safety studies [(b)(4)] (see Table 4, and described in the next section). Supporting studies included one population PK report and one CMC study. Datasets for all studies were submitted and available to the reviewers. The entire submission was in an all-electronic format.

The application also included a request for a Pediatric Exclusivity determination. In addition to dermatology studies, the Agency had requested three studies for the fluticasone propionate moiety as part of the pediatric Written Request. GSK chose to submit study reports in a rolling fashion. This submission included the final study two reports submitted to support Pediatric Exclusivity. The dermatology studies had been previously submitted, and resulted in labeling changes. One clinical HPA axis safety study (FNM40183) had been previously submitted [(b)(4)] Study FNM40183 was not reviewed as part of this efficacy supplement, but was reviewed for the Pediatric Exclusivity determination. [(b)(4)]

4.2. Overview of Clinical Trials

This submission includes two 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 was used. In the younger children, only an Aerochamber with a facemask was used.

The submission also contains two reports. The first is a CMC report for a [(b)(4)] study that sought to characterize the dose delivery from the fluticasone propionate CMC MDI with three different U.S.-marketed spacers/holding chambers. The second is a population PK report for the pharmacokinetics of fluticasone propionate CMC MDI administered with a spacer/holding chamber in the two submitted pediatric clinical studies.

Table 4. Summary of Studies and Reports for the Efficacy Supplement

Study or Report	Design	Dosage	Patients	Evaluations
FMS30058 77 centers in US	12-week, multicenter, randomized, double-blind, parallel group, placebo-controlled efficacy and safety study in 24 to 47 month old patients with asthma	Flovent CFC MDI 44mcg BID 88mcg BID Placebo Aerochamber and Optichamber with mask	332 111 108 113 ~50% ~50%	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

Study or Report	Design	Dosage	Patients	Evaluations
				AM PEF, subgroup analyses
FMS30059 54 centers in the US, Puerto Rico, and Chile	12-week, multicenter, randomized, double-blind, parallel group, placebo-controlled, efficacy and safety study in 6 to 23 month old patients with asthma	Flovent CFC MDI 44mcg BID 88mcg BID Placebo Aerochamber with mask	211 73 69 69 100%	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
RD2000/02054/00	*In Vitro* Study Report: Comparison of the particle size distribution (b) (4) 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		(b) (4) study
RM2002/00318/00	PK 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.
PK = pharmacokinetic.				

Source: Summary, p 24-5; summary.pdf

4.3. Postmarketing Experience

No post-marketing experience is submitted with this (b) (4) supplement.

4.4. Literature Review

Several articles published in the literature were submitted in support of this supplement. However, a literature review was not performed as part of this review.

5. CLINICAL REVIEW METHODS

5.1. Conduct of the Review

The review included evaluations of the two pivotal studies and two supporting reports, as outlined above. In addition, the Medical Officer review of the Flovent Rotadisk growth study was reviewed [(b) (4)] The Chemistry, Clinical Pharmacology and Biopharmaceutics, and Statistics reviewers were consulted throughout the course of this review, and this review contains summaries of all relevant information from those reviews.

[(b) (4)] Because of the Data Quality and Integrity issue, the Division did not attempt to duplicate any analyses.

5.2. Materials Consulted and Documentation

This was an all-electronic NDA submission. However, the Medical Officer Review of the Flovent Rotadisk growth study was not available electronically, and was reviewed from the paper version.

The submission is organized around the electronic Table of Contents (TOC) [ndatoc.pdf]. The electronic TOC has a hierarchical structure, which provides hypertext links and bookmarks to the rest of the NDA. The electronic pointers or bookmarks open sections and sub-sections within the submission that may or may not be within the same document. The TOC provides links to Form 356h [356h.pdf] and to the cover letter [cover.pdf]. Adobe Acrobat was used to open these documents and electronically 'mark it up' during the review process.

5.3. Data Quality and Integrity

This submission did include one minor and one major issue that involved data quality and integrity. [(b) (4)]

5.3.1. Minor Data Quality and Integrity Issue

During the course of the studies, GSK uncovered study conduct irregularities at one clinical site that affected both clinical studies. As a result, GSK made the decision prior to the final sign off of the reporting and analysis plan to establish a Reduced ITT (RITT) population for both studies. The RITT population excluded from the ITT population all four patients at site [(b) (4)] "because of study conduct irregularities." [(b) (4)] in study FMS30058 (1 FP88, 1 FP44, 1 placebo), and 1

patient in study FMS30059 (1 FP44). The RITT population also excluded any patients for whom study blind was broken (the most common cause was "flaking" of the blinding cover). (FMS30058, p 42, 134; FMS30058.pdf) (FMS30059, p 41, 124; FMS30059.pdf)

Therefore, the Division requested information regarding the specific study conduct irregularities noted by GSK in both study FMS30058 and study FMS30059. They responded that the irregularities were discovered by GSK personnel and the contract monitor assigned to this site during on-site visits [Submission of 02/14/2003]. The irregularities included:

(b) (4)

GSK reported that they discussed the discrepancies (b) (4) and developed an action plan to address issues at his site. This reviewer judged that, on the basis of these irregularities, GSK took appropriate actions to resolve those irregularities, and appropriately excluded the information from that site prior to unblinding of the data. It was judged that, based on the small number of patients enrolled at the affected site and the actions taken by GSK, the overall results of the studies were not affected. However, because of the seriousness of this information, the Division reported the information (b) (4) to the Division of Special Investigations during the review cycle.

5.3.2. Major Data Quality and Integrity Issue

During the review process, a significant data quality concern was raised regarding a major breech in data integrity for both studies. 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." [HPBio, PK Study, page 36; pkpopulation.pdf]

This raised the suspicion that patients in placebo groups might have received active drug. The Division attempted evaluate what happened to these patients by graphing the PK results for FP88, FP44, and placebo in each study. Figure 4 and Figure 5 illustrate that the range of detectable FP levels for the placebo group were quite comparable to the range of detectable FP levels found in patients assigned to active drug treatment. Figure 6 shows a concentration versus time plot (time relative to the morning dose of FP) for study FMS30058, showing that the positive results for the placebo patients occurred at various time points before and after dosing. Collectively, the analyses support the hypothesis that some patients in the placebo group may have received active treatment.

We next looked to see which sites the placebo patients with detectable FP levels came from. In study FMS30058, the ten placebo patients with detectable FP levels were from ten different sites (Table 5). In study FMS30059, two of the three patients were from the same site (Table 6). The fact that twelve sites were involved from all across the country and Puerto Rico implies that the problem was not site-specific. This appears to be confirmed by the fact that both studies were involved, and the sites having placebo patients with a detectable FP level were not the same sites in both studies. Note that many patients on active treatment did not have detectable FP levels, raising the possibility that the problem may have been larger than stated.

This reviewer can only conclude the problem was not a local problem, but a more general Quality Assurance (QA) problem. Because of this concern, the Division asked GSK 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 this issue. 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. These 13 patients had no record of receiving FP during the study, and were not exposed to FP on the day of PK testing. This information was not sufficient to resolve the Data Quality issue.

There are several possibilities that may explain these results. The Division believes that two major areas remain unevaluated: the allocation of drug to patients, and one of several problems involving the PK section of the clinical studies, as outlined below:

<u>QA issue at the level of the PK study</u>: A Quality Assurance issue within the PK study might explain these findings. Possibilities include, but may not be limited to, mismanagement of samples, invalid assay or assay failure, errors in correlating the assay results with the appropriate samples, etc. In these events, all results from the pop PK analysis would be obviated. All that one can conclude from the PK analysis is that with doses of either 44 or 88 (we don't know which), patients did receive drug through the spacer delivery device. Because of these findings, the Division judged that evaluation of any PK/PD relationship (dose vs cortisol or dose vs growth velocity) would not be useful. This is unfortunate, as these analyses would have yielded very helpful information.

QA issue at the level of drug allocation: One possible explanation for the PK observations is a drug allocation problem. Under such a scenario, some of the study drug sent as placebo was either contaminated with FP or was in fact FP canisters that had been mislabeled. In addition to implying that some patients in the placebo group received active drug, this might mean that some patients in the active treatment group received placebo. If active and placebo canisters were mixed up at GSK prior to sending the canisters to the sites, this would never be noted during the study. Nor would it be noted when the blind was broken because to break the blind one only breaks the allocation code. Breaking the study blind generally does not involve looking at each canister to confirm what drug each patient received. That might only be done by someone performing a QA/QI (Quality Assurance/Quality Improvement) audit, or for an individual patient with an AE.

How would such a Data Quality problem affect the study outcomes? If a problem occurred within the PK study, then the PK data would be worthless but the safety and efficacy data from the studies would not be affected, and the information from the clinical studies would be interpretable. However, it is impossible to know whether the problem was due to one of these etiologies. If the problem occurred at the level of drug allocation, it would be impossible to evaluate the actual patient exposure in the two clinical studies. Lacking any explanation to the contrary, this reviewer must assume that such a drug allocation problem might have occurred. 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. Therefore, the actual extent of exposure is impossible to determine. The effect would be to minimize any efficacy as well as safety findings. This would typically be detrimental to an efficacy claim, but the applicant is not seeking such a claim in this application. Of more concern is that the effect would be to minimize, blunt, or obscure any safety trends that might otherwise be present. The result is that due to this Data Quality and Integrity issue, the studies contained in this submission are uninterpretable.

Having made this statement, there were specific safety trends identified in one of the two studies, study FMS30058. The reader is again cautioned that the Data Quality and Integrity issue may have blunted any safety signals that might have been found in either study. Because of the Data Quality and Integrity issue, no attempt was made to combine the information into one unified safety assessment. Indeed, the two studies had different efficacy as well as safety findings, and any trends identified in one study did not appear to be reproduced in the second study.

(b) (4)

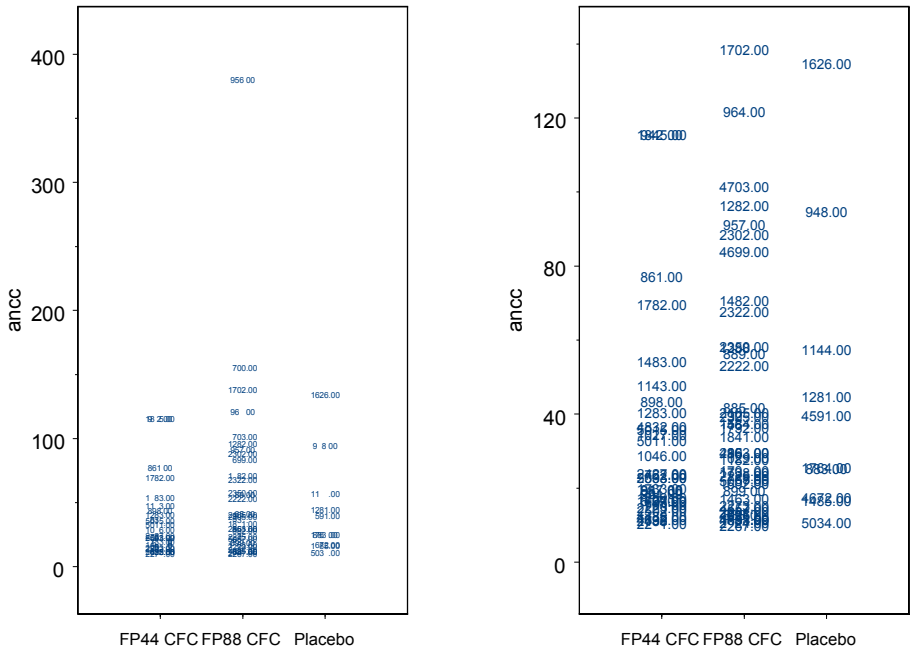

Figure 4. Study FMS30058, FP levels by treatment group

FP concentration in pg/mL. Figures show subject ID numbers. The left-hand figure shows the entire range of detectable FP results. The right-hand figure shows expanded information from the left-hand figure up to 150 pg/mL.
Source: Dr. He Sun, Office of Clinical Pharmacology and Biopharmaceutics, FDA

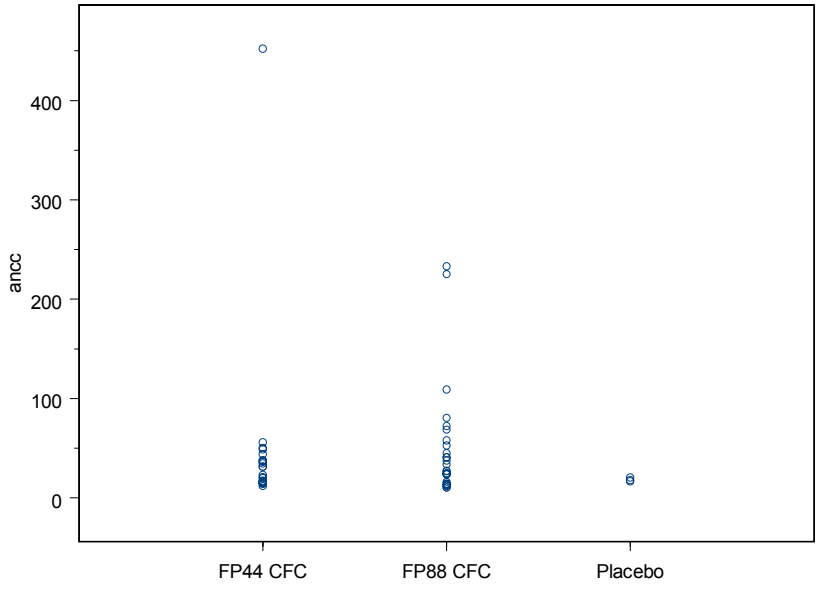

Figure 5. Study FMS30059, FP levels by treatment group

FP concentration in pg/mL. Each circle represents an individual data point.
Source: Dr. He Sun, Office of Clinical Pharmacology and Biopharmaceutics, FDA

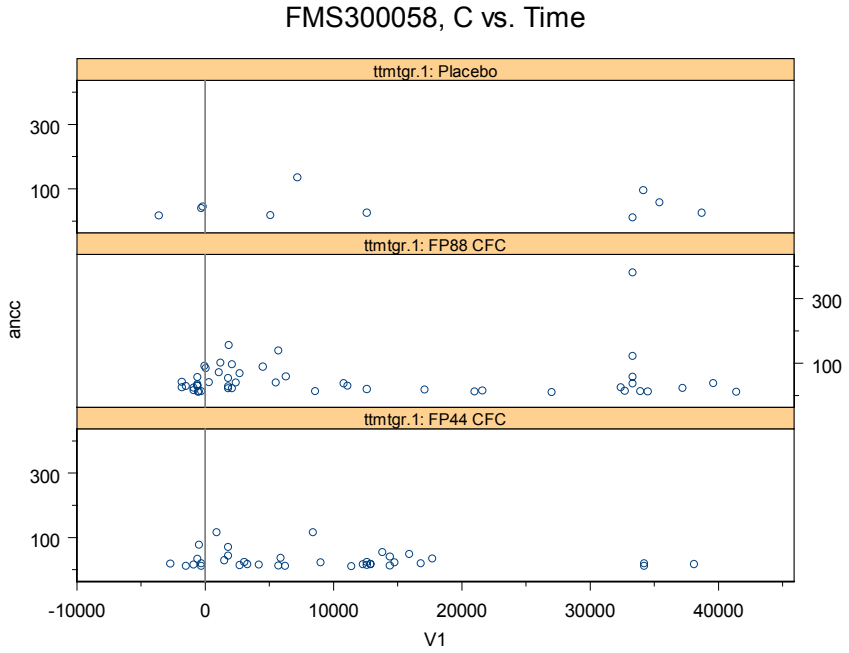

Figure 6. Study FMS30058. Concentration versus time plot for each study treatment

FP concentration in pg/mL. Each circle represents an individual data point.
Source: Dr. He Sun, Office of Clinical Pharmacology and Biopharmaceutics, FDA

Table 5. Study FMS30058, Placebo patients who had measurable FP levels

Subject ID	Site (Location)	Concentration	Ethnicity	Gender	Age (mo)	Holding chamber
883	Dr. J. Baker (OR)	25.8	White	Male	27	OPTICHAMBER
948	Dr. G. Bensch (CA)	95.1	White	Male	27	OPTICHAMBER
1144	Dr. D. Cook (CA)	57.9	White	Male	31	AEROCHAMBER
1281	Dr. S. Galant (CA)	45.1	White	Male	46	OPTICHAMBER
1485	Dr. M. Kraemer (WA)	17	White	Female	24	OPTICHAMBER
1626	Dr. F. Livingston (FL)	135	White	Male	36	AEROCHAMBER
1764	Dr. M. Mellon (CA)	26	Hispanic	Female	30	AEROCHAMBER
4591	Dr. M. Vu (CA)	40.1	Asian	Male	31	OPTICHAMBER
4672	Dr. G. Kerby (CO)	18	White	Male	39	AEROCHAMBER
5034	Dr. R. Levy (GA)	11.2	White	Male	26	OPTICHAMBER

FP concentration in pg/mL.

Source: Dr. He Sun, Office of Clinical Pharmacology and Biopharmaceutics, FDA
Clinical, Study FMS30058 Appendix, List of Investigators, pages 33-61; fms30058a.pdf

Table 6. Study FMS30059, Placebo patients who had measurable FP levels

Subject ID	Site (Location)	Concentration	Ethnicity	Gender
2649	Dr. K. Blake (FL)	16.5	Black	Female
6855	Dr. P. Goyco (PR)	17.9	Hispanic	Female
6858	Dr. P. Goyco (PR)	20.5	Hispanic	Female

FP concentration in pg/mL.

Source: Dr. He Sun, Office of Clinical Pharmacology and Biopharmaceutics, FDA
Clinical, Study FMS30059 Appendix, List of Investigators, pages 30-48; fms30059a.pdf

5.4. Ethical Standards

GSK states that each study was conducted in accordance with Good Clinical Practices (GCP) and all applicable regulations, including, where applicable, the Declaration of Helsinki, June 1964, as modified by the 48th World Medical Association, Republic of South Africa, October 1996 [Clinical, Study FMS30058, page 14; fms30058.pdf and Clinical, Study FMS30059, page 13; fms30059.pdf].

A DSI (Division of Special Investigations) audit was conducted with original NDAs for Flonase and Flovent. Since (b) (4) fluticasone propionate is not a new molecular entity, a DSI audit was not requested at the time of submission of this application. Because of the seriousness of the information regarding (b) (4) site, the Division reported the information to the Division of Special Investigations when the information came to light during the review cycle. However, the major Data Quality and Integrity issue arose late in the review process. This issue was discussed with DSI at the end of the review cycle.

5.5. Financial Disclosure

GSK states that a review was performed of the investigators participating in the clinical studies, and determined that no clinical investigator participating in the covered studies has a proprietary interest, as defined by payments at or above $25,000, or an equity interest in GSK of $50,000. (Section 19, Financial Disclosure by Clinical Investigators; financial.pdf)

6. INTEGRATED REVIEW OF EFFICACY

6.1. Brief Statement of Conclusions

(b) (4) 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. The applicant was not able to explain this observation. 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. Therefore, a drug allocation error must be assumed, and the actual extent of exposure is impossible to determine. Lack of ability to quantify exposure potentially blunted the efficacy findings from both studies. As a result, it is impossible to ascertain whether the studies derived an accurate assessment of efficacy. In addition, statistical comparisons were made without adjustment for multiplicity, both in the primary and secondary endpoints. Therefore, the Division judged that meaningful interpretation of the results of these studies is impossible. The results are presented for informational purposes.

The reader is cautioned that the results do not support or imply that either the FP44 or the FP88 dose is the appropriate dose for use in children in this age range. In this age range, these dosages may (or may not) be efficacious, and may (or may not) be associated with potential for systemic effects. If a clinician chooses to use this drug off-label in children below 12 years of age, the dose should be titrated to the lowest dose that appears to provide efficacy for that child, and the child should be monitored for signs and symptoms of systemic corticosteroid effects.

6.2. General Approach to the Efficacy Review

All studies were reviewed.

6.3. Summary of Trials

Efficacy for this application was derived from two clinical trials in young children spanning 6-47 months of age. Both were specifically designed to satisfy the requirements of the pediatric Written Request (see Appendix A). Both used Flovent Inhalation Aerosol (CFC MDI), which is currently approved for adolescents and adults 12 years of age and older. This application does not seek to lower the indicated age range.

The trials 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 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 in older children, two holding chambers were used, the

Aerochamber and the Optichamber. In study FMS30059 in younger children 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). Male and female 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. Prior to Visit 1, 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. To be eligible for randomization, patients had to have documented asthma symptoms 5 of the last 7 days of the 14 to 28 day screening period, and use of albuterol on at least 2 occasions during the 5 symptomatic screening days. Blinding between the different dosages and placebo was maintained by administration of one puff from each of two inhalers.

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 comparisons of both doses were made without adjustment for multiplicity.

6.4. Summary of Efficacy Results

(b)(4) Please refer to Section 5.3, Data Quality and Integrity on page 27, for a full discussion of the Data Quality and Integrity issues pertaining to this submission.

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. The applicant was not able to explain this observation. 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. Lack of ability to quantify exposure potentially blunted the efficacy findings from both studies. As a result, it is impossible to ascertain whether the studies derived an accurate assessment of efficacy. In addition, statistical comparisons were made without adjustment for multiplicity. Therefore, the Division judged that meaningful interpretation of the results of these studies is impossible.

The primary efficacy results for both studies are shown in Table 7. The efficacy results for each study are summarized below.

6.4.1. Study FMS30058

Primary efficacy results for study FMS30058 are summarized in Table 7. In study FMS30058, 80 outpatient centers were planned, 87 centers participated, and 77 centers enrolled patients (range 1 to 21 per center). Approximately 390 patients were planned, 493 enrolled, and 332 were randomized. The Intent to Treat (ITT) population included 113 placebo, 111 FP44, and 108 FP88 patients. The Reduced Intent to Treat (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.

At baseline daily asthma symptom scores for the RITT population were comparable, although the baseline score for the FP88 group was slightly higher than the other groups. At every week of treatment with the exception of Week 3 for FP44, there was a numerically greater reduction in asthma symptom scores in the FP88 and FP44 groups compared with placebo. The differences between FP44 and placebo for reductions in asthma symptom scores were significant at Weeks 5 and 6 but not at Endpoint ($p = 0.858$). However, the differences between FP88 and placebo for reductions in asthma symptom scores were significant at Weeks 1, 2, 6 and Endpoint ($p = 0.042$).

The percentage of symptom-free days and symptom- & albuterol-free days increased for all groups, but more for the FP88 group. This difference was significant for both the percentage of symptom-free days ($p=0.02$, FP88 vs placebo) and the percentage of symptom- & albuterol-free days ($p=0.017$, FP88 vs placebo). These results were consistent with the primary efficacy results. While the FP88 group experienced fewer daytime asthma symptoms than other treatment groups, the difference versus placebo was not significant. This difference was significant for nighttime asthma symptoms ($p=0.027$, FP88 vs placebo). These results were consistent with the primary efficacy results. The number of patients who experienced an asthma exacerbation over the 12 week treatment period was lower in both the FP88 and the FP44 groups ($n=13$ and $n=14$, respectively) compared with placebo

(n=24). The FP88 group had a greater probability of not experiencing an asthma exacerbation compared with those receiving FP44 or placebo. The difference versus placebo was statistically significant (p=0.044, FP88 vs placebo). All treatment groups experienced mean reductions in daily rescue albuterol use. Both FP groups experienced numerically greater mean reductions in daily rescue albuterol use than placebo; but the difference was only significant for FP88 (p=0.017, FP88 vs placebo). Both FP groups experienced greater mean reductions in daily rescue albuterol use than placebo; but the difference was only significant for FP88 (p=0.017, FP88 vs placebo).

Subgroup analyses included analysis by age group, holding chamber, and use of steroids within 8 weeks prior to study entry (GSK called this pre-treatment with corticosteroids). Subgroup analysis by age group showed results consistent with the full RITT population, with only FP88 treatment showing a consistent improvement in daily asthma scores compared to patients on either FP44 or placebo. Patients treated with FP44 experienced different results depending on their age group, with the 36-47 month FP44 sub-group showing a greater reduction in daily asthma symptom scores compared to placebo, but the 24-35 month FP44 age group showing less reduction than placebo. (*Note: It is possible that the difference in results based on age group could be related to the assay sensitivity, which may be higher in older children.*) Subgroup analysis by holding chamber showed results consistent with the full RITT population. Both the FP88 Aerochamber and Optichamber sub-groups showed a consistent improvement in daily asthma scores compared to patients on either FP44 or placebo. Patients treated with FP44 experienced different results depending on the holding chamber used. While the FP88 Aerochamber treatment group had a baseline score about 0.15 points higher than the rest of the groups, patients treated with FP44 or FP88 Aerochamber showed more improvement than patients assigned to the corresponding Optichamber groups. While patients using the Aerochamber device appeared to have a greater numerically reduction in asthma symptoms at endpoint than patients using the Optichamber, the difference in baselines for the two FP88 sub-groups makes precludes any interpretation of the results for these sub-groups. Subgroup analysis by pre-treatment with corticosteroids showed results consistent with the full RITT population. Both FP88 sub-groups showed a consistent improvement in daily asthma scores compared to patients on either FP44 or placebo.

In summary, FP88 demonstrated statistically significant reduction in mean daily asthma symptoms at endpoint, albuterol use, and nighttime asthma symptoms when compared with subjects treated with placebo. For FP88, there were also significantly more symptom-free days and symptom free and albuterol free days, and a significantly lower probability of treatment failure compared to subjects treated with placebo. For FP88, the improvement in daytime asthma symptoms was numerically but not significantly greater than placebo. Sub-group analyses showed that the treatment effect for FP88 was numerically greater in children 36 to 47 months than in children 24 to 35 months of age. While the FP44 dose showed greater numerical improvements in all efficacy parameters compared to placebo except daytime asthma symptoms, the differences in improvement were not significant. While patients using the Aerochamber device appeared to have a greater numerical reduction in asthma symptoms at endpoint than patients using the Optichamber, differences in baselines for the two sub-groups precludes any interpretation of the results by holding chamber sub-group.

6.4.2. Study FMS30059

Primary efficacy results for study FMS30059 are summarized in Table 7. In study FMS30059, 80 outpatient centers were planned, 71 centers participated, and 54 centers enrolled patients (range 1 to 17 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.

At baseline, daily asthma symptom scores for the RITT population were comparable only for the FP88 and placebo groups. The baseline score for the FP44 group was lower than the other groups. In the first five weeks, the reduction in asthma symptom scores for the FP88 group was numerically higher than the placebo group. After week six, any difference between these two groups disappeared, and the reduction in asthma symptom scores for the FP88 and placebo groups were comparable. Both of these treatment groups improved more than the FP44 group, which improved to about the same endpoint score as the other groups, but started with a lower baseline score. None of the differences between groups were significant.

The results for secondary endpoints were consistent with the primary efficacy results. Improvements in secondary endpoints including the percentage of symptom-free days, symptom- & albuterol-free days, daytime asthma symptoms, and nighttime asthma symptoms were comparable among treatment groups. The number of patients who experienced an asthma exacerbation over the 12 week treatment period was lower in the FP88 group (n = 6) than in either the FP44 or placebo groups (n=14 and n=10, respectively). The FP88 group had a greater probability of not experiencing an asthma exacerbation (time to treatment failure) compared with those receiving FP44 or placebo. The difference versus placebo was not statistically significant (p=0.165, FP88 vs placebo). All treatment groups experienced mean reductions in daily rescue albuterol use.

Subgroup analyses included analysis by age group and pre-treatment with corticosteroids. Subgroup analysis by age group showed no clear pattern, except that FP44 consistently showed less reduction in symptom scores than placebo. However, there were markedly different results between the two FP88 age sub-groups. In the older age sub-group of 12-23 months, the placebo treatment group showed greatest reduction in symptom scores, and the FP88 treatment group was comparable to the FP44 group. In the younger age sub-group of 6-11 months, the FP88 treatment group showed a greater numerical reduction in symptom scores than either placebo or FP44, and placebo showed a greater reduction than FP44. The

difference appears to be that FP44 showed less reduction in symptom scores in the younger age group than in the older age group.

Subgroup analysis by pre-treatment with corticosteroids showed results relatively consistent with the full RITT population, except that for the FP44 sub-group there was a marked difference in results based on whether patients had been pre-treated with corticosteroids. For patients who had pre-treatment with corticosteroids, the FP44 group showed a numerical reduction in symptom scores comparable to the other two treatment groups. For patients who had no pre-treatment with corticosteroids, the FP44 group did not show a reduction in symptom scores comparable to the other two treatment groups, and the results were consistent with those for the full RITT population.

(b) (4)

Treatment with Flovent did not demonstrate superior efficacy compared to placebo for either the primary or secondary endpoints. Improvements from baseline were observed for all efficacy parameters across all three treatment groups. Both of the FP88 and placebo treatment groups improved more than the FP44 group, which improved to about the same endpoint score as the other groups, but started with a lower baseline score. None of the differences between groups were significant.

Table 7. Studies FMS20058/9, Primary variable: Change from baseline in daily symptom scores at Endpoint, RITT population

	Placebo		FP44			FP88		
	n	mean (SE)	n	mean (SE)	p-value	n	mean (SE)	p-value
FMS30058	111		108			105		
Baseline*	109	1.16 (0.05)	106	1.14 (0.05)		105	1.23 (0.05)	
Endpoint*	92	0.67 (0.06)	100	0.63 (0.07)		100	0.49 (0.05)	
Change to Endpoint†	91	-0.49 (0.07)	99	-0.50 (0.07)	0.858	100	-0.75 (0.06)	**0.042**
FMS30059	69		71			69		
Baseline*	69	1.27 (0.06)	71	1.15 (0.06)		69	1.30 (0.07)	
Endpoint*	64	0.53 (0.07)	65	0.61 (0.07)		65	0.56 (0.08)	
Change to Endpoint†	64	-0.85 (0.09)	65	-0.77 (0.10)	0.375	65	-0.87 (0.10)	0.859

Baseline = the last week prior to randomization. Endpoint is the last two weeks of diary data prior to treatment stop date, asthma exacerbation, study withdrawal, or day 84. P-values are vs. placebo.

* Mean values for Baseline and Endpoint

† LS mean values for Change to Endpoint

Source: Clinical, Study FMS30058, Tables 14.1, 14.2, and 14.3, pages 1207-19; fms30058.pdf
Clinical, Study FMS30059, Tables 14.1, 14.2, and 14.3, pages 836-47; fms30059.pdf

6.5. Efficacy Discussion

Putting the Data Quality and Integrity issue aside for a moment, interpretation of the efficacy results for these studies would normally be tempered by an awareness of difficulties with assay sensitivity (using parent/guardian assessments) and dose delivery through an MDI/holding chamber combination with a facemask. Unfortunately, because of the Data Quality and Integrity issue, potential issues regarding both assay sensitivity and clinical dose delivery could not be fully explored.

The demonstration of efficacy of asthma drugs in young children is problematic. This is most likely due to difficulties with assay sensitivity, although in these studies there are also issues regarding how much drug is inhaled via a holding chamber. There are no simply applied techniques for evaluating pulmonary functions in young children that would allow a less empiric assessment of efficacy. Studies seeking to evaluate asthma endpoints in younger children must rely on parental/guardian evaluations of the child's status. It is well known that patients (both children and adults) may be experiencing significant reductions in pulmonary function without demonstrating much symptomatology. It is likely, therefore, that assay sensitivity for the primary efficacy variable that was chosen was relatively low. On the other hand, the NDA for Pulmicort Respules used a similar parent/guardian evaluation of efficacy (daytime and nighttime asthma symptom scores on a 0-3 scale by the parent/guardian), and was able to demonstrate significant efficacy over the entire age range that was approved (12 months to 8 years of age). In those studies, patients also who were old enough to undergo pulmonary function testing (PFT) showed improvement, but the correlation between an individual patient's scoring and improvement of PFTs is unknown. Therefore, while assay sensitivity is a concern, it is not an absolute barrier to demonstration of efficacy.

Study FMS30058 (b)(4) FP88 demonstrated significant reductions in mean daily asthma symptoms at endpoint, albuterol use, and nighttime asthma symptoms when compared with subjects treated with placebo. There was a greater but not significant improvement in daytime asthma symptoms, significantly more symptom-free days and symptom free and albuterol free days, and a significantly lower probability of treatment failure compared to subjects treated with placebo. While the FP44 dose showed greater numerical improvements in all efficacy parameters compared to placebo except daytime asthma symptoms, the differences in improvement were not significant. While patients using the Aerochamber device appeared to have a greater numerical reduction in asthma symptoms at endpoint than patients using the Optichamber, differences in baselines for the two sub-groups precludes any interpretation of the results by holding chamber sub-group.

These results were not duplicated in study FMS20059 in younger children. (b)(4) Treatment with Flovent did not demonstrate superior efficacy compared to placebo for either the primary or secondary endpoints. Improvements from baseline were observed for all efficacy parameters across all three treatment groups. Both of the FP88 and placebo treatment groups improved more than the FP44 group, which improved to about the same endpoint score as the other groups, but started with a lower baseline score. None of the differences between groups were significant.

The findings, (b)(4) may not be entirely accurate, as the allocation problem may have blunted any efficacy findings. No such finding were noted in younger children (study FMS30059), where placebo was as efficacious as FP88, and both were numerically superior to FP44. In addition, sub-group analysis for study FMS30058 showed that for he older subgroup FP88 appeared to have more efficacy than the younger sub-group. This may be explained by

variations in assay sensitivity by age. Sensitivity of parents to asthma signs and symptoms may change with increasing age, with changes in feedback from increasingly older children who are better able to express themselves both verbally and non-verbally, or with other factors that may change with age. Unfortunately, because of the Data Quality and Integrity issue, potential issues regarding assay sensitivity could not be fully explored.

