CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-433

MEDICAL REVIEW(S)

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

APPLICATION:	NDA 21-433	TRADE NAME:	Flovent® HFA
APPLICANT:	GlaxoSmithKline	USAN NAME:	Fluticasone propionate
MEDICAL OFFICER:	N/A		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	CATEGORY:	Corticosteroid
DUE DATE:	May 14, 2004	ROUTE:	Oral Inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
November 13, 2003	Electronic		Complete response to AE letter of December 27, 2002
April 2, 2004	Electronic		Updated labeling
April 29, 2004	Electronic	Safety Update	

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY: This is GSK's complete response to the Division's approvable letter of December 27, 2002.

In one of the long-term safety studies [FLTB3048], subjects were allowed to use spacers if they were using them prior to enrollment. In the NDA submission, the safety data for the subjects who used spacers were not analyzed separately from non spacer users in the ISS. In the approvable letter, the sponsor was asked to reanalyze the safety data from that study and separate the spacer users from the non-spacer users and resubmit an ISS excluding subjects who used spacers. In the AE letter preliminary labeling comments were also sent to the Applicant. GSK has satisfactorily addressed the Division's clinical comments in the complete response.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	___	FILEABLE	___	NOT FILEABLE	
	X	APPROVAL	___	APPROVABLE	___ NOT APPROVABLE
OTHER ACTION:	___		___		___

Background

GSK submitted an NDA for fluticasone propionate inhalation aerosol propelled by HFA-134a (Flovent HFA) on February 26, 2002 for the maintenance treatment of asthma. The clinical trials established efficacy of the three dosage strengths submitted in the NDA - Flovent ® HFA 44 mcg, 110 mcg and 220 mcg with an acceptable safety profile. The application was given an approvable action because of CMC deficiencies.

The development program consisted of 3 efficacy and safety studies and two long-term safety studies. The 3 efficacy studies were:

- Study FAP30007 - a placebo-controlled study with a 12-week treatment period in patients previously maintained on inhaled corticosteroids.
- Study FAP30008 - a placebo-controlled study with a 12-week treatment period in patients previously on bronchodilator therapy alone and
- Study FLTA3022 - a 16-week efficacy and safety study in patients previously maintained on oral corticosteroids.

The 2 long term safety studies were study FAP30001 and study FLTB3048. Study FAP30001 evaluated the safety of FP HFA 220 mcg BID (2x 110 BID) and FP HFA 440 mcg BID (2x 220 BID) over 6 months and was conducted in the U.S. Subjects enrolled in this study were prohibited from using a spacer during the trial. Study- FLTB3048 conducted in the U.K. evaluated the safety of FP HFA 440 mcg BID (2x 220 BID) and FP HFA 440 mcg BID (2x220 BID) over 12 months of treatment. In FLTB3048, the use of a spacer device for delivery of study medication was allowed if the subject had been using a spacer before. If spacer use was desired, subjects were provided with an [redacted]. Spacer and instructed to use it consistently during the study. Subjects could not discontinue spacer use during the study once they were started, neither could they change spacer devices during the study. In the NDA submission, the safety data of the subjects who used spacers were not analyzed separately from non spacer users in the ISS. In the approvable letter, the sponsor was asked to reanalyze the safety data from that study and separate the spacer users from the non-spacer users and resubmit an ISS excluding subjects who used spacers. In the AE letter preliminary labeling comments were also sent to the sponsor.

On November 13, 2003, GSK submitted a complete response to the AE letter of December 27, 2002. The clinical comments from the AE letter are stated or paraphrased below in italics followed by a review of the applicant's response.

Clinical Comment # 21
For study FLTB3048, present the safety data (including the cortisol data) from subjects using spacers separately form the non-spacer users. Resubmit an ISS excluding spacer users.

Clinical Comment # 22
The Division provided preliminary labeling changes to the Applicant.

GSK's Response:
The company submitted the requested reanalysis of the ISS and responded to the labeling comments in the revised label.

REVISED ISS
The population for the revised summaries was named the ITT Population Excluding Spacer Users. The resubmitted ISS contains a reanalysis of the safety data including morning serum cortisol concentration and biochemical markers of bone metabolism from the subjects in two long term studies who were not using spacers. No other modifications from the original ISS submitted to the Agency on February 26, 2002 have been made. The Applicant refers to the population excluding subjects who used spacers as the ITT population Excluding Spacer Users to distinguish them from the ITT population that included all the patients.

The total number of subjects excluding spacer users treated in the two long term studies was 379 as depicted in the table below

Subjects Treated in Long-term Studies – Excluding Spacer Users (FAP30001 and FLTB3048)

Study # (n = randomized)	HFA dose BID		CFC dose BID	Total
	FP220	FP440	FP440	
FAP30001 (n =182)	89	93	---	182
FLTB3048 (n=325)	---	96	101	197
Total				379

Of these subjects, 72 (81%) in the FP 220 HFA group, 159 (84%) in the FP 440 HFA group, and 94 (93%) in the FP 440 CFC group completed the study. The percentage of subjects completing the study in the ITT population [including spacer users] was similar (81, 84, and 90% respectively) and the extent of exposure ($\geq$ 81% of subjects for $\geq$6 months) was similar for both populations.

Long-term treatment effects (re-analysis with the exclusion of all subjects who used a spacer device during treatment in the FLTB3048 study)

Demographics
A total of 507 subjects participated in the long term-safety studies FAP30001 and FAP3048 and of these 379 did not use spacers. The results of the demographic characteristics for the ITT population Excluding Spacer Users were similar for the ITT population. Most of the subjects (>90%) were Caucasian, of similar age range and approximately half the subjects were female.

Adverse Events
To account for differences in the study design, as well as to provide an estimate of adverse events that occurred over time, adverse events that occurred during the first 6 months of treatment in the ITT population and the ITT Population Excluding Spacer

Users were compared with those that occurred during the last 6 months of treatment. The adverse events reported for the long-term safety studies for months 0 – 12 were consistent between the two populations except for an increase in upper respiratory infections in the FP 440 CFC Population Excluding Spacer Users (51%) compared to the ITT population (42%). This difference was not noted when the results for the 0 -6 months AEs were analyzed separately. Adverse events were most frequently reported in the ear, nose and throat, lower respiratory, neurological, gastrointestinal, and musculoskeletal system for both the ITT Population and the ITT Population Excluding Spacer Users in comparable frequency.

With respect to age, race, and sex, the AE profile for the long-term safety studies were the same for the ITT Population and the ITT Population Excluding Spacer Users.

When adverse events of interest (i.e. AEs that may be corticosteroid-related) were reviewed there was a slight increase in throat irritation in the 0 -6 month time frame for the FP 440 HFA and CFC groups in ITT Population excluding Spacer Users compared to the ITT Population. This difference was not appreciated at the 7 – 12 month time frame. Other than these differences, the overall AE profile was similar for the two populations displayed in the tables below.

Adverse Events of Interest ITT Population (FAP30001 and FLTB3048)

Adverse Event	0 – 6 months			7 -12 month	
	FP 220 HFA N = 89 N (%)	FP 440 HFA N = 256 N (%)	FP 440 CFC N = 162 N (%)	FP 440 HFA N = 151 N (%)	FP 440 CFC N =154 N (%)
Any Event	76 (85)	214 (84)	142 (88)	127 (84)	139 (90)
Ear Nose and Throat					
Throat irritation	9 (10)	33 (13)	15 (9)	18 (12)	11 (7)
Hoarseness/dysphonia	4 (4)	19 (7)	11 (7)	9 (6)	5 (3)
Pharyngitis/infection	2 (2)	8 (3)	11 (7)	5 (3)	7 (5)
Fungal infection mouth &throat	0	1 (<1)	0	1 (<1)	0
Lower Respiratory					
Cough	2(2)	18 (7)	14 (9)	14 (9)	11 (7)
Candidiasis					
Candidiasis mouth/throat	2 (2)	16 (6)	9 (6)	2 (1)	4 (3)
Candidiasis unspecified site	0	7(3)	7 (4)	4 (3)	4 (3)
Musculoskeletal					
Musculoskeletal Pain	6 (7)	28 (11)	13 (8)	16 (11)	15 (10)
Muscle cramps and spasm	1 (1)	4 (2)	2 (1)	0	1 (<1)

Adverse Events of Interest ITT Population Excluding Spacer Users FAP30001 and FLTB3048

Adverse Event	0 – 6 months			7 -12 month	
	FP 220	FP 440 HFA	FP 440 CFC	FP 440	FP 440 CFC

	HFA N = 89 N (%)	N =189 N (%)	N = 101 N (%)	HFA N =93 N (%)	N =96 N (%)
Any Event	76 (85)	157 (83)	87 (86)	75 (81)	88 (92)
Ear Nose and Throat					
Throat irritation	9 (10)	28 (15)	12 (12)	12 (13)	8 (8)
Hoarseness/dysphonia	4 (4)	18 (10)	4 (4)	4 (4)	4 (4)
Pharyngitis/infection	2 (2)	4 (2)	2 (2)	1 (1)	4 (4)
Fungal infection mouth & throat	0	1 (<1)	0	0	0
Lower Respiratory					
Cough	2(2)	12 (6)	9 (9)	5 (5)	9 (9)
Candidiasis					
Candidiasis mouth/throat	2 (2)	12(6)	6 (6)	1 (1)	2 (2
Candidiasis unspecified site	0	6 (3)	7 (7)	2 2	4 (4
Musculoskeletal					
Musculoskeletal Pain	6 (7)	20 (11)	6 (6)	10 (11)	9 (9)
Muscle cramps and spasm	1 (1)	3 (2)	2 (2)	0	1 (1)

In summary, overall, the incidence of subjects with predictable AEs of interest was consistent between the ITT Population and the ITT Population Excluding Spacer Users.

Eosinophilic Conditions

No subjects in the ITT Population Excluding Spacer Users experienced a hypereosinophilic illness. A total of 8 subjects in the ITT Population had AEs associated with elevated eosinophils. The adverse events were: the flu (1), viral respiratory infections (2), pharyngitis/throat infection (3), fungal skin infections (tinea pedis) (1), neuritis (1) and soft tissue injuries/insect sting (1). The cases of pharyngitis/throat infection and the viral respiratory infections cannot be ruled out as not drug-related.

Deaths and Serious Events

There were no deaths in the long term studies. The percentage of subjects who experienced a SAE was the same in the ITT Population [23/507 (5%)] as compared to the ITT Population Excluding Spacer Users [20 /379 (5%)]. One non-spacer using subject experience a spontaneous abortion that was reported as a serious adverse event in the post-treatment period. The association of this event to the study drug is unclear.

Withdrawals due to AEs and AEs with >3% incidence

Five (5) and four (4) percent of subjects in the ITT Population and the ITT Population Excluding Spacer Users respectively, withdrew from the study due to an AE. The Incidence of Adverse Events >3% regardless of relationship to study drug were similar between the ITT Population and the ITT Population excluding Spacer Users.

HPA Axis Effects

As described in the Medical Officer Review, the sponsor defined a Urine Cortisol Population comprised of subjects from the randomized population who had adequate urine volume collections and met criteria to allow for an assessment of the urine cortisol data. Mean urinary cortisol excretion values declined relative to baseline in both the population that included the spacer users and the population that excluded spacer users. In both populations, the decline in mean urinary cortisol was greatest in the FP 440 group. When data from the subjects using a spacer were compared to the data from the subjects not using a spacer the decline in urinary cortisol was numerically greater in the population not using a spacer. The tables below show the results for the FP 440 HFA and CFC. Note that the reduction from baseline in urinary cortisol with the CFC product is greater than for the HFA product. The data are extremely variable and more so for the CFC group and should be interpreted with caution. Nevertheless the results are consistent with the PK comparative data for Flovent CFC and Flovent HFA which showed that the systemic exposure to FP is higher with the CFC formulation compared to the HFA formulation *(See biopharmaceutics Officer Review).*

Mean 24-hour Urine Cortisol Excretion rates (mcg/24 hours) Urine cortisol population Excluding Spacer Users (Studies FAP30001, FLTB3048)

Timepoint	***FP 220 HFA N=60**	**FP 440 HFA N=101**		**FP 440 CFC N=35**	
		Spacer user	**Non-spacer users**	**Spacer users**	**Non-spacer users**
Baseline	24 .05 (13.06)	26.75 (23.99)	28.84 (25.52)	27.45 (25.49)	31.36 (30.94)
Month 6	21.89 (13.45)	21.92 (12.45)	22.77 (12.78)	20.34 (17.40)	18.71 (12.70)
Month 12	-----	22.12 (12.84)	23.49 (13.55)	28.56 (69.47)	34.85 (89.48)
* Study FAP30001 only where Spacers were not permitted					

SAFETY UPDATE

GSK submitted a safety update with their complete response that provided updated safety information from March 1, 2002 (the day after the cut-off data for the 120-Safety Update to the original NDA submission) through August 31, 2003. GSK also submitted a safety update on April 29, 2004 with updated safety information from September 1, 2003 through February 29, 2004. During these two reporting periods, no controlled US clinical studies with FP HFA in adolescents or adults 12 years of age and older were completed, or ongoing. During this last reporting period, GSK completed a safety and efficacy study in children 4 to 11 years of age with asthma (study FAP30010) and has one ongoing safety and efficacy study in children 1 to < 4years of age as part of their pediatric development program. There have been no deaths reported in any of the clinical studies using FP HFA. The adverse events reported in the completed pediatric study (FAP30010) were primarily in the Ear, Nose and Throat body system and included throat irritation, nasal

congestion/blockage, pharyngitis and sinusitis. These events do not raise any new safety concerns.

As of February 29, 2004, Fluticasone propionate inhalation aerosol propelled by HFA-134a has not been withdrawn from marketing for any reason related to safety or effectiveness. Currently, fluticasone propionate inhalation aerosol propelled by HFA-134a is marketed in several countries including Canada.

Summary/Conclusions

GSK presented the safety data for the subjects who used spacers separately from the non-spacer users as requested by the Agency. Analyzing the data in this fashion did not change the safety profile of the safety data as reviewed when the data were analyzed together and does not affect the approvability of the product from a clinical standpoint.

Labeling

Marked up labeling changes are provided in the label submitted by the sponsor. GSK has responded satisfactorily to the preliminary general labeling comments in the AE letter of December 27, 2002. Additional labeling comments/changes will be sent to the sponsor. One major labeling change would be the deletion of statements relating to a — claim cited in the CLINICAL PHARMACOLOGY section Mechanism of Action subsection, the DOSAGE and ADMINISTRATION section, and the Information for Patients section. Of note, the currently approved label for Flovent Inhalation Aerosol has similar language but the studies were not designed to demonstrate this claim and it should not be allowed in the label

Recommendation

Approval with labeling changes.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lydia McClain
5/10/04 10:22:53 AM
MEDICAL OFFICER

MEDICAL TEAM LEADER REVIEW

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

APPLICATION #:	NDA #21-433	APPLICATION TYPE:	Original NDA
SPONSOR:	GlaxoSmithKline	PRODUCT/PROPRIETARY NAME:	Flovent HFA Inhalation Aerosol
INDICATION:	Asthma	USAN / Established Name:	Fluticasone propionate
CATEGORY OF DRUG:	Corticosteroid	ROUTE OF ADMINISTRATION:	Orally inhaled
MEDICAL REVIEWER:	Purucker	REVIEW DATE:	20 December 2002

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	Document ID #:	Submission type/Comments:
26 February 2002	N 21 433 000	"Switch" program for replacement of Flovent CFC in all 3 strengths: 44, 110, 220 mcg/actuation; For the maintenance treatment of asthma in adults and adolescents ≥ 12 years.

RELATED APPLICATIONS

Document Date:	Document ID #:	Comments:
18 June 1997	IND 53,502 NDA 20-548	IND for Flovent HFA under which studies conducted
29 December 1994		Flovent CFC approved 27 March 1996

Overview of Application/Review In general, data provided in NDA 21-433 for Flovent HFA Inhalation Aerosol (MDI) is convincing of the efficacy of the new drug product compared to placebo in adults and adolescents age ≥ 12 years at all strengths tested. With regard to safety, there were no unique or unexpected findings specific to this formulation that might impact on drug product approvability. There are relatively minor issues in product labeling that will require re-analysis of existing data or a pharmacokinetic link to an approved Flovent product:

- The applicant has not supported the efficacy or risk benefit ratio of Flovent HFA at 880 mcg BID, and this dose should be removed from Table 3 of the DOSAGE AND INDICATIONS section of the product labeling.
- The HPA axis data is poorly collected, presented, and analyzed. A reanalysis should be considered, in which all urinary cortisol collections judged to be incomplete by reasonable physiologic standards are omitted. Alternatively, the sponsor should provide a more robust PK link to an approved Flovent product (Flovent CFC, Diskus, or Diskhaler).
- The applicant should reanalyze the AE data from clinical trial FLTB3048, providing separate listings for all subjects who had used a spacer during the one-year trial compared to subjects who did not. Only subjects who were treated without use of a spacer should be counted toward fulfillment of pre-marketing human exposure as recommended by ICH guidelines. Subjects enrolled in the 6-month safety study FAP30001 may be used to bolster this number, if required.

Outstanding Issues: Minor labeling issues

Recommended Regulatory Action:

NDA: ___X___ **Approvable** _____ **Not Approvable**

Signed: **Medical Team Leader:** Mary Purucker, MD, PhD **Date:** 23 December 2002

Acting Division Director: _____ **Date:** _____

ABBREVIATIONS

BID	twice daily
CFC	Chlorofluorocarbon propellant
FEV_1	forced expiratory volume in one second
FP	fluticasone propionate
GSK	GlaxoSmithKline
HFA	Hydrofluoroalkane propellant
ICS	Inhaled Corticosteroids
ICS (+)	Subject used inhaled CS at baseline
ICS (-)	Subject did not used inhaled CS at baseline
mcg	micrograms
MDI	metered dose inhaler
PEFR	Peak Expiratory Flow Rate/peak flow

SUMMARY AND RECOMMENDATIONS

This memorandum is to document the secondary review conclusions regarding the safety and efficacy of Flovent HFA Inhalation Aerosol, NDA 21-433. The drug product is manufactured as three strengths, 44 mcg, 110 mcg, and 220 mcg, measured as the dose delivered from the actuator and is analogous to the nominal dose *ex actuator* provided by the approved Flovent CFC comparator.

In general, the NDA for Flovent HFA has provided convincing evidence of efficacy of the new drug product compared to placebo in adults and adolescents age ≥ 12 years at all strengths tested. Similarly, there were no unique or unexpected safety findings specific to this formulation that might impact on drug product approvability.

That having been said, it should be noted that the clinical pharmacology studies submitted with this NDA demonstrated that systemic exposure for Flovent HFA was not reproducibly dose-proportional, and that there were inconsistencies between single and multiple dose studies. Overall systemic exposure compared to Flovent CFC also appeared to be lower.

Consistent with the finding of reduced systemic bioavailability, active controlled efficacy studies submitted with this NDA suggest that Flovent CFC is numerically superior to Flovent HFA on most clinical efficacy endpoints, although the difference was not consistently significant.

The applicant's data in support of the FP HFA 880 mcg BID dose is unconvincing, and reference to this dose should be removed from Table 3 in the **DOSAGE AND ADMINISTRATION** Section of the product label. It may be reasonable to mention in the text of this section that "higher doses" of Flovent HFA may be required for certain oral corticosteroid-dependent asthmatics.

There are several minor safety issues that the applicant should address, and which should not require new studies. In particular, the use of a spacer in clinical trial FLTB3048 and the poorly collected and analyzed HPA axis data from several trials. One path forward for the latter would be to provide a PK "link" to one of the better characterized approved Flovent products (Flovent Diskus, Flovent Diskhaler, data from other studies of Flovent CFC/inhalation aerosol).

In summary, from a clinical perspective, Flovent HFA inhalation aerosol is recommended for approval. The applicant should address the issues delineated in this review, which will impact on product labeling. Defining the differences between FP HFA and FP CFC will be challenging with the data at hand, but will be important for practitioners contemplating a switch to the new HFA product once the CFC formulation is no longer available.

OVERVIEW

Flovent® HFA Inhalation Aerosol is an orally inhaled presentation of the synthetic corticosteroid fluticasone propionate intended for the maintenance treatment of asthma for adults and adolescents age 12 years and older. The drug product is comprised of a pressurized canister containing the drug substance FP and the propellant HFA-134A (GR1066642X per GSK terminology) as a microcrystalline suspension. There are no emulsifiers or other excipients present in the formulation. Flovent HFA is manufactured as the same (three) nominal strengths as the Flovent CFC comparator, designated by the dose delivered *ex actuator,* 44, 110, and 220 mcg. This new drug product has been proposed as a non-CFC substitute for the approved Flovent MDI (NDA 20-548), which is planned to be phased out prior to the year 2007 in accordance with the Montreal Protocol, to which the US is a signatory. While the current NDA provides support for Flovent HFA in asthmatic subjects age 12 years and older, it should be noted that a separate pediatric program for children age 4 – 11 years is presently in phase 3 trials.

There are two other orally inhaled presentations of this moiety approved for marketing in the US, a dry powder formulation, Flovent Diskhaler (NDA 20-549; approved Nov., 1997) and a second dry powder formulation, Flovent Diskus (NDA 20-833; approved Sept., 2000). The products are similar in that the powder is contained in a double-foil blister that is opened and dispersed by patient activation and inhalation, but differ in the number of doses per device and in the overall weight of the excipients.

With regard to the inhalation aerosol formulations, it was noted that clear differences in performance characteristics between Flovent HFA and Flovent CFC could be identified relatively early in the development program. For this reason, among others, the applicant (GSK) chose to conduct a "stand-alone" program as opposed to employing a "switch" strategy. It should also be noted that the 44-mcg product was not fully developed until after the pivotal long-term safety study, FLTB3048, had been completed using the 110 and 220 mcg strengths. Although years separated completion of the pivotal safety portion of this NDA and several of the efficacy studies, discussion with the CMC reviewer Dr. Schroeder verified that the same to-be-marketed formulation was used for all studies.

EFFICACY

The pivotal placebo-controlled clinical trials submitted in support of the "stand alone" efficacy of Flovent HFA are comprised of two 12-week safety and efficacy studies in mild to moderate asthmatics and one 16-week oral corticosteroid sparing study. The two active-control 6- and 12-month studies will be discussed in the subsequent safety section (see table at end of

review for summary).

In general, the data presented in this NDA are supportive of the efficacy of Flovent HFA as maintenance therapy for treatment of asthma as BID therapy in either the ICS-naïve or the ICS-stabilized patient population. While a dose-response could not be convincingly demonstrated, each of the three strengths of Flovent HFA was statistically superior to placebo. This finding was replicated between the two trials FAP30007 and 30008. There was a numerical trend toward superior efficacy with higher doses of FP.

With regard to the oral corticosteroid sparing trial FLTA3022, active treatment was superior to placebo as measured by prednisone reduction and survival in study. Paradoxically, however, more than twice the subjects receiving the higher dose of FP HFA 880 BID withdrew from the study compared to the lower dose of FP HFA 440 BID (19% vs. 41%). The main reason for discontinuation was lack of efficacy (6% for 440 BID vs. 13% for 880 BID). With regard to the primary endpoint, while both doses of FP HFA were superior to placebo for mean daily prednisone use, FP HFA 440 BID was numerically (although not statistically) superior to FP HFA 880 BID (5.8% vs. 6.2%). With regard to safety, there were nine SAE's reported for this trial, four that occurred in the FP HFA 880 BID group compared to one each in the placebo and two in the FP CFC groups and 2 in the FP HFA group. Four of the nine SAE's lead to study withdrawal, and 3 of these were in the FP HFA 880 BID group.

In conclusion, neither the efficacy analysis nor the risk/benefit ratio support the use of FP HFA 880 mcg BID for the oral corticosteroid-sparing indication. However, the approved Flovent CFC product for inhalation carries an indication for the 880 mcg BID dosage, and it seems counter-intuitive to omit it from the reformulated product. Given the data, however, this reviewer would recommend omission of the 880 mcg BID dosage from *Table 3*, but would describe in the text that "certain oral corticosteroid-dependent" asthmatics may require higher doses to successfully reduce or eliminate oral CS.

SAFETY

The safety data for the drug substance fluticasone propionate by the inhalation route is extensive. Flovent HFA is a reformulation of a well-characterized moiety, and the safety analysis of this product ought to focus on any differences with the CFC comparator with regard to systemic bioavailability and any unique local toxicity attributable to its formulation with the novel propellant. Unfortunately, this application falls short in both categories. Specifically, the OCPB review conducted by Dr. Kofi Kumi concluded that neither PK nor PD (as measured by urinary or AM serum cortisol levels) could be shown to be dose proportional between the different HFA strengths when tested in asthmatics, and that a clear PK relationship with the comparator FP CFC could not be drawn. While not necessarily a "fatal flaw" in this program, it will be important to examine the relationship between the issues identified by the CMC reviewer and the inconsistencies noted in the Biopharm program. With regard to "PD", it will be important to document that urinary cortisol collections were complete, an issue repeatedly addressed with the applicant by Dr Gilbert-McClain, the primary medical reviewer. It is possible that several of these issues may be resolved through careful comparison of the two products on HPA axis function. Alternatively, the applicant may choose to develop a more acceptable PK relationship between Flovent HFA and one of the other approved Flovent oral inhalation product (Flovent Diskhaler, Diskus, or CFC MDI from a separate study).

One overriding issue that must be addressed is the presentation and quality of the safety data provided from the pivotal one-year safety study FLTB3048. Specifically, this trial was conducted at multiple non-US sites, and the demographic analysis supports differences in smoking habits (including recruitment of current smokers), ethnicity, availability and use of non-US baseline medication, and most importantly, the inclusion of an optional spacer to administer study drug (approximately 40%). The latter confounds the distribution between local and systemic CS adverse events, particularly for an ICS with poor oral bioavailability. The construction of an AE table for the product label will be compromised by mixing these data, and it is strongly recommended that the sponsor perform a reanalysis in which the two populations, all subjects who used a spacer during the trial and those who did not, are separately analyzed.

With regard to the AE profile defined by the pivotal 12-week trials, there appears to be no evidence supporting a substantial difference in safety between the two formulations of Flovent.

OVERALL CONCLUSIONS:
In general, I am in agreement with Dr. Gilbert-McClain's assessment of the approvability of this NDA. The applicant has provided (replicated) evidence in support of the efficacy of Flovent HFA at all three strengths and at doses of 88 mcg, 220 mcg, and 440 mcg BID. The applicant has not supported the efficacy or risk benefit ratio of Flovent HFA at 880 mcg BID, and recommendations for use of this dose should be removed from *Table 3* of the **DOSAGE AND ADMINISTRATION** SECTION of the product labeling. The requirement for higher doses of Flovent HFA for certain recalcitrant oral CS-dependent asthmatics could be discussed in the text of this section.

The applicant should provide a reanalysis of HPA axis data, omitting all urinary cortisol collections judged to be incomplete by reasonable physiologic standards. Alternatively, the applicant should provide an acceptable PK "link" to an approved Flovent product for oral inhalation.

The applicant should provide a reanalysis of AE data from clinical trial FLTB3048, separately reporting all subjects who had used a spacer during the one year study and the subjects who did not use a spacer. The impact of the spacer on delivery of study drug is unknown, but is expected to decrease local CS-related AE's and potentially increase the incidence of systemic CS-related AE's for fluticasone propionate, which has poor oral bioavailability. Only subjects not using a spacer device should be counted toward the ICH requirements for pre-marketing human exposure. To obtain adequate numbers of patients to fulfill ICH guidelines, the applicant may include safety data from subjects studied during the 6-month safety trial FAP30001.

CONTROLLED CLINICAL TRIALS FOR SAFETY AND EFFICACY: NDA 21-433 for FLOVENT HFA INHALATION AEROSOL (MDI)

Study	Population	Duration	Arms	Number Treated	1° Endpoint	Comments Effect Size
FAP30007	Adult and Adolescent ≥12 years **ICS-users**	*12 weeks*	Placebo FP HFA 44 2 puffs BID FP HFA 110 2 puffs BID FP HFA 220 2 puffs BID	104 103 106 102	Change from baseline in AM pre-dose FEV_1	Placebo = -0.260 L FP 88 = 0.100 ($p<0.001$) **0.360 L** FP 220 = 0.140 ($p<0.001$) **0.400 L** FP 440 = 0.180 ($p<0.001$) **0.440 L** No significant difference between Active Treatments
FAP30008	Adult and Adolescent ≥12 years **ICS-naive**	*12 weeks*	Placebo FP HFA 44 2 puffs BID FP HFA 110 2 puffs BID FP HFA 220 2 puffs BID	99 100 98 100	Change from baseline in AM pre-dose FEV_1	Placebo = 0.160 L FP 88 = 0.320 ($p<0.001$) **0.160 L** FP 220 = 0.350 ($p<0.001$) **0.190 L** FP 440 = 0.390 ($p<0.001$) **0.230 L** No significant difference between Active Treatments
FLTA3020	Adult and Adolescent	*12 weeks*	Placebo FP HFA 110 1 puff BID FP CFC 110 1 puff BID FP HFA 220 2 puffs BID FP CFC 220 2 puffs BID	43 37 38 35 38	Sensitivity to broncho-provocation stimulus	Placebo FP HFA 110 BID FP CFC 110 BID FP HFA 220 BID FP CFC 220 BID **no clear dose-response**
FLTA3022	*Adult* ≥18 years ***Oral CS sparing***	*16 weeks*	Placebo FP HFA 220 2 puffs BID FP CFC 220 2 puffs BID FP HFA 220 4 puffs BID FP CFC 220 4 puffs BID	33 37 32 34 32	Mean oral prednisone use during weeks 1 – 16 of the clinical trial period	Placebo **67% dropout** FP HFA 440 BID **19% dropout** FP CFC 440 BID **16% dropout** FP HFA 880 BID **41% dropout** FP CFC 880 BID **24% dropout**
FLTB3048	*Adult* ≥18 years **LT safety**	*One Year*	FP HFA 220 2 puffs BID FP CFC 220 2 puffs BID	163 162	Safety	FP HFA 440 BID FP CFC 440 BID ▪ Use of spacers by 41% of FP HFA and 38% of FP CFC subjects confounds these safety data with regard to local vs. systemic AE's and hence the AE table. This was a non-US study ▪ HPA-axis data analysis and collection was not adequately pre-specified and is uninterpretable
FAP30001	Adult and Adolescent ≥12 years **Intermediate-term safety**	*Six Months*	FP HFA 110 2 puffs BID FP HFA 220 2 puffs BID	89 93	Safety	FP HFA 220 BID FP HFA 440 BID ▪ May provide useful information to supplement safety data from FLTB3048

CC: Jafari/PM/HFD-570
Mann/DepDir/HFD-570
Chowdhury/ActingDivDir/HFD-570
Barnes/SupPM/HFD-570
Gilbert-McClain/MO/HFD-570
Schroeder/CMC/HFD-820
Poochikian/CMC TL/HFD-820
Fadiran/OCPB TL/HFD-870
Kumi/OCPB/HFD-870
Purucker/ClinTL/HFD-570 (now DD, HFD-970)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Purucker
12/26/02 03:26:03 PM
MEDICAL OFFICER

Medical Officer 45-day Filing Review

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

Application #:	NDA 21-433	**Category of Drug:**	Corticosteroid
Sponsor:	GlaxoWellcome Inc.	**Route of Administration:**	Oral Inhalation
Proprietary Name:	Flovent® HFA 44 mcg, 110 mcg, 220 mcg	**Medical Reviewer:**	Lydia I. Gilbert-McClain, MD, FCCP
USAN/Established Name:	Fluticasone propionate inhalation aerosol	**Review Date:**	March 20, 2002

Submissions Reviewed in This Document

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
February 26, 2002	Electronic submission	Original NDA	Indication for the maintenance treatment of asthma in adults and adolescents 12 years of age and older

Related Applications (if applicable)

June 18, 1997	IND 53,502	Fluticasone propionate/GR106642X inhalation aerosol (HFA)	Original IND under which drug development was done
September 26, 1986	IND 29,039	Fluticasone propionate inhalation aerosol	Original IND for the CFC formulation of the inhalation aerosol
October 23, 1998	IND 57,151	Salmeterol/Fluticasone propionate/GR106642X Inhalation Aerosol	Original IND under which drug development for the combination (Advair) aerosol product was done
December 29, 1994	NDA 20-548	Flovent ® Inhalation Aerosol (CFC)	Approved March 27, 1996
November 20, 1991	NDA 20-121	Flonase ® Nasal spray	Approved October 19, 1994
December 29, 1994	NDA 20-549	Flovent® Rotadisk	Approved November 07, 1997
September 26, 1996	NDA 20-770	Flovent Rotadisk	Pediatric application. Approved November 07, 1997
March 30, 1998	NDA 20-833	Flovent® Diskus	Approved September 29, 2000
March 24, 1999	NDA 21-077	Advair® Diskus	Approved August 24, 2000

Overview of Application: This is the 45-day review of NDA 21-433.

Outstanding Issues:

Recommended Regulatory Action

NDA/Supplements:

_____Approval

___ ___Approvable

_____ Not Approvable

Signature:_____ Date_____

Lydia I. Gilbert-McClain, MD, FCCP
Medical Reviewer

Medical Officer 45-day Filing Review

NDA 21-433
Drug: Fluticasone propionate/GR106642X (Flovent® HFA) Inhalation Aerosol
Indication: Maintenance treatment of asthma in adults and adolescents 12 years of age and older
Date of Submission: February 26, 2002
PDUFA Goal Date: December 27, 2002
45-day Filing review date:
Filing Date: April 27, 2002

Overview of Clinical Program

The sponsor is seeking the approval of three strengths of the inhaler, 44 mcg, 110 mcg, and 220 mcg ex-actuator for the maintenance treatment of asthma in adolescents and adults 12 years of age and older.
The U.S. drug development program for Flovent ® HFA consisted of three pivotal studies conducted in three specific populations - subjects maintained on inhaled corticosteroids (FAP30007), subjects maintained on short-acting bronchodilator therapy alone (FAP30008), and subjects who were oral corticosteroid-dependent (FLTA3022). All three studies were randomized, double-blind, parallel-group, placebo-controlled multicenter trials in adolescents and adults (≥ 12 years of age) with asthma.

Proposed dosage and administration

The recommended starting dose is based on the patients' current asthma therapy.

Previous therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators alone	88 mcg BID	440 mcg BID
Inhaled corticosteroids	88 – 220 mcg BID	440 mcg BID
Oral corticosteroids	—	880 mcg BID

Overview of Pivotal Studies

1. **FAP30007**
2. **FAP30008**
3. **FLTA3022**

FAP3007

A randomized, double-blind, parallel-group, placebo-controlled 12-week trial of inhaled fluticasone propionate 88 mcg bid, 220 mcg bid and 440 mcg bid versus placebo in propellant GR 106642X in adolescent and adult subjects with asthma who are maintained on inhaled corticosteroid therapy.

Brief trial description

Subjects enrolled in this study continued use of prescribed inhaled corticosteroids until randomization. Subjects were stratified according to the dose of ICS therapy used upon

entrance into the study and whether or not the study site was participating in PK assessments.

Study Objective

Efficacy and safety

Primary efficacy endpoint

Mean change from baseline to Endpoint in AM pre-dose percent-predicted FEV_1

Secondary

Include measurements to assess changes in FEV_1 throughout the treatment period, Ventolin® use, asthma symptom score, and nighttime awakenings.

Health outcome measures was assessed by the Asthma Quality of Life Questionnaire (AQLQ).

Safety measures include 24-hour urine cortisol for HPA-axis assessment.

Primary efficacy results

Mean Change from Baseline in AM Pre-Dose Percent Predicted FEV_1 at Week 12 (LOCF)

(ITT Population – Study FAP30007)

	PLA HFA (N=104)	FP 88 HFA (N=103)	FP 220 HFA (N=106)	FP 440 HFA (N=102)
Baseline (n)	104	103	106	101
Mean (%)	65.6	65.3	65.5	66.2
Week 12 (n)	102	100	105	98
Mean (%)	58.0	68.1	69.7	72.2
Mean Change	-7.7	2.9	4.2	5.9
LS Mean Change[b] (SE)	-8.3 (1.2)	2.2[a] (1.2)	3.2[a] (1.1)	4.6[a] (1.2)
95% CI[c]	---	(7.7, 13.3)	(8.8, 14.4)	(10.1, 15.8)
95% Dunnett CI[d]	---	(7.1, 13.8)	(8.2, 14.9)	(9.6, 16.4)

Source Data: Table 7.2, Table 7.3, Table 7.4

LOCF = last observation carried forward, LS = least square, SE = standard error

Post-baseline n's are the sample sizes used for LS mean change calculation

a p<0.001 vs. placebo (Hochberg multiplicity adjustment)

b ANCOVA, adjusted for baseline percent predicted FEV_1, region, age, gender, whether or not site had subject participating in PK assessments, and baseline dose level of ICS therapy (low/medium or high)

c 95% confidence interval for the difference between the FP groups and placebo

d 95% confidence interval for the difference between the FP groups and placebo, adjusted for multiple comparisons using Dunnett's method

Safety

There was one death during the study. A 60-year-old male (subject 51292-863) who received FP 440 bid. Approximately 6 days after discontinuing the study [for lack of efficacy] he suffered a cardiopulmonary arrest and died. Four (4) subjects, all in the placebo group experience serious adverse events. Two events were asthma exacerbations.

FAP 30008

This study was similarly designed to FAP30007 with identical primary and secondary measures, and safety assessments. The differences in design were that randomization was not stratified and subjects were not on

Mean Change from Baseline in AM Pre-Dose Percent Predicted FEV_1 at Week 12 (LOCF)
(ITT Population – Study FAP30008)

	PLA HFA (N=99)	FP 88 HFA (N=100)	FP 220 HFA (N=98)	FP 440 HFA (N=100)
Baseline (n)	99	99	98	100
Mean (%)	67.0	67.0	67.3	67.1
Week 12 (n)	96	95	95	99
Mean (%)	71.1	76.3	76.8	78.1
Mean Change	4.0	9.5	9.4	11.1
LS Mean Change[b] (SE)	3.4 (1.1)	9.0[a] (1.1)	9.8[a] (1.1)	11.2[a] (1.0)
95% CI[c]	---	(2.7, 8.6)	(3.4, 9.3)	(4.9, 10.7)
95% Dunnett CI[d]	---	(2.2, 9.2)	(2.8, 9.9)	(4.3, 11.3)

Source Data: Table 7.2 Table 7.3, Table 7.4
LOCF = last observation carried forward, LS = least square, SE = standard error
Post-baseline n's are the sample sizes used for LS mean change calculation
a p<0.001 vs. placebo (Hochberg multiplicity adjustment)
b ANCOVA, adjusted for baseline percent predicted FEV_1, region, age, and gender.
c 95% confidence interval for the difference between FP groups and placebo
d 95% confidence interval for the difference between FP groups and placebo adjusted for multiple comparisons using Dunnett's method

ICS.

Safety

There were no deaths during the study. Four subjects experienced serious adverse events during the treatment period. One subject was in the FP 88 mcg arm and 3 subjects were in the FP 440 mcg arm. The SAE's in the FP 440 mcg arm were possible adrenal suppression (subject 02525-8497) , status asthmaticus (subject 88226-3108), and bipolar exacerbation (subject 07237-3554). One subject experience serious adverse events (oral candidiasis, weakness, bleeding of internal hemorrhoids) during the follow-up period.

FLTA 3022

This study compared the dose-related efficacy of two doses (440 mcg bid and 880 mcg bid) of FP administered in HFA or CFC formulations in oral corticosteroid-dependant asthmatics. The study design was a multicenter double-blind, placebo-controlled study. Randomization was not stratified in FLTA3022. The treatment period was 16 weeks.

Primary efficacy measure

Mean daily oral prednisone use during the study (weeks 1 - 16). The dose of daily prednisone (maintenance dose and dose of prednisone bursts , if applicable) was recorded by the subject on the diary card.

Other efficacy measures
Reduction in oral prednisone dose
Mean dose of prednisone at baseline and endpoint
Mean change from baseline in prednisone dose
Rate of change of prednisone dose
Probability of attaining sustained elimination of prednisone
Duration of study participation
FEV_1, PEFR, symptom scores, nighttime awakenings and inhaled Ventolin® use.

Safety assessments
Included HPA-axis function assessed by the Cortrosyn stimulation tests.

Results summary
One hundred and sixty-eight subjects were enrolled at 39 sites and 113 (67%) completed. Of the 55 (33%) subjects who discontinued 22 were in the placebo group.

Summary of Subject Accountability: End of Study Record, n (%)
ITT Population

	Placebo HFA BID (N=33)	FP 440mcg HFA BID (N=32)	FP 880mcg HFA BID (N=32)	FP 440mcg CFC BID (N=37)	FP 880mcg CFC BID (N=34)	Total (N=168)
Completed	11 (33%)	26 (81%)	19 (59%)	31 (84%)	26 (76%)	113 (67%)
Prematurely discontinued	22 (67%)	6 (19%)	13 (41%)	6 (16%)	8 (24%)	55 (33%)
Reason for premature discontinuation						
Adverse event	0	0	3 (9%)	1 (3%)	1 (3%)	5 (3%)
Failed to return	0	0	0	0	0	0
Lack of efficacy	19 (58%)	2 (6%)	4 (13%)	3 (8%)	2 (6%)	30 (18%)
Inpatient hosp.	0	0	1 (3%)	0	0	1 (<1%)
↑ in asthma rx	9 (27%)	1 (3%)	3 (9%)	1 (3%)	1 (3%)	15 (9%)
3rd pred. burst	10 (30%)	1 (3%)	1 (3%)	2 (5%)	1 (3%)	15 (9%)
Other	3 (9%)	4 (13%)	6 (19%)	2 (5%)	5 (15%)	20 (12%)

Source Data, Table 3

Primary efficacy
A reduced ITT population was used for the efficacy analyses. A total of 3 subjects (1 subject who withdrew prior to any post-randomization assessments and all of the 2 from Dr. Edward's study site were excluded from the analyses.

Summary of Mean Daily Oral Prednisone Use, mg

Reduced ITT Population

	Placebo HFA BID (N=32)	FP 440mcg HFA BID (N=32)	FP 880mcg HFA BID (N=32)	FP 440mcg CFC BID (N=36)	FP 880mcg CFC BID (N=33)
Baseline	14.2	12.5	12.7	13.0	14.3
Weeks 1-16	14.9	5.8[a]	6.2[a]	4.9[a]	6.4[a]

Source Data: Tables 18 and 21
a Different from placebo, p<0.001

Safety
There were no deaths during the study. Nine subjects four of whom withdrew from the study experienced a serious adverse event.

The table below summarized the pivotal studies and the safety studies.

OVERVIEW OF PIVOTAL CLINICAL STUDIES
(the dosage administration is 2 puffs bid of the MDI. In the case of the 880 mcg dose, 2x 220 mcg strength MDIs were given to the subjects)

	FAP 3007	FAP 3008	FLTA 3022
Patient characteristics	Asthmatics maintained on ICS	Asthmatics maintained on bronchodilators alone	Oral corticosteroid-dependent asthmatics
Age	≥ 12 years	≥ 12 years	≥ 12 years
Study design	Multicenter, randomized double-blind, placebo-controlled	Multicenter, randomized double-blind, placebo-controlled	Multicenter, randomized double-blind, placebo-controlled
Stratification	Based on ICS dosage at study entry and performance of PK at study site	No	No
Treatment arms	FP 88 mcg, FP 220 mcg, FP 440 mcg bid, placebo bid	FP 88 mcg, FP 220 mcg, FP 440 mcg bid, placebo bid	FP 440 mcg, FP 880 mcg, (both HFA and CFC formulations)

			placebo
Study Duration	12 weeks	12 weeks	16 weeks
N Screened	1051	1146	
N randomized	415	397	168
N completed	288	312	113
N discontinued	127	85	55

SUPPORTING STUDIES

Several additional studies are submitted with this application. They included:

Supportive studies pertinent to this application and cited in the label

FAP30001
A randomized, double-blind parallel-group trial of inhaled Flovent® HFA 220 mcg BID and 440 mcg BID in adolescent and adult subjects with asthma.

Objectives
To assess the safety and efficacy of Flovent® HFA 220 mcg and 440 mcg BID over 26 weeks

Endpoints
1. Safety evaluations which consist of clinical adverse events, laboratory tests, assessment of HPA-axis function (by measurement of 24-hour urine cortisol excretion), 12 lead ECG, physical examinations and vital signs
2. Efficacy assessed by the usual lung function variables (FEV_1, PEFR), symptom scores, Ventolin ® use, and nighttime awakenings.

