

2.7.13 Single dose tolerability tests

The effects of single doses of study medication on actual FEV₁ were assessed at visit 2 in 76 patients at 4 centers, and analyzed for any declines that would be indicative of bronchospasm. Of the 76 patients, 13 received placebo, 33 received HFA treatment, and 30 received CFC treatment. Summary statistics were tabulated for each treatment group pre-dose, and 30 minutes, 1, 2, and 4 hours post dose. There were no significant differences between HFA flunisolide and placebo treatment groups (Table 2.7.13; applicant's in-text Table 41, vol.47). It should be noted that at all time points, all mean post dose FEV₁ values were higher than pre-dose values for the pooled HFA flunisolide group (applicant's in-text Table 40, vol.47). This was not true for the placebo and pooled CFC flunisolide groups.

Table 2.7.13 LSM Change in Actual FEV₁ (L) from Pre-dose to Post dose

Post dose Time point	LSM Change from Pre-dose			p-value ^a
	Placebo (n= 13)	HFA Flunisolide (n=33)	Difference (Placebo-HFA)	
30 minutes	0.026	-0.006	0.032	0.64
1 hour	0.034	0.052	-0.019	0.80
2 hours	0.103	0.068	0.032	0.65
4 hours	0.088	0.053	0.034	0.70

A minus sign for placebo of HFA flunisolide indicates a decrease from the pre-dose value
^a p-value based on the ABOVA model

Although significant reflex bronchospasm was not demonstrated in this small number of patients, it should be noted that at 30 minutes, a small decrease from pre-dose in FEV₁ was demonstrated for LSM change from pre-dose for the HFA flunisolide group and applicant claims that HFA flunisolide do not cause reflex bronchospasm are not unequivocally supported.

2.8 REVIEWER'S COMMENTS ON SAFETY

In general, treatment with HFA flunisolide resulted in a safety profile similar to, treatment with CFC flunisolide or placebo. The incidence of abnormal safety results, including chemistries, hematology, urinalysis, ECG findings and physical exam were low and similar among treatment groups. Incidence of oral candidiasis or clinical evidence of thrush infection was also similar across treatment groups. Additionally, urinary cortisol excretion and plasma cortisol values pre-and post cortrosyn stimulation were similar across all three treatment groups. No conclusions can be made about effects on metabolic bone activity due to results which show high variability and inconsistent treatment effect.

There were no deaths in this trial. Discontinuations due to adverse events occurred most frequently in the placebo group. The most common adverse event leading to patient withdrawal was asthma. The percentage of placebo-treated patients reporting TEAEs coded as asthma were 4 times that of patients in pooled HFA flunisolide treatment groups. The other most commonly reported TEAEs were headache and pharyngitis which were reported at a similar rate among treatment groups.

3.0 STUDY ANC-MD-03 (vol 1.67 et seq)

Initiation Date: August 13,1998

Completion Date: July 17, 1999

RÉSUMÉ

This dose ranging, active and placebo controlled efficacy and safety study, in 583 randomized pediatric patients age 4-11 years included mild to moderate asthmatic patients with a history of orally inhaled corticosteroid, cromolyn, or nedocromil use at a stable dose, or asthma symptoms requiring the use of a short acting β -agonist ≥ 3 times a week, for a minimum of 30 days prior to screening. 61 patients 4-5 years of age were randomized. Patients who met inclusion and exclusion criteria entered a 2-week open label run-in phase in which they all received treatment with CFC flunisolide 500 μ g twice daily, and albuterol as needed. They then entered a 12-week double-blind treatment phase in which they were randomly assigned to receive one or two puffs twice daily of either HFA flunisolide (85 μ g/puff), CFC flunisolide (250 μ g/puff), or placebo (HFA and/or CFC). Since the run-in phase included treatment with an active 500 μ g bid CFC flunisolide dose, 500 μ g bid CFC flunisolide and 170 μ g bid HFA flunisolide during the double-blind treatment phase would be expected to maintain the improvement observed during the run-in phase.

The study demonstrated statistically significant superiority of the 170 μ g doses of HFA flunisolide over placebo on the primary endpoint in 6-11 year old patients: change from baseline in percent predicted FEV₁ after 12 weeks treatment. FEV₁ assessment was optional in the 4-5 year old patients, and was assessed from baseline to the final visit in only 2 placebo patients, and 1 patient each who received 170 μ g bid HFA flunisolide and 250 μ g CFC flunisolide group, respectively. The study also demonstrated statistically significant superiority of 85 μ g dose of HFA flunisolide vs. placebo in percent predicted FEV₁.

No dose response relationship was demonstrated in the HFA flunisolide groups in 6-11 year old patients. There was an apparent dose-response relationship across the placebo, 250 and 500 mcg CFC flunisolide groups.

It should be noted that the statistically significant results for both HFA flunisolide doses demonstrated less than the 5% difference that the study was originally powered to detect, and the clinical relevance of the measured effect seen for this endpoint is difficult to determine. Information about actual FEV₁ change from baseline after 12 weeks was not evaluated in this trial, and even if it were, the clinical relevance of the magnitude of this change would vary by the height (age) of pediatric patients.

Numeric differences in change from baseline for in-clinic PEFr favored HFA and CFC flunisolide patients after 12 weeks of treatment, but were not statistically significant in either the 4-11 year old patients or 6-11 year old patients. No clear treatment difference was observed in any diary parameter, including AM and PM asthma symptoms, total daily asthma symptom, AM and PM PEFr, prn albuterol use, and nocturnal awakenings, and changes from baseline for all treatment groups for all diary parameters were small. Both 250 µg BID CFC flunisolide and 500µg BID CFC flunisolide doses were significantly superior to placebo for the primary efficacy parameter.

No additional benefit for the 170µg BID HFA dose over the 85µg BID HFA flunisolide dose could be inferred from dose response results, or time to drop out due to asthma exacerbation or insufficient therapeutic treatment effect.

With respect to safety, the incidences of TEAEs in the HFA and CFC flunisolide groups in 4-11 year old patients were comparable to the placebo group. The most commonly reported TEAEs were pharyngitis, rhinitis, and headache, which were reported at somewhat higher rates as compared to placebo. In the 4-5 year old patient subset, the most frequent TEAEs were fever, viral infection and rhinitis. Overall, no dose dependent increase in TEAEs was seen in either the HFA or CFC groups. Discontinuations due to adverse events in the 4-11 year old population occurred more often in the placebo group (12.1%) than in the 85µg bid HFA group (9.6%), 170µg bid dose of HFA group (10.3%), 250 µg bid CFC group (8.1%), or the 500 µg bid CFC group (7.1%). 1 SAE occurred in the 170µg bid dose of HFA group, 3 SAEs occurred in the 250 µg bid CFC group and 3 SAEs occurred in the placebo group. In the 4-5 year old subgroup, no patient in the HFA flunisolide-treated groups discontinued from the study due to asthma exacerbation or insufficient therapeutic effect, whereas 2 patients (11%) of the 4-5 year subset treated with placebo in this age did drop out.

Overall, incidences of abnormal laboratory values, ECG and physical exam abnormalities were small and similar among treatment groups. Pre and post cortrosyn stimulation cortisol levels were similar among HFA and CFC treatment groups and placebo. Timed urinary free cortisol, which may be a more sensitive measure of HPA-axis function, was not assessed in this study. It should also be noted that this study did not stratify patients based on their prior history of steroid exposure, however, prior history of inhaled steroid use was lowest in the placebo group (50.9% in

the placebo group versus 57% in both HFA flunisolide arms; 51% and 59% in the 250µg BID and 500µg BID CFC flunisolide arms, respectively). Prior use of oral or parenteral corticosteroid was low but not as similar across treatment arms (1.7% and lowest in the placebo group, 8.1% and highest in the 250 µg CFC flunisolide group. 4 cases of clinical moniliasis were reported, 2 in the HFA group, 2 in the CFC group and none in the placebo group. This result is not surprising for orally inhaled corticosteroids and will need to be addressed in the labeling.

In conclusion, this study provides evidence of efficacy and supports safety, with the caveat that HPA-axis effects were not assessed with sensitive tests, for 85µg bid HFA and 170µg bid doses of HFA flunisolide in pediatric patients 6-11 years of age in the treatment of mild-moderate asthma. It provides no clear evidence of efficacy, but supports safety, with the caveat that HPA-axis effects were not assessed adequately or in enough patients, in the 4-5 year old asthma patients. Although efficacy was demonstrated in the primary endpoint in 6-11 year old asthma patients, efficacy was not well supported by secondary efficacy parameters in 4-11 year old patients, or 6-11 year old patients, for either HFA or CFC formulations. This study provided no clear evidence that 170µg bid doses of HFA flunisolide in pediatric patients 6-11 years of age confers any additional benefit over 85µg bid doses of HFA flunisolide doses.

3.1 STUDY DESCRIPTION

DESIGN: Multi-center, randomized, double-blind, placebo and active controlled, dose-ranging 12 week efficacy and safety study of HFA flunisolide at BID doses of 83µg and 170µg, and CFC flunisolide at BID doses of 250µg and 500µg. HFA flunisolide dose (85 µg or 170 µg) selection was based on pharmacokinetic profiles in adults that were similar to CFC flunisolide (250µg or 500µg, respectively). The 500µg BID CFC flunisolide dose is the currently approved therapeutic dose in patients 6-15 years of age. No CFC and HFA flunisolide formulation comparative pharmacokinetic studies were submitted with this NDA.

POPULATION: 510 planned mild to moderate asthmatic patients 4-11 years of age, with a history of orally inhaled corticosteroid, nedocromil, or cromolyn use at stable doses, or asthma symptoms requiring the use of a short acting β-agonist ≥ 3 times a week, for a minimum of 30 days prior to enrollment. Up to seventy-five 4-5 year old patients were to be enrolled at 15 sites to randomize at least sixty 4-5 year old patients.

MATERIALS: Aerobid Inhaler System (CFC flunisolide) 250 µg/puff without Aerochamber spacer 1 or 2 puffs BID, Flunisolide HFA Inhaler System with built-in Bespak spacer 1 or 2 puffs BID, Albuterol Inhalation Aerosol (prn use), HFA placebo or CFC placebo, in children 6-11 years of age. Children 4-5 years of age, CFC flunisolide was to be administered with Aerochamber spacer.

OBJECTIVES: Primary - to demonstrate the efficacy and safety of 170 µg BID doses of HFA flunisolide hemihydrate after 12 weeks of treatment in pediatric patients in comparison to placebo. **Secondary** – to compare efficacy of 170 µg BID after 12 weeks of treatment for the following parameters: change in in-clinic PEFr, mean as-needed inhaled β-agonist use, AM and PM peak expiratory flow rate (PEFR), daily, mean AM and PM and total asthma symptom scores, and nocturnal awakenings requiring albuterol use.

The following additional secondary parameters were evaluated: to compare efficacy and safety of 170µg BID HFA flunisolide formulation with 500µg BID CFC; to evaluate 85µg BID HFA flunisolide vs. placebo; to evaluate the dose response relationship using change from baseline and screening; to evaluate time to drop-out for exacerbation of asthma; to evaluate safety of HFA and CFC formulations of flunisolide vs. placebo, and with respect to dose-dependent differences, if any.

CRITERIA: For patients 6-11 years of age, an FEV₁ of 45%-90% of predicted prior to inhalation of 180µg(2 puffs) albuterol after a washout period of various defined drugs (Vol 1.47, Section 5.3.6), a 12 % increase in their FEV₁ after 2 puffs of albuterol at or within 2 months prior to screening, and use of an orally inhaled corticosteroid, cromolyn, or nedocromil at a stable dose for a minimum of 30 days prior to Visit 1.

CONDUCT: Patients who met criteria at Visit 1 (Week-2) were entered into a 2-week, open label run-in period during which time they were all treated with 500µg BID of CFC flunisolide and as needed albuterol. Patients recorded asthma symptoms BID, AM and PM PEFr, use of prn albuterol, and the number of nocturnal awakenings secondary to asthma which required use of albuterol. PEFrs were measured at specified times, prior to administration of study medication and albuterol. PEFr readings obtained within 4 hours after albuterol administration were not to be recorded in the diary card. Patients were instructed not to take their morning dose of medication prior to their clinic visits. 6-11 year old patients were not permitted to use a facemask, spacer, or holding chamber device for any study medication.

At 12 selected sites, HPA axis was assessed by measuring effects of Cortrosyn stimulation on plasma cortisol. A normal response for the Cortrosyn stimulation test required a plasma cortisol increment of at least 7 mcg/100mL above the control value within 60 minutes after Cortrosyn administration and an absolute plasma cortisol value ≥ 18 mcg/ 100mL within 60 minutes.

Visit 1 assessments included, medical history, physical examination, vital signs, spirometry, (optional in 4-5 year of patients), in-clinic PEFr), clinical labs (to include mouth/throat smear and culture, hematology, chemistry, U/A) and 12-lead ECG were also assessed.

Visit 2 concluded the run-in period. Patients who had a pre-bronchodilator FEV₁ ≥ 80% predicted, total daily asthma symptom score ≤ 16 puffs per day for 5/7 days prior to Visit 2, and mean total albuterol intake ≤ 10 puffs/day during 5/7 days prior to Visit 2 were randomized into five treatment groups for the 12-week double-blind, double dummy phase of the trial. These patients were assigned to receive one or two puffs twice daily of HFA flunisolide (85 µg/puff), CFC flunisolide (250µg/puff), and/or placebo (HFA or CFC). Four canisters were dispensed and patients were instructed to always inhale from the canister labeled HFA first, followed by the CFC canister. HPA axis assessment was also performed at this visit.

Patients were instructed to return at three-week intervals for review of diary cards (AM and PM PEFR were to be recorded prior to taking their dose of study drug) and adverse events, concomitant medications, in-clinic PEFR, and spirometry (prebronchodilator) for Visits 3-6 (optional in 4-5 year old patients). At Visit 6 (Week 12), vital signs, physical examination, standard hematology and chemistry laboratory tests, 12-lead ECGs, and response to Cortrosyn stimulation were assessed. Additionally, adverse events, concomitant medications, and diary cards were reviewed and spirometry was performed. Spirometry was performed by an assessor blinded to the number of puffs/canister of study drug taken by the patient. All patients were instructed to withhold bronchodilator for at least six hours prior to spirometry assessments at each visit and were further instructed not to take their morning dose of study medication prior to their office visits.

DATA ANALYSIS: The protocol defined primary efficacy variable was change from baseline in percent predicted FEV₁ after twelve weeks treatment. This was expressed as least squares mean difference (LSM) from baseline of each HFA flunisolide compared with placebo in percent predicted FEV₁ after 12 weeks of treatment in patients 6-11 years of age. In 4-5 year old patients, in-clinic PEFR replaced FEV₁ in defining the primary efficacy parameter. Comparisons between CFC and HFA flunisolide formulations were made using an ANCOVA model. This model was also used to compare individual doses of CFC and HFA formulations to placebo. The Fisher's Least Significant Difference test was used to adjust for multiple comparisons. The same analytic approach was used for all secondary endpoints. Tukey's method was used to evaluate the dose response relationship, in which the most extreme p-value computed from a linear model with the original dose vs. a model with a log-transformed dose was taken. Kaplan Meier curves were used to analyze time to dropout due to asthma exacerbation. Adverse events were tabulated. Descriptive statistics were used to analyze results of primary efficacy parameters and all secondary parameters at 12 weeks and at each visit, and for laboratory tests, vital signs, and HPA axis assessments. Subgroups analyses for race, gender, patients 6-11, 4-11, and 4-5 were also performed. Missing data was imputed by the last observation carried forward (LOCF).

The Final Study Report analyzed patients based on the ITT population for efficacy (defined as all randomized patients who received at least one dose of study drug and had at least one follow-up assessment of the primary efficacy parameter after baseline (571 patients). A safety population (583 patients) was defined as all randomized patients who received at least one dose of study drug, i.e. all treated patients, for the analysis of safety. Sample size was calculated based on a 85% power to detect a 5% difference at the two-sided 0.05 significance level between 170µg BID HFA flunisolide and placebo in the primary efficacy parameter, assuming an 11% pooled standard deviation. The sample size for the 85µg BID HFA flunisolide group was matched to that of the higher dose group. In order to ensure at least 10% of patients age 4-5 years, randomization was stratified into 4-5 year old and 6-11 year old patients. 90 patients age 6-11 were randomized 1:1:1:1:1. For patients 4-5 years of age, 20 patients were to be randomized to placebo and 10 patients were to be randomized to each of the four active treatment groups.

It should be noted that as in the adult study, ANC-MD-01, the primary objective of this study, ANC-MD-03, analyzed in the final study report changed from the primary objective stated in the final protocol. Since this objective change and plans for the final SAP were made prior to unblinding of the data, and given the fact that the primary efficacy parameter did not change, this does not represent a significant review issue.