(b) (4)

Because of MDI/holding chamber care, handling, and usage issues, it not clear that the emitted dose accurately represents the delivered dose. While several studies have demonstrated clinical efficacy for asthma drugs administered to young children via a holding chamber with face mask, studies have also demonstrated that there are significant differences in delivered doses depending upon physical properties as well as the timing of use of the holding chamber/MDI combination. Such physical properties include whether the device has been washed, how it has been washed, and how it has been dried. (b) (4)

The timing of the puff in relation to the placement of the mask over the nose and mouth of the patient and how long the mask is kept in place (either by time or by respiratory cycles) are also thought to affect dose delivery. (b) (4)

Finally, statistical comparisons were made without adjustment for multiplicity, both in the primary and secondary endpoints. Therefore, the p-values stated in the results sections should be considered as exploratory only.

6.6. Efficacy Conclusions

(b) (4)

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. The applicant was not able to explain this observation. 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. Lack of ability to quantify exposure potentially blunted the efficacy findings from both studies. As a result, it is impossible to ascertain whether the

studies derived an accurate assessment of efficacy. In addition, statistical comparisons were made without adjustment for multiplicity, both in the primary and secondary endpoints. Therefore, the Division judged that meaningful interpretation of the results of these studies is impossible.

(b) (4)

The reader is cautioned that the results do not support or imply that either the FP44 or the FP88 dose is the appropriate dose for use in children in this age range. In this age range, these dosages may (or may not) be efficacious, and may (or may not) be associated with potential for systemic effects. If a clinician chooses to use this drug off-label in children below 12 years of age, the dose should be titrated to the lowest dose that appears to provide efficacy for that child, and the child should be monitored for signs and symptoms of systemic corticosteroid effects.

7. INTEGRATED REVIEW OF SAFETY

7.1. Brief Statement of Findings

(b) (4)

Prior to reading the results of the Safety Analyses in this section, the reader is cautioned to read Section 7.3, Description of Patient Exposure below, as well as Section 5.3 (Data Quality and Integrity) on page 27 for an in-depth discussion of Data Quality and Integrity issues and the implications for interpretation of the data in these studies. The Safety findings in Appendix B, Detailed Study Reviews were written prior to the uncovering of these Data Quality issues.

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. The applicant was not able to explain this observation. 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. Therefore, the actual extent of exposure is impossible to determine. Lack of ability to quantify exposure potentially blunted any safety signals found in either study, and minimized the true extent of the safety risk. (b) (4)

Nevertheless, several potential safety signals were noted in the studies, which are outlined in the sections below. Again, lack of ability to accurately quantify exposure potentially blunted any safety signals that may have been found in these studies. Therefore, an accurate assessment of the safety of Flovent CFC administered with a spacer/holding chamber with mask in younger children is impossible to determine.

The reader is cautioned that the results do not support or imply that either the FP44 or the FP88 dose is the appropriate dose for use in children in this age range. In this age range, these dosages may (or may not) be efficacious, and may (or may not) be associated with potential for systemic effects. If a clinician chooses to use this drug off-label in children below 12 years of age, the dose should be titrated to the lowest dose that appears to provide efficacy for that child, and the child should be monitored for signs and symptoms of systemic corticosteroid effects.

7.2. Methods and Content (Materials Utilized in Review)

All clinical data submitted to the application were reviewed.

7.3. Description of Patient Exposure

It is very difficult to evaluate the actual patient exposure in the two clinical studies submitted. Descriptions of exposure, as stated by GSK in the study reports, may be found within the detailed study reviews. However, this information may or may not be a realistic

statement of actual exposure in the clinical trials. This is specifically due to the results of the population PK analysis, in which 13 patients who were randomized to placebo treatment had measurable plasma FP concentrations. The reason for this observation was not explained either in the original submission or in response to a specific request by the Division during the review period. 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. In addition, the range of FP levels and timing of sampling for the placebo group were quite comparable to the range of FP levels and timing of sampling found in patients assigned to active drug treatment. This has raised the concern of a major Data Quality and Integrity issue in these studies.

One possible explanation for these findings is a problem with allocation to study drug. It is conceivable that patients randomized to placebo received active drug. It is also conceivable that patients randomized to active drug received placebo. Since many patients on active treatment did not have detectable FP levels, the true extent of exposure may have been larger than stated. Such errors in allocation would be expected to blunt any safety signals that might be present. This information significantly impacts the data presented below, and precludes interpretation of the safety data from these studies.

7.4. Safety Findings from Clinical Studies

[redacted] Prior to reading this section of the review, please read Section 7.3, Description of Patient Exposure and Section 5.3, Data Quality and Integrity.

Nevertheless, several safety trends identified, specifically in study FMS30058. The discussion that follows discusses the safety trends that were identified during the individual study review process. The reader is again cautioned that the Data Quality and Integrity issue may have blunted any safety signals that might have been found in either study, and minimized the true extent of the safety risk. Because of the Data Quality and Integrity issue, no attempt was made to combine the information into one unified safety assessment. Indeed, the two studies had different efficacy as well as safety findings, and any trends identified in one study did not appear to be reproduced in the second study.

7.4.1. Study FMS30058

The extent of exposure, as measured by diary responses, was comparable between groups. There were no deaths, but there were six serious adverse events (SAEs) reported by six patients during treatment (2 placebo, 0 FP44, 4 FP88). The SAEs included one each of the following: tooth abscess, dehydration, croup, behavior changes, near drowning, and right inguinal lymphadenitis. None of the events were judged by the investigator to be related to study drug. Shift tables for vital signs (systolic and diastolic BP and HR), physical examinations, and laboratory values showed no trends.

A total of 277 subjects (83%) reported at least one AE during treatment (93 [82%] placebo, 98 [88%] FP44, and 86 [80%] FP88). There was a minor trend toward higher incidences of fever in both the FP44 and FP88 groups (25 [22%] placebo, 32 [29%] FP44, and 30 [28%] FP88), the etiology of which is not clear. There was a trend toward higher incidence of

pharyngitis/throat infection in both the FP44 and FP88 groups (0 placebo, 7 [6%] FP44, and 3 [3%] FP88), presumably secondary to local effects of the active drug. There was a trend to higher incidence of candidiasis of the mouth/throat (2 [2%] placebo, 1 [<1%] FP44, and 5 [5%] FP88), or nasal cavity (0 placebo, 0 FP44, and 2 [2%] FP88) in the FP88 group), again presumably secondary to local effects of the active drug. All five cases of candidiasis of the mouth/throat were noted in the FP88 younger age group (24-35 months). Evaluation of adverse events by holding chamber showed no trends that appeared related to a specific holding chamber. Despite the candidiasis AEs, the incidence of oropharyngeal and nasopharyngeal examination and/or culture positive for Candida was comparable between treatment groups, and there were no trends toward shifts in exam or culture positive results by treatment group or sub-group. Evaluation of adverse events by pre-treatment with CS (any corticosteroids within 8 weeks of Visit 1) showed that, whereas the trend toward higher incidence of pharyngitis/throat infection spanned the two sub-groups, most instances of candidiasis of the mouth/throat and nasal cavity occurred in the group that had not received previous CS therapy. Evaluation of adverse events by gender showed revealed no specific trends. No rebound trends were noted during the follow-up period after stopping study drugs.

The Growth population was a subset of the IT population defined to exclude 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 Growth population included 71 placebo, 79 FP44, and 87 FP88 patients. Estimates for the growth velocity for the Growth population showed a dose-dependent reduction in growth velocity. Growth velocities were 20.8 mm/12 weeks for placebo, 19.1 mm/12 weeks for FP44, and 18.4 mm/12 weeks for FP88. The reduction in growth velocity compared to placebo was 1.680 mm/12 weeks ($p = 0.246$) and 2.388 mm/12 weeks ($p = 0.095$) for FP44 and FP88, respectively.

In general there are difficulties with extrapolation from short-term growth evaluations to longer-term growth. These difficulties include variability in measurement as well as variability in seasonal and in individual growth rates. Nevertheless, this reviewer extrapolated the data to place the results into context of what is known from other 1-year growth studies. The results of this 12-week study extrapolate to one-year linear growth effect sizes that are larger than those previously found in the Flovent Diskus growth study where the reduction in growth velocity compared to placebo for the 50-mcg group was -0.19 cm/year and for the 100-mcg group was 0.43 cm/year. In fact, the effect size seen in this limited study extrapolate to one-year linear growth effect sizes that are comparable to effect sizes that were considered clinically relevant in previous growth studies. Therefore, this reviewer believes that the differences in growth seen in this study between FP88, FP44 and placebo may be clinically relevant.

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 $>12 \pm 2$ 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. The Urine cortisol population included 26 placebo, 19 FP44, and 20 FP88 patients. Change from baseline for 12-hour overnight urinary cortisol was 0.6 (SD 2.54) (range -3.4 – 6.6), -0.8 (SD 2.08) (range -6.5 – 3.2), and -0.8 (SD 1.85) (range -4.2 – 2.6) for the placebo, FP44, and FP88 groups, respectively. GSK tried to suggest that 18 of 19 (95%) of the FP44 patients and 18 of 20 (90%) of the FP88 patients were contained within the range of the change from baseline in urine cortisol for the placebo group (-3.4 to 6.6mcg/12-hour). However, the cumulative distribution function reveals a clear separation between groups, with both the FP44 and the FP88 showing more change from baseline than the placebo group. This change is less obvious but still present in the data from the ITT population (data not shown here). (b) (4)

In summary, unlike study FMS30059, there were potentially significant safety trends noted in this study. There was a trend toward higher incidence of pharyngitis/throat infection in both the FP44 and FP88 groups, and a trend to higher incidence of candidiasis of the mouth/throat or nose, presumably secondary to local effects of the active drug. All five cases of candidiasis of the mouth/throat were noted in the FP88 younger age group (24-35 months). Estimates for the growth velocity for the Growth population showed a dose-dependent reduction in growth velocity. While the actual effect on longer-term growth was not evaluated and is unknown, the growth estimates based on 12 weeks of data may translate to clinically relevant effects on longer-term growth. Changes in 12-hour overnight urinary cortisol excretion showed a non-dose-dependent reduction in urinary cortisol. (b) (4)

7.4.2. Study FMS30059

The extent of exposure, as measured by diary responses, was comparable between groups. There were no deaths, but there were four SAEs reported by three patients during treatment (0 placebo, 1 FP44, 2 FP88), and three SAEs reported by two patients during the follow-up period (0 placebo, 2 FP44, 0 FP88). SAEs during the treatment period included one each of the following: perforated appendix with abdominal abscess, Rotaviral gastroenteritis, and viral gastroenteritis. SAEs during the follow-up period included the following: one patient with a seizure and an asthma exacerbation, and one patient with an asthma exacerbation. None of the events were judged by the investigator to be related to study drug. Shift tables for vital signs (systolic and diastolic BP and HR), physical examinations, and laboratory values showed no trends.

A total of 196 patients (93%) reported at least one AE during treatment (62 [90%] placebo, 68 [93%] FP44, and 66 [96%] FP88). There was a trend toward higher incidences of both upper respiratory tract infections (URTI) (21 [30%] placebo, 27 [37%] FP44, and 18 [26%] FP88) and ear, nose & throat infections (18 [26%] placebo, 30 [41%] FP44, and 15 [22%] FP88) in the FP44 group than in either the placebo or FP88 groups. During the course of the study the patients enrolled in the FP44 group experienced more upper respiratory related

infections than the placebo of FP88 groups. This increased incidence of illness may well explain the reduced efficacy of FP44 compared to placebo or FP88 seen in this study. Unlike study FMS30058, there was no trend to higher incidence of candidiasis of the mouth/throat (3 [4%] placebo, 3 [4%] FP44, and 4 [6%] FP88), however the FP88 group had a slightly higher incidence of candidiasis of the skin than the other two groups (1 [1%] placebo, 0 FP44, and 3 [4%] FP88). No rebound trends were noted during the follow-up period after stopping study drugs, except that the FP44 group continued to have a higher incidence of URTI and ENT infections than the other groups.

Evaluation of adverse events by age groups showed that the type and frequency of adverse events reported by subgroups were generally comparable. Evaluation of adverse events by previous CS therapy (any corticosteroids within 8 weeks of Visit 1) showed that the trend toward higher incidence of URT and ENT infections spanned the two sub-groups. Just as for study FMS30058, most instances of candidiasis of the mouth/throat occurred in the group that had not received previous CS therapy. Evaluation of adverse events by gender showed a comparable incidence of overall reported AEs in male and female placebo sub-groups (females: 92% placebo, 97% FP44, 96% FP88; males: 88% placebo, 90% FP44, 96% FP88).

Despite the fact that the number of reported AEs for oral or nasal candidiasis was not higher in the Flovent treatment groups, the numbers of patients who were exam or culture positive increased in all groups, and the incidence increased more in the FP88 than the other treatment groups. The FP88 treatment group also had a higher incidence in shift to a positive oropharyngeal culture for *Candida*.

The Growth population included 49 placebo, 48 FP44, and 52 FP88 patients. Unlike the growth velocity estimates in study FMS30058, the estimates in this study did not show a trend toward dose-dependent reduction in growth velocity. Growth velocities (change in body length as measured by an infantometer) by for the Growth population were 28.5 mm/12 weeks for placebo, 33.4 mm/12 weeks for FP44, and 29.9 mm/12 weeks for FP88. Patients on FP44 grew more than patients on placebo, while patients on FP88 grew slightly less. None of the differences in growth velocity between active drug and placebo groups were statistically significant.

These growth results are not surprising despite the 'presumptive positive' (although not statistically significant) growth results in study FMS30058. The lack of a growth effect may reflect a number of factors in the study. First, accurate assessment of growth in young children below 2 years of age is problematic, where the assessment must be performed by measurement of length rather than height. Second, it is not clear that the use of a holding chamber with mask allowed for adequate inhalation and dosing in this population, as evidenced by the lack of efficacy in this younger age group. But again, a lack of efficacy may have been related to other problems including the possible allocation problem. Third, the natural growth rate (and consequent variability in growth rate) is higher in serially younger populations. This may obscure any growth effect from the inhaled Flovent. Finally, 12 weeks of therapy may not be an adequate time interval in which to assess changes in growth.

The Urine Cortisol population included 7 placebo, 3 FP44, and 3 FP88 patients. Urinary cortisol analyses had too few patients to have meaningful results.

In summary, just as for the efficacy results for this study, the safety results for this study are difficult to interpret, and do not show any clear trends. Overall, the types and frequency of adverse events were comparable, except that more patients in the FP4 treatment groups developed upper respiratory and ear, nose and throat infections than the other two treatment groups. One possible explanation is that, combined with the lower baseline asthma symptom score, the increased incidence of illness may explain the reduced efficacy of FP44 compared to placebo or FP88 seen in this study. Unlike study FMS30058, there was no difference in clinical reports of candidiasis between placebo and the active treatment groups. However, more patients in the FP 88 CFC group developed positive *Candida* oropharyngeal cultures.

Unlike study FMS30058, estimates for the growth velocity for the Growth population did not show a dose-dependent reduction in growth velocity. Urinary cortisol analyses had too few patients to have meaningful results.

7.4.3. Safety Conclusions

(b) (4)

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. The applicant was not able to explain this observation. 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. Therefore, the actual extent of exposure is impossible to determine. Lack of ability to quantify exposure potentially blunted any safety signals found in either study, and minimized 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.

(b) (4)

The estimates for the growth velocity for the Growth population in study FMS30058 showed a dose-dependent reduction in growth velocity for both FP44 and FP88 compared to placebo. Growth velocities were 20.8 mm/12 weeks for placebo, 19.1 mm/12 weeks for FP44, and 18.4 mm/12 weeks for FP88. The reduction in growth velocity compared to placebo was 1.680 mm/12 weeks ($p = 0.246$) and 2.388 mm/12 weeks ($p = 0.095$) for FP44 and FP88, respectively. Surprisingly, this effect began within one week of the start of the study and continued throughout, making the results somewhat suspect, since in most growth studies with orally inhaled corticosteroids the effects on growth may not be seen for a period

of time. While the actual effect on longer-term growth was not evaluated and is unknown, the growth estimates based on 12 weeks of data may translate to clinically relevant effects on longer-term growth. Changes in 12-hour overnight urinary cortisol excretion showed a non-dose-dependent reduction in urinary cortisol in study FMS30058 for both FP44 and FP88 compared to placebo.

Measurement of overnight (8PM to 8AM) urine cortisol in this population has several associated problems. First, it is difficult to collect accurate urine samples in successively younger age ranges. Second, it is known that the overnight timing may not pick up the early morning rise in serum cortisol that may be reflected in the urine during the mid-morning hours after the urine collection is completed. In addition, growth effects have been noted in growth studies with other inhaled corticosteroids despite a lack of effect on HPA axis, implying that growth may be the more sensitive indicator of systemic effects of corticosteroids. While there is some question as to whether measurement of overnight urine cortisol may not be relied upon to accurately assess safety, previous HPA axis studies in adults using positive controls (oral corticosteroids) have shown effects on urinary cortisol when measured by 12-hour overnight urine sampling. (b) (4)

Other potentially significant safety trends noted in study FMS30058 included a trend toward higher incidence of pharyngitis/throat infection in both the FP44 and FP88 groups, and a trend to higher incidence of candidiasis of the mouth/throat or nose, presumably secondary to local effects of the active drug. All five cases of candidiasis of the mouth/throat were noted in the FP88 younger age group (24-35 months). No specific adverse event trends were noted in study FMS30059, except that patients on FP44 had higher incidences of upper respiratory infections.

(b) (4)

7.5. Miscellaneous Studies

No other clinical studies were performed.

7.6. Literature Review of Safety

No literature review was performed.

7.7. Postmarketing Surveillance – If Applicable

Although Flovent Inhalation Aerosol is not approved for this age range, it is clear that physicians prescribe this drug in the pediatric population below 12 years of age. Nevertheless, no postmarketing surveillance was submitted, and review of MedWatch reports was not attempted.

7.8. Safety Update – If Available

Since Flovent Inhalation Aerosol is not approved for this age range, no safety update was submitted.

7.9. Drug Withdrawal, Abuse, and Overdose Experience

Flovent Inhalation Aerosol is not approved for this age range. There is very little experience with withdrawal, abuse or overdose. The major clinical concern with this drug is the potential for systemic exposure and systemic effects with oral inhalation, even at doses that may be chosen by physicians prescribing this medication off-label.

7.10. Adequacy of Safety Testing

Please see Section 5.3 (Data Quality and Integrity) on page 27 for an in-depth discussion of Data Quality and Integrity issues and the implications for interpretation of the data in these studies. The detailed study reviews in Appendix B were written prior to the uncovering of the Data Quality issues. In light of this Data Quality information, the results of these studies are uninterpretable.

7.11. (b) (4) Postmarketing Commitments

(b) (4) No postmarketing commitments are needed.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

This supplement addresses the use of Flovent® Inhalation Aerosol (CFC MDI) when administered with a holding chamber with a mask in young children ages 6 to 47 months. Flovent CFC MDI is currently approved for the maintenance treatment of asthma in patients 12 years of age and above, and is not approved for use in children below 12 years of age. Other forms of orally inhaled fluticasone propionate, marketed as Flovent® Diskus® and Flovent® Rotadisk®, are currently approved for use in children 4 years of age and older. The use of a holding chamber is discussed in the CMC section of this review.

(b) (4)

The reader is cautioned that the results do not support or imply that either the FP44 or the FP88 dose is the appropriate dose for use in children in this age range. In this age range, these dosages may (or may not) be efficacious, and may (or may not) be associated with potential for systemic effects. If a clinician chooses to use this drug off-label in children below 12 years of age, the dose should be titrated to the lowest dose that appears to provide efficacy for that child, and the child should be monitored for signs and symptoms of systemic corticosteroid effects.

9. USE IN SPECIAL POPULATIONS

9.1. Evaluation of Applicant's Gender, Age, Race, or Ethnicity Efficacy and Safety Analyses and Adequacy of Investigation

While the applicant has tried to perform safety analyses for gender, age, race, and ethnicity, the information in this application is not interpretable regarding these safety analyses.

9.2. Pediatric Program

The clinical studies submitted in this application (b) (4) were prompted by the pediatric Written Request. (b) (4)

9.3. Comments on Data Available or Needed in Other Populations (Such as Renal or Hepatic Compromised Patients, Use in Pregnancy)

At this time, no further data is required in other populations.

10. CONCLUSIONS AND RECOMMENDATIONS

10.1. Conclusions Regarding Safety and Efficacy

This supplement addresses the use of Flovent CFC MDI when used with a holding chamber with a mask in young children ages 6 to 47 months. Flovent is currently approved for the maintenance treatment of asthma in patients 12 years of age and above, and is not approved for use in children below 12 years of age. GSK is not seeking an extension of the indicated age range below 12 years of age.

(b) (4)

10.2. Risk/benefit Analysis

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. The applicant was not able to explain this observation. 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. Therefore, the actual extent of exposure is impossible to determine. As a result, it is impossible to ascertain whether the studies derived an accurate assessment of efficacy or safety. Of major concern is that the potential allocation problem might be expected to minimize any efficacy findings as well as the true extent of the safety risk. In addition, statistical comparisons were made without adjustment for multiplicity. Therefore, the Division judged that meaningful interpretation of either the efficacy or safety results of these studies is impossible.

Nevertheless, some efficacy was demonstrated, and several potential safety signals were noted in the studies. Again, lack of ability to accurately quantify exposure potentially blunted any efficacy as well as any safety signals that may have been found in these studies, and the information presented below must be judged in this light.

Study FMS30058 (b) (4) FP88 demonstrated significant reductions in mean daily asthma symptoms at endpoint, albuterol use, and nighttime asthma symptoms when compared with subjects treated with placebo. There was a greater but not significant improvement in daytime asthma symptoms, significantly more symptom-free days and symptom free and albuterol free days, and a significantly lower probability of treatment failure compared to subjects treated with placebo. While the FP44 dose showed greater numerical improvements in all efficacy parameters compared to placebo except daytime asthma symptoms, the differences in improvement were not significant. In the active treatment groups, patients using the Aerochamber device demonstrated a greater numerical reduction in asthma symptoms at endpoint than patients using the Optichamber.

These results were not duplicated in study FMS20059 in younger children. [redacted] Treatment with Flovent did not demonstrate superior efficacy compared to placebo for either the primary or secondary endpoints. Improvements from baseline were observed for all efficacy parameters across all three treatment groups. Both of the FP88 and placebo treatment groups improved more than the FP44 group, which improved to about the same endpoint score as the other groups, but started with a lower baseline score. None of the differences between groups were significant.

[redacted]

Unfortunately, while the [redacted] study did to some extent characterize dose delivery from the inhaler with several holding chambers, as outlined in the Written Request, the Division assessed that the study was inadequate to fully address the emitted dose when a spacer/holding chamber is used in conjunction with an MDI.

The estimates for the growth velocity for the Growth population in study FMS30058 showed a dose-dependent reduction in growth velocity for both FP44 and FP88 compared to placebo. Surprisingly, this effect began within one week of the start of the study and continued throughout, making the results somewhat suspect, since in most growth studies with orally inhaled corticosteroids the effects on growth may not be seen for a period of time. While the actual effect on longer-term growth was not evaluated and is unknown, the growth estimates based on 12 weeks of data may translate to clinically relevant effects on longer-term growth. Changes in 12-hour overnight urinary cortisol excretion showed a non-dose-dependent reduction in urinary cortisol in study FMS30058 for both FP44 and FP88 compared to placebo.

Measurement of overnight (8PM to 8AM) urine cortisol in this population has several associated problems. First, it is difficult to collect accurate urine samples in successively younger age ranges. Second, it is known that the overnight timing may not pick up the early morning rise in serum cortisol that may be reflected in the urine during the mid-morning hours after the urine collection is completed. In addition, growth effects have been noted in growth studies with other inhaled corticosteroids despite a lack of effect on HPA axis,

implying that growth may be the more sensitive indicator of systemic effects of corticosteroids. While there is some question as to whether measurement of overnight urine cortisol may not be relied upon to accurately assess safety, previous HPA axis studies in adults using positive controls (oral corticosteroids) have shown effects on urinary cortisol when measured by 12-hour overnight urine sampling. [redacted]

Other potentially significant safety trends noted in study FMS30058 included a trend toward higher incidence of pharyngitis/throat infection in both the FP44 and FP88 groups, and a trend to higher incidence of candidiasis of the mouth/throat or nose, presumably secondary to local effects of the active drug. All five cases of candidiasis of the mouth/throat were noted in the FP88 younger age group (24-35 months).

In summary, while several efficacy and safety signals were noted, lack of ability to quantify exposure potentially blunted both the efficacy and safety findings from the studies. The potential allocation problem might be expected to minimize the assessment of efficacy and the true extent of the safety risk. Therefore, an accurate assessment of the risk/benefit of Flovent CFC administered with a spacer/holding chamber with mask in younger children is impossible to determine.

The reader is cautioned that the results do not support or imply that either the FP44 or the FP88 dose is the appropriate dose for use in children in this age range. In this age range, these dosages may (or may not) be efficacious, and may (or may not) be associated with potential for systemic effects. If a clinician chooses to use this drug off-label in children below 12 years of age, the dose should be titrated to the lowest dose that appears to provide efficacy for that child, and the child should be monitored for signs and symptoms of systemic corticosteroid effects.

10.3. Recommendations [redacted]

[redacted]

10.4. [redacted]

[redacted]

The Best Pharmaceutical Act for Children requires that, for supplements submitted after October of 2002, an Executive Summary of the review be placed in the Pediatric Section of the FDA website. Therefore, information from these studies will be available to the general public [redacted]

APPENDIX A

11. PEDIATRIC WRITTEN REQUEST: PULMONARY SECTION, AS AMENDED

The Written Request was issued June 25, 1999, and amended on May 21, 2001 and October 25, 2001. What follows below is the text of the Pulmonary section of the pediatric Written Request for the three studies that were requested. Wording that was amended is crossed out, and replaced by the newer wording of the amendment with the date of the amendment. The rationale for the particular studies that were requested will not be discussed here.

11.1. Type of studies:

Before starting the clinical program with the inhalation aerosol, characterize the dose delivery from the inhaler with two different U.S.-marketed spacers in *in vitro* studies to determine the optimum doses for Studies 1 and 2 (below).

Study 1: Efficacy and safety of fluticasone propionate inhalation aerosol for maintenance treatment of asthma in children between the ages of ≥2 years and <4years.

Study 2: Efficacy and safety of fluticasone propionate inhalation aerosol for maintenance treatment of asthma in children between the ages of ≥6 months and <2 years.

Study 3: Safety of fluticasone propionate nasal spray for the treatment of allergic rhinitis in children between the ages of ≥2 years and <4 years.

Perform the clinical program for asthma in sequence, so that Study 1 in older children is completed before initiating Study 2 in younger children. The results from Study 1 will guide you in the dose selection for Study 2.

11.2. Objective/rationale:

[redacted]–(Amendment 1; 5/21/01) Study 1: Assess the efficacy and safety of fluticasone propionate inhalation aerosol delivered with two different spacers in children between the ages of ≥2 years and <4 years, and ≥6 months and < 2 years with asthma. Study 2: Assess the efficacy and safety of fluticasone propionate inhalation aerosol in children between the ages of ≥2 years and <4 years, and ≥6 months and < 2 years with asthma. All patients may use one type of spacer.

Study 3: Assess the safety of fluticasone propionate nasal spray on the hypothalamic-pituitary-adrenal (HPA) axis in children between the ages of ≥2 years and <4 years with allergic rhinitis.

11.3. Indications to be studied:

Studies 1 and 2: Maintenance treatment of asthma.

Study 3: Allergic rhinitis.

11.4. Study design:

Studies 1 and 2: The studies must be randomized, double blind, placebo-controlled, and parallel group. Evaluate two doses of fluticasone in each of the two studies. In study 1, evaluate a fluticasone dose emitted from the spacers deemed comparable to a currently approved dose of fluticasone for children above 4 years of age, and a lower dose. The efficacy and safety results of study 1 will guide you in selecting the two fluticasone doses for study 2. In both studies, treat patients with conventional therapy for asthma, and fluticasone or a matching placebo for at least 12 weeks. Consider the use of rescue corticosteroids and beta$_2$-agonists in the study design.

Study 3: The study must be randomized, double-blind, placebo-controlled, and parallel group. Treat the patients with fluticasone or a matching placebo for at least 6 weeks.

11.5. Age group in which studies will be performed:

Study 1: Children between the ages of ≥2 years and <4 years. Half of the patients in each treatment group must be below age 3 years of age. [*Note: see Number of Patients section*]

Study 2: Children between the ages of ≥6 months and <2 years. Half of the patients in each treatment group must be below age 1 year of age. [*Note: see Number of Patients section*]

Study 3: Children between the ages of ≥2 years and <4 years. Half of the patients in each treatment group must be below age 3 years of age.

11.6. Number of patients to be studied:

[redacted] (Amendment 1; 5/21/01) Study 1: A minimum of 50 patients per group, **of which approximately 1/3 should be less than 12 months of age**, must complete the studies. Approximately one-half of the study patients must use one type of spacer, and the other patients must use a different type of spacer.

Study 2: A minimum of 50 patients per group, of which approximately 1/3 should be less than 12 months of age, must complete the studies. One type of spacer may be used for all patients in the study.

Study 3: A minimum of 24 patients per study group (2 groups) must complete the study.

11.7. Entry criteria:

[redacted]

(Amendment 1; 5/21/01) Studies 1 and 2: Children with asthma who are free from other clinically significant medical problems, and expected to derive benefit from inhaled corticosteroids. The patients must not have received treatment with greater than 2 courses of systemic or topical corticosteroids within the previous 6 months.

Study 3: Children with allergic rhinitis who may derive benefit from intranasal corticosteroids. The study patients must not have used any systemic or topical corticosteroids within 6 months of the study, and must be free from other clinically significant medical problems.

11.8. Clinical endpoints:

Studies 1 and 2: The primary efficacy endpoint must include asthma symptom scores such as wheeze, dyspnea, and cough. The secondary efficacy endpoints must include asthma symptom free days, use of rescue medications, treatment failures, and patients discontinuations. In study 1, attempt to measure peak expiratory flow rate. Safety endpoints must include recording of adverse events, vital signs, physical examination, linear growth, HPA-axis assessment, and clinical laboratory measures.

Study 3: Assess the effect of fluticasone propionate nasal spray on the hypothalamic-pituitary-adrenal (HPA) axis. A global efficacy assessment based on parent or caregiver ratings of patient symptoms at the start of the study period and at the completion of 6 weeks of treatment is optional.

11.9. Study evaluation:

(b) (4)

(b) (4)

[redacted]

Studies 1 and 2: Instruct patients or caregivers of the patients to record symptom scores and adverse events on daily diary cards. In study 1, attempt to record peak expiratory flow rates at least once daily. Conduct clinic visits at least every 4 weeks. During the clinic visits, record vital signs, perform a physical examination including assessment for linear growth, and perform oropharyngeal and nasal fungal cultures. Perform clinical laboratory measures and assessments of adrenal function before treatment and at the completion of 12 weeks of treatment. Assess adrenal function by an appropriate test for the study population such as by measurement of creatinine normalized timed urinary free cortisol excretion, or by an ACTH stimulation test. Assessment of A.M. serum cortisol levels alone will not be adequate.

In study 1, assess adrenal function in a sufficient number of patients to assure data from at least 24 patients per treatment arm who have completed the 12 weeks of treatment. In study 1, approximately half of the 24 patients must use one type of spacer, and the other patients must use a different type of spacer.

In study 2, assess adrenal function in a sufficient subset of patients to adequately relate the adrenal safety data for this age group to that obtained in study 1. Justify the number of patients studied based on the results in older children, pharmacokinetic data, and other relevant data. In study 2, all of the patients may use one type of spacer (see Drug Information).

For Study 2, approximately 1/3 of the patients studied should be less than 12 months of age. For convenience and standardization of the procedure, you may assess adrenal function at a limited number of study centers provided the selected study centers enroll a sufficient number of patients who complete the 12 weeks of treatment. Determine fluticasone plasma levels at the end of 12 weeks of treatment from a subset of an adequate number of patients at appropriate sampling times. If a sufficient amount of data is obtained, a population pharmacokinetic approach may be employed to obtain steady-state fluticasone pharmacokinetic parameters in these patients.

Study 3: Instruct parents or caregivers to record adverse events on daily diary cards. Perform a physical examination, clinical laboratory measures, an assessment of adrenal function before treatment and at the completion of 6 weeks of treatment, and an assessment

of fluticasone plasma levels at the completion of 6 weeks of treatment. Assess adrenal function by an appropriate test, such as by measurement of creatinine normalized timed urinary free cortisol excretion, or ACTH stimulation test. Assessment of AM serum cortisol levels alone will not be adequate. Determine fluticasone plasma levels at the end of 6 weeks of treatment from these patients at appropriate sampling times. If a sufficient amount of data is obtained, a population pharmacokinetic approach may be employed to obtain steady-state fluticasone pharmacokinetic parameters in these patients.

11.10. Drug information:

(b) (4)

(Amendment 1; 5/21/01) Studies 1 and 2: The spacers must not replace the actuator of the inhaler. In study 1, use fluticasone propionate inhalation aerosol in conjunction with two different U.S.-marketed spacers. In study 2, attach appropriate facemasks, available on the U.S. market, to the spacer to optimize drug delivery for the very young children. In study 1, approximately one-half of the patients in each dose group must use one kind of spacer, and the other patients must use a different kind of spacer. In study 2, all patients may use the same type of spacer.

Study 3: Use fluticasone propionate nasal spray (50 mcg/actuation) at a dose of 200 mcg/day.

11.11. Drug specific safety concerns:

The safety concerns with nasal and orally inhaled corticosteroids are suppression of adrenal function, suppression of linear growth, and adverse effects and other effects associated with corticosteroids. Oropharyngeal fungal overgrowth is also of concern with orally inhaled corticosteroids.

11.12. Statistical information, including power of study and statistical assessments:

Study 1 and 2: Analyze the efficacy data by analysis of variance or by an appropriate statistical test for the data. Perform standard statistical comparisons for adverse events, laboratory values, and other measures.

Study 3: Adrenal function data must be analyzed using Student's t-test with baseline as a covariate. Standard descriptive statistical analyses must be performed for adverse events, laboratory values, and other safety measures.