Summary
One-hundred eighty-two (182) subjects with asthma who were treated with daily low dose or high-dose inhaled corticosteroids and as needed beta-agonists were treated for 26 weeks with Flovent ® HFA 220 mcg BID or 440 mcg BID

Study design
Multicenter, randomized, double-blind, uncontrolled trial at 18 investigational sites in the U.S.
Brief summary of safety results
A total of 140 (77%) of subjects completed the study and 42 (23%) discontinued. There were no deaths and 2 subjects in the FP 440 mcg BID group experienced a serious adverse event (cholelithiasis and spontaneous abortion).

2. **FLTB3048**
A multicentre, randomised, double-blind parallel group clinical trial to assess the long-term (52 weeks) safety of FP 500 mcg BID administered by pressurised

metered dose inhaler propelled by HFA, in comparison with CFC in adolescents and adult subjects with asthma.

Summary

This multinational study enrolled 325 patients with asthma who had been treated daily with moderate to high doses of ICS (with or without concurrent use of salmeterol or albuterol at baseline). The study was conducted in centers in Belgium, Canada, Chile, Finland, New Zealand, and Norway.

Objectives

To compare the long-term safety of Flovent® HFA 440 mcg BID with Flovent ® MDI propelled by CFC propellants 11 and 12 administered over 52 weeks in adolescents and adults with asthma.

Safety measurements

Clinical adverse events, laboratory tests, HPA-axis function, biochemical markers of bone metabolism, asthma exacerbations, vital signs, ECGs, oropharyngeal examinations, physical examinations, and ophthalmic examinations.

HPA-axis evaluations

(1) morning serum cortisol AND
(2) Either 24-hour urinary cortisol OR short synacthen(Cortrosyn) test

Biochemical markers of bone

(1) Serum osteocalcin (a biochemical marker of bone formation)
(2) Urinary-N-telopeptide (a marker of bone resorption)

Summary results

A total of 292 (90%) patients completed the study. A total of 13 subjects were withdrawn for adverse events. There were no deaths. Twenty-two subjects, 12 in the Flovent ® HFA group and 10 in the Flovent® MDI (CFC) group experience serious adverse events. One subject in the post-treatment period experience a serious outcome to pregnancy (abortion, stillbirth).

Other supporting studies submitted in the NDA

These studies which will not be reviewed for this application include:

FLTA3020

A randomized, double-blind, placebo-controlled, dose-ranging, comparative trial of inhaled FP 110 mcg Bid and 220 mcg bid via CFC MDI or HFA in adolescents and adults subjects with asthma

FLIT 94
A multicentre, randomised, double-blind, parallel-group study to compare the efficacy and tolerability of FP 500 mcg bid administered by pressurised inhaler propelled by CFC or HFA for 12 months in adult patients with chronic reversible airway obstruction.

LABELING CLAIMS
Indications:
(1) Indicated for the maintenance treatment of asthma as prophylactic therapy in adolescent and adult patients 12 years of age and older
(2) Indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patents may be able to reduce or eliminate their requirement for oral corticosteroids over time.

(3) Onset of action: The sponsor cites

, in support of ar

The sponsor's method of determining onset of action will be carefully reviewed. Of note, in the Flovent® CFC formulation, there is no specific onset of action claim per se instead there is a general statement stating that asthma control following inhaled administration of FP can occur within 24 hours of beginning treatment although maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment.

(4) Health related outcomes: The sponsor cites

Financial Disclosure
One investigator held financial equity interest in the study sponsor. Investigator , study site held >$50,000 of equity interest in the study sponsor. The investigator participated in stud and enrolled (1.8%) subjects. This is a small number of patients and should not impact the study overall. It is noted however, that this study enrolled only

subjects at — study sites and with the exception of — most of them enrolled only — subjects.

Pediatric use information

In compliance with 21CFR 314.55 (b) and (c) the sponsor obtained a deferral for submission of an assessment of pediatric use with Flovent® HFA on July 26, 2000. A study FAP30010 in patients 4 to 11 years of age is ongoing, —

2002. Other non-US studies (FAS30007 and FAS30009)currently ongoing are to be used as supporting studies to support an indication in these pediatric age groups.

The sponsor is requesting a waiver to not evaluate Flovent® HFA in patients less than 12 months of age. The Agency indicated on June 19, 2001 during the pre-NDA meeting for Flovent ® HFA that an indication in children less than 12 months of age is unlikely to be approved because of (1) the difficulty in making a diagnosis of asthma in children under the age of 12 months, so extrapolation from older populations is not appropriate (2) no agreement among professional organizations that asthma, as defined in adults, exists in infants.

Fileability

This is an electronic submission and it was prepared in keeping with the draft guidance for industry on electronic submission of NDAs. The table of contents contains hyperlinks that allow the reviewer to navigate through the review. Datasets are in SAS transport files and can be easily imported into JMP. All the required elements of the NDA submission are present. There are no filing issues with the NDA. The sponsor did not submit a word version of the label however, they have been contacted and will submit a word version electronically to aid in the review process.

Audit

Sites from study FLTA3022 and from study FAP30007 will be submitted to DSI for auditing. Study FLTA3022 is the only study to support the oral corticosteroid reduction claim. Of particular concern is the large number of protocol violations noted in study FLTA3022 – 63 protocol violations in 52 subjects in a study with only 168 study participants. A total of 39 investigational sites participated in this study with most investigators enrolling 1 to 3 patients. The two investigators with the highest number of enrollees will be selected for audit.

(1) Edward M. Kerwin, MD, Investigator 7237. Site 19773
Clinical Research Institute of Southern Oregon, LLC
832 East Main Street, Suite, Medford, OR 97504
Number of subjects enrolled = 17 (10%). Eight protocol violations noted.
(2) Steven Weinstein, MD. Investigator # 4541. Site 10520
Allergy and Asthma Specialists Medical Group
17742 Beach Blvd., Suite, 310/340

Huntington Beach CA 92647
Number of subjects enrolled = 15 (9%). Six protocol violations.
Of note is that both of these investigators participated in the other two pivotal studies FAP30007 and FAP30008 as well.

Study FAP30008 was chosen for audit because this study evaluates the efficacy of Flovent® in asthmatic subjects previously maintained on inhaled beta-agonists alone. A total of 397subjects were randomized in this study and there were very few minor protocol violations. The site chosen for audit is based on the large number of enrollees.
The investigator selected for auditing is –
Michael J. Noonan, MD. Investigator # 2483. Site 10549
Allergy Associates Research Center, LLC
545 NE 47th Ave, Suite 310
Portland, OR 97213
Number of subjects enrolled = 21 (5%). Note that this study had 79 investigational sites, 54 of which had enrollment of 1 to 6 subjects. This investigator had by far the largest study site. This investigator also participated in study FAP30007 and had the largest enrollment [15] of study subjects.
A memo will be prepared to DSI requesting an audit of these sites.

Consults
At this time no consultations appear to be warranted for this application.

REVIEW TIMELINE
PDUFA Due Date: December 27, 2002
Reviewer Goal Date for Completion of NDA: November 15, 2002

Review schedule
In consideration of vacation times, holidays, meetings and other commitments the following schedule will attempt to keep the review process on track to fulfill the reviewer goal date but is subject to change.

Table of Proposed Review Schedule NDA 21-443 Flovent ® HFA
PDUFA Goal Date: December 27, 02
Reviewer Goal Date: November 15, 02

Study	Review Time	Concomitant out of office activities	Target Dates
FLTA3022	6 weeks	ATS May 17-22 Memorial day May 27	Start April 15, 02 Complete May 31, 02
FAP30007	3 weeks		June 3, 02 Complete June 24, 02
FAP30008	3 weeks	Annual leave – July 15th – July 22nd, 02 July 4th weekend	Begin July 8th, 02 complete August 2nd 02,
FAP30001	3 weeks	Annual leave Aug 19th – 30th. Labor day weekend Sept 2nd	Start Aug 5th 02, complete Sept 13th, 02
FLTB3048	3 weeks		Start Sept 16th Complete Oct 4th
ISS	2 weeks		Start Oct 7th complete October 21st, 02
ISE	2 weeks		Start October 22nd, complete Nov 5th
**Review template	2 weeks		Complete Nov 15th
Labeling	1 week		Complete Nov 15th
**Review template will be worked on simultaneously			

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lydia McClain
4/22/02 12:36:46 PM
MEDICAL OFFICER

Mary Purucker
4/23/02 09:27:51 AM
MEDICAL OFFICER

Medical Officer Review

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

Application #:	NDA 21-433	**Category of Drug:**	Corticosteroid
Sponsor:	GlaxoSmithKline	**Route of Administration:**	Oral Inhalation
Proprietary Name (s):	Flovent® HFA 44 mcg Inhalation Aerosol, Flovent® HFA, 110 mcg Inhalation Aerosol, Flovent® HFA 220 mcg Inhalation Aerosol	**Medical Reviewer:**	Lydia I. Gilbert-McClain, MD, FCCP
USAN/Established Name:	Fluticasone propionate Inhalation Aerosol	**PDUFA Date:**	December 27, 2002

Submissions Reviewed in This Document

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
February 26, 2002	Electronic submission	NDA	Flovent HFA indication asthma
April 16, 2002	Electronic Submission	Amendment	Sponsor submitted the archival copy of the dairy cards and questionnaires of the CRF that were left out of the electronic files
June 24, 2002	Electronic submission	Safety Update	120-day safety update
September 19, 2002	Electronic Submission	Response to questions	Sponsor submitted a line listing of abnormal cortisol values for the Urine Cortisol population for studies FAP30007 and FAP30008

Related Applications (if applicable)

		NDA 20-548	Original NDA for Flovent inhalation Aerosol (CFC propellants) approved March 27, 1996, in three dose strengths 44 mcg, 110 mcg, and 220 mcg ex-actuator.
		NDA 20-549	Original NDA for Flovent Inhalation powder approved November 7, 1997 in three dose strengths 44 mcg, 10 mcg, and 220 mcg
		NDA 20-833	Original NDA for Flovent Diskus approved September 29, 2000 in thee dose strengths 50 mcg, 100mcg, and 250 mcg
		NDA 21-077	Original NDA for Fluticasone propionate/salmeterol xinafoate powder inhalation (Advair Diskus) approved August 24, 2000 in three dose strengths 100/50, 250/50, and 500/50

Overview of Application: See Executive Summary.

Outstanding Issues:
Chemistry

Recommended Regulatory Action

NDA/Supplements:
__x____Approval
__Approvable
_____ Not Approvable

Signature:_____ Date_____
Lydia I. Gilbert-McClain, MD, FCCP
Medical Reviewer

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. RECOMMENDATIONS

A. Recommendation on Approvability

From a clinical standpoint, the drug product (s) Flovent HFA 44 mcg, 110 mcg, and 220 mcg can be approved for the maintenance treatment of asthma.

B. Recommendation on Phase 4 studies and Risk Management Steps

There are no recommendations for Phase 4 studies for this NDA approval. In a previous application (NDA 21-077 – Advair Diskus) the Agency asked GlaxoSmithKline (GSK) to conduct an assessment of the possible gender effects of Fluticasone. The studies have been completed and the results were submitted to the Division and are currently under review by the Biopharmaceutics team.

II. SUMMARY OF CLINICAL FINDINGS

A. Overview of clinical program

GSK undertook this clinical development program for Fluticasone Propionate (FP) GR106642X (hydrofluroalkane – 134a [HFA]) Inhalation Aerosol to develop an alternative formulation for their chlorofluorocarbon containing Metered Dose Inhaler (CFC MDI) which has been approved and marketed in the U.S. since 1996. CFC propellants are compounds known to deplete the ozone layer. Ozone depletion is acknowledged by the international community as a global problem with recognized environmental hazards. At a meeting in Montreal, Canada on September 16, 1987, a number of industrialized nations agreed and signed the Montreal Protocol to reduce emissions of chemicals that deplete the ozone layer.[1] To this end, the sponsor has been developing MDIs that are not propelled by CFCs and new formulations such as dry powder inhalers (DPIs) that do not use propellants.

The drug substance Fluticasone propionate was approved as an inhalation aerosol Metered Dose Inhaler (MDI) on March 27, 1996 under NDA 20-548 in three dose strengths 44 mcg, 110 mcg, and 220 mcg for the maintenance treatment of asthma. This MDI is propelled by CFC propellants 11/12. Two other non-CFC orally inhaled products Fluticasone propionate inhalation powder (Flovent® Rotadisk), and Fluticasone propionate Diskus (Flovent® Diskus) have also been approved.

[1] International Legal Materials Volume XXVI Number 6, November 1987

The Development program of Flovent HFA was designed to establish the safety and efficacy of Flovent HFA in the maintenance treatment of asthma in patients 12 years of age and older. The pivotal efficacy studies and the long-term safety studies were conducted in male and female asthmatic subjects aged 12 years and above. Studies FAP30007 and FAP30008 were 12-week studies that evaluated the efficacy and safety of Flovent HFA 88 mcg BID, 220 mcg BID, and 440 mcg BID using the 44 mcg, 110 mcg, and 220 mcg strength product. Study FAP30007 was conducted in subjects who had been maintained on inhaled corticosteroids (ICS), whereas, study FAP30008 was conducted in subjects who had been on bronchodilator therapy only. The oral corticosteroid-sparing trial FLTA3022 compared the highest doses of FP HFA and FP CFC 440 mcg BID, and 880 mcg BID with placebo in subjects who had been maintained on oral corticosteroids. Long-term safety data came from a one-year safety study FLTB3048 that compared the safety of FP HFA 440 BID with FP CFC 440 BID, and a 6-month safety study FAP30001 compared doses of FP HFA 220 BID with FP HFA 440 BID.

B. Efficacy

The two pivotal 12-week studies FAP30007 and FAP30008, showed that each dose of Flovent® HFA, 88 mcg BID, 220 mcg BID, and 440 mcg BID was efficacious compared to placebo in the long-term maintenance treatment of asthma. The primary endpoint in these two studies was mean change from baseline in pre-dose FEV_1 at Endpoint. The population studied in the two trials had a similar degree of asthma severity with baseline percent predicted FEV_1 of 65 – 67% predicted. A clear dose ordering relationship was not observed in either study but data trended in a positive fashion as dose increased. In study FAP30007, the LS mean difference (FP – placebo), was 10.5 , 11.5, and 12.9% respectively for the FP 88 mcg BID, the FP 220 mcg BID, and the FP 440 mcg BID treatment group respectively. In study FAP30008, the LS mean difference (FP- Placebo) was 5.6, 6.4 and 7.8% in the FP 88 mcg BID, the FP 220 mcg BID and the FP 440 mcg BID group respectively. There were no CFC comparator arms in these studies.

The secondary efficacy endpoints efficacy parameters evaluated were peak flow rates (AM and PM), asthma symptom scores, supplemental Ventolin® use, and discontinuations for lack of efficacy. These endpoints supported the primary finding of efficacy in both studies.

The Asthma Quality of Life Questionnaire (AQLQ) by Juniper was used to assesses patients' perception of the effect of their asthma on their overall "quality of life". Subjects in the FP 440 mcg BID treatment group in both studies had a clinically meaningful improvement (≥0.5) in their Overall Score and in the individual domains at Endpoint. In Study FAP30007, subjects in the lower dose treatment arms (88 mcg and 220 mcg BID) also had a clinically meaningful improvement in their Overall Score, but this finding was not replicated in study FAP30008.

In the oral corticosteroid sparing study FLTA3022, patients treated with either FP HFA 440 mcg BID or FP 880 mcg BID had a statistically significant reduction in oral corticosteroid usage over the 16-week treatment period compared with subjects treated with placebo. Subjects in the FP HFA 440 mcg BID and 880 mcg BID treatment groups had a mean daily oral prednisone usage of 5.8 mg/day and 6.2 mg/day respectively compared with 14.9 mg/day in subjects treated with placebo ($p<0.001$). In the two CFC comparator arms (440 and 880 BID), mean daily oral prednisone usage was similar: 4.9 mg/day and 6.4 mg/day respectively. As expected, discontinuations during the study due to lack of efficacy was markedly increased in the placebo group (58% of subjects discontinued due lack of efficacy whereas in the FP 440 and 880 mcg groups 6 – 13 % of subjects discontinued due to lack of efficacy.

In both active treatment groups, lung function as measured by mean change from baseline in FEV_1 and peak flow showed improvement whereas, in the placebo group there was a decline in lung function over the 16 weeks of treatment. At treatment Week 16, subjects in both the HFA and CFC treatment groups FP 440 mcg BID and FP 880 mcg BID had a mean increase of 240 mL from baseline in FEV_1 while in the placebo group, FEV_1 decreased by 250 mL from baseline.

The mean increase in AM PEF in study FLTA3022 ranged from 17.7 L/min to 36.5 L/min in the HFA and CFC treatment groups compared to a mean decrease from baseline of 18.9 L/min in the placebo group. In the other secondary efficacy measures – asthma symptom scores, Ventolin® use and nighttime awakenings requiring Ventolin® use, numerical improvements were noted in all the active treatment groups except that for the FP HFA 880 group nighttime awakenings increased slightly during the treatment period. At Week 16, the number of nighttime awakenings in the FP HFA 880 mcg BID group had increased to one awakening every 2 nights from one awakening every 3 nights at baseline. In the FP HFA 440 mcg BID group, the number of awakenings decreased to one every 2.5 nights compared to one every 2 nights at baseline. These small differences may not be clinically significant.

The efficacy findings do not appear to be affected by gender, ethnic origin, or age. Similar to what has been observed in other asthma development programs, there was a higher percentage of females (55%) compared to males (45%) overall. The efficacy findings were similar in both sexes. The population was predominantly Caucasian (84%) and an assessment of the effect of ethnic origin on efficacy could not be reliably determined. This caveat notwithstanding, there did not appear to be differences in efficacy among ethnic groups. With respect to age, 8% of the population was between the age of 12 – 17 years and 5% was $\geq$ 65 years. Efficacy appeared to be similar across age groups.

C. Safety

The safety profile of FP has been extensively studied in asthma trials. The drug substance has been approved and marketed in various formulations in the U.S. for over 6 years. The propellant hydrofluroalkane-134a (HFA) has also been extensively studied. Several other inhaled corticosteroids are approved and marketed in the U.S. for use in asthma and there are known and predictable adverse events that are associated with inhaled corticosteroids. Therefore, the safety assessment of FP HFA in addition to assessing for the known effects of ICS such as local (upper airway, oropharyngeal) and systemic (such HPA axis function, and glucose metabolism,) effects was also to evaluate for adverse events that might be unique to Flovent HFA, and that were not seen with Flovent CFC or other formulations of FP.

The adverse event profile in general was similar to what has been previously seen with inhaled corticosteroids. The most common adverse events were reported in the ear, nose and throat, upper respiratory, and neurological system. The most common events (> 5% frequency) included upper respiratory tract infection (URTI) , throat irritation, sinusitis, and headache. Local effects of ICS such as throat irritation, hoarseness/dysphonia, and oral candidiasis showed dose ordering as they were reported more frequently in subjects receiving the higher doses of FP. A gender effect was also noted in that oral candidiasis, throat irritation, and hoarseness/dysphonia were reported more frequently in females than males in the 12-week studies. However, this was not observed in the long-term (6-month and 1-year) studies.

In the one-year long-term study, which was conducted outside of the U.S., up to 40% of the subjects used a spacer . The local adverse events of throat irritation and hoarseness/dysphonia were reported with a slightly higher frequency in subjects without spacers compared to subjects who used spacers.

There was one death in the clinical development program and it was unrelated to the study drug or asthma.

A total of 50 events that met the regulatory definition of serious adverse events (SAEs) were reported during the drug development program. In the opinion of this reviewer, only one of these SAEs – i.e. adrenal suppression in a 24 year old female who was on the low dose of FP HFA (88 mcg BID) was definitely drug-related. However, it was noted that in study FLTA3022, there were three cases of serious pneumonia in subjects who were in the FP HFA 880 mcg BID treatment arm. These subjects were discontinued from the study. While it is not altogether clear that there is a direct relationship between Fluticasone propionate and pneumonia, the findings in this program are consistent with observations noted in other studies[2] with Fluticasone propionate that signal a slightly higher

[2] sNDA 21-077/S 003 – Advair Diskus, study SFCB 3023 submitted June 20, 2002, and Medical Officer review for sNDA 20-833/SE1-04 - Flovent Diskus submitted May 25, 20001

incidence of pneumonia in Fluticasone propionate-treated patients compared to controls or other active treatments.

Other events that did not meet the regulatory definition of SAE that in the opinion of this reviewer were drug-related and of clinical significance were a fungal infection on the vocal cords of a 50-year old female treated with FP HFA 440 BID that led to study discontinuation, and adrenal suppression in two subjects who received Flovent® CFC 440 mcg BID. One of these subjects who received Flovent® CFC was also described as having Cushing's syndrome. The final outcome of these two cases were not presented in the NDA submission. Given that these events occurred in the CFC treatment arm, this reviewer did not request additional information.

Systemic adverse events were monitored via clinical laboratory assessments that included routine chemistry and hematology evaluations, AM cortisol, 24-hour urinary cortisol and/or ACTH stimulation testing in all the studies. Non-specific serum/urinary markers of bone formation and resorption (serum osteocalcin and urinary N-telopeptide respectively) were measured in the one-year long-term study. Opthalmoscopic examinations were conducted in the one-year safety study as well.

Clinical chemistry and hematology data were not suggestive of a systemic corticosteroid effect. Serum and urinary cortisol measurements in general were lower in the FP treatment groups compared to placebo. A consistent dose ordering effect was not seen across studies. There are data limitations worth noting. In the first place, the data were insufficient to completely assess the relative effect of changes in exposure of FP HFA or CFC on serum/urine cortisol levels. Secondly, in the one-year study, a subset analysis of the systemic effects in subjects who were spacer users vs. non spacer users was not done.

There were no reports of cataracts or glaucoma in the one-year study. The study duration is probably too short to assess for these adverse events. However, one subject in the FP CFC 440 treatment arm was reported to have an opacity in one eye. Additional information was not provided.

Formal drug-drug interaction assessments were not done in the clinical studies. Subjects using other permitted asthma medications or Flonase ® nasal spray had similar adverse event profiles to patients who were not taking these medications.

D. Dosing

Fluticasone propionate Inhalation Aerosol GR1066X (Flovent ® HFA) is developed in three strengths: 44 mcg, 110 mcg and 220 mcg ex-actuator per inhalation. The proposed dosing regimen for the maintenance treatment of asthma is two inhalations twice a day with the option of using up to 4 inhalations

twice a day of the highest strength in subjects who are oral corticosteroid dependent. The lowest effective dose of corticosteroid should be employed depending on asthma severity.

E. Special Population

Formal pharmacokinetic studies using Flovent® HFA were not conducted to examine gender differences or in special populations, such as elderly patients specifically, or patients with hepatic, or renal impairment in the clinical studies. The sponsor conducted a population PK analysis and a PD meta-analysis to evaluate the potential gender effects of Flovent® to fulfill a phase 4 commitment to NDA 21-077 (Advair Diskus). These studies have been submitted and are under review in the Division by the Biopharmaceutics team.

Pediatric subjects 12 years of age and older were included in this clinical development program. At a meeting held with the Division on July 26, 2000, GSK requested and obtained a deferral for submission of an assessment of pediatric use in patients 1 to 11 years of age with Flovent® HFA. As part of their pediatric development program, GSK has an ongoing controlled study (FAP30010) in the U.S. comparing the efficacy and safety of Flovent® HFA 44 mcg versus placebo in asthmatic children aged 4 to 11 years. The sponsor has requested a waiver for the evaluation of Flovent® HFA in patients less than 12 months of age. During the pre-NDA meeting held June 19, 2001, the Division had indicated to the sponsor that an indication in children less than 12 months of age is unlikely to be approved because of the difficulty of making a diagnosis of asthma in children under the age of 12 months and extrapolation from older populations is not appropriate.

List of Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
AM	Morning
AQLQ	Asthma Quality of Life Questionnaire
ATS	American Thoracic Society
BID/bid/BD	Twice daily
CRF	Case report form
DPI	Dry powder inhaler
DSI	Division of Scientific Investigations
FEV_1	Forced expiratory flow rate in one second
FP	Fluticasone propionate
GI	Gastrointestinal
ICS	Inhaled corticosteroid
ITT	Intent to treat
IRB	Institutional Review Board
ISS	Integrated summary of safety
ISE	Integrated summary of efficacy
L	Liter
LFTs	Liver function tests
LLN	Lower limit of normal range
Mcg	microgram
MDI	Metered Dose Inhaler
Mins	Minutes
PEF/PEFR	Peak expiratory Flow [Peak expiratory flow rate]
PFT	Pulmonary function test
PD	Pharmacodynamic
PK	Pharmacokinetic
PM	Evening
PRN/prn	As needed
RBCs	Red blood cells
SAE/SE	Serious adverse event/Serious event
ULN	Upper limit of normal
WBCs	White blood cells

CLINICAL REVIEW

I. INTRODUCTION AND BACKGROUND

A. Drug Name, Indication, Dose, Regimens, Age Groups

The drug name(s) are : Fluticasone propionate Inhalation Aerosol metered dose inhaler GR1066X (Flovent HFA) 44, Fluticasone propionate Inhalation Aerosol metered dose inhaler GR1066X (Flovent HFA) 110 , and Fluticasone propionate Inhalation Aerosol metered dose inhaler GR1066X (Flovent HFA) 220. The proposed indication is for the long-term maintenance treatment of asthma in patients 12 years of age and older. The recommended dose is 2 puffs by oral inhalation BID. The starting dose depends on the degree of asthma severity. A dose of 880 mcg BID is proposed for asthmatics who are maintained on oral corticosteroids.

B. State of Armamentarium for Indication

Asthma is an inflammatory disease and the most effective long-term-control medications for asthma are those that reduce inflammation. Inhaled corticosteroids (ICS) are the most potent inhaled anti-inflammatory medication currently available[3].

There are several inhaled corticosteroids are approved and marketed in the U.S. for the maintenance treatment of asthma. This new MDI product will have the advantage of being propelled by hydrofluroalkanes (HFA) which do not deplete the ozone layer. Fluticasone propionate has been approved and marketed in various formulations; (i) in a pressurized MDI with CFC propellants (NDA 20-548) on March 27, 1996, (ii) as a dry powder inhalation (Flovent® Rotadisk) (NDA 20-549) on November 27, 1997 and (iii) as a dry powder inhalation Flovent® Diskus (NDA 20-833) on September 29, 2000. Fluticasone propionate is also formulated as a dry powder in a combination product – Advair Diskus (Fluticasone propionate/salmeterol xinafoate, NDA 21-077) which was approved August 24, 2000 for the long-term maintenance treatment of asthma.

C. Important Milestones in Product Development

Flovent® HFA was developed under IND 53, 502 which was initially submitted to the Agency on June 18, 1997. The sponsor met with the Division in March 1997 at a pre-IND meeting to discuss the development program for Flovent® HFA. At that time, the sponsor was considering a "switch program"[4] from Flovent® CFC to Flovent® HFA. During the initial development stages, the lowest strength of Flovent® 44 mcg was not available.

---

[3] NAEPP Guidelines, Diagnosis and Management of Asthma NIH Publication No. 97-4053, pg. 7
[4] Clinical Development Programs for MDI and DPI Drug Products. www.fda.gov/cder/guidance

Results of the dose proportionality study FLTA3020 failed to demonstrate a dose-response as required by the Agency and the sponsor changed the developmental approach from a "switch program" to a "stand-alone program". The sponsor met with the Division in May, 2000 and discussed the change in the development program. At the May 5, 2000 meeting, the sponsor also indicated that the 44 mcg product had since become available and that the clinical development program would now include all 3 strengths (44 mcg,110 mcg, and 220 mcg) of FP HFA.

At the May 2000 meeting, the sponsor proposed to use some of the studies already conducted under the "switch program" specifically, FLTA3022, FLTB3048, and FAP30001, and to conduct two additional pivotal efficacy studies, one in patients using inhaled corticosteroids (ICS) – study FAP30007, and one in patients using bronchodilators alone- study FAP30008. The Division agreed with the proposed clinical development plan.

At the time of the pre-IND meeting and the follow-up meeting with the Division in March 2000, the sponsor was GlaxoWellcome (GW). The sponsor subsequently merged with SmithKline and is now GlaxoSmithKline (GSK). The merger was completed on December 27, 2000.

At the pre-NDA meeting held June 19, 2001 the Division requested that the sponsor submit a sensitivity analyses (e.g. a worst case scenario) when considering the impact of missing data on the interpretation of the study results. The sponsor complied accordingly and conducted an acceptable sensitivity analysis.

The sponsor requested and obtained a deferral for submission of an assessment of pediatric use in patients 1 to 11 years of age with Flovent® HFA on July 26, 2000.

D. *Other Relevant Information*

See "Postmarketing Experience" section on page 17.

E. Important Issues with Pharmacologically Related Agents

N/A

II. Chemistry, Pharmacology/Toxicology, Statistics

Fluticasone propionate is a potent fluorinated glucocorticoid having the chemical name S-fluoromethyl 6α-methyl-3-oxo-17α-propionyloxyandrosta-1, 4-diene-17β-carbothioate. Fluticasone propionate is a white to off-white powder with a molecular formula of $C_{24}H_{31}F_3O_{5S}$ and molecular weight of 500.6. Flovent® HFA

Inhalation Aerosol was developed as pressurized, metered-dose aerosol units intended for oral inhalation only. Each unit contains a mocrocrystalline suspension of Fluticasone propionate (micronized) in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no excipients. After priming, each actuation of the inhaler delivers 50, 125, or 250 mcg of Fluticasone propionate from the valve and 44, 110, or 220 mcg respectively of Fluticasone propionate from the actuator. Each 10.6-g canister (44 mcg) and each 12-g canister (110 and 220 mcg) provides 120 inhalations.

The pre-clinical evaluation of both Fluticasone propionate and GR 106642X (HFA) have been previously established independently. To ensure that the administration of FP formulated in GR 106642X had a similar pre-clinical profile compared with that established for each component, the sponsor carried out additional toxicity studies of 3 months duration to "bridge" the existing databases. Dr. Larry Sancilio was the Pharmacology/Toxicology reviewer for this NDA *(see pharm tox review)*

Dr. Ted Guo Biostatistician conducted a detailed statistical review of the NDA.

III. Human Pharmacokinetics and Pharmacodynamics

Dr Kofi Kumi conducted the biopharmacology review of the NDA. The biopharmaceutics team concluded that systemic exposure of FP HFA in healthy volunteers was lower (30 –35% lower) compared to the same dose administered from the approved FP CFC product. After multiple dosing in asthmatic patients, a dose-related increase in systemic exposure was observed when FP HFA in doses of 88 mcg, 220 mcg, and 440 mcg was administered. The increase in systemic exposure was not dose proportional. Decreased serum cortisol levels were noted in all active treatment groups compared to placebo but these decreases were not dose-related. The Biopharm reviewer concluded that there were not sufficient data to completely compare the exposure of FP administered using the HFA-propelled MDI versus the CFC-propelled MDI however this is not considered an approvability issue since there are clinical safety and efficacy data available *(See Biopharm review for complete details)*.

IV. Description of Clinical Data and Sources

A. Overall Data

The data used in this review were obtained from the NDA 21-433 submission. Three pivotal efficacy trials were submitted: FAP30007, FAP30008 and FLTA3022. In study FAP30007, the asthma population were previously maintained on ICS, whereas, in study FAP30008 the subjects had not been maintained on ICS prior to enrollment. Both studies evaluated the efficacy of Flovent HFA 88 mcg BID , 220 mcg BID and 440 mcg BID for the maintenance treatment of asthma. Study FLTA3022, was an oral corticosteroid –sparing trial

that compared FP HFA and CFC 440 mcg and 880 mcg BID to placebo in reducing mean daily prednisone usage.

In addition to safety assessments in the efficacy trials, the sponsor conducted 2 long-term safety studies that assessed the safety of Flovent® HFA given for 6 months (study FAP30001) and one year (FLTB3048). The one-year study compared the safety of Flovent® HFA 440 mcg BID with Flovent CFC 440 mcg BID. Additional safety data were provided in the 120-day safety update that presented data for the period October 4th 2001 through February 28th 2002.

B. Table of Clinical Studies

TABLE 1. PIVOTAL CLINICAL STUDIES

Study #	Location	Study Design	Treatments Arms/ BID Dosage (mcg)	Primary Endpoints	N Randomized	N Completed
FAP30007	US	Randomized, double-blind, placebo-controlled parallel 12-week efficacy study in asthmatics previously maintained on ICS	Flovent HFA 88 , 220, 440 Placebo HFA	Change from baseline to Endpoint in pre-dose percent predicted FEV_1	415	289 (69%)
FAP30008	US	Randomized, double-blind, placebo-controlled parallel 12-week efficacy study in asthmatics previously maintained on bronchodilators alone	Flovent HFA 88 , 220, 440 Placebo HFA	Change from baseline to Endpoint in pre-dose percent predicted FEV_1	397	312 (79%)
FLTA3022	US	Randomized, double-blind, placebo-controlled 16- week comparative trial of FP HFA and FP CFC 440 and 880 mcg BID versus placebo	FP HFA 440, 880 FP CFC 440 , 880 Placebo HFA	Mean oral prednisone use during the study (weeks 1-16)	168	113 (67%)
FLTB3048	Non- US	Randomized, double-blind parallel group long-term safety (52 weeks) study	FP HFA 440 FP CFC 440	N/A Long term safety study	325	292 (90%)
FAP30001	US	Randomized, double-blind parallel group long-term safety (26 weeks) study	FP HFA 220 FP HFA 440	N/A Long term safety	182	140 (77%)

APPEARS THIS WAY
ON ORIGINAL

C. Foreign Marketing and Postmarketing Experience

As of February 28, 2002, FP HFA was approved in 61 countries
— Countries where FP HFA has been approved include Canada as Flovent® HFA in July 2001, Australia as FLIXOTIDE (CFC-free) Inhaler in June 1998, Germany as FLUTIDE N in February, 1997, New Zealand, as FLIXOTIDE inhaler (CFC-free) and the United Kingdom as FLIXOTIDE EVOHALER in June, 2000.

— There have been no withdrawals of FP HFA from marketing for any reason related to safety or effectiveness.

D. Literature Review

The sponsor submitted an extensive review in support of the use of corticosteroids in asthma and the rationale for developing a CFC-free inhalation aerosol. This reviewer did not conduct a literature review for this NDA. Evidence to support the use of ICS in the maintenance treatment of asthma is well established and substantiated in the literature. Inhalation aerosols containing HFA-134a as the propellant have been previously approved and marketed in the U.S.

V. CLINICAL REVIEW METHODS

A. Conduct of the Review

The three efficacy trials and the 2 long-term safety studies were reviewed in detail. The dose proportionality study FLTA3020 was briefly reviewed for safety only. Each trial was reviewed individually and then discussed with the Medical Team Leader, Dr. Mary Purucker.

B. Overview of Materials Consulted in the Review

N/A

C. Overview of Methods used to Evaluate Data Quality and integrity

At the request of this reviewer, the Division of Scientific Investigations (DSI) conducted an audit at 2 U.S. study sites. One site from study SFCA30008 and one site from study FLTA3022 were audited. The sites were site # 40057 Medford, Oregon - Principal Investigator Edward M. Kerwin from study FLTA3022 and site # 10549 Portland, Oregon - Principal Investigator Michael J. Noonnan from study FAP30008. There were no particular concerns for selecting these sites for audit other than they were some of the sites that enrolled the

largest number of patients. From the inspection DSI concluded that both sites followed FDA regulations governing the conduct of clinical investigations and the protection of human subjects and that the data submitted in the NDA were acceptable for use in making a determination of approvability of the drug.

D. Ethical Conduct of Trials

The studies were conducted in accordance with "Good Clinical Practice" (GCP) guidelines and all applicable regulations including the Declaration of Helsinki [June 1964] as modified by the 48th World Medical Association, Republic of South Africa, October 1996. The Principal Investigator or a medically qualified designee explained the study to the subjects who were interested in participating. Participation in the studies was voluntary and subjects signed an informed consent document prior to enrollment or the conduct of any procedures. For subjects less than 18 years of age, written informed consent was provided by the subject and the subject's parent or legal guardian. A copy of the signed consent form was given to the subject and the investigator retained the original.

E. Evaluation of Financial Disclosure

GlaxoSmithKline states in an organization-wide policy statement that "Glaxo does not compensate clinical investigators in such a way as the total amounts could vary with the outcome of the study". With regard to "significant payments of other sorts" from the sponsor, the $25,000 threshold for "payments of other sorts" was not exceeded in the case of any investigator. Relying on information available internally, GSK determined that no investigator participating in the Flovent® HFA development program had a proprietary interest in Flovent® HFA

Based on available financial data, a significant equity interest [> $50,000] was exceeded in the case of one principle investigator, —
(investigator # — . The center (site —) at which —
was based enrolled —1.8%) of the — subjects in — . The sponsor conducted a impact analysis on the intent-to treat population excluding all subjects from this center to assess the impact of this center on the overall outcome of this study. The results from the analysis excluding this center were not different from the analysis of all subjects. The sponsor concluded that the contribution of this site to the overall subject population did not have a clinically or statistically meaningful impact on the overall study outcome. This reviewer concurs with the sponsor's assessment.

VI. INTEGRATED REVIEW OF EFFICACY

A. Conclusions

In the two 12- week U.S. studies FAP30007 and FAP30008, each dose of FP HFA within each study was statistically superior to placebo. The primary efficacy endpoint "was mean change from Baseline in AM pre-dose percent predicted FEV_1 at Endpoint". Numerically, there was a very small difference among the three dosage strengths and this difference is too small to be regarded as a dose response relationship. This finding does not come as a surprise because the absence of a dose-response relationship was demonstrated in previous studies during the early stages of this drug development program. In FAP30007, the mean treatment effect (FP – Placebo) was 10.5, 11.5, and 12.9% for FP 88, 220, and 440 mcg BID respectively ($p<0.001$). Whereas, in FAP30008, the mean treatment effect was 5.6, 6.4, and 7.8% respectively ($p<0.001$).

The high percentage of drop outs [31%] in FAP30007 arguably would make determination of the effect size difficult. The sponsor attempted to address this with a sensitivity analysis using a recursive regression model in which musing values were imputed. The mean pre-dose percent predicted FEV_1 was greater in the FP HFA groups at endpoint compared with the placebo group ($p<0.001$)

The secondary endpoints change from baseline in AM PEF, discontinuation for lack of efficacy, asthma symptom scores, and supplemental Ventolin® use were adjusted for multiple comparisons and the primary treatment comparison was FP 88 mcg BID vs. placebo. In study FAP30007, FP HFA 88 mcg BID was significantly ($p<0.001$) superior to placebo in increasing AM PEF, in decreasing asthma symptoms and supplemental Ventolin® use, and in reducing discontinuations from the study for a lack of efficacy. In study FAP30008 only the improvement in AM PEF was statistically significant ($p<0.001$) in the FP HFA 88 mcg BID group compared with placebo and only subjects in the FP 440 mcg BID group had a significantly greater probability ($p =0.004$) of remaining in the study compared with those in the placebo group.

Subjects previously maintained on prednisone (5mg - < 45mg daily) were able to significantly reduce their daily prednisone usage during the 16-week treatment with FP HFA 440 mcg BID or 880 mcg BID. Subjects treated with FP 440 and 880 mcg BID had a mean daily oral prednisone use of 5.8 mg/day and 6.2 mg/day respectively compared with subjects treated with placebo who had a mean daily oral prednisone use of 14.9 mg/day ($p<0.001$). The FP 880 mcg BID treatment arm did not appear to have a treatment advantage compared to the FP 440 mcg BID treatment arm. Similarly, with the CFC formulation, a treatment advantage was not observed with the 880 mcg BID dose. In addition to the statistically significant reduction in mean daily prednisone usage, subjects treated with high doses of FP were able to maintain or improve their lung function (as measured by pre-dose FEV_1) whereas, subjects in the placebo group had

significant deterioration in lung function. As expected the majority of subjects in the placebo group (67%) prematurely discontinued mainly due to lack of efficacy.

Patient's perception of the effect of their asthma on their overall "quality of life" was assessed in the three efficacy studies using the Asthma Quality of Life Questionnaire. The data from the 16-week study is difficult to interpret because of the high percentage of drop outs (67%) in the placebo group. The sponsor used LOCF but this method of accounting for missing data is particularly problematic for a patient reported outcome measure. In both 12-week efficacy studies (FAP30007 and FAP30008), subjects treated with FP HFA 440 mcg BID had a clinically meaningful improvement (>0.5 point improvement above placebo) in their overall score and in each individual domain. Similar findings were observed for the FP HFA 88 mcg and 220 mcg BID treatment groups in study FAP30007 but not in study FAP30008.

B. General Approach to the Review of the Efficacy of the Drug

Described in section IV "Description of Clinical Data Sources" and section V "Clinical Review Methods".

C. DETAILED REVIEW OF CLINICAL TRIALS

The three efficacy trials for the clinical development program for Flovent HFA are:

FAP30007 "A randomized, double-blind, parallel-group, placebo-controlled 12-week trial of inhaled Fluticasone propionate 88 mcg BID, 220 mcg BID, and 440 mcg BID versus placebo in propellant GR106642X (HFA) in adolescent and adult subjects with asthma who are maintained on inhaled corticosteroid therapy (ICS)".

SFCA 30008 "A randomized, double-blind, parallel-group, placebo-controlled 12-week trial of inhaled Fluticasone propionate 88 mcg BID,220 mcg BID, and 440 mcg BID versus placebo in propellant GR106642X (HFA) in adolescent and adult subjects with asthma who are maintained on bronchodilator therapy alone. "

FLTA3022: "A randomized, double-blind, placebo-controlled comparative trial of Fluticasone propionate 440 mcg BID or 880 mcg BID versus placebo administered via metered-dose inhaler in propellant 11/12 or GR1066642X in adolescent and adult oral corticosteroid-dependent asthmatics."

All three studies were reviewed in detail. The trial design of FAP30007 and FAP30008 was identical except that subjects were not previously maintained on

ICS in study FAP30008. The trial design of these two studies is described together, followed by a description of the trial design for study FLTA3022.

TRIAL DESIGN of STUDIES FAP30007 AND FAP30008

OBJECTIVES

1. To assess the efficacy and safety of FP 88 mcg, 220 mcg and 440 mcg BID versus placebo in HFA propellant delivered from the 44 mcg, 110 mcg, and 220 mcg product administered over 12 weeks to adolescent and adult subjects with asthma who were previously maintained on ICS therapy (study FAP30007).

2. To assess the efficacy and safety of FP 88 mcg, 220 mcg and 440 mcg BID versus placebo in HFA propellant delivered from the 44 mcg, 110 mcg, and 220 mcg product administered over 12 weeks to adolescent and adult subjects with asthma who were previously maintained on bronchodilators alone (study FAP30008).

These trials were randomized, double blind, placebo-controlled, parallel group studies with a 12-week treatment period. In both studies, the Investigators assessed eligibility for enrollment during a 7 – 14 day screening period. The purpose of the screening period was to evaluate the subject's eligibility for the study and to obtain baseline measures of efficacy and safety. Subjects were allowed to continue on their stable doses of ICS during the screening period but were switched from their prescribed short-acting beta-agonists to open-label Ventolin® and were to continue using Ventolin® as needed for the remainder of the study.

At the end of the screening period, the Investigators re-assessed subjects to determine their eligibility for randomization. The subjects who had a best FEV_1 of 45-80% predicted, and who did not have signs of worsening asthma (defined below) were eligible for randomization. Subjects eligible for randomization were randomized to one of the following four treatment groups for 12 weeks:

- FP 88 mcg HFA (2 inhalations of 44 mcg product) BID
- FP 220 mcg HFA (2 inhalations of 110 mcg product) BID
- FP 440 mcg HFA (2 inhalations of 220 mcg product) BID
- Placebo HFA (2 inhalations) BID

Subjects were not allowed to use spacers in these studies.

Patients returned for follow up at out-patient clinics at Treatment Weeks 1, 2, 3, 4, 6, 8, and 12. Subjects who did not complete the study returned for a Post-Treatment visit 1 –2 weeks following discontinuation.