It should be further noted that this protocol design and analysis did not stratify patients based on prior use of either inhaled or systemic corticosteroid. This may limit interpretability of Cortrosyn stimulation assessments, if use of these drugs were not similar across treatment groups. Unlike the study in adults, no efforts were made to assess the effects of inhaled HFA flunisolide on bone metabolism.

3.2 PATIENT DISPOSITION

653 patients were enrolled at 51 sites; 583 were randomized to receive study drug. 571 patients had at least one follow-up assessment of the primary efficacy variable, and were included in the ITT analysis for efficacy. Of the 12 patients who were randomized but not included in the ITT analysis, 4 were in the placebo group, 4 were in the pooled HFA flunisolide groups, and 3 were in the pooled CFC flunisolide groups, as shown in Table 3.2A (applicant's in-text Table 1, vol.67).

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Table 3.2A Patient Disposition

	<i>Placebo</i>	<i>HFA 85 µg bid</i>	<i>HFA 170 µg bid</i>	<i>CFC 250 µg bid</i>	<i>CFC 500 µg bid</i>	<i>Total^a</i>
Patients Enrolled	---	---	---	---	---	653
Not Randomized	---	---	---	---	---	70
Patients Randomized	116	114	117	123	113	583
Did not take any study drug	0	0	0	0	0	0
Safety Population	116	114	117	123	113	583
No post-baseline efficacy data	4	2	2	1	3	12
ITT Efficacy Population	112	112	115	122	110	571
Completed Study^b (%)	89 (76.7)	94 (82.5)	98 (83.8)	105 (85.4)	91 (80.5)	477 (81.8)

Refer to Section 6.2 for definitions of study populations.

^a Total of all HFA flunisolide, CFC flunisolide, and placebo groups.

^b Patients who received 12 weeks of double-blind medication.

Cross-reference: After-text Tables 1.1, 1.2 and 1.3.

81.8% of randomized patients completed the study. The lowest percentage of patients completing the study were in the placebo group (76.7%) and the highest percentage were in the CFC flunisolide 250µg BID group (85.4%). The percentage of patients completing the study in the active groups were similar, with no observed statistically significant differences. The percentage of study completers in the active groups ranged from 80.5%-85.4%. Reasons for patient discontinuation are shown in Table 3.2B, (applicant's in-text Table 2, vol.65) shown below. For the 106 safety population patients who discontinued from the study, adverse event or intercurrent illness was the most frequent reason for patient discontinuation (55 patients, 9.4%). Safety population patient discontinuation was highest in the placebo group (12%). The highest percentage of patients who withdrew due to insufficient efficacy was also in the placebo group (2.6%). It should also be noted that discontinuations due to AEs or intercurrent illness were lowest in the CFC study groups, however, rates of discontinuation for insufficient efficacy were similar between HFA and CFC treatment groups.

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Table 3.2B Reasons for Patient Discontinuation

	<i>Placebo</i>	<i>HFA 85 µg bid</i>	<i>HFA 170 µg bid</i>	<i>CFC 250 µg bid</i>	<i>CFC 500 µg bid</i>	<i>Total</i>
Safety Population	116	114	117	123	113	583
Total discontinued from study	27 (23.3)	20 (17.5)	19 (16.2)	18 (14.6)	22 (19.5)	106 (18.2)
Adverse event/ intercurrent illness	14 (12.1)	11 (9.6)	12 (10.3)	10 (8.1)	8 (7.1)	55 (9.4)
Insufficient Efficacy	3 (2.6)	1 (0.9)	2 (1.7)	3 (2.4)	1 (0.9)	10 (1.7)
Lost to Follow-up	4 (3.4)	1 (0.9)	2 (1.7)	1 (0.8)	1 (0.9)	9 (1.5)
Non-compliance	1 (0.9)	2 (1.8)	0	1 (0.8)	4 (3.5)	8 (1.4)
Consent Withdrawn	2 (1.7)	0	2 (1.7)	1 (0.8)	3 (2.7)	8 (1.4)
Protocol Violation	2 (1.7)	3 (2.6)	0	2 (1.6)	0	7 (1.2)
Other^a	1 (0.9)	1 (0.9)	1 (0.9)	0	3 (2.7)	6 (1.0)
Administrative Reasons	0	1 (0.9)	0	0	2 (1.8)	3 (0.5)

^a Other reasons include: patient moved out of state, patient enrolled after the enrollment period ended, patient/parent unable to keep clinic appointments, and asthma status uncertain.

Cross-reference: After-text Table 1.3|

In the evaluation of the 4-5 year old subgroup of patients, the percentage who discontinued from the study in the CFC 500 µg flunisolide group (56%, 5/9 patients) was higher than in the percentage of the 6-11 year old subgroup (16.3%, 17/104 patients). The sponsor attributes this difference to the small sample size of the 4-5 year old patients in this treatment group and this reviewer agrees that sample size issues in the 4-5 year old population make interpretation of the data difficult.

3.3 PROTOCOL DEVIATIONS

A per-protocol population was not defined and there were no per-protocol analyses. Sixteen patients were randomized into the study despite their ineligibility by inclusion/exclusion criteria. Fourteen 6-11 year old patients were enrolled into the run-in phase with percent predicted FEV₁ outside the 45%-95% range at screening (2 patients < 45% and 12 patients >127%). Two patients had % predicted FEV₁ measurements at baseline that deteriorated more than 20% from the screening measurement. There were no deviations for total asthma symptom score or mean total albuterol intake criteria.

3.4 PATIENT CHARACTERISTICS

More male than female patients 4-11 years old were randomized (65.2% versus 34.8%, respectively). The majority of patients were white (69.5%) and the mean age was 8.5 ± 2.0 years. Sixty-one 4-5 year old patients were included and comprised 10% of the total safety population. CFC and HFA treatment groups had similar numbers and percentages (ranging from 9 patients and 7.9% to 13 patients and 10.6% per treatment group) of 4-5 year old patients, however, the placebo group had the highest number and percentage (18 patients, 15.5%). There were no overall important differences among treatment groups for height, weight, age, previous anti-asthma medication, or length of asthma history. Further, there were no overall important differences among treatment groups for efficacy variables at baseline for the ITT population. The enrolled study population had very mild asthma with a mean percent predicted $FEV_1 = 81.2$ at screening.

It should be noted, however, that inhaled corticosteroid prior use was about 51% in the placebo group, about 57% in both HFA flunisolide groups, and about 51% and 59% in the 250 μ g BID and 500 μ g BID CFC flunisolide groups, respectively. Prior use of oral or parenteral corticosteroid was low but not as similar across treatment arms (1.7% and lowest in the placebo group, 8.1% and highest in the 250 μ g CFC flunisolide group). Balance across treatment arms for this history of prior exposure is important in assessing the effects of the study treatment on the HPA axis. Unfortunately, this study did not stratify for this and it was not balanced for history of steroid use across treatment arms.

3.5 TREATMENT COMPLIANCE

Greater than 89% of all ITT patients were compliant at all visits and there were no apparent differences among the five treatment groups. Patient compliance was determined by dividing the actual total number of puffs of inhaled steroid used and recorded in the diary cards between each visit, by the predicted total number of puffs of inhaled steroid (total number of puffs the patient should have taken between each visit). It should be noted however, that diary data alone may be an unreliable assessment of compliance, especially in a pediatric population.

3.6 EFFICACY REVIEW

Efficacy was analyzed as change from baseline to 12 weeks of treatment in percent predicted FEV_1 using the ITT population and a LOCF method in 6-11 year old patients. This was assessed after a two-week run-in period in which patients received treatment with 500 μ g BID CFC flunisolide, and patients had generally well controlled asthma at the baseline. Improved pulmonary function was observed during the run-in phase, with a 6.2% increase in percent predicted FEV_1 and an 8.4L/min

(3.8%) improvement for in-clinic PEF_R, as assessed from screening to baseline. The goal of double blind treatment was to observe whether this improvement was maintained, exceeded or lost. At the conclusion of the trial, the measured effect size of the active treatments compared to placebo were due, in part, to any deteriorating pulmonary function in patients receiving placebo, and in part, to the effects of active treatment doses. It should be noted that in 4-5 year old patients, FEV₁ was not mandatory because young children have difficulty performing the assessment, and only four 4-5 year old patients were able to complete the assessment from baseline to the final visit. Results for the primary efficacy endpoint are reported for the 6-11 year old patient population.

3.6.1 Primary efficacy parameter: comparison of 170 µg BID HFA flunisolide to placebo for % predicted FEV₁ from baseline to 12 weeks (LOCF) in 6-11 year old patients

Using descriptive statistics, trial results in 6-11 year old patients demonstrated a mean decrease of 3.4% ± 13.41 in percent predicted FEV₁ for placebo treated patients, whereas patients treated with 170 µg BID HFA flunisolide maintained the level of improvement achieved during the run-in phase (mean change 0.2%± 12.18). A statistically significant improvement (p=0.034), in favor 170 µg BID HFA flunisolide compared with placebo, was demonstrated for LSM change in % predicted FEV₁ from baseline after 12 weeks treatment (table 3.6.1; applicant’s in-text table 14, vol. 67).

However, it should be noted that these results show less than a 5% difference as planned in the power analysis. It is difficult to determine whether this observed effect size has clinical meaning. Information about actual FEV₁ change from baseline after 12 weeks was not evaluated in this trial, and even if it were, the clinical relevance of the magnitude of this change would vary by the age (height) of the child. It is also interesting to note that after a 6.2% mean improvement in % predicted FEV₁ for all screened patients who were randomized at baseline, the placebo group declined 3.4%.

Table 3.6.1 Comparison of 170 µg BID HFA flunisolide to placebo for % predicted FEV₁ from baseline to 12 weeks (LOCF) in 6-11 year old patients

Percent Predicted FEV ₁	LSM ^a Placebo	LSM ^a 170 µg bid	Difference ^b	p-Value ^c
Change From Baseline to Week 12 (LOCF)	-3.53	0.35	3.88	0.034

^a LSM = least square mean for change from baseline.

^b LSM of change from baseline in flunisolide dose minus that of placebo.

^c p-value based on ANCOVA in testing the difference between 170 µg bid of HFA flunisolide and placebo.

Cross-reference: After-text Table 3.1 and Appendix VI.2

3.6.2 Secondary Objectives

Patients 6-11 years of age treated with 85µg BID HFA flunisolide demonstrated statistically significant improvement as compared with placebo for LSM change from baseline after 12 weeks treatment in 6-11 year old patients (p=0.008). As was demonstrated by the 170 µg BID HFA flunisolide dose, these patients maintained the improvement in percent predicted FEV₁ that was achieved during the run-in phase (mean 1.2% ± 12.03 increase) whereas patients randomized to placebo showed a mean % predicted FEV₁ decrease of 3.4% ± 13.41. It is interesting to note that the both the effect size demonstrated by descriptive statistics and the p-value obtained in the LSM analysis are more robust for this lower dose, and sample sizes for both active dose groups are equal (N=95). As observed in the primary endpoint analysis, it should be noted that these results also show less than a 5% difference as planned in the power analysis (table 3.6.2A, applicant's in-text table 16, vol.67).

Table 3.6.2A Comparison of 85 µg BID HFA flunisolide to placebo for % predicted FEV₁ from baseline to 12 weeks (LOCF) in 6-11 year old patients

Percent Predicted FEV ₁	LSM ^a Placebo	LSM 85 µg bid	Difference ^b	p-Value ^c
Change From Baseline to Week 12 (LOCF)	-3.55	1.32	4.87	0.008

^a LSM = least square mean for change from baseline.

^b LSM of change from baseline of flunisolide dose minus that of placebo.

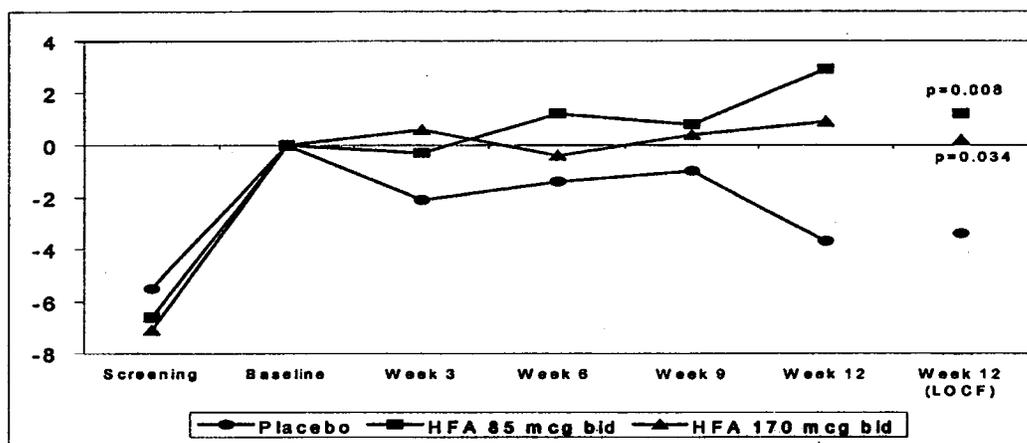
^c p-value is based on the ANCOVA in testing the difference between 85 µg bid of HFA flunisolide and placebo.

Cross-reference: After-text Table 3.1 and Appendix VI.2

Both formulations maintained their treatment effect, as measured by change from baseline by visit in % predicted FEV₁ in 6-11 year old patients, to a similar extent over the 12 week treatment period, whereas patients in the placebo group deteriorated over time (figure 3.6.2B; applicant's Figure 1, vol. 67)

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Figure 3.6.2B Change from Baseline by Visit in Percent Predicted FEV₁ HFA vs. Placebo: Patients age 6-11



p-values are based on the ANCOVA in testing the difference between each dose of HFA flunisolide and placebo. Cross-reference: After-text Tables 3.1 and 3.10.2.

Comparisons of the LSM change from baseline for the 250µg and 500µg BID CFC flunisolide doses with the LSM change from baseline for placebo for % predicted FEV₁ after 12 weeks treatment demonstrated statistically significant benefit for both treatment groups. Unlike the HFA formulation, dose ordering was observed, with a more robust benefit of the 500µg BID CFC flunisolide dose over the 250 µg BID CFC flunisolide dose demonstrated (table 3.6.3; applicants' in-text table 18, vol. 67).

Table 3.6.3 Comparison of CFC Flunisolide to Placebo: change from baseline in percent predicted FEV₁ after 12 weeks treatment in patients 6-11 years old

<i>Change From Baseline in Percent Predicted FEV₁</i>	<i>LSM^a Placebo</i>	<i>LSM</i>	<i>Difference^b</i>	<i>p-Value^c</i>
250 µg bid	-3.83	0.84	4.67	0.012
500 µg bid	-3.70	2.94	6.64	0.0001

^a LSM = least square mean for change from baseline.

^b LSM of change from baseline for flunisolide dose minus that of placebo.

^c p-value is based on the ANCOVA in testing the difference between each dose of CFC flunisolide and placebo.

Cross-reference: Appendix VI.2

Patients demonstrated a numeric difference in the change from baseline after 12 weeks treatment for in-clinic PEFr that favored both the 85µg BID HFA flunisolide and 170µg BID HFA flunisolide doses. Differences in the LSM change from baseline in in-clinic PEFr were not

statistically significant between 85µg BID HFA flunisolide and placebo, nor statistically significant for 170µg BID HFA flunisolide doses treatment groups versus placebo. These results were demonstrated for both the 4-11 year old age group and the 6-11 year old subgroup (please refer to applicant's after-text tables 3.2 and 3.2A, vol. 68). Mean change from baseline after 12 weeks for in-clinic PEFR were highly inconsistent in the 4-5 year old subgroup, in which the placebo group demonstrated a 6.8 ± 36.10 L/min **increase** for in-clinic PEFR, the 85 µg BID HFA flunisolide group demonstrated a 14.4 ± 26.03 L/min increase, the 170 µg BID HFA flunisolide group demonstrated a 5.0 ± 35.74 L/min increase, the 250 µg BID CFC flunisolide group demonstrated a 12.1 ± 30.26 L/min increase and the 500 µg BID CFC flunisolide group demonstrated a $19.4\% \pm 27.83$ L/min **decrease** (refer to applicant's after-text table 3.11.2.B, vol. 69).

It is interesting to note that among 4-11 year old patients, the group treated with placebo maintained the level of in-clinic PEFR from baseline after 12 weeks (mean increase 0.9 ± 46.20 L/min). One would have expected a decline in pulmonary function in this group after 12 weeks. However, among the 6-11 year old subset treated with placebo, a slight decline (-0.2 ± 47.87 L/min) for in-clinic PEFR after 12 weeks was observed. In 4-11 year old patients treated with 85µg BID HFA flunisolide and 170µg BID HFA flunisolide doses, 8.0 ± 36.62 L/min and 8.1 ± 49.15 L/min improvements from baseline after 12 weeks, respectively, were observed. Overall, these results seem to indicate a greater level of improvement with active treatment than with placebo.