11.13. (b) (4)

(b) (4)

Format of reports to be submitted:

Full study reports addressing the issues outlined in this request with full analysis, assessment, and interpretation must be submitted to the Agency.

11.14. Timeframe for submitting reports of the studies:

(b) (4)

(Amendments 1 and 2; 5/21/01 and 10/25/01) Reports of the studies that meet the terms of the Written Request dated June 25, 1999, as amended on May 21, 2001 and October 25, 2001, must be submitted to the Agency on or before July 31, 2003.

11.15. Other:

(b) (4)

APPENDIX B

12. DETAILED STUDY REVIEWS

NOTE: (b)(4)

Before reading the studies detailed below, the reader is strongly advised to read Section 5.3 (Data Quality and Integrity) on page 27 for an in-depth discussion of Data Quality and Integrity issue and the implications for interpretation of the data in these studies. The detailed study reviews in Appendix B were written prior to the uncovering of these Data Quality issue. Therefore, the results and discussion sections may minimize any potential safety concerns that are discussed in the individual reviews.

12.1. Study FMS30058, A multicenter, randomized, double-blind, 12-week study of Fluticasone Propionate 44mcg BID and 88mcg BID delivered via CFC MDI and a valved holding chamber with facemask in patients with asthma age 24 months to 47 months

Protocol #:	FMS30058
Title:	A multicenter, randomized, double-blind, parallel group, placebo-controlled, 12-week study of Fluticasone Propionate 44mcg BID and 88mcg BID delivered via CFC MDI and a valved holding chamber with facemask in subjects with asthma age 24 months to 47 months
Study Dates:	December 13, 1999 to May 8, 1999
Sites:	87 sites in the US, of which 77 sites enrolled patients
IRB:	IRB at each study site

Source: Clinical, FMS30058, pages 1-2, 14; fms30058.pdf

NOTE: (b)(4)

Before reading the results section of this study, the reader is strongly advised to read Section 5.3 (Data Quality and Integrity) on page 27 for an in-depth discussion of Data Quality and Integrity issue and the implications for interpretation of the data. This detailed study review was written prior to the uncovering of these Data Quality issue. Therefore, the results and discussion sections may minimize any potential safety concerns that are discussed in the review that follows.

12.1.1. Protocol/Study Design

The protocol for study FMS30059 was designed to satisfy the requirements of the pediatric Written Request. Please refer to Appendix A starting on page 56 for full details of the Written Request with Amendments.

12.1.1.1. Brief Summary of the Study Design

This was a 12-week, randomized, double-blind, parallel group, placebo-controlled multicenter (80 outpatient centers planned) study of fluticasone propionate 44mcg BID and 88mcg BID delivered via MDI with CFC propellants 11/12 and a valved holding chamber with a facemask in 332 patients with asthma age 24 months to 47 months. The study was designed to satisfy the requirements of the pediatric Written Request (see Appendix A). Two holding chambers were used, the Aerochamber and the Optichamber. The study was 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). Male and female patients aged 24-47 months inclusive with a documented history of symptomatic asthma and have experienced at least 2 episodes of increased symptoms of asthma requiring medical attention and asthma pharmacotherapy within the preceding 12 months. Prior to Visit 1, 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. To be eligible for randomization, patients had to have documented asthma symptoms 5 of the last 7 days of the 14 to 28 day screening period, and use of albuterol on at least 2 occasions during the 5 symptomatic screening days. Blinding was maintained by use of two inhalers throughout the study.

The primary efficacy endpoint was the average change from baseline in daytime and nighttime (daily) asthma symptom scores to Endpoint (the last two weeks of diary data prior to end of study, asthma exacerbation, or study withdrawal). 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. 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), the frequency of treatment failure, and patient discontinuations.

Safety was assessed by examining adverse events, physical examinations (including vital signs, linear growth assessments, oropharyngeal and nasal passage examinations), growth velocity, clinical laboratory tests (biochemistry and hematology), oropharyngeal and nasal passage *Candida* cultures, and hypothalamic-pituitary-adrenal (HPA) axis function (12-hour overnight urine cortisol). DNA samples and pharmacokinetic samples (one per patient) were collected during this study for analysis.

12.1.1.2. Objectives

The objective of this study was to evaluate the efficacy and safety of FP 44 mcg twice daily (BID) and 88 mcg BID versus placebo delivered via MDI with chlorofluorocarbon (CFC) propellants 11/12 plus either the Aerochamber or Optichamber valved holding chamber device with a facemask in the treatment of asthma in subjects aged 24- 47 months inclusive. [Clinical, FMS30058, pages 17, 2249; fms30058.pdf]

12.1.1.3. Population

Note: The pediatric Written Request (Amendment 1, 5/21/01) stated that the study should enroll "children with asthma who are free form other clinically significant medical problems, and expected to derive benefit from inhaled corticosteroids. The patients must not have received treatment with greater than 2 courses of systemic or topical corticosteroids with the previous 6 months."

12.1.1.3.1. Inclusion criteria [Clinical, FMS30058, pages 21-2, 2452-3; fms30058.pdf]

12.1.1.3.1.1. Screening period

A subject was eligible for inclusion into the screening period of the study if all of the following criteria applied:

1) Type of subject: outpatient
2) Age: 24 months to 47 months; inclusive. (Must not have reached their 4 th birthday before randomization.)
3) Sex: Male or female. A female was eligible to enter and participate in this study if she was of non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who was pre-menarchal.)
4) Clinical Presentation: All subjects had to have a history of symptomatic asthma and experienced at least 2 episodes of increased symptoms of asthma requiring medical attention and asthma pharmacotherapy within the preceding 12 months. In addition, all subjects also fulfilled the following criteria prior to Visit 1:
   - required therapy with a maintenance asthma medication (other than systemic corticosteroid) on a regular basis for the preceding 6 weeks

     AND/OR

   - required therapy with a short-acting beta-agonist for relief of respiratory symptoms at least twice per week over the preceding 3 weeks

   Maintenance medications included the following: theophylline, nedocromil, cromolyn, low dose inhaled corticosteroids [National Institutes of Health, 1997], long-acting inhaled β 2-agonist, sustained release beta-agonist tablet, and leukotriene receptor antagonists.
5) Parents/legal guardians: Subject's legally authorized representatives had to have the ability to read, comprehend and record diary information collected throughout the study.
6) Informed consent: A signed and dated written informed consent was obtained from the subject's legally authorized representative prior to study participation.

12.1.1.3.1.2. Treatment period

After meeting all inclusion criteria for the screening phase, a subject was eligible for inclusion into the treatment phase of the study at Visit 2 if all of the following randomization criteria applied:

1) Had symptoms of asthma (a score of ≥1 on either or both of the daytime and nighttime asthma symptom scales) recorded on the diary record on 5 of the last 7 days of the 14 to 28-day Screening Period.
2) Albuterol use documented on the diary record on at least 2 occasions during the 5 symptomatic screening days.
3) The subject's legally authorized representative demonstrated the ability to comply with use of the daily diary record defined as completion of all questions on at least 80% of the days during the Screening Period.
4) Subject was able to tolerate the use of an MDI and valved holding chamber with facemask.

Subjects who had an asthma exacerbation during the baseline period were not eligible for randomization. For purposes of this study, an asthma exacerbation was defined as increasing signs or symptoms of asthma, not controlled by as-needed albuterol and requiring asthma medications not allowed by this protocol, prior to an asthma exacerbation.

12.1.1.3.2. Exclusion criteria [Clinical, FMS30058, pages 21-2, 2453-5; fms30058.pdf]

A subject was not eligible for inclusion in this study if any of the following criteria applied:

1) Life-Threatening Asthma: A subject could not have life-threatening asthma. Life-threatening asthma was defined as a history of significant asthma episode(s) requiring admission to an intensive care unit for treatment of an acute asthma exacerbation within the 12 months prior to Visit 1.
2) Medications:
   - Inhaled corticosteroids: Use of inhaled corticosteroids at doses indicated in the following table within 8 weeks prior to Visit 1(Amendment 1):

Drug	Daily Dosage
Beclomethasone dipropionate	Greater than 336mcg (greater than 8 puffs of the 42mcg MDI or greater than 4 puffs of the 84mcg MDI)
Budesonide Turbuhaler	Greater than 200mcg (greater than 1 inhalation of the 200mcg Turbuhaler)
Flunisolide	Greater than 750mcg (greater than 3 puffs of the 250mcg MDI)
Fluticasone propionate MDI	Greater than 176mcg (greater than 4 puffs of the 44mcg MDI
Fluticasone propionate **ROTADISK**	Greater than 200mcg (greater than 4 inhalations of the 50mcg **ROTADISK** inhaler)
Triamcinolone acetonide	Greater than 800mcg (greater than 8 puffs of the 100mcg MDI)

   - Systemic corticosteroids:
     - Use of systemic corticosteroids within 8 weeks prior to Visit 1 (Amendment 1)
     - Treatment with greater than two courses (i.e., bursts) of systemic corticosteroids during the 6 months prior to Visit 1 (Amendments 1 and 6).

- Methylphenidate/Pemoline/Dextroamphetamine: Use of methylphenidate, pemoline or dextroamphetamine (Amendment 1) within 30 days prior to Visit 1.
- Investigational Medications: A subject could not have been exposed to an investigational drug or participated in another clinical study within 30 days prior to Visit 1 or within 10 half-lives (t½) of the prior investigational study drug (whichever is the longer of the two).

3) Concurrent Diseases/Abnormalities
   a) Historical or current evidence of significant diseases including, but not limited to those listed below. Significant was defined as any disease that in the opinion of the Investigator would put the subject at risk through study participation or which would affect the efficacy analysis if the disease exacerbated during the study.
      - Other significant pulmonary disease including cystic fibrosis, bronchiectasis, bronchopulmonary dysplasia
      - Unresolved upper or lower respiratory tract infection
      - Clinical or radiological evidence of pneumonia within the preceding 3 months
      - Disorders of the ears, nose, throat or sinuses likely to require surgical intervention during the study Treatment Period
      - Congenital heart disease that required pharmacotherapy or surgical correction within the preceding 12 months
      - Seizure disorder
      - Reflux esophagitis not controlled by pharmacotherapy and which might be contributing to or causing the subject's asthma symptoms.

        Amendment No. 5 amended the exclusion criteria to allow subjects with gastro-esophageal reflux disease (GERD) that was well controlled with pharmacotherapy and no longer contributing to the subject's asthma symptoms to be eligible for enrollment.

        Original wording: Reflux esophagitis that required pharmacotherapy with H2-antagonists, proton pump inhibitors, cisapride or metoclopramide within 3 months of entry into the study.
      - Cushing's Syndrome or hypoadrenalism
      - Renal disease
      - Severe hematological disease (Note: a history of idiopathic thrombocytopenia purpura was not an exclusion criterion if the platelet count had been within normal limits for 12 months. Asymptomatic hemoglobinopathy that had not required treatment was not an exclusion criterion.)
      - Hepatic disease (Note: Jaundice limited to the neonatal period that required phototherapy was not an exclusion criterion)
      - Malignancy
      - Disorder of cellular or humoral immunity
      - Juvenile rheumatoid arthritis, systemic lupus erythematous or other serious collagen-vascular disease
      - Inadequately controlled psychiatric disorder

- Endocrine disorders, including diabetes mellitus, pan-hypopituitarism
- Glaucoma or cataracts

b) Chickenpox: A subject was not eligible if he/she currently had chickenpox. If a subject had been exposed to chickenpox within 3 weeks preceding Visit 1 and the Investigator believed this exposure placed the subject at risk of developing infection, he/she was not eligible for the study. (Note: If a subject developed chickenpox during the study, he/she was discontinued from the study.)

c) Drug Allergy: Any immediate or delayed hypersensitivity to any sympathomimetic drug or any intranasal, inhaled or systemic corticosteroid therapy.

d) Chest x-ray abnormalities: A subject could not have any pulmonary abnormality that was not consistent with asthma. (Note: a chest x-ray was not required for this study.)

e) Clinically significant laboratory abnormalities: Laboratory tests were required to be reviewed prior to randomization.

4) Affiliation with the investigational site: A subject was not eligible if he/she was an immediate family member of the participating investigator, sub-investigator, or study coordinator.

5) Informed Consent: A subject was not eligible if he/she or his/her legally authorized representative had a history of psychiatric disease, intellectual deficiency, substance abuse, or other condition (e.g., inability to read, comprehend, and write) which would limit the validity of consent to participate in this study.

6) Attendance: A subject was not eligible if he/she or his/her legally authorized representative had any infirmity, disability or geographical location which seemed likely (in the opinion of the Investigator) to impair compliance with any aspect of this protocol or scheduled visits to the study center.

12.1.1.3.3. Concomitant, Excluded, and Rescue Medications, Washout Periods
[Clinical, FMS30058, pages 30-2, 2458-60; fms30058.pdf]

12.1.1.3.3.1. Permitted medications

Subjects were permitted to continue receiving cromolyn, nedocromil, theophylline or montelukast during the treatment period if the treatment was prescribed at least four weeks prior to Visit 1. During the screening period the dose could be titrated, but otherwise the dosing regimen was required to remain constant following randomization (Visit 2). However, theophylline dosage adjustment was permitted at the Investigator's discretion based on theophylline serum concentrations. The subject was not permitted to start any new maintenance therapies after the start of the study unless they experienced an asthma exacerbation. During and subsequent to an asthma exacerbation the Investigator could alter the subject's asthma pharmacotherapy regimen as deemed appropriate excluding administration of fluticasone propionate.

The following asthma and non-asthma medications were allowed during the study:

- Albuterol (study supplied as nebules or MDI)
- Cromolyn and nedocromil, if started at least four weeks prior to Visit 1 (Amendment 3)
- Theophylline, if started at least four weeks prior to Visit 1 (Amendment 3)

- Montelukast, if started at least four weeks prior to Visit 1 (Amendment 4)
- EMLA Cream (study supplied)
- Antibiotics
- Topical corticosteroid cream or ointment (hydrocortisone ≤1% or equivalent only)
- Acetaminophen
- Ibuprofen
- Guaifenesin
- Antihistamines
- Systemic decongestants (pseudoephedrine or phenylpropanolamine)
- Vaccinations recommended by the local public health department.

12.1.1.3.3.2. Prohibited medications

It was prohibited to start any new maintenance asthma medication on or after Visit 1 unless the subject experienced an asthma exacerbation. During and subsequent to an asthma exacerbation, the subject's pharmacotherapy regimen could be altered as deemed appropriate by the Investigator. However, inhaled fluticasone propionate (other than study drug could not be prescribed at any time. An asthma exacerbation was defined as "increasing signs or symptoms of asthma, not controlled by as-needed albuterol and requiring asthma medications not allowed by this protocol prior to an asthma exacerbation." Use of the following asthma medications was prohibited during the screening and treatment period prior to an asthma exacerbation:

- Inhaled corticosteroids
- Systemic corticosteroids
- Leukotriene inhibitors other than montelukast started at least four weeks prior to and continued after Visit 1 (Amendment 4)
- Beta-agonists, oral or inhaled, other than study supplied albuterol
- Cromolyn or nedocromil unless started at least four weeks prior to Visit 1 (Amendment 3)
- Theophylline unless started at least four weeks prior to Visit 1 (Amendment 3)
- Ipratropium bromide.

Use of the following non-asthma medications was prohibited:

- Intranasal corticosteroids
- Narcotic cough suppressants (e.g., codeine or products containing codeine)
- Non-narcotic cough suppressants (e.g., dextromethorphan (DM))
- >1% hydrocortisone dermatology products or equivalent
- Anticonvulsants
- beta-adrenergic antagonists (including ophthalmic)
- Central nervous system stimulants (methylphenidate or pemoline)
- Immunosuppressive agents (cyclosporine, methotrexate, gold salts)
- Ketoconazole.

12.1.1.3.4. Subject withdrawal [Clinical, FMS30058, pages 25-6; fms30058.pdf]

Children could be discontinued from the study at any time by a legally authorized representative or at the discretion of the Investigator. Subjects were not required to be prematurely discontinued if they experienced an asthma exacerbation, AE or serious adverse event (SAE).

If for any reason a child was prematurely discontinued from the study, the Investigator was to make every effort to perform the following evaluations and record the following information:

1) Review asthma symptom scores recorded on the daily diary record
2) AE and concomitant medication assessment
3) Conduct physical examination (including vital signs and linear growth assessment)
4) Examination of oropharyngeal and nasal passage
5) Oropharyngeal and nasal fungal culture
6) Obtain blood sample for clinical laboratory tests according to instructions in laboratory kit
7) Collect double-blind study medication
8) Collect used and unused albuterol
9) Phone the parent/guardian three days after study drug termination to assess for AEs.

Following these procedures, the Investigator could prescribe asthma medication follow the subject as judged medically appropriate. Subjects were to be followed or treated until a satisfactory resolution occurred for any clinically significant AEs, laboratory tests or physical examination abnormalities observed during the premature discontinuation visit.

12.1.1.3.5. Protocol Amendments [Clinical, FMS30058, pages 20-1; fms30058.pdf]

The original protocol, dated 09 September 1999, was amended 7 times.

Amendment 1 (04 Nov 1999): This amendment was implemented before enrollment started and applied to all participating clinical study sites. Amendment 1:

1) Revised exclusion criteria to:
   a) Exclude subjects who have received medium to high doses of inhaled corticosteroids 1 within 8 weeks prior to Visit 1
   b) Increase the washout period for systemic corticosteroids from 6 weeks to 8 weeks prior to Visit 1
   c) Exclude subjects with greater than 2 courses of systemic corticosteroids within the 12 months prior to Visit 1
   d) Exclude subjects with a history of use of dextroamphetamine within 4 weeks prior to Visit 1
2) Clarified stadiometry calibration. For measurements taken using stadiometers which require calibration, any measurements performed prior to appropriate stadiometer calibration will not be used in the analysis.
3) Revised requirements for urine specimen storage.

Amendment 2 (12 Dec 1999): This amendment was implemented before enrollment was ongoing and applied to all participating clinical study sites. Amendment 2 incorporated collection of DNA samples.

Amendment 3 (02 Feb 2000): This amendment was implemented while enrollment was ongoing and applied to all participating clinical study sites. Amendment 3:

1) Redefined the time period for baseline asthma symptom scores from 14 days prior to Visit 2 to 7 days prior, and
2) Defined the time period (4 weeks) that subjects who would be using cromolyn, nedocromil, or theophylline after Visit 1 must have been on a stable dose prior to Visit 1.

Amendment 4 (31 Mar 2000): This amendment was implemented while enrollment was ongoing and applied to all participating clinical study sites. Amendment 4 allowed concomitant use of montelukast provided a stable dose had been maintained for at least 4 weeks prior to Visit 1. If montelukast was continued after Visit 2, the dose was required to remain constant and the medication was not be discontinued during study participation.

Amendment 5 (08 Jun 2000): This amendment was implemented while enrollment was ongoing and applied to all participating clinical study sites. Amendment 5 amended the exclusion criteria to allow subjects with gastro-esophageal reflux disease (GERD) that was well controlled with pharmacotherapy and no longer contributing to the subject's asthma symptoms to be eligible for enrollment.

Amendment 6 (30 Mar 2001): This amendment was implemented while enrollment was ongoing and applied to all participating clinical study sites. Amendment 1 had earlier added a criteria which excluded subjects with a history of treatment with greater than 2 courses of systemic corticosteroids within the 12 months prior to Visit 1. This amendment revised this criteria to exclude only those subjects with greater than 2 courses of systemic corticosteroids within 6 months prior to Visit 1.

Amendment 7 (15 Jun 2001): This amendment was implemented while enrollment was ongoing and applied to all participating clinical study sites. Amendment 7 allowed the use of Proventil brand of albuterol sulfate inhalation solution as a substitute for Ventolin nebules.

12.1.1.4. Conduct

This was a 12-week, randomized, double-blind, parallel group, placebo-controlled multicenter study. While the protocol states that 80 outpatient centers were planned for subject enrollment, 87 sites participated, and 77 sites enrolled subjects. Table 8 shows the timing of events for the study. The study was conducted in two periods: a 2- to 4-week screening period, and a 12-week treatment period. Randomization was stratified by age at randomization: <36 months and >36 months, with separate blocks for each strata at each site. Subjects attended clinic visits at treatment weeks 1, 2, 4, 8, and 12 (Weeks 6 and 10 were phone contacts only). [Clinical, FMS30058, pages 18, 27-8, 30; fms30058.pdf]

Subjects were treated with either Flovent (fluticasone propionate) CFC MDI 44 mcg (1 puff), 88 mcg (2 puffs), or placebo CFC MDI administered twice daily with an Aerochamber or Optichamber valved holding chamber plus facemask. To maintain a dosing balance, two inhalers were distributed at each of Visits 2, 5, and 6, and parents/guardians

were instructed to administer one puff from each of the two inhalers twice daily. Parents/guardians were given instructions and demonstration kits for administration of medication and use of the valved holding chamber plus facemask. Approximately 50% of the sites distributed the Aerochamber device, and 50% distributed the Optichamber device (use of the holding chamber was unblinded). Asthma rescue medication included albuterol inhalation aerosol MDI (with a separate valved holding chamber) and/or nebules. [Clinical, FMS30058, pages 19, 28; fms30058.pdf]

Comments: The following comments reflect omissions in the protocol and study report that may have had a direct effect on the emitted dose from the combination of the MDI and the holding chamber with mask. Lack of this information constitutes a critical oversight in the study design.

1. (b)(4) *Washing and drying of the holding chamber, and timing of this care in relation to dosing may be strongly correlated with the dose emitted from the holding chamber, and therefore with the dose that the patient receives.*

2. Information regarding the timing of the puff in relation to the placement of the mask over the nose and mouth of the patient was not provided in either the protocol or the study report. Timing of the puff in relation to placement over the nose and mouth may be strongly correlated with the dose emitted from the holding chamber, and therefore with the dose that the patient receives.

3. Information regarding how long the mask was placed over the nose and mouth of the patient, either by time or by respiratory cycles, was not provided in either the protocol or the study report. How long the mask is kept over the nose and mouth may be strongly correlated with the dose that the patient receives.

A Peak Flow Meter was dispensed to the parents/guardians of those subjects capable of performing the maneuver and parents/guardians were instructed on proper method of performing PEF measurements. [Clinical, FMS30058, page 32; fms30058.pdf]

The batches of FP CFC MDI used were OZP1089, 9ZP1541, and W0388CC. Batches of placebo CFC MDI used were OZP0771 and 9ZP1542. [Clinical, FMS30058, page 27; fms30058.pdf]

Table 8. Study FMS30058, Time and events schedule

Visit	1	Phone Only	2	3	4	5	Phone Only	6	Phone Only	7	Early D/C	Phone Only
Week	Screening		0	1	2	4	6	8	10	12		
Day		14-21 and/or 28 days after Visit 1	1 (14-28 and/or 28 days after Visit 1)	8±3	15±3	29±4	43	57±4	71	85±4		3 days after termination of study drug
Informed consent	✓											
Review Inclusion/exclusion criteria and randomize patient if elig ble			✓									
Medical history	✓											

Appendix B, Study FMS30058

Visit	1	Phone Only	2	3	4	5	Phone Only	6	Phone Only	7	Early D/C	Phone Only
Week	Screening		0	1	2	4	6	8	10	12		
Day		14-21 and/or 28 days after Visit 1	1 (14-28 and/or 28 days after Visit 1)	8±3	15±3	29±4	43	57±4	71	85±4		3 days after termination of study drug
Concomitant medications assessments	✓		✓	✓	✓	✓		✓		✓	✓	
Assess adverse events			✓	✓	✓	✓		✓		✓	✓	✓
Review asthma symptom scores		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Review/dispense dairy	✓		✓	✓	✓	✓		✓	✓	✓	✓	
Physical examination	✓		✓			✓		✓		✓	✓	
Vital signs	✓		✓	✓	✓	✓		✓		✓	✓	
Linear growth (height)	✓		✓	✓	✓	✓		✓		✓	✓	
Oropharyngeal and nasal examination [a]	✓		✓	✓	✓	✓		✓		✓	✓	
Oropharyngeal and nasal fungal culture	✓									✓	✓	
Clinical laboratory tests	✓									✓	✓	
PK plasma sample										✓		
Review MDI / holding chamber technique			✓									
Demonstrate / dispense PEF meter [b]	✓		✓									
Dispense study drug [e]			✓			✓		✓				
Collect study drug						✓		✓		✓	✓	
Dispense/collect a buterol	✓		✓			✓		✓		✓	✓	
Dispense urine collection container	✓							✓				
Collect urine cortisol specimen [c]			✓							✓		
Phone call to home [d]		✓					✓		✓			✓

a Culture was required if patient has signs or symptoms of fungal infection

b PEF in capable patients

c Parents/guardians were required to collect overnight urine within two evenings prior to visit

d The investigator or study coordinator was required to call parent/guardian to assess compliance with daily diary record, medication, and child's health

e Each treatment pack included two inhalers (Inhaler A and Inhaler B). Each treatment pack was dispensed to each randomized subject for use over approximately four weeks. "Subjects inhaled one puff from Inhaler A and one puff from Inhaler B twice daily, approximately twelve hours apart using either an Aerochamber or Optichamber valved holding chamber with facemask. Parents/guardians were to attach the valved holding chamber directly to the actuator of the study drug inhaler. The instructions for administration of the medication were provided in the study reference manual and with the study drug. In addition, treatment demonstration kits were provided for instructional purposes." [page 28]

Source: Clinical, FMS30058, pages 28, 114, 2494; fms30058.pdf

12.1.1.5. Safety Evaluations

Note: The pediatric Written Request stated that study FMS30058 should "attempt to measure peak expiratory flow rate. Safety endpoints must include recording of adverse events, vital signs, physical examination, linear growth, HPA-axis assessment, and clinical laboratory measures."

Safety measures were assessed at each clinic visit by physical examinations (including vital signs and linear growth assessments), oropharyngeal and nasal passage examinations, oropharyngeal and nasal fungal culture, and adverse events reporting. Routine clinical laboratory tests and assessment of adrenal function by collection of an overnight urine for cortisol excretion were performed at baseline and following 12 weeks of treatment (parents were given two attempts for urine collection, within 48 hours prior to the scheduled visit). Parents/guardians were provided written instruction sheets for collection of the twelve-hour urine sample via bagged collection (non-toilet trained children) or pilgrim hat (toilet trained children) [Clinical, FMS30058, Attachments 1 and 2, pages 2429-2435; fms30058.pdf]. A medical history was obtained at screening (Visit 1), including a review of systems and information on the age of the onset of asthma, responses to provocative stimuli, pharmacotherapy, family history, daycare, pets, and household smoke exposure. For those patients capable of performing peak expiratory flow (PEF) measurements, parents/guardians were asked to record the morning PEF measurement in the diary daily. [Clinical, FMS30058, pages 33-5, 2467-70; fms30058.pdf]

The definition of an adverse event (AE) included: an exacerbation of a pre-existing illness, an increase in frequency or intensity of a pre-existing episodic event or condition, a condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study, continuous persistent disease or symptoms present at baseline that worsened following the start of the study. Surprisingly the definition of an AE excluded overdose of either study drug or concurrent medication without any signs or symptoms. [Clinical, FMS30058, pages 35-6; fms30058.pdf]

12.1.1.6. Efficacy and Compliance Evaluations

Efficacy was assessed by parent/guardian rating of the patient's daytime and nighttime asthma symptoms, as recorded on the daily diary card. The symptoms of wheeze, cough and shortness of breath were assessed and scored on a 0-3 severity scale. [Clinical, FMS30058, pages 33-4; fms30058.pdf]

Daytime symptoms:

0	None	no asthma symptoms (cough, wheeze, shortness of breath)
1	Mild	noticeable symptoms, but not interfering with daily activities
2	Moderate	symptoms present often, causing some interference with daily routine and activities
3	Severe	symptoms continuous or present most of the day, restricting daily routine and activities severely

Nighttime symptoms:

0	None	no asthma symptoms (cough, wheeze, shortness of breath)
1	Mild	noticeable symptoms but not interfering with sleep
2	Moderate	awakened once or more because of asthma symptoms
3	Severe	awake most of the night due to asthma symptoms

Compliance was assessed based on the administration of the morning and evening study medications as documented in the CRF Diary Card (Figure 7). [Clinical, FMS30058, page 30; fms30058.pdf]

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Subject Diary Card

Diary dispensed at Visit ☐

Parent's / guardian's initials[H] _____

Row number	Date (Month Day Year)	Asthma symptoms score: Last night's symptoms[A] (circle one)	Asthma symptoms score: Yesterday's day symptoms[B] (circle one)	Number of puffs of Ventolin[B] used over the past 24 hours[C]	Number of Ventolin[B] nebules used over the past 24 hours[D]	Today's AM Peak expiratory flow rate[E]	Did you take your study drug over the last 24 hours?[F] Y = YES N = NO: AM Canister A	AM Canister B	PM Canister A	PM Canister B	Record any medical problems and any medication used[G]
e.g.	09 22 99	(1) 1 2 3	0 1 2 (3)	2	1	300	(Y) N	(Y) N	(Y) N	(Y) N	
1		0 1 2 3	0 1 2 3				Y N	Y N	Y N	Y N	
2		0 1 2 3	0 1 2 3				Y N	Y N	Y N	Y N	
3		0 1 2 3	0 1 2 3				Y N	Y N	Y N	Y N	
4		0 1 2 3	0 1 2 3				Y N	Y N	Y N	Y N	
5		0 1 2 3	0 1 2 3				Y N	Y N	Y N	Y N	
6		0 1 2 3	0 1 2 3				Y N	Y N	Y N	Y N	
7		0 1 2 3	0 1 2 3				Y N	Y N	Y N	Y N	
8		0 1 2 3	0 1 2 3				Y N	Y N	Y N	Y N	
9		0 1 2 3	0 1 2 3				Y N	Y N	Y N	Y N	
10		0 1 2 3	0 1 2 3				Y N	Y N	Y N	Y N	

A. Night symptoms:
0 none; no asthma symptoms (cough, wheeze, shortness of breath)
1 mild; noticeable symptoms but not interfering with sleep
2 moderate; awakened once or more because of asthma symptoms
3 severe; awake most of the night due to asthma symptoms

B. Day symptoms:
0 none; no asthma symptoms (cough, wheeze, shortness of breath)
1 mild; noticeable symptoms, but not interfering with daily activities
2 moderate; symptoms present often, causing some interference with daily routine and activities
3 severe; symptoms continuous or present most day, restricting daily routine and activities severely

Figure 7. Study FMS30058, Sample CRF Diary Card, English version

12.1.1.7. Pharmacokinetic Evaluations

Pharmacokinetic sampling was performed at the end of 12 weeks of therapy. A modified population PK approach with sparse sampling was used. At Visit 7, subjects had a single blood sample of 5 mL collected at one of four randomized sampling times ranging from -1.0 to 0.0 hours (pre-dose), 0.25 to 2.5, 3 to 8, or 9 to 11 hours post-dose relative to the morning dose. Results were combined with population PK data from study FMS30059, and reported in a separate Clinical Pharmacology Study Report. [Clinical, FMS30058, pages 41, 2469-70; fms30058.pdf]

12.1.1.8. Statistical Plan

12.1.1.8.1. Definition of study populations

ITT population: The protocol defined the Intent-to-Treat (ITT) population as all subjects who were randomized and received at least one dose of study drug and had at least one observation taken while receiving study drug. However, the Intent-to-Treat (ITT) population that was used was all subjects who were randomized and received at least one dose of study drug. This was slightly more inclusive, as it included subjects who did not have any observations taken while receiving study drug, i.e. dropouts immediately after the first dose. [Clinical, FMS30058, pages 43-5; fms30058.pdf]

RITT population: GSK made the decision prior to the final sign off of the reporting and analysis plan to establish a Reduced ITT (RITT) population. The RITT population excluded from the ITT population all three subjects at (b) (4) site (1 placebo, 1 FP44, 1 FP88) because of study conduct irregularities and subjects at any investigative site for whom the treatment blind is broken (usually due to flaking of the blinding cover) (all at Visit 2). (See Ethical Standards, page 33) [Clinical, FMS30058, pages 42-3, 134; fms30058.pdf]

Growth population: The growth population was a subset of the ITT population defined to exclude subjects who did not have sufficient and reliable growth data to provide an estimate for 12-week growth velocity. Specifically, the growth population excluded subjects who had any one of the following:

1. Did not have growth assessments on at least three visits that included both baseline (Visit 2) and Week 12 (Visit 7).
2. Had a reduction in height measures from baseline to endpoint, i.e., the minimum of the triplicate height readings at baseline is larger than the maximum of the triplicate height readings at endpoint.
3. Received systemic (oral or injectable) corticosteroids or medium to high doses of inhaled corticosteroids within 8 weeks prior to any growth assessments.

Growth velocity was defined as the rate of increase in standing height over the 12-week Treatment Period. For each subject, the growth measurements were used to calculate the slope of the linear regression line fitted to the height measurements over the time (standardized to unit 1 in time). The three repeated measurements taken at each visit were considered as replicates in the regression analysis. The study report states that inconsistent measurements (i.e., outliers determined by regression diagnosis) were excluded, but the study report does not state whether the outliers were identified prior to breaking the blind on the data. [Clinical, FMS30058, page 44; fms30058.pdf]

Urine cortisol population: The urine cortisol population was defined to exclude subjects from ITT population whose urine samples were considered to have confounding factors that would affect the interpretation of the results. Specifically, the urine cortisol population excluded subjects who had any one of the following at either baseline or Week 12 [Clinical, FMS30058, pages 44-5; fms30058.pdf]:

1. Urine volume .80mL and a 12-hour creatinine excretion below the lower limit of threshold range of 6.5mg/kg/12hrs, regardless of sex.
2. Had collection time intervals outside 12 ± 2 hours.
3. Received systemic (oral or injectable) corticosteroids or medium to high doses of inhaled corticosteroids (see Exclusion Criteria) within 8 weeks prior to any start time of urine collection.
4. Used intranasal or topical corticosteroids (except ≤1% potency topical corticosteroids) within 30 days prior to any start time of urine collection.
5. Had been off study drug for more than one day at the start time of the post-baseline urine collection.