PATIENT POPULATION

The study population was comprised of male and female subjects at least 12 years of age with a diagnosis of asthma for ≥ 6 months as defined by the ATS. Subjects had an FEV_1 of 45% - 80% predicted and demonstrate reversibility (≥ 12% improvement in FEV_1) following 2 inhalations of Ventolin® at the screening visit. Subjects who did not demonstrate reversibility at screening were allowed to have a repeat reversibility assessment either at or before randomization and subjects who failed the reversibility assessment at that time were not eligible for randomization . For study FAP30007, all subjects had to be taking ICS for at least 3 months and had to be on a stable regimen for at least 30 days prior to the screening visit at or below the maximum dose allowed *(see Appendix I Table 1 page 76)*. In contrast, subjects in study FAP30008 were only using p.r.n bronchodilators.

The exclusion criteria were similar to those used in previous asthma trials such as the exclusion of subjects with history of life threatening asthma, upper or lower respiratory tract infections within 2 weeks prior to the screening visit, clinically significant ECG or clinical laboratory abnormalities, and significant concurrent medical conditions. Subjects with a history or current diagnosis of glaucoma or posterior subcapsular cataracts as well as subjects who had participated in any previous FP HFA clinical trial were excluded.

Disallowed medications included (i) Methotrexate, gold, cyclosporine, and other immunosuppressive medications, (ii) oral/systemic corticosteroids and other corticosteroids except for Flonase ® Nasal Spray and ≤ 1% hydrocortisone cream or ointment, (iii) Leukotriene modifiers, (iv) Inhaled cromolyn sodium and inhaled nedocromil sodium, (v) Serevent®, (vi) inhaled anticholinergics (e.g. Atrovent®, or atropine), and (vii) theophylline.

Subjects were discontinued for any of the following reasons:

- Lack of efficacy/worsening asthma. Subjects who met any of the following criteria during the 7 days preceding a study visit, (or at study visit in the case of FEV_1) were considered as having a lack of efficacy/worsening asthma:

  - AM PEF below the PEF stability Limit for > 3 days[5].The stability Limit was calculated at Visit 2 and was defined as 80% of the mean of the morning PEFs measured on the seven days preceding Treatment Day 0.
  - ≥12 puffs/day of Ventolin ® for >3 days
  - >3 nighttime awakenings due to asthma requiring treatment with Ventolin®
  - FEV_1 below the FEV_1 Stability Limit at a study visit. The Stability Limit was defined as 80% of the best FEV_1 measured on Treatment Day 0.

[5] Not necessarily consecutive

- Inadequate study medication compliance
- Breaking of the study blind
- Voluntary discontinuation
- Discontinuation at the discretion of the Investigator.

STATISTICAL AND ANALYTICAL PLAN

EFFICACY

Primary Efficacy Endpoint

The primary efficacy measure was mean change from Baseline to Endpoint in morning (AM) pre-dose percent-predicted FEV_1. Baseline FEV_1 was determined at randomization. Endpoint was the measurement taken at Week 12 or was the last observation carried forward (LOCF) for subjects who discontinued.

Secondary Efficacy Endpoints

There were four (4) key secondary endpoints.

1. Mean change from Baseline in AM and PM PEF at Weeks 1 through 12[6].
2. Duration of participation in the study
3. Mean change from Baseline in Ventolin® use
4. Mean change from Baseline in Asthma symptom scores at Weeks 1 through 12

The mean change from baseline in FEV_1 (measured as percent predicted, percent change from Baseline, and absolute change) at Weeks 1, 2, 3, 4, 6, 8, 12, and follow-up, and nighttime awakenings were also defined by the sponsor as secondary efficacy measures.

Health Outcomes Measures

The Asthma Quality of Life Questionnaire (AQLQ) developed by Juniper was used to asses the impact of asthma on the patient's quality of life. The AQLQ contains 32 items in four domains: activity limitation (11 items), symptoms (12 items), emotional function (5 items), and environmental stimuli (4 items). The response format consists of a 7-point scale where 1 indicates maximal impairment and 7 indicates no impairment. A clinically meaningful change for both overall quality of life score and individual domains was previously defined as 0.5 per item[7].

Subjects completed the questionnaire at the randomization visit and at Week 12 or at the discontinuation Visit. The mean Overall Score as well as the mean score in all four domains [Activity Limitation, Asthma symptoms, Emotional Function and Environmental Exposure] were analyzed. The sponsor defined *a priori* a reduced ITT population as the primary analysis population for the AQLQ

---

[6] Per the protocol procedures, morning PEF was taken before the AM dose of study medication. The evening PEF was taken before bedtime and could have been taken after the evening dose of study medication.

[7] Juniper, 1994, Determining the Clinically meaningful change

comprised of subjects with an overall AQLQ score of ≤5.8 at Baseline. Statistical analyses of AQLQ scores were based on mean change in response scores from baseline to endpoint.

Sample Size and Power Calculations

The sponsor estimated a standard deviation for percent predicted FEV_1 of 15% based on previous studies. A sample size of 98 subjects in each group would have 90% power to detect a difference between placebo and active groups of 7 percent of predicted FEV_1 in the change from baseline to endpoint using a two sample t-test with an α of 0.05. Therefore, a total of 392 evaluable subjects were needed for the study.

For the AQLQ the estimated standard deviation for the overall AQLQ score was 1.0 based on previous studies. The sponsor noted that if at least 64 subjects per treatment group would meet the criteria of an overall AQLQ score at baseline of ≤5.8, then the study would have at least 80% power to detect a difference in AQLQ of 0.5 points using a two-sample t-test with a two-sided significance level of 0.05. If all 98 subjects per group had a baseline score of ≤5.8 there would be 93% power to detect a difference of 0.5 points.

Handling of missing data

The sponsor used the last observation carried forward (LOCF) to Week 12 to account for data of subjects who discontinued prematurely from the study. The sponsor also used a recursive regression model to assess the impact of missing data on the interpretation of the FEV_1 results.

Multiple comparisons and multiplicity adjustment

For the primary endpoint, there were 3 pair-wise comparisons between active treatment and placebo. Therefore, the hypothesis that correspond to the primary analyses were:

H_{01}:FP440mcg = P H_{A1}:FP440mcg ≠ P
H_{02}:FP220mcg = P H_{A2}:FP220mcg ≠ P
H_{03}: FP88mcg = P H_{A3}: FP88mcg ≠ P

The multiple comparisons of active treatment groups with placebo were adjusted using Hochberg's method. This method controlled the type I error rate at 0.05. The p values from the comparisons of active treatment groups with placebo were ranked from the least to the greatest i.e. p1 ≤ p2 ≤ p3 and superiority claims were made according to the following:

If p3 < 0.05 then all pairwise comparisons were considered significant
If p2 < 0.025 then significance was claimed for p1 and p2 only
If p1 < 0.0167 then significance was claimed for p1 only.

Four of the secondary endpoints were adjusted for multiplicity. These endpoints were:

- change from baseline in morning PEF,
- duration of participation in the study,
- change from baseline in supplemental Ventolin® use,
- change from baseline in asthma symptom scores.

The Hochberg method described above was used for multiplicity adjustment. The primary treatment comparison was FP 88mcg vs. placebo, with the comparisons of FP220 mcg and FP440 mcg vs. placebo as supportive.

SAFETY

Safety assessments included adverse events, clinical laboratory data, HPA-axis function, 12-lead EKGs, oropharyngeal examinations, and vital signs. HPA-axis function was assessed using 24-hour urine cortisol.

Compliance

Compliance was assessed during the 12-week period based on information from the diary card. Compliance was calculated as the number of doses actually used by the subject divided by the expected number of doses used, multiplied by 100.

STUDY DESIGN FLTA3022

Title: "A randomized, double-blind, placebo-controlled comparative trial of Fluticasone propionate 440 mcg BID or 880 mcg BID versus placebo administered via metered-dose inhaler in propellant 11/12 or GR1066642X in adolescent and adult oral corticosteroid-dependent asthmatics".

STUDY DESIGN

The study was a randomized, double-blind, parallel-group, placebo-controlled trial with a 16 week treatment period. The double-blind treatment period started 14± 2 days after the initial screening. Follow up visits were scheduled weekly.

The HFA and the CFC formulations of the Fluticasone propionate 220 mcg strength products were used in this study. Subjects were randomized to one of the following treatment arms.

- Placebo HFA
- FP HFA 440 mcg BID
- FP HFA 880 mcg BID
- FP CFC 440 mcg BID
- FP CFC 880 mcg BID

In order to maintain the blind all subjects received 2 inhalers. For the 440 mcg BID arm subjects took 2 puffs of the active inhaler BID and 2 puffs of the placebo inhaler. For the 880 mcg BID arm, subjects took 2 puffs BID of two active inhalers.

STUDY POPULATION

Subjects were enrolled in the study if they were at least 12 years of age and had a diagnosis of asthma for at least 1 year. Subjects had to be oral corticosteroid-dependent for the past 6 months and had to be on their minimum effective dose of oral corticosteroid. The minimum dose of prednisone allowed at study entry was 5 mg daily (QD) or 10 mg every other day (QOD) and the maximum dose allowed at entry was 40 mg QD or 80 mg QOD. Subjects taking inhaled corticosteroids except Flovent ® were also eligible for enrollment. Concurrent inhaled corticosteroids were discontinued at randomization. As with other asthma studies, subjects had to demonstrate reversibility by demonstrating an increase in FEV_1 of ≥12% approximately 15 minutes following inhalation of 2 puffs of Ventolin® at Visit 1 (screening visit) or as a result of other pharmacotherapy (e.g. prednisone treatment or nebulized albuterol) during the previous 6 months.

Subjects had to have been maintained on the same dose of oral corticosteroid for at least 2 weeks prior to Visit 2 (baseline). Subjects were allowed to take inhaled corticosteroids prior to randomization up to the following doses displayed in Table 2 as long as those doses remained constant within 4 weeks prior to randomization. All ICS had to be discontinued the evening prior to randomization and for the duration of the study.

Table 2 Maximum Dose of ICS allowed prior to randomization

Generic Name	Brand Name	Maximum dose
Beclomethasone dipropionate	Beclovent® Vanceril®	Up to 16 inhalations/day
Dexamethasone sodium phosphate	Decadron phosphate Respihaler ®	Up to 12 inhalations/day
Triamcinolone acetonide	Azmacort ®	Up to 16 inhalations/day
Flunisolide	Aerobid ®	Up to 6 inhalations/day
Note: concurrent use of Flovent® is not allowed and should not have been used within the 4 weeks prior to Visit 1		

Subjects were to be excluded if any of the exclusion criteria were met. These exclusion criteria were essentially the same as those described for the previous asthma trials discussed.

Disallowed Medications included (i) Ophthalmologic, dermatologic (except topical hydrocortisone cream or ointment of ≤ 1%, (ii) injectable corticosteroid therapy during the 1 month prior to Visit 1, (iii) Ketoconazole (other antifungals were allowed), and (iv) Influenza vaccination within 4 weeks of Visit 2 (Baseline).

Permitted medications included (i) long-acting beta$_2$-agonists and theophylline at the same constant dose and frequency, (ii) topical hydrocortisone cream or ointment of ≤ 1%, (iii) topical nasal medications: Nasalcrom®, Flonase®, Afrin®

Claritin® and OTC antihistamines (must be withheld prior to study visits), and (iv) regularly scheduled immunotherapy provided that the subject has received his/her usual stable maintenance dose for 12 weeks prior to Visit 1.

STUDY PROCEDURE

Patients eligible for enrollment entered a 2-week screening period. During this time, they continued taking all anti-asthma medications including inhaled corticosteroids (ICS) without adjustment in dosage or dosing interval with the exception that Ventolin® replaced all other short-acting inhaled beta$_2$- agonists. All subjects received a supply of prednisone tablets and were instructed to use them in place of and at the same dose as the prednisone used during the 2 weeks prior to screening. During the 2-week screening period subjects recorded peak flow measurements, and subjective assessments of asthma (i.e. symptoms, Ventolin® use, nighttime awakenings) in a diary card.

At visit 2 subjects were assigned to one of five double-blind treatment arms if they had a best FEV_1 of 40 –85% predicted, met all the criteria for enrollment, and demonstrated compliance (i.e. were able to complete the diary cards, and withhold medication for the time defined in the protocol). Subjects had weekly follow up visits in the clinic.

Prednisone Dose adjustment

Subjects continued to take their current prednisone dose for a 2-week post-randomization stabilization period and thereafter the investigator titrated the dose once a week according to the prednisone modification chart outlined below.

Table 3 Prednisone titration chart

Prednisone Maintenance Dose Modification Chart

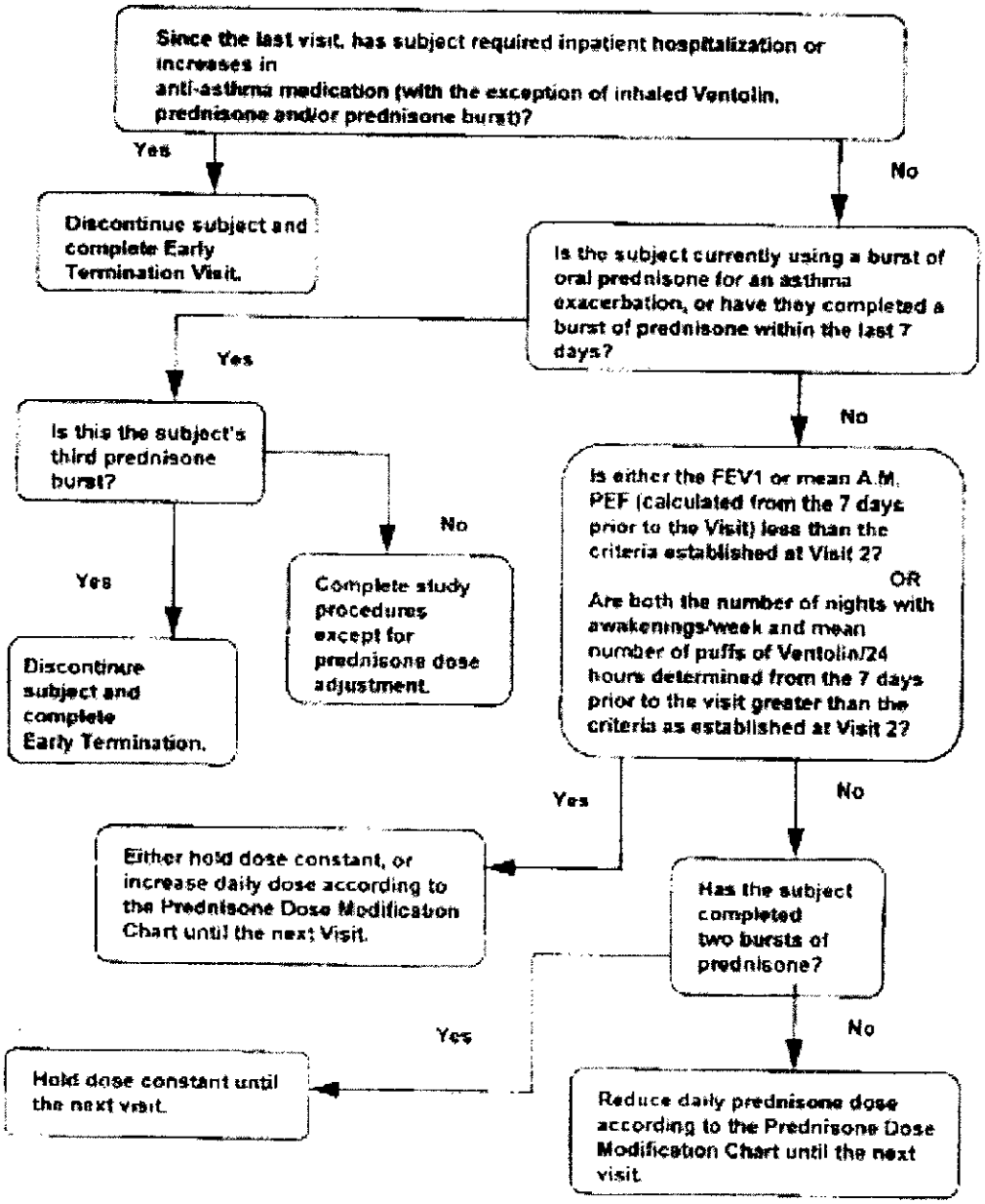
Maintenance Dose	Dose Reduction/Increase
≥30mg QD (60mg QOD)	10mg QD(20mg QOD)
>10mg QD <30mg QD (>20mg QOD to <60mg QOD)	5mg QD(10mg QOD)
>5mg QD ≤10mg QD(>10mg QOD to ≤20mg QOD)	2.5mg QD(5mg QOD)
≤5mg QD (≤10mg QOD)	1.25mg QD (2.5mg QOD)

(Table source: Pg. 25 FLTA3022.pdf)

All investigators followed a prespecified decision diagram for prednisone dose adjustment to determine whether the daily prednisone dose should be reduced. The decision diagram is depicted below *(source pg. 1536 FLTA3022.pdf)*.

DIAGRAM 2

**DECISION DIAGRAM FOR PREDNISONE DOSE ADJUSTMENT
VISITS 4-18 (WEEKS 2-16)**



STATISTICAL AND ANALYTICAL PLAN

Efficacy

Primary efficacy measurement

The primary measure of efficacy was mean oral prednisone use over the treatment period (Weeks 1-16). This included both maintenance prednisone and any prednisone prescribed as part of a prednisone burst. The primary efficacy endpoint was mean daily oral prednisone use. The mean daily oral prednisone use was calculated by adding each day's total daily dose for the time period of interest and dividing by the total number of days in that time period.

Secondary efficacy measurements

The sponsor looked at ten (10) secondary efficacy endpoints which are numerated below:

1. Reduction in oral prednisone use
2. Mean dose of prednisone at baseline and endpoint
3. Mean change from baseline in prednisone dose
4. Time to sustained elimination of prednisone dose
5. Duration of study participation
6. FEV_1
7. PEF (subject-administered)
8. Daily symptom scores
9. Nighttime awakenings requiring Ventolin ® use
10. Inhaled Ventolin® use

The same questionnaire used in the other studies the Asthma Quality of Life Questionnaire (AQLQ) by Juniper was used to assess patient reported outcomes. The questionnaire was administered at baseline and after 16 weeks of treatment or earlier in the case of withdrawal from the study.

The last observation carried forward (LOCF) was used as a method to handle missing data from subjects who were withdrawn from the study. The sponsor also conducted completer analysis (analysis in which the discontinued subjects' last value was not carried forward) to distinguish between LOCF.

Sample Size considerations

The standard deviation of average daily oral prednisone use adjusted for baseline was assumed to be 10mg based on previous studies. With 33 subjects per arm there will be > 80% power to detect a difference in average daily oral prednisone use of 7 mg between any 2 treatment groups using a 2- tailed test with an α level of 0.05.

Multiple comparisons
Pairwise comparisons to placebo were performed in a sequential manner, beginning with the FP HFA 880 mcg BID group and the FP CFC 880 mcg group. If neither of these comparisons was significantly different from placebo, further p-values were not interpreted. If these p-values were significant, comparisons to placebo were interpreted for the FP 440 mcg groups.

Safety
Safety assessments included adverse events assessment, clinical laboratory tests, physical examination including oropharyngeal exams, assessment of HPA-axis function (Cortrosyn® stimulation testing), 12-lead ECG and vital signs.

Medication compliance
Medication was assessed based on the data recorded in the patient diary cards.

EFFICACY RESULTS

The primary efficacy results for FAP30007 and FAP 30008 are presented first, followed by the secondary endpoints for these studies. Next the efficacy findings for FLTA3022 are presented.

The baseline asthma characteristics of the subjects in both studies were similar. The baseline FEV_1 was between 65% and 67% predicted normal and over half of the subjects (52 –63%) had asthma for ≥ 15 years

Primary Efficacy Results FAP30007

Change from baseline to Endpoint in mean morning pre-dose percent-predicted FEV_1

The efficacy results were as expected with subjects in the placebo group, having a decrease in FEV_1 and subjects in the active treatment groups showing improvement in lung function as measured by FEV_1 throughout the 12- week treatment period and realizing a statistically significant increase in percent predicted FEV_1 compared with placebo at Endpoint for all three doses of FP. The table below depicts these results.

Table 4: FAP 30007 Primary Efficacy Results
Mean change from Baseline in AM pre-dose FEV_1 % predicted at Week 12 (LOCF)

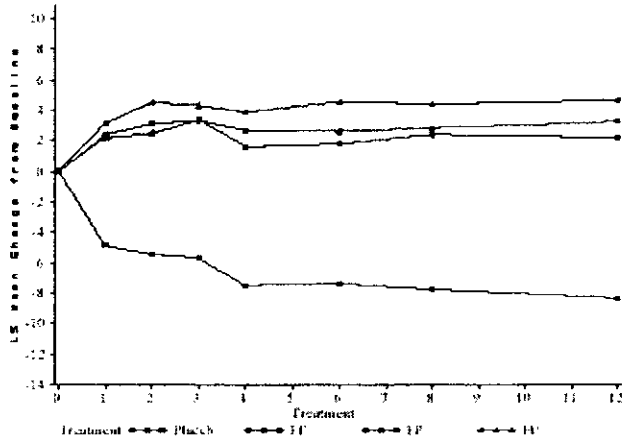
	Placebo HFA	FP 88 HFA	FP 220 HFA	FP 440 HFA
Baseline (n)	104	103	106	102
Mean FEV_1 (%)	65.6	65.3	65.5	66.2
Baseline FEV1 (L) (SE)	2.22 L (0.06)	2.14 L (0.05)	2.16 L (0.05)	2.11 L (0.05)
Week 12 (n)	102	100	105	98
Mean FEV_1 (L) (SE)	1.96 L (0.06)	2.24 L (0.07)	2.30 L (0.07)	2.29 L (0.06)
Mean FEV_1 (%)	58.0	68.1	69.7	72.2
LS mean change %	-8.3 (1.2)	2.2 (1.2)	3.2 (1.1)	4.6 (1.2)

predicted (SE)				
95% CI	-	(7.7,13.3)	(8.8, 14.4)	(10.1, 15.8)
LS mean difference FP – placebo	-	10.5 (p < 0.001)	11.5 (p<0.001)	12.9 (p<0.001)

As seen in the table, numerically, the higher doses of FP had a slightly greater improvement in FEV_1 at Endpoint but the differences are too small to constitute a true dose-response relationship.

The adjusted mean change in FEV_1 (L) from baseline at Week 12 for the placebo group was – 0.26L. The effect size (active – placebo) was 0.36L, 0.40L, and 0.44L for the FP 88, FP 220, and FP 440 treatment groups respectively. A graphic display of the primary efficacy results is depicted below copied from the sponsor's submission. The curves from top to bottom are for the FP 440, 220, 88 mcg arms, and placebo respectively.

LS Mean Change from Baseline in AM Pre-Dose Percent Predicted FEV_1
(ITT Population with LOCF – Study FAP30007)



The sponsor also did a post-hoc analysis of the primary endpoint without LOCF and the results were similar to those of the primary analysis with LOCF for the active treatment arms. In the placebo arm a change in lung function was not observed. The table below is copied from the sponsor's submission FAP 30007.pdf and displays those results.

Table 5 – Primary Efficacy Endpoint FAP30007 without LOCF

Mean Change from Baseline in AM Pre-Dose Percent Predicted FEV_1 at Week 12 for Subjects who Completed the Study (Without LOCF)

(ITT Population – Study FAP30007)

	PLA HFA (N=104)	FP 88 HFA (N=103)	FP 220 HFA (N=106)	FP 440 HFA (N=102)
Baseline (n)	104	103	106	101
Mean (%)	65.6	65.3	65.5	66.2
Week 12 (n)	40	85	84	79
Mean (%)	66.5	70.2	73.1	74.5
Mean Change	-0.1	4.8	6.4	7.7
LS Mean Chg[b] (SE)	0.02 (1.50)	5.1[a] (1.10)	6.3[a] (1.11)	7.2[a] (1.15)
95% CI[c]	---	(1.9, 8.3)	(3.1, 9.5)	(3.9, 10.4)
95% Dunnett's CI[d]	---	(1.3, 8.8)	(2.5, 10.0)	(3.4, 11.0)

Reviewer comment
It is interesting that > 1/3 of subjects receiving ICS at the time of recruitment were able to maintain control of their asthma at least as measured by mean FEV_1 for the full 12 weeks of the trial while on placebo. This is a strong argument for practitioners to taper ICS during periods of asthma stability, in order to limit exposing patients to the risk of ICS without deriving any tangible benefit.

Sensitivity Analysis

As expected, there was an excessive number of dropouts in the placebo group. To address the impact of missing data on the results the sponsor designed a recursive regression model using covariates that included sex, age, Baseline % predicted FEV_1, site cluster, and the previous visit's percent predicted FEV_1. For each successive visit, the model was fitted to impute the missing values using the observed or the imputed (wherever missing) values from the previous visit. At Week 12, a complete set of data on percent predicted FEV_1 were obtained for all subjects who had baseline and at least one post-baseline assessment on percent predicted FEV_1. These data were then fitted in an ANCOVA model. To address a worse case scenario, a 5% penalty was made for the subjects in the active treatment groups (i.e. using 95% of the imputed value at Week 12 prior to calculating the residuals and testing for treatment effect. Placebo-treated subjects or FP-treated subjects who had the observed (instead of imputed) percent predicted FEV_1 did not have a penalty applied to their data.

The residuals mean AM pre-dose percent predicted FEV_1 were greater in the FP HFA groups at week 12 (0.87% to 2.57%) compared with the placebo group (-4.91%) , $p < 0.001$. When the 5% penalty was applied the results were still statistically significant.

Primary Efficacy Results FAP30008

Primary efficacy endpoint – Mean change from baseline in AM pre-dose percent predicted FEV_1 at Endpoint

Similar to study FAP30007, there was a statistically significant improvement in AM pre-dose percent predicted FEV_1 at endpoint for all three FP arms compared to placebo ($p < 0.001$). There was no strong evidence for a dose-response relationship. The results are summarized in Table 6 below.

Table 6 Primary Efficacy Endpoint FAP 30008

	Placebo HFA N =99	FP HFA 88 mcg N= 100	FP HFA 220 mcg N =98	FP HFA 440 mcg N = 100
Baseline (n)	99	99	98	100
Mean FEV_1 L (SE)	2.40 L (0.06)	2.35 L (0.06)	2.50 L (0.06)	2.30 L (0.05)
Mean FEV_1 (%)	67.0	67.0	67.3	67.1
Week 12 (n)	96	95	95	99
Mean FEV_1 L (SE)	2.56 L (0.07)	2.67 L (0.07)	2.85 L (0.07)	2.69 L (0.06)
Mean FEV_1 (%)	71.1	76.3	76.8	78.1
LS Mean change (SE)	3.4	9.0 (1.1)[a]	9.8 (1.1)[a]	11.2 (1.0)[a]
a = $p < 0.001$ Vs placebo (Hochberg multiplicity adjustment)				

The analysis of the primary efficacy endpoint without LOCF, as well as the sensitivity analysis (described for study FAP30007), also showed statistically significant differences between the three FP treatment groups and placebo. There was no clinically meaningful difference within the active treatment groups At Week 12, the improvement from baseline in FEV_1 (L) in the placebo group was 160 mL. The effect size (active – placebo) in the treatment arms was smaller than what was observed for study FAP30007 and was 0.16L, 0.19L, and 0.23L in the FP 88, FP 220, and FP 440 treatment arms respectively.

Secondary Efficacy Results FAP30007 and FAP30008

The secondary efficacy endpoints evaluated were:

1. AM PEF
2. Supplemental Ventolin® use
3. Asthma symptom scores
4. Duration of study participation(discontinuations due to lack of efficacy)

In study FAP 30007, there was statistically significant improvement in all four secondary efficacy endpoints for the FP HFA 88 mcg treatment groups. However, in study FAP30008 there was a statistically significant improvement only for AM peak flow and discontinuations due to lack of efficacy was statistically significant for only the FP 440 mcg BID treatment arm.

Table 7 Secondary endpoints, AM PEF, Ventolin use and asthma symptom scores
FAP 30007

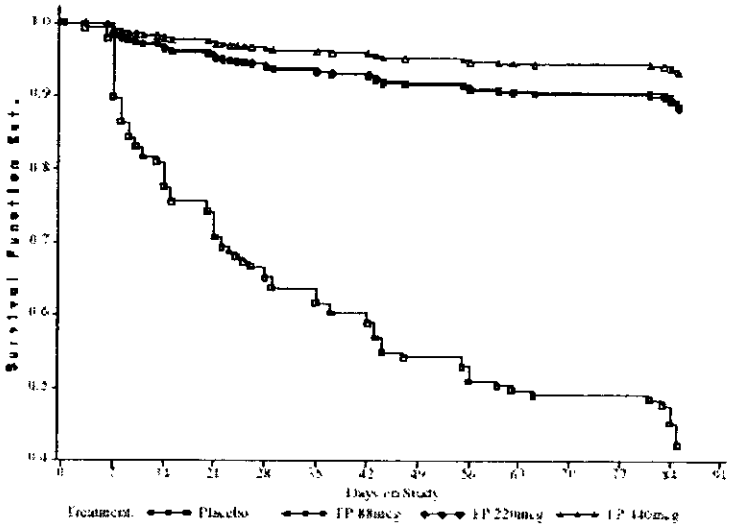
Endpoint	Placebo (n = 104)	FP 88 HFA (n=103)	FP 220 HFA (n=106)	FP 440 HFA (n=102)
AM PEF (L/min)				
Baseline (n)	104	103	106	102
Mean (L/min)	346.0	334.8	329.0	333.1
Week 12 (n)	102	100	105	100
Mean (L/min)	326.6	356.9	348.9	356.0
LS mean change (SE)	-20.7	20.8	20.9	20.9
Supplemental Ventolin® Use				
Baseline (n)	104	102	105	102
Mean (puffs/24hr)	2.38	2.69	2.52	2.72
Week 12 (n)	102	100	105 1	00
Mean (puffs/24hr)	3.24	2.20	1.86	1.96
LS mean change (SE)	1.09 (0.20)	-0.16(0.21)	-0.44(0.20)	-0.43(0.21)
Asthma symptom scores*				
Baseline (n)	103	101	105	100
Mean (points)	1.79	1.77	1.77	1.61
Week 12 (n)	101	98	105	98
Mean (points)	2.09	1.38	1.46 1.1	9
LS mean change (SE)	0.38 (0.10)	-0.32(0.10)	-0.26(0.10)	-0.40(0.10)

Discontinuation for lack of efficacy (duration of study participation) in study FAP 30007

The estimated probability of remaining in the study was assessed at 2-week intervals using Kaplan- Meier estimates. The probability of remaining in the study was higher for each FP treatment group compared with placebo at each two-week interval. At week 1, the probability of remaining in the study in the FP HFA treatment groups was 0.89 for the FP 88 treatment group, 0.90 for the FP 220 treatment group, and 0.94 for the FP 440 treatment group compared with 0.45 for placebo-treated subjects ($p<0.001$). The figure below copied from the sponsor's submission depicts the survival in the study. As shown in the graph, the FP 440 mcg arm (top curve) had some separation from the from the FP 88 and 220 mcg arms which are almost superimposible.

APPEARS THIS WAY
ON ORIGINAL

Duration of Subject Participation in the Study - SDF Estimates
(ITT Population – Study FAP30007)



(Data source FAP30007.PDF pg. 85)
Survival curve is based on discontinuations due to lack of efficacy. Subjects who discontinued for other reasons were censored in this analysis.

As mentioned earlier, only AM PEF was statistically significant in study FAP30008. Table 8 displays the secondary endpoint results for FAP30008.

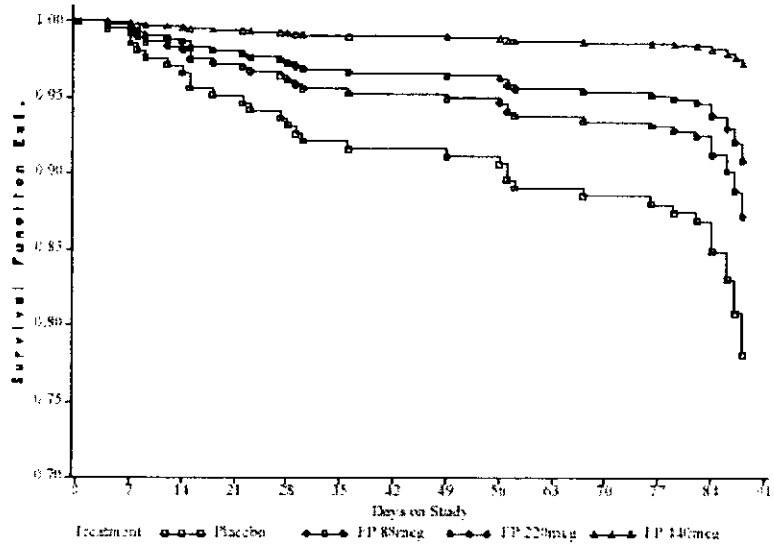
Table 8 - Secondary Endpoints – FAP 30008
AM peak flow, supplemental Ventolin® use and asthma symptom scores.

	Placebo HFA N =99	**FP HFA 88 mcg N= 100**	**FP HFA 220 mcg N =98**	**FP HFA 440 mcg N = 100**
AM Peak flow – change from baseline in AM peak flow (L/min) at Week 12 (LOCF)				
Baseline (n) Mean (L/min)	99 353.4	100 344.9	98 372.7	99 335.6
Week 12 (n) Mean (L/min) *LS mean change (SE)	98 363.4 11.4 (6.0)	97 384.1 41.7 (6.0) ***[p<0.001]**	97 415.5 47.6 (6.0)	99 390.0 54.1 (5.9)
Supplemental Ventolin ® use –Change from baseline in supplemental Ventolin use (puffs/24hrs)				
Baseline (n) Mean (puffs/24hr)	992.79	100 3.67	98 3.17	99 2.86
Week 12 (n) Mean (puffs/24hr) LS mean change (SE)	98 2.19 -0.76 (0.18)	97 2.21 -1.17 (0.18)	97 1.63 -1.51 (0.18)	99 1.09 -1.90 (0,17)
Asthma symptom scores- Change from baseline in asthma symptom scores (points) at Week 12				
Baseline (n) Mean (points)	99 1.98	100 2.07	98 2.19	98 2.01
Week 12 (n) Mean (points) LS mean change (SE)	98 1.68 -0.33(0.10)	97 1.45 -0.61 (0.10)	97 1.49 -0.65 (0.10)	98 1.12 -0.92 (0.10)

Duration of study participation (Discontinuations for lack of efficacy) in FAP30008

There was a higher probability of remaining in the study for each FP treatment group compared with placebo at each two-week interval. However, the difference in survival between the FP 88 and the placebo group, or between the FP 220 and the placebo group was not statistically significant. However, subjects treated with FP 440 mcg had a significantly greater probability (p = 0.004) of remaining in the study compared with those in the placebo group. The graph of the survival curves is displayed below copied from the sponsor's submission FAP30008.pdf. the curves from top to bottom represent the FP 440, 220, and 88 mcg treatment arms, and placebo.

Duration of Subject Participation in the Study - SDF Estimates
(ITT Population – Study FAP30008)



Health Outcomes Results FAP30007 and FAP30008

Subjects whose total score at baseline was ≤ 5.8 made up the "asthma quality of life population". In study FAP30007, subjects in each of the active treatment groups had an improvement of at least the minimum clinically important change (≥0.5) in each of the 4 domains and in the overall score at Week 12 *(See Appendix I, Table 7 pg. 87 and Appendix II, Table 15, pg. 97)*. Each of the FP treated groups when compared with placebo had clinically significant improvements in the overall score (≥ 0.5) and in the individual domains of Activity limitation, Asthma symptoms and Emotional Function at Week 12. In

study FAP30008, only the FP 440 treatment group had a clinically significant improvement (≥ 0.5) in the overall score and in each individual domain.

EFFICACY RESULTS FLTA3022

Three subjects were excluded from the 168 subjects that made up the ITT population. The efficacy analyses were conducted on this reduced ITT population (n = 165). The three subjects who were excluded were one subject who received study drug but withdrew prior to any post-randomization assessments being done, and the 2 subjects at Dr. — site[8]. (During the conduct of this study, the FDA imposed regulatory and administrative sanctions on Dr for violations identified in the conduct of ***other studies*** at his investigative site). Therefore, results from his site were excluded from the analyses.

Primary efficacy endpoint: Mean daily oral prednisone dose

The mean results are summarized in the table below copied from the sponsor's submission. Each FP treatment arm had a statistically significantly lower mean daily oral prednisone use compared to placebo. The highest FP dose 880 mcg Bid (both the HFA and the CFC) did not demonstrate a treatment advantage over FP 440 BID.

Table 9 – Mean Daily Prednisone Use, Mg

Summary of Mean Daily Oral Prednisone Use, mg Reduced ITT Population					
	Placebo HFA BID (N=32)	FP 440mcg HFA BID (N=32)	FP 880mcg HFA BID (N=32)	FP 440mcg CFC BID (N=36)	FP 880mcg CFC BID (N=33)
Baseline	14.2	12.5	12.7	13.0	14.3
Weeks 1-16	14.9	5.8[a]	6.2[a]	4.9[a]	6.4[a]

Source Data: Tables 18 and 21

a Different from placebo, p<0 001

Other Efficacy Measures

- Reduction in prednisone use

Prednisone reduction response was defined by the following categories:

A complete response:	100% reduction
A major response:	50 – 99% reduction
A minor response:	1- 49% reduction
No response:	0% reduction
A negative response:	Any increase in prednisone

8 — One subject was enrolled in the FP CFC 440 arm and the other in the FP CFC 880 arm.

Table 10 – Summary of Reduction in Prednisone Dose
Summary of Reduction in Oral Prednisone Dose
From Baseline to Study Completion: Reduced ITT Population

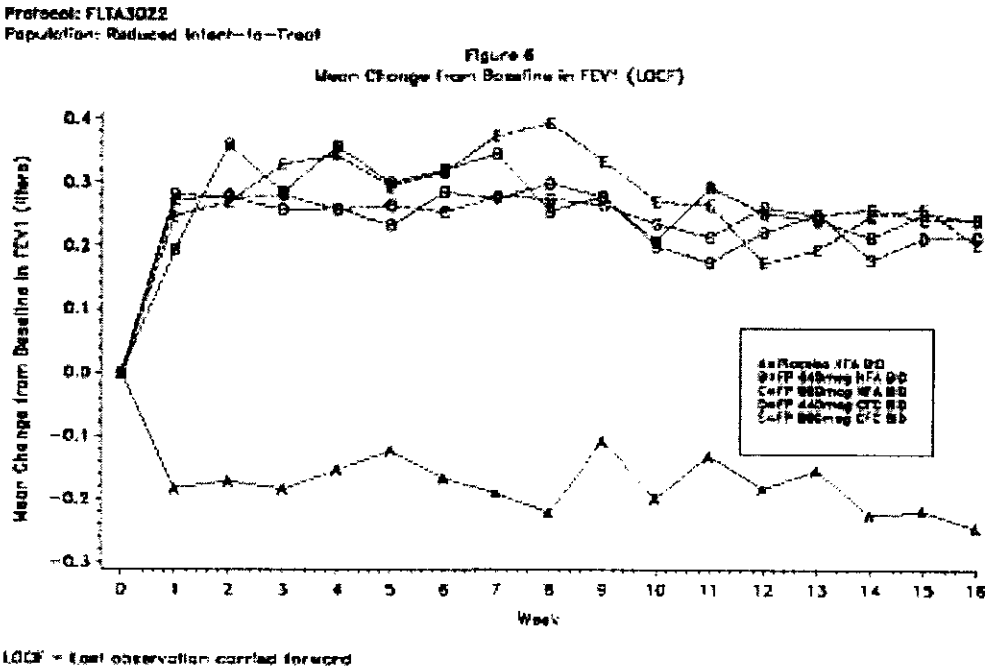
Categorical response, n (%)	Placebo HFA BID (N=32)	FP 440mcg HFA BID (N=32)	FP 880mcg HFA BID (N=32)	FP 440mcg CFC BID (N=36)	FP 880mcg CFC BID (N=33)
Complete response (100% reduction)	4 (13%)	19 (59%)	18 (56%)	30 (83%)	26 (79%)
Major response 50-99% reduction)	9 (28%)	11 (34%)	12 (38%)	4 (11%)	3 (9%)
Minor response (1-49% reduction)	4 (13%)	1 (3%)	1 (3%)	1 (3%)	3 (9%)
No response (0% reduction)	3 (9%)	0	1 (3%)	1 (3%)	0
Negative response any increase)	12 (38%)	1 (3%)	0	0	1 (3%)
Combined complete response and major response	13 (41%)	30 (94%)	30 (94%)	34 (94%)	29 (88%)

Source Data: Table 19

Interestingly, A total of 13 subjects (41%) in the placebo group had a reduction of oral prednisone dose of 50 to 100% and of these subjects 4 (13%) had a complete response (100% reduction in oral corticosteroids. One potential reason for this finding is that patients may not have been on the minimum effective dose of corticosteroids on entering the study but were actually on higher than needed maintenance doses of oral corticosteroids. In the FP treatment groups, a 50 to 100% reduction in prednisone dose was achieved by 94% of subjects.

- FEV_1

The mean FEV_1 and the mean change from baseline in FEV_1 were followed. All four active treatment groups had an increase in the mean change from baseline in FEV_1 and the mean change in percent predicted FEV_1 from baseline over the 16-week treatment period. Whereas, in the placebo group, mean FEV_1 declined or did not improve over the 16 weeks of treatment. Both doses of FP, 440 mcg and 880 mcg BID, had identical mean improvements in FEV_1 from baseline (0.24 L) compared with a decrease in FEV_1 in the placebo group (-0.25L) at Week 16 The improvements in FEV_1 seen with the HFA and the CFC products were similar. The FEV_1 changes are depicted in the graph below.



- Diary Data

➢ Peak Flow

Numerical improvements were seen in mean morning and evening PEF (L/min) in all active treatment groups whereas, mean PEF declined in the placebo group over the 16-week treatment period. The mean increase in PEF from baseline was numerically greater for AM PEF compared to evening PEF. The change in AM PEF ranged from 16.3 L/min to 36.5 L/min for the HFA groups and from 17.4. to 36.5 for the CFC groups. Interestingly, the HFA groups showed dose ordering, whereas the CFC groups did not. This finding may reflect the variability that is often seen with PEF measurements. *(See Appendix III, Table 28, pg116).*

➢ Asthma symptom scores, Ventolin® use, nighttime awakenings

Asthma symptom scores, Ventolin® use and nighttime awakenings requiring Ventolin® were recorded in patient diaries. Numerical improvements were noted in all the active treatment groups except that for the FP HFA 880 group nighttime awakenings increased slightly during the study and was slightly increased at week 16 from baseline. At Week 16, subjects in the FP HFA 880 mcg BID group were reporting 1 nighttime awakening every 2 nights compared with one awakening every 3 nights at baseline. Subjects in the FP HFA 440 were reporting one awakening every 2.5 nights compared to one awakening every 2 nights at baseline. *(See Appendix III, Table 29, pg.116).*

Patient-reported Outcomes
The AQLQ was used in this study also. However, over two-thirds of the subject sin the placebo arm did not complete the study making it difficult to make any conclusions from the AQLQ data.

EFFICACY SUMMARY

The data confirm that Flovent HFA 88 mcg BID, 220 mcg, BID and 440 mcg BID are statistically superior to placebo in improving lung function in asthmatic patients previously maintained on inhaled corticosteroids or previously maintained on bronchodilator therapy alone. Asthmatic subjects maintained on oral corticosteroids were able to significantly reduce daily prednisone usage when treated with FP HFA 440 mcg BID or 880 mcg BID.

None of the studies showed a clear dose-ordering effect study although there were small numerical differences in favor of a dose response in the 12-week studies.

Of the many secondary efficacy endpoints evaluated, statistical improvement in AM PEF was replicated for FP 88 mcg BID treatment group in the 12-week studies. An Increased probability of survival in the study was replicated for the FP 440 mcg BID arm in both 12-week studies.

Clinically significant improvement in Patient reported outcomes measures was replicated for the FP 440 mcg BID treatment arm but not for the lower doses in the 12-week studies. Patient reported outcome data for the oral corticosteroid - sparing study was uninterpretable because of the 67% drop out rate in the placebo arm and the perils of LOCF for this type of questionnaire.