Results for in-clinic PEFR for both the 250 µg and 500 µg BID CFC flunisolide doses yielded similar results, which were similar in magnitude to the 85µg BID HFA flunisolide and 170µg BID HFA flunisolide doses. As for the HFA groups, these differences were not statistically significant.

The applicant performed a post-hoc observed case analysis at week 12 for in-clinic PEFR in the 170µg BID HFA flunisolide treatment group versus placebo, in 4-11 year old and 6-11 year old subgroups. Although this analysis demonstrated statistical significance for in-clinic PEFR in both subgroups for this dose, it should be noted that the 4-11 year old population results in a less favorable treatment mean (table 3.6.4; applicant's in-text table 20, vol. 67). This result would also suggest that in 4-5 year old patients, there was no demonstrated efficacy for in-clinic PEFR. This was an important efficacy parameter in this subset of patients unable to perform FEV₁ assessments. It is possible that the PEFR assessment may also be highly variable and unreliable in this young population, this trial enrolled patients with very mild asthma, and the placebo treated patients unexpectedly did not demonstrate a reduction in PEFR after randomization and sample size was not powered to assess in-clinic PEFR.

Table 3.6.4 Observed Case Comparison of 170µg BID HFA flunisolide to Placebo: Change from Baseline in In-clinic PEFR (L/min) after 12 weeks treatment

	<i>LSM^a Placebo</i>	<i>LSM 170 µg bid</i>	<i>Difference^b</i>	<i>p-value^c</i>
4-11 Years Old	3.54	18.93	15.39	0.023
6-11 Years Old	2.73	20.38	17.65	0.018

^a LSM = least square mean for change from baseline.

^b LSM of change from baseline of flunisolide dose minus that of placebo.

^c p-value based on ANCOVA in testing the difference between 170 µg bid of HFA flunisolide and placebo.

Cross-reference: After-text Table 3.1, 3.1A, and Appendix VI.2

Diary data in patient 4-11 years old for change from baseline after 12 weeks treatment were highly variable and no statistical differences were observed between placebo and any active treatment group. These results are shown below (table 3.6.5; applicant's in-text table 23, vol. 67). Of note, the AM PEFR improved most in the CFC 500 µg BID group (8.3), followed by placebo (6.7). The PM PEFR improved most in the **placebo** group (7.4), followed by the HFA 85 µg BID group (3.5). On the other hand, AM, PM and total asthma symptom scores trended in favor of the HFA 85 µg BID and CFC 500 µg BID groups, where as prn albuterol use trended in favor of HFA 170 µg BID and CFC 500 µg BID groups.

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Table 3.6.5 Descriptive Statistics for Diary Data after 12 weeks of Treatment in Patients age 4-11

	<i>Placebo</i>		<i>HFA 85 µg bid</i>		<i>HFA 170 µg bid</i>		<i>CFC 250 µg bid</i>		<i>CFC 500 µg bid</i>	
	<i>N</i>	<i>Mean</i>	<i>N</i>	<i>Mean</i>	<i>N</i>	<i>Mean</i>	<i>N</i>	<i>Mean</i>	<i>N</i>	<i>Mean</i>
PRN Albuterol Use (Puffs/Day)										
Baseline	110	1.7	111	1.5	112	1.6	120	1.6	109	1.7
12 Weeks (LOCF)	107	1.9	106	1.5	113	1.5	121	1.7	106	1.6
Change ^a	106	0.1	105	0.0	110	-0.1	119	0.1	106	-0.2
AM Diary PEFR (L/min)										
Baseline	111	221.3	112	231.7	115	221.3	122	233.7	108	237.1
12 Weeks (LOCF)	108	230.3	108	238.6	113	226.0	121	238.9	106	244.5
Change ^a	108	6.7	108	5.0	113	4.6	121	5.9	105	8.3
PM Diary PEFR (L/min)										
Baseline	111	230.8	111	235.8	115	229.9	122	240.0	108	245.1
12 Weeks (LOCF)	108	240.3	108	241.3	113	231.9	121	241.6	106	245.4
Change ^a	108	7.4	107	3.5	113	2.4	121	2.1	105	1.1
AM Asthma Symptom Score										
Baseline	111	0.8	112	0.9	115	0.9	122	0.9	109	1.1
12 Weeks (LOCF)	107	1.2	106	0.9	113	1.0	121	1.2	105	1.1
Change ^a	107	0.4	106	-0.1	113	0.1	121	0.2	105	0.0
PM Asthma Symptom Score										
Baseline	111	1.0	111	1.0	115	1.1	122	1.1	108	1.2
12 Weeks (LOCF)	107	1.2	106	0.8	113	1.1	121	1.1	105	1.2
Change ^a	107	0.1	105	-0.2	113	0.0	121	0.0	104	-0.1
Mean Total Daily Asthma Symptom Score										
Baseline	111	1.9	112	1.9	115	2.0	122	2.0	109	2.3
12 Weeks (LOCF)	107	2.3	106	1.7	113	2.0	121	2.3	105	2.3
Change ^a	107	0.4	106	-0.2	113	0.1	121	0.3	105	-0.1
Nocturnal Awakenings (per night)										
Baseline	108	0.0	109	0.1	112	0.0	117	0.0	104	0.0
12 Weeks (LOCF)	107	0.1	104	0.1	112	0.1	121	0.1	106	0.1
Change ^a	104	0.1	102	0.0	110	0.1	116	0.1	101	0.0

^a Change from baseline after 12 weeks of treatment

Cross-reference: After-text Table 3.3 - 3.9 and 3.12.1 - 3.18.2

No significant differences, in change from baseline after 12 weeks treatment, between HFA 170 µg BID flunisolide and CFC 500 µg BID flunisolide groups were demonstrated for the primary efficacy parameter or any of the secondary efficacy parameters in 6-11 year old patients (see applicant's in-text table 24, vol. 67). However, no comparison between the 85 µg BID flunisolide and CFC 500 µg BID flunisolide groups were submitted with the Final Study report. It should be noted that there was no apparent dose response between the 85 µg BID flunisolide and 170 µg BID flunisolide doses, which may be a reflection that in children 6-11 years of age, the 85 µg BID flunisolide may be at the dose response plateau. It would therefore be informative to compare this lower HFA flunisolide dose with the approved CFC flunisolide dose for all assessed efficacy endpoints. This information was requested and is pending, however, the following table assessing the primary endpoint, percent predicted FEV₁ change from baseline after 12 weeks, was generated by this reviewer, in consultation with FDA statistician, James Gebert, PhD. (table 3.6.6)

3.6.6 Comparability of 85µg BID HFA Flunisolide and 500µg BID CFC Flunisolide: difference in change from baseline after 12 weeks of treatment (LOCF) in 6-11 year old patients

Efficacy Parameter	LSM Difference (HFA-CFC)	95% CI	p-Value
Primary % predicted FEV₁	-1.302	-4.248, 1.64	0.38

The p-value is even less significant (p=0.38) for the 85µg BID HFA flunisolide to 500µg BID CFC flunisolide comparison of the primary efficacy parameter, than in the 170µg BID HFA flunisolide to 500µg BID CFC flunisolide comparison (p= 0.108). The sponsor will therefore not be able to make dose comparability claims between specific HFA and CFC doses, especially in light of no existing HFA pharmacokinetic data in children assessing dosing comparability.

The absence of dose response in percent predicted FEV₁ at 12 weeks in 6-11 year old patients are presented below. There was an apparent dose-response relationship across the placebo, 250 and 500 mcg CFC flunisolide groups. (figures 3.6.7A and 3.6.7B; applicant's figures 3 and 4, vol. 67).

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Figure 3.6.7A Dose response change from baseline in percent predicted FEV₁ at 12 weeks (LOCF) in patients 6-11

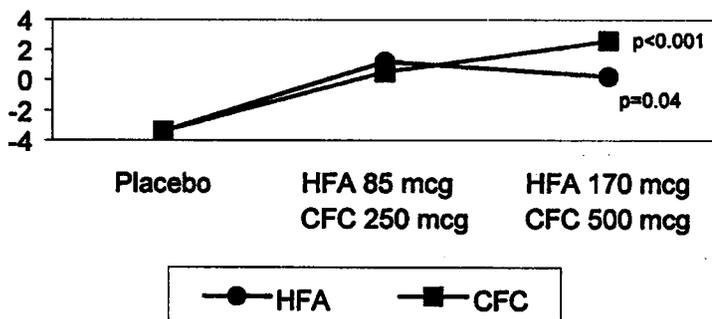
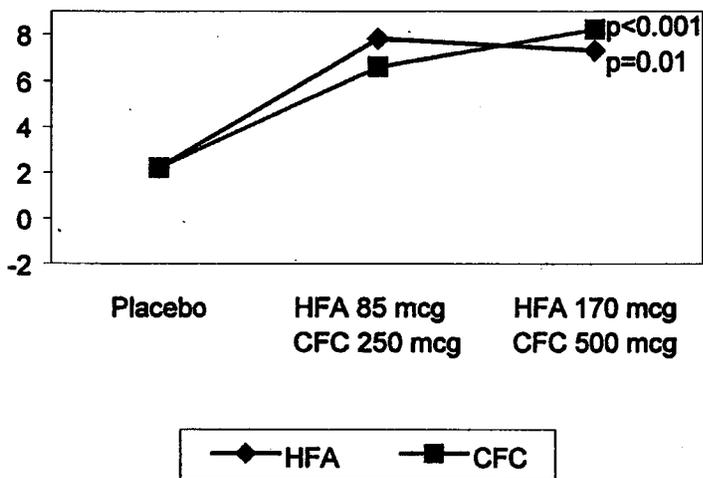


Figure 3.6.7B Dose response change from screening in percent predicted FEV₁ at 12 weeks (LOCF) in patients 6-11



As seen in table 3.6.8 below (applicant's in-text table 26, vol. 67) more 4-11 year old patients discontinued from the study due to asthma exacerbation or insufficient treatment effect in the placebo group throughout this study (placebo=13.8%; 85 µg BID flunisolide=7.9%; 170µg BID flunisolide=10.3%). However, these numerical differences in favor of the HFA treatment did not reach statistical significance, and it should also be noted that the 85 µg BID flunisolide group had a lower percentage of patient discontinuation after week three, than the higher 170µg BID flunisolide group. Kaplan Meier curves generated to compare placebo to both HFA groups for time to drop-out due to asthma or insufficient treatment effect did not show clear separation between groups, for the overall 4-11 year old population, 6-11 year old subset, or 4-5 year old subset (applicant's after text tables 3.19, 3.19A and 3.19B, vol. 68 and 69). The applicant did not compare CFC flunisolide groups and placebo for this efficacy parameter in the Final Study Report.

Table 3.6.8 Cumulative Frequency of Patient Discontinuations due to Lack of Efficacy or Asthma Exacerbation in 4-11 year old Patients

<i>Visit Number</i>	<i>Placebo (n = 116)</i>	<i>HFA 85 µg bid (n = 114)</i>	<i>HFA 170 µg bid (n = 117)</i>
Week 3	6 (5.2%)	5 (4.4%)	2 (1.7%)
Week 6	11 (9.5%)	7 (6.1%)	9 (7.7%)
Week 9	12 (10.3%)	8 (7.0%)	12 (10.3%)
Week 12	16 (13.8%)	9 (7.9%)	12 (10.3%)
p-Value ^a		0.1384	0.3136

^a p-Value for comparison with placebo based on the log-rank tests.
Cross-Reference: After-text Table 3.19

The sponsor performed subgroup analysis comparisons by gender, age, ethnic group and prior steroid use in patient subsets. Overall, 65% were male and 35% were female. Male and female patients 6-11 years of age responded comparably to each flunisolide formulation for both FEV₁ and PEFR efficacy parameters.

Baseline and change from baseline for PEFR in the 4-5 year old patients were similar across the treatment groups, with the numerically greatest improvement observed after 12 weeks in the 85µg HFA flunisolide group. Baseline values for PEFR were lower in the 4-5 year old subset compared to the 6-11 year old subset. After 12 weeks of treatment, the mean in-clinic PEFR and change from baseline in the 4-5 year old patients were comparable to the 6-11 year old subset of patients. While mean PEFR deteriorated in the placebo treated 6-11 year old subset of patients (-0.2 ± 47.87 L/min), this did not occur in the 4-5 year old population (6.8 ± 36.10 L/min).

Analyses of the mean value at each visit, and the mean change from baseline, in percent predicted FEV₁ (6-11 year old patients) and in-clinic PEFr (4-11 year old patient) by ethnic group (White, Black, Hispanic, and Other) were performed. No consistent pattern was observed for Hispanic patients across treatment groups for change from baseline FEV₁ was observed.. Both White and Black patients in the placebo group showed a mean decrease in FEV₁ from baseline at every visit, whereas in the HFA and CFC treatment groups, both White and Black patients maintained the improvement achieved at baseline from screening, or showed an improvement from baseline. Mean in-clinic PEFr did not change from baseline among White placebo-treated patients, but increased from baseline in all other treatment groups. No consistent pattern for in-clinic PEFr was observed in Black or Hispanic patients.

In patients who received prior steroids, the placebo group showed a mean decrease from baseline after 12 weeks of treatment for percent predicted FEV₁ and PEFr, whereas HFA and CFC flunisolide treatment groups maintained the improvement in asthma control from baseline. In patients who did not have a prior history of steroid use, mean increases from baseline for PEFr were observed in the placebo group after 12 weeks of treatment, however, increases in the HFA flunisolide group were greater than the mean increase observed with placebo. A mean decrease from baseline after 12 weeks treatment for FEV₁ was observed in the no prior steroid placebo group, whereas the HFA and CFC flunisolide treatment groups demonstrated increases from baseline.

3.7 REVIEWER COMMENTS ON EFFICACY

This study demonstrated statistically significant superiority of the 170µg BID doses of HFA flunisolide over placebo on the primary endpoint in 6-11 year old patients with mild to moderate asthma, change from baseline in percent predicted FEV₁ after 12 weeks treatment. The study also demonstrated statistically significant superiority of 85µg BID dose of HFA flunisolide vs. placebo in percent predicted FEV₁. However, it should be noted that these results show less than a 5% difference as planned in the power analysis. It is difficult to determine whether this observed effect size has clinical meaning. Information about actual FEV₁ change from baseline after 12 weeks was not evaluated in this trial, and even if it were, the clinical relevance of the magnitude of this change would vary by the age (height) of the child. Further, no dose response relationship was demonstrated in the HFA flunisolide groups for 6-11 year old patients.

Secondary endpoints do not provide strong evidence of efficacy in 4-11 year old patients with mild to moderate asthma. Numeric differences in change from baseline for in-clinic PEFr favored HFA and CFC flunisolide patients after 12 weeks of treatment, but were not statistically significant in either the 4-11 year old patients or 6-11 year old patients. No clear treatment difference, for either the HFA or CFC formulations, was observed in 4-11 year old patients in any diary parameter, including AM and PM asthma symptoms, total daily asthma symptom, AM and PM PEFr, prn

albuterol use, and nocturnal awakenings, and changes from baseline for all treatment groups for all diary parameters were small. It should also be noted that the 85µg dose of HFA flunisolide had numerically superior results in some secondary efficacy parameters when compared to the 170µg dose of HFA flunisolide and placebo (AM, PM and total daily asthma symptom scores). Further, when assessing dropouts due to ineffective therapy or asthma exacerbation, 85µg BID dose of HFA flunisolide was numerically superior to both placebo and 170µg HFA flunisolide.

Based on the efficacy results of this one pediatric study, there is no clear evidence that 170 µg HFA flunisolide confers any additional benefit over 85 µg HFA flunisolide doses.

Both 250 µg BID CFC flunisolide and 500µg BID CFC flunisolide doses were significantly superior to placebo for the primary efficacy parameter. It should be further noted that only the 500µg BID CFC flunisolide formulation achieved the 5% difference after 12 weeks for the primary efficacy variable formulations that was used to power the study (6.64% difference in change from baseline for CFC flunisolide compared with placebo). There was an apparent dose-response relationship across the placebo, 250 and 500 mcg CFC flunisolide groups, but no dose response relationship was established across the 85 and 170 mcg HFA flunisolide groups.

The difference between HFA and CFC flunisolide treatment groups was not statistically significant for any of the efficacy parameters. Efficacy in both doses of HFA flunisolide was similar, overall, in the subgroup analyses by age, gender, and ethnic group, as well as in prior steroid exposed and prior non-steroid exposed subgroups.

No support of efficacy was seen for either HFA or CFC formulations in the 4-5 year old subset of patients.

3.8 SAFETY REVIEW

3.8.1 Patient exposure

583 patients age 4-11 were exposed to double-blind medication during the treatment phase of the study for an average duration of 76.6 ± 21.6 days; the median for all five treatment groups was 84 days. The mean duration of exposure to study drug was lowest in the placebo group (72.7 days). This which may reflect early dropouts due to insufficient therapeutic effect, however, there were no significant differences among treatment groups. (Table 3.8.1; applicant's in-text table 27, vol. 67). Mean extent of exposure in the 6-11 and 4-5 year subsets were comparable to the overall population.