Completer population: A completer was defined as a subject who completed at least 81 days of study treatment, had a clinic visit at Week 12, and did not withdraw from the study. [Submission of 02-14-2003, page 1; cover.pdf]

12.1.1.8.2. Primary endpoint and analysis

Note: The pediatric Written Request stated that 'the primary efficacy endpoint must include asthma symptom scores such as wheeze, dyspnea, and cough. The secondary efficacy endpoints must include asthma symptom free days, use of rescue medications, treatment failures, and patients discontinuations."

In addition, no adjustment was made for multiple comparisons for either the primary or the secondary endpoints.

The primary efficacy endpoint was the average of the change from baseline in daily asthma symptom scores during the last two weeks of diary data prior to end of study, asthma exacerbation or study withdrawal. The daily asthma symptom scores were a composite of the parent/guardian's rating of daytime and nighttime (average of the AM and PM) asthma symptom scores for wheeze, cough, and shortness of breath. Baseline was defined as the average of the daytime and nighttime (composite) asthma symptom scores recorded for the last 7 days prior to Visit 2. [Clinical, FMS30058, pages 33-4, 50; fms30058.pdf]

12.1.1.8.3. Secondary endpoints and analyses

Secondary 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. Treatment failure was defined as the first asthma exacerbation. [Clinical, FMS30058, pages 34; fms30058.pdf]

12.1.1.8.4. Other endpoints and analyses

Other efficacy endpoints included the diary AM Peak expiratory flow rate (PEF), the frequency of treatment failure, and subject discontinuations. [Clinical, FMS30058, page 34; fms30058.pdf]

12.1.1.8.5. Sample size considerations and data analysis methodology

The study was designed around a Written Request (WR) issued by the FDA. Therefore, the sample size calculations typically found in a study protocol were not used to estimate the powering of this study. The original WR required a minimum of 100 completed patients per group with ½ less than 3 years of age. Amendment #1 (5/21/2001) stated that "a minimum of 50 patients per group, of which approximately 1/3 should be less than 12 months of age" were required. This was a typographical error that applied to study FMS30059, and was never corrected. Because of this, GSK used the population size from the original WR.

With an estimated dropout rate of 20%, the study planned 130 subjects per group, or a total of 390 subjects to be enrolled. Based on a previous study with a nebulized steroid product, a sample size of 95 in each group had at least 80% power to detect a difference of 0.30 in the average of the change from baseline in daytime and night-time symptom scores between

treatment groups using the two-sample t-test with a 0.05 two-sided significance level. Assuming a similar standard deviation (0.73 if 94 subjects/group), 100 per group would provide 82% power, with a power of 91% using last observation carried forward (130 subjects/group). Again per the Written Request, randomization was stratified by age group (24 to less than 36 months, 36 to less than 48 months) within each center. Enrollment was planned from 80 sites in the United States, with an average number of five subjects per site. [Clinical, FMS30058, pages 2472-3; fms30058.pdf]

Safety analyses (except for cortisol and growth) were based on the ITT population. All efficacy analyses were based on the RITT population, with the additional inferential analysis performed on the primary efficacy endpoint for the ITT population as the sensitivity analysis. No interim analysis was planned or conducted. The primary contrasts of interest were the two pairwise comparisons between the two active treatments and placebo. The primary analysis methodology was an analysis of covariance (ANCOVA) using the covariates of baseline value, age group, holding chamber, sex, region, previous corticosteroid (CS) therapy (yes/no), family history of asthma, and subject history of allergy. Although the randomization was stratified by age (24 to less than 36 months, 36 to less than 48 months) at each site, the analysis model did not include site as a covariate, as most sites had a small number of subjects. The analyses used two-sided statistical tests with results considered statistically significant where $p \leq 0.05$. When specified, 95% confidence intervals were calculated. No multiplicity adjustment was made for the secondary efficacy measures as the study was designed to fulfill the Pediatric Exclusivity determination requirements. [Clinical, FMS30058, pages 42, 45-6, 2473; fms30058.pdf]

For premature discontinuations, the primary efficacy endpoint was considered as missing if a subject had less than 7 days recorded diary data prior to the efficacy cut-off date. If a subject had between 7 and 14 days of recorded diary data prior to efficacy cut-off date, the endpoint was calculated as the average of daily asthma symptom scores from all available data during the Treatment Period. For missing data, the weekly mean for a given efficacy measure was reported as the mean of non-missing observations if two or more daily asthma symptom scores were present. Since the daily asthma symptom score was defined to be the average of AM and PM (composite) asthma symptom scores as recorded on the diary card, the daily asthma symptom score was considered as missing unless both AM and PM symptom scores were available. [Clinical, FMS30058, page 47; fms30058.pdf]

12.1.2. Results

NOTE: (b) (4)

12.1.2.1. Description of Study Population

12.1.2.1.1. Disposition

Patient disposition is summarized in Table 9. In this study, 80 outpatient centers were planned, 87 centers participated, and 77 centers enrolled patients (range 1 to 21 per center). Approximately 390 patients were planned, 493 enrolled, and 332 were randomized.

Slightly more patients in the placebo group discontinued than in either of the Flovent groups, with the majority of discontinuations in the placebo groups due to being lost to follow-up. One patient in the SP44 group discontinued at the discretion of the principal investigator secondary to worsening asthma. This patient was coded in the 'Other' category, and should have been coded as a discontinuation due to an adverse event. [Clinical, Study FMS30058, page 60, Tables 13.5 and 13.6, pages 152-4; fMS30058.pdf]

Table 9. Study FMS30058, Patient disposition, ITT population

Disposition	Placebo	FP44	FP88	Total
ITT population	113	111	108	332
Completed	95 (84%)	99 (89%)	102 (94%)	296 (89%)
Discontinued	18 (16%)	12 (11%)	6 (6%)	36 (1%)
Adverse event	3	0	0	3
Consent withdrawn	2	2	2	6
Lost to follow-up	9	2	2	13
Protocol violation	3	4	1	8
Lack of efficacy	1	2	0	3
Other *	0	2	1	3

* The Other group included: patient had surgery/parent decided to discontinue (1), principal investigator discretion for worsening asthma (1), stopped study drug after first dose (1).

Source: Clinical, Study FMS30058, Tables 13.5 and 13.6, pages 152-4; fMS30058.pdf

12.1.2.1.2. Protocol Violations

Protocol deviations are summarized in Table 10. Major violations included enrollment and/or randomization of subjects to who did not meet the inclusion, exclusion and/or randomization criteria. Other protocol deviations included use of prohibited concomitant medications, incorrect stratification, incorrect study drug dispensing, and any other deviations that were deemed to have the potential for influencing the results.

There were more protocol violations in the placebo group (60%) than in the Flovent groups (46-47%). This appears to be due predominantly to more frequent use of prohibited medications during the treatment period and a higher incidence of other deviations in the placebo group. The majority of patient visits were within the protocol specified visit windows (65-94%), with similar results for all treatment groups (results not shown). [Clinical, FMS30058, Table 13.10, pages 213-4; fms30058.pdf]

There were six patients unblinded during the study (1 placebo, 3 FP 44, 2 FP 88). All six were unintentionally unblinded due to breaking or flaking of the label, but nevertheless completed the study. [Clinical, FMS30058, Table 13.11, pages 215-28; fms30058.pdf]

Table 10. Study FMS30058, Protocol violations, ITT population

Protocol Violation	Placebo	FP44	FP88
ITT population	113	111	108
Protocol violations †	68 (60%)	52 (47%)	50 (46%)
Failed to meet inclusion criteria	2	1	0
Failed to meet exclusion criteria	19	16	21
Failed to meet randomization criteria	17	12	8
Prohibited medication	41	33	31
Pre-screening	18	16	20

Protocol Violation	Placebo	FP44	FP88
During screening	26	23	24
During treatment	29	23	18
Prohibited concurrent medication *	2	2	2
Treatment medication violation	2	3	7
Stadiometer calibration violation	0	1	0
Other	26	20	16

† Note; patients may have violated more than one criterion.

* Prohibited concurrent medication was checked on Protocol Violations Summary CRF page, but medication was not specified on the concurrent medications CRF page.

Source: Clinical, Study FMS30058, page 61 and Table 13.8, pages 156-63; fMS30058.pdf

12.1.2.1.3. Analysis populations

As defined above, there were several analysis populations defined in the protocol, before unblinding, and *post-hoc*. These included the ITT, RITT, Completer, Growth, and Cortisol populations. The numbers of patients in each population are shown in Table 11. 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 patients excluded from the ITT to create the RITT population included 8 patients: 3 from (b) (4) site (one in each of the three treatment groups), and 5 for whom study drug accidentally was unblinded (1 placebo, 2 FP44, 2 FP88). The majority of patients excluded from the urine cortisol population were due to missing data (57-59%) and due to low 12-hour weight-adjusted creatinine and urine volume (20-28%) [Clinical, Study FMS30058, page 61; fMS30058.pdf]. This is not unexpected, due to difficulties with urine collection from bagged specimens in a partially toilet-trained population.

The Completer population was defined specifically *post-hoc* to meet the Written Request. This population included 283 patients (100 FP88, 95 FP44, 88 placebo), of which 141 patients (50%) were 24-35 months of age and 142 patients (50%) 36-47 months of age, and of which 132 patients (47%) used an Aerochamber and 151 patients (53%) used an Optichamber. [Submission of 2/14/03, p 1, cover.pdf; Table 3, p 24-6, fms3005859tables.pdf].

Table 11. Study FMS30058, Summary of analysis populations

Population	Placebo	FP44	FP88
ITT	113	111	108
RITT	111	108	105
Completer	88	95	100
Growth	71	79	87
Urine cortisol	26	19	20

Source: Clinical, Study FMS30058, page 61; fMS30058.pdf
Submission of 2/14/03, Table 3, p 24-6, fms3005859tables.pdf

12.1.2.1.4. Demographics and baseline characteristics

Demographic and other baseline characteristics of the patients in the ITT population are summarized in Table 12. As shown, the demographics of the treatment groups were comparable. The history of asthma and allergies, including family history of asthma, is

summarized in Table 13. Again, the groups were comparable. The incidence of other medical conditions (not shown) was comparable among groups.

Prior use of corticosteroids and other asthma medications are shown in Table 14. The FP44 group had a slightly lower baseline use of corticosteroids, both within six months (both oral and inhaled) and eight weeks (inhaled only) prior to Visit 1. There was a low use of oral corticosteroids in all groups within eight weeks of Visit 1. Prior use of other asthma medications was comparable among groups.

Use of non-asthma concurrent medications both before and during the treatment period was comparable among groups [Clinical, Study FMS30058, pages 708, 837; fms30058.pdf]. As expected, during the treatment period the active treatment groups used less concurrent asthma medications (38-40%) than the placebo group (52%), with the most commonly used asthma medications being sodium cromoglycate (24-29%) and prednisolone (4-13%) [Clinical, Study FMS30058, Table 13.29, page 626; fms30058.pdf]. Post-treatment, both active groups (30%) used less asthma medications than the placebo group (40%) [Clinical, Study FMS30058, page 66; fms30058.pdf].

Table 12. Study FMS30058, Demographics and Baseline Characteristics, ITT pop

Demographics	Placebo n = 113	FP44 n = 111	FP88 n = 108	Total n = 332
Age (months)			5	
Mean (range)	35.7 (24-48)	35.6 (24-47)	35.5 (24-47)	35.6 (24-47)
24-35 months	54 (48%)	56 (50%)	53 (49%)	163 (49%)
36-47 months	59 (52%)	55 (50%)	55 (51%)	169 (51%)
Male	71 (63%)	70 (63%)	63 (58%)	204 (61%)
Female	42 (37%)	41 (37%)	45 (42%)	128 (39%)
Ethnicity:				
White	84	70	77	231
Black	10	19	13	42
Asian	1	2	2	5
Hispanic	11	14	12	38
Other*	6	6	4	16
Height (cm) (mean, range)	94.9 (83-109)	94.2 (78-109)	94.8 (79-109)	94.6 (78-109)
Weight (kg) (mean, range)	15.2 (10-24)	14.8 (10-24)	15.2 (10-33)	15.1 (10-33)
Device type				
Aerochamber	52	56	50	158
Optichamber	61	55	58	174
Other demographics				
Smoking exposure*	25 (22%)	21 (19%)	17 (16%)	63 (19%)
Pet exposure*	62 (55%)	58 (52%)	58 (54%)	178 (54%)
Attend daycare	67 (59%)	63 (57%)	63 (58%)	193 (58%)

* History of smoking or pet exposure in household or daycare environment.

Source: Clinical, Study FMS30058, Table 13.18, pages 362-4; fms30058.pdf

Table 13. Study FMS30058, Asthma and allergy history, ITT population

Asthma	Placebo n = 113	FP44 n = 111	FP88 n = 108
Age at Onset (months)			
<6 months	31 (27%)	33 (30%)	39 (36%)
≥6 months to <1 year	32 (28%)	28 (25%)	22 (20%)
≥1 year to <2 years	31 (27%)	39 (35%)	34 (31%)
≥2 years to <3 years	19 (17%)	10 (9%)	11 (10%)
≥3 years to <4 years	1 (<1%)	1 (<1%)	2 (2%)
Duration of Asthma (months)			
Mean (range)	23.3 (2-43)	25 (6-46)	24.4 (4-46)
History of Allergy	95 (84%)	91 (82%)	78 (72%)
SAR	46	37	34
PAR	55	59	50
Eczema	30	27	26
Food allergy	27	18	22
Other	25	19	23
Immediate Family History of Asthma			
Yes	74 (65%)	83 (75%)	78 (72%)
Mother	37	34	41
Father	23	35	26
Siblings	38	39	45
Maternal GP	27	31	30
Paternal GP	9	16	16
No	38	25	27
Unknown	1	3	3

Source: Clinical, Study FMS30058, Table 13.20, pages 383-4; fms30058.pdf

Table 14. Study FMS30058, Pre-study corticosteroid use, ITT population

Corticosteroid use	Placebo n = 113	FP44 n = 111	FP88 n = 108
Last 6 months prior to Visit 1			
Have used	53 (47%)	42 (38%)	49 (45%)
Oral	21 (19%)	16 (14%)	25 (23%)
Inhaled	40 (35%)	27 (24%)	31 (29%)
Last 8 weeks prior to Visit 1			
Have used	34 (30%)	27 (24%)	31 (29%)
Oral	1 (<1%)	2 (2%)	3 (3%)
Inhaled	32 (28%)	24 (22%)	29 (27%)
Medium-high dose	1	2	1
Low dose	29	22	28
Dose unknown	2	1	1
Last 6 months prior to Visit 1			
Have used	109 (96%)	109 (98%)	106 (98%)
Salbutamol	103	105	102
Cromolyn	39	36	40
Montelukast	13	14	11
Levalbuterol	9	8	3
Ipratropium	4	7	6
Salmeterol	3	1	4

Corticosteroid use	Placebo n = 113	FP44 n = 111	FP88 n = 108
Theophylline	0	1	0
Intranasal corticosteroids			
Used within 6 months	4 (4%)	3 (3%)	3 (3%)
Used within 8 weeks	4 (4%)	3 (3%)	3 (3%)

Source: Clinical, Study FMS30058, Table 13.25, pages 472-3 and Table 13.26, page 475; fms30058.pdf

12.1.2.1.5. Compliance

Compliance with study drug treatment (as measured by dairy records, and not by returned medications) is shown in Table 15. Rates increased with an increasing dose of Flovent.

Table 15. Study FMS30058, Compliance rates, ITT population

Compliance	Placebo n = 113	FP44 n = 111	FP88 n = 108
Compliance rate* (mean)	88.0	92.0	97.6
n ≥ 90%	82	84	84
n >=80-90%	14	13	16
n < 80%	17	13	8

* Based on dairy data. Compliance rate = the number of days all AM and PM medications were taken divided by the number of days in the treatment period.

Source: Clinical, Study FMS30058, Table 13.39, page 1197; fms30058.pdf

12.1.2.2. Efficacy Endpoint Outcomes

12.1.2.2.1. Primary efficacy measure

The primary efficacy measure was defined as the mean change from baseline in daily (24-hours) asthma symptom scores that were collected during the last two weeks of the study, but prior to the efficacy cut-off date (i.e., treatment stop date, asthma exacerbation, study withdrawal, or Day 84, whichever occurred first). These results were reported for the RITT population. The daily asthma symptom scores and the change from baseline in daily asthma symptom scores were summarized at baseline, weekly and at endpoint.

Daily asthma symptom scores at baseline, weekly, and at endpoint are summarized in Table 16 and shown graphically in Figure 8. The change from baseline in daily asthma symptom scores at baseline, weekly, and at Endpoint are summarized in Table 17, and shown graphically in Figure 9 (daily asthma scores). Figure 10 shows the asthma symptom scores broken down by daytime and nighttime asthma scores. In Table 16 and Table 17 the primary efficacy endpoint is shown in *italics*. In Table 17 all statistically significant differences are shown in **bold**.

At baseline daily asthma symptoms scores for the RITT population were comparable, although the baseline score for the FP88 group was slightly higher than the other groups. At every week of treatment with the exception of Week 3 for FP44, there was a greater reduction in asthma symptom scores in the FP88 and FP44 groups compared with placebo. The differences between FP44 and placebo for reductions in asthma symptom scores were significant at Weeks 5 and 6 but not at Endpoint (p = 0.858). However, the differences

between FP88 and placebo for reductions in asthma symptom scores were significant at Weeks 1, 2, 6 and Endpoint (p = 0.42).

Table 16. Study FMS30058, Daily symptom scores by week and at Endpoint, RITT population

Daily symptom scores	Placebo n = 111		FP44 n = 108		FP88 n = 105	
	n	mean (SE)	n	mean (SE)	n	mean (SE)
Baseline	109	1.16 (0.05)	106	1.14 (0.05)	105	1.23 (0.05)
Week 1	108	0.98 (0.06)	106	0.88 (0.06)	104	0.78 (0.05)
Week 2	106	0.83 (0.06)	105	0.78 (0.06)	102	0.63 (0.05)
Week 3	103	0.70 (0.06)	104	0.71 (0.06)	101	0.62 (0.05)
Week 4	101	0.71 (0.06)	103	0.65 (0.06)	101	0.56 (0.06)
Week 5	100	0.72 (0.06)	102	0.56 (0.06)	100	0.55 (0.06)
Week 6	99	0.69 (0.06)	101	0.53 (0.06)	100	0.49 (0.06)
Week 7	99	0.68 (0.06)	100	0.64 (0.06)	100	0.59 (0.06)
Week 8	97	0.72 (0.06)	98	0.61 (0.06)	100	0.54 (0.06)
Week 9	95	0.59 (0.06)	98	0.55 (0.06)	100	0.50 (0.06)
Week 10	93	0.52 (0.06)	97	0.52 (0.06)	99	0.46 (0.06)
Week 11	92	0.60 (0.06)	97	0.56 (0.07)	98	0.45 (0.06)
Week 12	87	0.58 (0.07)	92	0.59 (0.07)	98	0.40 (0.06)
Endpoint	*92*	*0.67 (0.06)*	*100*	*0.63 (0.07)*	*100*	*0.49 (0.05)*

Baseline = the last week prior to randomization. Endpoint is the last two weeks of diary data prior to treatment stop date, asthma exacerbation, study withdrawal, or day 84.

Source: Clinical, Study FMS30058, Table 14.1, pages 1207-10; fms30058.pdf

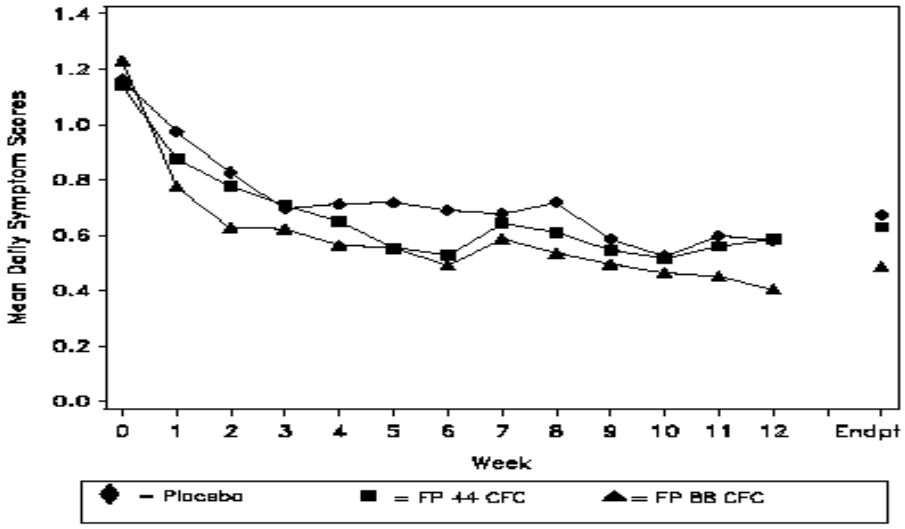

Figure 8. Study FMS30058, Daily symptom scores over time, RITT population

Source; Clinical, Study FMS30058, Figure 14.1, page 1200; fms30058.pdf

Table 17. Study FMS30058, Change from baseline in daily symptom scores by week and at Endpoint, RITT population

Change from baseline in daily symptom scores	Placebo n = 111		FP44 n = 108			FP88 n = 105		
	n	mean (SE)	n	mean (SE)	p-value	n	mean (SE)	p-value
Baseline*	109	1.16 (0.05)	106	1.14 (0.05)		105	1.23 (0.05)	
Week 1	107	-0.19 (0.05)	105	-0.26 (0.05)	0.324	104	-0.45 (0.05)	**<0.001**
Week 2	105	-0.34 (0.06)	104	-0.37 (0.06)	0.409	102	-0.61 (0.05)	**0.001**
Week 3	102	-0.45 (0.06)	103	-0.45 (0.06)	0.802	101	-0.61 (0.06)	0.419
Week 4	100	-0.45 (0.06)	102	-0.51 (0.07)	0.528	101	-0.67 (0.07)	0.130
Week 5	99	-0.44 (0.07)	101	-0.60 (0.06)	**0.035**	100	-0.68 (0.07)	0.060
Week 6	98	-0.47 (0.07)	100	-0.62 (0.07)	**0.047**	100	-0.74 (0.06)	**0.026**
Week 7	98	-0.48 (0.07)	99	-0.50 (0.06)	0.689	100	-0.65 (0.07)	0.337
Week 8	96	-0.45 (0.07)	97	-0.55 (0.07)	0.311	100	-0.70 (0.06)	0.109
Week 9	94	-0.60 (0.07)	97	-0.60 (0.07)	0.727	100	-0.75 (0.06)	0.390
Week 10	92	-0.66 (0.07)	96	-0.63 (0.07)	0.987	99	-0.78 (0.07)	0.733
Week 11	91	-0.58 (0.07)	96	-0.59 (0.08)	0.857	98	-0.79 (0.06)	0.270
Week 12	86	-0.59 (0.08)	92	-0.56 (0.08)	0.813	98	-0.84 (0.06)	0.096
Endpoint†	*91*	*-0.49 (0.07)*	*99*	*-0.50 (0.07)*	*0.858*	*100*	*-0.75 (0.06)*	***0.042***

Baseline = the last week prior to randomization. Endpoint is the last two weeks of diary data prior to treatment stop date, asthma exacerbation, study withdrawal, or day 84. P-values are vs. placebo.

* Mean values for Baseline

† LS mean values for Weeks 1-12 and Endpoint

Source: Clinical, Study FMS30058, Tables 14.2, and 14.3, pages 1211-9; fms30058.pdf

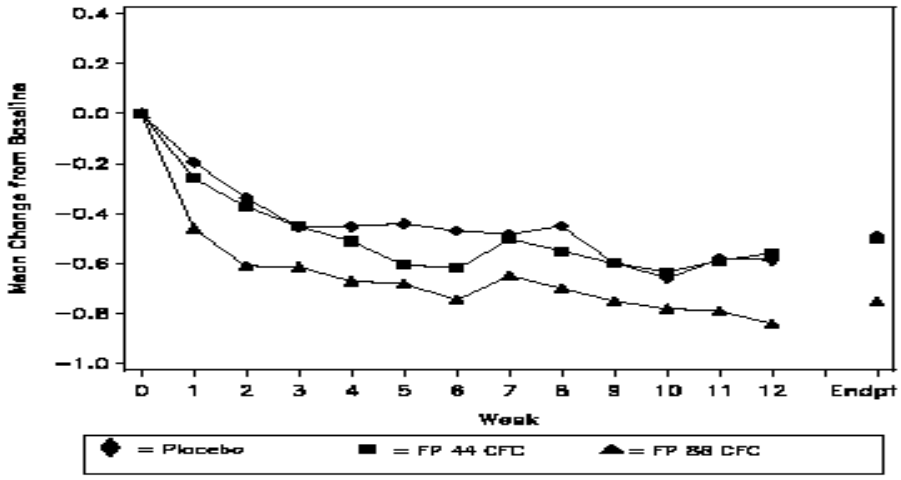

Figure 9. Study FMS30058, Change from baseline in daily symptom scores over time, RITT population

Source; Clinical, Study FMS30058, Figure 14.2, page 1201; fms30058.pdf

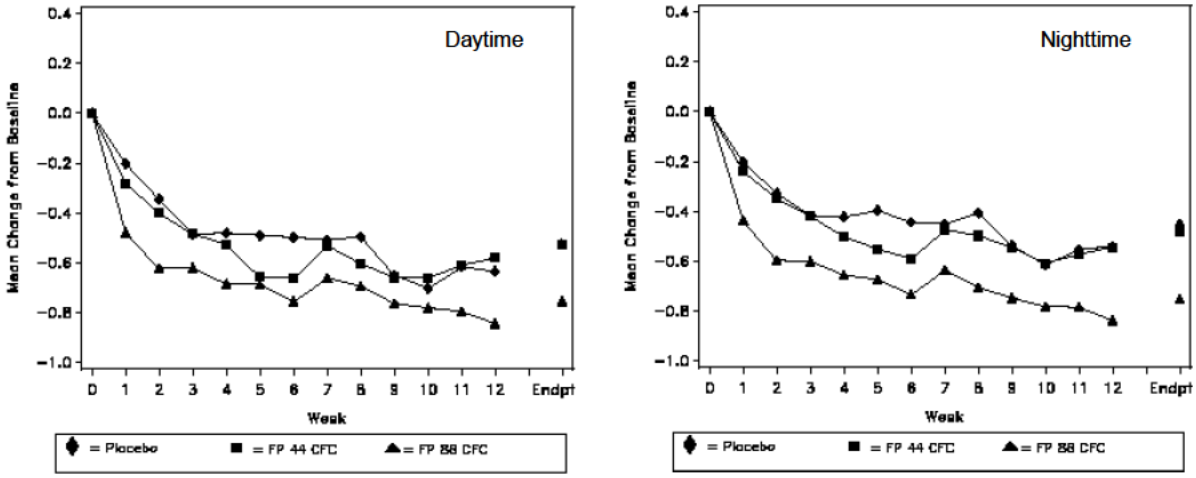

Figure 10. Study FMS30058, Change from baseline in daytime and nighttime symptom scores over time, RITT population

Source; Clinical, Study FMS30058, Figures 14.3 and 14.4, pages 1202-3; fms30058.pdf

12.1.2.2.2. Secondary efficacy measures

Secondary efficacy measures included the percentage of symptom-free days, percentage of symptom- and albuterol-free days, daytime and nighttime asthma scores, time to treatment failure, daily rescue albuterol use, and total daily albuterol use.

The percentages of symptom-free days and symptom- & albuterol-free days are shown in Table 18. A symptom-free day was defined as a day in which a patient had a daytime symptom score of zero and a nighttime symptom score of zero. A symptom-free & albuterol-free day was defined as a day in which a patient had both daytime and nighttime symptom scores of zero and required no albuterol use. The percentage of symptom-free days and symptom- & albuterol-free days increased for all groups, but more for the FP88 group. This difference was significant for both the percentage of symptom-free days (p=0.02, FP88 vs placebo) and the percentage of symptom- & albuterol-free days (p=0.017, FP88 vs placebo). These results were consistent with the primary efficacy results.

Table 18. Study FMS30058, Percentage of symptom-free and symptom- & albuterol-free days, RITT population

% of symptom-free and symptom- & albuterol-free days	Placebo n = 111		FP44 n = 108			FP88 n = 105		
	n	Mean (SEM)	n	Mean (SEM) (95% CI)	p-value	n	Mean (SEM) (95% CI)	p-value
Percentage of symptom-free days, RITT population								
Baseline*	109	10.2 (1.45)	106	10.6 (1.77)		105	7.0 (1.03)	
Weeks 1-12†	108	30.09 (4.79)	105	38.09 (4.76)	0.04	104	43.40 (4.57)	<0.001
Endpoint†	91	33.80 (7.30)	99	38.24 (7.06) (-6.34, 15.23)	0.418	100	46.71 (6.71) (2.04, 23.79)	0.02

% of symptom-free and symptom- & albuterol-free days	Placebo n = 111		FP44 n = 108			FP88 n = 105		
	n	Mean (SEM)	n	Mean (SEM) (95% CI)	p-value	n	Mean (SEM) (95% CI)	p-value
Percentage of symptom- and albuterol-free days, RITT population								
Baseline*	109	8.1 (1.33)	106	9.1 (1.70)		104	5.7 (1.03)	
Weeks 1-12†	108	29.92 (4.88)	105	38.57 (4.85)	0.03	103	43.16 (4.66)	0.001
Endpoint†	90	34.69 (7.39)	98	40.62 (7.16) (-5.07, 16.92)	0.289	100	48.13 (6.80) (2.42, 24.45)	0.017

ANCOVA adjusted for baseline value, region, age group, sex, holding chamber, previous corticosteroid use, family history of asthma, and patient history of allergies. P-values are vs. placebo.

* Mean values for Baseline

† LS mean values for Weeks 1-12 and Endpoint

Source: Clinical, Study FMS30058, Tables 10 and 11, pages 70-1; fms30058.pdf

Daytime and nighttime asthma symptom scores are shown in Table 19. All treatment groups experienced a reduction in daytime and nighttime symptom scores. While the FP88 group experienced fewer daytime asthma symptoms than other treatment groups, the difference versus placebo was not significant. This difference was significant for nighttime asthma symptoms (p=0.027, FP88 vs placebo). These results were consistent with the primary efficacy results.

Table 19. Study FMS30058, Daytime and nighttime asthma symptom scores, RITT population

Daytime and nighttime asthma symptom scores	Placebo n = 111		FP44 n = 108			FP88 n = 105		
	n	Mean (SEM)	n	Mean (SEM) (95% CI)	p-value	n	Mean (SEM) (95% CI)	p-value
Daytime asthma symptom scores, RITT population								
Baseline*	109	1.23 (0.05)	106	1.20 (0.05)		105	1.26 (0.05)	
Endpoint*	92	0.70 (0.06)	100	0.66 (0.07)		100	0.51 (0.06)	
Change to Endpoint†	91	-0.58 (0.11)	99	-0.58 (0.11) (-0.17, 0.17)	0.985	100	-0.73 (0.11) (-0.32, 0.02)	0.081
Nighttime asthma symptom scores, RITT population								
Baseline*	109	1.10 (0.05)	106	1.08 (0.06)		105	1.20 (0.06)	
Endpoint*	92	0.65 (0.06)	100	0.60 (0.07)		100	0.46 (0.05)	
Change to Endpoint†	91	-0.48 (0.11)	99	-0.51 (0.11) (-0.19, 0.13)	0.733	100	-0.67 (0.10) (-0.35, 0.02)	0.027

ANCOVA adjusted for baseline value, region, age group, sex, holding chamber, previous corticosteroid use, family history of asthma, and patient history of allergies. P-values are vs. placebo.

* Mean values for Baseline and Endpoint

† LS mean values for Change to Endpoint

Source: Clinical, Study FMS30058, Tables 12 and 13, pages 72-3; fms30058.pdf

The number of patients who experienced an asthma exacerbation over the 12 week treatment period was lower in both the FP88 and FP44 groups (n=13 and n=14, respectively) compared with placebo (n=24). A Kaplan Meier plot of time to treatment failure for the RITT population is shown in Figure 11. Treatment failure was defined as the patient's first asthma exacerbation for a patient and was measured as the time from the date of treatment initiation to the date of first asthma exacerbation or the date of treatment termination. The FP88 group had a greater estimated probability of not experiencing an asthma exacerbation

compared with those receiving FP44 or placebo. The difference was statistically significant (p=0.044, FP88 vs placebo). [Clinical, Study FMS30058, pages 73-5; fms30058.pdf]

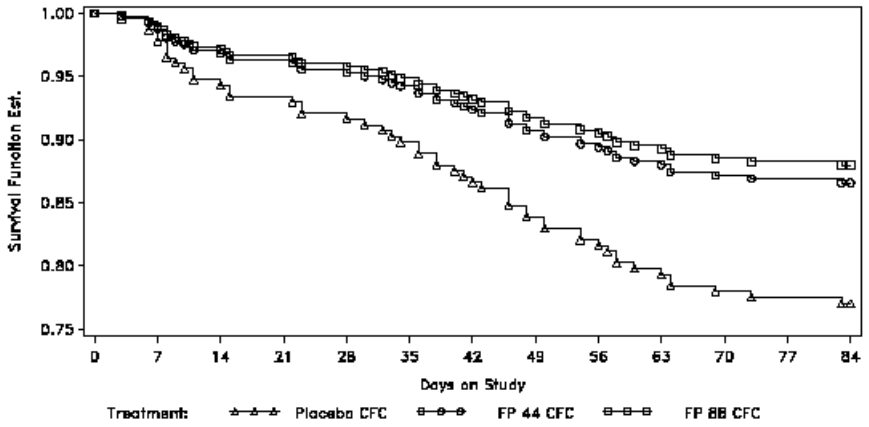

Figure 11. Study FMS30058, Time to treatment failure, RITT population

Source; Clinical, Study FMS30058, Figure 14.5, page 1204; fms30058.pdf

Daily rescue albuterol use was defined as the number of treatments of albuterol per day. One treatment equaled two puffs from albuterol MDI or one albuterol nebule. All treatment groups experienced mean reductions in daily rescue albuterol use. Both FP groups experienced greater mean reductions in daily rescue albuterol use than placebo; but the difference was only significant for FP88 (p=0.017, FP88 vs placebo).