The highest FP HFA dose 880 mcg BID did not demonstrate any treatment advantage compared with the lower dose of 440 mcg BID in the oral corticosteroid – sparing trial but neither did the FP CFC 880 mcg BID dose. These findings may just be reflective of the variability of the findings that can sometimes be seen with a very severe asthma population as was studied in FLTA3022. The current label for Flovent® MDI (CFC formulation) recommends 880 mcg BID as the starting and the maximum dose for oral corticosteroid. The results of this study justifies a recommendation of FP HFA 440 mcg BID as the starting dose for oral corticosteroid sparing. A dose of 880 mcg BID could potentially be beneficial in some patients and subjects who do not achieve improvement with 440 mcg BID could increase the dose to 880 mcg BID.

VII. INTEGRATED REVIEW OF SAFETY

A. CONCLUSIONS

A total of 1678 subjects participated in the clinical studies in support of this application. Of these 1090, were exposed to FP HFA in different doses. The adverse event profile for Flovent ® HFA was relatively similar to the adverse event profile for Flovent ® CFC. Adverse events were reported more frequently in the ear, nose and throat, respiratory, neurological, and gastrointestinal systems. Some of the more commonly ($\geq$ 5%) reported AEs were upper respiratory tract infections, sinusitis, headache, throat irritation, hoarseness/dysphonia, and candidiasis.

In the efficacy studies and the long term safety studies, there tended to be a slightly higher frequency of local effects (throat irritation, candidiasis, hoarseness and dysphonia) in females compared to males.

One subject died during the study but the death did not appear to be related to the study medication. Of the 50 serious adverse events reported only one was definitely drug related. This was a case of adrenal suppression in a 24 year old female who was randomized to FP 88 mcg BID in one of the 12-week efficacy studies. There were 2 other reports of adrenal suppression but they were reported in subjects who had been on FP CFC.

There were 3 cases of serious pneumonia in the oral corticosteroid sparing trial in subjects in the FP 880 mcg BID arm. It is not clear that there is a relationship between FP and pneumonia but previous studies have reported results that are suggestive of a safety signal.

The data from the one-year study show that overall, subjects using or not using spacers had essentially the same incidence of adverse events. Local effects of throat irritation and hoarseness/dysphonia were reported with a slightly higher frequency in spacer users vs. non-spacer users. It is not clear if there is a difference in systemic effects in spacer users vs. non-spacer users.

Results of general chemistry and hematology evaluations did not raise any particular concerns. There were some reports of elevations in blood glucose above the threshold limit (170 mg/dl). The majority of these cases were in subjects who were enrolled with blood glucose levels above the normal range or who had a history of diabetes. One case of hyperglycemia in a subject with previously normal blood glucose was reported in a placebo subject and in a subject who received FP 88 mcg BID. Hypereosinophilia and/or signs/symptoms or Churg Strauss were not detected in this program.

Serum and 24-hr urine cortisol levels were higher in the placebo groups compared with the FP groups. There was not a consistent dose response effect on cortisol levels.

Markers of bone formation /resorption serum osteocalcin and urine N-telopeptide were measured in the one-year study but these markers are exploratory and firm conclusions cannot be based on these tests.

B. PATIENT EXPOSURE AND DEMOGRAPHICS

A total of 1,171 patients were treated in the two12-week efficacy studies, the 12-week dose proportionality study, and the 16-week corticosteroid-sparing study. Of these, 745 subjects received FP HFA, 147 received FP CFC, and 279 received placebo. The studies from which safety data are obtained are outlined in the table below.

Table 11- Studies that provide safety data

Study	Study type/ design	Duration	*Treatment Dose (s) (mcg)	Number exposed
FAP30007	Pivotal Efficacy Randomized, double-blind, placebo-controlled parallel (subjects maintained on ICS)	12 Weeks	FP 88 BID FP 220 BID FP 440 BID PLA BID	103 106 102 104
FAP30008	Pivotal Efficacy/Randomized, double-blind, placebo-controlled parallel (subjects maintained on bronchodilators alone)	12 Weeks	FP 88 BID FP 220 BID FP 440 BID PLA BID	100 98 100 99
FLTA3020	Dose-proportionality study Randomized double-blind placebo controlled	12 Weeks	FP 110 BID (CFC) FP 110 BID (HFA) FP 220 BID (CFC) FP 220 BID (HFA) PLA BID (HFA)	38 37 38 35 43
FLTA 3022	Pivotal efficacy/randomized, double-blind, placebo-controlled parallel	16 weeks	FP 440 BID (HFA) FP 880 BID (HFA) FP 440 BID (CFC) FP 880 BID (CFC) PLA BID (HFA)	32 32 37 34 33
FLTB3048	Long-term safety (non-US)	52 weeks	FP 440 mcg BID (HFA) FP 440 mcg BID CFC)	163 162
FAP30001	Long-term safety	26 weeks	FP 220 mcg BID (HFA) FP 440 mcg BID (HFA)	89 93
*Drug product is HFA formulation unless otherwise stated				
Number exposed to FP HFA formulation in 12 week studies = 681				
Number exposed to FP HFA product in 16-week study = 64				
Number exposed to FP HFA product in 52-week safety study = 163				
Number exposed to FP HFA product in 26-week safety study = 182				

The mean age of subjects exposed to HFA (FP and placebo) in the placebo-controlled clinical studies ranged from 31.6 – 50.1 years. Eight (8%) percent of subjects were aged 12-17 years, 86% were age 18 – 64 years, 4 % were 65 to 74 years of age and 1% were 75 years or older. The majority of subjects (84%)

were Caucasians. The table below summarizes the main demographic characteristics of the subjects in these studies.

Table 12 - Demographics for subjects exposed to Flovent and placebo HFA Placebo-controlled trials (FAP30007, FAP30008, FLTA3020 and FLTA3022)

	Placebo HFA	FP 88 mcg BID (44 mcg Product)	FP 220 mcg BID (110 mcg product)	FP 440 mcg BID (220 mcg product)	FP 880 mcg BID (220 mcg product)	FP HFA 110 BID (110 mcg product)	Totals
Studies	30007,30008, 3020, 3022	30007, 30008	30007,30008, 3020	30007,30008, 3022	3022	3020	
N	279	203	239	234	32	37	1024
Mean age (range)	43.9 (12-88)	39.9 (12-84)	38.1 (12-73)	45 (12-83)	50.1 (26-79)	31.6 (12-53)	
Age distribution n (%)							
12-17 yrs	24 (10%)	15 (7%)	18 (8%)	19 (9%)	0	6 (16)	82 (8%)
18-64 yrs	238 (85%)	176 (87%)	216 (90%)	199 (85%)	25 (78%)	31 (84%)	885 (86%)
65-74 yrs	12 (4%)	10 (5%)	5 (2%)	12 (5%)	6 (19%)	0	45 (4%)
≥ 75 yrs	5 (2%)	2 (<1%)	0	4 (1%)	1 (3%)	0	12 (1%)
Gender (%) M/F	45/56	41/59	49/51	40/60	44/56	54/46	45/55
Ethic origin (%): *W/B/O	81/12/8	83/10/7	80/10/10	87/9/6	84/9/6	86/8/6	83.8/9.6/ 7.6
Exposure (mean)							
W/B/O = White/Black/Other							

In the long-term safety studies, FLTB3048 and FAP30001, a total of 507 subjects were exposed to study treatment with FP HFA and CFC formulations. Of these, 89 subjects and 93 subjects were exposed to FP 220 mcg (HFA) BID and FP 440 (HFA) mcg BID respectively, in the 6- month study (FAP30001), and in the one-year study (FLTB3048), 163 were exposed to FP 440 mcg BID (HFA) and 162 subjects were exposed to FP 440 BID (CFC).

In the 6-month study, FAP30001, the mean duration of exposure was 156.8 – 160.0 days in the 2 treatment groups. The mean age ranged from 37.2 to 39.6 years, up to 61% of subjects were female, and 88% were Caucasian. In the one-year safety study, FLTB3048, the study population was essentially all Caucasian (98%). There were slightly more females (55%) enrolled. The mean age of subjects ranged between 37.2 – 44.7 years. The mean exposure ranged between 345 – 349 days. About 40% of subjects in the one year study used a spacer prior to enrolling in the study and continued to use one during the study. Table 12 summarizes the demographic characteristics in the long term studies. The table is copied from the sponsor's submission.

Table 13 – Demographic Characteristics FAP30001 and FLTB3048

Demographic Characteristics (FAP30001, FLTB3048)

	FP220 HFA N=89	FP440 HFA N=256	FP440 CFC N=162
Protocols	**FAP30001**	**FAP30001, FLTB3048**	**FLTB3048**
Age Mean (range)	37.2 (12-73)	43.8 (12-79)	44.7 (18-76)
Age Distribution, n (%)			
12-17 yrs	11 (12)	4 (2)	0
18-64 yrs	74 (83)	232 (91)	146 (90)
65-74 yrs	4 (4)	17 (7)	14 (9)
≥75 yrs	0	3 (1)	2 (1)
Sex (%) Male/Female	48/52	41/59	48/52
Ethnic Origin (%) W/B/O	87/7/7	95/2/3	98/<1/2

Source Data: Table 17.1
W/B/O=White/Black/Other

C. METHODS AND SPECIFIC FINDINGS OF SAFETY REVIEW

The safety findings for all the studies were reviewed in detail.

The safety findings from the pivotal efficacy studies are presented first followed by A description of the design of the long term safety studies and the safety results. Finally a summary of the safety data submitted in the 120-day safety update is presented.

SAFETY RESULTS FAP30007

Adverse Events

Of the 415 subjects randomized in the treatment period, a total of 253 experienced at least one adverse event (AE) during the treatment period. The most frequently reported AEs were upper respiratory tract infection, headaches, and throat irritation. Adverse events that occurred with an incidence of > 3% and more frequently than in the placebo group are displayed in the table below.

Table 14 Adverse Events at a rate > 3% and more common than in placebo group regardless of causality (Source: data table 9.3 FAP30007.pdf)

Adverse Event N (%)	Placebo HFA (n = 104)	FP 88 HFA N=103	FP 220 HFA N=106	FP 440 HFA N=102
ANY EVENT	54 (52%)	70 (68%)	67 (63%)	62 (61%)
URTI	16 (15%)	22 (21%)	16 (15%)	19 (19%)
Headaches	4 (4%)	15 (15%)	8 (8%)	3 (3%)
Throat Irritation	3 (3%)	7 (7%)	7 (7%)	8 (8%)
***Sinusitis/sinus infection	3 (3%)	10 (10%)	10 (10%)	6 (6%)
Cough	7 (7%)	5 (5%)	11 (10%)	3 (3%)
Candidiasis mouth/throat	2 (2%)	4 (4%)	3 (3%)	9 (9%)

Hoarseness/dysphonia	**1 (<1%)**	**1 (<1%)**	**5 (5%)**	**8 (8%)**
Upper respiratory inflammation	**2 (2%)**	**2 (2%)**	**5 (5%)**	**6 (6%)**
Nasal congestion/blockage	3 (3%)	5 (5%)	2 (2%)	4 (4%)
Musculoskeletal pain	2 (2%)	3 (3%)	5 (5%)	2 (2%)
Diarrhea	0	5 (5%)	2 (2%)	0
***This reviewer combined the AEs from the sponsor's two distinct AE names of sinusitis and sinusitis/sinus infection. There is no apparent rationale for having two distinct AEs "sinusitis" and "sinusitis/sinus infection". AEs in bold showed dose ordering.				

As shown in the table, AEs that are know to be associated with inhaled corticosteroids – namely candidiasis mouth/throat, throat irritation and hoarseness/dysphonia were reported with higher frequency in the active treatment groups and appeared to show dose-ordering.

Drug related adverse events and events associated with local or systemic corticosteroid effects

A total of 48 subjects (12%) experienced at least one event recorded by the investigator as possibly drug related. The most common of these events were candidiasis (n=16) hoarseness/dysphonia (n=14), throat irritation (n=22). Other AEs recorded by the Investigator as drug-related but could not be assessed for causality by this reviewer because case narratives were not provided include mood swings (1), anxiety (1), and headache (2).

Deaths and Serious Adverse Events (SAE)

Deaths
One subject died during the study. This was a 60-year old male subject (subject #863) with a history of nocturnal seizure disorder, who received FP 440 mcg BID. Approximately 9 days after starting the treatment period he was withdrawn from the study due to lack of efficacy. The subject reported that he was having trouble breathing deeply. He was started concurrently on inhaled fluticasone (formulation unknown) and intranasal sodium cromoglycate. Approximately 6 days after discontinuation of the study medication, the subject died. He was found dead in his bed four days after the estimated date of death. The family did not give consent for an autopsy. The investigator believed that the cause of death was cardiac.

Serious Adverse Events
There were no serious adverse events in the active treatment arms. Four (4) subjects in the placebo group experienced serious adverse events. These events were (a) pneumonia and asthma exacerbation in one subject, (b) diverticulitis in one subject , (c) asthma exacerbation in one subject, and (d) right knee cellulitis in one subject.

Pregnancies
Three pregnancies occurred during treatment period. One subject in the placebo group was exposed during the first trimester. The other two subjects were in the

FP 220 group and were exposed to study medication before conception and for up to 4 weeks gestation. The sponsor reported in the 120-day safety update that 2 of the subjects each gave birth to a healthy baby and information on the third patient was pending.

Discontinuations due to Adverse Events

A total of 11 (3%) subjects had AEs that resulted in withdrawal from the study. Of these subjects, 4 were in the placebo group, 1 was in the FP 88 group and 3 each were in the FP 220 and FP 440 group. In 4 of the 11 subjects the adverse event was possibly related to the study medication. These events were asthma and copious oral secretions in 2 subjects in the placebo group, puritus in one subject in the FP 220 group and hoarseness/dysphonia in one subject in the FP 440 group.

Clinical Laboratory Results

There were no clinically significant changes in laboratory parameters that required a change in treatment or initiation of clinical treatment.

In hematology parameters, there were no values outside the predefined threshold range for RBCs, lymphocytes, monocytes, eosinophils, basophils and platelets. Two subjects in the FP 220 group and one subject in the FP 440 group had hemoglobin, WBC, and neutrophils below the threshold range at Week 12. These subjects had entered the study with values either below the threshold range (e.g. subject # 2121) in FP 220 arm with baseline hemoglobin of 8.7 g/dl) or with values below the normal range (e.g. subject #1568 in the FP 440 arm with a baseline hemoglobin of 10.5 g/dl). The changes during the study were not significantly different from their baseline.

Although there were some shifts to high outside of the normal range for eosinophils in 13 subjects, there were no reports of shifts to high outside of the pre-specified threshold. Of the 13 subjects with shifts to high eosinophils, 5 were in the placebo group, 6 were in the FP 88 group and 2 were in the FP 220 group. There were no subjects in the FP 440 group with shifts to high eosinophils.

Increased neutrophils and low lymphocytes could be due to a systemic corticosteroid effect. Although there were some shifts in neutrophil counts, there were no shifts to levels outside the threshold range (high or low) for neutrophils or lymphocytes.

Liver function abnormalities above the threshold were noted in three (3) subjects but all three subjects had entered the study with liver transaminases either above the normal range or above the threshold value. Subject # 5624 who was in the FP 440 BID treatment arm, entered the study with an elevated ALT (above the threshold) and withdrew from the study 2 weeks later. Subject #5538 who was also in the FP 440 BID treatment arm, entered the study with a GGT value of 144 U/L which was above the normal range and at Week 12 the value

was 182 U/L which was above the threshold range. Another subject, #2242, in the FP 220 group also entered the study with a GGT value above the normal range (102 U/L) and at Week 12 the value was 202 U/L which was above the threshold range.

A total of 6 subjects had blood sugar levels above the threshold range - one subject in the placebo group, 2 in the FP 88 group and 3 in the FP 440 group. All six subjects entered the study with blood sugar levels either above the normal or the threshold range. The values of the elevated liver function and blood glucose results are shown in the table below.
As shown in the table, subjects in the highest ICS group did not have clinically significant worsening of their blood glucose levels from study entry.

Table 15 - Liver Function and Glucose Values Above the Threshold Value
Study FAP 30007

	Treatment arm	Lab value at study entry	Lab value at follow up (Week 12)*
Liver Function abnormalities			
Subject # 2242 - GGT	FP 220	102 U/L	202U/L
Subject # 5624 – ALT *(subject withdrew at Week 2 result for repeat test 1 week after withdrawal)	FP 440	148 U/L	117 U/L
Subject # 5538 - GGT	FP 440	144 U/L	182 U/L
Elevate blood glucose			
Subject # 5499	Placebo	134 mg/dl	234 mg/dl
Subject #2240	FP 88	193 mg/dl	264 mg/dl
Subject # 5688	FP 88	184 mg/dl	256 mg/dl
Subject # 4195	FP 440	154 mg/dl	203 mg/dl
Subject # 1272	FP 440	265 mg/dl	221 mg/dl
Subject # 1894	FP 440	209 mg/dl	178 mg/dl

HPA Axis Function Assessment

Twenty-four hour urine cortisols were collected at randomization visit (Baseline) and at Week 12 or study discontinuation. Subjects whose urine samples were considered to have confounding factors that could affect the interpretation of the results were excluded from this analysis. Urine samples of subjects who had any one of the following findings were not included in the analysis.

- Incomplete samples noted on the CRF

- Urine volumes of < 600 ml for female subjects and < 800 ml for male subjects and 24-hour creatinine excretion below the lower limit of threshold range
- Collection time interval outside 24 ± 4 hours
- Off study drug for more than one day at the start of post baseline urine collection period
- Used corticosteroids (except Flonase® or < 1% hydrocortisone cream) within 30 days of the screening visit or during the treatment period

Based on these criteria, a total of 225 (54%) of the randomized subjects (defined as the urine cortisol population) had urine cortisol samples that were eligible for analysis. Table 15 shows the mean baseline and Week 12/discontinuation values for the 24 hr urine cortisols and the mean change from baseline. A normal range for urine cortisol was unavailable for urine cortisol for subjects under 18 years. The cited normal range for 24 hour cortisol was 5 – 55 mcg / 24 hours for subjects 18 years of age and older. As shown in the table, subjects in the FP groups had lower urine cortisol levels than placebo-treated subjects. The decrease in urine cortisol was not proportional to the FP dose administered.

Table 16 - 24 hr urine cortisol FAP30007

	Placebo (n=32)	FP 88 (n=69)	FP 220 (n=64)	FP 440 (n=70)
Randomized n	104	103	106	102
Baseline mean (SD)	15.92 (13.96)	16.88 (14.56)	15.17 (13.50)	18.62 (16.65)
Week 12/Discontinuation mean (SD)	19.47 (14.50)	17.40 (16.50)	17.77 (14.28)	16.73 (15.56)
*Mean Δ change from Baseline (SD)	3.55 (17.47)	0.52 (15.12)	2.60 (13.79)	-1.89 (17.47)
* Raw means not LS means				

SAFETY RESULTS FAP30008

Adverse Events

Of the 397 subjects randomized in the treatment period, 222 (56%) had at least one AE during the study. The most frequently reported adverse events were similar to those previously described for FAP30007. Adverse events most frequently seen were upper respiratory tract infections (URTI) (13%-17%), followed by throat irritation (8% - 12%), headaches (7%-8%) and nausea and vomiting (5%-7%). Adverse events that occurred at a frequency of > 3% in the FP groups and more frequently than in the placebo group are depicted in the table below.

Table 17 Adverse Events at a rate > 3% and more common than in placebo group regardless of causality (Source: data table 9.3 FAP30008.pdf)

Adverse Event N (%)	Placebo HFA (n = 99)	FP 88 HFA N=100	FP 220 HFA N=98	FP 440 HFA N=100
ANY EVENT	54 (55%)	53 (53%)	52 (53%)	63 (63%)
Ear Nose and Throat				
URTI	13 (13)	14 (14%)	17 (17%)	14 (14%)
Throat irritation	8 (8%)	9 (9%)	10 (10%)	12 (12%)
Headaches	8 (8%)	7 (7%)	7 (7%)	8 (8%)
Viral respiratory infections	3 (3%)	4 (4%)	4 (4%)	5 (5%)
Upper respiratory inflammation	1 (1%)	3 (3%)	5 (5%)	5 (5%)
Cough	3 (3%)	4 (4%)	2 (2%)	5 (5%)
Bronchitis	3 (3%)	1 (1%)	0	7 (7%)
Hoarseness/dysphonia	1 (1%)	4 (4%)	1(1%)	4 (4%)
Fever	1 (1%)	1 (1%)	3 (3%)	4 (4%)
Candidiasis	0	3 (3%)	1 (1%)	2 (2%)
Muscle injuries	2 (2%)	1 (1%)	5 (5%)	0
GI signs and symptoms*	1 (1%)	1 (1%)	4 (4%)	2 (2%)

* sponsor did not specify. However, this category was distinct from nausea/vomiting, diarrhea, dyspeptic symptoms, and abdominal discomfort.

Drug-related Adverse events and events associated with local or systemic corticosteroid effects.

Most of the adverse events described as drug-related were events that are known to be associated with a local corticosteroid effect. This reviewer could not assess some events that the sponsor reported as drug-related (such as nausea and vomiting and lymphatic signs and symptoms) because the sponsor did not provide case narratives for these reports. Throat irritation occurred with similar frequency among all treatment groups (including placebo) and this event could be related to the propellant as well as the ICS. Hoarseness/dysphonia and candidiasis were not frequent events but were more common in the FP treatment groups. In the placebo group there were no cases of candidiasis and only one case of hoarseness/dysphonia.

Deaths and Serious adverse events

There were no deaths during the study. Three (3) serious adverse events occurred during the treatment period,. One of these SAEs was in the FP 88 HFA treatment group, and the other two events occurred in the FP 440 HFA treatment group.

The serious adverse events are briefly described below.

Subject 8497: Adrenal suppression occurred in a 24 year old female who was randomized to FP HFA 88 mcg BID . One day following the final dose of study medication laboratory studies revealed a blood glucose of 42 mg/dl, an undetectable 24-hour urine cortisol level (< 3.2 mcg/24 hours) and increased eosinophils (2.06). Eleven days later, the subject still had low blood glucose (57 mg/dl) and high eosinophils (2.78). The subject was diagnosed with possible adrenal suppression based on the laboratory results. The subject was

asymptomatic. Three weeks after discontinuing the study medication, the cortisol level, cortisol stimulation and urine cortisol were normal.

Subject 3554: Exacerbation of bipolar disorder occurred in a 54 year old female with a history of bipolar disorder. She was randomized to FP 440 mcg BID . Fourteen days after starting the study medication the subject was reported to have increased stress and was hospitalized. She was treated with risperidone. The event resolved after 5 days and the subject was seen in the clinic that same day for a study visit. She was found to have rapid and rambling speech, and study drug was discontinued and she was withdrawn from the study. The investigator was unable to obtain details about her hospitalization.

Subject 3108: Status asthmaticus occurred in a 72 year old female with a history of GERD, post-traumatic splenectomy, and hypothyroidism who presented to the emergency room with symptoms of worsening asthma 3 weeks after starting study treatment. She reported exposure to ammonia and "cleaning fumes" earlier in the week. She was treated and sent home and returned to the ER the following day because her symptoms did not improve and she was admitted to the hospital. Her hospital stay was prolonged by oral candidiasis, rectal bleeding (bleeding internal hemorrhoids) and weakness.

Pregnancies

There were 2 pregnancies during the study. One subject was receiving FP HFA 88 mcg (subject 7816) and the other, FP 440 mcg (subject 3116). Both subjects were found to be pregnant after completing the treatment phase of the study. The outcomes of the pregnancies were not available at the time of the NDA nor the 120 – day safety update report.

Discontinuations due to Adverse Events

Six (6) subjects had adverse events that resulted in treatment withdrawal. These events are tabulated below. Of these adverse events, candidiasis of the mouth and throat is most likely due to the corticosteroid. There were no discontinuations due to AEs in the FP 88 treatment group.

Table 18 - Discontinuations due to AEs
Study FAP30008

	Placebo	FP HFA 220	FP HFA 440
Dizzy spells	Subject 3559 32y/o W M		
Abnormal menses		Subject 7412, 43 y/o W F	
Exacerbation bipolar disorder			*Subject 3554, 53 y/o W F
Allergic conjunctivitis			Subject 2377, 35 y/o W M
Candidiasis mouth/throat			Subject 8403, 47 y/o W F
Status asthmaticus			*Subject 3108 72 y/o W F

* Had serious adverse events discussed previously. Subject 3108 also had oral candidiasis, but this was not the adverse event that led to withdrawal.

Clinical Laboratory Results

There were no clinically significant changes in hematology, or clinical chemistry values during the 12-week treatment period. There were no shifts (high or low) outside of the threshold range.

A total of 17 subjects had shifts to high in blood glucose: 4 in the placebo group, 3 in the FP 88 group 5 in the FP 220, and 5 in the FP 440 groups. Of the subjects with shifts to high in blood glucose, six had blood sugar levels above the threshold range (>170 mg/dl). Five of these subjects entered the study with blood sugar levels already above the threshold value. These six subjects are briefly described in the table below. One subject in the FP 88 group was reported to have hyperglycemia as an adverse event.

Table 19 - Elevated Blood glucose levels
Study FAP 30008

	Treatment Arm	Blood glucose at study entry	Blood glucose at follow up
*Subject 3657	FP 88	112 mg/dl	408 mg/dl at Week 10 and 336 mg/dl at week 11. No further testing available
Subject 8782	FP 88	159 mg/dl	184 mg/dl at Week 12. Repeat one week later 162 mg/dl
Subject 8502	FP 220	167 mg/dl	254 mg/dl at Week 12
Subject 3890	FP 220	245 mg/dl	195 mg/dl at Week 12
Subject 8942	FP 220	218 mg/dl	215 mg/dl at week 12
Subject 8989	FP 440	284 mg/dl	295 mg/dl at week 12
*Reported as an adverse event (hyperglycemia)			

HPA Axis Function

Twenty-four hour urine cortisols were collected at randomization visit (Baseline) and Week 12 or study discontinuation. Subjects whose urine samples were considered to have confounding factors that could affect the interpretation of the results were excluded from this analysis using the same criteria as described for study FAP 30007. (*See pages 47 - 48).* Based on these criteria, a total of 262 (66%) of the randomized subjects had urine cortisol samples analyzed. Table 20 shows the mean baseline and Week 12/discontinuation values for the 24 hr urine cortisols and the mean change from baseline. Similar to what was seen in FAP30007, the FP arms had slightly lower urine cortisol levels than the placebo arm. The greatest changes from baseline are seen in the two higher dose FP arms consistent with drug effect systemically.

Table 20 - 24-hr urine cortisols
Study FAP30008

	Placebo (n=63)	FP 88 (n=58)	FP 220 (n=68)	FP 440 (n=73)
Randomized n	99	100	98	100
Baseline mean (SD)	22.41(22.96)	17.45 (15.32)	24.07 (21.85)	21.26 (17.01)
Week	18.69 (12.53)	17.57 (14.41)	18.12 (13.41)	16.43 (16.85)

12/Discontinuation mean (SD)				
Δ change from Baseline (SD)	-3.72 (24.10)	0.12 (17.65)	-5.95 (21.73)	-4.83 (21.27)

SAFETY RESULTS FLTA3022

Of the 168 subjects enrolled in the study, 160 (95%) reported at least one adverse event. The most commonly reported adverse events were seen in the ear, nose and throat (61%-75%), gastrointestinal (24%-53%), musculoskeletal (24%-44%), lower respiratory (22% -32%), neurology (15%-38%) and the dermatologic (13%-29%) systems. Adverse events that did not fall into any specific system made up 32%-44%.

More patients in the FP CFC 880 mcg bid group reported throat irritation (26%), candidiasis of the mouth/throat (29%), candidiasis at an unspecified site (12%) and lower respiratory events (32%) compared with patients in the placebo and or other active treatment groups. Adverse events that occurred at a rate of over 3% in the FP groups and were reported more frequently than in the placebo group are depicted in the table below.

Table 21 Adverse Events at a rate > 3% and more common than in placebo group regardless of causality (Source: data table 58)

	Placebo HFA BID (N = 33)	FP 440 HFA BID (N =32)	FP 880 HFA BID (N = 32)	FP 440 CFC BID (N =37)	FP 880 CFC BID (N =34)
ANY EVENT	28 (85%)	31 (97%)	32 (100%)	36 (97%)	33 (97%)
Ear Nose and Throat					
ANY EVENT	20 (61%)	22 (69%)	24 (75%)	27 (73%)	24 (71%)
URTI	12 (36%)	13 (41%)	12 (38%)	11 (30%)	8 (24%)
Sinusitis	7 (21%)	4 (13%)	5 (16%)	8 (22%)	5 (15%)
Throat irritation	2 (6%)	3 (9%)	5 (16%)	6 (16%)	9 (26%)
Rhinitis	3 (9%)	6 (19%)	3 (9%)	2 (5%)	4 (12%)
Pharyngitis/throat infection	0	0	2 (6%)	4 (11%)	3 (9%)
Gastrointestinal					
ANY EVENT	8 (24%)	16 (50%)	16 (50%)	14 (38%)	18 (53%)
Candidiasis mouth/throat	2 (6%)	11 (34%)	6 (19%)	5 (14%)	10 (29%)
Nausea/vomiting	1 (3%)	4 (13%)	5 (16%)	3 (8%)	3 (9%)
Diarrhea	1 (3%)	4 (13%)	5 (16%)	3 (8%)	3 (9%)
Dyspeptic symptoms	1 (3%)	0	2 (6%)	3 (8%)	1 (3%)
Gastroenteritis	0	0	0	3 (8%)	3 (9%)
Constipation	0	0	1 (3%)	1 (3%)	2 (6%)
Viral gastrointestinal infections	0	1 (3%)	0	0	2 (6%)
Non-site specific *ANY EVENT*	11 (33%)	11 (34%)	14 (44%)	15 (41%)	11 (32%)
Malaise & fatigue	3 (9%)	7 (22%)	7 (22%)	5 (14%)	3 (9%)
Candidiasis unspecified site	1 (3%)	1 (3%)	2 (6%)	4 (11%)	4(12%)
Fever	1 (3%)	1 (3%)	2 (6%)	4 (11%)	0

Pain	1 (3%)	1 (3%)	1 (3%)	*2 (5%)*	*2 (6%)*
Viral infections	0	*2 (6%)*	0	1 (3%)	1 (3%)
Musculoskeletal					
ANY EVENT	8 (24%)	14 (44%)	14 (44%)	13 (35%)	8 (24%)
Arthralgia & articular rheumatism	4 (12%)	*7 (22%)*	*4 (13%)*	*6 (16%)*	1 (3%)
Musculoskeletal pain	3 (9%)	*5 (16%)*	*6 (19%)*	*4 (11%)*	1 (3%)
Muscle pain	1 (3%)	*3 (9%)*	*4 (13%)*	*2 (5%)*	*2 (6%)*
Arthritis	0	1 (3%)	1 (3%)	1 (3%)	*2 (6%)*
Lower Respiratory					
ANY EVENT	8 (24%)	7 (22%)	9 (28%)	8 (22%)	11 (32%)
Cough	0	0	*2 (6%)*	*3 (8%)*	*2 (6%)*
Pneumonia	0	0	*3 (9%)*	0	0
Neurology					
ANY EVENT	6 (18%)	8 (25%)	12 (38%)	7 (19%)	5 (15%)
Headaches	4 (12%)	3 (9%)	*8 (25%)*	4 (11%)	3 (9%)
Sleep disorders	2 (6%)	0	*4 (13%)*	0	*3 (9%)*
Dizziness		2 (6%)	0	2 (5%)	
SKIN					
ANY EVENT	6 (18%)	4 (13%)	5 (16%)	9 (24%)	10 (29%)
Pruritus	0	0	1 (3%)	*2 (5%)*	*3 (9%)*
Skin rashes	0	1 (3%)	1 (3%)	*2 (5%)*	*2 (6%)*
Eczema	0	0	*3 (9%)*	0	*2 (6%)*
Fungal skin infections	1(3%)	0	0	1 (3%)	*2 (6%)*
Drug interaction overdose & trauma					
ANY EVENT	1 (3%)	3 (9%)	2 (6%)	4 (11%)	2 (6%)
Muscle injuries	0	1 (3%)	0	*2 (5%)*	1(3%)
Cardiovascular					
ANY EVENT	1 (3%)	1 (3%)	4 (13%)	2 (5%)	3 (9%)
Hypertension	0	0	*3 (9%)*	0	1(3%)
Psychiatry					
ANY EVENT	0	3 (9%)	4 (13%)	2 (5%)	2 (6%)
Depressive disorders	0	*2 (6%)*	*2 (6%)*	0	1 (3%)
Anxiety	0	0	*2 (6%)*	0	1 (3%)
Endocrine and metabolic					
ANY EVENT	0	3 (9%)	2 (6%)	2 (5%)	2 (6%)
Appetite disturbances	0	*2 (6%)*	1 (3 (%)	0	0

Hoarseness and dysphonia were very uncommon and only occurred in one subject in the FP 440 CFC BID treatment group.

Deaths

There were no deaths during the study.

Serious Adverse Events

Nine subjects experienced a serious adverse event (SAE) during the study. The SAEs were the 3 serious pneumonia in the FP HFA880 treatment group previously described in addition to the other events outlined in the table below.

Table 22 – Serious Adverse Events

Subjects with Serious Adverse Events

Treatment	Investigator – Subject #	Age/ Sex	Adverse Event	Time to onset from first dose	Maximum intensity/ Outcome	Withdrawn due to adverse event/ Related to Study Drug
Placebo HFA	7237-27786	68/F	Biliary tract disorders	61 days	Severe/ Resolved	No/ No
FP 440mcg HFA BID	2483-27661	62/M	Primary malignant skin neoplasia	18 days	Mild/ Resolved	No/ No
	4541-27647	51/F	Depressive disorders	101 days	Severe/ Resolved	No/ No
FP 880mcg HFA BID	5165-27697	63/F	Pneumonia. asthma	31 days	Severe/ Resolved	Yes/ No
	9913-27742	32/M	Pneumonia	88 days	Severe/ Resolved	Yes/ No
	43099-27568	66/F	Cholelithiasis	110 days	Severe/ Resolved	No/ No
	44618-27733	74/F	Pneumonia	93 days	Severe/ Resolved	Yes/ No
FP 440mcg CFC BID	45683-27747	53/F	Asthma	88 days	Moderate/ Resolved	Yes/ No
FP 880mcg CFC BID	46139-27548	44/M	Depressive disorders	10 days	Severe/ Resolved with sequelae	No/ No

Source Data: Table 63

Systemic corticosteroid-related effects

The following events displayed in Table 22 were reported as adverse events.

Table 23 Adverse events suggestive of a systemic effect

	Placebo HFA BID (N = 33)	FP 440 HFA BID (N =32)	FP 880 HFA BID (N = 32)	FP 440 CFC BID (N =37)	FP 880 CFC BID (N =34)
Cataracts	0	1 (3%)	0	0	0
Contusions and hematomas	0	1 (3%)	0	1 (3%)	0
Fractures	0	0	0	1 (3%)	0
Hypertension	0	0	3 (9%)	0	1 (3%)
Diabetes mellitus	0	0	1 (3%)	0	0
Hyperglycemia	0	0	0	0	1 (3%)
Hypofunction of adrenal cortex	0	1 (3%)	0	0	0

Pregnancies

There were no pregnancies during the study.

Clinical Laboratory Evaluations

FP Plasma Concentrations

Trough (pre-dose) FP plasma concentrations were obtained in a sub-set of subjects (n = 63) two weeks after the start of dosing. The median trough concentrations for the FP CFC 440 BID and 880 BID group was 47.3 pg./ml(range 23.1 – 162.11 pg./ml) and 52.9 pg./ml (range 22.9 –113.6 pg./ml). The median trough concentrations for the FP HFA 440 BID and 880 BID groups were 27.3 pg./ml (range 21.3 – 351.2 pg./ml) and 55.9 pg./ml (range 21.0 – 223.1 pg./ml). The ranges are extremely large and this may be a reflection of the variability that could in a test where very low concentrations are being measured. At the same time, it could also be a reflection of the fact that the severe asthmatic population under study show more variability in the absorption of FP because of their severe bronchoconstriction. The results at best suggest that FP HFA is less bioavailable that FP CFC in more severe asthmatics. In future studies, it may be more helpful to evaluate systemic concentrations of ICS in milder asthmatics.

Laboratory abnormalities outside the threshold range were uncommon. Laboratory abnormalities that could possibly be related to systemic corticosteroid exposure such as elevated glucose levels, increased white blood cell counts (WBC) and neutrophils and decreased lymphocytes and eosinophils were rarely noted. There were no shifts to low (below the threshold range) for eosinophils or lymphocytes and no shifts to high (above the threshold range) for neutrophils. One subject in the FP HFA 440 BID group had a shift to high in WBC counts and two subjects in the FP HFA 880 had a shift to high in glucose levels.
One subject had a shift to low in potassium levels. There were no reported abnormalities in alkaline phosphatase or sodium bicarbonate levels.

A total of 11 (12%)subjects distributed over all the treatment groups (including placebo) had eosinophil shifts to high. There were no cases of pneumonia reported in any of the subjects with eosinophil shifts to high. However, two subjects reported upper respiratory tract infections, one patient reported mild bronchitis, and two subjects reported sinusitis. No subjects were withdrawn from the study because of eosinophil elevations.

HPA Axis function

HPA axis was assessed at screening and at Week 16 or early termination by AM plasma cortisol and Cortrosyn testing. An abnormal response was defined as:

Morning cortisol < 5 mcg/dl
Post-stimulation rise in cortisol of < 7 mcg/dl or
Post-stimulation cortisol of < 18 mcg/dl

The majority of subjects in the study had low AM (up to 64% of subjects) and post-stimulation (up to 81% of subjects) plasma cortisol levels. This is not an

unexpected finding given that the subjects enrolled in this study had been on maintenance corticosteroids. At Week 16, subjects who completed the study still showed low AM cortisol levels however the percentage of subjects having low AM cortisol and post-stimulation cortisol were lower in the FP treated groups compared to the placebo group. At Week 16 the percentage of subjects with abnormal cortisol levels was higher (as expected) in FP 880 treatment groups compared to the FP 440 treatment groups. A higher percentage of subjects in the placebo group had abnormal cortisol responses, however the numbers are very small and it is difficult to draw any conclusions from this observation.

Table 24 Summary of plasma cortisol abnormalities

	Placebo HFA BID (n= 32)	FP HFA 440 BID (n = 32)	FP HFA 880 BID (n = 32)	FP CFC 440 BID (n = 36)	FP CFC 880 BID (n = 34)
Screening, n	32	32	32	36	34
AM cortisol < 5 mcg/dl	16 (50%)	20 (63%)	13 (43%)	23 (64%)	14 (45%)
Post-stimulation cortisol < 18 mcg/dl	22 (69%)	25 (78%)	23 (72%)	29 (81%)	24 (71%)
Week 16, n	12	26	19	31	26
AM cortisol < 5 mcg/dl	5 (42%)	5 (19%)	9 (47%)	7 (23%)	10 (38%)
Post-stimulation cortisol < 18 mcg/dl	8 (73%)	14 (54%)	13 (68%)	16 (52%)	16 (62%)

SAFETY STUDY FLTB3048

Title: "A multi-centre, randomised, double-blind parallel group clinical trial to assess the long-term (52 weeks) safety of Fluticasone propionate 500 mcg BID administered by pressurised metered dose inhaler propelled by GR106642X propellant in comparison with propellants 11 and 12 in adolescent and adult subjects with asthma".

STUDY DESIGN

The study was a multicenter, randomized, double-blind, parallel-group study designed to compare the long-term safety of Fluticasone propionate (FP) HFA 440 mcg BID, with FP CFC 440 mcg BID for 52 weeks in adolescent and adult subjects with asthma. The study was conducted at 26 sites in Belgium, Canada, Chile, Finland, New Zealand, and Norway. There was a 7 –14 day screening (run-in) period followed by a 52-week treatment period and a 7-14 day follow-up period. Subjects were randomised to FP HFA or FP CFC 440 mcg BID administered using the 220 mcg product.

STUDY POPULATION

The study population was made up of adolescent and adult subjects age 16 years or older, with mild to moderate reversible obstructive airways disease who had stable lung function. Subjects were included in the study if they met the following criteria:

1. Male or female subjects with asthma aged ≥16 years inclusive at the time of the screening visit (Clinic Visit 1).

2. Were receiving ≥ 800mcg to ≥ 2000mcg/day of beclomethasone dipropionate, budesonide, Triamcinolone acetonide, or flunisolide or ≥400mcg to ≥1000mcg/day inhaled fluticasone propionate on entry to the study.

3. Had a forced expiratory volume at one second (FEV_1) ≥ 60% of predicted value at the screening visit. [European Community for Coal and Steel (ECCS) predicted lung function values were used for subjects ages ≥18 years and Polgar predicted lung function values were used for subjects less than 18 years of age]

4. Had historical documentation within the 12 months prior to Visit 1 (excluding any screening visit pulmonary function tests), of a ≥15% variation in FEV_1, or demonstrated at the screening visit an increase in FEV_1 of ≥15% following inhalation of 2 actuations of albuterol from a pressurized MDI (propellants 11 and 12).

5. Were able to use a pressurized MDI correctly, understand and complete a daily record card, and record their peak expiratory flow (PEF) using a Mini-Wright peak flow meter.

6. Were willing to give written informed consent to participate in the study. In the case of adolescents, the parent or legal guardians also had to give written informed consent for them to participate in the study.

The exclusion criteria were similar to those previously described. Patients were permitted to continue on most of their routine asthma/anti-allergy medications such as long-acting inhaled β_2-agonists, oral xanthine derivatives such as theophylline and aminophylline, anticholinergic bronchodilators, oral anti-allergics such as ketotifen and sodium cromoglycate and nedocromil. Patients were not permitted to take oral/parenteral/depot corticosteroids, short-acting β_2-agonists other than albuterol dispensed in the study, or inhaled combination products containing a short-acting β_2-agonist.

Subjects could discontinue the study at the discretion of the Investigator or by the subject's own volition. Subjects with more than 3 asthma exacerbations during the 52-week treatment period, or subjects who experienced an asthma exacerbation that required a course of oral corticosteroids for longer than 10 days were withdrawn from the study.

MEASUREMENTS AND EVALUATIONS

The sponsor conducted an extensive safety evaluation that included the following assessments:

- Adverse Events – assessed at every clinic visit

- Clinical laboratory tests – Clinical chemistry, hematology, and renal function tests were conducted at screening, Weeks 24, and 52
- Evaluation of HPA Axis Function – Assessed by AM cortisol and either 24-hour urinary cortisol, or the ACTH stimulation test at screening, and Weeks 24 and 52. The test selected was at the discretion of the Investigator
- Biochemical Markers of Bone – Blood and urine samples were obtained at Screening, and after Weeks 24 and 52. Serum osteocalcin (biochemical marker of bone formation) and urinary N-telopeptide concentrations (marker of bone resorption) were measured.
- Asthma exacerbations – Were defined as worsening in asthma symptoms requiring increased use of bronchodilators and being seen in clinic within 24 hours of onset of worsening symptoms. The Investigator determined whether a short course of oral corticosteroids was indicated.
- Vital signs, ECG findings and oral candidiasis – Vital signs were done at Screening and at Weeks 12, 24, 36, and 52 and as necessary at the Early withdrawal visit or during follow-up. The 12-lead ECG tracings were obtained at screening and at Week 52. Oropharyngeal examinations were performed at every visit to evaluate for the presence of oral candidiasis.
- Physical and ophthalmic examinations – Physical exams were performed at Screening, Week 52 and the Withdrawal visit. Ophthalmic exams were performed at Screening, Weeks 24, and 52

Sample size considerations

The sample size was selected to ensure that data from at least 100 subjects on FP HFA would be obtained at the one year timepoint. Therefore the sponsor planned to randomize a maximum of 300 subjects to each treatment arm. These numbers were based on the International Conference on Harmonization (ICH) and the FDA guidelines for long-term safety exposure information for new molecular entities.

SAFETY RESULTS

A total of 325 subjects were randomized to study treatment – 163 subjects in the FP HFA group and 162 subjects in the FP CFC group.