Table 3.8.1 Treatment Duration^a (Days): Safety Population Patients 4-11 Years of Age

	Placebo (n = 116)	HFA Flunisolide		CFC Flunisolide		Total (n = 583)	p-Value ^b
		85 µg bid (n = 114)	170 µg bid (n = 117)	250 µg bid (n = 123)	500 µg bid (n = 113)		
Mean	72.7	76.2	78.2	79.1	76.5	76.6	0.097
SD	25.96	22.06	18.20	19.88	21.23	21.64	
Median	84.0	84.0	84.0	84.0	84.0	84.0	
Range	1-98	1-98	12-108	1-113	8-112	1-113	

^a Duration = number of days treated during the double-blind phase

^b p-Value based on Kruskal-Wallis test across all five treatments.

Cross-reference: After-text Table 1.5.2

3.8.2 Treatment Emergent Adverse Events (TEAE)

78 (67.2%) of patients in the placebo group, 162 (70.1%) of patients in the pooled HFA flunisolide groups, and 165 (69%) of patients in the pooled CFC flunisolide groups reported at least one TEAE by body system. The incidence of TEAEs by body system were similar in the 6-11 year old subgroup to the overall 4-11 year old population. In the 4-5 year old subset, the incidence of TEAEs by body system were higher in the placebo group (72.2%) than in the 85µg BID HFA flunisolide (33.3%), 170µg BID µg BID HFA flunisolide (66.7%), 250µg BID CFC flunisolide (69.2%), or 500µg BID CFC flunisolide group (66.7%).

The most common TEAEs (>10%) inpatients receiving flunisolide formulation were pharyngitis, rhinitis and headache. Asthma was reported as a TEAE in 14.7%, 10.0%, and 11% of patients in the placebo, pooled HFA flunisolide and CFC flunisolide groups, respectively. It should be noted, however that rates of pharyngitis, rhinitis, headache, sinusitis, vomiting, bacterial infection, pain, and epistaxis exceeded both the placebo and 85µg BID HFA flunisolide groups (table 3.8.2A; applicant's in-text table 31).

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3.8.2A TEAEs Reported by $\geq 3\%$ of all Safety Patients: number (%) of Patients

<i>Preferred Term</i>	<i>Placebo</i>	<i>HFA flunisolide pooled^b</i>	<i>CFC flunisolide pooled^b</i>
	<i>(N=116)</i>	<i>(n=231)</i>	<i>(n=236)</i>
One or more ^c	78 (67.2)	162 (70.1)	165 (69.9)
Pharyngitis	19 (16.4)	44 (19.0)	39 (16.5)
Rhinitis	17 (14.7)	37 (16.0)	34 (14.4)
Headache	11 (9.5)	30 (13.0)	35 (14.8)
Cough Increased	9 (7.8)	23 (10.0)	30 (12.7)
Asthma	17 (14.7)	23 (10.0)	26 (11.0)
Fever	10 (8.6)	19 (8.2)	19 (8.1)
Sinusitis	7 (6.0)	19 (8.2)	10 (4.2)
Viral Infection	15 (12.9)	15 (6.5)	23 (9.7)
Vomiting	6 (5.2)	15 (6.5)	10 (4.2)
Otitis Media	9 (7.8)	10 (4.3)	11 (4.7)
Rash	4 (3.4)	9 (3.9)	13 (5.5)
Bacterial Infection	2 (1.7)	8 (3.5)	6 (2.5)
Pain	1 (0.9)	8 (3.5)	8 (3.4)
Accidental Injury	1 (0.9)	7 (3.0)	11 (4.7)
Epistaxis	2 (1.7)	6 (2.6)	1 (0.4)

^a Patients are counted once for each adverse event.

^b Frequency $> 3\%$ in any one dose group. Dose groups for each formulation are pooled.

^c "One or more" includes the number of patients who reported at least one TEAE.

Cross-reference: After-text Table 5.1.

There did not appear to be a dose dependant increase in the incidence of TEAEs among HFA treatment groups. It is noted that pharyngitis, rhinitis, headache, increased cough, sinusitis, vomiting, pain, accidental injury, and epistaxis all occurred in the HFA flunisolide groups at higher rates than placebo. Pharyngitis, rhinitis, sinusitis, vomiting, bacterial infection, pain and epistaxis also occurred at higher rates in the pooled HFA flunisolide groups than in the CFC flunisolide groups. TEAEs that occurred at an incidence of $\geq 5\%$ in one or more HFA dose groups and at a frequency of twice more than placebo included bacterial infection (6.1% in the 85 μg BID HFA dose group), epistaxis (5.3% in the 85 μg BID HFA dose group) and pain (5.1% in the 170 μg BID HFA dose group).

Overall, asthma as an AE was reported less frequently in the pooled HFA flunisolide group than in either the placebo or pooled CFC flunisolide groups. Asthma as an AE was reported most frequently in the placebo group (14.7%), followed by the 170 μg BID HFA group (10.3%), and the 85 μg BID HFA group (9.6%). (table 3.8.2B; applicant's in-text table 32, vol. 67).

Table 3.8.2B TEAEs Reported by > 3% of all Patients: HFA Flunisolide vs. Placebo: Number (%) of Safety Patients

<i>Body System</i>	<i>Placebo</i>	<i>HFA Flunisolide 85 µg bid</i>	<i>HFA flunisolide 170 µg bid</i>
	<i>(n=116)</i>	<i>(n=114)</i>	<i>(n=117)</i>
BODY AS A WHOLE			
Abdominal Pain	4 (3.4%)	4 (3.5%)	5 (4.3%)
Accidental Injury	1 (0.9%)	2 (1.8%)	5 (4.3%)
Fever	10 (8.6%)	11 (9.6%)	8 (6.8%)
Headache	11 (9.5%)	11 (9.6%)	19 (16.2%)
Infection Bacterial	2 (1.7%)	7 (6.1%)	1 (0.9%)
Pain	1 (0.9%)	2 (1.8%)	6 (5.1%)
Viral Infection	15 (12.9%)	7 (6.1%)	8 (6.8%)
DIGESTIVE SYSTEM			
Diarrhea	1 (0.9%)	2 (1.8%)	5 (4.3%)
Nausea	1 (0.9%)	4 (3.5%)	4 (3.4%)
Vomiting	6 (5.2%)	6 (5.3%)	9 (7.7%)
RESPIRATORY SYSTEM			
Asthma	17 (14.7%)	11 (9.6%)	12 (10.3%)
Cough Increased	9 (7.8%)	12 (10.5%)	11 (9.4%)
Epistaxis	2 (1.7%)	6 (5.3%)	0 (0.0%)
Laryngitis	0 (0.0%)	4 (3.5%)	0 (0.0%)
Pharyngitis	19 (16.4%)	22 (19.3%)	22 (18.8%)
Rhinitis	17 (14.7%)	13 (11.4%)	24 (20.5%)
Sinusitis	7 (6.0%)	12 (10.5%)	7 (6.0%)
SKIN AND APPENDAGES			
Rash	4 (3.4%)	4 (3.5%)	5 (4.3%)
SPECIAL SENSES			
Otitis Media	9 (7.8%)	5 (4.4%)	5 (4.3%)

*Patients are counted once for each preferred term.
Cross-reference: After-text Table 5.1.3 PCT.

Overall, mild or moderate TEAEs were most frequently reported (63%) in all treatment groups. Severe TEAEs were reported by 36 (6.2%) of patients overall, with 8.6%, 5.6%, and 5.5% in the placebo, pooled HFA flunisolide, pooled CFC flunisolide groups, respectively. The most frequently reported severe TEAE was asthma, reported as 5% in the placebo group, 1% in the 85µg BID HFA, 4% in the 170µg BID HFA, 5% in the 250 µg BID CFC, and 1% in the 500 µg BID CFC groups respectively.

3.8.3 Treatment Discontinuation due to Adverse Events (AEs)

Overall, no single adverse event lead to an increased rate of discontinuation in any of the HFA or CFC flunisolide groups compared to placebo. More patients discontinued due to an AE in the placebo group (12%) than in the pooled HFA (10%) or CFC (7.6) flunisolide groups. The most common adverse event leading to discontinuation in > 1% of patients was asthma, which was highest in the placebo group (13 patients, 11.2%), followed by the pooled HFA flunisolide group (7.8%) and then the CFC flunisolide group (6.3%). Zero placebo patients discontinued due to pharyngitis but 1.7% and 1.3% discontinued in the pooled HFA and CFC flunisolide groups, respectively (table 3.8.3; applicant’s in-text table 35, vol. 67).

Table 3.8.3 Adverse Events (> 1%) Resulting in Discontinuations of Treatment in Double – Blind Treatment Phase

<i>Adverse Event</i>	<i>No. (%) of Patients</i>		
	<i>Placebo (n = 116)</i>	<i>HFA Flunisolide Pooled (n = 231)</i>	<i>CFC Flunisolide Pooled (n = 236)</i>
<i>Preferred term</i>			
One or more^a	14 (12.1%)	23 (10.0%)	18 (7.6%)
Asthma	13 (11.2%)	18 (7.8%)	15 (6.3%)
Pharyngitis	0	4 (1.7%)	3 (1.3%)

^a“One or more” includes any patients for whom treatment was discontinued for one or more adverse event. Patients are counted once for “one or more” adverse events and once for each adverse event.
Cross-Reference: After-text Table 5.1 ADO.

The incidence of AEs leading to patient discontinuation is similar in the 4-5 year old and 6-11 year old patient subsets to the overall 4-11 year old population. 6 patients discontinued due to an AE in the 4-5 year old subset, including 2 in the placebo group, 1 in the HFA flunisolide group and 3 in the CFC flunisolide group. None of these events were considered SAEs, but included 4 cases of asthma exacerbation, 2 viral infections, and 1 case each of fever and rhinitis.

3.8.4 Serious Adverse events (SAEs) and Deaths

There were no deaths in this trial. Seven 6-11 year old patients experienced SAEs during the double blind phase of the study, with only 1 patient having received HFA study treatment, as follows:

- ◆ Asthma exacerbation and hypoxia in an 8 year old white male randomized to placebo, eight weeks after beginning study drug
- ◆ Asthma exacerbation in a 7 year old black female, randomized to 170 µg BID HFA flunisolide, 7 weeks after beginning study drug

- ◆ Viral respiratory infection in a 10 year old white female, randomized to placebo, 9 days after beginning study drug. Although this patient was not coded as having had an asthma exacerbation, she was treated with oral and IV corticosteroids
- ◆ Infection, requiring appendectomy in an 8 year old white female, randomized to 250 µg BID CFC flunisolide, 8 weeks after beginning treatment with study drug
- ◆ Otitis media with elective tonsillectomy, adenoidectomy, and bilateral placement of tympanostomy tubes in a 6 year of white female, randomized to 250 µg BID CFC flunisolide. Study medication was never discontinued during the trial.
- ◆ Asthma exacerbation in an 11 year old white female, randomized to placebo, 10 weeks after beginning study drug

One patient, a 6 year old male, experienced an asthma exacerbation during the run-in phase and was not randomized. There were no SAEs in the 4-5 year old patient subset. A total of four patients discontinued from the study due to these adverse events. It is notable that 2 SAEs, (possibly 3) due to asthma occurred in the placebo group, whereas 1 SAE due to asthma occurred in the HFA patient group, and no SAEs due to asthma occurred in the CFC patient group.

Fourteen patients withdrew from the trial during the single blind, 2 week run-in phase, where all patients were being treated with 500 µg BID CFC flunisolide. 5 of these patients discontinued secondary to asthma exacerbation.

3.8.5 Clinical Laboratory Evaluations

Mean hematology values at Visit 1 and 6, as well as change from screening to Visit 6 for all hematology parameters were comparable among all treatment groups in the 4-11 year old population, as well as the 6-11 and 4-11 year old subset. None of these changes from screening were clinically important, and may be considered part of normal variation. The incidence of potentially clinically significant (PCS) abnormal hematology values was very low (0-2%) and was similar across treatment groups. Individual patient findings of PCS were considered clinically important.

Mean chemistry values at screening and at Visit 6, as well as change from screening to Visit 6 for all chemistry parameters were comparable among all treatment groups. None of these changes were considered clinically important, and there were no differences in the change from screening values among the five treatment groups. The most commonly reported individual patient abnormalities coded as potentially clinically significant were high serum triglycerides (16.5%, 16.7%, 12.8%, 19.6%, and 6.6%, in the placebo, 85 µg BID HFA flunisolide, 170 µg BID HFA flunisolide, 250 µg BID CFC flunisolide, and 500µg BID CFC flunisolide groups, respectively), and high cholesterol (6.0%, 9.0%, 3.9%, 3.6%, and 6.4%, in the placebo, 85 µg HFA flunisolide, 170 µg HFA BID flunisolide, 250 µg BID CFC flunisolide, and 500 µg BID CFC flunisolide groups, respectively).

There were no differences in mean urinalysis values at screening and at Visit 6, as well as change from screening to Visit 6, among the 5 treatment groups. There were no PCS abnormal urine tests.

3.8.6 Vital Signs

Vital sign parameter at baseline as well as change from baseline to week 12 (LOCF) for all parameters except temperature were similar among treatment groups in the 4-11 year old population as well as the 6-11 and 4-11 year old subsets. None of these changes from screening were . Mean change from baseline to week 12 (LOCF) ranged from a decrease of 0.1⁰F in the 500 µg BID CFC flunisolide group to an increase of 0.3⁰F in the 250 µg BID CFC flunisolide group. The between group difference was statistically significant (p=0.002) but was not considered clinically important.

There were no clinically important differences in the incidences of OCS vital sign values for systolic BP, diastolic BP, and pulse among the treatment groups and none of the individual patient findings were considered clinically important.

3.8.7 Electrocardiograms (ECGs)

The Final Study report states that there were no differences between treatment groups in the number of patients with abnormal ECGs at endpoint, or clinically significant changes since visit 1. However, a review of After-text table 5.8.6 and the individual patient listings of ECGs in Appendix 9 revealed that 1 patient in the 170 µg HFA BID flunisolide group who was normal at screening, changed to abnormal (borderline prolonged QT) at endpoint). The relevance of this finding to study drug is unclear.

3.8.8 Physical Examination (PE)

The number of patients with PE transitions from normal at baseline to abnormal at endpoint was most frequently reported in the Eyes, Ears, Nose and throat and Pulmonary body systems. The highest percentages of PE transitions overall occurred in the 250 µg BID CFC flunisolide group (15.5%, 18.4%, 17.1%, 28.5%, and 11.5%, reported in the placebo, 85 µg HFA flunisolide, 170 µg HFA BID flunisolide, 250 µg BID CFC flunisolide, and 500 µg BID CFC flunisolide groups, respectively). The incidence of these PE transitions was similar in the 6-11 and 4-5 year old subsets, as to the 4-11 year old overall population.

3.8.9 Lung Examination

Lung examination was performed at every study visit. The incidences of abnormal lung function at baseline, and transition from normal to abnormal were comparable among the treatment groups. There were no between group differences after 12 weeks treatment, however, it should be noted that in looking at shift from normal to abnormal change from baseline at 12 weeks, the placebo group was higher (11.5%) than either HFA group (8.7%, 8.7%), and that the CFC groups were highest (13.2%, 13.2%).

3.8.10 Plasma cortisol after Cortrosyn stimulation

The plasma cortisol levels in all HFA and CFC flunisolide groups were generally stimulated to the same extent at 30 and 60 minutes as the placebo groups, at both baseline and at the end of the study, as measured by mean plasma cortisol. At baseline, the placebo group had the highest mean change at both 30 and 60 minutes from pre-Cortrosyn stimulation, possibly reflecting the fact that this group also had the lowest history of prior steroid exposure at screening. By the end of the study, however, mean change from baseline was comparable among all study groups.

The percentage of patients who were responders at baseline and changed to non-responders at the end of the study was similar among treatment groups (table 3.6.10A; applicant's in-text Table 44, vol.67).

Table 3.8.10A Nonresponders^a to Cortrosyn Stimulation Test Results: Percent (number) of Patients

Time Point	Placebo	HFA 85 µg	HFA 170 µg	CFC 250 µg	CFC 500 µg
Baseline ^b	2.4 (1/41)	10.9 (5/46)	11.6 (5/43)	15.2 (7/46)	17.5 (7/40)
End of Study ^b	10.7 (3/28)	10.5 (4/38)	8.6 (3/35)	14.3 (5/35)	3.7 (1/27)
New Non-responders at End of Study ^c	7.5 (3/40)	7.3 (3/41)	2.6 (1/38)	10.3 (4/39)	3.0 (1/33)

^a Non-responder = a patient who does not have an increase in plasma cortisol ≥ 7 µg/dL or does not have an absolute value ≥ 18 µg/dL after cortrosyn injection.