Table 20. Study FMS30058, Daily rescue albuterol use, RITT population

Daily albuterol use	Placebo n = 111		FP44 n = 108			FP88 n = 105		
	n	Mean (SEM)	n	Mean (SEM) (95% CI)	p-value	n	Mean (SEM) (95% CI)	p-value
Baseline*	108	1.2 (0.09)	106	1.1 (0.09)		104	1.3 (0.12)	
Endpoint*	91	0.6 (0.09)	99	0.5 (0.07)		100	0.4 (0.06)	
Change to Endpoint†	90	-0.57 (0.14)	98	-0.75 (0.14) (-0.39, 0.03)	0.094	100	-0.82 (0.13) (-0.47, -0.05)	0.017

ANCOVA adjusted for baseline value, region, age group, sex, holding chamber, previous corticosteroid use, family history of asthma, and patient history of allergies. P-values are vs. placebo.

* Mean values for Baseline and Endpoint

† LS mean values for Change to Endpoint

Source: Clinical, Study FMS30058, Table 15, page 75; fms30058.pdf

12.1.2.2.3. Other efficacy measures

Other efficacy measures included the diary AM PEF (Table 21), frequency of treatment failure (see previous section), and discontinuations (see Table 9). Due to the age of the children participating in this study, only about 25% of the total population were able to perform a PEF maneuver. For these patients, all treatment groups experienced a reduction in PEF, with a minor but insignificant trend toward the FP44 and FP88 groups. The percent of patient discontinuations trended in favor of treatment with Flovent, with fewer discontinuations corresponding to increasing doses.

Table 21. Study FMS30058, AM PEF, RITT population

AM PEF L/min	Placebo n = 111			FP44 n = 108			FP88 n = 105		
	n	Mean (SEM)	% Δ	n	Mean (SEM)	% Δ	n	Mean (SEM)	% Δ
Baseline*	22	85.4 (6.42)		28	88.4 (5.53)		30	91.0 (5.89)	
Endpoint*	17	96.3 (7.23)		23	115.7 (7.22)		26	116.9 (7.53)	
Change to Endpoint†	15	12.8 (7.37)	21.8	21	23.3 (5.19)	27.5	26	23.9 (4.67)	30.1

* Mean values for Baseline and Endpoint
† LS mean values for Change to Endpoint.

Source: Clinical, Study FMS30058, Table 16, page 76; fms30058.pdf

12.1.2.2.4. Subgroup analyses

Subgroup analyses including analysis by age group, holding chamber, and treatment with corticosteroids within 8 weeks prior to Visit 1 (GSK called this pre-treatment CS) are shown in Table 22. As per the Written Request, similar numbers of patients were randomized both by age and holding chamber. However, there were approximately 2 to 3-fold more patients in the no previous CS treatment sub-group than in the previous CS treatment sub-group.

Subgroup analysis by age group showed results consistent with the full RITT population, with only FP88 treatment showing a consistent improvement in daily asthma scores compared to patients on either FP44 or placebo. Patients treated with FP44 experienced different results depending on their age group, with the 36-47 month FP44 sub-group showing a greater reduction in daily asthma symptom scores compared to placebo, but the 24-35 month FP44 age group showing less reduction than placebo.

Subgroup analysis by holding chamber showed results consistent with the full RITT population. Both the FP88 Aerochamber and Optichamber sub-groups showed a consistent improvement in daily asthma scores compared to patients on either FP44 or placebo. Patients treated with FP44 experienced different results depending on the holding chamber used. While the FP88 Aerochamber treatment group had a baseline score about 0.15 points higher than the rest of the groups, patients treated with FP44 or FP88 Aerochamber showed more improvement than patients assigned to the corresponding Optichamber groups.

Subgroup analysis by pre-treatment with corticosteroids showed results consistent with the full RITT population. Both FP88 sub-groups showed a consistent improvement in daily asthma scores compared to patients on either FP44 or placebo.

Table 22. Study FMS30058, Asthma symptom scores by sub-group of age, holding chamber, and pre-treatment with corticosteroids, RITT population

Daily asthma symptom scores	Placebo n = 111		FP44 n = 108		FP88 n = 105	
Subgroup analyses	n	mean (SEM)	n	mean (SEM)	n	mean (SEM)
Total RITT pop						
Baseline	109	1.16 (0.05)	106	1.14 (0.05)	105	1.23 (0.05)
Endpoint	91	–0.49 (0.07)	99	–0.50 (0.07)	100	–0.75 (0.06)
Age 24-35 months						
Baseline	52	1.15 (0.07)	56	1.11 (0.07)	50	1.24 (0.08)
Endpoint	42	–0.52 (0.10)	54	–0.37 (0.11)	49	–0.71 (0.09)
Age 36-47 months						

Daily asthma symptom scores	Placebo		FP44		FP88	
	n = 111		n = 108		n = 105	
Subgroup analyses	n	mean (SEM)	n	mean (SEM)	n	mean (SEM)
Baseline	57	1.18 (0.07)	50	1.18 (0.07)	55	1.22 (0.05)
Endpoint	49	–0.46 (0.09)	45	–0.66 (0.09)	51	–0.79 (0.08)
Aerochamber						
Baseline	51	1.14 (0.06)	53	1.13 (0.07)	50	1.31 (0.07)
Endpoint	44	–0.48 (0.09)	50	–0.59 (0.09)	48	–0.81 (0.09)
Optichamber						
Baseline	58	1.18 (0.07)	53	1.15 (0.07)	55	1.16 (0.06)
Endpoint	47	–0.50 (0.10)	49	–0.42 (0.11)	52	–0.69 (0.08)
Pre-treatment CS*						
Baseline	33	1.20 (0.09)	25	1.16 (0.10)	30	1.20 (0.09)
Endpoint	28	–0.54 (0.14)	25	–0.40 (0.15)	28	–0.85 (0.12)
No pre-treatment CS*						
Baseline	76	1.15 (0.06)	81	1.14 (0.06)	75	1.24 (0.05)
Endpoint	63	–0.47 (0.08)	74	–0.54 (0.08)	72	–0.71 (0.07)
* Pre-treatment CS was defined as treatment with CS within 8 weeks of visit 1						

Source: Clinical, Study FMS30058, Tables 17, 18, 19, pages 78-80; fms30058.pdf

12.1.2.3. Safety Outcomes

All safety results were reported for the ITT population, except that the growth and cortisol results reported the results for the predefined growth and cortisol populations as well as the ITT populations.

12.1.2.3.1. Extent of exposure

The mean number of treatment days is shown in Table 23. Most patients had a treatment duration of 12 weeks or more (percentages were 71% for the placebo group, 77% for the FP44 group, and 81% for the FP88 treatment group).

Table 23. Study FMS30058, Extent of exposure, ITT population

	Placebo	FP44	FP88
	n = 113	n = 111	n = 108
Treatment Duration			
0-< 1 Week (1- 6 Days)	1	0	3
1-< 2 Weeks (7- 13 Days)	2	1	0
2-< 3 Weeks (14- 20 Days)	4	1	0
3-< 4 Weeks (21- 27 Days)	1	2	0
4-< 6 Weeks (28- 41 Days)	4	5	1
6-< 8 Weeks (42- 55 Days)	3	0	0
8-< 12 Weeks (56- 83 Days)	18 (16%)	17 (15%)	16 (15%)
>= 12 Weeks (>= 84 Days)	80 (71%)	85 (77%)	88 (81%)
Treatment Days, mean (SD)	78.8 (23.0)	81.6 (17.6)	83.5 (83.5)

Source: Clinical, Study FMS30058, Tables 15.1, page 1345; fms30058.pdf

12.1.2.3.2. Clinical adverse events

Adverse events (AEs) were summarized by body system, AE group term, and treatment group, and sorted (within patient) by the date of onset; treatment group, investigator number,

subject number, demographic details (e.g., age, holding chamber, sex, race, and weight), body system, event (preferred term), resolution status, and action taken.

A total of 277 patients (83%) reported at least one AE during treatment (93 [82%] placebo, 98 [88%] FP44, and 86 [80%] FP88). Adverse events reported with an incidence greater than 3% and greater than the incidence in the placebo treatment group, regardless of causality, are presented in Table 24. There was a minor trend toward higher incidences of fever in both the FP44 and FP88 groups (25 [22%] placebo, 32 [29%] FP44, and 30 [28%] FP88), the etiology of which is not clear. There was a trend toward higher incidence of pharyngitis/throat infection in both the FP44 and FP88 groups (0 placebo, 7 [6%] FP44, and 3 [3%] FP88), presumably secondary to local effects of the active drug. There was a trend to higher incidence of candidiasis of the mouth/throat (2 [2%] placebo, 1 [<1%] FP44, and 5 [5%] FP88), or nasal cavity (0 placebo, 0 FP44, and 2 [2%] FP88) in the FP88 group), again presumably secondary to local effects of the active drug. No rebound trends were noted during the follow-up period after stopping study drugs. [Clinical, Study FMS30058, pages 82-5; fms30058.pdf]

> *Note: The study report does not state whether parents/guardians were instructed to ask the children to rinse out their mouths after inhalations. In this age group most children are not able to gargle, and rinsing out a mouth may or may not be sufficient. Indeed, gargling or rinsing would not have prevented the 2 episodes of candidiasis of the nose. This is likely secondary to the use of the spacer with mask, and consequent inhalation through the nose.* (b) (4)

Evaluation of adverse events by age groups did not lead to any trends not already noted above. Just as the breakdown of patients by age and treatment group were roughly equal, the incidence of adverse events were about the same. While the 24-35 month placebo group experienced more episodes of URTI than their treatment counterparts (39% placebo, 29% FP 44, and 26% FP88), this did not hold true for the 36-48 month group. The trend toward increased incidence of pharyngitis/throat infection was seen across both age groups. Both cases of candidiasis of the nose were noted in the FP88 older age group (36-48 months). All five cases of candidiasis of the mouth/throat were noted in the FP88 younger age group (24-35 months). [Clinical, Study FMS30058, Tables 15.15 and 15.16, pages 1842-1856; fms30058.pdf]

Evaluation of adverse events by holding chamber showed no trends that appeared related to a specific holding chamber [Clinical, Study FMS30058, Tables 15.17and 15.18, pages 1857-1871; fms30058.pdf].

Evaluation of adverse events by previous CS therapy (any corticosteroids within 8 weeks of Visit 1) showed that, whereas the trend toward higher incidence of pharyngitis/throat infection spanned the two sub-groups, most instances of candidiasis of the mouth/throat and nasal cavity occurred in the group that had not received previous CS therapy. [Clinical, Study FMS30058, Tables 15.19 and 15.20, pages 1872-1885; fms30058.pdf]

Evaluation of adverse events by gender showed a slight difference in reported AEs in male and female placebo sub-groups (females: 95% placebo, 85% FP44, 78% FP88; males: 75% placebo, 90% FP44, 81% FP88) primarily due to a difference in the incidence of gastrointestinal AEs, but the type and frequency of adverse for both gender sub-groups were

generally similar to each other and to the ITT population. [Clinical, Study FMS30058, Tables 15.21 and 15.22, pages 1886-1900; fms30058.pdf]

Table 24. Study FMS30058, Adverse events reported with an incidence greater than 3% and greater than the incidence in the placebo treatment group, regardless of causality, ITT population

AEs >3% and >than placebo, ITT population	Placebo n = 113 n (%)	FP44 n = 111 n (%)	FP88 n = 108 n (%)
Mean duration of exposure (days)	78.8	81.6	83.5
Number of subjects with any AEs	93 (82)	98 (88)	86 (80)
Ear Nose & Throat			
Ear, nose & throat infections	27 (24)	25 (23)	26 (24)
Rhinorrhea/post nasal drip	12 (11)	13 (12)	9 (8)
Nasal congestion/blockage	4 (4)	8 (7)	9 (8)
Sinusitis	6 (5)	8 (7)	6 (6)
Rhinitis	5 (4)	7 (6)	2 (2)
Upper respiratory inflammation	3 (3)	5 (5)	3 (3)
Pharyngitis/throat infection	0	7 (6)	3 (3)
Tympanum disorders	2 (2)	1 (<1)	4 (4)
Non-site Specific			
Fever	25 (22)	32 (29)	30 (28)
Viral infections	4 (4)	10 (9)	6 (6)
Gastrointestinal			
Candidiasis mouth/throat	2 (2)	1 (<1)	5 (5)
Candidiasis of nasal cavity	0	0	2 (2)
Candidiasis unspecified site	0	2 (2)	0
Lower Respiratory			
Cough	3 (3)	7 (6)	4 (4)
Bronchitis	4 (4)	3 (3)	4 (4)
Viral respiratory infections	3 (3)	4 (4)	4 (4)
Skin			
Skin rashes	4 (4)	8 (7)	7 (6)
Eczema	0	3 (3)	4 (4)
Neurology			
Headaches	6 (5)	5 (5)	6 (6)

Source: Clinical, Study FMS30058, Tables 20 and 15.7, pages 84 and 1821-2; fms30058.pdf

12.1.2.3.3. Drug-related clinical adverse events

A total of 18 patients reported at least one AE during treatment that was judged by the investigator to be drug-related (6 [5%] placebo, 5 [5%] FP44, and 7 [6%] FP88). Again, candidiasis of the nose and throat were the only trends. [Clinical, Study FMS30058, pages 85-6 and 1829-31; fms30058.pdf]

12.1.2.3.4. Serious adverse events, Deaths, and Discontinuations

There were no deaths, but there were six SAEs reported by six patients during treatment (Table 25), and no SAEs during the follow-up period. There were also four SAEs during the screening period in three patients who were not subsequently randomized: pneumonia NOS,

ankle fracture, asthma aggravated/infectious croup. All six patients with SAEs during treatment were hospitalized, but none were withdrawn. None of the events were judged by the investigator to be related to study drug. [Clinical, Study FMS30058, pages 88-9; fms30058.pdf]

Table 25. Study FMS30058, Serious adverse events during the treatment period, ITT population

ID#	Treatment	Device	Age/Gender/Race	SAE (verbatim text)
1022	Placebo CFC	OC	42m Hispanic male	TOOTH ABSCESS – UPPER
2426	Placebo CFC	AC	24m White female	DEHYDRATION
1345	FP 88 CFC	OC	39m White female	CROUP
2107	FP 88 CFC	AC	31m White female	BEHAVIOR CHANGES
2345	FP 88 CFC	AC	42m White male	NEAR DROWNING
4953	FP 88 CFC	AC	36m White male	RIGHT INGUINAL LYMPHADENITIS
AC = Aerochamber, OC = Optichamber				

Source: Clinical, Study FMS30058, Table 15.23, pages 1901-3; fms30058.pdf

The study report states that three patients were withdrawn from the study due to an adverse event, that all were in the placebo treatment group, and that none of the events were serious. The report states that all events were considered by the investigator to be related to study drug. However, one AE (Subject 1043) occurred 2 days prior the first dose of study drug. If this is correct, it means that this patient had not yet been randomized, and the study report should have considered this patient to be a non-randomized patient secondary to an AE during the screening period rather than a withdrawal from treatment. The events are listed below. [Clinical, Study FMS30058, pages 88-90 and Table 15.24, page 1904; fms30058.pdf]

- Subject 1122, White male, 34 months, using Optichamber, was withdrawn due to hyperactivity. The event occurred two days after starting treatment and the Investigator considered the event related to study drug. The event resolved with sequelae 7 days after onset. (Investigator 49423)
- Subject 1043, White male, 47 months, using Optichamber, was withdrawn due to hyperactivity. The event occurred two days prior to the first dose and the Investigator considered the event related to study drug. The event resolved 30 days after onset. (Investigator 501)
- Subject 1728, Hispanic female, 31 months, using Aerochamber, was withdrawn due to nasal 'stinging' when administering the inhaler. The event occurred five days after starting treatment and the Investigator considered the event related to study drug. The event resolved eight days after onset. (Investigator 73037)

One patient in the placebo treatment group discontinued treatment prematurely due to an AE, but was not withdrawn from the study. Interestingly, this was the same investigator who reported a patient withdrawal due to an AE related to study drug use two days prior to starting study drug (see discussion above). [Clinical, Study FMS30058, page 90 and Table 15.25, page 1905; fms30058.pdf]

- Subject 1042, White female, 26 months, using Optichamber, had study medication permanently discontinued after 11 days of study treatment due to an upper respiratory

infection but was not withdrawn from the study. The event was not considered related to study drug and was resolved 11 days after onset. (Investigator 501)

There were five subjects that had AEs requiring concomitant asthma therapy with a non-study drug (1 placebo, 2 FP44, 2 FP88). These therapies included prednisolone (3 patients), ipratropium bromide (1 patient), and non-study supplied albuterol (2 patients). [Clinical, Study FMS30058, page 90 and Table 15.26, page 1906; fms30058.pdf]

12.1.2.3.5. Height and Growth velocity

The changes in standing height (mm) over the course of the study for the Growth population are shown in Table 26. Table 26 also shows the changes in standing height (mm) for all sub-populations within the Growth population. The estimated growth velocity for the Growth and ITT populations is shown in Table 27, and graphically in Figure 12. Figure 13 shows a histogram of estimated growth velocity illustrating the large range in growth within the Growth population that is consistent with what is found for range of growth in growth studies. Figure 14 shows the empirical cumulative distribution function (CDF) (cumulative frequencies of change from baseline in height) for the growth population.

Estimates for the growth velocity for the Growth population showed a not statistically significant dose-dependent trend toward a reduction in growth velocity. Growth velocities were 20.8 mm/12 weeks for placebo, 19.1 mm/12 weeks for FP44, and 18.4 mm/12 weeks for FP88. The reduction in growth velocity compared to placebo was 1.680 mm/12 weeks ($p = 0.246$) and 2.388 mm/12 weeks ($p = 0.095$) for FP44 and FP88, respectively.

Investigation of treatment-by-age showed a dose-dependent trend for change in height over 12 weeks only in the older sub-group (36-47 months). In the younger sub-group (24-35 months) the changes in height over the study were comparable among treatment groups. Investigation of treatment-by-gender and treatment-by-holding chamber showed no clear trends. Investigation of treatment-by-pretreatment with corticosteroids showed a trend for patients pretreated with corticosteroids. Patients pretreated with corticosteroids and treated with Flovent grew less than those on placebo. All trends were minor and not statistically significant.

Table 26. Study FMS30058, Changes in standing height (mm), Growth population

Standing height (mm)	Placebo n = 71		FP44 n = 79		FP88 n = 87	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Screening	71	947.2 (7.0)	79	934.2 (7.4)	87	941.7 (7.1)
Baseline	71	949.5 (7.0)	78	938.5 (7.3)	87	946.3 (6.9)
Range		834 - 1092		782 - 1097		792 - 1093
At Week 12	44	970.8 (6.9)	79	956.0 (7.1)	87	964.2 (6.8)
Range		858 - 1109		798 - 1119		810 - 1093
Change from baseline						
Week 1	71	4.1 (1.4)	79	2.7 (0.5)	87	2.1 (0.5)
Week 2	70	4.9 (1.3)	77	4.0 (0.7)	85	3.4 (0.6)
Week 4	68	9.2 (1.4)	75	7.5 (0.8)	84	5.9 (0.7)
Week 8	69	14.0 (0.9)	76	13.3 (0.8)	85	11.5 (0.9)
Week 12	71	21.3 (1.5)	79	18.7 (1.0)	87	18.0 (1.0)

Standing height (mm)	Placebo n = 71		FP44 n = 79		FP88 n = 87	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Age 24-35 months						
Baseline	33	907.3 (7.5)	39	892.3 (8.2)	46	902.8 (6.7)
At Week 12	33	926.4 (7.4)	40	912.3 (7.9)	46	923.0 (6.9)
Change from baseline	33	19.1 (1.4)	39	21.3 (1.4)	46	20.2 (1.4)
Age 36-47 months						
Baseline	38	986.1 (7.2)	39	984.8 (6.1)	41	995.1 (7.0)
At Week 12	38	1009 (6.5)	39	1001 (6.2)	41	1011 (7.0)
Change from baseline	38	23.2 (2.5)	39	16.0 (1.1)	41	15.4 (1.4)
Aerochamber						
Baseline	32	942.3 (10.3)	38	931.8 (10.9)	43	939.4 (10.2)
At Week 12	32	962.2 (10.4)	38	948.7 (10.6)	43	957.3 (10.1)
Change from baseline	32	20.0 (1.6)	38	16.9 (1.5)	43	17.9 (1.6)
Optichamber						
Baseline	39	955.4 (9.5)	40	945.0 (9.9)	44	953.0 (9.4)
At Week 12	39	977.8 (9.2)	41	962.7 (9.5)	44	971.0 (9.2)
Change from baseline	39	22.4 (2.3)	40	20.3 (1.2)	44	18.0 (1.3)
Males						
Baseline	44	952.8 (9.1)	50	945.2 (8.1)	52	957.0 (9.0)
At Week 12	44	972.0 (9.0)	51	962.9 (7.8)	52	974.9 (8.8)
Change from baseline	44	19.2 (1.5)	50	19.7 (1.1)	52	17.9 (1.1)
Females						
Baseline	27	944.1 (11.0)	28	926.6 (14.4)	35	930.3 (10.5)
At Week 12	27	968.9 (11.1)	28	943.4 (14.0)	35	948.3 (10.3)
Change from baseline	27	24.7 (3.0)	28	16.7 (1.8)	35	18.0 (1.9)
Pre-treatment CS*						
Baseline	17	942.6 (14.4)	16	937.8 (13.6)	23	952.2 (12.9)
At Week 12	17	966.1 (14.6)	16	956.5 (12.1)	23	970.0 (12.3)
Change from baseline	17	23.5 (2.2)	16	18.8 (2.2)	23	17.8 (2.0)
No pre-treatment CS*						
Baseline	54	951.7 (8.0)	62	938.7 (8.6)	64	944.1 (8.2)
At Week 12	54	972.3 (7.9)	63	955.8 (8.4)	64	962.2 (8.2)
Change from baseline	54	20.6 (1.8)	62	18.6 (1.1)	64	18.0 (1.2)

* Pre-treatment CS was defined as treatment with CS within 8 weeks of visit 1

Source: Clinical, Study FMS30058, Tables 15.32 to 15.43, pages 2026-47; fms30058.pdf

Table 27. Study FMS30058, Estimated growth velocity, Growth and ITT populations

Estimated growth rate (mm/12 weeks)	Placebo	FP44	FP88
Growth population	n = 71	n = 79	n = 87
Mean, SD	19.7 (9.15)	18.1 (7.89)	17.0 (9.25)
Range	1.0 - 45.5	0.0 - 43.0	-1.3 - 46.9
LS mean	20.8 (2.09)	19.1 (2.05)	18.4 (1.93)
LS mean difference		-1.680	-2.388
P-value vs placebo		0.246	0.095
95% CI		(-4.53, 1.17)	(-5.19, 0.41)
ITT population	n = 113	n = 111	n = 107
Mean, SD	17.0 (15.73)	17.5 (11.17)	17.0 (9.56)
LS mean	16.5 (2.11)	17.1 (2.05)	16.4 (2.02)
LS mean difference		0.556	-0.114
P-value vs placebo		0.741	0.947
95% CI		(-2.75, 3.86)	(-3.47, 3.24)

P- values based on analysis of covariance (ANCOVA) adjusting for baseline value, region, age group, sex, holding chamber, pre- treatment steroid use, family history of asthma, weight and subject history of allergies.

Source: Clinical, Study FMS30058, Table 15.33 and 15.35, pages 2028 and 2031; fms30058.pdf

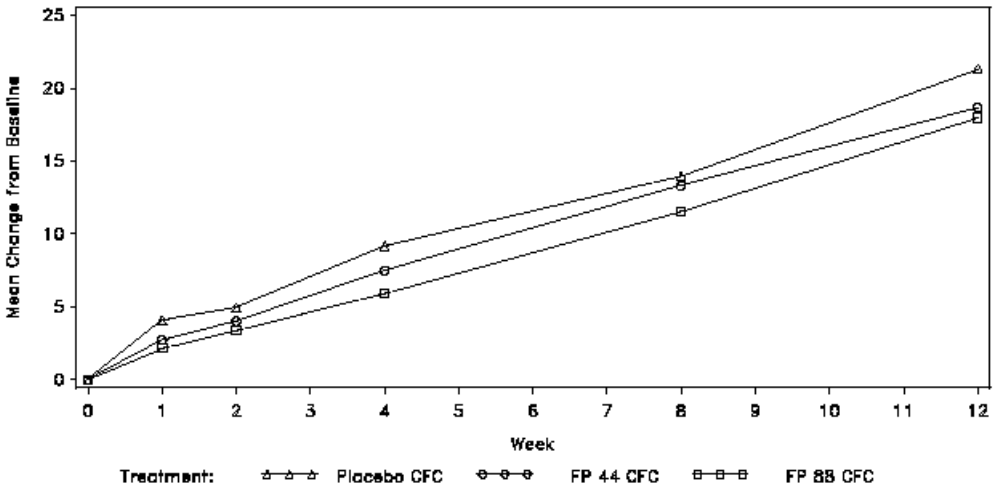

Figure 12. Study FMS30058, Mean change in height over time, Growth population

Source; Clinical, Study FMS30058, Figure 15.1, page 1333; fms30058.pdf

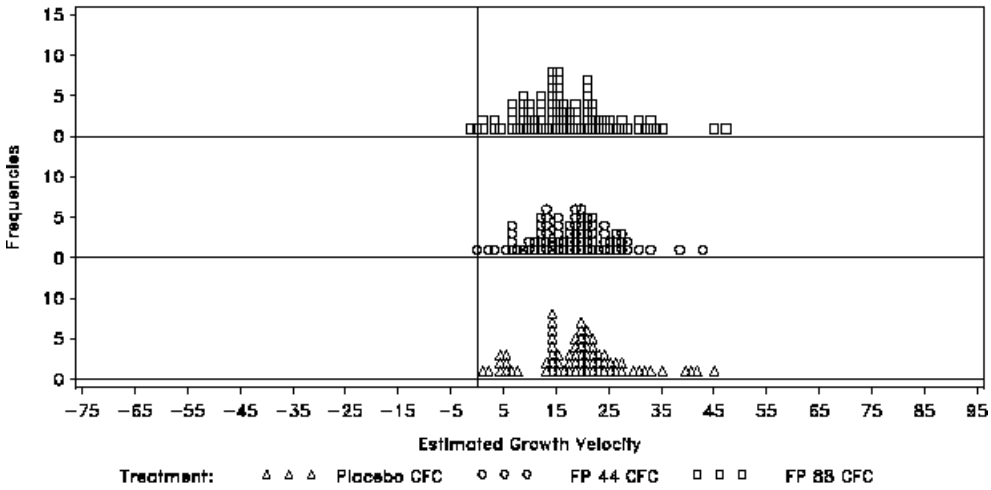

Figure 13. Study FMS30058, Histogram of estimated growth velocity, Growth population

Source: Clinical, Study FMS30058, Figure 15.2, page 1334; fms30058.pdf

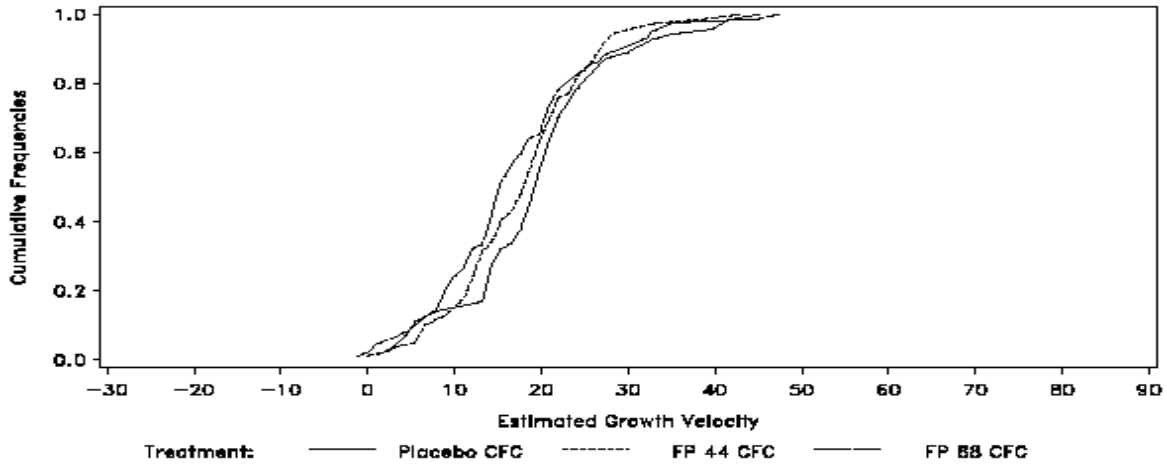

Figure 14. Study FMS30058, Empirical CDF of the estimated growth velocity, Growth population

Source: Submission of 05/19/03, Clinical, FMS30058 graphs, Figure 15.3, page 1; fms30058graphs.pdf

12.1.2.3.6. Urinary cortisol

The 12-hour overnight urinary cortisol excretion (mcg/12hr) was calculated by multiplying the total volume of urine in (dL) by the concentration of urinary cortisol. The urinary cortisol population was defined as those subjects from the ITT population whose urine samples were considered to have no confounding factors that would affect the interpretation of the results.

The urinary cortisol data for the urinary Cortisol population (including sub-group analyses) are summarized at baseline, at the end of the study (Week 12), and for the change from

baseline in Table 28. Sub-group analyses by age, holding chamber, and pre-treatment with corticosteroids were performed, but a gender analysis was not performed. A histogram of the individual patient 12-hour urinary cortisol excretions is shown in Figure 15. Figure 16 illustrates the distribution of the change from baseline to endpoint in 12-hour overnight cortisol via an empirical cumulative distribution function (cumulative frequencies of change from baseline in urinary cortisol) for each treatment group.