Adverse Events

Nearly all subjects (91% -98%) reported at least one adverse event the study. This is not unexpected given the duration of the study. The body systems with the most commonly reported adverse events were the ears, nose and throat (64% -77%), lower respiratory (63%-65%), neurology, gastrointestinal, musculoskeletal and non-site specific (20% -22%). The table below, displays the adverse events that occurred with a frequency of ≥ 5%.

Table 25 - Adverse Events at a frequency of ≥ 5% - FLTB 3048
Data source Table 23 FLTB. pdf pgs. 192- 207

Adverse Event , n (%) N= # of subjects reporting the event	FP HFA 440 mcg BID N = 163	FP CFC 440 mcg BID N = 162
Any Event	149 (91%)	158 (98%)
Ear, Nose, Throat		
Upper resp. Tract infection (URTI)	56 (34%)	68 (42%)
Throat Irritation	27 (17%)	24 (15%)
Sinusitis	22 (13%)	17 (10%)
Rhinitis	16 (10%)	20 (12%)
Upper respiratory inflammation	9 (6%)	20 (12%)
Pharyngitis/Throat infection	11 (7%)	17 (10%)
Hoarseness/dysphonia	13 (8%)	14 (9%)
Laryngitis	2 (1%)	8 (5%)
Lower Respiratory		
Bronchitis	50 (31%)	47 (29%)
Viral respiratory infections	42 (26%)	34 (21%)
Asthma	36 (22%)	23 (14%)
Cough	28 (17%)	22 (14%)
Lower respiratory tract infection	8 (5%)	5 (3%)
Pneumonia*	5 (3%)	5 (3%)
Neurology		
Headache	52 (32%)	48 (30%)
Gastrointestinal		
Diarrhea	14 (9%)	14 (9%)
Nausea/vomiting	13 (8%)	11 (7%)
Candidiasis mouth/throat	10 (6%)	12 (7%)
Gastroenteritis	8 (5%)	10 (6%)
Dental discomfort and pain	8 (5%)	6 (4%)
Musculoskeletal		
Musculoskeletal pain	27 (17%)	24 (15%)
Non-site specific		
Candidiasis unspecified site	8 (5%)	9 (6%)
Chest symptoms	10 (6%)	5 (3%)
Endocrine & metabolic		
Decreased cortisol*	1 (<1%)	3 (2%)
Hypofunction of the adrenal cortex*	0	2 (1%)
Cushing's syndrome*	0	1 (<1%)
* < than 5% frequency but listed because of clinical importance		

Overall, the frequency of adverse events was relatively similar among the treatment groups. Some events occurred at a somewhat higher frequency in one group compared with the other, but this observation may not be of clinical significance. For example, upper respiratory inflammation was reported by 12% of subjects in the FP CFC group compared with 6% in the FP HFA group, and upper respiratory tract infection was reported by 42% of subjects in the FP CFC group compared with 34% of subjects in the FP HFA group. Cough was reported more frequently in the FP HFA group (17%) compared with 14% in the FP CFC group. Candidiasis of the mouth/throat occurred at a similar frequency in both treatment groups. Pneumonia was reported in 3% of subjects in both groups. Adverse events known to be associated with inhaled corticosteroids are summarized in the table below. The results appear to be similar among the two formulations.

Table 26 Adverse Events know to be associated with FP – FLTB3048

	FP HFA 440 BID	FP CFC 440 BID
Throat Irritation	27 (17%)	24 (15%)
Hoarseness/dysphonia	13 (8%)	14 (9%)
Candidiasis mouth/throat	10 (6%)	12 (7%)
Candidiasis site unspecified	8 (5%)	9 (6%)
Fungal infections*	1 (<1%)	1 (<1%)
Fungal skin infections*	2 (1%)	3 (2%)
Decreased cortisol	1 (<1%)	3 (2%)
Fungal infections (<1%) and fungal skin infections (1-2%) were also listed as adverse events however the sponsor did not provide more specific information about these.		

Adverse Events in Subjects with and without spacers

The frequency of adverse events was similar among subjects who used or did not use a spacer device during the study although throat irritation and hoarseness/dysphonia were reported with a slightly higher frequency in subjects who did not use a spacer device compared with subjects who did. The degree of difference was similar for both the HFA and the CFC formulations. The table below summarizes the local adverse events know to be associated with FP in subjects using and not using a spacer device.

Table 27 - Adverse Events associated with FP in subjects with and without spacer Device –FLTB 3048

	FP HFA 440 BID N =163		FP CFC 40 BID N =162	
	With Spacer N = 67 (41%)	Without Spacer N = 96 (59%)	With Spacer N = 61 (38%)	Without Spacer N=101 (62%)
Any Event	63 (94%)	86 (90%)	60 (98%)	98 (97%)
Throat Irritation	9 (13%)	18 (19%)	6 (10%)	18 (18%)
Hoarseness/dysphonia	4 (6%)	9 (9%)	7 (11%)	7 (7%)
Candidiasis mouth/throat	5 (7%)	5 (5%)	5 (8%)	7 (7%)
Candidiasis site unspecified	2 (3%)	6 (6%)	0	9 (9%)
Fungal skin infections	1 (1%)	1 (1%)	2 (3%)	1 (1%)

Deaths and Serious Adverse Events

There were no deaths during the study. A total of 22 subjects - 12 in the FP HFA group and 10 in the FP CFC group experienced serious adverse events during the treatment period. This reviewer concluded that possibly. One of these events might be drug-related. There was one serious event of pneumonia in a 31-year old man (#7847) that occurred about 7 months after treatment with FP HFA 440 BID. He developed an upper respiratory tract infection and pneumonia (confirmed by radiology) for which he was hospitalized and received intravenous antibiotics. The event resolved after 22 days and the subject continued on in the study.

One serious adverse event led to discontinuation from the study. This event occurred in a 72-year old man who had been on FP CFC 440 BID who was hospitalized and had surgery for a herniation of an intervertebral disc. The patient had received 21 weeks of treatment with the study drug when the SAE occurred.

Clinical Laboratory Evaluations
There were no clinically significant hematology or chemistry abnormalities in either treatment group during the study. Two subjects had an increase in eosinophil count during the study. One subject had an elevated eosinophil level at screening and this increased further during the study.

Subject #7575 is a 38-year old female with normal eosinophil (0.51 GI/L) at screening. At Week 24 eosinophil level was 1.26 GI/L and 1.00 GI/L at the end of treatment.

Subject #7870 is a 42-year old female with elevated eosinophil count at screening (1.07 GI/L). the eosinophil count remained elevated at Week 24 (1.00 GI/L) and at the end of treatment (1.30 GI/L).

One subject (#7823) was withdrawn because of abnormal LFTs. This was a 31-year old male in the FP CFC group. The subject had elevated AST (86U/L) and elevated ALT (134 U/L) at enrollment. At Week 12, both his AST (117 U/L) and Alt (217 U/L) had continued to increase. The subject was withdrawn at that time. He was asymtomatic. No further lab work was collected. One subject in the FP HFA group and 5 subjects in the FP CFC group had glucose levels that were at or above the high threshold level.

HPA Axis Assessments and biochemical markers of bone
The sponsor evaluated HPA axis using morning serum cortisol measurements and 24-hour urine cortisol or short ACTH stimulation testing. Investigators had to choose one test or the other at their discretion. There were no predefined criteria for selecting a test. The data are presented as cortisol/creatinine ratios and it is difficult to make a comparison between the HFA an the CFC formulations. The sponsor did not separate out the subjects using spacers from those who did not. The use of spacer while decreasing local effects could potentially result in increased systemic exposure and the cortisol data should be analyzed for these two subsets.

Asthma exacerbations
More subjects in the FP HFA group experienced asthma exacerbations during the study (22%) compared with subjects in the FP CFC group (14%). More subjects in the FP HFA group had more than one asthma exacerbation (7%) compared with subjects in the FP CFC group (2%).

Ophthalmic examinations
There were no reports of cataracts or glaucoma. One subject in the FP CFC group, a 26 year-old Caucasian woman, was found to have an opacity in one eye (report does not state which) upon examination at endpoint. But this was not reported as an adverse event and details about this are not available.

Discontinuations from the study

A total of 13 subjects discontinued due to an adverse event. In the opinion of this reviewer, 8 of the adverse events that led to discontinuations are possibly drug related. These events are listed in the table below. This reviewer's assessment of causality is noted in the last column. A brief narrative of each subject's AE is presented below. An interesting observation is that 7 of the 8 subjects with drug-related AEs that led to withdrawal are female and all the events that are definitely or possibly related to the drug occurred in females. None of these adverse events satisfied the regulatory definition of a serious adverse event

Table 28 - Withdrawals due to Adverse Events that are possibly drug-related – FLTB3048
Data source pg. 44 FLTB3048

Treatment Arm	Investigator - Subject #	Adverse Event	Time to onset from first dose of study medication	Relationship to study drug (per reviewer)
FP HFA 440 BID	5375-7790	Fungal infection of mouth and throat	32 weeks	Definitely related
	34910-7925	Fluid retention	12 weeks	Probably
	37568-7869	Throat irritation	1 week	Possibly
	46637-7667	Urticaria	40 weeks	Possibly
FP CFC 440 BID	5371-7902	Hypofunction of adrenal cortex and Cushing's syndrome	27 weeks	Definitely
	10392-7377	Rhinorrhea; hoarseness	Not stated	Possibly
	36758-7585	Hoarseness	15 weeks	Possibly
	46635-7678	Hypofunction of adrenal cortex	Not stated	Definitely

Subject # 7790 is 50-year old female who developed oral thrush after 25 weeks of treatment with FP HFA 440 BID. She was treated with Nystatin and the event resolved with 11 days. The subject continued in the study until at 32 weeks of study treatment she developed a fungal infection of the mouth and throat including yeast on the vocal cords. The study drug was discontinued and the subject was withdrawn from the study.

Subject #7925 is a 77 year-old-man treated with FP HFA 440 BID who developed mild fluid retention after 12 weeks of study medication. The subject had previously complained of muscle cramps, and spasms in the foot and leg, epistaxis, and arthralgia and articular rheumatism (joint pain). Review of the CRF showed that the only past medical history for this subject was allergic rhinitis and Chron's disease for which he had an ileostomy in —

Subject # 7869 is a 32-year-old female who was treated with FP HFA 440 BID and developed moderate throat irritation described as a sore and dry throat after 8 days of treatment. The event resolved within 25 days.

Subject # 7667 is a 45-year-old female treated with FP 440 BID who developed severe urticaria that lasted for 11 days. This event developed 40 weeks into the study. The CRF did not provide additional details of this event. The patient had a

history of hypothyroidism and a past surgical history of surgery on the ischias. She was also taking a thyroid preparation, piroxicam for headache and paralgin forte for lumbago (back pain).

Subject # 7902 is a 35-year-old female treated with FP CFC 440 BID who developed adrenal suppression and Cushing's syndrome 27 weeks after starting treatment. The subject had a morning serum cortisol concentration of 502 nmol/L at baseline and at week 24 the morning cortisol concentration was 94 nmol/L (144 nmol/L upon repeat). Urinary cortisol was 21 µg/L/24 hours at screening and 9 µg/L/24 hours at Week 24. Serum osteocalcin and urinary N-telopeptides were increased from baseline. This subject also reported other adverse events including candidiasis mouth/throat, chest congestion, cough, and menstrual cramps. The adverse event of Cushing's syndrome remained unresolved as of the last follow-up visit.

Subject # 7377 Is a 54 year-old female who was treated with FP CFC 440 BID developed mild intermittent rhinorrhea/post nasal drip and hoarseness/dysphonia. The duration of time on treatment prior to these events was not specified. The hoarseness resolved after the subject was withdrawn from the study.

Subject #7585: Is a 46-year old female who received FP CFC 440 BID. She developed hoarseness/dysphonia 15 weeks after starting treatment. The event resolved with 46 days.

Subject # 7678 Is a 61-year old female who received FP CFC 440 BID. At screening her morning serum cortisol was 469 nmol/L and at Weeks 24, 28, and 32, her morning serum cortisol values were 128nmol/L, 61 nmol/L and 164 nmol/L respectively. Concurrently, her urinary cortisol excretion was 49 µg/ml/24 hours at Screening and decreased to 21 µg/ml and 23 µg/ml at Weeks 24 and 32 respectively. The patient was not taking concurrent oral corticosteroids.

Pregnancies
Three subjects became pregnant and were discontinued. One subject was on FP HFA 440 mcg BID and 2 subjects were on FP CFC 440 BID. One subject (on FP CFC) had a spontaneous abortion after approximately 5 weeks of pregnancy. She was a 33-year old female who had been on the FP for approximately 6 months prior to becoming pregnant. The other 2 subjects delivered healthy babies. There is not enough information to make an assessment of causality with respect to the spontaneous abortion.

SAFETY STUDY FAP30001

Title: "A randomized, double-blind, parallel-group trial of inhaled Fluticasone propionate/GR1066642X (FP HFA) 220 BID and 440 BID in adolescent and adult subjects with asthma"

STUDY DESIGN

The study was designed to assess the safety of FP HFA 220 BID via the 110 mcg strength product and FP HFA 440 BID via the 220 mcg strength product for 6 months (26 weeks) in asthmatic subjects 12 years of age and older.

STUDY POPULATION

The study population and the inclusion and exclusion criteria were similar to that of the other studies. Subjects had to have an FEV_1 of ≥ 45%. Subjects could have been taking ICS but had to have been maintained on a stable regimen for at least 30 days prior to Visit 1. Subjects could have been on the maximum recommended dose of ICS. Subjects on theophylline, cromolyn or nedocromil, leukotriene receptor antagonists and 5-lipoxygenases inhibitors were allowed to continue taking them during the study if they were on a stable regimen. Subjects who had a history of oral corticosteroid use must not have required more than one systemic corticosteroid burst (defined as course of systemic corticosteroid < 14 days and the highest dose must not have exceeded 60 mg) during the 6 months prior to visit 1, and subjects must have discontinued the use of oral corticosteroids at least 6 weeks prior to Visit 1.

MEASUREMENTS AND EVALUATIONS

The primary objective of the study was safety. Safety measures similar to what was assessed in the other studies were evaluated. Efficacy was measured as mean change in percent predicted FEV_1 and mean change in morning pre-bronchodilator FEV_1.

SAFETY RESULTS

A total of 182 subjects were randomized to double-blind treatment, 89 in the FP HFA 220 mcg Bid arm and 93 in the FP HFA 440 mcg BID treatment arm. Eighty-five to eighty-six percent of subjects reported at least one adverse event during the study treatment. Although the percentage of subjects reporting at least one adverse events was similar in both treatment groups, adverse events that are related to ICS use such as throat irritation, hoarseness/dysphonia, candidiasis of the mouth/throat, and musculoskeletal pain were reported more frequent in the FP 440 group. Bronchitis, nausea/vomiting, and sinusitis were also reported more frequently in the FP 440 treatment group. Overall, the adverse event profile in both treatment groups was similar to that seen in the other FP studies in this program. Adverse events reported by ≥ 5% of subjects are displayed in the table below as copied from the sponsor's submission.

Table 29 - Adverse Events summary FAP 30001

Summary of Adverse Events Reported by ≥5% Subjects, n (%)

	FP 220mcg HFA BID (N=89)	FP 440mcg HFA BID (N=93)
Any event	76 (85%)	80 (86%)
Upper respiratory tract infection (URTI)	30 (34%)	32 (34%)
Throat irritation	9 (10%)	17 (18%)
Hoarseness/dysphonia	4 (4%)	11 (12%)
Sinusitis	4 (4%)	7 (8%)
Upper respiratory inflammation	7 (8%)	3 (3%)
Headaches	24 (27%)	19 (20%)
Viral respiratory infections	9 (10%)	8(9%)
Bronchitis	3 (3%)	9 (10%)
Asthma	4 (4%)	5 (5%)
Nausea and Vomiting	2 (2%)	6 (6%)
Candidiasis mouth/throat	2 (2%)	8 (9%)
Musculoskeletal pain	6 (7%)	13 (14%)
Muscle pain	6 (7%)	7 (8%)
Pain	5 (6%)	3 (3%)

Deaths and Serious Adverse Events

There were no deaths during the study. Two subjects in the FP 440 BID group had a serious adverse event but these events in the opinion of this reviewer (cholelithiasis and spontaneous abortion) are not related to the study drug.

Withdrawals due to Adverse Events

Eleven subjects were withdrawn from the study because of adverse events – 3 subjects in the FP 220 treatment group and 8 subjects in the FP 440 treatment group. Five of the subjects had events that were in the opinion of this reviewer drug-related. One subject in the FP 220 group – a 26 year old man developed a generalized rash after being on study drug for 4 days. The drug was stopped and the rash resolved after 14 days. Three subjects in the FP 440 group were discontinued because of throat irritation, sore throat, and dysphonia/hoarseness, and one subject in the FP 440 group was discontinued because of candidiasis mouth/throat.

Pregnancies

Two subjects became pregnant during the study. Both subjects were in the FP 440 treatment group. One subject was lost to follow up and the other subject had a spontaneous abortion. This subject # 392, a 30-year-old female became pregnant approximately four months after initiating study treatment. An ultrasound revealed that the pregnancy was not viable and the subject spontaneously aborted the fetus approximately 5 weeks after becoming pregnant. In the opinion of this reviewer, there is not enough information to make a determination of causality (if any) with the study drug.

Clinical Laboratory Findings

There were no clinically significant laboratory findings during the study. Shifts in laboratory values outside of the normal reference ranges was rare (≤2%) and not clinically significant. Four (4%) of subjects in the FP 220 group and one (1%) subject in the FP 440 group had shifts to high in eosinophil counts but these shifts were below the threshold range and there were no clinical signs of Churg – Strauss syndrome. One subject reported a high glucose at Week 26 but this did not reach threshold limits (170 mg/dl).

Urinary Cortisol

The sponsor presented 24-hour urinary cortisol as a cortisol/creatinine ratio and mean urinary cortisols. This study did not have a placebo arm and the findings in the 220 mcg BID treatment arm were not particularly different from the FP 440 arm. These data do not provide useful information and will not be discussed further.

Conclusions

The adverse event profile of Flovent HFA in this study is similar to the adverse event profile seen in other studies, although a clear dose-response in corticosteroid-related AE's was demonstrated between the FP 220 BID and FP 440 BID groups. Withdrawals due to adverse events and adverse events related to ICS were reported more frequently in FP 440 BID group compared with the FP 220 group. With respect to efficacy, the study was not designed or powered to detect a difference on an efficacy endpoint. However, FP 220 BID was not substantially different from FP 440 BID, although the survival-in-study endpoint clearly favored the lower dose. The finding of no clear dose-response on most efficacy endpoints is similar to what was seen in the pivotal efficacy trials. This trial suffers from the same deficiency as the previous (non-US) study in the inadequacy of the HPA-axis data.

120-Safety Update

The 120-day safety update (SUR), includes safety information from October 4th, 2001 – February 28th, 2002. The safety information in the NDA included safety information through the NDA cut-off date of October 3rd, 2001. Information from the following studies was submitted in the report:

Completed studies

Study FAS30007 – a controlled clinical study conducted in the US in pediatric patients age 1 – 4 years.

Ongoing Studies

FAS40019 – non-US local study is being conducted in children with asthma aged 3 – 4 years and adolescents aged 12- 15 years
SAM30013 – non-US local study in adolescents and adults aged 12-55 years
FAP40002 – post-marketing observational study

Studies initiated during the reporting period
FAP30010 – US controlled pediatric clinical study in children aged 4 – 11 years.

Adverse Events
In the pediatric study FAS30007 adverse events that occurred with a frequency of ≥ 5% in both placebo and HFA treatment groups included URTI, fever, rhinitis, ENT infections, asthma, tonsillitis, upper respiratory inflammation, diarrhea, viral infections and nausea and vomiting. Adverse events that occurred with greater frequency in FP HFA group compared with placebo were (1) URTI [27% FP vs. 20 % placebo], (2) rhinitis [9% FP vs. 6% placebo], (3)tonsillitis [5% FP vs. 2% placebo. There were no other completed studies in this SUR and no details of AEs are available because data remain blinded.

Deaths, Serious Adverse Events
There were no deaths, reported for any of the completed, or ongoing studies. The only reports of serious adverse events were in the completed pediatric study FAP30007, where 9 subjects (6%) experienced at least one serious adverse events. None of these events appear to be drug related. Asthma aggravation was the most common serious AE. In the ongoing post-marketing observational study no deaths, SAEs or pregnancies were reported

Pregnancies
There were no pregnancies reported in the completed or ongoing clinical studies. Glaxo provided follow up information for pregnancies reported as ongoing in the U.S. pivotal studies FAP30007 and FAP30008. Two of the subjects #44154-5407 and #89758-4011 each gave birth to a healthy baby. The outcome of the pregnancy for the third subject #04758-4294 is still pending.

Post-Marketing Experience - Spontaneous reports of SAEs
There were no spontaneous reports of deaths, serious adverse events, or pregnancies in patients using FP HFA during the reporting period. There were 2 spontaneous reports of death in subjects who used an unknown inhaled formulation of FP. One subject was a 57 year old male from Denmark who died of a brain tumor and the other subject was a 66 year old female from Poland who died of cardiopulmonary insufficiency, and pneumonia. The deaths do not appear to be related to FP. There were no reports of Churg-Strauss in subjects taking FP during the reporting period.

Safety Conclusions

The safety profile of Flovent HFA appears similar to the safety profile of Flovent CFC. The most common adverse events were in the ear, nose and throat and respiratory system. The most common drug-related adverse events were those that could be attributed to inhaled corticosteroids such as throat irritation, hoarseness/dysphonia, and oral candidiasis. This observation is supported by the finding that the higher dosage strengths (FP 440 BID and FP 880 BID) had higher percentages of throat irritation, hoarseness/dysphonia and oral candidiasis than the lower dosage strengths of FP. In the 12 - week studies there a gender difference in the frequency of adverse events was seen with females having a slightly higher frequency of throat irritation and hoarseness/dysphonia compared to males. This observation was not present in the long term studies however. In the Advair Diskus asthma development program, in study SFCB3019 (a study with 28 weeks of active treatment), females had more adverse events overall (85%) compared to males (63%) *[Medical officer Review, Dr Susan Johnson, NDA21-077].* Pharmacokinetic observations suggested that there might be an increased bioavailability of FP in females compared with males. In compliance with a phase 4 commitment for NDA21-077 (Advair Diskus) to study the apparent gender effects of Fluticasone propionate, GlaxoSmithKline has conducted studies to address this issue and the results of these studies are currently under review by the Biopharm team in the Division.

VIII. Dosing, Regimen, and Administration Issues

Flovent® HFA comes in three strengths: 44 mcg, 220 mcg, and 440 mcg ex-actuator. The sponsor is seeking approval for all three strengths for the long term maintenance treatment of asthma. The proposed dosing regimen is two inhalations twice daily. In addition, the sponsor is seeking approval of 880 mcg (4 inhalations of the 440 mcg strength) BID for oral corticosteroid sparing in subjects maintained on oral corticosteroid

The proposed dosing regimen of 2 inhalations BID is acceptable. The dosage strength selected should be dependent on the degree of asthma severity. Practitioners should always titrate patients to the lowest effective dose in order to reduce the potential for steroid-related side effects. This is particularly important for this product given that a clear dose response relationship was not demonstrated during the study. The data do not support a starting dose [redacted] for oral corticosteroid sparing. For this indication, subjects should be started on 440 mcg BID (2 inhalations of the 220 mcg product). Subjects who do not improve on this dose may increase the dose to 880 mcg BID (4 inhalations of the 220 mcg product).

IX. Use in Special Populations

A. Gender Effects

A greater percentage (55%) of subjects participating in the efficacy clinical studies was female. The incidence of candidiasis mouth/throat, throat irritation, and hoarseness/dysphonia tended to be lower in males compared to females in the 12-week studies (see table below) but not in the longer term studies. There were no gender differences for other adverse events. There were no gender-related differences in effectiveness.

Table 30 - Adverse Events by Gender U.S. 12-Week studies (data from table 8.2, 8.3 iss.pdf page 270 – 327)

	Placebo		HFA treatment groups	
	Male N = 116	Female N = 130	Male N=299	Female N = 382
Candidiasis mouth/throat	0	2 (<1%)	7 (2%)	15 (4%)
URTI	17 (15%)	24 (18%)	47 (16%)	73 (19%)
Throat Irritation	4 (3%)	8 (6%)	18 (6%)	39 (10%)
Hoarseness/dysphonia	1 (<1%)	1 (<1%)	6 (2%)	19 (5%)

B. Age, Race/Ethnicity effects on Safety or Efficacy

Subjects in this development program were 12 years and older. The majority of subjects (86%) were 18 – 64 years of age and the majority of subjects (84%) were Caucasian. There was not a representative number of patients in the other ethnic groups to allow for meaningful statistical comparisons. There did not appear to be any age-related or ethic origin-related differences in efficacy or safety.

C. Pediatric Program

In compliance with 21 CFR 314.55(c)(3) Glaxo requested and obtained a deferral for submission of an assessment of pediatric use with Flovent® HFA on July 26, 2000. This development program included patients 12 years of age and older.

For patients less than 12 months of age, GSK is requesting a waiver to not evaluate Flovent® HFA as it was indicated by the Agency on June 19, 2001 (during the pre-NDA meeting) that an indication in children less than 12 months of age was unlikely to be approved because of:

(1) the difficulty of making a diagnosis of asthma in children under the age of 12 months so extrapolation form older populations is not appropriate
(2) No agreement among professional organizations that asthma, as defined in adults exists in infants (under 12 months of age).

Also, given the recent U.S. District court ruling, GSK is not obligated to do a pediatric assessment.

D. Other Populations i.e. Pregnancy, Renal, or Hepatic Compromise

Formal studies were not conducted in subjects with renal impairment or hepatic compromise. Since FP is predominantly cleared by hepatic metabolism impairment of liver function may lead to accumulation of FP in plasma. Therefore, patients with hepatic disease should be closely monitored. There are no adequate and well-controlled studies with Flovent® HFA in pregnant women. A total of 10 pregnancies were reported in this development program. Follow up information is available for 5 subjects. One subject had a spontaneous abortion and the other 4 subjects had healthy babies. Flovent® HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

X. Conclusions and Recommendations

A. Conclusions

- Flovent ® HFA 44 mcg, 110 mcg, and 220 mcg administered as 2 inhalations BID are effective in the maintenance treatment of asthma.

- For oral corticosteroid sparing, both doses of Flovent 440 mcg BID and 880 mcg BID are effective, however the 880 mcg BID dose offers no demonstrable advantage over the 440 mcg BID and may even have some safety disadvantage as noted by the higher incidence of local events with this dose and the occurrence of 3 cases of serious pneumonia.

- A clear dose response relationship was not established for Flovent ® HFA.

- The adverse event profile for Flovent® HFA was generally similar to what was previously observed with Flovent® CFC.

- The data are insufficient to completely assess the comparative systemic effects of FP HFA compared with FP CFC, however, available biopharm data suggests that FP HFA is less systemically bioavailable than FP CFC.

- Long term data suggests that FP HFA might be less efficacious that FP CFC as demonstrated by the finding of 22% of asthma exacerbations in the FP HFA group compared with 14% in the FP CFC group in the one- year safety study.

B. Recommendations

From a clinical standpoint, Flovent ® HFA 44 mcg, 110 mcg , and 220 mcg Inhalation Aerosols can be approved for the long-term maintenance treatment of asthma.

For oral corticosteroid sparing, the starting dose should be 440 mcg BID For subjects who do not respond the dose can be increased to 880 mcg BID. Doses higher that 880 mcg BID are not recommended.

For all indications, the Lowest effective dose of ICS should be used.

Labeling and General Comments to the sponsor

A complete labeling review was not conducted during this review cycle since it was determined that this product will receive an APPROVABLE action because of unresolved Chemistry issues. The following labeling comments to be forwarded to the sponsor are general comments only and are not inclusive. More detailed comments will be sent when the approvable issues are resolved and the drug is ready for approval.

Preliminary labeling comments

These are general labeling comments are not all-inclusive. More detailed labeling comments will be forthcoming when the approvable issues have been addressed.

- In the **CLINICAL TRIALS** section page 8 delete the paragraph that begins

Rationale: cannot be used to establish an claim.

- In the **DOSAGE AND ADMINISTRATION** section of the label, in Table 3. Page 19,"Recommended Dosages of FLOVENT HFA": For Oral corticosteroids, under the "Recommended Starting Dosage" column, replace with 440 mcg twice daily. Leave 880 mcg BID as the highest recommended dosage.

Rationale: The data do not support a starting dose of or oral corticosteroid sparing.

General comments

For study FLTB3048, present the safety data (including the cortisol data) for subejcts using spacers separately from the nonspacer users. Resubmit an ISS excluding spacer users.

Rationale: While the spacer use may have decreased local AEs, inhaled drugs with a high first pass metabolism may show increased systemic effects when used with a spacer.

APPENDICES

Appendix I. STUDY FAP30007

TITLE: A randomized, double-blind, parallel-group, placebo-controlled 12-week trial of inhaled fluticasone propionate 88 mcg BID, 220 mcg BID, and 440 mcg BID versus placebo in propellant GR106642X (HFA) in adolescent and adult subjects with asthma who are maintained on inhaled corticosteroid therapy (ICS).

Protocol amendments

The original protocol dated August 2, 2000 was amended twice. The first amendment added a genotyping substudy to the protocol. This substudy assessed the association of polymorphisms in the glucocorticoid receptor and possibly other factors associated with response to glucocorticoids such as the glucocorticoid response element and transcription factors such as AP-1 and NFκB. Other genes assessed were CYP3A4, the $beta_2$-adrenergic receptor and enzymes involved in the synthesis of leukotrienes (5-lipoxygenase, LTC4 synthase) and the leukotriene receptors CysLT1 and CysLT2.

The second amendment was implemented on August 31, 2001 after enrollment was completed but before the clinical trial database was authorized and unblinded. The amendment replaced section 6 of the protocol entitled "data Analysis plan" with an attachment to the protocol entitled "FAP30007 Data Analysis Plan" and revised and expanded the section to included details on how planned analyses were to be conducted.

Objectives

The objective of the study was to assess the efficacy and safety of FP 88 mcg, 220 mcg and 440 mcg BID versus placebo in HFA propellant delivered from the 44 mcg, 110 mcg, and 220 mcg product administered over 12 weeks to adolescent and adult subjects with asthma who were previously maintained on ICS therapy.

Study period: October 26, 2000 – July 31, 2001

Study Design

The study was a multicenter randomized, double-blind, parallel-group, placebo-controlled trial with a 12 week treatment period. The double-blind treatment period started 14± 2 days after the initial screening and follow up visits were scheduled weekly for the first 4 weeks of the treatment period, then at treatment Week 6, 8, and 12.

Study Medication

The study medication was fluticasone propionate MDI in HFA propellant in the following strengths:
FP 44 mcg/actuation for the 88 mcg BID arm
FP 110 mcg/actuation for the 220 mcg BID arm
FP 220 mcg/actuation for the 440 mcg BID arm

Study Population

The study population was comprised of male and female subjects at least 12 years of age with a diagnosis of asthma for ≥ 6 months as defined by the ATS. Subjects should have an FEV_1 of 45% - 80% predicted and demonstrate reversibility (≥ 12%) following 2 inhalations of Ventolin® at the screening visit. Subjects who did not demonstrate reversibility at screening were allowed to have a repeat reversibility assessment either at or before randomization. If the subject failed to demonstrate an increase in FEV_1 ≥ 12%, then the subject was not eligible for the study. All subjects had to be taking ICS for at least 3 months and had to be on a stable regimen for at least 30 days prior to the screening visit at or below the maximum dose allowed, as outlined in the following table copied from the sponsor's submission:

Table 1 maximum allowable ICS doses (sponsor's table FAP30007.pdf pg. 29)

Maximum Allowable Inhaled Corticosteroid Doses
(Study FAP30007)

Generic Name	Brand Name	Maximum Daily Dose	
fluticasone propionate (FP)	**FLOVENT** Inhalation Aerosol	44mcg/inhalation: 20 inhalations/day 110mcg/inhalation: 8 inhalations/day 220mcg/inhalation: 4 inhalations/day	880mcg/day
	FLOVENT ROTADISK†	50mcg/blister: 20 blisters/day 100mcg/blister: 10 blisters/day 250mcg/blister: 4 blisters/day	1000mcg/day
beclomethasone dipropionate (BDP)	**BECLOVENT**†, **VANCERIL**† **VANCERIL DS**	42mcg/inhalation 20 inhalations/day 84mcg/inhalation: 10 inhalations/day	840mcg/day
budesonide (BUD)	**PULMICORT**† Turbohaler	200mcg/inhalation: 8 inhalations/day	1600mcg/day
flunisolide (FLN)	**AEROBID**†, **AEROBID-M**	250mcg/inhalation: 8 inhalations/day	2000mcg/day
triamcinolone acetonide (TA)	**AZMACORT**†	100mcg/inhalation: 16 inhalations/day	1600mcg/day

Smokers were eligible provided that they had a history of tobacco use of < 10 pack-years.

Exclusion Criteria

The exclusion criteria were similar to those used in previous asthma trials such as the exclusion of subjects with history of life threatening asthma, upper or lower respiratory tract infections within 2 weeks prior to the Screening visit, clinically significant ECG or clinical laboratory abnormalities, and significant

concurrent medical conditions. Subjects with a history or current diagnosis of glaucoma or posterior subcapsular cataracts were excluded.
Subjects who participated in any previous FP HFA clinical trial were also excluded.

Disallowed medications

- Methotrexate, gold, cyclosporine, and other immunosuppressive medications
- Oral/systemic corticosteroids and other corticosteroids except for Flonase ® Nasal Spray and ≤ 1% hydrocortisone cream or ointment
- Leukotriene modifiers
- Inhaled cromolyn sodium and inhaled nedocromil sodium
- Serevent®, inhaled anticholinergics (e.g. Atrovent®, or atropine), and theophylline

Study Procedure

After obtaining informed consent, subjects entered a Screening period which lasted 7 – 14 days. The purpose of the screening period was to evaluate the subject's eligibility for the study and to obtain baseline measures of efficacy and safety. Subjects were allowed to continue on their stable doses of ICS during the screening period. Subjects were switched from their prescribed short-acting beta-agonists to open-label Ventolin® and were to continue using Ventolin® as needed for the remainder of the study. At the end of the screening period, the Investigators re-assessed subjects to determine their eligibility for randomization. The subjects who had a best FEV_1 of 45-80% predicted, and who did not have signs of worsening asthma (defined below) were eligible for randomization. Subjects eligible for randomization were randomized to one of the following four treatment groups for 12 weeks:

- FP 88 mcg HFA (2 inhalations of 44 mcg/actuation) BID
- FP 220 mcg HFA (2 inhalations of 110 mcg/actuation) BID
- FP 440 mcg HFA (2 inhalations of 220 mcg/actuation) BID
- Placebo HFA (2 inhalations) BID

Subjects were not allowed to use spacers during the study. Patients returned for follow up at out-patient clinics at Treatment Weeks 1, 2, 3, 4, 6, 8, and 12. Subjects returned for a Post-Treatment visit 1 –2 weeks after discontinuation from the study.

Study discontinuation criteria

Subjects were discontinued for any of the reasons:

- Lack of efficacy/worsening asthma. Subjects who met any of the following criteria during the 7 days preceding a study visit (or at study visit in the case of FEV_1) were considered as having a lack of efficacy/worsening asthma:

- AM PEF below the PEF stability Limit for > 3 days. The stability was Limit was calculated at Visit 2 and was defined as 80% of the mean of the morning PEFs measured on the seven days preceding Treatment Day 0.
- ≥12 puffs/day of Ventolin ® for 3 days
- >3 nighttime awakenings due to asthma requiring treatment with Ventolin®
- FEV_1 below the FEV_1 Stability Limit at a study visit. The Stability Limit was defined as 80% of the best FEV_1 measured on Treatment Day 0.

- Inadequate study medication compliance
- Breaking of study blind
- Voluntary discontinuation
- Discontinuation at the discretion of the Investigator.

Statistical and Analytical Plan

Efficacy

- Primary

The primary efficacy measure was mean change from Baseline to Endpoint in morning (AM) pre-dose percent-predicted FEV_1. Baseline FEV_1 was determined at randomization. Endpoint was the measurement taken at Week 12 or was the last observation carried forward (LOCF) for subjects who discontinued.

- Secondary

There were four (4) key secondary endpoints.

5. Mean change from Baseline in AM and PM PEF at Weeks 1 through 12[9].
6. Duration of participation in the study
7. Mean change from Baseline in Ventolin use
8. Mean change from Baseline in Asthma symptom scores at Weeks 1 through 12

The mean change from baseline in FEV_1 (measured as percent predicted, percent change from Baseline, and absolute change) at Weeks 1, 2, 3, 4, 6, 8, 12, and Follow-up, and Nighttime awakenings were defined as secondary efficacy measures.

Health Outcomes Measures

The Asthma Quality of Life Questionnaire (AQLQ) developed by Juniper was used to asses the impact of asthma on the patient's quality of life. The AQLQ contains 32 items in four domains: activity limitation (11 items), symptoms (12 items), emotional function (5 items), and environmental stimuli (4 items). The response format consists of a 7-point scale where 1 indicates maximal impairment and 7 indicates no impairment. A clinically meaningful change for

[9] *Per the protocol procedures, morning PEF was taken before the AM dose of study medication. The evening PEF was taken before bedtime and could have been taken after the evening dose of study medication.*

both overall quality of life score and individual domains has been previously defined as 0.5 per item (Juniper, 1994).

Subjects completed the questionnaire at the randomization visit and at Week 12 or at the discontinuation Visit. The mean Overall Score as well as the mean score in all four domains [Activity Limitation, Asthma symptoms, Emotional Function and Environmental Exposure] were analyzed. The sponsor defined *a priori* a reduced ITT population comprised of subjects with an overall AQLQ score of ≤5.8 at Baseline as the primary analysis population for the AQLQ. Statistical analyses of AQLQ scores were based on mean change in response scores from baseline to endpoint.
int.

Sample size and power calculations
The sponsor estimated a standard deviation for percent predicted FEV_1 of 15% based on previous studies. A sample size of 98 subjects in each group would have 90% power to detect a difference between placebo and active groups of 7 percent of predicted FEV_1 in the change from baseline to endpoint using a two sample t-test with an α of 0.05. Therefore, a total of 392 available subjects were needed for the study.

For the AQLQ the estimated standard deviation for the overall AQLQ score was 1.0 based on previous studies. The sponsor noted that if at least 64 subjects per treatment group would meet the criteria of an overall AQLQ score at baseline of ≤5.8, then the study would have at least 80% power to detect a difference in AQLQ of 0.5 points using a two-sample t-test with a two-sided significance level of 0.05. If all 98 subjects per group had a baseline score of ≤5.8 there would be 93% power to detect a difference of 0.5 points.

Handling of missing data
The sponsor used the last observation carried forward (LOCF) to Week 12 to account for data of subjects who discontinued prematurely from the study. The sponsor also used a recursive regression model to assess the impact of missing data on the interpretation of the FEV1 results.

Multiple comparisons and multiplicity adjustment
For the primary endpoint, there are 3 pair-wise comparisons between active treatment and placebo. Therefore, the hypothesis that correspond to the primary analyses are:

H_{01}:FP440mcg = P H_{A1}:FP440mcg ≠ P
H_{02}:FP220mcg = P H_{A2}:FP220mcg ≠ P
H_{03}: FP88mcg = P H_{A3}: FP88mcg ≠ P

The multiple comparisons of active treatment groups with placebo were adjusted using Hochberg's method. This method controlled the type I error rate at 0.05. The p values from the comparisons of active treatment groups with placebo were

ranked from the least to the greatest i.e. p1 ≤ p2 ≤ p3 and superiority claims were made according to the following:

If p3 < 0.05 then all pairwise comparisons were considered significant
If p2 < 0.025 then significance was claimed for p1 and p2 only
If p1 < 0.0167 then significance was claimed for p1 only.

Four of the secondary endpoints were adjusted for multiplicity. These endpoints were:

- change from baseline in morning PEF,
- duration of participation in the study,
- change from baseline in supplemental Ventolin® use,
- change from baseline in asthma symptom scores.

The Hochberg method described above was used for multiplicity adjustment. The multiple comparisons were focused on FP 88mcg vs. placebo, with the comparisons of FP220 mcg and FP440 mcg vs. placebo as supportive.

Safety Analyses

Safety assessments included adverse events, clinical laboratory data, HPA-axis function, 12-lead EKGs, oropharyngeal examinations, and vital signs. HPA-axis function was assessed using 24-hour urine cortisol.

Compliance

Compliance was assessed during the 12-week period based on information from the diary card. Compliance was calculated as the number of doses actually used by the subject divided by the expected number of doses used, multiplied by 100.

RESULTS

Population Results

Of the 1051 subjects screened for this study, 636 failed screening and 415 were randomized to study treatment. The most common reason for failing to meet screening and/or randomization criteria was FEV_1 outside of the required range of <45%>80% predicted. Subject accountability is depicted in the table ---below.

Table 2 Summary of subject Accountability study FAP 30007

	Placebo HFA	FP 88 HFA	FP 220 HFA	FP 440 HFA	Total
Randomized (n)	104	103	106	102	415
Completed	40 (38%)	85 (83%)	84 (79%)	79 (77%)	288 (69%)
Discontinued	64 (62%)	18 (17%)	2 (21%)	23 (23%)	127 (31%)

Reasons for discontinuation					
Lack of efficacy	52 (50%)	11 (11%)	11 (10%)	6 (6%)	80 (19%)
Protocol violation	4 (4%)	1 (<1%)	4 (4%)	7 (7%)	16 (4%)
Adverse event	4 (4%)	1 (<1%)	3 (3%)	3 (3%)	11 (3%)
Consent withdrawn	1 (<1%)	2 (2%)	1 (<1%)	3 (3%)	7 (2%)
Noncompliance	0	0	0	1 (<1%)	1 (<1%)
Other	3 (3%)	3 (3%)	3 (3%)	3 (3%)	12 (3%)
Percentages are based on totals in treatment arm					

The distribution of subjects was relatively similar throughout the treatment arms. Only 38% of subjects in the placebo arm completed the study whereas, 77% - 83% of subjects in the active treatment groups completed. The high dropout rate in the placebo group was not unexpected given that these subjects were previously maintained on inhaled corticosteroids. Lack of efficacy was the most common reason for withdrawal both in the placebo and the active treatment groups. Among the "other" reasons for withdrawal was pregnancy in 2 subjects.

Protocol violations

Sixteen (16) subjects had protocol violations that resulted in discontinuation from the study. Some subjects had more than one violation that led to study discontinuation. The protocol deviations responsible for the 16 subject discontinuations were: (i) failed screening (3 subjects), (ii) failed randomization criteria (8 subjects), (iii) prohibited medications (3 subjects), (iv) late for Week 2 visit then missed Week 3 visit and follow-up (1 subject) and (v) final AQLQ not done (1 subjects).

Population baseline characteristics and demographics

The baseline characteristics and demographics are depicted in the table below as copied from the sponsor's submission FAP30007.pdf

Table 3 - Population Characteristics

Summary of Demographic and Baseline Characteristics
(ITT Population – Study FAP30007)

	PLA HFA (N=104)	FP 88 HFA (N=103)	FP 220 HFA (N=106)	FP 440 HFA (N=102)
Age (years), n (%)				
Mean (range)	44.5 (13-88)	45.6 (12-84)	42.3 (12-73)	42.3 (12-76)
12 – 17	8 (8)	7 (7)	8 (8)	8 (8)
18 – 64	86 (83)	86 (83)	94 (89)	88 (86)
65 – 74	6 (6)	8 (8)	4 (4)	5 (5)
≥75	4 (4)	2 (2)	0	1 (<1)
Gender, n (%)				
Male	46 (44)	45 (44)	45 (42)	34 (33)
Female	58 (56)	58 (56)	61 (58)	68 (67)
Ethnic Origin, n (%)				
White	92 (88)	90 (87)	92 (87)	86 (84)
Black	5 (5)	6 (6)	8 (8)	9 (9)
Other[a]	7 (7)	7 (7)	6 (5)	7 (7)
Steroid Strata, n (%)				
Low/Medium	88 (85)	85 (83)	87 (82)	88 (86)
High	16 (15)	18 (17)	19 (18)	14 (14)
PK Assessments, n (%)	14 (13)	20 (19)	15 (14)	17 (17)
Duration of Asthma, n (%)				
≥6mo–<1yr	1 (<1)	2 (2)	1 (<1)	0
≥1yr–<5yr	9 (9)	9 (9)	17 (16)	5 (5)
≥5yr–<10yr	11 (11)	15 (15)	17 (16)	14 (14)
≥10yr–<15yr	17 (16)	13 (13)	16 (15)	20 (20)
≥15yr	66 (63)	64 (62)	55 (52)	63 (62)
Smoking Status, n (%)				
Never smoked	75 (72)	76 (74)	68 (64)	72 (71)
Current smoker	5 (5)	1 (<1)	1 (<1)	5 (5)
Former smoker	24 (23)	26 (25)	37 (35)	25 (25)

The study population was predominantly white (84%) with Blacks making up 9% of the study population and other races making up 7%. Two-thirds of the subjects (67%) were female. Five percent of subjects in the study were current smokers. About 71% of subjects had never smoked and 25% were former smokers The mean age range was 42.3 – 45.6 years. Subjects in the lower age ranges were very poorly represented. There were only 19 subjects (6%) aged 14 years or younger in the study. Eighty-nine percent of subjects had asthma for 5 years of longer. The percent predicted FEV_1 at baseline was almost identical across treatment groups and ranged from 65.3 % (FEV_1=2.14 L) to 66.2 % (FEV_1 =2.11L). All subjects demonstrated a similar degree of reversibility which ranged between 22.0 and 22.7 %.