^b Percentages are based on the no. of patients with post-Cortrosyn stimulation test results at respective time point.

^c Non-responders at week 12, who were responders at baseline. Percentages are based on number of responders at baseline.

Cross-reference: After-text Table 5.11.1 and Table 5.11.2.

Cortisol values at each time point, and change from baseline in cortisol values at each time point, in the 6-11 subset of patients were similar to the overall population. In the 4-5 year old subset, there was wider variability in the mean and mean change from pre-dosing values, than in either the

overall 4-11 year old population, or the 6-11 year old subset, however, there were very few patients in this subset who had this variable assessed (1 patient in the placebo group, 3 patients in each HFA group, 6 patient in the 250µg BID CFC flunisolide and 1 patient in the 500µg BID CFC flunisolide).

If one assesses the simple change from baseline to end of study in non-responders to Cortrosyn stimulation (Table 3.8.10B), placebo group patients had the highest number of non-responders overall.

Table 3.8.10B Change from Baseline to End of Study in Non-responders to Cortrosyn Stimulation Test: Percent of Patients

Delta ^a	Placebo	HFA 85 µg	HFA 170 µg	CFC 250 µg	CFC 500µg
	8.3	-0.4	-3.0	-0.9	-13.8

^a Delta is defined as percent of non-responder patients at the end of the study minus percentage of non-responder patients at baseline

3.8.11 Mouth/Throat cultures for *Candida Albicans*

The incidence of tests newly positive for yeast was higher in all active treatment groups than placebo, after 12 weeks treatment. Four cases of clinical oral moniliasis were reported at Visit 6, with none reported in the placebo group: 2 (1.8%) in the HFA85µg group, 1(0.8%) in the CFC 250µg group, and 1(0.8%) in the CFC 500µg group.

3.9 REVIEWER'S COMMENTS ON SAFETY

In general, treatment with HFA flunisolide resulted in a safety profile similar to treatment with CFC flunisolide or placebo. The most commonly reported TEAEs were pharyngitis, rhinitis and headache, which were reported at a somewhat higher rate than placebo. Incidence of abnormal safety results including chemistries, hematology, and vital signs were low and similar among treatment groups. There were no clear clinically relevant safety findings from ECGs or PE for the HFA flunisolide groups, compared with placebo. There was an increased incidence of new positive yeast infections in both HFA and CFC flunisolide groups, as compared to placebo, however, this is not unexpected for this class of drug and will need to be addressed in labeling. Pre- and post-cortrosyn stimulation plasma cortisol levels did not demonstrate cortisol suppression as compared to placebo, however, past experience has shown that timed urinary cortisol may be a more sensitive safety parameter for adrenal suppression, and this was not assessed in this trial. There were too few 4-5 year old patients who had any HPA axis assessments to determine whether HFA flunisolide had any effects in this subgroup.

There were no deaths in this study. For the HFA flunisolide groups, there did not appear to be a dose-dependant increase in the frequency of reported TEAEs. TEAEs that occurred at an incidence of $\geq 5\%$ in one or more HFA dose groups and at a frequency of twice more than placebo included bacterial infection (6.1% in the 85 μg BID HFA dose group), epistaxis (5.3% in the 85 μg BID HFA dose group) and pain (5.1% in the 170 μg BID HFA dose group).

Overall, a larger percentage of patients discontinued due to adverse events in the placebo group, than from the pooled HFA or CFC flunisolide groups. Asthma was the most frequently reported TEAE that resulted in discontinuation from the study, and it occurred most frequently in the placebo group (11.2% vs. 7.8% and 6.3% in the pooled HFA flunisolide and CFC flunisolide groups, respectively).

4.0 120-DAY SAFETY UPDATE and ANNUAL REPORT to IND 51, 456

Full Study Reports for two long-term clinical safety studies, ANC-MD-02 and ANC-MD-04, were submitted, along with an updated Integrated Summary of Safety and a synopsis for another clinical study ANC-MD-05-000, "A Taste Perception Evaluation of Methods of Delivery of Flunisolide in Adult Asthma Patients." SAE and ADO data prior to May 1, 2000 from studies ANC-MD-07 and ANC-MD-08 were provided. Review of the two long-term safety studies follow in Sections 5.0 and 6.0. Additional safety information for clinically complete and ongoing clinical studies was also provided with the Annual Report submitted to IND 51, 456 on 10/25/00. Synopses of these reports from these additional studies follow below.

4.1 Other Studies

Study ANC-MD-05, a four-way assessor blinded crossover study which included 52 stable adult asthmatic patients 18-67 years of age, treated with a single 2 puff dose of either Aerobid M, Aerobid M with Aerochamber, HFA flunisolide, or HFA, placebo, will not receive detailed Medical Officer review. The objective of this study was to evaluate the taste characteristics of three different systems for the delivery of flunisolide: Aerobid-M, Aerobid M with Aerochamber, and Flunisolide HFA Inhaler system, compared to placebo. Adverse events, SAEs, deaths, and discontinuations due to AEs were the only safety data collected during this study. No deaths or SAEs were reported. AEs were reported by 11 patients, including headache (5 patients), nausea (2 patients), infection, glossitis, dizziness, nervousness, and dyspnea, each reported by 1 patient. No patient discontinued due to an adverse event.

HFA flunisolide treatment had the highest number of patients with at least one AE (4 patients, which was twice the rate seen in the Aerobid M (without Aerochamber) and the HFA placebo groups. Headache was reported by 3 patients with HFA flunisolide treatment (highest number among treatment groups), whereas glossitis, nausea and dyspnea, and infection were reported by no patient with HFA flunisolide treatment. Nervousness was reported by one patient with HFA flunisolide treatment.

Overall, ANC-MD-05 adds modest information to the HFA flunisolide database, and supports general safety and tolerability of a single dose of 170 µg HFA flunisolide in adult asthma patients.

_____ is an ongoing, : _____

_____ Analyses are on-going and not included in the NDA 120-day Safety Update or Annual report to the IND.

5.0 STUDY ANC-MD-02 ((vol. 4.1 et seq)

Initiation Date: June 25, 1998

Completion Date: October 12, 1999

RÉSUMÉ

This was a 1-year, open label, active controlled, flexible-dose safety study, in 215 randomized adult and adolescent mild-moderate asthmatic patients age 12-62 years. It included patients with a history of leukotriene antagonist, nedocromil, cromolyn, or orally inhaled corticosteroid at a stable dose for a minimum of 30 days prior to enrollment, or patients with a history of asthma symptoms requiring the use of an inhaled β-agonist at least 3 times a week, FEV₁ ≥ 60% of predicted prior to inhalation of albuterol, or an ability to demonstrate FEV₁ increase of ≥ 12% after inhalation of albuterol at or within 12 months prior to enrollment. Non-smoking, non-pregnant, enrolled patients entered into a 1-week run-in period, during which time they continued their usual stable dose of asthma controller medication and prn albuterol. Eligible patients then entered into the 52 week open-label phase of the study, in which they were assigned to receive either HFA flunisolide (85µg/puff) or beclomethasone (84µg/puff) in a 3:1, HFA flunisolide: beclomethasone randomization scheme, at a dosage of 2-4 puffs, depending on prior treatment history. The investigator could increase or decrease the dose of study medication, as necessary,

per protocol pre-specified criteria during the next 52 weeks. A beclomethasone dose range of three – eight puffs daily (252 µg - 672 µg total daily dose) and an HFA flunisolide dose range of two – eight puffs (170 µg - 680 µg total daily dose) were allowed by the protocol. The protocol does not specify whether patients were permitted to use a spacer in the beclomethasone treatment arm.

The primary objective of the study was to evaluate the safety of HFA Flunisolide Inhaler System over a 1-year course of treatment, as compared to beclomethasone treatment. Secondary objectives of the study included evaluation for maintenance of pulmonary function across treatment groups

TEAE frequency was comparable, but slightly higher for patients treated with HFA flunisolide (82.7%) compared with patients treated with beclomethasone (81.1%). It is noteworthy that patient discontinuation due to AEs occurred at twice the rate in the HFA flunisolide group (12 patients, 7.4%) as compared to patients treated with beclomethasone (2 patients, 3.8%), however, absence of a placebo control group, small sample size and unbalanced randomization makes it difficult to interpret the meaning of this result. AEs most frequently resulting in discontinuation in the HFA flunisolide group were taste perversion (5 patients, 3.1%) and asthma exacerbation (3 patients, 1.9%). Accidental injury, allergic reaction, increased cough, dyspepsia, taste perversion and dizziness occurred in ≥ 3% of the population and at ≥ twice the rate in the HFA flunisolide group, as compared to the beclomethasone group.

The percentages of patients who discontinued from the study due to asthma exacerbation or insufficient therapeutic effect were low in both treatment groups (<5%), but slightly higher in the HFA flunisolide group as compared to beclomethasone (4.3% vs. 3.8%, respectively).

No patient died in this study. SAEs were reported for 3 patients in the HFA flunisolide group (asthma in two patients, and GI disorder/hemorrhage in 1 patient) compared with 2 SAEs in the beclomethasone group (1 patient with asthma, 1 patient with migraine).

More patients experienced weight gain (18.3% vs. 11.6%, HFA flunisolide vs. beclomethasone, respectively), in the HFA flunisolide group (mean change at the end of the study 2.5 ± 9.1 lbs), as compared with beclomethasone (mean change at the end of the study -0.7lbs ± 12.0). Two patients in the HFA flunisolide group shifted from normal ECGs at baseline, to clinically significant ECG changes at the end of the study (WPW in one patient and prolonged QT interval with normal QT_c in the other), whereas no patients in the beclomethasone group had clinically significant ECGs at either baseline or at the end of the study.

HPA axis assessments were performed on 136 patients at 15 sites. These patients were not randomized by prior steroid exposure history, a design flaw that together with unequal randomization between groups, limits data interpretability. 24-hour urinary cortisol excretion

and plasma cortisol levels at 30 minutes and 60 minutes following Cortrosyn stimulation showed no clear evidence of cortisol suppression in either the HFA flunisolide or beclomethasone groups. However, the percentages of patients who changed from responder to non-responder following Cortrosyn stimulation were slightly higher in the HFA flunisolide group (9.1% vs. 7.4%).

The incidence of clinical thrush was higher in the beclomethasone group than in the HFA flunisolide group (9.4% vs. 1.2 %). It is not known whether patients in the beclomethasone group used a spacer when delivering their dose of study medication.

Most patients had no exacerbations of asthma (72% of HFA flunisolide patients vs. 69.8% beclomethasone patients) and no study patient had 4 or more asthma exacerbations during the 52 weeks of this trial. The greatest incidence of first asthma exacerbation for the HFA flunisolide group occurred between Week 4 and 8, and the greatest incidence of first asthma exacerbation for the beclomethasone group occurred between Week 8 and 16. Since this trial assessed maintenance of well controlled asthma following a run-in period, this may be a signal of weaker efficacy as compared with beclomethasone, in range the doses used by patients in this trial.

It is noteworthy that compliance was not fully evaluated in this trial. Non-compliance was a reason for study termination, defined as being off study medication for 14 days. However, procedural assessment for non-compliance was not described in the protocol. HFA flunisolide was associated with taste perversion, whereas beclomethasone did not have this association. It is possible that if HFA flunisolide has a bad taste, there may have been lower patient compliance in that group, as compared to beclomethasone.

Efficacy analyses were performed on all randomized patients who received at least one dose of study medication and who had at least one follow-up visit. Pulmonary function as measured by percent predicted FEV₁, PEFR, prn albuterol use, asthma symptoms, and number of nocturnal awakenings due to asthma requiring albuterol over the 52 week was generally well maintained in the beclomethasone group. However, in the HFA Flunisolide group, % predicted FEV₁ declined very slightly from baseline at the end of the study (-0.7% ± 10.5), but without decline in actual FEV₁, decline in AM PEFR, and without increase in mean daily prn asthma use, asthma symptom score, or nocturnal awakenings. It is unlikely that this very slight decline without other signals of HFA flunisolide loss of efficacy at the end of the study has clear clinical relevance, however, it is noted there was no placebo group in this study and the trial was not powered to assess efficacy.

Overall, this flawed study demonstrated a 1 year HFA flunisolide safety profile consistent with this class of medication, without a clear signal for loss of efficacy, for mild to moderate asthma in adults and adolescent patients ≥ 12 years of age. Other long-term glucocorticoid class effects were not addressed in this study (effects on bone density and development of cataracts and glaucoma).

5.1 STUDY DESCRIPTION

DESIGN: Multi-center, randomized, open-label, active controlled, flexible dose, 1-year, safety study comparing HFA flunisolide (85µg/puff) at BID doses of 170µg - 340µg, and beclomethasone dipropionate (84µg/puff) at daily doses of 252 µg –672 µg.

POPULATION: 200 mild to moderate, asthmatic patients 12-60 years of age.

MATERIALS: HFA Flunisolide Inhaler System (85µg/puff); Beclomethasone dipropionate Oral Inhaler (Vanceril DS 84µg/puff); Albuterol Oral Inhaler (Proventil 90µg/puff); Mini-Wright Peak Flow Meter. The protocol specifies no spacer or holding chamber, but does not indicate whether use of a spacer or holding chamber was prohibited in the study for either albuterol or beclomethasone. HFA Flunisolide System has a built-in Bepak spacer.

OBJECTIVES: Primary - to evaluate safety of HFA flunisolide hemihydrate over a 1 year period weeks in adult and adolescent mild-moderate asthmatic patients in comparison to beclomethasone treatment. Primary parameters for safety evaluation included AEs, physical examination, vital signs, ECGs, laboratory assessments of hematology, chemistry, U/A, mouth and throat smear and cultures, 24-hour urinary cortisol excretion, and response to Cortrosyn stimulation. **Secondary** – to evaluate efficacy of HFA flunisolide in patients transferred from prior inhaled anti-inflammatory therapy to HFA flunisolide compared to inhaled beclomethasone dipropionate using the following parameters: percent predicted FEV₁, as-needed inhaled β-agonist use, AM and PM peak expiratory flow rate (PEFR), daily asthma symptom scores, nocturnal awakenings requiring albuterol use, frequency of asthma exacerbation, number of asthma exacerbations, time to first asthma exacerbation and time to dropout due to asthma exacerbation or insufficient therapeutic effect.

CRITERIA: non-smoking, non-pregnant/non-lactating, women and men with a history of orally inhaled corticosteroid, nedocromil, cromolyn, or leukotriene antagonist use at stable doses for 30 days prior to Visit 1, or asthma symptoms requiring the use of a short acting β-agonist ≥ 3 times a week. The maximum allowed daily dose for flunisolide was 8 puffs; for triamcinolone, 10 puffs; for beclomethasone, 16 puffs; for fluticasone, 6 puffs; and for budesonide 3 puffs. FEV₁ had to be ≥ 60% of predicted prior to inhalation of 2 puffs of albuterol and abstaining from the use of protocol specified medications for certain periods of time prior to enrollment, with demonstration of reversible bronchoconstriction (≥ 12% increase in FEV₁ following 2 puffs of albuterol). Eligibility for randomization included the best pre-bronchodilator FEV₁ ≥ 90% of the best prebronchodilator FEV₁ at Visit 1, with mean daily asthma symptom score ≤ 2.5 and mean total albuterol intake ≤ 6 puffs over the 7 day period prior to randomization.

CONDUCT: Patients first entered a 1-week run-in phase, in which they received their usual dose of inhaled asthma controller medication and prn albuterol. For those patients in Study ANC-MD-01, the last week of that study was considered the run-in period for this study. Patients then entered the 52-week open label phase, using a 3:1 HFA flunisolide: beclomethasone randomization scheme, and returned to clinic for evaluation at weeks 4, 8, 16, 26, 39, 45, and 52. Patients randomly assigned to receive either open label HFA flunisolide or beclomethasone were each initiated at a dose of 2 or 4 puffs bid, depending upon prior therapy. The investigator could increase or decrease the dose of study medication, based on protocol-defined criteria, during the 52 week study period. All patients were instructed to take their study medication at specified times during the day, and on the day of a study visit, to withhold their morning dose of their medication and withhold use of albuterol at least 6 hours prior to the visit.

Physical examination, hematology, chemistry, U/A, and mouth and throat culture, were assessed at screening and at weeks 26 and 52. Vital signs and lung auscultation, and adverse events were assessed at all visits and diary cards were dispensed at all visits except at the final visit. Spirometry was performed at screening, baseline, and weeks 4, 8, 26, 45 and 52. A 12 lead ECG was performed at the first visit (screening visit, week-1)) and final visit (Week 52).

At selected sites, HPA axis effects were assessed baseline (week 2), and at weeks 26 and 52 by measuring 24-hour urinary free cortisol and effects of Cortrosyn stimulation on plasma cortisol. A normal response for the Cortrosyn stimulation test required a plasma cortisol increment of at least 7 mcg/100mL above the control value within 60 minutes after Cortrosyn administration and an absolute plasma cortisol value \geq 18 mcg/ 100mL within 60 minutes.