Change from baseline for 12-hour overnight urinary cortisol was 0.6 (SD 2.54) (range -3.4 – 6.6), -0.8 (SD 2.08) (range -6.5 – 3.2), and -0.8 (SD 1.85) (range -4.2 – 2.6) for the placebo, FP44, and FP88 groups, respectively. GSK tried to suggest that 18 of 19 (95%) of the FP44 patients and 18 of 20 (90%) of the FP88 patients were contained within the range of the change from baseline in urine cortisol for the placebo group (-3.4 to 6.6mcg/12-hour) (Figure 15). However, the cumulative distribution function shown in Figure 16 reveals a clear separation between groups, with both the FP44 and the FP88 showing more change from baseline than the placebo group. This change is less obvious but still present in the data from the ITT population (data not shown here). [(b)(4)]

[(b)(4)]

Table 28. Study FMS30058, 12-hour urine cortisol excretion, Cortisol population

12-hour urinary cortisol	Placebo	FP44	FP88
	Mean, (SD) (Range)	Mean, (SD) (Range)	Mean, (SD) (Range)
Cortisol population	n = 26	n = 19	n = 20
Baseline	2.4 (2.17) (0.4 – 9.2)	2.6 (2.10) (0.4 – 9.7)	2.5 (1.41) (0.2 – 4.6)
Week 12	3.1 (2.55) (0.3 – 9.0)	1.8 (1.56) (0.1 – 6.9)	1.6 (1.55) (0.2 – 7.1)
Change to Week 12	0.6 (2.54) (-3.4 – 6.6)	-0.8 (2.08) (-6.5 – 3.2)	-0.8 (1.85) (-4.2 – 2.6)
Age 24-35 months	n = 6	n = 5	n = 4
Baseline	2.5 (3.33) (0.4 – 9.2)	1.4 (0.55) (0.4 – 1.7)	1.3 (0.90) (0.2 – 2.1)
At Week 12	2.3 (3.29) (0.3 – 9.0)	1.2 (1.01) (0.4 – 3.0)	1.4 (0.79) (0.2 – 1.9)
Change from baseline	-0.2 (0.80) (-0.9 – 1.3)	-0.1 (1.13) (-1.1 – 1.3)	0.1 (0.37) (-0.2 – 0.6)
Age 36-47 months	n = 20	n = 14	n = 16
Baseline	2.4 (1.80) (0.5 – 5.7)	3.0 (2.28) (0.7 – 9.7)	2.8 (1.36) (0.5 – 4.6)
At Week 12	3.3 (2.35) (0.5 – 8.2)	1.9 (1.71) (0.1 – 6.9)	1.7 (1.70) (0.2 – 7.1)
Change from baseline	0.9 (2.83) (-3.4 – 6.6)	-1.1 (2.31) (-6.5 – 3.2)	-1.1 (2.00) (-4.2 – 2.6)
Aerochamber	n = 16	n = 13	n = 10
Baseline	2.0 (2.13) (0.4 – 9.2)	2.6 (2.39) (0.7 – 9.7)	2.7 (1.55) (0.2 – 4.6)
At Week 12	2.6 (2.77) (0.5 – 9.0)	2.1 (1.76) (0.4 – 6.9)	1.4 (1.14) (0.2 – 3.1)
Change from baseline	0.7 (2.35) (-2.6 – 6.1)	-0.6 (2.32) (-6.5 – 3.2)	-1.3 (2.15) (-4.2 – 2.6)
Optichamber	n = 10	n = 6	n = 10
Baseline	3.1 (2.14) (0.7 – 5.7)	2.5 (1.42) (0.4 – 4.5)	2.2 (1.30) (0.6 – 4.5)
At Week 12	3.7 (2.13) (0.3 – 7.5)	1.0 (0.67) (0.1 – 2.1)	1.8 (1.92) (0.2 – 7.1)
Change from baseline	0.6 (2.94) (-3.4 – 6.6)	-1.5 (1.40) (-2.8 – 0.9)	-0.4 (1.48) (-3.0 – 2.6)
Pre-treatment CS*	n = 9	n = 3	n = 5
Baseline	2.7 (2.86) (0.5 – 9.2)	1.7 (0.35) (1.3 – 2.0)	1.9 (1.47) (0.5 – 3.9)
At Week 12	2.7 (2.67) (0.3 – 9.0)	1.9 (1.07) (0.8 – 3.0)	1.7 (1.11) (0.2 – 3.1)
Change from baseline	0.0 (1.39) (-1.8 – 3.2)	0.2 (1.27) (-1.2 – 1.3)	-0.2 (1.63) (-1.5 – 2.6)
No pre-treatment CS*	n = 17	n = 16	n = 15
Baseline	2.3 (1.79) (0.4 - 5.7)	2.8 (2.25) (0.4 - 9.7)	2.7 (1.39) (0.2 - 4.6)
At Week 12	3.3 (2.55) (0.5 - 8.2)	1.7 (1.67) (0.1 – 6.9)	1.6 (1.71) (0.2 – 7.1)
Change from baseline	1.0 (2.96) (-3.4 – 6.6)	-1.0 (2.17) (-6.5 – 3.2)	-1.1 (1.92) (-4.2 – 2.6)
* Pre-treatment CS was defined as treatment with CS within 8 weeks of visit 1			

Source: Clinical, Study FMS30058, Table 15.44, page 2048, and Tables 15.46-15.51, pages 2196-2201; fms30058.pdf

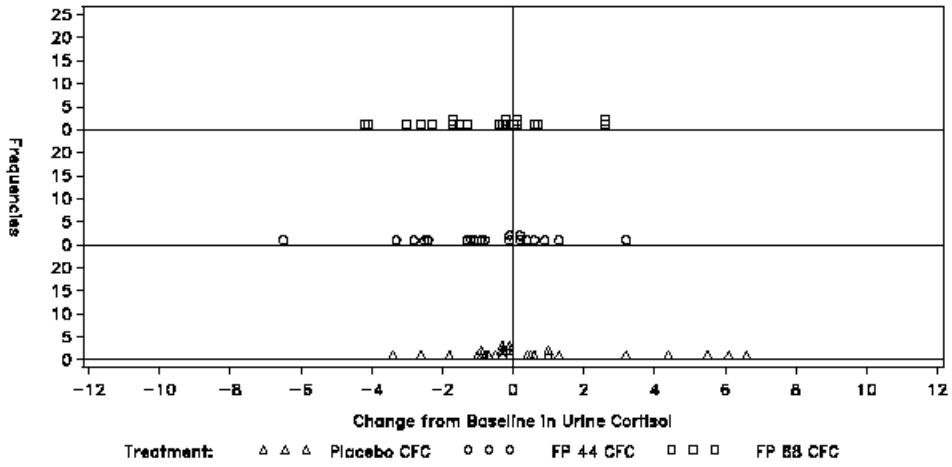

Figure 15. Study FMS30058, Histogram of individual patient 12-hour urine cortisol excretion by treatment, Cortisol population

Source; Clinical, Study FMS30058, Figure 15.8, page 1340; fms30058.pdf

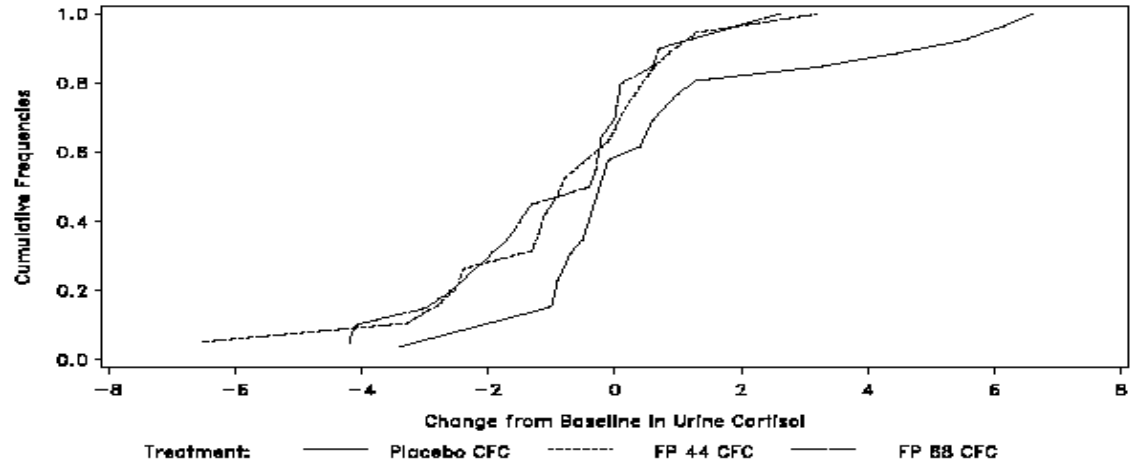

Figure 16. Study FMS30058, Cumulative frequencies of change from baseline in 12-hour urine cortisol excretion, Cortisol population

Source: Submission of 05/19/03, Clinical, FMS30058 graphs, Figure 15.9, page 3; fms30058graphs.pdf

12.1.2.3.7. Nasal and oropharyngeal examinations and cultures

Physical examinations included clinical findings of candidiasis by examination of the oropharynx and nasal passage as well as fungal cultures of the oropharynx and nose at screening and at Week 12 or discontinuation. Results of the oropharyngeal and nasopharyngeal examination and/or culture positive for Candida at the beginning and end of the study are shown in Table 29. No specific trends are noted. No trends were noted for sub-groups by holding chamber, age, or pre-treatment with corticosteroids (results not shown) [Submission of 4/22/2003, FMS30058 Tables, Tables 15.52 and 15.53, pages 1-14; fms30058tables.pdf]

Shift tables for changes in oropharyngeal or nasal passage exams (not shown) or cultures did not show any trends (Table 30). Breakdowns by sub-group also did not show any trends (results not shown) [Submission of 4/22/2003, FMS30058 Tables, Tables 15.55 to 15.56a, pages 15-42; fms30058tables.pdf].

Table 29. Study FMS30058, Exam and/or culture positive results for Candida, ITT pop

Exam and/or culture positive for Candida	Placebo				FP44				FP88			
	E+ C-	E- C+	E+ C+	E+ or C+ n (%)	E+ C-	E- C+	E+ C+	E+ or C+	E+ C-	E- C+	E+ C+	E+ or C+ n (%)
Oropharyngx	n = 95				n = 103				n = 102			
Baseline	1	31	0	32 (34)	0	45	0	45 (44)	1	38	0	41 (40)
Week 12	0	29	0	29 (31)	0	41	0	41 (40)	0	40	0	42 (41)
Change	-1	-2	0	-3	0	-4	0	-4	-1	2	0	1
Nasal passage	n = 95				n = 103				n = 102			
Baseline	0	1	0	1 (1)	0	6	0	6 (6)	0	2	0	2 (2)
Week 12	0	3	0	3 (3)	0	2	0	2 (2)	0	1	0	1 (<1)
Change	0	2	0	2	0	-4	0	-4	0	-1	0	-1

E+C- = Exam positive and culture negative; E-C+ = Exam negative and culture positive; E+C+ = Exam positive **and** culture positive; E+ or C+ = Exam positive **or** culture positive.

Source: Submission of 4/22/2003, FMS30058 Tables, Tables 15.52, 15.53, pages 1, 8; fms30058tables.pdf

Table 30. Study FMS30058, Shifts in culture positive results for Candida, ITT pop

Culture positive for Candida	Placebo n = 113	FP44 N = 111	FP88 N = 108
Oropharyngx n	95	103	102
Remains negative	52 (55)	50 (49)	48 (47)
Negative to positive	12 (13)	8 (8)	14 (14)
Positive to negative	14 (15)	12 (12)	12 (12)
Remains positive	17 (18)	33 (32)	28 (27)
Nasal passage n	94	103	102
Remains negative	90 (96)	95 (92)	99 (97)
Negative to positive	3 (3)	2 (2)	1 (<1)
Positive to negative	1 (1)	6 (6)	2 (2)
Remains positive	0	0	0

Source: Clinical, Study FMS30058, Tables 15.55 and 15.56, pages 2278-83 ; fms30058.pdf

12.1.2.3.8. Vital signs and Physical examinations

Shift tables for vital signs (systolic and diastolic BP and HR), and physical examinations were examined. There were no trends noted. [Source: Clinical, Study FMS30058, Table 15.58, pages 2285-2299 and Table 15.60, pages 2416-21; fms30058.pdf]

12.1.2.3.9. Laboratory Adverse Events

Laboratory shift tables were reviewed. There were no trends noted in laboratory shifts for hematology parameters. Shifts for hepatic function tests were comparable for the active treatment groups and placebo. The only ALT shift to abnormally high value occurred in the FP88 group. Creatinine shifts to abnormally high values occurred most often in the FP88 group and less frequently in the other two treatment groups (3% placebo, 4% FP44, 8%

FP88). Shifts to abnormally high glucose values occurred at a comparable frequency across treatment groups (1% placebo, 3% FP44, 2% FP88). [Clinical, Study FMS30058, page 91-4 and Tables 15.27, 1528, page 1909-19; fms30058.pdf]

Hematology values outside the threshold range were generally comparable between treatment groups. Clinical chemistry values outside the threshold range were infrequent and generally comparable between treatment groups. [Clinical, Study FMS30058, page 95-6; fms30058.pdf]

12.1.2.3.10. Medical device incidents or malfunctions

There were no incidents, near incidents or malfunctions reported with the use of the medical device(s) manufactured or marketed, by GSK or by a third party for GSK. [Clinical, Study FMS30058, page 106; fms30058.pdf]

12.1.3. Discussion

In study FMS30058, 80 outpatient centers were planned, 87 centers participated, and 77 centers enrolled patients (range 1 to 21 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.

The demonstration of efficacy of asthma drugs in young children is problematic. This is likely due to assay sensitivity, although in this study there are also issues regarding how much drug is inhaled via a holding chamber. There are no simply applied techniques for evaluating pulmonary functions in young children. Studies seeking to evaluate asthma endpoints in younger children must rely on parental/guardian evaluations of the child's status. It is well known that patients (both children and adults) may be experiencing significant reductions in pulmonary function without demonstrating much symptomatology. It is likely, therefore, that assay sensitivity for the primary efficacy variable that was chosen for this study was quite low.

While several studies have demonstrated clinical efficacy for asthma drugs administered to young children via a holding chamber with face mask, studies have also demonstrated that there are significant differences in delivered doses depending upon physical properties as well as the timing of use of the holding chamber/MDI combination. Such physical properties include whether the device has been washed, how it has been washed, and how it has been dried. (b) (4) The timing of the puff in relation to the placement of the mask over the nose and mouth of the patient and how long the mask is kept in place (either by time or by respiratory cycles) are also thought to affect dose delivery. (b) (4)

The primary efficacy measure was the mean change from baseline in parent/guardian-assessed daily asthma symptom scores during the last two weeks of participation in the study. At baseline daily asthma symptom scores for the RITT population were comparable, although the baseline score for the FP88 group was slightly higher than the other groups. At every week of treatment with the exception of Week 3 for FP44, there was a greater reduction in asthma symptom scores in the FP88 and FP44 groups compared with placebo. The differences between FP44 and placebo for reductions in asthma symptom scores were significant at Weeks 5 and 6 but not at Endpoint ($p = 0.858$). However, the differences between FP88 and placebo for reductions in asthma symptom scores were significant at Weeks 1, 2, 6 and Endpoint ($p = 0.42$).

While patients using the Aerochamber device appeared to have a greater reduction in asthma symptoms at endpoint than patients using the Optichamber, the difference in baselines for the two FP88 sub-groups makes such a conclusion difficult to support.

The percentage of symptom-free days and symptom- & albuterol-free days increased for all groups, but more for the FP88 group. This difference was significant for both the percentage of symptom-free days ($p=0.02$, FP88 vs placebo) and the percentage of symptom- & albuterol-free days ($p=0.017$, FP88 vs placebo). These results were consistent with the primary efficacy results. While the FP88 group experienced fewer daytime asthma symptoms than other treatment groups, the difference versus placebo was not significant. This difference was significant for nighttime asthma symptoms ($p=0.027$, FP88 vs placebo). These results were consistent with the primary efficacy results. The number of patients who experienced an asthma exacerbation over the 12 week treatment period was lower in both the FP88 and the FP44 groups ($n=13$ and $n=14$, respectively) compared with placebo ($n=24$). The FP88 group had a greater probability of not experiencing an asthma exacerbation compared with those receiving FP44 or placebo. The difference versus placebo was statistically significant ($p=0.044$, FP88 vs placebo). All treatment groups experienced mean reductions in daily rescue albuterol use. Both FP groups experienced greater mean reductions in daily rescue albuterol use than placebo; but the difference was only significant for FP88 ($p=0.017$, FP88 vs placebo). Both FP groups experienced greater mean reductions in daily rescue albuterol use than placebo; but the difference was only significant for FP88 ($p=0.017$, FP88 vs placebo).

Subgroup analyses included analysis by age group, holding chamber, and pre-treatment with corticosteroids. Subgroup analysis by age group showed results consistent with the full RITT population, with only FP88 treatment showing a consistent improvement in daily asthma scores compared to patients on either FP44 or placebo. Patients treated with FP44 experienced different results depending on their age group, with the 36-47 month FP44 sub-group showing a greater reduction in daily asthma symptom scores compared to placebo, but the 24-35 month FP44 age group showing less reduction than placebo. Subgroup analysis by holding chamber showed results consistent with the full RITT population. Both the FP88 Aerochamber and Optichamber sub-groups showed a consistent improvement in daily asthma scores compared to patients on either FP44 or placebo. Patients treated with FP44 experienced different results depending on the holding chamber used. While the FP88

Aerochamber treatment group had a baseline score about 0.15 points higher than the rest of the groups, patients treated with FP44 or FP88 Aerochamber showed more improvement than patients assigned to the corresponding Optichamber groups. Subgroup analysis by pre-treatment with corticosteroids showed results consistent with the full RITT population. Both FP88 sub-groups showed a consistent improvement in daily asthma scores compared to patients on either FP44 or placebo.

The extent of exposure, as measured by diary responses, was comparable between groups. There were no deaths, but there were six SAEs reported by six patients during treatment, but none of the events were judged by the investigator to be related to study drug. There were no incidents, near incidents or malfunctions reported with the use of the medical device(s) manufactured or marketed, by GSK or by a third party for GSK. Shift tables for vital signs (systolic and diastolic BP and HR), physical examinations, and laboratory values showed no trends.

A total of 277 subjects (83%) reported at least one AE during treatment (93 [82%] placebo, 98 [88%] FP44, and 86 [80%] FP88). There was a minor trend toward higher incidences of fever in both the FP44 and FP88 groups (25 [22%] placebo, 32 [29%] FP44, and 30 [28%] FP88), the etiology of which is not clear. There was a trend toward higher incidence of pharyngitis/throat infection in both the FP44 and FP88 groups (0 placebo, 7 [6%] FP44, and 3 [3%] FP88), presumably secondary to local effects of the active drug. There was a trend to higher incidence of candidiasis of the mouth/throat (2 [2%] placebo, 1 [<1%] FP44, and 5 [5%] FP88), or nasal cavity (0 placebo, 0 FP44, and 2 [2%] FP88) in the FP88 group), again presumably secondary to local effects of the active drug. All five cases of candidiasis of the mouth/throat were noted in the FP88 younger age group (24-35 months). Evaluation of adverse events by holding chamber showed no trends that appeared related to a specific holding chamber. Despite the candidiasis AEs, the incidence of oropharyngeal and nasopharyngeal examination and/or culture positive for Candida was comparable between treatment groups, and there were no trends toward shifts in exam or culture positive results by treatment group or sub-group. Evaluation of adverse events by previous CS therapy (any corticosteroids within 8 weeks of Visit 1) showed that, whereas the trend toward higher incidence of pharyngitis/throat infection spanned the two sub-groups, most instances of candidiasis of the mouth/throat and nasal cavity occurred in the group that had not received previous CS therapy. Evaluation of adverse events by gender showed revealed no specific trends. No rebound trends were noted during the follow-up period after stopping study drugs.

The growth population included 71 placebo, 79 FP44, and 87 FP88 patients. Estimates for the growth velocity for the Growth population showed a dose-dependent reduction in growth velocity. Growth velocities were 20.8 mm/12 weeks for placebo, 19.1 mm/12 weeks for FP44, and 18.4 mm/12 weeks for FP88. The reduction in growth velocity compared to placebo was 1.680 mm/12 weeks ($p = 0.246$) and 2.388 mm/12 weeks ($p = 0.095$) for FP44 and FP88, respectively.

In general there are difficulties with extrapolation from short-term growth evaluations to longer-term growth. These difficulties include variability in measurement as well as variability in seasonal and in individual growth rates. Nevertheless, this reviewer extrapolated the data to place the results into context of what is known from other 1-year

growth studies. The results of this 12-week study extrapolate to one-year linear growth effect sizes that are larger than those previously found in the Flovent Diskus growth study where the reduction in growth velocity compared to placebo for the 50-mcg group was -0.19 cm/year and for the 100-mcg group was 0.43 cm/year. In fact, the effect size seen in this limited study extrapolate to one-year linear growth effect sizes that are comparable to effect sizes that were considered clinically relevant in previous growth studies. Therefore, this reviewer believes that the differences in growth seen in this study between FP88, FP44 and placebo may be clinically relevant.

The urine cortisol population included 26 placebo, 19 FP44, and 20 FP88 patients. Change from baseline for 12-hour overnight urinary cortisol was 0.6 (SD 2.54) (range -3.4 – 6.6), -0.8 (SD 2.08) (range -6.5 – 3.2), and -0.8 (SD 1.85) (range -4.2 – 2.6) for the placebo, FP44, and FP88 groups, respectively. GSK tried to suggest that 18 of 19 (95%) of the FP44 patients and 18 of 20 (90%) of the FP88 patients were contained within the range of the change from baseline in urine cortisol for the placebo group (-3.4 to 6.6mcg/12-hour). However, the cumulative distribution function reveals a clear separation between groups, with both the FP44 and the FP88 showing more change from baseline than the placebo group. This change is less obvious but still present in the data from the ITT population (data not shown here). [redacted]

In summary, the FP88 CFC-MDI administered BID with a holding chamber demonstrated superior efficacy compared to placebo, whereas the FP44 dose did not. FP 88 also demonstrated significant reductions in mean daily asthma symptoms, albuterol use, and nighttime asthma symptoms when compared with subjects treated with placebo. There was a greater but not significant improvement in daytime asthma symptoms, significantly more symptom-free days and symptom free and albuterol free days, and a significantly lower probability of treatment failure compared to subjects treated with placebo. While the FP44 dose showed greater improvements in all efficacy parameters compared to placebo except daytime asthma symptoms, the differences in improvement were not significant. Although most of the clinical trials in adolescents and adults used doses of 88mcg and above, clinical trials with Flovent Inhalation Aerosol have demonstrated efficacy at doses as low as 22mcg. Therefore, it is somewhat surprising that the FP88 appeared to show efficacy whereas the FP44 did not. This may have been due to one of several reasons, including assay sensitivity and issues with how much drug is inhaled via a holding chamber.

Unlike study FMS30059, there were potentially significant safety trends noted in this study. There was a trend toward higher incidence of pharyngitis/throat infection in both the FP44 and FP88 groups, and a trend to higher incidence of candidiasis of the mouth/throat or nose, presumably secondary to local effects of the active drug. All five cases of candidiasis of the mouth/throat were noted in the FP88 younger age group (24-35 months). Estimates for the growth velocity for the Growth population showed a dose-dependent reduction in growth velocity. While the actual effect on longer-term growth was not evaluated and is unknown, the growth estimates based on 12 weeks of data may translate to clinically relevant effects on longer-term growth. Changes in 12-hour overnight urinary cortisol excretion showed a non-dose-dependent reduction in urinary cortisol. [redacted]

(b) (4)

12.1.4. Conclusions

Interpretation of the efficacy results for this study would normally be tempered by an awareness of difficulties with assay sensitivity (using parent/guardian assessments) and dose delivery through an MDI/holding chamber combination with a facemask. Putting the Data Quality and Integrity issue aside for a moment, there are a number of possible implications from the data. (b) (4)

Of most significance for this study is the Data Quality and Integrity issue arising as a result of the PK measurements that found detectable FP levels in 10 patients assigned to placebo treatment. This issue totally confuses what dose was delivered to which patient, and make any meaningful interpretation of the efficacy results from this study impossible.

The reader is cautioned that the results do not support or imply that either the FP44 or the FP88 dose is the appropriate dose for use in children in this age range. In this age range, these dosages may (or may not) be efficacious, and may (or may not) be associated with potential for systemic effects. If a clinician chooses to use this drug off-label in children below 12 years of age, the dose should be titrated to the lowest dose that appears to provide efficacy for that child, and the child should be monitored for signs and symptoms of systemic corticosteroid effects.

12.2. Study FMS30059, A multicenter, randomized, double-blind, 12-week study of Fluticasone Propionate 44mcg BID and 88mcg BID delivered via CFC MDI and a valved holding chamber with facemask in patients with asthma age 6 months to 23 months

Protocol #:	FMS30059
Title:	A multicenter, randomized, double-blind, parallel group, placebo-controlled, 12-week study of Fluticasone Propionate 44mcg BID and 88mcg BID delivered via CFC MDI and a valved holding chamber with facemask in subjects with asthma age 6 months to 23 months
Study Dates:	March 8, 2000 to March 28, 2002
Sites:	71 sites in the US, Puerto Rico, and Chile, of which 54 sites enrolled patients
IRB:	IRB at each study site

Source: Clinical, FMS30059, pages 1-2, 13-4; fms30059.pdf

NOTE: (b) (4)

12.2.1. Protocol/Study Design

This was a 12-week, randomized, double-blind, parallel group, placebo-controlled multicenter study of fluticasone propionate 44mcg BID and 88mcg BID delivered via MDI with CFC propellants 11/12 and a valved holding chamber with a facemask in 337 patients with asthma age 6 months to 23 months. The protocol for study FMS30059 was designed to satisfy the requirements of the pediatric Written Request (see Appendix A, page 56). Except for minor differences as stipulated in the Written Request, the protocol was identical to that for study FMS30058. The major difference between the two studies was that study FMS30058 was conducted in children ages 24 to 47 months, and this study was conducted in children ages 6 to 23 months. Because the protocols are almost identical, the protocol/study design for study FMS30059 will not be repeated here, and the reader is referred to study FMS30058 for protocol/study design details and the Written Request for details of what was requested in the two studies. This section contains a brief discussion of the protocol study design differences between study FMS30059 in younger (6-23 months) children compared to study FMS30058 in the older (24-47 months) children.

The protocol was amended 5 times [Clinical, FMS30059, pages 18-9; fms30059.pdf]. Inclusion and exclusion criteria, permitted and prohibited medications were identical to those for study FMS30058 except for inclusion criterion #3which defined the age for subjects to be 6 months to 23 months inclusive (Must not have reached their 2nd birthday before randomization.), and the prohibition of leukotriene inhibitors. Withdrawal criteria, permitted, and excluded medications were the same as for study FMS30058.

The conduct of the study was identical to study FMS30058 except that 80 centers were planned, 71 sites participated, and 54 sites enrolled subjects. These sites were in the United States (49), Puerto Rico (2), and Chile (3) [Clinical, Study FMS30059, Table 13.12, pages

184-6; fMS30059.pdf]. The original pediatric Written Request stated that a minimum of 100 patients in each group must complete the study. However, Amendment 1 (May 21, 2001) lowered the numbers of patients to specify that a minimum of 50 patients per group, of which approximately 1/3 should be less than 12 months of age, must complete the studies. GSK states that approximately 390 subjects were planned, 227 enrolled, and 211 were randomized to study treatment, with about 1/3 of the randomized patients between 6 and 12 months of age (randomization was stratified by age). Unlike the study in older children, the Written Request specified that only one holding chamber need be used, and GSK chose to use the Aerochamber plus mask. Powering based on the revised number of 65 planned patients per treatment group. This provided a 67% power to detect a difference of 0.3 in mean change from baseline in daytime and nighttime symptom scores between active drug and placebo assuming a standard deviation of 0.73 and using a two-sided t-test with a significance 0.05.

Safety and efficacy evaluations, including efficacy scoring, variables, and endpoints were identical to those for study FMS30058 except that PEF measurements were not obtained. A single blood sample was taken at the end of 12 weeks of therapy for pharmacokinetic analysis using a modified population PK approach in combination with the results from study FMS30058. The statistical plan was also the same, and a RITT population was defined for this study as for study FMS30058 excluding the data from one patient at (b) (4) site (0 placebo, 1 FP44, 0 FP88) [Clinical, Study FMS30059, Table 13.3, page 124; fMS30059.pdf]. In these younger children for whom standing height measurements are not appropriate, body length assessment used an infantometer with triplicate measurements at the same time of day for each subject.

The batches of FP CFC MDI used were OZM2355, OZP1089, and 9ZP1541. Batches of placebo CFC MDI used were OZP0771 and 9ZP1542. [Clinical, FMS30059, page 25; fms30059.pdf]

12.2.2. Brief Summary of the Study Design

This was a 12-week, randomized, double-blind, parallel group, placebo-controlled multicenter (80 outpatient centers planned) study of fluticasone propionate 44mcg BID and 88mcg BID delivered via MDI with CFC propellants 11/12 and a valved holding chamber with a facemask in 337 patients with asthma age 6 months to 23 months. The study was designed to satisfy the requirements of the pediatric Written Request (see Appendix A). The study was identical in design to study FMS30058 except that only one holding chamber was used. It was 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). Male and female patients aged 6-23 months inclusive with a documented history of symptomatic asthma and have experienced at least 2 episodes of increased symptoms of asthma requiring medical attention and asthma pharmacotherapy within the preceding 12 months. Prior to Visit 1, 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. To be eligible for randomization, patients had to have documented asthma symptoms 5 of the last 7 days of the 14 to 28 day screening period, and use of albuterol on at least 2 occasions during the 5

symptomatic screening days. Blinding was maintained by use of two inhalers throughout the study.

The primary efficacy endpoint was the average change from baseline in daytime and nighttime (daily) asthma symptom scores to Endpoint (the last two weeks of diary data prior to end of study, asthma exacerbation, or study withdrawal). The daily asthma symptom score was the average of daytime and nighttime asthma symptom scores as 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. 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), the frequency of treatment failure, and patient discontinuations.

Safety was assessed by examining adverse events, physical examinations (including vital signs, linear growth assessments, oropharyngeal and nasal passage examinations), growth velocity, clinical laboratory tests (biochemistry and hematology), oropharyngeal and nasal passage *Candida* cultures, and hypothalamic-pituitary-adrenal (HPA) axis function (12-hour overnight urine cortisol). DNA samples and pharmacokinetic samples (one per patient) were collected during this study for analysis.

12.2.3. Results

<u>NOTICE</u>: Before reading the results section of this study, the reader is strongly advised to read Section 5.3 (Data Quality and Integrity) on page 27 for an in-depth discussion of Data Quality and Integrity issues and the implications for interpretation of the data. This detailed study review was written prior to the uncovering of these Data Quality issues. Therefore, the results and discussion sections may no longer be applicable.

12.2.3.1. Description of Study Population

12.2.3.1.1. Disposition

Patient disposition is summarized in Table 31. Two-hundred and eleven patients participated in this study at 54 study sites (range 1 to 17 per site). Slightly more patients in the FP88 and FP44 groups discontinued than in the placebo group, with the majority of discontinuations in the placebo groups due to being lost to follow-up. [Clinical, Study FMS30059, pages 56-7; fMS30059.pdf]

Table 31. Study FMS30059, Patient disposition, ITT population

Disposition	Placebo	FP44	FP88	Total
ITT population	69	73	69	211
Completed	65 (94%)	64 (88%)	58 (84%)	187 (89%)
Discontinued	4 (6%)	9 (12%)	11 (16%)	24 (11%)
Adverse event	0	2	0	2
Consent withdrawn	2	1	0	3
Lost to follow-up	0	3	6	9
Protocol violation	1	1	0	2
Lack of efficacy	0	1	3	4
Other *	1	1	2	4

* Other reasons included: moved out of state (1), parent became ill (1), noncompliance (1), going away for extended period of time (1)

Source: Clinical, Study FMS30059, Tables 13.5 and 13.6, pages 134-137; fMS30059.pdf

12.2.3.1.2. Protocol Violations

Protocol deviations are summarized in Table 32. Major violations included enrollment and/or randomization of subjects to who did not meet the inclusion, exclusion and/or randomization criteria. Other protocol deviations included use of prohibited concomitant medications, incorrect stratification, incorrect study drug dispensing, and any other deviations that were deemed to have the potential for influencing the results.

There were comparable numbers of protocol violations in all treatment groups. The majority of patient visits were within the protocol specified visit windows (68-94%), with similar results for all treatment groups (results not shown). [Clinical, FMS30059, Table 13.10, pages 173-4; fms30059.pdf]

There was one patient in the FP 44 group was unintentionally unblinded during the study due to damage to the label while removing the medication from the treatment box. The patient was discontinued one week after this event. [Clinical, FMS30059, Tables 13.11 and 13.15, pages 179, 198; fms30059.pdf]

Table 32. Study FMS30059, Protocol violations, ITT population

Protocol Violation	Placebo	FP44	FP88
ITT population	69	73	69
Protocol violations †	33 (48%)	37 (51%)	35 (51%)
Failed to meet inclusion criteria	0	1	0
Failed to meet exclusion criteria	11	16	13
Failed to meet randomization criteria	5	7	10
Prohibited medication	19	23	19
Pre-screening	11	16	11
During screening	15	19	15
During treatment	10	9	10
Prohibited concurrent medication *	0	3	0
Treatment medication violation	4	1	5
Stadiometer calibration violation	0	1	0
Other	10	13	10

Protocol Violation	Placebo	FP44	FP88
† Note; patients may have violated more than one criterion. * Prohibited concurrent medication was checked on Protocol Violations Summary CRF page, but medication was not specified on the concurrent medications CRF page.			

Source: Clinical, Study FMS30059, page 57-8 and Table 13.8, pages 139-44; fMS30059.pdf

12.2.3.1.3. Analysis populations

As defined above, there were several analysis populations defined in the protocol, before unblinding, and *post-hoc*. These included the ITT, RITT, Completer, Growth, and Cortisol populations. The numbers of patients in each population are shown in Table 33. The ITT population included 69 placebo, 73 FP44, and 69 FP88 patients. The RITT population included 69 placebo, 71 FP44, and 69 FP88 patients. The patients excluded from the ITT to create the RITT population included 2 patients in the FP44 group: 1 from (b) (4) site and 1 for whom study drug accidentally was unblinded. The majority of patients excluded from the urine cortisol population were due to missing data (71-75%) and due to low 12-hour weight-adjusted creatinine and urine volume (22-33%) [Clinical, Study FMS30059, page 59; fMS30059.pdf]. This is not unexpected, due to difficulties with urine collection from bagged specimens in a non-toilet-trained population.

The Completer population was defined specifically *post-hoc* to meet the Written Request. This population included 182 patients (57 FP88, 63 FP44, 62 placebo), of which 60 patients (33%) were 6-11 months of age and 122 patients (67%) were 12-23 months of age. [Submission of 2/14/03, p 1, cover.pdf; Table 7, p 30-1, fms3005859tables.pdf].

Table 33. Study FMS30059, Summary of analysis populations

Population	Placebo	FP44	FP88
ITT	69	73	69
RITT	69	71*	69
Completer	62	63	57
Growth	49	48	52
Urine cortisol	7	3	3
* One patient at (b) (4) site, and one patient who was unintentionally unblinded			

Source: Clinical, Study FMS30059, page 59; fMS30059.pdf
Submission of 2/14/03, Table 7, p 30-1, fms3005859tables.pdf

12.2.3.1.4. Demographics and baseline characteristics

Demographic and other baseline characteristics of the patients in the ITT population are summarized in Table 34. As shown, the demographics of the treatment groups were comparable. 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 history of asthma and allergies, including family history of asthma, is summarized in Table 35. Again, the groups were comparable. The incidence of other medical conditions (not shown) was comparable among groups [Clinical, Study FMS30059, Table 13.22, pages 313-7; fms30059.pdf].

Prior use of corticosteroids and other asthma medications are shown in Table 36. The placebo group had a slightly higher baseline use of corticosteroids (both oral and inhaled) within the six months prior to Visit 1. There was a low use of oral corticosteroids in all groups within eight weeks of Visit 1. Prior use of other asthma medications was comparable among groups.

Use of non-asthma concurrent medications both before and during the treatment period was comparable among groups [Clinical, Study FMS30059, pages 62, 560; fms30059.pdf]. As expected, during the treatment period the active treatment groups used less concurrent asthma medications (23-27%) than the placebo group (32%), with the most commonly used asthma medications being salbutamol (6-10%), sodium cromoglycate 4-13%) and prednisolone (4-13%) [Clinical, Study FMS30059, Table 13.29, page 448; fms30059.pdf]. Post-treatment, both active groups (17-19%) used slightly less asthma medications than the placebo group (23%) [Clinical, Study FMS30059, page 470; fms30059.pdf].

Table 34. Study FMS30059, Demographics and Baseline Characteristics, ITT pop

Demographics	Placebo n = 69	FP44 n = 73	FP88 n = 69	Total n = 211
Age (months)				
Mean (range)	15.3 (7-23)	15.26 (6-23)	14.2 (6-23)	35.6 (6-23)
6-11 months	20 (29%)	22 (30%)	24 (35%)	66 (31%)
12-23 months	49 (71%)	51 (70%)	45 (65%)	145 (69%)
Male	43 (62%)	42 (58%)	45 (65%)	130 (62%)
Female	26 (38%)	31 (42%)	24 (35%)	81 (38%)
Ethnicity:				
White	28	35	32	95
Black	11	9	8	28
Asian	2	1	0	3
Hispanic	26	25	27	78
Other*	2	3	2	7
Length (cm) (mean, range)	77.4 (54-91)	76.9 (50-89)	76.9 (56-88)	77.1 (50-91)
Weight (kg) (mean, range)	10.9 (7.5-15.8)	10.8 (6.5-19.0)	11.0 (6.8-19.0)	10.9 (6.5-19.0)
Other demographics				
Smoking exposure*	16 (23%)	15 (21%)	16 (23%)	47 (22%)
Pet exposure*	22 (32%)	31 (42%)	30 (43%)	83 (39%)
Attend daycare	28 (41%)	23 (32%)	20 (29%)	71 (34%)

* History of smoking or pet exposure in household or daycare environment.