Treatment compliance

Mean compliance (assessed by diary data) ranged from 94% - 97% across treatment groups. Six subjects had treatment compliance of < 70%. Five of these six subjects discontinued within the first 3 days of treatment and one subject withdrew after 14 days.

EFFICACY RESULTS

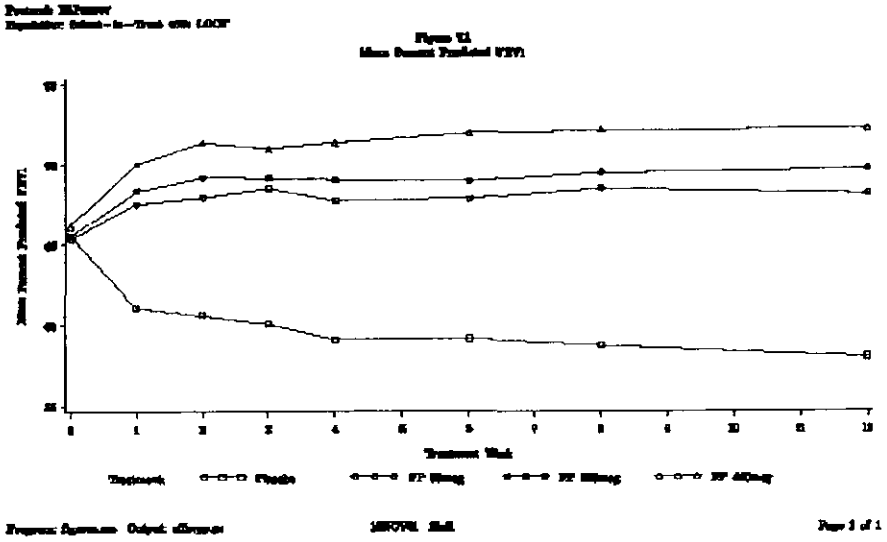
Primary Efficacy Endpoint

The primary efficacy endpoint was mean change from Baseline in AM pre-dose percent predicted FEV_1 at Endpoint (Week 12 with LOCF). The efficacy results were as expected with subjects in the placebo group having a decrease in FEV_1 and subjects in the active treatment groups maintaining their FEV_1 and even having a small increase from Baseline. The table below depicts these results.

Table 4 - FAP 30007 Primary efficacy results
Mean change from Baseline in AM pre-dose FEV_1 % predicted at Week 12 (LOCF)

	Placebo HFA	FP 88 HFA	FP 220 HFA	FP 440 HFA
Baseline (n) Mean FEV_1 (%) Baseline FEV1 (L) (SE)	104 65.6 2.22 L (0.06)	103 65.3 2.14 L (0.05)	106 65.5 2.16 L (0.05)	102 66.2 2.11 L (0.05)
Week 12 (n) Mean FEV_1 (L) (SE) Mean FEV_1 (%) LS mean change % predicted (SE)	102 1.96 L (0.06) 58.0 -8.3 (1.2)	100 2.24 L (0.07) 68.1 2.2 (1.2)	105 2.30 L (0.07) 69.7 3.2 (1.1)	98 2.29 L (0.06) 72.2 4.6 (1.2)
95% CI	-	(7.7,13.3)	(8.8, 14.4)	(10.1, 15.8)
LS mean difference FP – placebo	-	10.5 (p < 0.001)	11.5 (p<0.001)	12.9 (p<0.001)

With Hochberg multiplicity adjustment, all three doses of FP are significantly superior to placebo. The higher doses of FP had a slightly greater improvement in FEV_1 at Endpoint but the differences are probably too small to constitute a true dose-response relationship. The results are displayed in the graph below



The sponsor also did a post-hoc analysis of the primary endpoint without LOCF and the results were similar to those of the primary analysis with LOCF, with the exception of the placebo arm. The table below is copied from the sponsor's submission FAP 30007.pdf and displays those results.

Reviewer comment: For the primary analysis using LOCF, the change in FEV_1 (L) from baseline at Week 12 for the placebo group was –260 mL. The effect size (active – placebo) was 360 mL, 400 mL, and 440 mL for the FP 88, FP 220, and FP 440 group respectively.

Table 5 – Primary Efficacy Results – Completer Analysis

Mean Change from Baseline in AM Pre-Dose Percent Predicted FEV_1 at Week 12 for Subjects who Completed the Study (Without LOCF)

(ITT Population – Study FAP30007)

	PLA HFA (N=104)	FP 88 HFA (N=103)	FP 220 HFA (N=106)	FP 440 HFA (N=102)
Baseline (n)	104	103	106	101
Mean (%)	65.6	65.3	65.5	66.2
Week 12 (n)	40	85	84	79
Mean (%)	66.5	70.2	73.1	74.5
Mean Change	-0.1	4.8	6.4	7.7
LS Mean Chg[b] (SE)	0.02 (1.50)	5.1[a] (1.10)	6.3[a] (1.11)	7.2[a] (1.15)
95% CI[c]	---	(1.9, 8.3)	(3.1, 9.5)	(3.9, 10.4)
95% Dunnett's CI[d]	---	(1.3, 8.8)	(2.5, 10.0)	(3.4, 11.0)

In the above table the post-baseline n's are the sample sizes used for the LS mean change calculation. The comparison here is with inhaled corticosteroid-dependent asthmatics who were on placebo for 12 weeks compared with inhaled corticosteroid-dependent asthmatics on inhaled corticosteroid treatment. This analysis represents the worse case scenario where the subjects previously on corticosteroids were able to withstand 12 weeks without ICS and still retain asthma control compared to the active subjects who have not undergone such a challenge.

Reviewer comment
It is interesting that > 1/3 of subjects receiving ICS at the time of recruitment were able to maintain control of their asthma for the full 12 weeks of the trial, at least as measured by mean FEV_1. This constitutes a powerful argument for practitioners to taper ICS during periods of asthma stability, in order to limit exposing patients to the risk of ICS without deriving any tangible benefit.

Sensitivity Analysis

As expected, there was an excessive number of dropouts in the placebo group. At a pre-NDA meeting (June 19, 2001) the FDA requested an alternative method to LOCF to analyze the primary endpoint to assess the impact of missing data on the interpretation of the results. To address this requirement, a recursive regression model using covariates that included sex, age, Baseline % predicted FEV_1, site cluster, and the previous visit's percent predicted FEV_1, was designed.

For each successive visit, the model was fitted to impute the missing values using the observed or the imputed (wherever missing) values from the previous visit. At Week 12, a complete set of data on percent predicted FEV_1 were obtained for all subjects who had baseline and at least one post-baseline assessment on percent predicted FEV_1. These data were then fitted in an ANCOVA model. To address a worse case scenario, a 5% penalty was made for the subjects in the active treatment groups (i.e. using 95% of the imputed value at Week 12 prior to calculating the residuals and testing for treatment effect. Placebo-treated subjects or FP-treated subjects who had the observed (instead of imputed) percent predicted FEV_1 did not have a penalty applied to their data.

The residuals mean AM pre-dose percent predicted FEV_1 were greater in the FP HFA groups at week 12 (0.87% to 2.57%) compared with the placebo group (-4.91%, $p < 0.001$). When the 5% penalty was applied the results were still statistically significant.

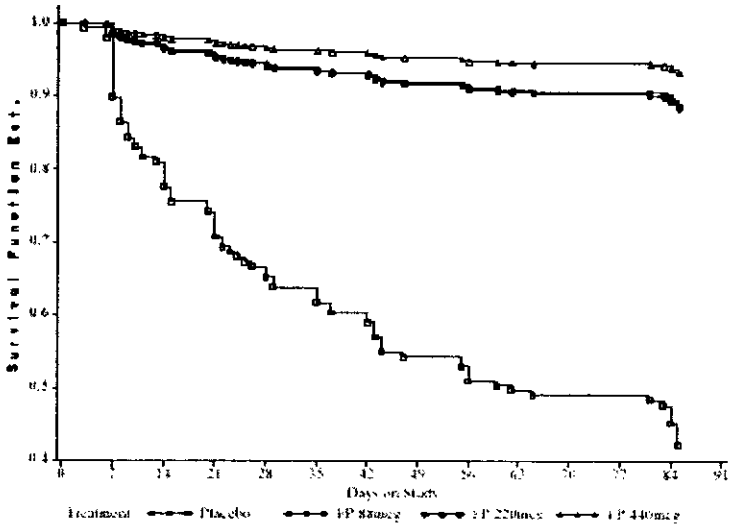
Secondary Endpoints

The four secondary endpoints change from baseline in morning PEF, discontinuation for lack of efficacy (duration of study participation), Asthma symptom scores and change from baseline in supplemental Ventolin® use were adjusted for multiple comparisons using the Hochberg method previously described in the statistical and analytical section *(see page 78)*. The comparison of interest was FP 88 HFA vs placebo.

Discontinuation for lack of efficacy (duration of study participation)

The estimated probability of remaining in the study was assessed at 2-week intervals using Kaplan- Meier estimates. The probability of remaining in the study was higher for each FP treatment group compared with placebo at each two-week interval. At week 1, the probability of remaining in the study in the FP HFA treatment groups was 0.89 for the FP 88 treatment group, 0.90 for the FP 220 treatment group, and 0.94 for the FP 440 treatment group compared with 0.45 for placebo-treated subjects ($p<0.001$). The figure below copied from the sponsor's submission depicts the survival in the study.

Duration of Subject Participation in the Study - SDF Estimates
(ITT Population – Study FAP30007)



(Source: FAP30007.pdf, pg. 85)
Survival curve is based on discontinuations due to lack of efficacy. Subjects who completed the study or discontinued for other reasons were censored in this analysis.

The results for the secondary measures AM PEF, supplemental Ventolin® use, and asthma symptom scores are displayed in the table below. Using the Hochberg multiplicity method, there was a statistically significant improvement in AM PEF, Ventolin® use, and asthma symptom scores ($p<0.001$) for the FP 88 HFA-treated subjects compared with placebo. The results seen in the FP 220 and FP 440 groups were supportive of the findings in the FP 88 treatment group.

Table 6- Secondary endpoints, AM PEF, Ventolin use and asthma symptom scores FAP 30007

Endpoint	Placebo (n = 104)	FP 88 HFA (n=103)	FP 220 HFA (n=106)	FP 440 HFA (n=102)
AM PEF (L/min)				
Baseline (n)	104	103	106	102
Mean (L/min)	346.0	334.8	329.0	333.1
Week 12 (n)	102	100	105	100
Mean (L/min)	326.6	356.9	348.9	356.0
LS mean change (SE)	-20.7	20.8	20.9	20.9
Supplemental Ventolin® Use				
Baseline (n)	104	102	105	102
Mean (puffs/24hr)	2.38	2.69	2.52	2.72
Week 12 (n)	102	100	105 1	00
Mean (puffs/24hr)	3.24	2.20	1.86	1.96
LS mean change (SE)	1.09 (0.20)	-0.16(0.21)	-0.44(0.20)	-0.43(0.21)
Asthma symptom scores				
Baseline (n)	103	101	105	100
Mean (points)	1.79	1.77	1.77	1.61
Week 12 (n)	101	98	105	98
Mean (points)	2.09	1.38	1.46 1.1	9
LS mean change (SE)	0.38 (0.10)	-0.32(0.10)	-0.26(0.10)	-0.40(0.10)
Asthma symptom scores were scored on a 6-point incremental rating scale where 0= no symptoms to 5 = severe symptoms prohibiting normal daily activities.				

Health Outcomes Results

Subjects whose total score at baseline was ≤ 5.8 made up the "asthma quality of life population". Subjects in each of the active treatment groups had an improvement of at least the minimum clinically important change (≥0.5) in each of the 4 domains and in the overall score at Week 12. The FP treated groups when compared with placebo had clinically significant improvements in the overall score (≥ 0.5) and in the individual domains of Activity limitation, Asthma symptoms and Emotional Function at Week 12. Given that the patient population was made up of subjects who were previously maintained on ICS, the lack of improvement in the placebo group is not unexpected. The results of the AQLQ are displayed in the table below.

Table 7 - Health Outcomes Results FAP 30007

	Placebo (n=83)	**FP 88 (n=87)**	**FP 220 (n=87)**	**FP 440 (n=80)**
Randomized n	104	103	106	102
AQLQ Score				
Overall Score				
Baseline (SD)	4.53 (0.75)	4.41 (0.91)	4.35 (0.90)	4.69 (0.79)
Week 12	4.40 (1.10)	5.51 (1.06)	5.12 (1.18)	5.30 (0.93)
FP Δ from baseline – placebo (at Week 12)	-	0.79	0.79	0.75
Activity limitation				
Baseline (SD)	4.65 (0.79)	4.50 (0.95)	4.40 (0.98)	4.87 (0.83)
Week 12	4.61 (1.16)	5.25 (1.10)	5.25 (1.18)	5.55 (0.92)
FP Δ from baseline – placebo (at Week 12)	-	0.69	0.72	0.76
Asthma symptoms				
Baseline (SD)	4.62(0.81)	4.47 (0.91)	4.45 (0.96)	4.69 (0.82)
Week 12	4.27 (1.21)	5.25 (1.05)	5.15 (1.25)	5.28 (1.01)
FP Δ from baseline – placebo (at Week 12)	-	0.67	0.58	0.58
Emotional Function				
Baseline (SD)	4.27 (1.28)	4.20 (1.41)	4.27 (1.34)	4.48 (1.21)
Week 12	4.08 (1.53)	4.93 (1.51)	5.05 (1.42)	5.12 (1.36)
FP Δ from baseline – placebo (at Week 12)	-	0.50	0.60	0.60
Environmental stimuli				
Baseline (SD)	4.27 (1.20)	4.22 (1.41)	3.98 (1.15)	4.46 (1.27)
Week 12	4.52 (1.21)	4.86 (1.36)	4.83 (1.52)	4.98 (1.13)
FP Δ from baseline – placebo (at Week 12)	-	0.34	0.49	0.33

SAFETY RESULTS – FAP 30007

Exposure

The mean duration of exposure was lowest (as expected) in the placebo group (48.7 days). The mean duration of exposure was similar across the active treatment arms and ranged from 74.1 to 72.8 days. Exposure to active treatment was highest for the FP 88 group where 70% of subjects completed the entire 12 weeks of study medication.

Adverse Events

Of the 415 subjects randomized to the treatment period, a total of 253 experienced at least one adverse event (AE) during the study. The most frequently reported AEs were similar to those previously reported in other asthma studies with inhaled corticosteroids. The most frequently reported AEs were upper respiratory tract infection, headaches, and throat irritation. Adverse events that occurred with an incidence of > 3% and more frequently than in the placebo group are displayed in the table below.

Table 8 Adverse Events at a rate > 3% and more common than in placebo group regardless of causality (Source: data table 9.3 FAP30007.pdf)

Adverse Event N (%)	Placebo HFA (n = 104)	FP 88 HFA N=103	FP 220 HFA N=106	FP 440 HFA N=102
ANY EVENT	54 (52%)	70 (68%)	67 (63%)	62 (61%)
URTI	16 (15)	22 (21%)	16 (15%)	19 (19%)
Headaches	4 (4%)	15 (15%)	8 (8%)	3 (3%)
Throat Irritation	3 (3%)	7 (7%)	7 (7%)	8 (8%)
***Sinusitis/sinus infection	3 (3%)	10 (10%)	10 (10%)	6 (6%)
Cough	7 (7%)	5 (5%)	11 (10%)	3 (3%)
Candidiasis mouth/throat	2 (2%)	4 (4%)	3 (3%)	9 (9%)
Hoarseness/dysphonia	1 (<1%)	1 (<1%)	5 (5%)	8 (8%)
Upper respiratory inflammation	2 (2%)	2 (2%)	5 (5%)	6 (6%)
Nasal congestion/blockage	3 (3%)	5 (5%)	2 (2%)	4 (4%)
Musculoskeletal pain	2 (2%)	3 (3%)	5 (5%)	2 (2%)
Diarrhea	0	5 (5%)	2 (2%)	0

***This reviewer combined the AEs from the sponsor's two distinct AE names of sinusitis and sinusitis/sinus infection. There is no apparent rationale having two distinct AEs "sinusitis" and "sinusitis/sinus infection".

As displayed in the table, local AEs that are know to be associated with inhaled corticosteroids such as namely candidiasis mouth/throat, throat irritation and hoarseness/dysphonia were reported with higher frequency in the active treatment groups and appeared to show dose-ordering.

Drug related adverse events and events associated with local or systemic corticosteroid effects

In addition to the more frequently observed AEs of candidiasis, hoarseness/dysphonia, throat irritation and musculoskeletal pain associated with ICS, there were four (4) additional AEs reported by the investigator as drug-related. Because no case narratives were provided for these events this reviewer is unable to make an assessment of causality of these events.

Deaths and Serious Adverse Events (SAE)

- Deaths

One subject died during the study. This was a 60-year old male subject (subject #863) with a history of nocturnal seizure disorder, who received FP 440 mcg BID Approximately 9 days after starting the treatment period he was withdrawn from the study due to lack of efficacy. The subject reported that he was having trouble breathing deeply. He was started concurrently on inhaled fluticasone (formulation unknown) and intranasal sodium cromoglycate. Approximately 6 days after discontinuation of the study medication, the subject died. He was found dead in his bed four days after the estimated date of death and the family did not allow an autopsy. The investigator believed that the cause of death was cardiac.

- Serious Adverse Events

There were no serious adverse events in the active treatment arms. Four (4) subjects in the placebo group experienced serious adverse events. These events were (a) pneumonia and asthma exacerbation in one subject, (b) diverticulitis in one subject , (c) asthma exacerbation in one subject, and (d) right knee cellulitis in one subject.

Pregnancies

Three pregnancies occurred during treatment period. One subject in the placebo group was exposed during the first trimester. The other two subjects were in the FP 220 group and were exposed to study medication before conception and for up to 4 weeks gestation. The outcome of these pregnancies is pending.

Discontinuations due to Adverse Events

A total of 11 (3%) subjects had AEs that resulted in withdrawal from the study. Of these subjects, 4 (4%) were in the placebo group, 1 (<1%) was in the FP 88 group and 3 (3%) each were in the FP 220 and FP 440 group. In 4 of the 11 subjects the adverse event was possibly related to the study medication. These events were asthma and copious oral secretions in 2 subjects in the placebo group, puritus in one subject in the FP 220 group and hoarseness/dysphonia in one subject in the FP 440 group.

Clinical Laboratory Results

There were no clinically significant changes in laboratory parameters that required a change in or clinical treatment.

Hematology

There were no values outside the predefined threshold range for RBCs, lymphocytes, monocytes, eosinophils, basophils and platelets. Two subjects in the FP 220 group and one subject in the FP 440 group had hemoglobin, WBC, and neutrophils below the threshold range at Week 12. These subjects entered

the study with values either below the threshold range (e.g. subject # 2121) in FP 220 arm with baseline hemoglobin of 8.7 g/dl) or with values below the normal range (e.g. subject #1568 in the FP 440 arm with a baseline hemoglobin of 10.5 g/dl). The changes were not clinically significant and did not result in a change in treatment.

Although there were some shifts to high outside of the normal range for eosinophils in 13 subjects, there were no reports of shifts to high outside of the pre-specified threshold. Of the 13 subjects with shifts to high eosinophils, 5 were in the placebo group, 6 were in the FP 88 group and 2 were in the FP 220 group. There were no subjects in the FP 440 group with shifts to high eosinophils.

Increased neutrophils and low lymphocytes could be due to a systemic corticosteroid effect. A total of 9 subjects (3 in the placebo group, 1 in the FP 88 group, 4 in the FP 220 group and 1 in the FP 440 group had shifts to high (but not outside the threshold) in neutrophil counts. Three subjects, two in the FP 220 and one in the FP 440 group had shifts to low (but not outside the threshold value) in lymphocyte count.

Chemistry

Liver function abnormalities above the threshold were noted in three (3) subjects but all three subjects entered the study with liver transaminases either above the normal range or above the threshold value. Subject # 5624 entered the study with an elevated ALT (above the threshold) and withdrew from the study 2 weeks later. Subject #5538 entered the study with a GGT value of 144 U/L which was above the normal range and at Week 12 the value was 182 U/L which was above the threshold range. Another subject, in the FP 220 group also entered the study with a GGT value above the normal range (102 U/L) and at Week 12 the value was 202 U/L which was above the threshold range.

A total of 6 subjects had blood sugar levels above the threshold range - one subject in the placebo group, 2 in the FP 88 group and 3 in the FP 440 group. All six subjects entered the study with blood sugar levels either above the normal or the threshold range. The values of the elevated liver function and blood glucose results are shown in the table below.
As shown in the table, subjects in the highest ICS group did not have clinically significant worsening of their blood glucose levels from study entry.

Table 8 - liver function and glucose values above the threshold value
Study FAP 30007

	Treatment arm	Lab value at study entry	Lab value at follow up (Week 12)*
Liver Function abnormalities			
Subject # 2242 - GGT	FP 220	102 U/L	202U/L
Subject # 5624 – ALT *(subject withdrew at Week 2 result for repeat test 1 week after	FP 440	148 U/L	117 U/L

withdrawal)			
Subject # 5538 - GGT	FP 440	144 U/L	182 U/L
Elevate blood glucose			
Subject # 5499	Placebo	134 mg/dl	234 mg/dl
Subject #2240	FP 88	193 mg/dl	264 mg/dl
Subject # 5688	FP 88	184 mg/dl	256 mg/dl
Subject # 4195	FP 440	154 mg/dl	203 mg/dl
Subject # 1272	FP 440	265 mg/dl	221 mg/dl
Subject # 1894	FP 440	209 mg/dl	178 mg/dl

HPA Axis Function Assessment

Twenty-four hour urine cortisols were collected at randomization visit (Baseline) and at Week 12 or study discontinuation. Subjects whose urine samples were considered to have confounding factors that could affect the interpretation of the results were excluded from this analysis. Urine samples of subjects who had any one of the following findings were not included in the analysis.

- Incomplete samples noted on the CRF
- Urine volumes of < 600 ml for female subjects and < 800 ml for male subjects and 24-hour creatinine excretion below the lower limit of threshold range
- Collection time interval outside 24 ± 4 hours
- Off study drug for more than one day at the start of post baseline urine collection period
- Used corticosteroids (except Flonase® or < 1% hydrocortisone cream) within 30 days of the screening visit or during the treatment period

Based on these criteria, a total of 225 (54%) of the randomized subjects (defined as the urine cortisol population) had urine cortisol samples that were eligible for analysis. Table 10 shows the mean baseline and Week 12/discontinuation values for the 24 hr urine cortisols and the mean change from baseline. A normal range for urine cortisol was unavailable for urine cortisol for subjects under 18 years. The cited normal range for 24 hour cortisol was 5 – 55 mcg / 24 hours for subjects 18 years of age and older.

Reviewer comment. A review of the line listings revealed that the sponsor submitted line listings for the 24 hr cortisol for the ITT population, but did not include a separate listing of the urine cortisol population. This information would provide more useful information than the mean results presented in the submission. The results of the ITT population contain all the abnormal results including those from inadequate collections. Outliers cannot be determined from mean results and the sponsor was asked to submit the line listings for the "urine

cortisol population". A separate line listing of the "cortisol population" was submitted. There were no trends that raised particular concerns. The subjects in the placebo group generally had higher cortisol levels than the subjects in the FP groups.

Table 10 - 24 hr urine cortisol FAP30007

	Placebo (n=32)	FP 88 (n=69)	FP 220 (n=64)	FP 440 (n=70)
Randomized n	104	103	106	102
Baseline mean (SD)	15.92 (13.96)	16.88 (14.56)	15.17 (13.50)	18.62 (16.65)
Week 12/Discontinuation mean (SD)	19.47 (14.50)	17.40 (16.50)	17.77 (14.28)	16.73 (15.56)
*Mean Δ change from Baseline (SD)	3.55 (17.47)	0.52 (15.12)	2.60 (13.79)	-1.89 (17.47)
* Raw means not LS means				

APPEARS THIS WAY
ON ORIGINAL

Appendix II. STUDY FAP30008

This study was a 12-week, randomized, double-blind parallel-group, placebo-controlled, multicenter trial to compare the efficacy and safety of FP HFA 88 mcg BID , 220 mcg BID , and 440 mcg BID versus placebo HFA in adolescent and adult subjects with asthma maintained on bronchodilator therapy alone.

The study was of identical design to study FAP30007 except that subjects enrolled in this study were not previously maintained on ICS.

RESULTS

POPULATION RESULTS

A total of 1146 subjects were screened for this study and 749 subjects failed to meet the screening and /or randomization criteria. The most common reason for failure was not meeting the FEV_1 criteria of FEV_1 45 – 80% predicted. A total of 397 subjects were randomized to study treatment and constituted the ITT population.

The subject accountability is displayed in the table below. The distribution of patients in the treatment arms was relatively similar. More subjects in the placebo group discontinued compared to the FP-treated subjects. However, the percentage of subjects discontinuing placebo group and the FP 88 mcg group was not very different (30% placebo vs. 26% FP 88 group). Lack of efficacy was the most common reason (8%) for discontinuing the study across all treatment groups. The percentage of discontinuations due to lack of efficacy was highest in the placebo group (15%). A total of 12 subjects discontinued because of protocol violations. Of these, 11 subjects had violations due to failed screening or randomization criteria.

Table 11- Subject Accountability FAP 30008

	Placebo HFA	FP 88 HFA	FP 220 HFA	FP 440 HFA	Total
Randomized (n)	99	100	98	100	397
Completed	69 (70%)	74 (74%)	80 (82%)	89 (89%)	312 (79%)
Discontinued	30 (30%)	26 (26%)	18 (18%)	11 (11%)	85 (21%)
Reasons for discontinuation					
Lack of efficacy	15 (15%)	9 (9%)	6 (6%)	2 (2%)	32 (8%)
Consent withdrawn	6 (6%)	5 (5%)	4 (4%)	2 (2%)	17 (4%)
Protocol violation	4 (4%)	5 (5%)	1 (1%)	2 (2%)	12 (3%)
Adverse event	1 (1%)	0	1 (1%)	4 (4%)	6 (2%)
Lost to follow up	1 (1%)	2 (2%)	1 (1%)	1 (1%)	5 (1%)
Noncompliance	1 (1%)	2 (2%)	0	0	3 (<1%)
Other	2 (2%)	3 (3%)	5 (5%)	0	10 (3%)
Percentages are based on totals in treatment arm					

Baseline Characteristics and demographics of the study population were similar across treatments group and similar to that of the study population in FAP30007. The majority of subjects were white and females made up 56% - 62% of the population. The table below copied from the sponsor's submission summarizes the study population characteristics and demographics. The age range was 12 to 83 years and the mean age range was 31.9 to 36.1 years. Subjects aged 12 to 14 years of age represented only 4% (n= 17) of the patient population. Most of the subjects (78%- 83%) had never smoked.

Table 12 – Population Demographics and Baseline Characteristics

Summary of Demographic and Baseline Characteristics
(ITT Population – Study FAP30008)

	PLA HFA (N=99)	FP 88 HFA (N=100)	FP 220 HFA (N=98)	FP 440 HFA (N=100)
Age (years), n (%)				
Mean (range)	31.9 (12-70)	34.0 (12-67)	34.4 (12-66)	36.1 (12-83)
12 – 17	14 (14)	8 (8)	9 (9)	11 (11)
18 – 64	84 (85)	90 (90)	88 (90)	86 (86)
65 – 74	1 (1)	2 (2)	1 (1)	2 (2)
≥75	0	0	0	1 (1)
Gender, n (%)				
Male	47 (47)	38 (38)	56 (57)	44 (44)
Female	52 (53)	62 (62)	42 (43)	56 (56)
Ethnic Origin, n (%)				
White	75 (76)	78 (78)	76 (78)	88 (88)
Black	16 (16)	15 (15)	9 (9)	9 (9)
Other[a]	8 (8)	7 (7)	13 (13)	3 (3)
Duration of Asthma, n (%)				
≥6mo–<1yr	2 (2)	1 (1)	0	1 (1)
≥1yr–<5yr	11 (11)	10 (10)	15 (15)	15 (15)
≥5yr–<10yr	16 (16)	12 (12)	16 (16)	13 (13)
≥10yr–<15yr	15 (15)	18 (18)	13 (13)	18 (18)
≥15yr	55 (56)	59 (59)	54 (55)	53 (53)
Smoking Status, n (%)				
Never smoked	77 (78)	82 (82)	78 (80)	83 (83)
Current smoker	6 (6)	6 (6)	1 (1)	2 (2)
Former smoker	16 (16)	12 (12)	19 (19)	15 (15)

Spirometry

Mean FEV_1 at baseline ranged from 2.34 L (67% predicted) to 2.51 L (67.3% predicted). Baseline FEV_1 was similar among treatment groups.

Treatment Compliance

The mean compliance as assessed by diary data ranged from 90% - 97%. Only 8 subjects (2%) had a reported compliance of <70%. Of these subjects one each was in the placebo group and the FP 220 group and the other 6 subjects were in the FP 88 group.

EFFICACY RESULTS

Primary efficacy endpoint – Mean change from baseline in AM pre-dose percent predicted FEV_1 at Endpoint

There was a statistically significant improvement in AM pre-dose percent predicted FEV_1 at endpoint for all three FP arms compared to placebo ($p < 0.001$) with the Hochberg multiplicity adjustment. There was no apparent dose-response relationship. The results are summarized in Table 13 below.

Table 13 - Primary Efficacy Endpoint FAP 30008

	Placebo HFA N =99	**FP HFA 88 mcg N= 100**	**FP HFA 220 mcg N =98**	**FP HFA 440 mcg N = 100**
Baseline (n) Mean FEV_1 L (SE) Mean FEV_1 (%)	99 2.40 L (0.06) 67.0	99 2.35 L (0.06) 67.0	98 2.50 L (0.06) 67.3	100 2.30 L (0.05) 67.1
Week 12 (n) Mean FEV_1 L (SE) Mean FEV_1 (%) LS Mean change (SE)	96 2.56 L (0.07) 71.1 3.4	95 2.67 L (0.07) 76.3 9.0 (1.1)[a]	95 2.85 L (0.07) 76.8 9.8 (1.1)[a]	99 2.69 L (0.06) 78.1 11.2 (1.0)[a]
a = $p < 0.001$ Vs placebo (Hochberg multiplicity adjustment)				

The analysis of the primary efficacy endpoint without LOCF, as well as the sensitivity analysis (described in study FAP30007), also showed statistically significant differences between the three FP treatment groups and placebo. There was no clinically meaningful difference within the active treatment groups At Week 12, the improvement from baseline in FEV_1 (L) in the placebo group was 160 mL. The effect size (active – placebo) in the treatment arms was 160 mL, 190 mL, and 230 mL in the FP 88, FP 220, and FP 440 treatment arms respectively.

SECONDARY EFFICACY ENDPOINTS

There was a statistically significant improvement in AM peak flow, in the FP HFA 88 mcg treatment group compared with placebo ($p < 0.001$ with Hochberg multiplicity adjustment as described for FAP30007). However, the asthma symptom scores and Ventolin® use were not inferentially significant compared with placebo The results of these key endpoints are depicted in the table below.

Table 14 -SECONDARY ENDPOINTS – FAP 30008
AM peak flow, supplemental Ventolin® use and asthma symptom scores.

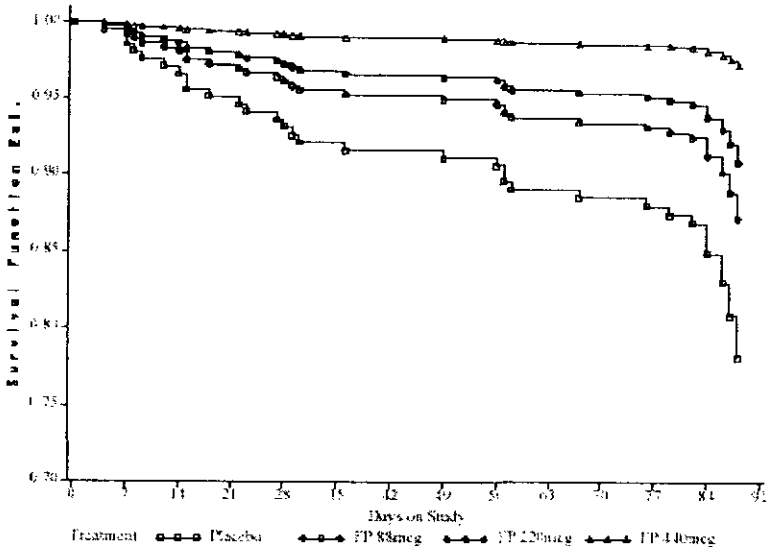
	Placebo HFA N =99	**FP HFA 88 mcg N= 100**	**FP HFA 220 mcg N =98**	**FP HFA 440 mcg N = 100**
AM Peak flow – change from baseline in AM peak flow (L/min) at Week 12 (LOCF)				
Baseline (n) Mean (L/min)	99 353.4	100 344.9	98 372.7	99 335.6
Week 12 (n) Mean (L/min) LS mean change	98 363.4	97 384.1	97 415.5	99 390.0

(SE)	11.4 (6.0)	41.7 (6.0)	47.6 (6.0)	54.1 (5.9)
Supplemental Ventolin ® use --Change from baseline in supplemental Ventolin use (puffs/24hrs)				
Baseline (n) Mean (puffs/24hr)	992.79	100 3.67	98 3.17	99 2.86
Week 12 (n) Mean (puffs/24hr) LS mean change (SE)	98 2.19 -0.76 (0.18)	97 2.21 -1.17 (0.18)	97 1.63 -1.51 (0.18)	99 1.09 -1.90 (0,17)
Asthma symptom scores- Change from baseline in asthma symptom scores (points) at Week 12				
Baseline (n) Mean (points)	99 1.98	100 2.07	98 2.19	98 2.01
Week 12 (n) Mean (points) LS mean change (SE)	98 1.68 -0.33(0.10)	97 1.45 -0.61 (0.10)	97 1.49 -0.65 (0.10)	98 1.12 -0.92 (0.10)

Duration of study participation (Discontinuations for lack of efficacy)

There was a higher probability of remaining in the study for each FP treatment group compared with placebo at each two-week interval. However, the difference in survival between the FP 88 and the placebo group, or between the FP 220 and the placebo group was not statistically significant. However, subjects treated with FP 440 mcg had a significantly greater probability (p = 0.004) of remaining in the study compared with those in the placebo group. The graph of the survival curves is displayed below copied from the sponsor's submission FAP30008.pdf.

Duration of Subject Participation in the Study - SDF Estimates
(ITT Population – Study FAP30008)



Health Outcomes Results

The Asthma Quality of Life Questionnaire (AQLQ), Juniper and Guyatt, was also used in this study to assess the impact of treatment on the subjects' perception

of their asthma-related health. Similarly, as done in study FAP30007, a reduced ITT population, comprised of subjects whose total score at baseline was ≤ 5.8 was used in this analysis. A total of 344 subjects (86%) of the 397 randomized subjects qualified. Only the FP 440 treatment group had a clinically significant improvement (≥ 0.5) in the overall score and in each individual domain. These results displayed in the table below are taken from the sponsor's submission (FAP30008. pdf pg. 96). The change from baseline is based on the LS means adjusted for baseline score, region, age, and gender.

Table 15 Health Outcomes Results
FAP 30008

	Placebo (n=89)	**FP 88 (n=85)**	**FP 220 (n=83)**	**FP 440 (n=87)**
Randomized n	99	100	98	100
AQLQ Score				
Overall Score				
Baseline (SD)	4.43 (0.82)	4.25 (0.85)	4.35 (0.83)	4.26 (0.86)
FP Δ from baseline – placebo (at Week 12)	-	0.40	0.40	0.66
Activity limitation				
Baseline (SD)	4.71 (0.87)	4.51 (0.89)	4.48 (0.95)	4.52 (0.92)
FP Δ from baseline – placebo (at Week 12)	-	0.43	0.27	0.59
Asthma symptoms				
Baseline (SD)	4.32 (0.89)	4.29 (0.89)	4.26 (0.87)	4.15 (0.90)
FP Δ from baseline – placebo (at Week 12)	-	0.37	0.52	0.64
Emotional Function				
Baseline (SD)	4.33 (1.18)	4.05 (1.18)	4.29 (1.27)	4.26 (1.36)
FP Δ from baseline – placebo (at Week 12)	-	0.34	0.46	0.80
Environmental stimuli				
Baseline (SD)	4.17 (1.27)	4.00 (1.23)	4.33 (1.15)	3.84 (1.34)
FP Δ from baseline – placebo (at Week 12)	-	0.52	0.38	0.76

SAFETY RESULTS

Exposure

The mean duration of exposure was 71 to 80 days. The subjects in the active treatment arms were exposed to medication an average of 73 to 80 days compared with an average of 71 days in the placebo group. Exposure across treatment groups was highest in the FP 440 group in which 75% of subjects completed the entire 12 weeks of study treatment.

Adverse Events

Of the 397 subjects randomized in the treatment period, 222 (56%) had at least one AE during the study. The most frequently reported adverse events were similar to those previously described for the other studies in this development program and similar to the most frequently reported adverse events reported in other asthma studies with inhaled corticosteroids. Adverse events most frequently seen were upper respiratory tract infections (URTI) (13%-17%), followed by throat irritation (8% - 12%), headaches (7%-8%) and nausea and vomiting (5%-7%). Adverse events that occurred at a frequency of > 3% in the FP groups and more frequently than in the placebo group are depicted in the table below.

Table 16 - Adverse Events at a rate > 3% and more common than in placebo group regardless of causality (Source: data table 9.3 FAP30008.pdf)

Adverse Event N (%)	Placebo HFA (n = 99)	**FP 88 HFA N=100**	**FP 220 HFA N=98**	**FP 440 HFA N=100**
ANY EVENT	54 (55%)	53 (53%)	52 (53%)	63 (63%)
Ear Nose and Throat				
URTI	13 (13)	14 (14%)	17 (17%)	14 (14%)
Throat irritation	8 (8%)	9 (9%)	10 (10%)	12 (12%)
Headaches	8 (8%)	7 (7%)	7 (7%)	8 (8%)
Viral respiratory infections	3 (3%)	4 (4%)	4 (4%)	5 (5%)
Upper respiratory inflammation	1 (1%)	3 (3%)	5 (5%)	5 (5%)
Cough	3 (3%)	4 (4%)	2 (2%)	5 (5%)
Bronchitis	3 (3%)	1 (1%)	0	7 (7%)
Hoarseness/dysphonia	1 (1%)	4 (4%)	1(1%)	4 (4%)
Fever	*1 (1%)*	*1 (1%)*	*3 (3%)*	*4 (4%)*
Candidiasis	*0*	*3 (3%)*	*1 (1%)*	*2 (2%)*
Muscle injuries	*2 (2%)*	*1 (1%)*	*5 (5%)*	*0*
GI signs and symptoms*	*1 (1%)*	1 (1%)	*4 (4%)*	*2 (2%)*
* sponsor did not specify. However, this category was distinct from nausea/vomiting, diarrhea, dyspeptic symptoms, and abdominal discomfort.				

Drug-related Adverse events and events associated with local or systemic corticosteroid effects.

Most of the adverse events described as drug-related were events that are known to be associated with a local corticosteroid effect. This reviewer could not assess some events reported as drug-related (such as nausea and vomiting and lymphatic signs and symptoms) because the sponsor did not provide case narratives for these cases. Events that could be associated with a local corticosteroid effect are displayed in the table below. Throat irritation occurred with similar frequency among all treatment groups and this event may be related to the propellant. Hoarseness/dysphonia and candidiasis were not frequent events but were more common in the FP treatment groups. In the placebo group there were no cases of candidiasis and only one case of hoarseness/dysphonia.

Table 17 Local Corticosteroid effects
Study FAP 30008.

Adverse Event N (%)	Placebo HFA (n = 99)	FP 88 HFA N=100	FP 220 HFA N=98	FP 440 HFA N=100
Throat irritation	8 (8%)	9 (9%)	10 (10%)	12 (12%)
Hoarseness/dysphonia	1 (1%)	4 (4%)	1(1%)	4 (4%)
Candidiasis mouth/throat	0	3 (3%)	1 (1%)	2 (2%)

Deaths and Serious adverse events
There were no deaths during the study. Three (3) serious adverse events occurred during the treatment period,. One of these SAEs was in the FP 88 HFA treatment group, and the other two events occurred in the FP 440 HFA treatment group.

The serious adverse events are briefly described below.

Subject 8497- Adrenal suppression occurred in a 24 year old female who was randomized to FP HFA 88 mcg BID . One day following the final dose of study medication laboratory studies revealed a blood glucose of 42 mg/dl, an undetectable 24-hour urine cortisol level (< 3.2 mcg/24 hours) and increased eosinophils (2.06). Eleven days later, the subject still had low blood glucose (57 mg/dl) and high eosinophils (2.78). The subject was diagnosed with possible adrenal suppression based on the laboratory results. The subject was asymptomatic. Three weeks after discontinuing the study medication, the cortisol level, cortisol stimulation and urine cortisol were normal.

Subject 3554: Exacerbation of bipolar disorder occurred in a 54 year old female with a history of bipolar disorder. She was randomized to FP 440 mcg BID . Fourteen days after starting the study medication the subject was reported to have increased stress and was hospitalized. She was treated with risperidone. The event resolved after 5 days and the subject was seen in the clinic that same day for a study visit. She was found to have rapid and rambling speech, and study drug was discontinued and she was withdrawn from the study. The investigator was unable to obtain details about her hospitalization.

Subject 3108: Status asthmaticus occurred in a 72 year old female with a history of GERD, post-traumatic splenectomy, and hypothyroidism who presented to the emergency room with symptoms of worsening asthma 3 weeks after starting study treatment. She reported exposure to ammonia and "cleaning fumes" earlier in the week. She was treated and sent home and returned to the ER the following day because her symptoms did not improve and she was admitted to the hospital. Her hospital stay was prolonged by oral candidiasis, rectal bleeding (bleeding internal hemorrhoids) and weakness.

Pregnancies

There were 2 pregnancies during the study. One subject was receiving FP HFA 88 mcg (subject 7816) and the other, FP 440 mcg (subject 3116). Both subjects were found to be pregnant after completing the treatment phase of the study. The outcomes of the pregnancies were not available at the time of reporting.

Discontinuations due to Adverse Events

Six (6) subjects had adverse events that resulted in treatment withdrawal. These events are tabulated below. Of these adverse events, candidiasis of the mouth and throat is most likely due to the corticosteroid.

Table 18 - Discontinuations due to AEs
Study FAP30008

	Placebo	FP HFA 220	FP HFA 440
Dizzy spells	Subject 3559 32y/o W M		
Abnormal menses		Subject 7412, 43 y/o W F	
Exacerbation bipolar disorder			*Subject 3554, 53 y/o W F
Allergic conjunctivitis			Subject 2377, 35 y/o W M
Candidiasis mouth/throat			Subject 8403, 47 y/o W F
Status asthmaticus			*Subject 3108 72 y/o W F
* Had serious adverse events discussed previously. Subject 3108 also had oral candidiasis, but this was not the adverse event that led to withdrawal.			