DATA ANALYSIS: All hypothesis tests were conducted using the two-sided 0.05 level of significance. Hypothesis tests were used to compare demographics, asthma history and baseline efficacy parameters, only. All safety analyses were done on the safety population, which was defined as all randomized patients who received at least one dose of study drug. Descriptive statistics were presented for the safety population at baseline (Week 0) and comparisons between treatment groups were performed using the Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables.

Adverse events were presented by body system and treatment group, as well as severity and relationship to study drug. Physical exam, lung exam and vital signs at each study visit and change from baseline were summarized for each treatment group. The results of ECG, mouth and throat smear and cultures were reported as normal, abnormal, not clinically significant, and abnormal, clinically significant, and tabulated by treatment group. Descriptive statistics for baseline, 30 minute, 60 minute, and 30 and 60 minute differences from baseline were presented for Cortrosyn stimulation tests. The rates of normal response of patients at 30 and 60 minutes at the visit were also tabulated. Descriptive statistics for baseline, Visit 6, Visit 8 and differences for each of the groups were presented.

All efficacy analyses were done of the ITT population, defined as all randomized patients who received at least one dose of study drug and had at least one follow-up assessment of FEV₁. Missing data was imputed by the LOCF. The actual value and change from baseline at each

follow-up visit post-randomization in percent predicted FEV₁, actual FEV₁, mean daily prn albuterol use, mean daily asthma symptom scores, mean PEF_R, and mean number of nocturnal awakenings due to asthma requiring albuterol was summarized for both treatment groups. The number of asthma exacerbations was tabulated by treatment group, and Kaplan-Meier estimates of survival function were generated for time to first exacerbation and time to discontinuation for lack of efficacy.

5.2 PATIENT DISPOSITION

230 patients enrolled at 24 investigator sites, and 215 were randomized (2 withdrew due to AEs/intercurrent illness, 2 withdrew consent, 9 did not meet randomization criteria, 2 withdrew for “other” reasons. 215 were included in the safety analyses, however, 4 (3.7%) patients in the HFA flunisolide group and 4 in the beclomethasone group did not have follow-up assessment of FEV₁, and were not included in the ITT population.

Approximately 65% (140/215) of randomized patients completed the study: 61% (100/162) in the HFA flunisolide group and 75% (40/53) in the beclomethasone group (p=0.69). The most common reasons for the 75 patients who discontinued from the study prematurely were consent withdrawn (13.6% vs. 9.4% for HFA flunisolide and beclomethasone, respectively), AE/intercurrent illness (7.4% vs. 3.8% for HFA flunisolide and beclomethasone, respectively), and lost to follow-up (6.2% vs. 7.5% for HFA flunisolide and beclomethasone, respectively). It should be noted that insufficient efficacy (2.5% vs. 1.9%), and non-compliance (3.1% vs. 1.9%) occurred at a higher rate in the HFA flunisolide group. It is unclear how non-compliance was assessed, since that was neither specified in the protocol, nor further evaluated in the Final Study Report.

Four patients at 2 investigator sites entered this study after completing Study ANC-MD-01. Three of these patients had received HFA flunisolide and one patient was treated with placebo.

5.3 BASELINE CHARACTERISTICS

No important differences were noted for any demographic variable between treatment groups. There were 33 patients (20.4%) under 18 years of age in the HFA flunisolide group, and 12 patients (22.6%) in the beclomethasone group. The majority of patients were white (88.8%) and female (53%), with a mean age of 33.1 ± 13.76 years (range at randomization was 12 years-62 years). All patients met ATS criteria for non-smokers. Recalculated percent predicted FEV₁ (Knudson formula, with 12% race correction for African Americans) and actual FEV₁ at screening (83.8%±12.5; 2.78L±0.60) and baseline (87.4%±14.1; 2.90L±0.67) reflected mild to moderate asthma in the safety population

During the run-in phase of this study, most patients used an anti-asthma medication other than albuterol (80.9% and 75.5% in the HFA flunisolide and beclomethasone groups, respectively). In the safety population, the daily dose of the five inhaled corticosteroids most commonly used during the run-in phase was similar between treatment groups.

Asthma history was similar between treatment groups, although the HFA flunisolide group numerically appeared to have slightly better asthma control as measured by asthma symptoms. The HFA flunisolide group had asthma 16.7±years and 21.6% (35/162) of these patients had <3 mean days per week with asthma symptoms 4 weeks prior to enrollment. The beclomethasone group had asthma 18.1±13.1 years and 17% (9/53) of these patients had <3 mean days per week with asthma symptoms 4 weeks prior to enrollment.

Medical and surgical history were similar between treatment groups, and vital signs at baseline were within normal ranges and similar between treatment groups. Efficacy parameters at screening and at baseline were quite similar between treatment groups and are shown in table 5.3A (applicant's in-text table 18, vol.4.1).

5.3A Efficacy Parameters at Screening and Baseline – Safety Population

Parameter	HFA flunisolide (N=162)		Beclomethasone (N=53)		Total (N=215)		p-value ^a
	N	Mean±SD	N	Mean±SD	N	Mean±SD	
SCREENING							
Percent Predicted FEV ₁	162	83.6 ± 13.0	53	84.4 ± 11.1	215	83.8 ± 12.5	0.547
BASELINE							
Percent Predicted FEV ₁	162	87.1 ± 13.9	53	88.5 ± 14.5	215	87.4 ± 14.1	0.689
Actual FEV ₁ (L)	162	2.90 ± 0.69	53	2.91 ± 0.60	215	2.90 ± 0.67	0.831
PRN Albuterol Use (puffs/day)	161	2.3 ± 2.02	53	2.5 ± 1.85	214	2.4 ± 1.98	0.348
Daily Asthma Symptoms Score	161	0.8 ± 0.61	53	1.0 ± 0.51	214	0.9 ± 0.59	0.118
Nocturnal Awakenings (per night)	157	0.1 ± 0.24	51	0.1 ± 0.21	208	0.1 ± 0.23	0.479
AM PEFR (L/min)	160	389 ± 99.4	53	380 ± 80.8	213	387 ± 95.0	0.467

^a P-values are based on the Kruskal-Wallis test.

Cross-reference: After-text Table 2.2 and 2.10

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5.4 SAFETY RESULTS

5.4.1 Extent of Exposure

162 patients were treated with HFA flunisolide for a mean duration of 279 (\pm 127) days and 53 patients were treated with beclomethasone for a mean duration of 304 (\pm 127 days). Of patients who received HFA flunisolide, 100 (61.7%) were treated for more than 48 weeks, whereas 39 (73.6%) beclomethasone group patients were treated for more than 48 weeks. Differences in duration of exposure might be attributed to the higher rate of patient discontinuation seen in the HFA flunisolide group.

The mean daily dose of HFA flunisolide was 447 (\pm 155 mcg/day) and the mean daily dose of beclomethasone was 463 (\pm 153 mcg/day). Median daily doses and last daily dose received by the patient prior to study termination were similar between groups (340 mcg/day in the HFA flunisolide group and 336 mcg/day in the beclomethasone group).

The most frequently used anti-asthma concomitant medications, other than study medications during the study were oral or parenteral steroids (24.7% of HFA flunisolide patients and 32.1% of beclomethasone patients) and long acting beta-agonists, salmeterol and theophylline, (24.7% of HFA flunisolide patients and 31.2% of beclomethasone patients). It is interesting that patients treated with beclomethasone had higher rates of use for these medications.

The most frequently used concomitant medications other than anti-asthma medications were analgesics, anti-bacterials, anti-inflammatory and anti-rheumatic products, topical nasal preparations, cough and cold preparations, and antihistamines. There were no consistent differences between the two treatment groups across classes of medications.

5.4.2 Treatment emergent Adverse Events (TEAEs)

TEAEs were reported by 134 (82%) of HFA flunisolide patients and 43 (81.1) of beclomethasone patients. Among AEs reported by \geq 3% of the safety population, pharyngitis was the most frequent TEAE reported in both the HFA flunisolide group (27.8%) and the Beclomethasone group (32.1%). The next most frequently reported TEAEs in the HFA flunisolide group were viral infection, headache, sinusitis, and pain. These were all reported at higher rates in the beclomethasone group. Oral moniliasis was also reported at a higher rate in the beclomethasone group. It is noteworthy that increased cough, asthma, dyspepsia, myalgia, and accidental injury occurred at higher rates in the HFA flunisolide group, and also noteworthy that allergic reaction, taste perversion and dizziness occurred only in the HFA flunisolide group (Table 5.4.2A; applicant's in-text table 22, vol. 4.1).

Table 5.4.2A TEAEs by Body System Reported by ≥ 3% of Patients in either Treatment Group-Safety Population

<i>Body System^a</i>	<i>HFA flunisolide (N=162)</i>	<i>Beclomethasone (N=53)</i>
One or more^b	134 (82.7)	43 (81.1)
Body as a whole	97 (59.9)	32 (60.4)
Viral infection	36 (22.2)	12 (22.6)
Headache	28 (17.3)	15 (28.3)
Pain	23 (14.2)	11 (20.8)
Flu syndrome	22 (13.6)	7 (13.2)
Accidental injury	20 (12.3)	3 (5.7)
Infection	5 (3.1)	5 (9.4)
Allergic reaction	7 (4.3)	0
Back pain	5 (3.1)	2 (3.8)
Fever	2 (1.2)	3 (5.7)
Infection bacterial	2 (1.2)	2 (3.8)
Respiratory system	86 (53.1)	31 (58.5)
Pharyngitis	45 (27.8)	17 (32.1)
Sinusitis	23 (14.2)	14 (26.4)
Rhinitis	14 (8.6)	8 (15.1)
Bronchitis	11 (6.8)	7 (13.2)
Cough increased	13 (8.0)	2 (3.8)
Asthma	8 (4.9)	2 (3.8)
Laryngitis	1 (0.6)	2 (3.8)
Digestive system	40 (24.7)	11 (20.8)
Dyspepsia	13 (8.0)	2 (3.8)
Nausea	5 (3.1)	2 (3.8)
Oral moniliasis	2 (1.2)	5 (9.4)
Vomiting	2 (1.2)	2 (3.8)

(cont)

<i>Body System^a</i>	<i>HFA flunisolide (N=162)</i>	<i>Beclomethasone (N=53)</i>
Special senses	23 (14.2)	3 (5.7)
Otitis media	7 (4.3)	2 (3.8)
Taste perversion	9 (5.6)	0
Conjunctivitis	5 (3.1)	0
Musculoskeletal system	7 (4.3)	5 (9.4)
Myalgia	8 (4.9)	2 (3.8)
Arthritis	2 (1.2)	2 (3.8)
Urogenital system	3 (1.9)	6 (11.3)
Dysmenorrhea	3 (1.9)	3 (5.7)
Nervous system	15 (9.3)	6 (11.3)
Depression	4 (2.5)	2 (3.8)
Dizziness	5 (3.1)	0
Skin and appendages	11 (6.8)	3 (5.7)
Rash	2 (1.2)	2 (3.8)
Cardiovascular system	9 (5.6)	4 (7.5)
Migraine	5 (3.1)	3 (5.7)

^a Patients are counted once within each body system.

^b "One or more" includes the number of patients who reported at least one TEAE.

Cross-reference: After-text Table 4.1.

Severe TEAEs were reported more frequently in the beclomethasone patients than in the HFA flunisolide patients (37.7% vs. 22.2%, respectively). In both treatment groups, headache was the TEAE most frequently reported as severe.

Taste perversion was the TEAE most frequently reported as related to study drug in the HFA flunisolide group (9/162, 3.1%) and oral moniliasis was the most frequently reported causally related TEAE in the beclomethasone group.

5.4.3 Treatment Discontinuation due to AEs

Twelve HFA flunisolide patients (7.4%) and two beclomethasone patients (3.8%) discontinued from the study due to AEs. Three HFA flunisolide patients and one beclomethasone discontinued due to asthma, and 5 HFA flunisolide patients discontinued due to taste perversion. All cases of asthma and taste perversion were considered drug related. It is noteworthy that laryngitis, pharyngitis, and voice alteration (Table 5.4.3.A; applicant's in-text table 25, vol. 4.1) each were reported as the AE resulting in patient discontinuation in the HFA flunisolide group, and considered drug related. Each of these events resolved spontaneously within 1-4 days of stopping the study drug.

Table 5.4.3A Adverse Events resulting in Patient Discontinuation of Treatment –Safety Population

<i>Body System^a</i>	<i>No. (%) of Patients</i>	
<i>Preferred Term</i>	<i>HFA flunisolide (N=162)</i>	<i>Beclomethasone (N=53)</i>
One or more^b	12 (7.4%)	2 (3.8%)
Cardiovascular system	1 (0.6%)	0
Electrocardiogram abnormal	1 (0.6%)	0
Palpitation	1 (0.6%)	0
Digestive system	1 (0.6%)	0
Nausea	1 (0.6%)	0
Musculoskeletal system	1 (0.6%)	1 (1.9%)
Arthritis	0	1 (1.9%)
Bursitis	1 (0.6%)	0
Nervous system	1 (0.6%)	0
Dizziness	1 (0.6%)	0
Respiratory system	5 (3.1%)	1 (1.9%)
Asthma	3 (1.9%)	1 (1.9%)
Laryngitis	1 (0.6%)	0
Pharyngitis	1 (0.6%)	0
Voice alteration	1 (0.6%)	0
Special senses	6 (3.7%)	0
Taste perversion	5 (3.1%)	0
Vitreous disorder	1 (0.6%)	0

^a Patients are counted once within each body system.

^b "One or more" includes any patients for whom treatment was discontinued for one or more AE. Patients are counted once for "One or more" and once for each AE.

Cross-reference: After-text Table 4.4

5.5 Deaths and Serious Adverse Events

There were no deaths among patients in this study.

- ◆ Five patients experienced SAEs, 3 (1.9%) in the HFA flunisolide group (2 patients with asthma – who were both discontinued from the study; one patient with acute GI ulcer and hemorrhage, that did not lead to medication or study discontinuation)
- ◆ Two patients experienced (3.8%) in the beclomethasone group (1 patient with asthma who was discontinued from the study; 1 patient with migraine, who remained in the study)

5.6 Clinical Laboratory Evaluation, U/A, Vital Signs, ECG, PE, and Lung Examination

Mean changes from screening at Week 26, Week 52, and at the end of the study in hematology parameters were comparable and without clinically important trends in both study groups. PCS values were reported in 3 patients (low HCT in 2 patients, low hemoglobin and low HCT in 1 patient – reported as an AE - anemia, and low RBC in 1 patient. All occurred in the in the HFA flunisolide group.

Mean changes from screening at Week 26, Week 52, and at the end of the study in chemistry parameters were comparable and without clinically important trends in both study groups. Among PCS laboratory parameters in the HFA flunisolide group, one patient had elevated fasting glucose at screening and at the end of the study, another patient had normal fasting glucose at screening, and low fasting glucose at the end of the study (50 mg/dL), one patient had an elevated AST (146 U/L) at the end of the study, which returned to baseline within a month of completing the study, and 1 patient had an elevated potassium (5.8 mmol/L) at study visit 6, which was normal at the last study visit. Cholesterol and triglyceride elevations were noted in both HFA flunisolide and beclomethasone groups, but these low incidences of events were both higher in the beclomethasone group.

Mean changes from screening, at Week 26, Week 52, and at the end of the study in U/A and Vital Signs were similar between treatment groups and no clinically significant trends were noted, with the possible exception of increased weight in the HFA flunisolide group. 24/131 (18.3%) of HFA flunisolide patients and 5/43 (11.6%) of beclomethasone patients experienced weight gain.

Two patients in the HFA flunisolide group shifted from normal ECGs at baseline, to clinically significant ECG changes at the end of the study (WPW in one patient and prolonged QT interval with normal QT_c in the other), whereas no patients in the beclomethasone group had clinically significant ECGs at either baseline or at the end of the study. These ECG changes are unexpected for this class of medication and their low rate of occurrence in this trial in the HFA flunisolide group is difficult to interpret.

The incidence of abnormal lung examination at each visit among treatment groups ranged from 0%-15.2%, but as not consistently higher in one group than the other across study visits. It is noteworthy that the incidence of patients who transitioned from a normal EENT exam at baseline to abnormal at the end of the study was higher in the HFA flunisolide group (23.8% vs. 14.3%).

5.7 HPA axis analyses

24 hour urine cortisol excretion was assessed in 136 patients at 15 sites. Urinary cortisol excretion increased in both HFA flunisolide and beclomethasone as measured from baseline to the end of the study. However, the single measured decrease in cortisol excretion occurred in the HFA flunisolide group at Week 6 (table 5.6A; applicant's in-text table 35). These results expressed as the cortisol/creatinine ratio were similar to those observed for the absolute cortisol excretion. It is not clear that randomization balanced differences between groups in prior history of steroid exposure, among those patients that had HPA axis assessments. If there were differences in this history between groups, these results would then be uninterpretable.