Source: Clinical, Study FMS30059, Table 13.18, pages 281-4; fms30059.pdf

Table 35. Study FMS30059, Asthma and allergy history, ITT population

Asthma	Placebo n = 69	FP44 n = 73	FP88 n = 69
Age at onset (months)			
<6 months	44 (64%)	48 (66%)	47 (68%)
≥6 months to <1 year	22 (32%)	19 (26%)	20 (29%)
≥1 year to <2 years	3 (4%)	6 (8%)	2 (3%)
Duration of Asthma (months)			
Mean (range)	10.9 (1-23)	10.3 (1-22)	10.0 (0-21)
History of Allergy	41 (59%)	44 (62%)	48 (70%)
SAR	8	19	12

Asthma	Placebo n = 69	FP44 n = 73	FP88 n = 69
PAR	20	19	27
Eczema	17	13	15
Food allergy	9	9	9
Other	9	7	11
Immediate Family History of Asthma			
Yes	51 (74%)	51 (72%)	56 (81%)
Mother	13	14	15
Father	23	28	16
Siblings	30	30	25
Maternal GP	20	9	18
Paternal GP	4	6	11
No	13	18	12
Unknown	5	2	1

Source: Clinical, Study FMS30059, Table 13.20, pages 294-7; fms30059.pdf

Table 36. Study FMS30059, Pre-study corticosteroid use, ITT population

Corticosteroid use	Placebo n = 69	FP44 n = 73	FP88 n = 69
Last 6 months prior to Visit 1			
Have used	34 (51%)	35 (48%)	29 (42%)
Oral	20 (29%)	15 (21%)	16 (23%)
Inhaled	26 (38%)	20 (27%)	18 (26%)
Last 8 weeks prior to Visit 1			
Have used	22 (32%)	20 (27%)	19 (28%)
Oral	2 (3%)	1 (1%)	2 (3%)
Inhaled	20 (29%)	17 (23%)	17 (25%)
Medium-high dose	2	1	0
Low dose	17	12	16
Dose unknown	1	4	1
Last 6 months prior to Visit 1			
Have used	68 (99%)	71 (97%)	65 (94%)
Salbutamol	66	65	63
Cromolyn	12	13	16
Levalbuterol	9	10	5
Montelukast	3	2	2
Sodium chloride	2	1	1
Ipratropium	2	0	0
Salmeterol	0	1	1
Aminophylline	1	0	0
Terbutaline	1	0	0
Investigational drug, unspecified	0	1	0
Intranasal corticosteroids			
Used within 6 months	0	1 (1%)	1 (1%)
Used within 8 weeks	0	1 (1%)	1 (1%)

Source: Clinical, Study FMS30059, Table 13.25, pages 355-8 and Table 13.26, page 359-60; fms30059.pdf

12.2.3.1.5. Compliance

Compliance with study drug treatment (as measured by dairy records, and not by returned medications) is shown in Table 37. Rates were comparable across treatment groups.

Table 37. Study FMS30059, Compliance rates, ITT population

Compliance	Placebo n = 69	FP44 n = 73	FP88 n = 69
Compliance rate* (mean)	91.2	92.6	91.3
n ≥ 90%	53	58	53
n >=80-90%	8	7	8
n < 80%	8	8	8
* Based on dairy data. Compliance rate = the number of days all AM and PM medications were taken divided by the number of days in the treatment period.			

Source: Clinical, Study FMS30059, Table 13.39, page 826; fms30059.pdf

12.2.3.2. Efficacy Endpoint Outcomes

12.2.3.2.1. Primary efficacy measure

The primary efficacy measure was defined as the mean change from baseline in daily (24-hours) asthma symptom scores that were collected during the last two weeks of the study, but prior to the efficacy cut-off date (i.e., treatment stop date, asthma exacerbation, study withdrawal, or Day 84, whichever occurred first). These results were reported for the RITT population. The daily asthma symptom scores and the change from baseline in daily asthma symptom scores were summarized at baseline, weekly and at endpoint.

Daily asthma symptom scores at baseline, weekly, and at endpoint are summarized in Table 38 and shown graphically in Figure 17. The change from baseline in daily asthma symptom scores at baseline, weekly, and at Endpoint are summarized in Table 39, and shown graphically in Figure 18 (daily asthma scores). Figure 19 shows the asthma symptom scores broken down by daytime and nighttime asthma scores. In Table 38 and Table 39 the primary efficacy endpoint is shown in *italics*. In Table 39 all statistically significant differences are shown in **bold**.

At baseline daily asthma symptoms scores for the RITT population were comparable, although the baseline score for the FP44 group was slightly lower than the other groups. There was no significant difference in the reduction in asthma symptom scores in either the FP88 and FP44 groups compared with placebo. Surprisingly, the placebo and FP88 groups both improved by comparable amounts, and both did better than the FP44 group.

Table 38. Study FMS30059, Daily symptom scores by week and at Endpoint, RITT population

Daily symptom scores	Placebo n = 69		FP44 n = 71		FP88 n = 69	
	n	mean (SE)	n	mean (SE)	n	mean (SE)
Baseline	69	1.27 (0.06)	71	1.15 (0.06)	69	1.30 (0.07)
Week 1	69	1.02 (0.08)	71	0.88 (0.07)	68	0.97 (0.08)
Week 2	68	0.83 (0.07)	68	0.75 (0.07)	68	0.81 (0.08)
Week 3	68	0.78 (0.08)	68	0.66 (0.07)	68	0.74 (0.08)
Week 4	67	0.75 (0.08)	69	0.63 (0.07)	67	0.65 (0.06)
Week 5	66	0.72 (0.08)	66	0.65 (0.08)	67	0.62 (0.06)
Week 6	66	0.64 (0.07)	67	0.63 (0.07)	63	0.64 (0.06)
Week 7	66	0.65 (0.08)	67	0.59 (0.08)	63	0.55 (0.06)
Week 8	66	0.69 (0.09)	65	0.68 (0.08)	62	0.63 (0.09)
Week 9	66	0.62 (0.07)	64	0.68 (0.09)	59	0.58 (0.09)
Week 10	66	0.56 (0.07)	64	0.58 (0.08)	58	0.58 (0.09)
Week 11	64	0.45 (0.06)	63	0.51 (0.08)	59	0.51 (0.08)
Week 12	60	0.48 (0.07)	63	0.53 (0.08)	58	0.53 (0.08)
Endpoint	*64*	*0.53 (0.07)*	*65*	*0.61 (0.07)*	*65*	*0.56 (0.08)*

Baseline = the last week prior to randomization. Endpoint is the last two weeks of diary data prior to treatment stop date, asthma exacerbation, study withdrawal, or day 84.

Source: Clinical, Study FMS30059, Table 14.1, pages 836-9; fms30059.pdf

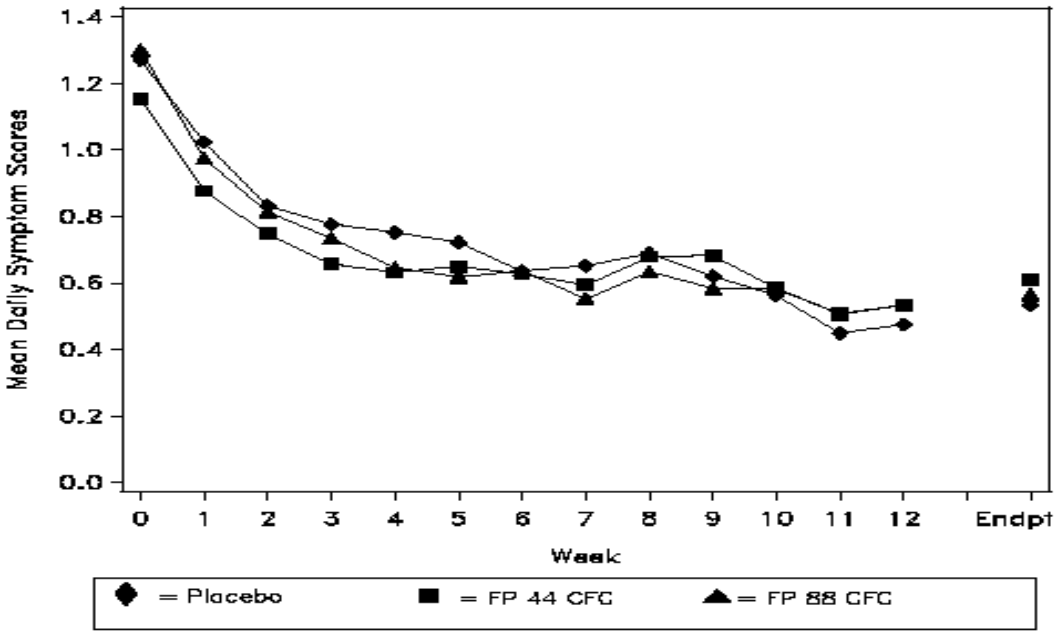

Figure 17. Study FMS30059, Daily symptom scores over time, RITT population

Source; Clinical, Study FMS30059, Figure 14.1, page 829; fms30059.pdf

Table 39. Study FMS30059, Change from baseline in daily symptom scores by week and at Endpoint, RITT population

Change from baseline in daily symptom scores	Placebo n = 69		FP44 n = 71			FP88 n = 69		
	n	mean (SE)	n	mean (SE)	p-value	n	mean (SE)	p-value
Baseline*	69	1.27 (0.06)	71	1.15 (0.06)		69	1.30 (0.07)	
Week 1	69	-0.27 (0.08)	71	-0.32 (0.09)	0.535	68	-0.36 (0.09)	0.325
Week 2	68	-0.58 (0.09)	68	-0.61 (0.09)	0.761	68	-0.67 (0.10)	0.327
Week 3	68	-0.63 (0.09)	68	-0.71 (0.10)	0.387	68	-0.74 (0.11)	0.266
Week 4	67	-0.64 (0.09)	69	-0.72 (0.10)	0.382	67	-0.82 (0.11)	0.076
Week 5	66	-0.70 (0.10)	66	-0.77 (0.11)	0.538	67	-0.90 (0.11)	0.061
Week 6	66	-0.74 (0.10)	67	-0.73 (0.10)	0.965	63	-0.77 (0.11)	0.709
Week 7	66	-0.69 (0.10)	67	-0.75 (0.11)	0.518	63	-0.83 (0.11)	0.189
Week 8	66	-0.70 (0.11)	65	-0.70 (0.12)	0.984	62	-0.85 (0.13)	0.240
Week 9	66	-0.74 (0.11)	64	-0.64 (0.12)	0.382	59	-0.83 (0.13)	0.445
Week 10	66	-0.77 (0.10)	64	-0.71 (0.11)	0.589	58	-0.80 (0.12)	0.770
Week 11	64	-0.83 (0.10)	63	-0.75 (0.11)	0.433	59	-0.83 (0.12)	0.966
Week 12	60	-0.85 (0.11)	63	-0.78 (0.11)	0.518	58	-0.87 (0.12)	0.870
Endpoint†	*64*	*-0.85 (0.09)*	*65*	*-0.77 (0.10)*	*0.375*	*65*	*-0.87 (0.10)*	*0.859*

Baseline = the last week prior to randomization. Endpoint is the last two weeks of diary data prior to treatment stop date, asthma exacerbation, study withdrawal, or day 84. P-values are vs. placebo.

* Mean values for Baseline

† LS mean values for Weeks 1-12 and Endpoint

Source: Clinical, Study FMS30059, Tables 14.2, and 14.3, pages 840-7; fms30059.pdf

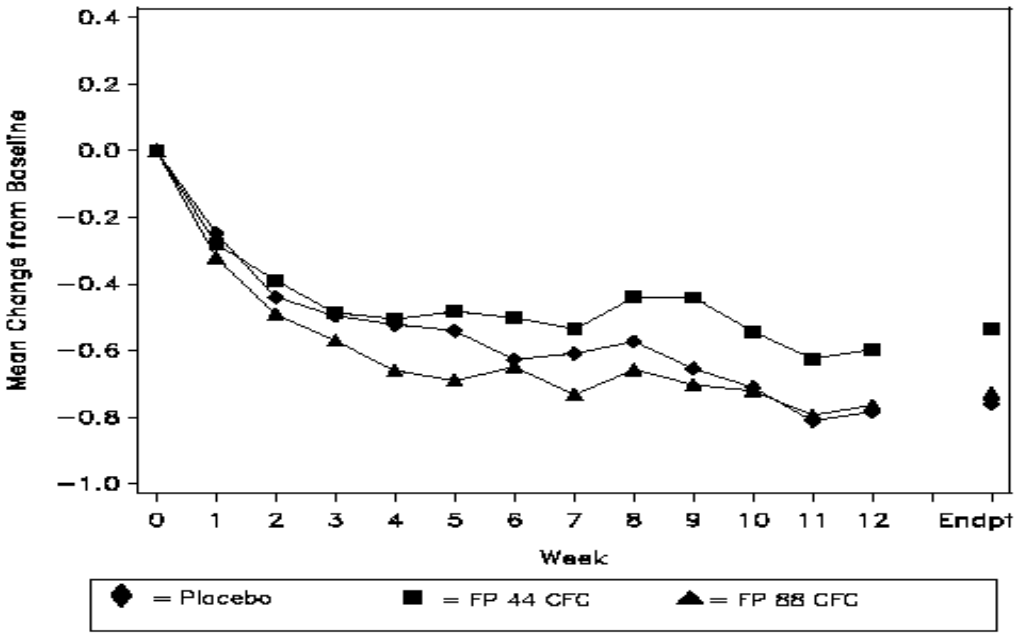

Figure 18. Study FMS30059, Change from baseline in daily symptom scores over time, RITT population

Source; Clinical, Study FMS30059, Figure 14.2, page 830; fms30059.pdf

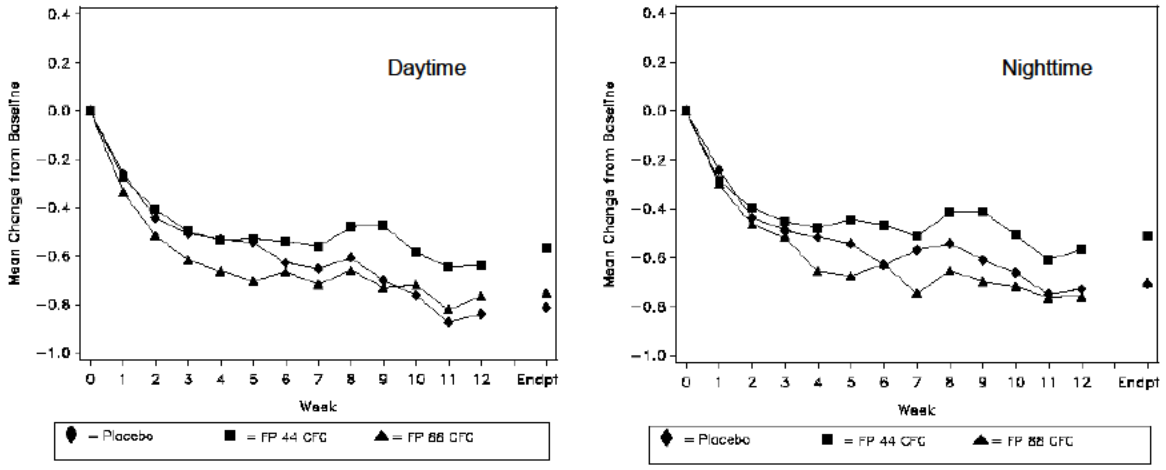

Figure 19. Study FMS30059, Change from baseline in daytime and nighttime symptom scores over time, RITT population

Source; Clinical, Study FMS30059, Figures 14.3 and 14.4, pages 1202-3; fms30059.pdf

12.2.3.2.2. Secondary efficacy measures

Secondary efficacy measures included the percentage of symptom-free days, percentage of symptom- and albuterol-free days, daytime and nighttime asthma scores, time to treatment failure, daily rescue albuterol use, and total daily albuterol use.

The percentages of symptom-free days and symptom- & albuterol-free days are shown in Table 40. A symptom-free day was defined as a day in which a patient had a daytime symptom score of zero and a nighttime symptom score of zero. A symptom-free & albuterol-free day was defined as a day in which a patient had both daytime and nighttime symptom scores of zero and required no albuterol use. The percentage of symptom-free days and symptom- & albuterol-free days increased comparably for all treatment groups. These results were consistent with the primary efficacy results.

Table 40. Study FMS30059, Percentage of symptom-free and symptom- & albuterol-free days, RITT population

% of symptom-free and symptom- & albuterol-free days	Placebo n = 69		FP44 n = 71			FP88 n = 69		
	n	Mean (SEM)	n	Mean (SEM) (95% CI)	p-value	n	Mean (SEM) (95% CI)	p-value
Percentage of symptom-free days, RITT population								
Baseline*	69	6.2 (1.37)	71	8.1 (1.59)		69	6.7 (1.80)	
Weeks 1-12†	69	41.33 (4.83)	71	43.09 (5.10)	0.727	69	45.73 (5.34)	0.388
Endpoint†	64	54.59 (6.27)	65	52.17 (6.72) (-15.64, 10.79)	0.718	65	57.53 (6.98) (-10.37, 16.24)	0.664
Percentage of symptom- and albuterol-free days, RITT population								
Baseline*	68	5.7 (1.28)	69	6.5 (1.46)		67	6.1 (1.77)	
Weeks 1-12†	68	40.81 (4.98)	69	41.56 (5.28)	0.885	67	42.67 (5.52)	0.724
Endpoint†	62	55.05 (6.39)	62	51.41 (6.84) (-17.10, 9.83)	0.595	64	53.57 (7.06) (-14.93, 11.97)	0.828

% of symptom-free and symptom- & albuterol-free days	Placebo n = 69		FP44 n = 71			FP88 n = 69		
	n	Mean (SEM)	n	Mean (SEM) (95% CI)	p-value	n	Mean (SEM) (95% CI)	p-value
ANCOVA adjusted for baseline value, region, age group, sex, holding chamber, previous corticosteroid use, family history of asthma, and patient history of allergies. P-values are vs. placebo. * Mean values for Baseline † LS mean values for Weeks 1-12 and Endpoint								

Source: Clinical, Study FMS30059, Tables 10 and 11, pages 66-7; fms30059.pdf

Daytime and nighttime asthma symptom scores are shown in Table 19. All treatment groups experienced comparable reductions in daytime and nighttime symptom scores. These results were consistent with the primary efficacy results.

Table 41. Study FMS30059, Daytime and nighttime asthma symptom scores, RITT population

Daytime and nighttime asthma symptom scores	Placebo n = 69		FP44 n = 71			FP88 n = 69		
	n	Mean (SEM)	n	Mean (SEM) (95% CI)	p-value	n	Mean (SEM) (95% CI)	p-value
Daytime asthma symptom scores, RITT population								
Baseline*	69	1.33 (0.06)	71	1.19 (0.06)		69	1.34 (0.07)	
Endpoint*	64	0.54 (0.07)	65	0.61 (0.07)		65	0.57 (0.08)	
Change to Endpoint†	64	-0.88 (0.09)	65	-0.81 (0.10) (-0.13, 0.27)	0.482	65	-0.90 (0.11) (-0.22, 0.19)	0.883
Nighttime asthma symptom scores, RITT population								
Baseline*	69	1.22 (0.07)	71	1.12 (0.07)		69	1.26 (0.07)	
Endpoint*	64	0.52 (0.07)	65	0.61 (0.08)		65	0.55 (0.08)	
Change to Endpoint†	64	-0.82 (0.10)	65	-0.73 (0.10) (-0.11, 0.29)	0.376	65	-0.85 (0.11) (-0.23, 0.18)	0.805
ANCOVA adjusted for baseline value, region, age group, sex, holding chamber, previous corticosteroid use, family history of asthma, and patient history of allergies. P-values are vs. placebo. * Mean values for Baseline and Endpoint † LS mean values for Change to Endpoint								

Source: Clinical, Study FMS30059, Tables 12 and 13, pages 68-9; fms30059.pdf

The number of patients who experienced an asthma exacerbation over the 12 week treatment period was lower in the FP88 groups (n=6) than in the FP44 and placebo groups (n=14 and n=10, respectively). A Kaplan Meier plot of time to treatment failure for the RITT population is shown in Figure 20. Treatment failure was defined as the patient's first asthma exacerbation for a patient and was measured as the time from the date of treatment initiation to the date of first asthma exacerbation or the date of treatment termination. The FP88 group had a greater estimated probability of]\not experiencing an asthma exacerbation compared with those receiving FP44 or placebo, although the difference was not inferentially significant (p=0.165, FP88 vs placebo). [Clinical, Study FMS30059, pages 70-1; fms30059.pdf]

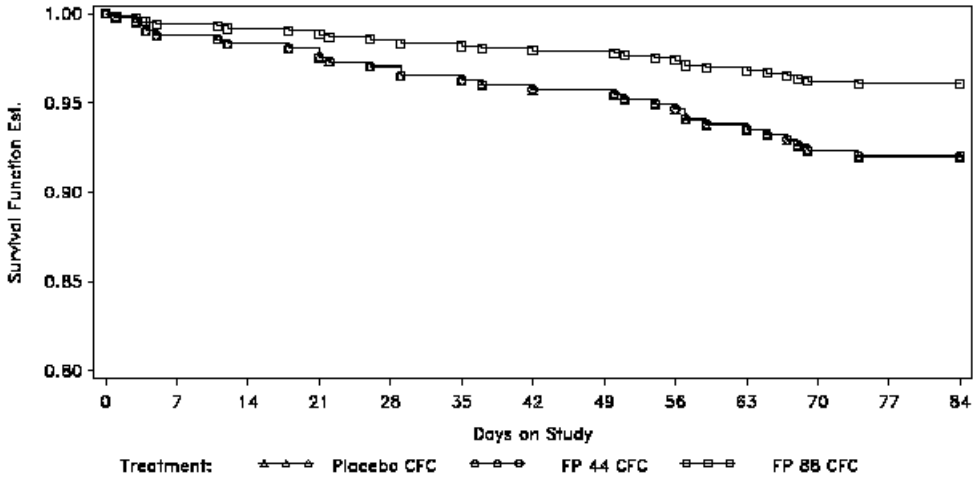

Figure 20. Study FMS30059, Time to treatment failure, RITT population

Source; Clinical, Study FMS30059, Figure 14.5, page 833; fms30059.pdf

Daily rescue albuterol use (Table 42) was defined as the number of treatments of albuterol per day. One treatment equaled two puffs from albuterol MDI or one albuterol nebule. All treatment groups experienced comparable mean reductions in daily rescue albuterol use. These results are consistent with the primary and other secondary efficacy measures.

Table 42. Study FMS30059, Daily rescue albuterol use, RITT population

Daily albuterol use	Placebo n = 69		FP44 n = 71			FP88 n = 69		
	n	Mean (SEM)	n	Mean (SEM) (95% CI)	p-value	n	Mean (SEM) (95% CI)	p-value
Baseline*	68	1.6 (0.15)	69	1.4 (0.15)		67	1.7 (0.20)	
Endpoint*	64	0.5 (0.09)	63	0.6 (0.12)		65	0.5 (0.13)	
Change to Endpoint†	63	-1.21 (0.15)	62	-1.02 (0.16) (-0.13, 0.50)	0.238	64	-1.20 (0.16) (-0.30, 0.32)	0.948

ANCOVA adjusted for baseline value, region, age group, sex, holding chamber, previous corticosteroid use, family history of asthma, and patient history of allergies. P-values are vs. placebo.

* Mean values for Baseline and Endpoint

† LS mean values for Change to Endpoint

Source: Clinical, Study FMS30059, Table 15, page 71; fms30059.pdf

12.2.3.2.3. Other efficacy measures

Other efficacy measures included the frequency of treatment failure (see previous section), and discontinuations (see Table 31). Due to the age of the children participating in this study, PEF measurements were no included in this study as was the case for study FMS30058. The percent of patient discontinuations was lower for the placebo group than either of the two Flovent groups.

12.2.3.2.4. Subgroup analyses

Subgroup analyses including analysis by age group and treatment with corticosteroids within 8 weeks prior to Visit 1 (GSK called this pre-treatment CS) are shown in Table 43. The

study used only one type of holding chamber. As per the Written Request, about one-third of the patients were below 1 year of age. Just as for study FMS30058, there were approximately 2 to 3-fold more patients in the no previous CS treatment sub-group than in the previous CS treatment sub-group.

Subgroup analysis by age group showed no clear pattern, except that FP44 consistently showed less reduction in symptom scores than placebo. There were markedly different results between the two FP88 age sub-groups. In the older age sub-group of 12-23 months, the placebo treatment group showed greatest reduction in symptom scores, and the FP88 treatment group was comparable to the FP44 group. In the younger age sub-group of 6-11 months, the FP88 treatment group showed a greater reduction in symptom scores than either placebo or FP44, and placebo showed a greater reduction than FP44. The difference appears to be that FP44 showed less reduction in symptom scores in the younger age group than in the older age group.

Subgroup analysis by pre-treatment with corticosteroids showed results relatively consistent with the full RITT population, except that for the FP44 sub-group there was a marked difference in results based on whether patients had been pre-treated with corticosteroids. For patients who had pre-treatment with corticosteroids, the FP44 group showed a reduction in symptom scores comparable to the other two treatment groups. For patients who had no pre-treatment with corticosteroids, the FP44 group did not show a reduction in symptom scores comparable to the other two treatment groups, and the results were consistent with those for the full RITT population.

Table 43. Study FMS30059, Asthma symptom scores by sub-group of age and pre-treatment with corticosteroids, RITT population

Daily asthma symptom scores	Placebo		FP44		FP88	
	n = 69		n = 71		n = 69	
Subgroup analyses	n	mean (SEM)	n	mean (SEM)	n	mean (SEM)
Total RITT pop						
Baseline	69	1.27 (0.06)	71	1.15 (0.06)	69	1.30 (0.07)
Endpoint	64	–0.76 (0.08)	65	–0.54 (0.07)	65	–0.73 (0.09)
Age 6-11 months						
Baseline	20	1.26 (0.15)	21	1.03 (0.09)	24	1.46 (0.12)
Endpoint	19	–0.83 (0.14)	18	–0.39 (0.10)	23	–1.02 (0.17)
Age 12-23 months						
Baseline	49	1.28 (0.07)	50	1.21 (0.07)	45	1.21 (0.08)
Endpoint	45	–0.73 (0.09)	47	–0.59 (0.09)	42	–0.57 (0.11)
Pre-treatment CS*						
Baseline	21	1.20 (0.13)	19	1.22 (0.12)	17	1.15 (0.14)
Endpoint	20	–0.70 (0.17)	18	–0.84 (0.17)	16	–0.74 (0.19)
No pre-treatment CS*						
Baseline	48	1.30 (0.07)	52	1.13 (0.07)	52	1.35 (0.08)
Endpoint	44	–0.79 (0.09)	47	–0.42 (0.07)	49	–0.72 (0.11)

* Pre-treatment CS was defined as treatment with CS within 8 weeks of visit 1

Source: Clinical, Study FMS30059, Tables 16 and 17, pages 73-4; fms30059.pdf

12.2.3.3. Safety Outcomes

All safety results were reported for the ITT population, except that the growth and cortisol results reported the results for the predefined growth and cortisol populations as well as the ITT populations.

12.2.3.3.1. Extent of exposure

The mean number of treatment days is shown in Table 44. Most patients had a treatment duration of 12 weeks or more (percentages were 81% for the placebo group, and 75% for both the FP44 and FP88 treatment groups).

Table 44. Study FMS30059, Extent of exposure, ITT population

	Placebo n = 69	**FP44** n = 73	**FP88** n = 69
Treatment Duration			
0-< 1 Week (1- 6 Days)	1	1	1
1-< 2 Weeks (7- 13 Days)	0	2	0
2-< 3 Weeks (14- 20 Days)	1	0	1
3-< 4 Weeks (21- 27 Days)	0	2	0
4-< 6 Weeks (28- 41 Days)	0	0	4
6-< 8 Weeks (42- 55 Days)	0	1	1
8-< 12 Weeks (56- 83 Days)	11 (16%)	12 (16%)	10 (14%)
>= 12 Weeks (>= 84 Days)	56 (81%)	55 (75%)	52 (75%)
Treatment Days, mean (SD)	84.1 (14.4)	80.7 (19.5)	79.7 (18.5)

Source: Clinical, Study FMS30059, Tables 15.1, page 953; fms30059.pdf

12.2.3.3.2. Clinical adverse events

Adverse events (AEs) were summarized by body system, AE group term, and treatment group, and sorted (within patient) by the date of onset; treatment group, investigator number, subject number, demographic details (e.g., age, holding chamber, sex, race, and weight), body system, event (preferred term), resolution status, and action taken.

A total of 196 patients (93%) reported at least one AE during treatment (62 [90%] placebo, 68 [93%] FP44, and 66 [96%] FP88). Adverse events reported with an incidence greater than 3% and greater than the incidence in the placebo treatment group, regardless of causality, are presented in Table 45. There was a trend toward higher incidences of both upper respiratory tract infections (URTI) (21 [30%] placebo, 27 [37%] FP44, and 18 [26%] FP88) and ear, nose & throat infections (18 [26%] placebo, 30 [41%] FP44, and 15 [22%] FP88) in the FP44 group than in either the placebo or FP88 groups. During the course of the study the patients enrolled in the FP44 group just happened to become more ill with upper respiratory related infections than the placebo of FP88 groups. This increased incidence of illness may well explain the reduced efficacy of FP44 compared to placebo or FP88 seen in this study. Unlike study FMS30058, there was no trend to higher incidence of candidiasis of the mouth/throat (3 [4%] placebo, 3 [4%] FP44, and 4 [6%] FP88), however the FP88 group had a slightly higher incidence of candidiasis of the skin than the other two groups (1 [1%] placebo, 0 FP44, and 3 [4%] FP88). No rebound trends were noted during the follow-up period after stopping study drugs, except that the FP44 group continued to have a higher

incidence of URTI and ENT infections than the other groups [Clinical, Study FMS30059, Table 15.9, page 1324; fms30059.pdf].

Evaluation of adverse events by age groups did not lead to any trends not already noted above. The type and frequency of adverse events reported by subgroups were generally similar to each other and to the ITT population. [Clinical, Study FMS30059, Tables 15.13 and 15.14, pages 1346-57; fms30059.pdf]

Evaluation of adverse events by previous CS therapy (any corticosteroids within 8 weeks of Visit 1) showed that the trend toward higher incidence of URT and ENT infections spanned the two sub-groups. Just as for study FMS30058, most instances of candidiasis of the mouth/throat occurred in the group that had not received previous CS therapy. [Clinical, Study FMS30059, Tables 15.15 and 15.16, pages 1358-69; fms30059.pdf]

Evaluation of adverse events by gender showed a comparable incidence of overall reported AEs in male and female placebo sub-groups (females: 92% placebo, 97% FP44, 96% FP88; males: 88% placebo, 90% FP44, 96% FP88). [Clinical, Study FMS30059, Tables 15.17 and 15.18, pages 1370-82; fms30059.pdf]

Table 45. Study FMS30059, Adverse events reported with an incidence greater than 3% and greater than the incidence in the placebo treatment group, regardless of causality, ITT population

AEs >3% and >than placebo, ITT population	Placebo n = 69 n (%)	FP44 n = 73 n (%)	FP88 n = 69 n (%)
Mean duration of exposure (days)	84.1	80.7	79.7
Number of subjects with any AEs	62 (90)	68 (93)	66 (96)
Ear Nose & Throat			
Upper respiratory tract infection (URTI)	21 (30)	27 (37)	18 (26)
Ear, nose & throat infections	18 (26)	30 (41)	15 (22)
Rhinorrhea/post nasal drip	8 (12)	10 (14)	4 (6)
Rhinitis	3 (4)	7 (10)	4 (6)
Pharyngitis/throat infection	5 (7)	2 (3)	6 (9)
Upper respiratory inflammation	2 (3)	3 (4)	5 (7)
Sinusitis	4 (6)	5 (7)	0
Tympanum disorders	1 (1)	3 (4)	4 (6)
Ear signs and symptoms	1 (1)	4 (5)	2 (3)
Tonsillitis	1 (1)	1 (1)	3 (4)
Non-site Specific			
Fever	21 (30)	24 (33)	23 (33)
Viral infections	5 (7)	7 (10)	3 (4)
Allergies and allergic reactions	0	3 (4)	2 (3)
Gastrointestinal			
Diarrhea	8 (12)	9 (12)	9 (13)
Candidiasis mouth/throat	3 (4)	3 (4)	4 (6)
Skin			
Skin rashes	4 (6)	5 (7)	8 (12)
Dermatitis and dermatosis	5 (7)	4 (5)	7 (10)
Fungal skin infections	1 (1)	0	3 (4)
Lower Respiratory			

AEs >3% and >than placebo, ITT population	Placebo n = 69 n (%)	FP44 n = 73 n (%)	FP88 n = 69 n (%)
Cough	4 (6)	6 (8)	4 (6)
Lower respiratory infections	2 (3)	0	4 (6)
Drug Interaction, Overdose, & Trauma			
Soft tissue injuries	4 (6)	2 (3)	5 (7)
Blood & Lymphatic			
Lymphatic signs & symptoms	2 (3)	2 (3)	5 (7)

Source: Clinical, Study FMS30059, Tables 18 and 15.7, pages 77 and 1318-9; fms30059.pdf

12.2.3.3.3. Drug-related clinical adverse events

A total of 18 patients reported at least one AE during treatment that was judged by the investigator to be drug-related (7 [10%] placebo, 4 [5%] FP44, and 7 [10%] FP88). Again, candidiasis of the nose and throat were the only trends, but was spread across all treatment groups (2 [3%] placebo, 3 [4%] FP44, and 4 [6%] FP88). [Clinical, Study FMS30059, pages 79 and 1335-6; fms30059.pdf]

12.2.3.3.4. Serious adverse events, Deaths, and Discontinuations

There were no deaths, but there were four SAEs reported by three patients during treatment (Table 46), and three SAEs reported by two patients during the follow-up period (Table 47). There were also four SAEs during the screening period in four patients who were not subsequently randomized: constipation (1), gastroenteritis rotavirus (1), asthma aggravated (2). All three patients with SAEs during treatment were hospitalized, and one was withdrawn. None of the events were judged by the investigator to be related to study drug. [Clinical, Study FMS30059, pages 81-2; fms30059.pdf]

Table 46, Study FMS30059, Serious adverse events during the treatment period, ITT population

ID#	Treatment	Age/Gender/Race	SAE (verbatim text)	Withdrawal?
3119	FP44	19m White female	PERFORATED APPENDIX ABDOMINAL ABSCESS	Yes
6812	FP88	14m Hispanic male	ROTAVIRAL GASTROENTERITIS	No
3172	FP88	18m White male	VIRAL GASTROENTERITIS	No

Source: Clinical, Study FMS30059, Table 15.19, pages 1383-4; fms30059.pdf

Table 47. Study FMS30059, Serious adverse events during the post-treatment period, ITT population

ID#	Treatment	Age/Gender/Race	SAE (verbatim text)
2652	FP44	14m Black male	SEIZURE ASTHMA EXACERBATION
2902	FP44	8m White female	ASTHMA EXACERBATION

Source: Clinical, Study FMS30059, Table 15.20, page 1385; fms30059.pdf

The study report states that two patients were withdrawn from the study due to an adverse event, that both were in the FP44 treatment group, and that one of the events was considered serious (Subject 3119). The report states that none of the events were considered by the investigator to be related to study drug. The events are listed below. No patients

discontinued treatment prematurely due to an AE, but were not withdrawn from the study. [Clinical, Study FMS30059, pages 82-3 and Table 15.21, page 1386; fms30059.pdf]

- Subject 3119, 19m White female, was withdrawn due to severe abdominal abscess and perforated appendix. The event was not considered related to study drug and was resolved 9 days after onset. (Investigator 73037)
- Subject 5931, 12m black male, was withdrawn due to severe pneumonia. The event was not considered related to study drug and was not resolved. (Investigator 49258)

There were five patients that had AEs requiring concomitant asthma therapy with a non-study drug (3 placebo, 2 FP44, 0 FP88). These therapies included prednisolone (4 patients), prednisone (1 patient), and non-study supplied albuterol (1 patient). [Clinical, Study FMS30059, page 83 and Table 15.22, pages 1387-8; fms30059.pdf]

12.2.3.3.5. Body length and Growth velocity

The changes in recumbent body length (mm) as measured by an infantometer over the course of the study for the Growth population are shown in Table 48, and graphically in Figure 21. Table 48 also shows the changes in body length (mm) for all sub-populations within the Growth population. The estimated growth velocities for the Growth and ITT populations are shown in Table 49. Figure 22 shows a histogram of estimated growth velocity illustrating the large range in growth within the Growth population. While most growth studies are not performed in populations this young, the range of growth noted in this study appears to be is consistent with what is found for range of growth in growth studies. Figure 23 shows the empirical cumulative distribution function (CDF) (cumulative frequencies of change from baseline in body length) for the growth population.