Clinical Laboratory Results

There were no clinically significant changes in hematology, or clinical chemistry values during the 12-week treatment period. One subject in the placebo group and 2 subjects in the FP 440 group had a shift to the low range in lymphocytes, while 2 subjects in the placebo group and 4 subjects each in the FP 88 and the FP 440 group had shifts to the high range in eosinophils. Also shifts to high in neutrophils were noted in 1 subject in the placebo group, 4 subjects in the FP 88 group and 2 subjects in the FP 220 group.

A total of 17 subjects had shifts to high in blood glucose – 4 in the placebo group, 3 in the FP 88 group and 5 each in the FP 220 and FP 440 groups. Of the subjects with shifts to high in blood glucose, six had blood sugar levels above the threshold range (>170 mg/dl). Five of these subjects entered the study with blood sugar levels already above the threshold value. These six subjects are briefly described in the table below. One subject in the FP 88 group was reported to have hyperglycemia as an adverse event.

Table 19 - Elevated Blood glucose levels
Study FAP 30008

	Treatment Arm	Blood glucose at study entry	Blood glucose at follow up
*Subject 3657	FP 88	112 mg/dl	408 mg/dl at Week 10 and 336 mg/dl at week 11. No further testing available
Subject 8782	FP 88	159 mg/dl	184 mg/dl at Week 12. Repeat one week later 162 mg/dl
Subject 8502	FP 220	167 mg/dl	254 mg/dl at Week 12
Subject 3890	FP 220	245 mg/dl	195 mg/dl at Week 12
Subject 8942	FP 220	218 mg/dl	215 mg/dl at week 12
Subject 8989	FP 440	284 mg/dl	295 mg/dl at week 12
*Reported as an adverse event (hyperglycemia)			

HPA Axis Function

Twenty-four hour urine cortisols were collected at randomization visit (Baseline) and Week 12 or study discontinuation. Subjects whose urine samples were considered to have confounding factors that could affect the interpretation of the results were excluded from this analysis using the same criteria as described for study FAP 30007. (*See page 91).* Based on these criteria, a total of 262 (66%) of the randomized subjects had urine cortisol samples analyzed. Table 20 shows the mean baseline and Week 12/discontinuation values for the 24 hr urine cortisols and the mean change from baseline. A normal range for urine cortisol was unavailable for urine cortisol for subjects under 18 years. The cited normal range for 24 hour cortisol was 5 – 55 mcg / 24 hours for subjects 18 years of age and older.

Reviewer comment. The sponsor submitted line listings for the 24 hr cortisol for the entire ITT population with abnormal cortisol results , but did not include a separate listing of the urine cortisol population. This information may provide more useful information than the mean results presented in the submission. The results of the ITT population contain all the abnormal results including those from inadequate collections. The sponsor was asked to submit the listings for the Urine Cortisol Population. The sponsor has since submitted the line listings for the "cortisol population". The findings do not reveal any trends of concern.

Table 20 - 24 hr urine cortisols
Study FAP30008

	Placebo (n=63)	FP 88 (n=58)	FP 220 (n=68)	FP 440 (n=73)
Randomized n	99	100	98	100
Baseline mean (SD)	22.41(22.96)	17.45 (15.32)	24.07 (21.85)	21.26 (17.01)
Week 12/Discontinuation mean (SD)	18.69 (12.53)	17.57 (14.41)	18.12 (13.41)	16.43 (16.85)
Δ change from Baseline (SD)	-3.72 (24.10)	0.12 (17.65)	-5.95 (21.73)	-4.83 (21.27)

Conclusions

The efficacy of FP HFA in the maintenance treatment of asthma was established and replicated in the two studies FAP 30007 and 30008. A dose response relationship was not clearly seen in either of the two studies. The safety profile of FP HFA was similar to that seen in the previous asthma studies with FP CFC.

APPEARS THIS WAY
ON ORIGINAL

Appendix III. STUDY FLTA 3022

Title: A randomized, double-blind, placebo-controlled comparative trial of fluticasone propionate 440 mcg BID or 880 mcg BID versus placebo administered via metered-dose inhaler in propellant 11/12 or GR1066642X in adolescent and adult oral corticosteroid-dependent asthmatics.

The study was conducted under IND 53,502 at 27 centers in the U.S.

Protocol Amendments
There were 2 amendments to the protocol that were implemented prior to the enrollment of any subjects. The first amendment applied to selected investigators and provided for an assessment of FP plasma concentrations after 2 weeks of double-blind treatment. The amendment specified that a blood sample would be obtained 12 hours post-dose. The second amendment applied to all investigators and specified how a 50% increase in Ventolin® use should be calculated if the subject was taking concomitant Serevent®.

Objectives
To compare the dose related efficacy and safety of fluticasone propionate 440 mcg BID and 880 mcg BID using the 220 mcg formulation administered by pressurized metered-dose inhaler propelled by CFC propellants 11/12 (CFC) or HFA propellant GR106642X 9HFA) for 16 weeks in adolescent and adult oral corticosteroid dependent asthmatics.

Study Period: September 4, 1997 – May 4, 1999

Study Design
The study was a randomized, double-blind, parallel-group, placebo-controlled trial with a 16 week treatment period. The double-blind treatment period started 14± 2 days after the initial screening. Follow up visits were scheduled weekly.

Study Medication
The HFA and the CFC formulations of the fluticasone propionate 220 mcg products were used in this study.

Subjects were randomized to the following treatment arms.
- Placebo HFA
- FP HFA 440 mcg BID
- FP HFA 880 mcg BID
- FP CFC 440 mcg BID
- FP CFC 880 mcg BID

In order to maintain the blind all subjects received 2 inhalers. For the 440 mcg BID arm subjects took 2 puffs of the active inhaler BID and 2 puffs of the placebo inhaler. For the 880 mcg BID arm, subjects took 2 puffs BID of two active inhalers.

Study Population
Subjects were enrolled in the study if they were at least 12 years of age and had diagnosis of asthma. Subjects had to be oral corticosteroid-dependent for the past 6 months and had to be on their minimum effective dose of oral corticosteroid. The minimum dose of prednisone allowed at study entry was 5 mg daily (QD) or 10 mg every other day (QOD) and the maximum dose allowed at entry was 40 mg QD or 80 mg QOD. Subjects taking inhaled corticosteroids except Flovent ® were also eligible for enrollment. Concurrent inhaled corticosteroids were discontinued at randomization.

Inclusion Criteria

- Asthma as defined by the ATS diagnosed for at least 1 year
- Required oral steroids ≥ 5 mg QD or ≥ 10 mg QOD for the past 6 months prior to randomization.
- Best FEV_1 of 40 – 85% predicted at screening
- Demonstrate reversibility by demonstrating an increase in FEV_1 of ≥12% approximately 15 minutes following inhalation of 2 puffs of Ventolin® at Visit 1 (screening visit) or as a result of other pharmacotherapy (e.g. prednisone treatment or nebulized albuterol) during the previous 6 months.
- Must be maintained on the same dose of oral corticosteroid for at least 2 weeks prior to Visit 2 (baseline).
- Minimum dose of prednisone allowed at entry is 5 mg QD or 10 mg QOD
- Maximum dose of prednisone allowed at entry is 40 mg QD or 80 mg QOD
- Subjects may also be taking inhaled corticosteroids prior to randomization up to the following doses displayed in Table 21.
- Inhaled corticosteroids must remain at a constant dose and frequency within 4 weeks prior to Visit 2.
- All in ICS must be discontinued the evening prior to Visit 2 and for the duration of the study.

Table 21 - Maximum Dose of ICS allowed prior to randomization

Generic Name	Brand Name	Maximum dose
Beclomethasone dipropionate	Beclovent® Vanceril®	Up to 16 inhalations/day
Dexamethasone sodium phosphate	Decadron phosphate Respihaler ®	Up to 12 inhalations/day
Triamcinolone acetonide	Azmacort ®	Up to 16 inhalations/day
Flunisolide	Aerobid ®	Up to 6 inhalations/day
Note: concurrent use of Flovent® is not allowed and should not have been used within the 4 weeks prior to Visit 1		

Exclusion Criteria

Subjects were to be excluded if any of the exclusion criteria were met. These exclusion criteria were the same as those used in previous asthma trials such as the exclusion of subjects with history of life threatening asthma, upper respiratory tract infections or influenza vaccination two weeks prior to Visit 1 (Screening), clinically significant ECG or clinical laboratory abnormalities, and significant concurrent medical conditions. Also, subjects with a history or current diagnosis of glaucoma or posterior subcapsular cataracts were to be excluded. Subjects using any tobacco products within 1 year of Visit 1 or subjects having a 10-pack year or greater history of cigarette smoking (including pipes and cigars) were to be excluded.

Disallowed Medications

- Ophthalmologic, dermatologic (except topical hydrocortisone cream or ointment of ≤ 1%, or injectable corticosteroid therapy during the 1 month prior to Visit 1 is prohibited.
- Ketoconazole (other antifungals are allowed)
- Influenza vaccination within 4 weeks of Visit 2 (Baseline).

Permitted medications

- Long-acting $beta_2$-agonists and theophylline at the same constant dose and frequency. Subjects must be able to withhold their long-acting $beta_2$-agonists for ≥ 12 hours and theophylline preparations for the appropriate time (≥12 - ≥ 36 hours depending on the formulation) prior to all study visits.

- Topical hydrocortisone cream or ointment of ≤ 1%

- Topical nasal medications: Nasalcrom®, Flonase®, Afrin®

- Claritin® and OTC antihistamines (must be withheld prior to study visits).

- Regularly scheduled immunotherapy provided that the subject has received his/her usual stable maintenance dose for 12 weeks prior to Visit 1.

Study Procedures

Patients eligible for enrollment entered a 2-week screening period. During this time, they continued taking all anti-asthma medications including inhaled

corticosteroids (ICS) without adjustment in dosage or dosing interval with the exception that Ventolin® replaced all other short-acting inhaled $beta_2$- agonists. All subjects received a supply of prednisone tablets and were instructed to use them in place of and at the same dose as the prednisone used during the 2 weeks prior to screening. During the 2-week screening period subjects recorded peak flow measurements, and subjective assessments of asthma (i.e. symptoms, Ventolin® use, nighttime awakenings) in a diary card.

At visit 2 subjects were assigned to one of five double-blind treatment arms if they had a best FEV_1 of 40 –85% predicted, met all the inclusion and exclusion criteria, and demonstrated compliance (i.e. able to complete the diary cards, and withhold medication for the time defined in the protocol). Subjects had weekly follow up visits in the clinic.

Prednisone Dose adjustment
Subjects continued to take their current prednisone dose for a 2-week post-randomization stabilization period and thereafter the investigator titrated the dose once a week according to the prednisone modification chart outlined below.

Table 22 – Prednisone Dose Modification Chart
Prednisone Maintenance Dose Modification Chart

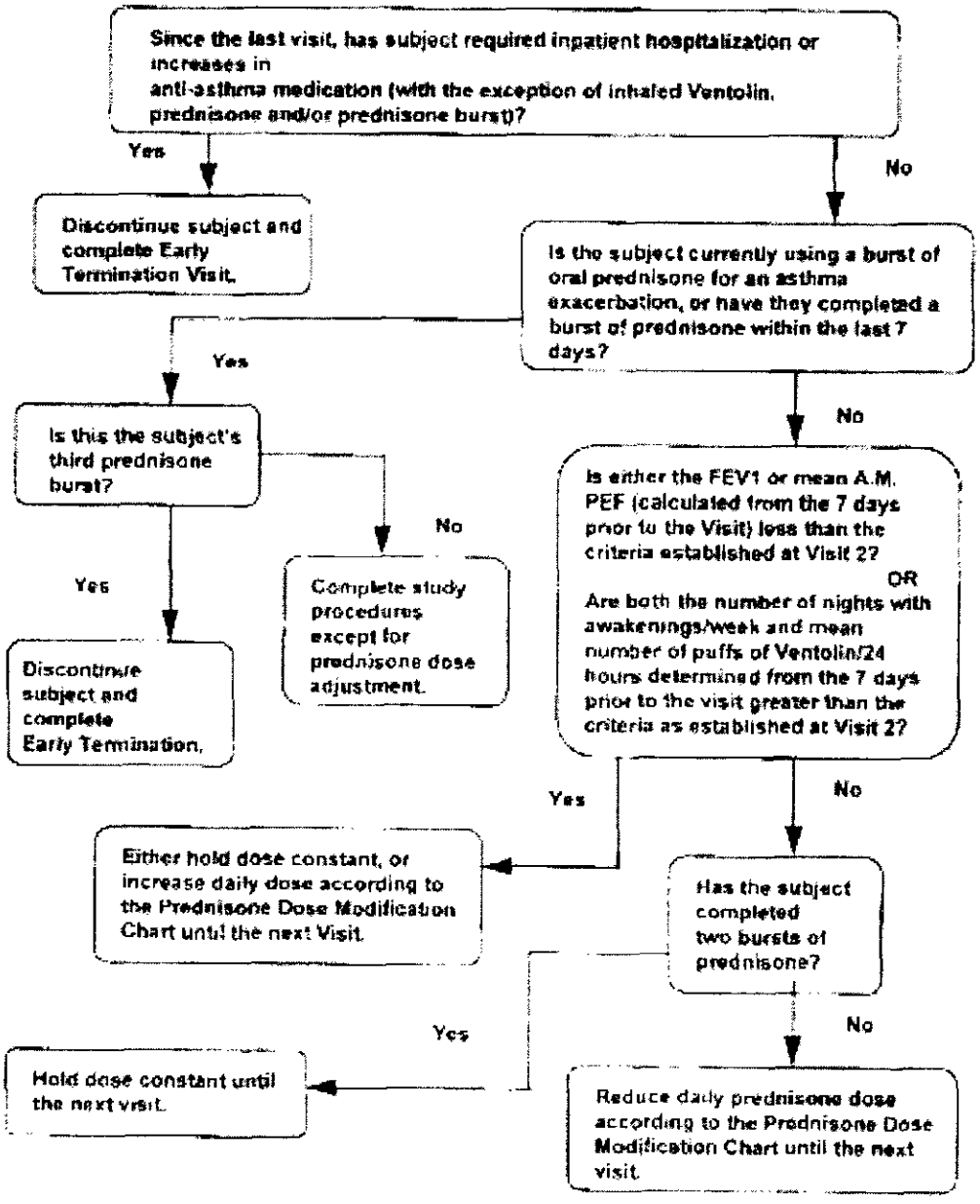
Maintenance Dose	Dose Reduction/Increase
≥30mg QD (60mg QOD)	10mg QD(20mg QOD)
>10mg QD <30mg QD (>20mg QOD to <60mg QOD)	5mg QD(10mg QOD)
>5mg QD ≤10mg QD(>10mg QOD to ≤20mg QOD)	2.5mg QD(5mg QOD)
≤5mg QD (≤10mg QOD)	1.25mg QD (2.5mg QOD)

Table source: Pg. 25 FLTA3022.pdf

All investigators followed a prespecified decision diagram for prednisone dose adjustment to determine whether the daily prednisone dose should be reduced. The decision diagram is depicted below (source pg. 1536 FLTA3022.pdf).

DIAGRAM 2

DECISION DIAGRAM FOR PREDNISONE DOSE ADJUSTMENT VISITS 4-18 (WEEKS 2-16)



Definitions

- **Clinical asthma exacerbations**

Any breakthrough signs and symptoms of asthma that in the opinion of the investigator require:

- Inpatient hospitalization
- A tapering burst of oral prednisone or
- Increases in any anti-asthma medication (except inhaled Ventolin®), including prednisone dose increases outside of those allowed by protocol.

- **Discontinuations for lack of efficacy**

Subjects were to be discontinued from the study for lack of efficacy if they required:

- Inpatient hospitalization for asthma
- Increases in, or introduction of any anti-asthma medication other than inhaled Ventolin® and oral prednisone bursts to a dose greater than specified; or
- A third burst of oral prednisone

- **Endpoint**

- For dairy data: the last 7 days of available data where the subject was still on study drug
- For clinical data: data obtained at the last visit where the subject was still on study drug or had only been off study drug for at most one day.

Protocol-defined procedure for prednisone bursts

The protocol provided specific guidance for how to administer a prednisone burst based on a subject's current maintenance prednisone dose.

- For subjects currently maintained on > 10 mg or prednisone per day or > 20 mg QOD

1. The prednisone burst will begin with 60 mg for 1 day
2. The dose will be tapered by 5 mg per day to 5 mg more than the dose the subject was taking at the time the exacerbation and prednisone burst began.
3. When reached, this dose must be held constant for 7 days prior to making any further prednisone reductions.

- For subjects currently maintained on ≤ 10 mg of prednisone per day (≤20 mg QOD):

1. The prednisone burst will begin with 40 mg for 1 day
2. The dose will be tapered by 5 mg per day to 2.5 mg more than the dose the subject was taking at the time the exacerbation and prednisone burst began.
3. When reached, this dose must be held constant for 7 days prior to making any further prednisone reductions.

Statistical and Analytical Plan

Efficacy

Primary efficacy measurement
The primary measure of efficacy is mean oral prednisone use during the study (weeks 1-16). This included both maintenance prednisone and any prednisone prescribed as part of a prednisone burst. The primary efficacy endpoint is mean daily oral prednisone use.
The mean daily oral prednisone use was calculated by adding each days' total daily dose for the time period of interest and dividing by the total number of days in that time period.

- Secondary efficacy measurements

1. Reduction in oral prednisone use
2. Mean dose of prednisone at baseline and endpoint
3. Mean change from baseline in prednisone dose
4. Time to sustained elimination of prednisone dose
5. Duration of study participation
6. FEV_1
7. PEF (subject-administered)
8. Daily symptom scores
9. Nighttime awakenings requiring Ventolin ® use
10. Inhaled Ventolin® use

- Patient-reported outcome evaluations

The Asthma Quality of Life Questionnaire (AQLQ) was used to assess patient reported outcomes. The questionnaire was administered at baseline and after 16 weeks of treatment or earlier in the case of withdrawal from the study.

Calculation of last observed value carried forward (LOCF)
The last observation carried forward (LOCF) was used as a method to handle missing data from subjects who were withdrawn from the study. The sponsor also conducted completer analysis (analysis in which the discontinued subjects' last value was not carried forward) to distinguish between LOCF.

Sample Size considerations
The standard deviation of average daily oral prednisone use adjusted for baseline was assumed to be 10mg based on previous studies. With 33 subjects per arm there will be > 80% power to detect a difference in average daily oral prednisone use of 7 mg between any 2 treatment groups using a 2- tailed test with an α level of 0.05.

Multiple comparisons

Pairwise comparisons to placebo were performed in a sequential manner, beginning with the FP HFA 880 mcg BID group and the FP CFC 880 mcg group. If neither of these comparisons was significantly different from placebo, further p-values were not interpreted. If these p-values were significant, comparisons to placebo were interpreted for the FP 440 mcg groups.

Safety

Safety assessments included adverse events assessment, clinical laboratory tests, physical examination including oropharyngeal exams, assessment of HPA-axis function (Cortrosyn® stimulation testing), 12-lead ECG and vital signs.

Medication compliance

Medication was assessed based on the data recorded in the patient diary cards.

RESULTS

Study Population Characteristics

The main demographic characteristics and baseline lung function are depicted in the table below. The patient population was an older population with the majority of the patients (134 [78%]) being 40 years of age or above. The mean age of the patients ranged from 50.1 years to 53.5 years. Thirty-four patients were < 40 years of age and of these only 14 patients were under 30 years of age. The youngest patient was 14 years old (n =1). There were more female patients enrolled (90 [54%]) compared to male patients (78 [46%]). One hundred and thirty-four (134) subjects (80%) were white, 24 (14%) were black, and the remainder were Asian, American Hispanic and Other. Over half of the patients (55%) had asthma for ≥ 15 years duration. There were no patients with asthma duration of less than 1 year. Salmeterol xinafoate and theophylline were the most frequently used concomitant asthma medications. Forty four (44%) to 56% of subjects were also taking salmeterol, and 35% - 57% of subjects were taking theophylline during the study.

Table 23 - Study Population Characteristics

	Placebo HFA BID (n= 33)	FP HFA 440 BID (n = 32)	FP HFA 880 BID (n = 32)	FP CFC 440 BID (n = 37)	FP CFC 880 BID (n = 34)
Age (yr)	50.8	50.7	50.1	52.5	53.5
Gender					
Females	19 (58%)	19 (59%)	18 (56%)	19 (51%)	15 (44%)
Males	14 (42%)	13 (41%)	14 (44%)	18 (49%)	19 (56%)
Race					
White	26 (79%)	23 (72%)	27 (84%)	29 (78%)	29 (85%)
Black	4 (12%)	7 (22%)	3 (9%)	6 (16%)	4 (12%)
Asian	2 (6%)	0	0	0	0
American Hispanic	1 (3%)	2 (6%)	0	1 (3%)	0
Other	0	0	2 (6%)	1 (3%)	1 (3%)
Asthma duration					
≥ 15 years	17 (52%)	19 (59%)	19 (59%)	19 (51%)	18 (53%)
> 1 < 15 years	18 (48%)	13 (41%)	13 (41%)	18 (49%)	16 (47%)
Concurrent					

asthma medications					
Salmeterol	17 (52%)	18 (56%)	17 (53%)	18 (49%)	15 (44%)
Theophylline	17 (52%)	14 (44%)	14 (44%)	21 (57%)	12 (35%)
Baseline FEV_1 (% pred)	1.81 L (58.7%)	1.95 L (61.5%)	1.89 L (60.5%)	1.90 L (59.9%)	2.04 L 58.9%)

Baseline daily prednisone dose

A total of 97 subjects (58%) had baseline prednisone dose between 5 and < 15 mg. Fifty-two (52) subjects (31%) had daily prednisone dose of 15 - < 25 mg and 16 subjects (9%) had daily prednisone dose of 25 or greater. A total of 5 subjects, all in the FP CFC treatment groups, had prednisone dose of 40 - < 45 mg. The table below shows the baseline prednisone dose for each treatment arm in the reduced ITT population.

Table 24

Distribution of Baseline Prednisone Dose, n (%)

Reduced ITT Population

	Placebo HFA BID (N=32)	FP 440mcg HFA BID (N=32)	FP 880mcg HFA BID (N=32)	FP 440mcg CFC BID (N=36)	FP 880mcg CFC BID (N=33)	Total (N=165)
5 - <10mg	3 (9%)	10 (31%)	10 (31%)	13 (36%)	11 (33%)	47 (28%)
10 - <15mg	17 (53%)	11 (34%)	6 (19%)	8 (22%)	8 (24%)	50 (30%)
15 - <20mg	4 (13%)	2 (6%)	10 (31%)	5 (14%)	4 (12%)	25 (15%)
20 - <25mg	4 (13%)	6 (19%)	4 (13%)	8 (22%)	5 (15%)	27 (16%)
25 - <30mg	1 (3%)	2 (6%)	0	0	1 (3%)	4 (2%)
30 - <35mg	2 (6%)	1 (3%)	1 (3%)	0	1 (3%)	5 (3%)
35 - <40mg	1 (3%)	0	1 (3%)	0	0	2 (1%)
40 - <45mg	0	0	0	2 (6%)	3 (9%)	5 (3%)

Source Data: Table 8

Subject accountability

A total of 168 subjects enrolled in the study at 39 sites. Of these, 113 (67%) completed the study and 55 (33%) discontinued. Of the 55 subjects who discontinued, 22 (40%) were in the placebo group. This was not unexpected, since the patients enrolled in this study were previously maintained on oral corticosteroid therapy. Both the FP HFA and CFC 880 mcg BID groups unexpectedly had a higher percentage of discontinuations compared to the next lower dose of fluticasone, respectively . Of the adverse events leading to discontinuations in the FP HFA 880 mcg BID group, 3 of them were cases of serious pneumonia. These results are depicted in the table below copied from the sponsor's submission. There is a discrepancy in the number of subjects in the FP HFA 800 mcg group who were discontinued because of adverse events (n =3) as stated in the table below, compared to what is stated on page 86-87 (n = 4). This is because one of the subjects was classified as withdrawing due to "lack of efficacy" in the Subject Accountability table shown below instead of withdrawing due to adverse events.

Table 25

Summary of Subject Accountability: End of Study Record, n (%)
ITT Population

	Placebo HFA BID (N=33)	FP 440mcg HFA BID (N=32)	FP 880mcg HFA BID (N=32)	FP 440mcg CFC BID (N=37)	FP 880mcg CFC BID (N=34)	Total (N=168)
Completed	11 (33%)	26 (81%)	19 (59%)	31 (84%)	26 (76%)	113 (67%)
Prematurely discontinued	22 (67%)	6 (19%)	13 (41%)	6 (16%)	8 (24%)	55 (33%)
Reason for premature discontinuation						
Adverse event	0	0	3 (9%)	1 (3%)	1 (3%)	5 (3%)
Failed to return	0	0	0	0	0	0
Lack of efficacy	19 (58%)	2 (6%)	4 (13%)	3 (8%)	2 (6%)	30 (18%)
Inpatient hosp.	0	0	1 (3%)	0	0	1 (<1%)
↑ in asthma rx	9 (27%)	1 (3%)	3 (9%)	1 (3%)	1 (3%)	15 (9%)
3rd pred. burst	10 (30%)	1 (3%)	1 (3%)	2 (5%)	1 (3%)	15 (9%)
Other	3 (9%)	4 (13%)	6 (19%)	2 (5%)	5 (15%)	20 (12%)

Source Data: Table 3

Subject discontinuations

- Discontinuations due to adverse events

A total of 6 subjects were withdrawn from the study due to adverse events. Four of these subjects (3 in the FP HFA 880 mcg group and 1 in the FP CFC 440 mcg group) experienced serious adverse events. The serious events were pneumonia (n= 3) in three subjects from the FP 800 mcg HFA group, and one case of asthma in the FP CFC 440 mcg group.
The other two withdrawals were for musculoskeletal pain in one subject in the FP HFA 880 mcg group and for prostate disorders in one man in the FP CFC 880 mcg group. The three cases of serious pneumonia are briefly described below. None of the cases were associated with hypereosinopilia.

Serious pneumonia in the FP 880 mcg HFA group

Subject 27697 is a 63 year old female who developed bilateral pneumonia approximately 31 days after initiating study treatment and was hospitalized. She also experienced an asthma exacerbation. She had positive blood cultures for gram positive cocci and rods. The pneumonia resolved 26 days after onset.

Subject 27742 is a 33 year old male who developed pneumonia 12 weeks after starting study medication. The dose of prednisone that the patient was on at the beginning of the study was being discontinued according to the protocol and after 8 weeks of study medication, the prednisone was completed eliminated. About 4 weeks later the patient developed pneumonia and was hospitalized.

Subject 27733 is a 74 year old female who developed pneumonia approximately 13 weeks after beginning study treatment and was hospitalized. She was treated

for 2 days and then discharged to home care. Of interest is that in the case narrative for this case, the list of medications does not include an antibiotic (only prednisone, theophylline, Robitussin AC ™, albuterol, and ipratropium bromide). The treatment regimen is more consistent with treatment for an acute exacerbation of COPD. The case narrative states that a chest x-ray done three and a half weeks later showed that the pneumonia had resolved.
Review of the case report list the same medications as stated before. Antibiotics are not listed as part of the treatment regimen. It would be highly unusual for an elderly patient with prior corticosteroid use to be admitted to hospital with pneumonia and not receive antibiotics. Therefore it is very likely that this was this case was miscoded as pneumonia.

Discontinuations due to lack of efficacy
A total of 30 subjects were discontinued due to lack of efficacy. The majority, 19 subjects were in the placebo group. The most common cited reason for lack of efficacy was that an increase in anti-asthma medication was required (15 subjects) and a third burst of oral prednisone was required (15 subjects).

Discontinuations due to "other" reasons
A total of 20 subjects discontinued due to "other" reasons. Reasons cited included use of excluded medications (3), non-compliance (3), abnormal laboratory results at baseline (1), withdrawal of consent (4), use of systemic corticosteroids for other conditions (7) and travel out of state (2).

EFFICACY RESULTS

- ITT population

Three subjects were excluded from the ITT population. The efficacy analyses were conducted on this reduced ITT population. The three subjects who were excluded were one subject who received study drug but withdrew prior to any post-randomization assessments being done, and the 2 subjects at Dr. [redacted] site. (During the conduct of this study, the FDA imposed regulatory and administrative sanctions on Dr. [redacted] for violations identified in the conduct of other studies conducted at his investigative site). Therefore, results for this study were excluded from the analyses.

- Primary efficacy endpoint: Mean daily oral prednisone dose

The mean results are summarized in the table below copied from the sponsor's submission. Each FP treatment arm had a statistically significantly lower mean daily oral prednisone use compared to placebo. The highest prednisone doses FP 880 BID (both the HFA and the CFC) did not confer a treatment advantage over FP 440 BID. In fact, the lower FP dose of 440 BID both HFA and CFC, had a numerical advantage over FP 880 in terms of lowering the man daily oral prednisone usage. The sponsor conducted a post-hoc analysis excluding

---

One subject was enrolled in the FP CFC 440 mcg BID group and the other was in the FP CFC 880 mcg BID group.

subjects taking > 40 mg prednisone at baseline (most of these patients were in the CFC treatment arms of the study) and the results were similar to the overall results.

Table 26

Summary of Mean Daily Oral Prednisone Use, mg

Reduced ITT Population

	Placebo HFA BID (N=32)	FP 440mcg HFA BID (N=32)	FP 880mcg HFA BID (N=32)	FP 440mcg CFC BID (N=36)	FP 880mcg CFC BID (N=33)
Baseline	14.2	12.5	12.7	13.0	14.3
Weeks 1-16	14.9	5.8[a]	6.2[a]	4.9[a]	6.4[a]

Source Data: Tables 18 and 21

a Different from placebo, p<0.001

Other Efficacy Measures

- Reduction in prednisone use

Prednisone reduction response was defined by the following categories:

A complete response: 100% reduction
A major response: 50 – 99% reduction
A minor response: 1- 49% reduction
No response: 0% reduction
A negative response: Any increase in prednisone

Table 27
Summary of Reduction in Oral Prednisone Dose
From Baseline to Study Completion: Reduced ITT Population

Categorical response, n (%)	Placebo HFA BID (N=32)	FP 440mcg HFA BID (N=32)	FP 880mcg HFA BID (N=32)	FP 440mcg CFC BID (N=36)	FP 880mcg CFC BID (N=33)
Complete response (100% reduction)	4 (13%)	19 (59%)	18 (56%)	30 (83%)	26 (79%)
Major response 50-99% reduction)	9 (28%)	11 (34%)	12 (38%)	4 (11%)	3 (9%)
Minor response (1-49% reduction)	4 (13%)	1 (3%)	1 (3%)	1 (3%)	3 (9%)
No response (0% reduction)	3 (9%)	0	1 (3%)	1 (3%)	0
Negative response any increase)	12 (38%)	1 (3%)	0	0	1 (3%)
Combined complete response and major response	13 (41%)	30 (94%)	30 (94%)	34 (94%)	29 (88%)

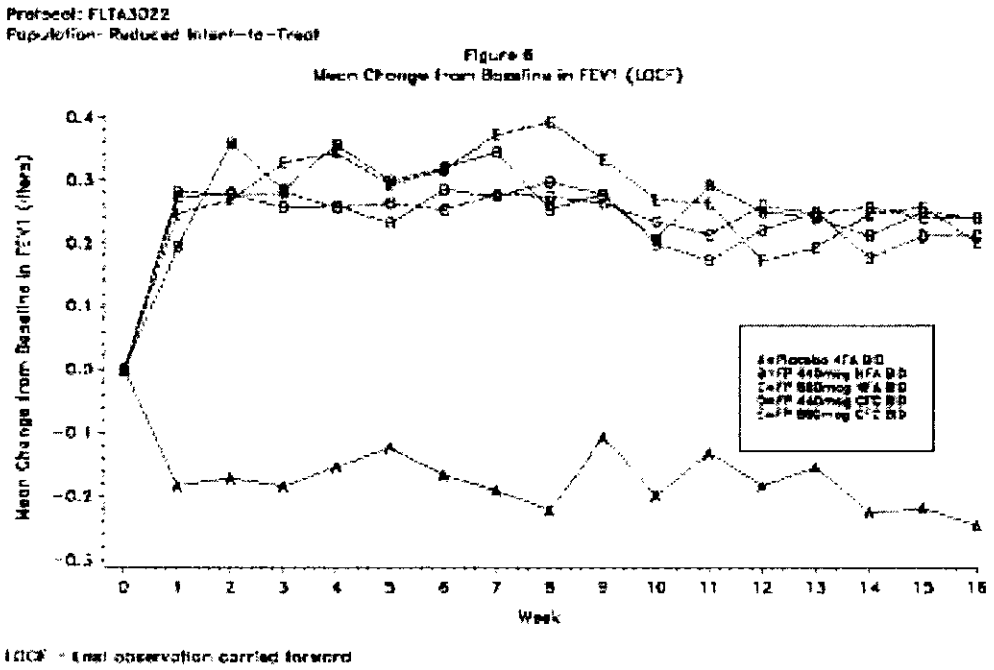
Source Data: Table 19

A total of 13 subjects (41%) in the placebo group had a reduction of oral prednisone dose of 50 to 100% and of these subjects 4 (13%) had a complete response. One reason for this finding is that patients may not have been on the

minimum effective dose of corticosteroids but were actually on higher than needed maintenance doses of oral corticosteroids. In the FP treatment groups, a 50 to 100% reduction in prednisone dose was achieved by 88% - 94% of subjects. The CFC treatment groups (both doses) had a greater percentage of subjects with complete response than the HFA treatment groups.

- *FEV_1*

The mean FEV_1 and the mean change from baseline in FEV_1 were followed. All four active treatment groups had an increase in the mean change from baseline in FEV_1 and the mean change in percent predicted FEV_1 from baseline over the 16-week treatment period. Whereas, in the placebo group, mean FEV_1 declined or did not improve over the 16 weeks of treatment. Both doses of FP, 440 mcg and 880 mcg BID, had similar improvements in FEV_1. The improvements in FEV_1 seen with the HFA and the CFC products were similar. The FEV_1 changes are depicted in the graph below.



- Diary Data

➢ Peak Flow

Numerical improvements were seen in mean morning and evening PEF (L/min) in all active treatment groups whereas, mean PEF declined in the placebo group over the 16-week treatment period. The mean increase in PEF from baseline was numerically greater for AM PEF compared to evening PEF. The change in AM PEF ranged from 16.3 L/min to 36.5 L/min for the HFA groups and from 17.4. to 36.5 for the CFC groups. Interestingly, the HFA groups showed dose ordering,

whereas the CFC groups did not. This finding may reflect the variability that is often seen with PEF measurements. The AM PEF results are showed in the table below.

Table 28 Morning PEF FLTA3022

Mean Baseline Morning PEF and Mean Change from Baseline in Morning PEF (Completers), L/min (SE): Reduced ITT Population

	Placebo HFA BID (N=32)		FP 440mcg HFA BID (N=32)		FP 880mcg HFA BID (N=32)		FP 440mcg CFC BID (N=36)		FP 880mcg CFC BID (N=33)	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Baseline	32	307 (13.8)	32	340 (16.3)	32	328 (16.5)	36	339 (14.5)	33	377[a] (21.4)
Week 1	32	-3.0 (5.1)	32	19.0[a] (5.5)	32	27.2[a] (6.6)	36	22.2[a] (6.7)	33	17.4[a] (6.3)
Week 4	30	-6.6 (7.7)	32	30.2[a] (9.2)	32	38.0[a] (9.5)	36	31.6[a] (9.5)	32	35.7[a] (8.1)
Week 8	24	-3.9 (11.6)	30	21.0 (10.6)	30	44.8[a] (12.3)	36	36.4[a] (10.2)	29	29.2[a] (9.4)
Week 12	18	13.9 (14.1)	27	35.2 (11.3)	24	22.9 (11.2)	34	32.7 (12.4)	27	9.4 (8.5)
Week 16	11	13.6 (22.4)	24	26.8 (14.1)	19	33.1 (11.8)	29	46.9 (11.7)	23	17.5 (11.2)

Source Data Tables 37 and 38

a Significant difference versus placebo p<0.05

(Source FLTA3022.pdf pg. 73)

➢ Asthma symptom scores, Ventolin® use, nighttime awakenings

Asthma symptom scores, Ventolin® use and nighttime awakenings requiring Ventolin® were recorded in patient diaries. Numerical improvements were noted in all the active treatment groups except that for the FP HFA 880 group nighttime awakenings increased slightly at the later weeks of the study and was slightly increased at week 16 from baseline. Results for nighttime awakenings are shown in the table. Data are from tables 48, 49 and 50 in FLTA3022.pdf.

Table -29- Nighttime Awakenings

	Placebo HFA BID (n= 33)	FP HFA 440 BID (n = 32)	FP HFA 880 BID (n = 32)	FP CFC 440 BID (n = 37)	FP CFC 880 BID (n = 34)
Baseline	0.67 (1 awakening every 1.5 nights)	0.49 (1 awakening every 2 nights)	0.33 (1 awakening every 3 nights)	0.62 (1 awakening every 1.6 nights)	0.43 (1 awakening every 2 nights)
Week 4	0.82	0.25	0.25	0.32	0.18
Week 8	0.88	0.40	0.25	0.25	0.18
Week 12	1.01	0.36	0.37	0.22	0.19
Week 16	1.17 (1 awakening every night)	0.39 (1 awakening every 2.5 nights)	0.44 (1 awakening every 2 nights)	0.17 (1 awakening every 6 nights)	0.18 (1 awakening every 5.5 nights)

At week 16 subjects in the CFC treatment groups had fewer nighttime awakenings than subjects in the HFA treatment groups.

Patient-reported Outcomes

The Asthma Quality of Life Questionnaire (Juniper) was used to evaluate patient-reported outcomes (PRO). The AQLQ was completed at baseline and after 16 weeks of treatment or earlier in the case of withdrawal from the study. The population analyzed was made up of the subjects whose baseline overall AQLQ score was < 5.8. A total of 13 subjects had baseline AQLQ overall score of > 5.8 and were therefore excluded for the patient-reported outcomes analysis. Therefore the PRO population consisted of 152 subjects. The high percentage of dropouts (64%) in the placebo group, makes it extremely difficult to interpret these data. LOCF is very problematic for a QOL instrument making any interpretation of the data questionable. Nevertheless, the results are shown below as copied from the sponsor submission.

Table 30
Mean Baseline AQLQ Scores and Mean Change from Baseline in AQLQ Scores: QOL Population

	Placebo HFA BID (N=30)		FP 440mcg HFA BID (N=30)		FP 880mcg HFA BID (N=28)		FP 440mcg CFC BID (N=34)		FP 880mcg CFC BID (N=30)	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Overall AQLQ Score										
Baseline	29	3.80	29	3.99	26	4.02	34	3.87	29	4.23
Endpoint	29	-0.26	29	1.02[a,b]	25	1.03[a,b]	34	1.16[a,b]	29	1.03[a,b]
Activity Limitation										
Baseline	29	3.71	29	3.92	26	4.05	34	3.99	29	4.28
Endpoint	29	-0.05	29	1.14[a,b]	25	0.87[a,b]	34	1.07[a,b]	29	1.03[a,b]
Asthma symptoms										
Baseline	29	3.94	29	4.18	26	4.09	34	4.05	29	4.23
Endpoint	29	-0.52	29	0.93[a,b]	25	1.27[a,b]	34	1.24[a,b]	29	1.04[a,b]
Emotional function										
Baseline	29	3.71	29	3.73	26	3.88	34	3.51	29	4.03
Endpoint	29	-0.42	29	1.02[a,b]	25	0.95[a,b]	34	1.25[a,b]	29	1.09[a,b]
Environmental stimuli										
Baseline	29	3.76	29	3.97	26	3.88	34	3.49	29	4.29
Endpoint	29	0.15	29	0.96[a,b]	25	0.92[a,b]	34	1.01[a,b]	29	0.86[a,b]

Source Data: Tables 52 and 53

SAFETY RESULTS

Extent of Exposure

The mean duration of exposure ranged from 104 to 107 days in the FP treatment groups and 77 days in the placebo group.

Adverse Events

Of the 168 subjects enrolled in the study, 160 reported at least one adverse event. A total of 28/33 (85%) subjects in the placebo group, 31/32 (97%) subjects in the FP HFA 400 mcg group, 32/32 (100%) in the FP HFA 880 group 36/37 (97%) in the FP CFC 440 group and 33/34 (97%) in the FP CFC 880 group. The most commonly reported adverse events were seen in the ear, nose and throat

(61%-75%), gastrointestinal (24%-53%), musculoskeletal (24%-44%), lower respiratory (22% -32%), neurology (15%-38%) and the dermatologic (13%-29%) systems. Adverse events that did not fit into any specific system made up 32%-44%.

More patients in the FP CFC 880 mcg bid group reported throat irritation (26%), candidiasis of the mouth/throat (29%), candidiasis at an unspecified site (12%) and lower respiratory events (32%) compared with patients in the placebo and or other active treatment groups. Adverse events that occurred at a rate of over 3% in the FP groups and were common than in the placebo group are depicted in the table below.

Table 31 Adverse Events at a rate > 3% and more common than in placebo group regardless of causality (Source: data table 58)

	Placebo HFA BID (N = 33)	FP 440 HFA BID (N =32)	FP 880 HFA BID (N = 32)	FP 440 CFC BID (N =37)	FP 880 CFC BID (N =34)
ANY EVENT	28 (85%)	31 (97%)	32 (100%)	36 (97%)	33 (97%)
Ear Nose and Throat					
ANY EVENT	20 (61%)	22 (69%)	24 (75%)	27 (73%)	24 (71%)
URTI	12 (36%)	13 (41%)	12 (38%)	11 (30%)	8 (24%)
Sinusitis	7 (21%)	4 (13%)	5 (16%)	8 (22%)	5 (15%)
Throat irritation	2 (6%)	3 (9%)	5 (16%)	6 (16%)	9 (26%)
Rhinitis	3 (9%)	6 (19%)	3 (9%)	2 (5%)	4 (12%)
Pharyngitis/throat infection	0	0	2 (6%)	4 (11%)	3 (9%)
Gastrointestinal					
ANY EVENT	8 (24%)	16 (50%)	16 (50%)	14 (38%)	18 (53%)
Candidiasis mouth/throat	2 (6%)	11 (34%)	6 (19%)	5 (14%)	10 (29%)
Nausea/vomiting	1 (3%)	4 (13%)	5 (16%)	3 (8%)	3 (9%)
Diarrhea	1 (3%)	4 (13%)	5 (16%)	3 (8%)	3 (9%)
Dyspeptic symptoms	1 (3%)	0	2 (6%)	3 (8%)	1 (3%)
Gastroenteritis	0	0	0	3 (8%)	3 (9%)
Constipation	0	0	1 (3%)	1 (3%)	2 (6%)
Viral gastrointestinal infections	0	1 (3%)	0	0	2 (6%)
Non-site specific					
ANY EVENT	11 (33%)	11 (34%)	14 (44%)	15 (41%)	11 (32%)
Candidiasis unspecified site	1 (3%)	1 (3%)	2 (6%)	4 (11%)	*4(12%)*
Fever	1 (3%)	1 (3%)	2 (6%)	4 (11%)	0
Pain	1 (3%)	1 (3%)	1 (3%)	2 (5%)	*2 (6%)*
Viral infections	0	2 (6%)	0	1 (3%)	1 (3%)
Musculoskeletal					
ANY EVENT	8 (24%)	14 (44%)	14 (44%)	13 (35%)	8 (24%)
Arthralgia & articular rheumatism	4 (12%)	7 (22%)	4 (13%)	6 (16%)	1 (3%)
Musculoskeletal pain	3 (9%)	5 (16%)	6 (19%)	4 (11%)	1 (3%)
Muscle pain	1 (3%)	3 (9%)	4 (13%)	2 (5%)	2 (6%)
Arthritis	0	1 (3%)	1 (3%)	1 (3%)	*2 (6%)*
Lower Respiratory					
ANY EVENT	8 (24%)	7 (22%)	9 (28%)	8 (22%)	11 (32%)
Cough	0	0	2 (6%)	3 (8%)	2 (6%)

Pneumonia	0	0	3 (9%)	0	0
Neurology					
ANY EVENT	6 (18%)	8 (25%)	12 (38%)	7 (19%)	5 (15%)
Headaches	4 (12%)	3 (9%)	8 (25%)	4 (11%)	3 (9%)
Sleep disorders	2 (6%)	0	4 (13%)	0	3 (9%)
Dizziness		2 (6%)	0	2 (5%)	
SKIN					
ANY EVENT	6 (18%)	4 (13%)	5 (16%)	9 (24%)	10 (29%)
Pruritus	0	0	1 (3%)	2 (5%)	3 (9%)
Skin rashes	0	1 (3%)	1 (3%)	2 (5%)	2 (6%)
Eczema	0	0	3 (9%)	0	2 (6%)
Fungal skin infections	1(3%)	0	0	1 (3%)	2 (6%)
Drug interaction overdose & trauma					
ANY EVENT	1 (3%)	3 (9%)	2 (6%)	4 (11%)	2 (6%)
Muscle injuries	0	1 (3%)	0	2 (5%)	1(3%)
Cardiovascular					
ANY EVENT	1 (3%)	1 (3%)	4 (13%)	2 (5%)	3 (9%)
Hypertension	0	0	3 (9%)	0	1(3%)
Psychiatry					
ANY EVENT	0	3 (9%)	4 (13%)	2 (5%)	2 (6%)
Depressive disorders	0	2 (6%)	2 (6%)	0	1 (3%)
Anxiety	0	0	2 (6%)	0	1 (3%)
Endocrine and metabolic					
ANY EVENT	0	3 (9%)	2 (6%)	2 (5%)	2 (6%)
Appetite disturbances	0	2 (6%)	1 (3 (%)	0	0

Hoarseness and dysphonia were very uncommon and only occurred in one subject in the FP 440 CFC BID treatment group.