Table 5.7A 24-Hour Urine Cortisol (mcg/dL) tests in Safety Patients at Selected Centers

<i>Visit</i>	<i>HFA flunisolide</i>			<i>Beclomethasone</i>		
	<i>N^a</i>	<i>Value</i>	<i>Change^b</i>	<i>N^a</i>	<i>Value</i>	<i>Change^b</i>
Baseline	102	31.8 ± 40.0		33	26.3 ± 18.5	
Visit 6 (Week 26)	86	24.1 ± 20.2	-3.6 ± 22.8	28	28.8 ± 38.8	2.5 ± 43.6
Visit 8 (Week 52)	63	41.3 ± 62.5	12.8 ± 67.5	24	27.8 ± 19.8	5.0 ± 23.2
End of Study	87	36.1 ± 54.5	8.5 ± 59.1	28	27.1 ± 18.9	0.7 ± 25.6

^a N is the total number of patients at each visit. N for the changes may be smaller at each visit due to missing values at baseline.

^b change from baseline at each time point.

Cross-reference: After-text Table 4.12.

Cortrosyn stimulation tests were also performed at 15 sites. Mean baseline plasma cortisol levels at baseline and at 30 and 60 minutes following cortrosyn stimulation, as well as end of study. Mean baseline plasma cortisol levels at baseline and at 30 and 60 minutes following cortrosyn stimulation, were similar across treatment groups (applicant's in-text table 36)

The number and percentage of new non-responders following cortrosyn stimulation as measured from baseline to end of study was higher in the HFA flunisolide group (7/77 or 9.1% vs. 2/27 or 7.4%), however, total numbers of assessed patients in the beclomethasone group were very small.

5.8 Culture for Candida

The incidence rates for yeast cell presence in the HFA flunisolide group were similar to or lower than in the beclomethasone group. The incidence of clinical thrush was higher in the beclomethasone group than in the HFA flunisolide group (9.4% vs. 1.2 %). It is not known whether patients in the beclomethasone group used a spacer when delivering their dose of study medication.

5.9 Asthma exacerbations

Most patients had no exacerbations of asthma (72% of HFA flunisolide patients vs. 69.8% beclomethasone patients) and no study patient had 4 or more asthma exacerbations during the 52 weeks of this trial. The greatest incidence of first asthma exacerbation for the HFA flunisolide group occurred between Week 4 and 8, and the greatest incidence of first asthma exacerbation for the beclomethasone group occurred between Week 8 and 16. Since this trial assessed maintenance of well-controlled asthma following a run-in period, this may be a signal of weaker efficacy as compared with beclomethasone, in range the doses used by patients in this trial.

The number of patients who discontinued from the study due to asthma or insufficient therapeutic effect was similar, but slightly higher in the HFA flunisolide group (4.3%) as compared to the beclomethasone group (3.8%). (table 5.9; applicant's in-text table 41).

Table 5.9 Cumulative Number of Patients who Discontinued Treatment due to Asthma Exacerbation or Insufficient Therapeutic Effect during the Study – Safety Population

<i>Weeks in Study</i>	<i>HFA Flunisolide (N=162)</i>	<i>Beclomethasone (N=53)</i>	<i>Total (N=215)</i>
Week 4	0	0	0
Week 8	3 (1.9)	0	3 (1.4%)
Week 16	5 (3.1%)	1 (1.9%)	6 (2.8%)
Week 26	6 (3.7%)	1 (1.9%)	7 (3.3%)
Week 39	7 (4.3%)	2 (3.8%)	9 (4.2%)
Week 45	7 (4.3%)	2 (3.8%)	9 (4.2%)
Week 52	7 (4.3%)	2 (3.8%)	9 (4.2%)

Cross-reference: After-text Table 4.17.

5.10 REVIEWER'S COMMENTS ON SAFETY

Over a 1-year course of treatment, HFA flunisolide treated patients had comparable TEAEs as patients treated with beclomethasone. However, twice as many patients in the HFA flunisolide group withdrew from AEs as compared to those patients treated with beclomethasone (7.4% vs. 3.8%). The most frequent reasons for patient discontinuation in the HFA flunisolide group were taste perversion (5 patients) and asthma (3 patients). Serious AEs were reported for 3 patients in the HFA flunisolide group (2 with asthma; 1 with GI hemorrhage) and 2 patients in the beclomethasone group (1 with asthma and 1 with migraine). It is noteworthy that local AEs associated with the corticosteroid class (laryngitis, pharyngitis, and voice alteration) each were reported as an AE resulting in patient discontinuation in the HFA flunisolide group, and considered drug related. Clinical oral moniliasis was more frequently reported in the beclomethasone group, but it was unclear whether patients in this group were allowed to use a spacer. HFA flunisolide has a built -in spacer.

The number of patients who discontinued from the study due to asthma or insufficient therapeutic effect was similar, but slightly higher in the HFA flunisolide group (4.3%) as compared to the beclomethasone group. Unequal randomization (3:1, HFA flunisolide: beclomethasone) makes interpretation of these small differences difficult.

The greatest incidence of first asthma exacerbation for the HFA flunisolide group occurred between Week 4 and 8, and the greatest incidence of first asthma exacerbation for the beclomethasone group occurred between Week 8 and 16. Since this trial assessed maintenance of well controlled asthma following a run-in period, this may be a signal of weaker efficacy as compared with beclomethasone, in range the doses used by patients in this trial.

Urinary cortisol and response to Cortrosyn stimulation was similar across treatment groups, without clear evidence of cortisol suppression in either group. However, the percentages of patients who changed from responder to non-responder following Cortrosyn stimulation were slightly higher in the HFA flunisolide group (9.1% vs. 7.4%). Unequal randomization, lack of randomization according to prior history of steroid exposure, and small sample size for HPA axis assessment in the beclomethasone arm render interpretation of small differences difficult.

There were no clinically important trends in laboratory values, vital signs, or PE, associated with either the HFA flunisolide or beclomethasone groups, other than a greater incidence of increased weight observed in the HFA flunisolide group. ECG changes seen in 2 in the patients in the HFA flunisolide group were interpreted as clinically unimportant by the applicant, but will be added to the overall safety database.

Overall this study generally supports HFA flunisolide safety within this class of inhaled glucocorticoid over 1-year of use, although design flaws limit full interpretation of the safety data. Other long-term glucocorticoid class effects were not addressed in this study (effects on bone density and development of cataracts and glaucoma).

5.11 EFFICACY RESULTS and REVIEWER'S COMMENTS ON EFFICACY

Demographic data for the ITT population was similar to the safety population. At baseline, no significant differences were observed in any efficacy parameter, except daily asthma symptom score, which was higher in the beclomethasone group ($p=0.039$).

Change from baseline in percent predicted FEV₁ to the end of the study showed a slight decrease in the HFA flunisolide group, whereas patients in the beclomethasone group showed a slight increase. However, actual FEV₁, AM PEF, PRN albuterol use, asthma symptom scores and nocturnal awakenings requiring albuterol did not reinforce this suggestion of efficacy loss in the HFA flunisolide group (Table 5.11; applicant's in-text table 42).

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Table 5.11 Efficacy parameters – ITT population

Parameter	HFA flunisolide (N=158)			Beclomethasone (N=49)		
		Value	Change from Baseline ^a		Value	Change from Baseline ^a
	N	Mean ± SD	Mean ± SD	N	Mean ± SD	Mean ± SD
PERCENT PREDICTED FEV₁ (%)						
Baseline (week 0)	158	87.0 ± 14.1		49	89.6 ± 13.9	
Visit 6 (week 26)	131	86.2 ± 16.0	-1.4 ± 9.97	43	93.0 ± 12.8	3.2 ± 10.0
Visit 8 (week 52)	96	86.4 ± 15.7	-0.3 ± 9.45	34	91.9 ± 13.5	2.0 ± 11.5
End of Study	158	86.2 ± 16.8	-0.7 ± 10.5	49	92.1 ± 13.8	2.5 ± 11.3
ACTUAL FEV₁ (L)						
Baseline (week 0)	158	2.89 ± 0.69		49	2.93 ± 0.62	
Visit 6 (week 26)	131	2.86 ± 0.70	-0.03 ± 0.31	43	3.12 ± 0.69	0.15 ± 0.34
Visit 8 (week 52)	96	2.93 ± 0.69	0.02 ± 0.34	34	3.11 ± 0.74	0.12 ± 0.39
End of Study	158	2.90 ± 0.72	0.00 ± 0.36	49	3.07 ± 0.71	0.14 ± 0.37
AM PEAK EXPIRATORY FLOW RATE (L/MIN)						
Baseline (week 0)	156	391 ± 97.7		49	382 ± 82.0	
Visit 6 (week 26)	125	390 ± 96.1	-1.3 ± 41.0	43	397 ± 77.1	5.5 ± 34.7
Visit 8 (week 52)	93	409 ± 93.2	5.7 ± 42.0	30	401 ± 85.3	10.5 ± 36.1
End of Study	157	392 ± 99.4	1.6 ± 49.0	49	397 ± 90.2	14.9 ± 41.7
MEAN DAILY PRN ALBUTEROL USE (PUFFS/DAY)						
Baseline (week 0)	157	2.3 ± 2.02		49	2.5 ± 1.86	
Visit 6 (week 26)	125	1.9 ± 2.21	-0.2 ± 1.67	43	2.0 ± 1.86	-0.6 ± 1.90
Visit 8 (week 52)	93	1.6 ± 2.11	-0.4 ± 1.63	30	1.8 ± 2.08	-0.3 ± 2.52
End of Study	157	2.3 ± 2.42	-0.1 ± 1.76	49	2.1 ± 2.25	-0.4 ± 2.38

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<i>Parameter</i>	<i>HFA flunisolide (N=158)</i>			<i>Beclomethasone (N=49)</i>		
		<i>Value</i>	<i>Change from Baseline*</i>		<i>Value</i>	<i>Change from Baseline*</i>
	<i>N</i>	<i>Mean ± SD</i>	<i>Mean ± SD</i>	<i>N</i>	<i>Mean ± SD</i>	<i>Mean ± SD</i>
DAILY ASTHMA SYMPTOMS SCORE						
Baseline (week 0)	157	0.8 ± 0.62		49	1.0 ± 0.49	
Visit 6 (week 26)	125	0.7 ± 0.64	-0.1 ± 0.54	43	0.9 ± 0.59	-0.1 ± 0.44
Visit 8 (week 52)	93	0.6 ± 0.63	-0.2 ± 0.50	30	0.8 ± 0.61	-0.2 ± 0.60
End of Study	157	0.7 ± 0.67	-0.1 ± 0.57	49	0.8 ± 0.66	-0.2 ± 0.60
NOCTURNAL AWAKENINGS (NUMBER/NIGHT) DUE TO ASTHMA REQUIRING ALBUTEROL						
Baseline (week 0)	153	0.1 ± 0.24		47	0.1 ± 0.17	
Visit 6 (week 26)	125	0.1 ± 0.17	-0.0 ± 0.20	43	0.1 ± 0.19	0.0 ± 0.21
Visit 8 (week 52)	93	0.1 ± 0.20	-0.0 ± 0.20	30	0.1 ± 0.47	0.1 ± 0.43
End of Study	157	0.1 ± 0.31	0.0 ± 0.29	49	0.1 ± 0.41	0.1 ± 0.42

* N is the total number of patients at each visit. N for the changes in all parameters may be smaller at each visit due to missing values at baseline.

Cross-reference: After-text Tables 5.1 - 5.6

It is unlikely that this very slight decline in percent predicted FEV₁ without other signals of HFA flunisolide loss of efficacy at the end of the study has clear clinical relevance, however, it is noted there was no placebo group in this study and the trial was not powered to assess efficacy. Unfortunately, full assessment of compliance with treatment was not described in the protocol or the Final Study Report. Further diary data alone, even if it were assessed, is inadequate to address patient compliance.

Overall, this study does not suggest loss of HFA flunisolide pulmonary function over 1-year, however, there were weak signals that it may be less effective than beclomethasone at the doses used in this study. A larger comparative study powered to an efficacy endpoint would be necessary to assess whether or not this is the case.

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6.0 STUDY ANC-MD-04 ((vol. 4.10 et seq.)

Initiation Date: July 06, 1998

Completion Date: November 30, 1999

RÉSUMÉ

This was a 1-year, open label, active controlled, flexible-dose safety study, in 235 randomized pediatric mild-moderate asthmatic patients age 4-11 years. It included patients with a history of inhaled bronchodilator, or inhaled anti-inflammatory agent at a stable dose for a minimum of 30 days prior to enrollment, or patients with a history of asthma symptoms requiring the use of an inhaled β -agonist at least 3 times a week, $FEV_1 \geq 60\%$ of predicted prior to inhalation of albuterol, and an ability to demonstrate FEV_1 increase of $\geq 12\%$ after inhalation of albuterol at or within 12 months prior to enrollment. All female children were to be pre-menarchal. The protocol did not specify Tanner staging prior to enrollment, at randomization or at specified study visits during the trial.

Enrolled patients entered into a 1-week run-in period, during which time they continued their usual stable dose of asthma controller medication and prn albuterol. Eligible patients then entered into the 52-week open-label phase of the study, with in-clinic evaluations at weeks 4, 8, 16, 26, 39, 45, and 52. Patients 6-11 were randomized to receive open dose HFA flunisolide (85 μ g/puff) 2 puffs BID, beclomethasone dipropionate (84 μ g/puff) 2 puffs BID, or cromolyn sodium (800 μ g/puff) 2 puffs QID treatment groups in a 3: 3: 1 ratio. Patients 4-5 were not randomized, but assigned to receive open dose HFA flunisolide 2 puffs BID for 52 weeks. The investigator could increase or decrease the dose of study medication, as necessary, per protocol pre-specified criteria during the next 52 weeks. A beclomethasone dose range of two – four puffs daily (168 μ g - 336 μ g total daily dose), an HFA flunisolide dose range of two – four puffs daily (170 μ g - 340 μ g total daily dose) and a cromolyn dose range of four -eight puffs daily (3200 μ g - 6400 μ g total daily dose) were protocol specified. Patients < 6 years of age could use a spacer for albuterol inhalation if they were accustomed to using one. Neither the Final Study report nor the protocol specified whether a spacer was permitted for either beclomethasone or cromolyn inhalation in this subgroup or overall population.

The primary objective of the study was to evaluate the safety of HFA Flunisolide Inhaler System over a 1-year course of treatment, as compared to beclomethasone or cromolyn treatment. Secondary objectives of the study included evaluation of growth by stadiometry across treatment groups, and to compare maintenance of pulmonary function.

Baseline demographic variable were comparable across treatment groups. Efficacy parameters at baseline were also comparable across treatment groups, with the exception of AM PEFr. Diary AM PEFr was about 100 L/min lower in the 4-5 year old subset in the HFA flunisolide group, as

compared to the 6-11 year old group, which therefore lowered the overall AM PEFr in the HFA flunisolide group as compared to cromolyn and beclomethasone. This is expected since all 4-5 year old patients received HFA flunisolide.

Mean duration of exposure was highest in the beclomethasone group (364 days \pm 95.8 days), followed by HFA flunisolide (295 \pm 119.9 days) and cromolyn (271 \pm 141.9 days). Mean daily HFA flunisolide dose was 351 μ g \pm 87.3, mean daily beclomethasone dose was 314 μ g \pm 79.7, and mean daily cromolyn dose was 6355 μ g \pm 3964.

Overall TEAE frequency was comparable, but slightly lower for patients treated with HFA flunisolide (88.8%) compared with patients treated with beclomethasone (94.9%) or cromolyn (93.2%). Pharyngitis, viral infection, headache, increased cough, and sinusitis were the most frequent TEAEs reported at >20% of patients in the HFA flunisolide group, and were reported at comparable rates in the other active treatment groups.

Local adverse events including laryngitis (in 5/152 HFA flunisolide patients), voice alteration (in 2/152 HFA flunisolide patients), glossitis (in 1/152 HFA flunisolide patients), oral moniliasis (in 4/152 HFA flunisolide patients), dry mouth (in 2/152 HFA flunisolide patients) were seen in the HFA flunisolide exposed group. In contrast, these events were seen in no patient treated with either cromolyn or beclomethasone in this trial. Epistaxis occurred at almost twice the rate seen in either the cromolyn or beclomethasone groups, however, this rate was driven by the high rate seen in the under 6 year old subset. It is notable that no pediatric patient reported taste perversion in this trial, whereas it was reported and cited as a cause for patient termination in the 1-year adult safety trial (ANC-MD-02).

No patient died in this study. SAEs were reported for 8 (5.3%) patients, including asthma in six patients in the HFA flunisolide group. Four SAEs were reported in the cromolyn group. It is notable that no patient in the beclomethasone group experienced an SAE.