Unlike the growth velocity estimates in study FMS30058, the estimates in this study did not show a trend toward dose-dependent reduction in growth velocity. Growth velocities for the Growth population were 28.5 mm/12 weeks for placebo, 33.4 mm/12 weeks for FP44, and 29.9 mm/12 weeks for FP88. Patients on FP44 grew more than patients on placebo, while patients on FP88 grew slightly less. None of the differences in growth velocity between active drug and placebo groups were statistically significant. However, visually there appears to be a trend to separation for the FP88 group, seen in Figure 21.

Investigation of treatment-by-age showed no clear trends. In the older sub-group (12-23 months), children treated with Flovent grew less than those on placebo, with a slight dose-ordering to the trend. In the younger sub-group (6-11 months) the children on Flovent grew more, particularly in the FP44 group. Investigation of treatment-by-gender showed no clear trends. Investigation of treatment-by-pretreatment with corticosteroids showed a trend for patients pretreated with corticosteroids. Patients pretreated with corticosteroids and treated with Flovent grew less than those on placebo. This was not seen in the no-pretreatment group. All trends were minor and not statistically significant.

Comment: The lack of a growth effect may reflect a number of factors in the study. First, it is not clear that the use of a holding chamber with mask allowed for adequate inhalation and dosing in this population, as evidenced by the lack of efficacy in this age group. Second, the natural growth rate (and consequent variability in growth rate) is higher in serially younger populations. This may obscure any growth effect from the

inhaled Flovent. Finally, 12 weeks of therapy may not be an adequate time interval in which to assess changes in growth.

Table 48. Study FMS30059, Changes in body length (mm), Growth population

Body length (mm)	Placebo n = 49		FP44 n = 48		FP88 n = 52	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Screening	49	767.0 (11.1)	47	753.3 (12.2)	51	771.2 (9.1)
Baseline	45	773.9 (11.9)	48	757.3 (11.9)	51	778.4 (9.2)
Range		539 - 906		498 - 884		555 - 881
At Week 12	49	808.1 (11.8)	48	792.8 (11.0)	51	807.7 (8.9)
Range		549 - 974		558 - 923		566 - 920
Change from baseline						
Week 1	44	4.1 (1.3)	48	5.1 (1.3)	50	3.3 (1.1)
Week 2	45	10.0 (2.2)	48	11.1 (2.6)	51	6.4 (1.2)
Week 4	44	15.2 (1.9)	46	11.6 (1.8)	48	10.2 (1.4)
Week 8	45	23.6 (2.3)	46	24.6 (3.2)	49	19.7 (1.7)
Week 12	45	32.2 (2.7)	48	35.5 (2.8)	50	29.4 (2.0)
Age 6-11 months						
Baseline	13	716.8 (8.3)	17	681.2 (15.0)	16	724.9 (8.0)
At Week 12	14	751.2 (5.5)	17	729.2 (13.7)	17	761.9 (7.8)
Change from baseline	13	33.6 (4.9)	17	48.0 (4.7)	16	36.5 (3.9)
Age 12-23 months						
Baseline	32	797.1 (14.5)	31	799.1 (10.7)	35	802.9 (10.6)
At Week 12	35	830.9 (14.7)	31	827.7 (11.0)	34	830.7 (10.8)
Change from baseline	32	31.6 (3.3)	31	28.6 (2.8)	34	26.1 (2.2)
Males						
Baseline	29	788.4 (12.0)	25	759.8 (13.7)	34	779.3 (10.6)
At Week 12	29	823.9 (12.1)	25	798.3 (11.9)	33	810.8 (10.1)
Change from baseline	26	33.0 (3.4)	25	38.4 (4.2)	33	30.4 (2.8)
Females						
Baseline	19	753.9 (22.4)	23	754.6 (20.2)	17	776.5 (18.0)
At Week 12	20	785.2 (22.3)	23	786.9 (19.1)	18	802.2 (17.4)
Change from baseline	19	31.0 (4.5)	23	32.3 (3.5)	17	27.5 (2.7)
Pre-treatment CS*						
Baseline	10	733.7 (37.1)	7	748.6 (38.2)	12	791.8 (26.2)
At Week 12	12	768.3 (33.8)	7	772.8 (39.9)	12	817.4 (26.3)
Change from baseline	10	33.1 (5.0)	7	24.2 (4.5)	12	25.6 (3.6)
No pre-treatment CS*						
Baseline	35	785.4 (10.6)	41	758.8 (12.5)	39	774.3 (9.1)
At Week 12	37	821.0 (10.6)	41	796.2 (11.1)	39	804.8 (8.5)
Change from baseline	35	31.9 (3.2)	41	37.4 (3.1)	38	30.6 (2.4)

* Pre-treatment CS was defined as treatment with CS within 8 weeks of visit 1

Source: Clinical, Study FMS30059, Tables 15.29 to 15.38, pages 1548-65; fms30059.pdf

Table 49. Study FMS30059, Estimated growth velocity, Growth and ITT populations

Estimated growth rate (mm/12 weeks)	Placebo	FP44	FP88
Growth population	n = 49	n = 48	n = 52
Mean (SD)	28.5 (14.64)	33.4 (18.42)	29.9 (15.00)
Range	1.0 - 78.8	-1.4 - 107.8	1.8 - 71.2
LS mean (SE)	26.79 (3.30)	30.50 (3.59)	26.83 (3.66)
LS mean difference		3.710	0.041
P-value vs placebo		0.219	0.989
95% CI		(-2.23, 9.65)	(-5.83, 5.91)
ITT population	n = 69	n = 73	n = 69
Mean (SD)	30.1 (18.50)	25.1 (26.74)	31.0 (25.66)
LS mean (SE)	30.97 (3.80)	26.90 (3.98)	31.03 (4.19)
LS mean difference		-4.073	0.060
P-value vs placebo		0.294	0.988
95% CI		(-11.71, 3.56)	(-7.71, 7.83)

P- values based on analysis of covariance (ANCOVA) adjusting for baseline value, region, age group, sex, pre- treatment steroid use, family history of asthma, weight, and subject history of allergies.

Source: Clinical, Study FMS30059, Table 15.30 and 15.32, pages 1550 and 1553; fms30059.pdf

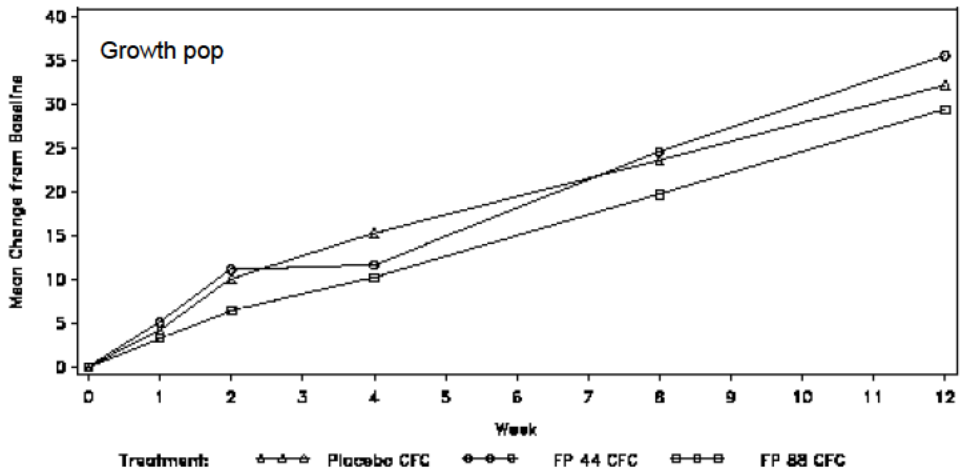

Figure 21. Study FMS30059, Mean change in body length, Growth population

Source: Clinical, Study FMS30059, Figure 15.1, page 941; fms30059.pdf

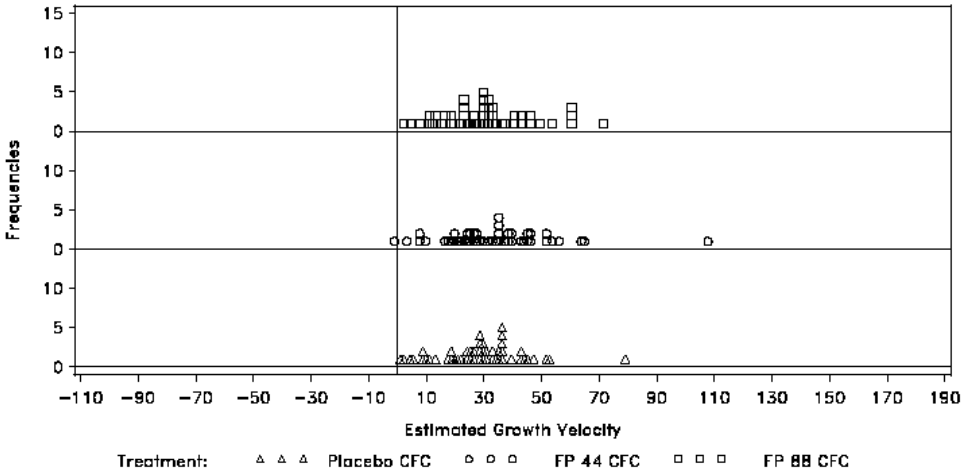

Figure 22. Study FMS30059, Histogram of estimated growth velocity, Growth pop

Source: Clinical, Study FMS30059, Figure 15.2, page 942; fms30059.pdf

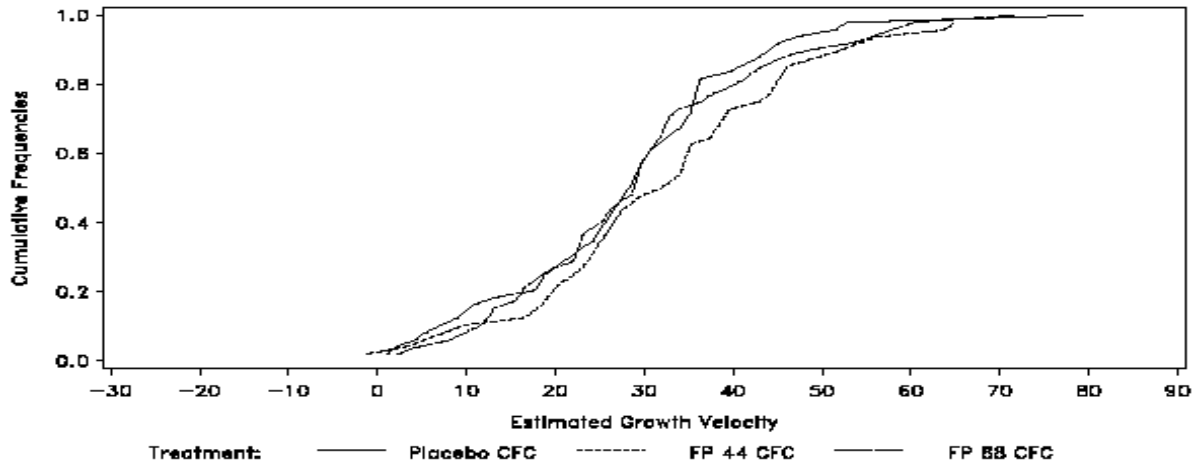

Figure 23. Study FMS30059, Empirical CDF of the estimated growth velocity, Growth pop

Source: Submission of 5/19/03, Clinical, FMS30059 graphs, Figure 15.3, page 1; fms30059graphs.pdf

12.2.3.3.6. Urinary cortisol

The 12-hour overnight urinary cortisol excretion (mcg/12hr) was calculated by multiplying the total volume of urine in (dL) by the concentration of urinary cortisol. The urinary cortisol population was defined as those subjects from the ITT population whose urine samples were considered to have no confounding factors that would affect the interpretation of the results.

The urinary cortisol data for the urinary Cortisol population (including sub-group analyses) are summarized at baseline, at the end of the study (Week 12), and for the change from baseline in Table 50. Sub-group analyses by age and pretreatment with corticosteroids were performed, but a gender analysis was not performed. A histogram of the individual patient 12-hour urinary cortisol excretions is shown in Figure 24. Figure 25 illustrates the

distribution of the change from baseline to endpoint in 12-hour overnight cortisol via an empirical cumulative distribution function (cumulative frequencies of change from baseline in urinary cortisol) for each treatment group.

Urinary cortisol analyses had too few patients to have meaningful results, and the data are shown for completeness only.

Table 50. Study FMS30059, 12-hour urine cortisol excretion, Cortisol population

12-hour urinary cortisol	Placebo	FP44	FP88
	Mean, (SD) (Range)	Mean, (SD) (Range)	Mean, (SD) (Range)
Cortisol population	n = 7	n = 3	n = 5
Baseline	1.2 (1.64) (0.2 – 4.9)	2.0 (1.85) (0.4 – 4.0)	1.4 (2.07) (0.2 – 5.1)
Week 12	2.3 (2.83) (0.2 – 7.7)	4.2 (1.56) (0.7 – 8.2)	1.2 (1.67) (0.2 – 4.2)
Change to Week 12	1.1 (2.57) (-0.6 – 6.7)	2.2 (1.95) (0.3 – 4.2)	-0.2 (0.57) (-0.9 – 0.4)

Source: Clinical, Study FMS30059, Table 15.39, page 1993; fms30059.pdf

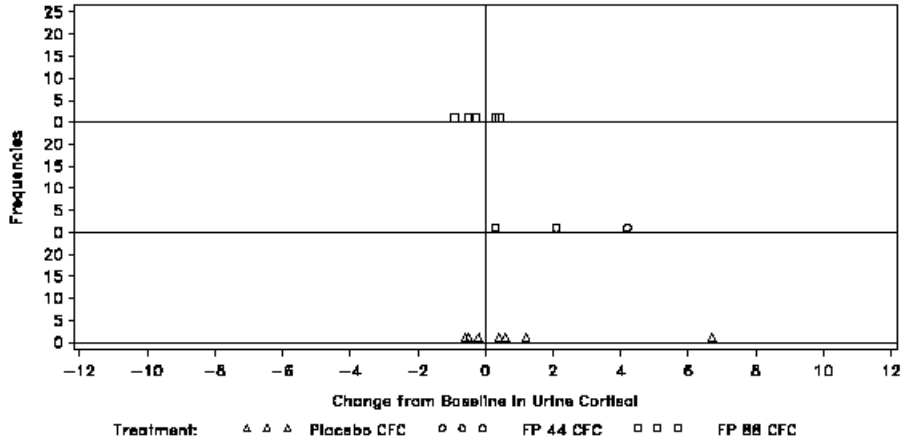

Figure 24. Study FMS30059, Histogram of individual patient 12-hour urine cortisol excretion by treatment, Cortisol population

Source: Clinical, Study FMS30059, Figure 15.8, page 948; fms30059.pdf

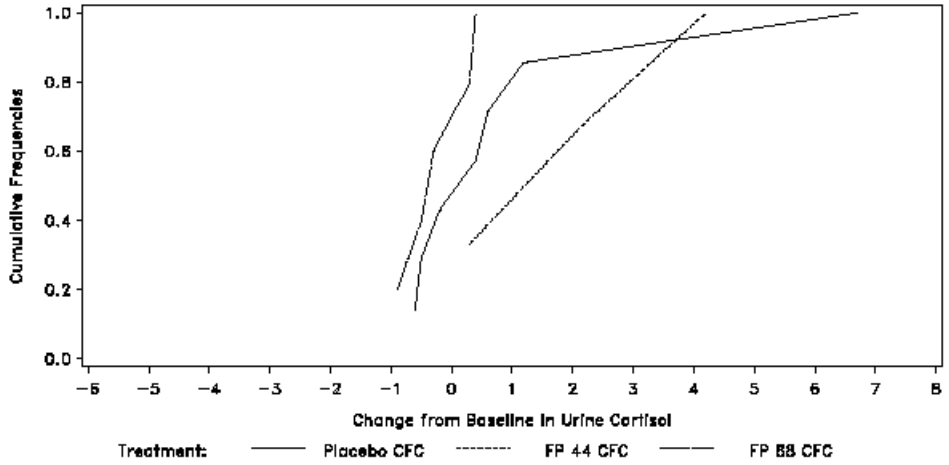

Figure 25. Study FMS30059, Cumulative frequencies of change from baseline in 12-hour urine cortisol excretion, Cortisol population

Source: Submission of 5/19/03, Clinical, FMS30059 graphs, Figure 15.9, page 949; fms30059graphs.pdf

12.2.3.3.7. Nasal and oropharyngeal examinations and cultures

Physical examinations included clinical findings of candidiasis by examination of the oropharynx and nasal passage as well as fungal cultures of the oropharynx and nose at screening and at Week 12 or discontinuation. Results of the oropharyngeal and nasopharyngeal examination and/or culture positive for Candida at the beginning and end of the study are shown in Table 51. While the numbers of patients who were exam or culture positive increased in all groups, the incidence increased more in the FP88 than the other treatment groups. No trends were noted for sub-groups by holding chamber, age, or pre-treatment with corticosteroids (results not shown) [Submission of 4/22/2003, FMS30059 Tables, Tables 15.52 and 15.53, pages 1-10; fms30059tables.pdf]

Shift tables for changes in oropharyngeal or nasal passage exams (not shown) or cultures (Table 52) confirmed that there were more patients who shifted from negative to positive in oropharyngeal cultures in the FP88 than in the other treatment groups. This trend was not seen for nasal passage cultures. Breakdown by sub-group (results not shown) revealed a slightly higher incidence in shift to a positive oropharyngeal culture for Candida in the no-pre-treatment CS FP88 group [Submission of 4/22/2003, FMS30059 Tables, Tables 15.48 to 49a, pages 11-30; fms30059tables.pdf].

Table 51. Study FMS30059, Exam and/or culture positive results for Candida, ITT pop

Exam and/or culture positive for Candida	Placebo				FP44				FP88			
	E+ C-	E- C+	E+ C+	E+ or C+ n (%)	E+ C-	E- C+	E+ C+	E+ or C+ n (%)	E+ C-	E- C+	E+ C+	E+ or C+ n (%)
Oropharyngx	n = 67				n = 61				n = 59			
Baseline	0	35	0	35 (52)	0	29	0	29 (44)	0	28	0	28 (47)
Week 12	0	38	1	39 (58)	0	31	1	32 (52)	0	39	0	39 (66)
Change	0	3	1	4	0	2	1	3	0	11	0	11
Nasal passage	n = 66				n = 61				n = 59			
Baseline	0	2	0	2 (3)	0	6	0	6 (10)	0	3	0	3 (5)
Week 12	0	2	0	2 (3)	0	2	1	3 (5)	0	4	0	4 (7)
Change	0	0	0	0	0	-4	1	-3	0	1	0	1

Source: Submission of 4/22/2003, FMS30059 Tables, Tables 15.45, 15.46, pages 1, 6; fms30059tables.pdf

Table 52. Study FMS30059, Shifts in culture positive results for Candida, ITT pop

Culture positive for Candida	Placebo	FP44	FP88
Oropharyngx	67	61	59
Remains negative	22 (33)	24 (39)	16 (27)
Negative to positive	10 (15)	8 (13)	15 (25)
Positive to negative	6 (9)	5 (8)	4 (7)
Remains positive	29 (43)	24 (39)	24 (41)
Nasal passage	66	61	59
Remains negative	62 (94)	52 (85)	53 (90)
Negative to positive	2 (3)	3 (5)	3 (5)
Positive to negative	2 (3)	6 (10)	2 (3)
Remains positive	0	0	1 (2)

Source: Submission of 4/22/2003, FMS30059 Tables, Tables 15.48, 15.49, pages 11, 21; fms30059tables.pdf

12.2.3.3.8. Vital signs and Physical examinations

Shift tables for vital signs (systolic and diastolic BP and HR), and physical examinations were examined. There were no trends noted. [Source: Clinical, Study FMS30059, Table 15.51, pages 1686-1700 and Table 15.53, pages 1773-8; fms30059.pdf]

12.2.3.3.9. Laboratory Adverse Events

Laboratory shift tables were reviewed. The only minor trend noted in laboratory shifts for hematology parameters was a more frequent shift to high in WBC (6% placebo, 11% FP44, 20% FP88) for the Flovent treatment groups. Shifts for hepatic function tests were roughly comparable for the Flovent treatment groups, while the placebo group experienced more shifts to high in AST (16% placebo, 11% FP44, 10% FP88) and Alk Phos (20% placebo, 11% FP44, 6% FP88). Shifts to abnormally high glucose values occurred at a comparable frequency across treatment groups (5% placebo, 7% FP44, 2% FP88). [Clinical, Study FMS30059, pages 83-7 and Tables 15.24, page 1392-9; fms30059.pdf]

Hematology values outside the threshold range were generally comparable between treatment groups. Clinical chemistry values outside the threshold range were infrequent and generally comparable between treatment groups. [Clinical, Study FMS30059, page 87-9; fms30059.pdf]

12.2.3.3.10. Medical device incidents or malfunctions

There were no incidents, near incidents or malfunctions reported with the use of the medical device(s) manufactured or marketed, by GSK or by a third party for GSK. [Clinical, Study FMS30059, page 99; fms30059.pdf]

12.2.4. Discussion

In study FMS30059, 80 outpatient centers were planned, 71 centers participated, and 54 centers enrolled patients (range 1 to 17 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. 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.

The demonstration of efficacy of asthma drugs in young children is problematic. This is likely due to assay sensitivity, although in this study there are also issues regarding how much drug is inhaled via a holding chamber. There are no simply applied techniques for evaluating pulmonary functions in young children. Studies seeking to evaluate asthma endpoints in younger children must rely on parental/guardian evaluations of the child's status. It is well known that patients (both children and adults) may be experiencing

significant reductions in pulmonary function without demonstrating much symptomatology. It is likely, therefore, that assay sensitivity for the primary efficacy variable that was chosen for this study was quite low.

While several studies have demonstrated clinical efficacy for asthma drugs administered to young children via a holding chamber with face mask, studies have also demonstrated that there are significant differences in delivered doses depending upon physical properties as well as the timing of use of the holding chamber/MDI combination. Such physical properties include whether the device has been washed, how it has been washed, and how it has been dried. (b) (4) The timing of the puff in relation to the placement of the mask over the nose and mouth of the patient and how long the mask is kept in place (either by time or by respiratory cycles) are also thought to affect dose delivery. (b) (4)

The primary efficacy measure was the mean change from baseline in parent/guardian-assessed daily asthma symptom scores during the last two weeks of participation in the study. At baseline, daily asthma symptom scores for the RITT population were comparable for the FP88 and placebo groups, but the baseline score for the FP44 group was lower than the other groups. In the first five weeks, the reduction in asthma symptom scores for the FP88 group was higher than the placebo group. After week six, any difference between these two groups disappeared, and the reduction in asthma symptom scores for the FP88 and placebo groups were comparable. Both of these treatment groups improved more than the FP44 group, which improved to about the same endpoint score as the other groups, but started with a lower baseline score. None of the differences between groups were significant.

The results for secondary endpoints were consistent with the primary efficacy results. Improvements in secondary endpoints including the percentage of symptom-free days, symptom- & albuterol-free days, daytime asthma symptoms, and nighttime asthma symptoms were comparable among treatment groups. The number of patients who experienced an asthma exacerbation over the 12 week treatment period was lower in the FP88 group (n = 6) than in either the FP44 or placebo groups (n=14 and n=10, respectively). The FP88 group had a greater probability of not experiencing an asthma exacerbation (time to treatment failure) compared with those receiving FP44 or placebo. The difference versus placebo was not inferentially significant (p=0.165, FP88 vs placebo). All treatment groups experienced mean reductions in daily rescue albuterol use.

Subgroup analyses included analysis by age group and pre-treatment with corticosteroids. Subgroup analysis by age group showed no clear pattern, except that FP44 consistently showed less reduction in symptom scores than placebo. However, there were markedly different results between the two FP88 age sub-groups. In the older age sub-group of 12-23 months, the placebo treatment group showed greatest reduction in symptom scores, and the FP88 treatment group was comparable to the FP44 group. In the younger age sub-group of

6-11 months, the FP88 treatment group showed a greater reduction in symptom scores than either placebo or FP44, and placebo showed a greater reduction than FP44. The difference appears to be that FP44 showed less reduction in symptom scores in the younger age group than in the older age group.

Subgroup analysis by pre-treatment with corticosteroids showed results relatively consistent with the full RITT population, except that for the FP44 sub-group there was a marked difference in results based on whether patients had been pre-treated with corticosteroids. For patients who had pre-treatment with corticosteroids, the FP44 group showed a reduction in symptom scores comparable to the other two treatment groups. For patients who had no pre-treatment with corticosteroids, the FP44 group did not show a reduction in symptom scores comparable to the other two treatment groups, and the results were consistent with those for the full RITT population.

The extent of exposure, as measured by diary responses, was comparable between groups. There were no deaths, but there were four SAEs reported by three patients during treatment, and three SAEs reported by two patients during the follow-up period, but none of the events were judged by the investigator to be related to study drug. There were no incidents, near incidents or malfunctions reported with the use of the medical device(s) manufactured or marketed, by GSK or by a third party for GSK. Shift tables for vital signs (systolic and diastolic BP and HR), physical examinations, and laboratory values showed no trends.

A total of 196 patients (93%) reported at least one AE during treatment (62 [90%] placebo, 68 [93%] FP44, and 66 [96%] FP88). There was a trend toward higher incidences of both upper respiratory tract infections (URTI) (21 [30%] placebo, 27 [37%] FP44, and 18 [26%] FP88) and ear, nose & throat infections (18 [26%] placebo, 30 [41%] FP44, and 15 [22%] FP88) in the FP44 group than in either the placebo or FP88 groups. During the course of the study the patients enrolled in the FP44 group just happened to become more ill with upper respiratory related infections than the placebo of FP88 groups. This increased incidence of illness may well explain the reduced efficacy of FP44 compared to placebo or FP88 seen in this study. Unlike study FMS30058, there was no trend to higher incidence of candidiasis of the mouth/throat (3 [4%] placebo, 3 [4%] FP44, and 4 [6%] FP88), however the FP88 group had a slightly higher incidence of candidiasis of the skin than the other two groups (1 [1%] placebo, 0 FP44, and 3 [4%] FP88). No rebound trends were noted during the follow-up period after stopping study drugs, except that the FP44 group continued to have a higher incidence of URTI and ENT infections than the other groups.

Evaluation of adverse events by age groups showed that the type and frequency of adverse events reported by subgroups were generally comparable. Evaluation of adverse events by previous CS therapy (any corticosteroids within 8 weeks of Visit 1) showed that the trend toward higher incidence of URT and ENT infections spanned the two sub-groups. Just as for study FMS30058, most instances of candidiasis of the mouth/throat occurred in the group that had not received previous CS therapy. Evaluation of adverse events by gender showed a comparable incidence of overall reported AEs in male and female placebo sub-groups (females: 92% placebo, 97% FP44, 96% FP88; males: 88% placebo, 90% FP44, 96% FP88).

Despite the fact that the number of reported AEs for oral or nasal candidiasis was not higher in the Flovent treatment groups, the numbers of patients who were exam or culture positive

increased in all groups, and the incidence increased more in the FP88 than the other treatment groups. The FP88 treatment group also had a higher incidence in shift to a positive oropharyngeal culture for Candida.

The urine cortisol population included 7 placebo, 3 FP44, and 3 FP88 patients. Urinary cortisol analyses had too few patients to have meaningful results.

The growth population included 49 placebo, 48 FP44, and 52 FP88 patients. Unlike the growth velocity estimates in study FMS30058, the estimates in this study did not show a trend toward dose-dependent reduction in growth velocity. Growth velocities for the Growth population were 28.5 mm/12 weeks for placebo, 33.4 mm/12 weeks for FP44, and 29.9 mm/12 weeks for FP88. Patients on FP44 grew more than patients on placebo, while patients on FP88 grew slightly less. None of the differences in growth velocity between active drug and placebo groups were statistically significant.

These growth results are surprising, given the 'presumptive positive' (although not statistically significant) growth results in study FMS30058. The lack of a growth effect may reflect a number of factors in the study. First, it is not clear that the use of a holding chamber with mask allowed for adequate inhalation and dosing in this population, as evidenced by the lack of efficacy in this age group. Second, the natural growth rate (and consequent variability in growth rate) is higher in serially younger populations. This may obscure any growth effect from the inhaled Flovent. Finally, 12 weeks of therapy may not be an adequate time interval in which to assess changes in growth.

Note: Because of the results outlined above, of concern is how much drug the patients actually received. GSK's report of the PK results revealed that in this study three patients (at two sites) who were randomized to placebo had detectable levels of FP at the 12 week visit. Please refer to Section 5.3 (Data Quality and Integrity) on page 27 for an in-depth discussion of the Data Quality and Integrity issue and the implications for interpretation of the data.

(b) (4)

Treatment with Flovent did not demonstrate superior efficacy compared to placebo for either the primary or secondary endpoints. Improvements from baseline were observed for all efficacy parameters across all three treatment groups. Both of the FP88 and placebo treatment groups improved more than the FP44 group, which improved to about the same endpoint score as the other groups, but started with a lower baseline score. None of the differences between groups were significant.

Just as for the efficacy results, the safety results for this study are difficult to interpret, and do not show any clear trends. Overall, the types and frequency of adverse events were comparable, except that more patients in the FP4 treatment groups developed upper respiratory and ear, nose and throat infections than the other two treatment groups. Combined with the lower baseline asthma symptom score, this increased incidence of illness may explain the reduced efficacy of FP44 compared to placebo or FP88 seen in this study. Unlike study FMS30058, there was no difference in clinical reports of candidiasis between placebo and the active treatment groups. However, more patients in the FP 88 CFC group developed positive *Candida* oropharyngeal cultures. (b) (4)

(b) (4)

12.2.5. Conclusions

Interpretation of the efficacy results for this study would normally be tempered by an awareness of difficulties with assay sensitivity (using parent/guardian assessments) and dose delivery through an MDI/holding chamber combination with a facemask. Putting the Data Quality and Integrity issue aside for a moment, there are a number of possible implications from the data. (b) (4)

Of most significance for this study is the Data Quality and Integrity issue arising as a result of the PK measurements that found detectable FP levels in 3 patients assigned to placebo treatment. This issue totally confuses what dose was delivered to which patient, and make any meaningful interpretation of the efficacy results from this study impossible at this time.

The reader is cautioned that the results do not support or imply that either the FP44 or the FP88 dose is the appropriate dose for use in children in this age range. In this age range, these dosages may (or may not) be efficacious, and may (or may not) be associated with potential for systemic effects. If a clinician chooses to use this drug off-label in children below 12 years of age, the dose should be titrated to the lowest dose that appears to provide efficacy for that child, and the child should be monitored for signs and symptoms of systemic corticosteroid effects.

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