Deaths

There were no deaths during the study.

Serious Adverse Events

Nine subjects experienced a serious adverse event (SAE) during the study. The SAEs occurred in 1 (3%) subject each in the placebo, FP 440 CFC mcg and FP CFC 880 mcg groups, 2 (6%) in the FP 440 mcg HFA group and 4 (13%) in the FP 880 mcg HFA group. Of the 9 subjects with serious adverse events, 4 were withdrawn from the study – three in the FP-HFA 880 mcg group and one in the FP-CFC 440 bid group.

Systemic corticosteroid-related effects

Adverse events associated with systemic corticosteroid effects such as ocular effects, adrenal dysfunction, hyperglycemia, skin manifestations, and fractures that were not displayed in the previous table are summarized in the table below.

Table 32 Adverse events suggestive of a systemic effect

	Placebo HFA BID (N = 33)	FP 440 HFA BID (N =32)	FP 880 HFA BID (N = 32)	FP 440 CFC BID (N =37)	FP 880 CFC BID (N =34)
Cataracts	0	1 (3%)	0	0	0
Contusions and hematomas	0	1 (3%)	0	1 (3%)	0
Fractures	0	0	0	1 (3%)	0

Hypertension	0	0	3 (9%)	0	1 (3%)
Diabetes mellitus	0	0	1 (3%)	0	0
Hyperglycemia	0	0	0	0	1 (3%)
Hypofunction of adrenal cortex	0	1 (3%)	0	0	0

Pregnancies
There were no pregnancies during the study.

Clinical Laboratory Evaluations

FP Plasma Concentrations
Trough (pre-dose) FP plasma concentrations were obtained in a sub-set of subjects (n = 63) two weeks after the start of dosing. The median trough concentrations for the FP CFC 440 BID and 880 BID group was 47.3 pg./ml(range [illegible] and 52.9 pg./ml (rang[illegible] ml).
The median trough concentrations for the FP HFA 440 BID and 880 BID groups were 27.3 pg./ml (range [illegible] pg./ml) and 55.9 pg./ml (range [illegible] pg./ml). The ranges are extremely large and this may be a reflection of the variability that could in a test where very low concentrations are being measured. At the same time, it could also be a reflection of the fact that the severe asthmatic population under study show more variability in the absorption of FP because of their severe bronchoconstriction. The results at best suggest that FP HFA is less bioavailable that FP CFC.

Reviewer Comment
In future studies, it may be more helpful to evaluate systemic concentrations of ICS in milder asthmatics.

Laboratory abnormalities outside the threshold range were uncommon. Laboratory abnormalities that could possibly be related to systemic corticosteroid exposure such as elevated glucose levels, increased white blood cell counts (WBC) and neutrophils and decreased lymphocytes and eosinophils were rarely noted. There were no shifts to low (below the threshold range) for eosinophils or lymphocytes and no shifts to high (above the threshold range) for neutrophils. One subject in the FP HFA 440 BID group had a shift to high in WBC counts and two subjects in the FP HFA 880 had a shift to high in glucose levels.
One subject had a shift to low in potassium levels. There were no reported abnormalities in alkaline phosphatase or sodium bicarbonate levels.

A total of 11 (12%)subjects distributed over all the treatment groups (including placebo) had eosinophil shifts to high. There were no cases of pneumonia reported in any of the subjects with eosinophil shifts to high. However, two subjects reported upper respiratory tract infections, one patient reported mild bronchitis, and two subjects reported sinusitis. No subjects were withdrawn from the study because of eosinophil elevations.

HPA Axis function

HPA axis was assessed at screening and at Week 16 or early termination by AM plasma cortisol and Cortrosyn testing. An abnormal response was defined as:

Morning cortisol < 5 mcg/dl
Post-stimulation rise in cortisol of < 7 mcg/dl or
Post-stimulation cortisol of < 18 mcg/dl

The majority of subjects in the study had low AM (up to 64% of subjects) and post-stimulation (up to 81% of subjects) plasma cortisol levels. This is not an unexpected finding given that the subjects enrolled in this study had been on maintenance corticosteroids. At Week 16, subjects who completed the study still showed low AM cortisol levels however the percentage of subjects having low AM cortisol and post-stimulation cortisol were lower in the FP treated groups compared to the placebo group. At Week 16 the percentage of subjects with abnormal cortisol levels was higher (as expected) in FP 880 treatment groups compared to the FP 440 treatment groups.

Table 33 - Summary of plasma cortisol abnormalities

	Placebo HFA BID (n= 32)	FP HFA 440 BID (n = 32)	FP HFA 880 BID (n = 32)	FP CFC 440 BID (n = 36)	FP CFC 880 BID (n = 34)
Screening, n	32	32	32	36	34
AM cortisol < 5 mcg/dl	16 (50%)	20 (63%)	13 (43%)	23 (64%)	14 (45%)
Post-stimulation cortisol < 18 mcg/dl	22 (69%)	25 (78%)	23 (72%)	29 (81%)	24 (71%)
Week 16, n	12	26	19	31	26
AM cortisol < 5 mcg/dl	5 (42%)	5 (19%)	9 (47%)	7 (23%)	10 (38%)
Post-stimulation cortisol < 18 mcg/dl	8 (73%)	14 (54%)	13 (68%)	16 (52%)	16 (62%)

Summary/Conclusions

This study demonstrated that asthmatic patients previously maintained on oral prednisone can achieve a significant reduction in their oral prednisone use when treated with FP HFA 440 mcg BID, or 880 mcg BID. The reduction in oral prednisone use was also accompanied by improvements in FEV_1, peak flows, asthma symptom scores and Ventolin ® use. The study did not demonstrate a dose response relationship between doses of 440 mcg BID and 880 mcg BID. It is noteworthy that subjects in the FP HFA 440 mcg BID group had a numerically greater reduction in mean daily prednisone use than subjects in the FP HFA 880 mcg BID group. Similar results were seen with the FP CFC products.
The current label for Flovent ® MDI (CFC formulation) has the 880 mcg BID as the highest recommended dose for this patient population. In this study, there was no advantage to using FP HFA 880 mcg BID dose. The proposed label for Flovent ® HFA proposes the same dosage recommendation (? for label

consistency) however the need to use doses as high as 880 mcg BID was not established in this study.

Adverse events noted in the study were similar to adverse events seen in other trials with inhaled corticosteroids at these high doses.

The patient population was an older population with mean ages ranging from 50 – 53.5 years across treatment groups. The youngest subject was one 14 year Given the historical data available for the moiety fluticasone propionate, it is acceptable to extrapolate the results of this study down to age 12.

Appendix IV. FLTB3048

TITLE: "A multi-centre, randomised, double-blind parallel group clinical trial to assess the long-term (52 weeks) safety of fluticasone propionate 500 mcg BID administered by pressurised metered dose inhaler propelled by GR106642X propellant in comparison with propellants 11 and 12 in adolescent and adult subjects with asthma".

Study objectives:
The objective of this study was to compare the long-term safety of fluticasone propionate (FP) HFA 440 mcg BID, with FP CFC 440 mcg BID for 52 weeks in adolescent and adult subjects with asthma.

Study Period and Study Sites
The study was conducted between January 28, 1997 and July 10, 1998. The study sites were locate in Belgium, Canada, Chile, Finland, New Zealand, and Norway.

Study Design
The study was multinational, non-US, multicenter, randomized, double-blind, and parallel-group in design. There was a 7 – 14 day screening (run-in) period followed by a 52-week treatment period followed by a 7-14 day follow-up period.

Study Medication
Fluticasone Propionate HFA 440 mcg BID
Fluticasone propionate CFC 440 mcg BID

Study Population
The study population was made up of adolescent and adult subjects age 16 years or older, with mild to moderate reversible airways obstruction who had stable lung function. In order to be considered as having reversible disease, subjects had to demonstrate improvement in lung function in response to two actuations (180 mcg) of albuterol. Subjects were included in the study if they met the following criteria:

Inclusion Criteria

7. Male or female subjects with asthma aged ≥16 years inclusive at the time of the screening visit (Clinic Visit 1).

8. Were receiving ≥ 800mcg to ≥ 2000mcg/day of beclomethasone dipropionate, budesonide, Triamcinolone acetonide, or flunisolide or ≥400mcg to ≥1000mcg/day inhaled fluticasone propionate on entry to the study.

9. Had a forced expiratory volume at one second (FEV_1) ≥ 60% of predicted value at the screening visit. [European Community for Coal and Steel (ECCS) predicted lung function

values were used for subjects ages ≥18 years and Polgar predicted lung function values were used for subjects less than 18 years of age]

10. Had historical documentation within the 12 months prior to Visit 1 (excluding any screening visit pulmonary function tests), of a ≥15% variation in FEV_1, or demonstrated at the screening visit an increase in FEV_1 of ≥15% following inhalation of 2 actuations of albuterol from a pressurized MDI (propellants 11 and 12).

11. Were able to use a pressurized MDI correctly, understand and complete a daily record card, and record their peak expiratory flow (PEF) using a Mini-Wright peak flow meter.

12. Were willing to give written informed consent to participate in the study. In the case of adolescents, the parent or legal guardians had also to give written informed consent for them to participate in the study.

The exclusion criteria were similar to those used in previous asthma trials such as the exclusion of subjects with a history of life threatening asthma, upper or lower respiratory tract infections within 2 weeks prior to the Screening visit, clinically significant ECG or clinical laboratory abnormalities, and significant concurrent medical conditions. Subjects with a ≥10-pack year smoking history were not eligible.

Allowed Medications
Patients were permitted to continue on the following asthma/anti-allergy medications during the 12-month treatment period.
Long-acting inhaled β_2-agonists such as salmeterol and formoterol
Oral xanthine derivatives such as theophylline and aminophylline
Anticholinergic bronchodilators
Oral anti-allergics such as ketotifen
Sodium cromoglycate and nedocromil

Disallowed Medications
Patients were not permitted to take oral/parenteral/depot corticosteroids, short-acting β_2-agonists other than albuterol dispensed in the study, inhaled combination products containing a short-acting β_2-agonist.

Discontinuations from the study
Subjects could discontinue the study at the discretion of the Investigator or by the subject's own volition. Subjects with more than 3 asthma exacerbations during the 52-week treatment period, or subjects who experienced an asthma exacerbation that required more than 10 days of corticosteroid therapy were withdrawn from the study.

Measurements and Evaluations
The sponsor conducted an extensive safety evaluation that included the following assessments:

- Adverse Events – assessed at every clinic visit

- Clinical laboratory tests – Clinical chemistry, hematology, and renal function tests were conducted at screening, Weeks 24, and 52

- Evaluation of HPA Axis Function – Assessed by AM cortisol and either 24-hour urinary cortisol, or the ACTH stimulation test at screening, and Weeks 24 and 52. The test selected was at the discretion of the Investigator

- Biochemical Markers of Bone – Blood and urine samples were obtained at Screening, and after Weeks 24 and 52. Serum osteocalcin (biochemical marker of bone formation) and urinary N-telopeptide concentrations (marker of bone resorption) were measured.

- Asthma exacerbations –defined as worsening in asthma symptoms requiring increased use of bronchodilators and being seen in clinic within 24 hours of onset of worsening symptoms. The Investigator determined whether a short course of oral corticosteroids was indicated.

- Vital signs, ECG findings and oral candidiasis – Vital signs were done at Screening and at Weeks 12, 24, 36, and 52 and as necessary at the Early withdrawal visit or during follow-up. The 12-lead ECG tracings were obtained at screening and at Week 52. Oropharyngeal examinations were performed at every visit to evaluate for the presence of oral candidiasis.

- Physical and ophthalmic examinations – Physical exams were performed at Screening, Week 52 and the Withdrawal visit. Ophthalmic exams were performed at Screening, Weeks 24, and 52

Sample size considerations

The sample size was selected to ensure that data from at least 100 subjects on FP HFA would be obtained at the one year timepoint. Therefore the sponsor planned to randomize a maximum of 300 subjects to each treatment arm. These numbers were based on the International Conference on Harmonization (ICH) and the FDA guidelines for long-term safety exposure information for new molecular entities.

STUDY POPULATION RESULTS

A total of 325 subjects were randomized to study treatment – 163 subjects in the FP HFA group and 162 subjects in the FP CFC group. The two treatment groups had similar demographic and baseline characteristics. The population was almost exclusively white (98%) and females made up 55%. The percentage of subjects using spacers was 41% and 38% in the HFA and CFC group respectively. The majority of subjects (up to 57%) never used tobacco and only about 7 - 9% were current tobacco users. Subjects had a history of reversible airways disease for 5 years or more. The treatment groups were also similar with respect to current medical conditions. The most frequently affected body systems were

ears/nose/throat, neurology, musculoskeletal, gastrointestinal and eye. Concurrent asthma medications taken during the trial were similar among treatment groups with 26%-30% of subjects taking salmeterol and 7%-9% of subjects taking theophylline. Thirty-one to forty-one (31 –41%) percent of subjects continued to use a spacer device during the trial. Subjects who used spacers were provided with an — Spacer and instructed to use it consistently during the study. The lung function at Baseline was 2.47 L in the FP HFA group and 2.63 L in the FP CFC group. The baseline characteristics and demographics of the study population are summarized in the table below.

Table 34 - Baseline Demographics and Population Characteristics FLTB3048

	FP HFA 440 BID N =163	FP CFC 440 BID N=162
Age (years) mean, Range (years)	46.2 18 – 79	44.7 18 -76
Gender, n (%) Male Female	69 (42%) 94 (58%)	78 (48%) 84 (52%)
Ethnic Origin, n (%) Caucasian Black Other	161 (99%) 1 (<1%) 1 (<1%)	158 (98%) 1 (<1%) 3 (1%)
Use of Spacer device, n (%) No Yes	96 (59%) 67 (41%)	101 (62%) 61 (38%)
Tobacco Use, n (%) Never used Former tobacco user Current Tobacco User	93 (57%) 55 (34%) 15 (9%)	89 (55%) 61 (38%) 12 (7%)
Concurrent Salmeterol use, n (%) Yes No	42 (26%) 121 (74%)	49 (30%) 113 (70%)
Concurrent Theophylline use, n (%) Yes No	15 (9%) 154 (91%)	11 (7%) 151 (93%)
Mean Baseline FEV1 (L)	2.474 L	2.632 L

Subject Accountability

After randomization, a total of 33 subjects were withdrawn from the study. The table below is a summary of subject accountability for this study.

Table 35 - Subject Accountability – FLTB3048

	FP HFA 440 BID	FP CFC 440 BID	Total
Randomized	N= 163	N = 162	N =325
# withdrawn	16 (10%)	17 (10%)	33 (10%)
Reason for Withdrawal			
Did not fulfill entry	2 (< 1%)	0	2 (<1%)

criteria			
***Adverse event	6 (4%)	7 (4%)	13 (4%)
Failure to return	1 (<1%)	3 (2%)	4 (<1%)
Non-compliance	0	3 (2%)	3(<1%)
Other*	7 (4%)	4 (2%)	11 (3%)
***Does not include pregnancy. Page 62 of the sponsor's submission refer to 16 subjects withdrawing due to AEs but that number includes 3 pregnancies. "Other" reasons include withdrawal of consent, illicit drug use, moving, pregnancy, elevated liver function tests (one subject on FP CFC), taking prohibited medication (FP), not feeling happy on the trial.			

Study Discontinuations

Due to Adverse Events

A total of 13 subjects discontinued due to an adverse event. In the opinion of this reviewer, 8 of the adverse events that led to discontinuations are possibly drug related. These events are listed in the table below. This reviewer's assessment of causality is noted in the last column. A brief narrative of each subject's AE is presented below. An interesting observation is that 7 of the 8 subjects with drug-related AEs that led to withdrawal are female and all the events that are definitely or possibly related to the drug occurred in females. None of these adverse events satisfied the regulatory definition of a serious adverse event.

Table 36 Withdrawals due to Adverse Events that are possibly drug-related – FLTB3048
Data source pg. 44 FLTB3048

Treatment	Investigator - Subject #	Adverse Event	Time to onset from first dose of study medication	Relationship to study drug
FP HFA 440 BID	5375-7790	Fungal infection of mouth and throat	32 weeks	Definitely related
	34910-7925	Fluid retention	12 weeks	Probably
	37568-7869	Throat irritation	1 week	Possibly
	46637-7667	Urticaria	40 weeks	Possibly
FP CFC 440 BID	5371-7902	Hypofunction of adrenal cortex and Cushing's syndrome	27 weeks	Definitely
	10392-7377	Rhinorrhea; hoarseness	Not stated	Possibly
	36758-7585	Hoarseness	15 weeks	Possibly
	46635-7678	Hypofunction of adrenal cortex	Not stated	Definitely

Subject # 7790 is 50-year old female who developed oral thrush after 25 weeks of treatment with FP HFA 440 BID. She was treated with Nystatin and the event resolved with 11 days. The subject continued in the study until at 32 weeks of study treatment she developed a fungal infection of the mouth and throat including yeast on the vocal cords. The study drug was discontinued and the subject was withdrawn from the study.

Subject #7925 is a 77 year-old-man treated with FP HFA 440 BID who developed mild fluid retention after 12 weeks of study medication. The subject had previously complained of muscle cramps, and spasms in the foot and leg, epistaxis, and arthralgia and articular rheumatism (joint pain). Review of the CRF showed that the only past medical history for this subject was allergic rhinitis and Chron's disease for which he had an ileostomy in ___

Subject # 7869 is a 32-year-old female who was treated with FP HFA 440 BID and developed moderate throat irritation described as a sore and dry throat after 8 days of treatment. The event resolved within 25 days.

Subject # 7667 is a 45-year-old female treated with FP 440 BID who developed severe urticaria that lasted for 11 days. This event developed 40 weeks into the study. The CRF did not provide additional details of this event. The patient had a history of hypothyroidism and a past surgical history of surgery on the ischias. She was also taking a thyroid preparation, piroxicam for headache and paralgin forte for lumbago (back pain).

Subject # 7902 is a 35-year-old female treated with FP CFC 440 BID who developed adrenal suppression and Cushing's syndrome 27 weeks after starting treatment. The subject had a morning serum cortisol concentration of 502 nmol/L at baseline and at week 24 the morning cortisol concentration was 94 nmol/L (144 nmol/L upon repeat). Urinary cortisol was 21 µg/L/24 hours at screening and 9 µg/L/24 hours at Week 24. Serum osteocalcin and urinary N-telopeptides were increased from baseline. This subject also reported other adverse events including candidiasis mouth/throat, chest congestion, cough, and menstrual cramps. The adverse event of Cushing's syndrome remained unresolved as of the last follow-up visit.

Subject # 7377 is a 54 year-old female who was treated with FP CFC 440 BID developed mild intermittent rhinorrhea/post nasal drip and hoarseness/dysphonia. The duration of time on treatment prior to these events was not specified. The hoarseness resolved after the subject was withdrawn from the study.

Subject #7585 is a 46-year old female who received FP CFC 440 BID. She developed hoarseness/dysphonia 15 weeks after starting treatment. The event resolved with 46 days.

Subject # 7678 is a 61-year old female who received FP CFC 440 BID. At screening her morning serum cortisol was 469 nmol/L and at Weeks 24, 28, and 32, her morning serum cortisol values were 128nmol/L, 61 nmol/L and 164 nmol/L respectively. Concurrently, her urinary cortisol excretion was 49 µg/ml/24 hours at Screening and decreased to 21 µg/ml and 23 µg/ml at Weeks 24 and 32 respectively. The patient was not taking concurrent oral corticosteroids.

Discontinuations due to other reasons

Elevated LFTs

One subject in the FP CFC group (mentioned under "other" reasons) withdrew because of elevated liver function tests. This subject, #34560 -7823, was a 31 year-old male who had an elevated AST (86 U/) and ALT (134 U/L) at screening. After 12 weeks both enzymes were still elevated (AST 117 U/L, ALT 271 U/L). The GGT was in the normal range. The subject was withdrawn from the study and no further laboratory studies were collected. The subject had no complaints except for a sprained ankle.

Pregnancies

Three subjects became pregnant and were discontinued. One subject was on FP HFA 440 mcg BID and 2 subjects were on FP CFC 440 BID. One subject (on FP CFC) had a spontaneous abortion after approximately 5 weeks of pregnancy. She was a 33-year old female who had been on the FP for approximately 6 months prior to becoming pregnant. The other 2 subjects delivered healthy babies. There is not enough information to make an assessment of causality with respect to the spontaneous abortion.

SAFTEY RESULTS

Exposure

The mean exposure was similar for the two treatment groups – 344.9 days for FP HFA and 349.1 days for FP CFC. The majority of subjects were exposed for ≥ 360 days as displayed in the table below.

Table 37 Summary of Duration of Exposure to Study Medication- FLTB 3048
Data source Table 22 FLTB3048.pdf pg. 191

Treatment duration (days)	FP HFA 440 BID N =163	FP CFC 440 BID N = 162
≤ 300 days	16 (9%)	17 (11%)
331-360 days	19 (12%)	20 (12%)
361- 390 days	117 (72%)	119 (73%)
> 390 days	11 (7%)	6 (4%)

Compliance

The sponsor did not have specific measures for assessing compliance during the study. Subject compliance with study medication and all study procedures were reinforced at each clinic visit.

Adverse Events

Nearly all subjects (91% -98%) reported at least one adverse event the study. This is not unexpected given the duration of the study. The body systems with the most commonly reported adverse events were the ears, nose and throat (64% -77%), lower respiratory (63%-65%), neurology, gastrointestinal, musculoskeletal and non-site specific (20% -22%). The table below, displays the adverse events that occurred with a frequency of ≥ 5%.

Table 38 - Adverse Events at a frequency of ≥ 5% FLTB 3048
Data source Table 23 FLTB. pdf pgs. 192 - 207

Adverse Event , n (%) N= # of subjects reporting the event	**FP HFA 440 mcg BID N = 163**	**FP CFC 440 mcg BID N = 162**
Any Event	149 (91%)	158 (98%)
Ear, Nose, Throat		
Upper resp. Tract infection (URTI)	56 (34%)	68 (42%)
Throat Irritation	27 (17%)	24 (15%)
Sinusitis	22 (13%)	17 (10%)
Rhinitis	16 (10%)	20 (12%)
Upper respiratory inflammation	9 (6%)	20 (12%)
Pharyngitis/Throat infection	11 (7%)	17 (10%)
Hoarseness/dysphonia	13 (8%)	14 (9%)
Laryngitis	2 (1%)	8 (5%)
Lower Respiratory		
Bronchitis	50 (31%)	47 (29%)
Viral respiratory infections	42 (26%)	34 (21%)
Asthma	36 (22%)	23 (14%)
Cough	28 (17%)	22 (14%)
Lower respiratory tract infection	8 (5%)	5 (3%)
Pneumonia*	5 (3%)	5 (3%)
Neurology		
Headache	52 (32%)	48 (30%)
Gastrointestinal		
Diarrhea	14 (9%)	14 (9%)
Nausea/vomiting	13 (8%)	11 (7%)
Candidiasis mouth/throat	10 (6%)	12 (7%)
Gastroenteritis	8 (5%)	10 (6%)
Dental discomfort and pain	8 (5%)	6 (4%)
Musculoskeletal		
Musculoskeletal pain	27 (17%)	24 (15%)
Non-site specific		
Candidiasis unspecified site	8 (5%)	9 (6%)
Chest symptoms	10 (6%)	5 (3%)
Endocrine & metabolic		
Decreased cortisol*	1 (<1%)	3 (2%)
Hypofunction of the adrenal cortex*	0	2 (1%)
Cushing's syndrome*	0	1 (<1%)
*< than 5% frequency but listed because of clinical importance		

Overall, the frequency of adverse events was relatively similar among the treatment groups. Some events occurred at a somewhat higher frequency in one group compared with the other, but this observation may not be of clinical significance. For example, upper respiratory inflammation was reported by 12% of subjects in the FP CFC group compared with 6% in the FP HFA group, and upper respiratory tract infection was reported by 42% of subjects in the FP CFC group compared with 34% of subjects in the FP HFA group. Cough was reported more frequently in the FP HFA group (17%) compared with 14% in the FP CFC

group. Candidiasis of the mouth/throat occurred at a similar frequency in both treatment groups. Pneumonia was reported in 3% of subjects in both groups. Adverse events known to be associated with inhaled corticosteroids are summarized in the table below. The results appear to be similar among the two formulations.

Table 39 - Adverse Events know to be associated with FP – FLTB3048

	FP HFA 440 BID	FP CFC 440 BID
Throat Irritation	27 (17%)	24 (15%)
Hoarseness/dysphonia	13 (8%)	14 (9%)
Candidiasis mouth/throat	10 (6%)	12 (7%)
Candidiasis site unspecified	8 (5%)	9 (6%)
Fungal infections*	1 (<1%)	1 (<1%)
Fungal skin infections*	2 (1%)	3 (2%)
Fungal infections (<1%) and fungal skin infections (1-2%) were also listed as adverse events however the sponsor did not provide more specific information about these.		

Adverse Events in Subjects with and without spacers

The frequency of adverse events was similar among subjects who used or did not use a spacer device during the study. However, some adverse events were different among spacer users and non-spacer uses. Throat irritation and hoarseness/dysphonia was reported with a higher frequency in subjects who did not use a spacer device compared with subjects who did. The degree of difference was similar for both the HFA and the CFC formulations. The table below summarizes the adverse events know to be associated with FP in subjects using and not using a spacer device.

Table 40 - Adverse Events associated with FP in subjects with and without spacer Device – FLTB 3048

	FP HFA 440 BID N =163		FP CFC 40 BID N =162	
	With Spacer N = 67 (41%)	Without Spacer N = 96 (59%)	With Spacer N = 61 (38%)	Without Spacer N=101 (62%)
Any Event	63 (94%)	86 (90%)	60 (98%)	98 (97%)
Throat Irritation	9 (13%)	18 (19%)	6 (10%)	18 (18%)
Hoarseness/dysphonia	4 (6%)	9 (9%)	7 (11%)	7 (7%)
Candidiasis mouth/throat	5 (7%)	5 (5%)	5 (8%)	7 (7%)
Candidiasis site unspecified	2 (3%)	6 (6%)	0	9 (9%)
Fungal skin infections	1 (1%)	1 (1%)	2 (3%)	1 (1%)

Deaths and Serious Adverse Events

There were no deaths during the study. A total of 22 subjects - 12 in the FP HFA group and 10 in the FP CFC group experienced serious adverse events during the treatment period. This reviewer concluded that none of these events are drug-related. There was one serious event of pneumonia in a 31-year old man (#7847) that occurred about 7 months after treatment with FP HFA 440 BID. He developed an upper respiratory tract infection and subsequently pneumonia (confirmed by radiology) for which he was hospitalize and received intravenous antibiotics. The event resolved after 22 days and the subject continued on in the

study. Only one serious adverse event led to discontinuation from the study. This event occurred in a 72-year old man who had been on FP CFC 440 BID who was hospitalized and had surgery for a herniation of an intervertebral disc. The patient had received 21 weeks of treatment with the study drug when the SAE occurred.

Clinical Laboratory Evaluations
There were no clinically significant hematology or chemistry abnormalities in either treatment group during the study. Two subjects had an increase in eosinophil count during the study. One subject had an elevated eosinophil level at screening and this increased further during the study.

Subject #7575 is a 38-year old female with normal eosinophil (0.51 GI/L) at screening. At Week 24 eosinophil level was 1.26 GI/L and 1.00 GI/L at the end of treatment.

Subject #7870 is a 42-year old female with elevated eosinophil count at screening (1.07 GI/L). the eosinophil count remained elevated at Week 24 (1.00 GI/L) and at the end of treatment (1.30 GI/L).
One subject was withdrawn because of abnormal LFTs (described on pg.---).
One subject in the FP HFA group and 5 subjects in the FP CFC group had glucose levels that were at the high threshold level.

HPA Axis Assessments and biochemical markers of bone
The sponsor attempted to evaluate HPA axis using morning serum cortisol measurements and 24-hour urine cortisol or short ACTH stimulation testing. Investigators had to choose one test or the other at their discretion. There were no predefined criteria for selecting a test. The data are inadequate to completely compare the two products FP HFA and FP CFC. The sponsor does not refer to these data in the proposed label and this reviewer is unable to make any conclusions from these data and therefore, they will not be addressed further in this review.

Asthma exacerbations
More subjects in the FP HFA group experienced asthma exacerbations during the study (22%) compared with subjects in the FP CFC group (14%). More subjects in the FP HFA group had more than one asthma exacerbation (7%) compared with subjects in the FP CFC group (2%).

Ophthalmic examinations
There were no reports of cataracts or glaucoma. One subject in the FP CFC group, a 26 year-old Caucasian woman was found to have an opacity in one eye (report does not state which) upon examination at endpoint. But this was not reported as an adverse event and details about this are not available.

Efficacy

Efficacy was not the primary objective of this study. However, lung function was assessed by FEV_1 and clinic PEF measurements at different timepoints throughout the treatment period. These results indicate that lung function remained stable and even showed numerical improvement throughout the treatment period. The findings were similar for both formulations as displayed in the table below.

Table 41 - Summary of Efficacy Findings FLTB3048

	FP 440 HFA BID (n=163)		FP 440 CFC BID (n =162)	
Efficacy Measure	n		n	
Mean FEV_1 (SE) [%predicted]				
Baseline FEV_1 L (SD)	163	2.474 (0.761)	162	2.63 (0.741)
Week 12 FEV_1 L (SE)	155	2.57 (0.026)	159	2.592 (0.026)
Week 32 FEV_1 L (SE)	150	2.512 (0.024)	150	2.591 (0.025)
Week 52 FEV_1 L (SE)	147	2.527 (0.026)	147	2.529 (0.027)
Clinic PEF (L)				
Baseline PEF L (SD)	163	413.3 (99.3)	162	436.0 (96.7)
Week 12 PEF L (SE)	154	434.9 (4.5)	159	437.2 (4.4)
Week 32 PEF L (SE)	147	426.3 (4.1)	149	438.3 (4.1)
Week 52 PEF L (SE)	146	435.8 (4.5)	144	439.1 (4.6)

Summary

This was a 1-year safety study conducted at multiple non-US sites, and therefore the safety conclusions discussed below must take this information into consideration. Compared to trials enrolling a US population, there were differences in ethnicity, smoking habits (current smoking was allowed during the study), availability and use of baseline medication, and the allowance of a spacer to administer the study drug.

Given these caveats, the safety profile of FP HFA 440 BID was similar to the safety profile seen in the 12-week studies, although it should be noted that such conclusions must be tempered by the absence of data supporting adherence of the subjects to study medication. Lung function was maintained throughout the 52 week – period. There was not a clear difference between adverse events in subjects using the CFC formulation compared with subjects using the HFA formulation, although the HFA subjects had numerically more asthma exacerbations, both overall and per subject. The explanation for this finding is unclear, and could be attributable to poor tolerability of the HFA formulation in some subjects. Alternatively, the CFC product may have greater efficacy in this population (not a primary endpoint of this study, however). Subjects using spacers had a lower incidence of local AE's such as throat irritation and hoarseness/dysphonia, however systemic corticosteroid AE's were not specifically addressed.

Appendix V. STUDY FAP30001

Title: "A randomized, double-blind, parallel-group trial of inhaled fluticasone propionate/GR1066642X (FP HFA) 220 BID and 440 BID in adolescent and adult subjects with asthma."

Objective
The objective of the study was to assess the safety of FP HFA 220 BID via the 110 mcg strength product and FP HFA 440 BID via the 220 mcg strength product for 6 months (26 weeks) in asthmatic subjects 12 years of age and older.

Study period and Sites
The study was conducted between November 20, 1998 and November 3rd, 1999. The study was conducted at 18 investigational sites in the United States.

Study Medication
Fluticasone Propionate HFA 110 mcg strength 220 BID
Fluticasone Propionate HFA 220 mcg strength 440 BID

Study Population
The study population and the inclusion and exclusion criteria were similar to that of the other studies. Subjects had to have an FEV_1 of ≥ 45%. Subjects could have been taking ICS but had to have been maintained on a stable regimen for at least 30 days prior to Visit 1. Subjects could have been on the maximum recommended dose of ICS. Subjects on theophylline, cromolyn or nedocromil, leukotriene receptor antagonists and 5-lipoxygenases inhibitors were allowed to continue taking them during the study if they were on a stable regimen. Subjects who had a history of oral corticosteroid use must not have required more than one systemic corticosteroid burst (defined as course of systemic corticosteroid < 14 days and the highest dose must not exceed 60 mg) during the 6 months prior to visit 1, and must have discontinued the use of oral corticosteroids at least 6 weeks prior to Visit 1.

Measurements and Evaluations
The primary objective of the study was safety. Safety measures similar to what was assessed in the other studies were evaluated. Efficacy was measured as mean change in percent predicted FEV_1 and mean change in morning pre-bronchodilator FEV_1.

Statistical methods
Statistical testing comparing the two treatment groups for safety or efficacy was not conducted. Safety and efficacy data were summarized on tables that provided sample sizes, means, medians, standard errors, minimums and maximums.

Study population results

A total of 182 subjects were randomized to double-blind treatment; 89 in the FP HFA 220 BID group and 93 in the FP HFA 440 BID group. A total of 42 (23%) subjects discontinued the study. The percentage was higher in the FP 440 BID group compared with the FP 220 BID group. Also, more subjects in the FP 440 BID group discontinued because of adverse events (9%) compared with the FP 220 BID group (3%). The table below summarizes the subject accountability findings.

Table 42 Subject Accountability FAP30001

Summary of Subject Accountability: End of Study Record, n (%)

	FP 220mcg HFA BID (N=89)	FP 440mcg HFA BID (N=93)
Completed	72 (81%)	68 (73%)
Prematurely discontinued	17 (19%)	25 (27%)
Reason for premature discontinuation		
Adverse event	3 (3%)	8 (9%)
Consent withdrawn	2 (2%)	3 (3%)
Lack of efficacy	0	0
Lost to follow-up	2 (2%)	2 (2%)
Other	3 (3%)	4 (4%)
Systemic corticosteroid	5 (6%)	6 (6%)
Protocol violation	2 (2%)	2 (2%)
Pregnancy	0	2 (4%)*
Death	0	0

Study Population Characteristics

The characteristics of the subjects in the study were similar to that of the subjects in other studies. The mean age ranged from 37.2 years in the FP 220 group to 39.6 years in the FP 440 group. Fifty-two to sixty-one (52 -61%) percent of subjects were females and 87 – 88% were Caucasian, 97 –98% were non-smokers and 44 –49% of the subjects had asthma for ≥ 15 years. At screening the percent predicted FEV_1 ranged from 70.1% in the FP 220 group to 72.3% in the FP 440 group. Subjects had similar concurrent medical conditions and disorders. Salmeterol (28 – 30% of subjects) and theophylline (9 – 10% of subjects) were the most common concurrent asthma medications taken by subjects during the study followed by zarfirlukast (≤ 8% of subjects) and montelukast (≤4% of subjects).

SAFETY RESULTS

Exposure

Mean exposure to the study drug was similar for the two treatment groups and ranged from 156.8 days (FP 440 BID group) to 160.0 days (FP 220 BID group). A total of 141 (77%) subjects had ≥175 days of exposure to study medication.

Compliance

Compliance as assessed by responses on the diary card was reported to be high (≥ 95%) in both treatment groups.

Adverse Events

Eighty-five to eighty-six percent of subjects reported at least one adverse event during the study treatment. Although the percentage of subjects reporting at least one adverse events was similar in both treatment groups, adverse events that are related to ICS use such as throat irritation, hoarseness/dysphonia, candidiasis of the mouth/throat, and musculoskeletal pain were notably more frequent in the FP 440 group. Bronchitis, nausea/vomiting, and sinusitis were also reported more frequently in the FP 440 treatment group. Overall, the adverse event profile in both treatment groups was similar to that seen in the other FP studies in this program. Adverse events reported by ≥ 5% of subjects are displayed in the table below as copied from the sponsor's submission.

Table 43 - Adverse Events summary FAP 30001

Summary of Adverse Events Reported by ≥5% Subjects, n (%)

	FP 220mcg HFA BID (N=89)	FP 440mcg HFA BID (N=93)
Any event	76 (85%)	80 (86%)
Upper respiratory tract infection (URTI)	30 (34%)	32 (34%)
Throat irritation	9 (10%)	17 (18%)
Hoarseness/dysphonia	4 (4%)	11 (12%)
Sinusitis	4 (4%)	7 (8%)
Upper respiratory inflammation	7 (8%)	3 (3%)
Headaches	24 (27%)	19 (20%)
Viral respiratory infections	9 (10%)	8(9%)
Bronchitis	3 (3%)	9 (10%)
Asthma	4 (4%)	5 (5%)
Nausea and Vomiting	2 (2%)	6 (6%)
Candidiasis mouth/throat	2 (2%)	8 (9%)
Musculoskeletal pain	6 (7%)	13 (14%)
Muscle pain	6 (7%)	7 (8%)
Pain	5 (6%)	3 (3%)

Deaths and Serious Adverse Events

There were no deaths during the study. Two subjects in the FP 440 BID group had a serious adverse event but these events in the opinion of this reviewer (cholelithiasis and spontaneous abortion) are not related to the study drug.

Withdrawals due to Adverse Events

Eleven subjects were withdrawn from the study because of adverse events – 3 subjects in the FP 220 treatment group and 8 subjects in the FP 440 treatment group. Five of the subjects had events that were in the opinion of this reviewer drug-related. One subject in the FP 220 group – a 26 year old man developed a generalized rash after being on study drug for 4 days. The drug was stopped and the rash resolved after 14 days. Three subjects in the FP 440 group were discontinued because of throat irritation, sore throat, and dysphonia/hoarseness, and one subject in the FP 440 group was discontinued because of candidiasis mouth/throat.

Pregnancies

Two subjects became pregnant during the study. Both subjects were in the FP 440 treatment group. One subject was lost to follow up and the other subject had a spontaneous abortion. This subject # 392, a 30-year-old female became pregnant approximately four months after initiating study treatment. An ultrasound revealed that the pregnancy was not viable and the subject spontaneously aborted the fetus approximately 5 weeks after becoming pregnant. In the opinion of this reviewer, there is not enough information to make a determination of relationship (if any) with the study drug.

Clinical Laboratory Findings

There were no clinically significant laboratory findings during the study. Shifts in laboratory values outside of the normal reference ranges was rare (≤2%) and not clinically significant. Four (4%) of subjects in the FP 220 group and one (1%) subject in the FP 440 group had shifts to high in eosinophil counts. One subject reported a high glucose at Week 26 but this did not reach threshold limits (170 mg/dl).

Urinary Cortisol

The sponsor presented 24-hour urinary cortisol as a cortisol/creatinine ratio and mean urinary cortisols. The data compare FP 220 mcg BID with FP 440 mcg BID. There is no placebo arm. The sponsor does not refer to these data in the label and this comparison is not very helpful in exploring the systemic effects of the two products given that the PK data did not show that exposure had a clear dose proportional relationship.

EFFICACY

Efficacy measures assessed were FEV_1, PEF, symptom scores, nighttime awakenings requiring Ventolin® use, and rescue Ventolin® use. The FEV_1, PEF, and Ventolin® use data are presented as mean change from Baseline to Endpoint in the table below.

Table 44 - Summary of Efficacy Findings FAP30001

	FP 220 HFA BID (n=89)		FP 440 HFA BID (n =93)	
Efficacy Measure	n		n	
Mean FEV_1 (SE) [%predicted]				
Baseline	89	2.65 (0.09) [75.0%]	93	2.49 (0.06) [74.0%]
Endpoint	86	2.96 (0.09) [84.6%]	92	2.79 (0.08) [82.2%]
Change from Baseline		+0.30 (0.05) [+9.1%]		+0.30(0.05) [+8.2%]
AM PEF (L) (SE)				
Baseline	88	416.9 (10.8)	93	400.0 (8.9)
Endpoint	87	446.7 (10.9)	93	427.0 (9.7)
Change		+26.3 (6.0)		+27.0 (5.4)
PM PEF (L) (SE)				
Baseline	89	435.8 (10.5)	93	422.2 (8.8)
Endpoint	87	462.8 (10.2)	93	439.9 (9.1)
Change		+25.0 (5.8)		+17.7 (4.7)
Ventolin Use (Puffs/day)				

Baseline	89	2.63 (0.30)	93	3.41 (0.80)
Endpoint	87	1.54 (0.23)	93	1.85 (0.23)
Change		-1.08 (0.20)		-1.57 (0.77)

As shown in the table, the two treatment groups had similar efficacy at endpoint.

Conclusions

The adverse event profile of Flovent HFA in this study is similar to the adverse event profile seen in other studies, although a clear dose-response in corticosteroid-related AE's was demonstrated between the FP 220 BID and FP 440 BID groups. Withdrawals due to adverse events and adverse events related to ICS were reported more frequently in FP 440 BID group compared with the FP 220 group. With respect to efficacy, the study was not designed or powered to detect a difference on an efficacy endpoint. However, FP 220 BID was not substantially different from FP 440 BID, although the survival-in-study endpoint clearly favored the lower dose. The finding of no clear dose-response on most efficacy endpoints is similar to what was seen in the pivotal efficacy trials. This trial suffers from the same deficiency as the previous (non-US) study in the inadequacy of the HPA-axis data.

Appendix VI. Other Studies – FLTA3020

FLTA3020 : "A twelve-week randomized, multicenter, double-blind, placebo-controlled, parallel-group study to assess dose ranging, safety and efficacy of the 110 mcg CFC and HFA fluticasone propionate products".

The study was conducted between October 1997 and 1998 and was a ranging study using bronchoconstrictive response to methacholine challenge as the assay. Subjects with mild asthma were recruited and used to compare FP doses of 110 mcg (1 x 110 mcg) and 220 mcg (2 x110 mcg) twice daily of both CFC and HFA products, and placebo HFA. A total of 191 subjects between the ages of 12 and 65 years with a diagnosis of asthma and a FEV_1 of 60 – 90% were eligible. Subjects could not have been using inhaled corticosteroid prior to entry into the study.

The study failed to demonstrate a dose-response relationship but was able to show that both FP HFA 110 mcg and 220 mcg produced protection against methacholine-induced bronchial hyperresponsiveness.

A total of 191 subjects were in the study distributed as follows: 43 in the placebo group, 72 in the FP HFA groups and 76 in the FP CFC groups. Mean exposure was 62.1 days in the placebo group and ranged from 72.6 to 82.2 days in the FP groups.

The adverse event profile was similar to what has been previously seen in studies with ICS and were more commonly reported in the ear, nose and throat system (43 – 47%). There were no reports of oral candidiasis or candidiasis at unspecified sites in this study.

There were no deaths in the study. Two serious adverse events were reported during the study but were unrelated to the study drug. One was a fractured pelvis and the other was a case of a ruptured appendix.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lydia McClain
12/17/02 08:19:43 AM
MEDICAL OFFICER

Marianne Mann
12/17/02 11:20:00 AM
MEDICAL OFFICER