Results of routine laboratory assessments, vital signs, physical and lung examination, and ECGs comparable across all treatment groups. There were no clinically significant results or trends for these parameters.

Response to Cortrosyn stimulation was assessed by demonstrating increase in mean plasma cortisol levels at 30 and 60 minutes following 250 mcg IV injection. This study did not assess timed urinary cortisol excretion, which is thought to be a more sensitive assessment of HPA axis function. In this study, all study groups had similar increases in plasma cortisol at 30 and 60 minutes following cortrosyn stimulation at baseline Week 52 and at the end of the study. The percentage of responders at baseline who became non-responders at the end of the study included 1 (2.94%) patient in the HFA flunisolide group, 1 (7.7%) patient in the beclomethasone group, and zero patients in the cromolyn group. Although this study did not demonstrate an appreciable HPA

axis effect within or between study groups, study design flaws that include insensitive HPA axis testing, 3:1:1 randomization without stratification based on prior history of steroid exposure, and small sample size in the active comparator arms, does not allow clear assessment for HFA flunisolide's effect on the HPA axis.

Clinical thrush was reported in the HFA flunisolide group (n=4), without any reports of clinical thrush in either beclomethasone or cromolyn groups. Cromolyn had the lowest incidence of positive fungal cultures and smears, as compared to beclomethasone (highest) and HFA flunisolide. This is not unexpected for the glucocorticoid class and will need to be addressed in labeling.

Although growth was evaluated in this study, study design was not adequate to allow interpretation of the results. There was no assessment of Tanner staging at any point during the trial, calibration of the assessment tool (stadiometer) was not protocol specified, and the manner in which physiologically improbable data points were handled were not protocol specified or described in the Final Study Report. Further, a descriptive comparison of growth velocities between girls and boys were also omitted, and there was some imbalance for sex among treatment arms. Therefore, study results indicating equal mean change in baseline height at week 52 in 6-11 year old patients for cromolyn and HFA flunisolide groups (6.2 cm/yr) vs. a mean change of 5.1 cm/yr in the beclomethasone group is uninterpretable (mean change from baseline in the 4-5 year old HFA flunisolide group was 5.8cm/yr). Similarly, growth velocity assessments between groups that the applicant reports as showing no statistically significant differences between HFA and cromolyn are not definitively meaningful.

Patient discontinuation due to AEs occurred at a higher rate in the HFA flunisolide group (9 patients, 5.9%) as compared to patients treated with beclomethasone (1 patient, 2.6%), but at a slightly lower rate than cromolyn (3 patients, 6.8%). The AE most frequently resulting in discontinuation in the HFA flunisolide group was asthma (6/142, (4%) and it was the only AE cited for discontinued patients in both beclomethasone (1/39, 2.6%) and cromolyn (3/44, 6.8%) treatment groups).

Overall, similar percentages of patients experienced asthma exacerbation over 52 weeks across treatment groups, with the highest rate seen in the cromolyn group (22/44, 50%), followed by HFA flunisolide (69/152, 45.4%) and beclomethasone (15/39, 38.5%) treatment groups. The greatest incidence of first asthma exacerbation in the HFA flunisolide treatment group occurred in the first 4 weeks of the trial, whereas this occurred between week 8-16 in the beclomethasone and cromolyn groups. Further, among patients who received HFA flunisolide, asthma exacerbation was more frequent in the 4-5 year old subset, than in the 6-11 year old groups, particularly during the first eight weeks of the study. This may be a signal that HFA flunisolide may be less effective in maintaining asthma control at tested dose regimens over one year, either as a result of drug activity differences, drug delivery system differences, or compliance differences, especially in the 4-5 year old subset, as compared with the active comparator.

Efficacy analyses were performed on all randomized patients who received at least one dose of study medication and who had at least one follow-up visit. Pulmonary function as measured by percent predicted FEV₁, PEFR, prn albuterol use, asthma symptoms, and number of nocturnal awakenings due to asthma requiring albuterol over the 52 week was generally well maintained in the beclomethasone group. However, in the HFA Flunisolide group, % predicted FEV₁ declined very slightly from baseline at the end of the study (-0.5% ± 13.7), but without decline in AM PEFR, and without increase in mean daily prn albuterol use, or asthma symptom score. This decline was not seen in either the beclomethasone or cromolyn groups. This very slight decline without other signals of HFA flunisolide loss of efficacy at the end of the study has no clear clinical relevance, however, it is noted there was no placebo group in this study and the trial was not powered to assess efficacy.

Compliance was not fully evaluated in this trial. Non-compliance was a reason for study termination, defined as being off study medication for 14 days. Procedural assessment for non-compliance was not described in the protocol, however.

In conclusion, trial design does not allow for adequate assessment of 2 specific safety concerns associated with inhaled glucocorticoids in children: HPA axis effects and growth. This study, although flawed, demonstrated a 1- year HFA flunisolide safety profile otherwise consistent with this class of medication. The trial did not demonstrate any clear signal for loss of efficacy in 6-11 year old mild asthma patients, however, the higher rate of asthma exacerbations in the 4-5 year old patients, especially during the first 8 weeks of the study, requires further evaluation. Other long-term glucocorticoid class effects were not addressed in this study (effects on bone density and development of cataracts and glaucoma).

6.1 STUDY DESCRIPTION

DESIGN: Multi-center (25), randomized, open-label, active controlled, flexible dose, 1-year, safety study comparing HFA flunisolide (85µg/puff) at BID doses of 85 µg - 170 µg (1-2 puffs BID), beclomethasone dipropionate (84µg/puff) at BID doses of 84 µg - 168 µg (1-2 puffs BID), and cromolyn sodium (800µg/puff) at daily doses of 3200 µg - 6400 µg (2 puffs BID- 2 puffs qid).

POPULATION: 250 mild to moderate, asthmatic patients 4-11 years of age; 4-5 year old patients were assigned to receive HFA flunisolide only

MATERIALS: HFA Flunisolide Inhaler System (85µg/puff); Beclomethasone dipropionate Oral Inhaler (Vanceril DS 84µg/puff); cromolyn sodium (Intal 8µg/puff) Albuterol Oral Inhaler (Proventil 90µg/puff); Mini-Wright Peak Flow Meter. Children less than 6 years of age could use a spacer device with albuterol, if they were accustomed to using one.

OBJECTIVES: Primary - to evaluate safety of HFA flunisolide hemihydrate over a 1 year period weeks in mild-moderate asthmatic children in comparison to beclomethasone treatment or cromolyn sodium. Primary parameters for safety evaluation included AEs, physical examination, lung examination, vital signs, ECGs, laboratory assessments of hematology, chemistry, U/A, mouth and throat smear and cultures, 24-hour urinary cortisol excretion, and response to Cortrosyn stimulation. **Secondary** – to evaluate the effect of HFA flunisolide on growth (by stadiometry, assessing height and growth velocity) as compared to beclomethasone or cromolyn; to compare the efficacy of HFA flunisolide to inhaled beclomethasone and cromolyn using the following parameters: percent predicted FEV₁, as-needed inhaled β-agonist use, AM peak expiratory flow rate (PEFR), daily asthma symptom scores, nocturnal awakenings requiring albuterol use, frequency of asthma exacerbation, time to first asthma exacerbation and time to dropout due to asthma exacerbation or insufficient therapeutic effect. Spirometry was not required in patients 4-5 years of age.

CRITERIA: Male and female (pre-menarchal) children 4-11 with a diagnosis of asthma; asthma symptoms at least 3 times per week, which required use of a bronchodilator or inhaled anti-inflammatory agent at least 30 days prior to enrollment; FEV₁ ≥ 60% of predicted after abstaining from the use of protocol specified medications for certain periods of time prior to enrollment; demonstration of reversible bronchoconstriction (≥ 12% increase in FEV₁ following 2 puffs of albuterol in those children capable of spirometry assessments). A clinical diagnosis of asthma was the entry criterion in the 4-5 year old age group. Patients were excluded from participation if they used specified disallowed drugs within a defined period prior to Visit 1 or 2, or used an orally inhaled corticosteroid at a dose greater than the approved product labeling within 30 days of Visit 1. Eligibility for randomization included the best pre-bronchodilator FEV₁ within 15% of the best prebronchodilator FEV₁ at Visit 1, with mean daily asthma symptom score ≤ 2.5 over 7 days prior to Visit 2, and mean total albuterol intake ≤ 6 puffs over the 7 day period prior to randomization.

CONDUCT: Patients first entered a 1-week run-in phase, in which they received their usual dose of anti-asthma medication and prn albuterol. An anticipated 220 6-11 year old patients were to enter the 52-week open label phase, using a 3:1:1 HFA flunisolide: beclomethasone: cromolyn randomization scheme, and returned to clinic for evaluation at weeks 4, 8, 16, 26, 39, 45, and 52. Patients randomly assigned to receive either open label HFA flunisolide or beclomethasone were each initiated at a dose of 2 puffs bid for HFA flunisolide or beclomethasone, or 2 puff qid for cromolyn, the maximum dose allowed in this study. An anticipated 25-30 four-five year old patients were to be assigned to receive HFA flunisolide 2 puffs BID. The investigator could change the dose of study medication, based on protocol-defined criteria, during the 52-week study period. All patients were instructed to take their study medication at specified times during the day, and on the day of a study visit, to withhold their morning dose of their medication and withhold use of albuterol at least 6 hours, Theo-Dur for 12 hours, an Theo-24 for 24 hours prior to the visit.

Physical examination, hematology, chemistry, U/A, and mouth and throat culture, were assessed at screening and at weeks 26 and 52. Vital signs, lung auscultation, spirometry and adverse events were assessed at all visits and diary cards were dispensed at all visits except at the final visit. Spirometry was performed at screening, baseline, and weeks 4, 8, 26, 45 and 52. A 12 lead ECG was performed at the first visit (screening visit, week-1) and final visit (Week 52). All patients were instructed to take their study medication at specified times during the day, and on the day of a study visit, to withhold their morning dose of their medication and withhold use of albuterol at least 6 hours prior to the visit.

At selected sites, HPA axis effects were assessed baseline (week 2), and at week 52 by measuring effects of Cortrosyn stimulation on plasma cortisol. A normal response for the Cortrosyn stimulation test required a plasma cortisol increment of at least 7 mcg/100mL above the control value within 60 minutes after Cortrosyn administration and an absolute plasma cortisol value \geq 18 mcg/ 100mL within 60 minutes.

DATA ANALYSIS: All hypothesis tests were conducted using the two-sided 0.05 level of significance. Hypothesis tests were used to compare demographics, asthma history and baseline efficacy parameters, only. All safety analyses were done on the safety population, which was defined as all randomized patients who received at least one dose of study drug. Descriptive statistics were presented for the safety population at baseline (Week 0) and comparisons between treatment groups were performed using the Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables.

Adverse events were presented by body system and treatment group, as well as severity and relationship to study drug. Physical exam, lung exam and vital signs at each study visit and change from baseline were summarized for each treatment group. The results of ECG, mouth and throat smear and cultures were reported as normal, abnormal, not clinically significant, and abnormal, clinically significant, and tabulated by treatment group. Descriptive statistics for baseline, 30 minute, 60 minute, and 30 and 60 minute differences from baseline were presented for Cortrosyn stimulation tests. The rates of normal response of patients at 30 and 60 minutes at the visit were also tabulated. Descriptive statistics for baseline, Visit 6, Visit 8 and differences for each of the groups were presented for each visit and the change from baseline at each post-baseline visit were summarized. Growth (height) was assessed and summarized by descriptive statistics and growth velocity was estimated by linear regression of height over time for each patient.

All efficacy analyses were done of the ITT population, defined as all randomized patients who received at least one dose of study drug and had at least one follow-up assessment of FEV₁. Missing data was imputed by the LOCF. To avoid inconsistencies between study centers, percent predicted FEV₁ was recalculated using the Knudson formula. The actual value and change from

baseline at each follow-up visit post-randomization in percent predicted FEV₁, mean daily prn albuterol use, mean daily asthma symptom scores, mean PEF, and mean number of nocturnal awakenings due to asthma requiring albuterol was summarized for both treatment groups. The number of asthma exacerbations, time to first exacerbation and time to discontinuation for lack of efficacy was tabulated by treatment group.

No hypothesis tests of efficacy were performed. All analyses were done at the 5% significance level on a two-sided bases. Sample size was determined such that at least 100 patients would be treated with HFA flunisolide for 1 year.

6.2 PATIENT DISPOSITION

241 patients were enrolled at 24 sites, with 211 patients in the 6-11 year old age group and 30 patients in the 4-5 year old age group. 6 patients failed to meet entry criteria after the one-week run-in period. 235 patients were assigned to treatment groups and comprise the safety population and of these, 224 patients had a follow-up efficacy assessment and are included in the ITT analysis. 11 patients (8 in the HFA flunisolide group and 3 in the cromolyn group) did not have an efficacy assessment and were excluded from ITT analysis. No patients rolled over from study ANC-MD-03.

There were no significant differences in the percentage of patients completing the study across treatment groups, although there were numeric differences (69.7%, 82.1%, and 63.6% completed the study in the HFA flunisolide, beclomethasone, and cromolyn groups, respectively; p=0.3).

29% (69 patients) discontinued from the study prematurely, most commonly due to lost to follow-up (7.2%), withdrawn consent (5.5%) and AE/intercurrent illness (5.5%). The discontinuation rates and reasons were similar in the 4-5 year old population as in the 6-11 year old population. Discontinuation due to AE/intercurrent illness was numerically higher in the HFA flunisolide group (9/152 patients, 5.9%) than in the beclomethasone group (1/39 patients, 2.6%), but lower than the cromolyn group (3/34 patients, 6.8%). It was notable that no patient in the beclomethasone group discontinued for insufficient effect or non-compliance. 3.3% of HFA flunisolide patients and 6.8% of cromolyn patients discontinued for non-compliance, and 2% of HFA flunisolide patients and 6.8% of cromolyn patients discontinued due to insufficient effect. It is not clear how non-compliance was assessed, however, since that was not specified in the protocol or further evaluated in the final study report.

106 patients in the HFA flunisolide group completed the study, including twenty 4-5 year old patients.

6.3 BASELINE CHARACTERISTICS

No significant differences were noted for any demographic variable between treatment groups. However, numerical differences were noted for age (related to the fact that all 4-5 year old patients received HFA flunisolide) and sex (% female patients differed across treatment arms such that only 25.6%(10/39) patients in the beclomethasone group were female, compared to 40.1% (61/152) in the HFA flunisolide arm, and 43.2% (19/44) in the cromolyn arm. Differences in age and sex across treatment arms may have an important effect on growth parameters, especially since this study did not assess Tanner staging at any point in this trial.

The majority of patients were white (75.7%) and male (61.7%), with a mean age 8.3 ± 2.1 years.

Enrolled and randomized patients had very mild asthma, with mean percent predicted FEV₁ recalculated by the Knudson formula of $88.3\% \pm 13.1$ at screening and 90.0 ± 12.9 at baseline. All patients used some anti-asthma medication prior to enrollment and about 66.4% used inhaled corticosteroids. More than 60% of patients used inhaled corticosteroids and about 12% used cromolyn /nedocromil during the run-in phase of the study. The mean number of years with asthma was 2.9 years in the 4-5 year old population (HFA flunisolide), 5.3 years in the 6-11 year old HFA flunisolide group, 5.5 years in the beclomethasone group and 5.8 years in the cromolyn group.

There were no significant differences in medical and surgical history, vital sign measurements at baseline or most efficacy parameters at baseline between treatment groups or between the 4-5 year old population and the 6-11 year old population. The one exception was AM PEF_R diary parameter in the 4-5 year old group, which was 100 L/min lower than the 6-11 year old HFA flunisolide group, therefore, overall AM PEF_R in the HFA flunisolide group was lower at baseline compared to the other groups. This is not unexpected, since the AM PEF_R was not corrected for height of the patient.

6.4 SAFETY RESULTS

6.4.1 Extent of Exposure

235 patients were exposed for a median duration of 361 days in the HFA flunisolide group, 364 days in the beclomethasone group, and 361 days in the cromolyn group. Among those exposed to HFA flunisolide, 106/152 patients completed the study, of which 102/152 (67.1%) received treatment for more than 48 weeks, versus 32/39 (82.1%) in the beclomethasone group, and 28/44 (63.6%) in the cromolyn group. The mean daily doses for HFA flunisolide was $351\mu\text{g} \pm 87.3$, versus beclomethasone $314\mu\text{g} \pm 79.7$ and cromolyn $6355\mu\text{g} \pm 3964$. Last mean daily dose received by the patient prior to study termination was very similar to mean daily dose.

There were no important differences noted in concomitant anti-asthma medication used during the study, however, there was slight numerically higher use of oral and parenteral steroid use among patients in the beclomethasone group (17/39, 43.6%) versus the HFA flunisolide group (58/152, 38.2%) or cromolyn groups (16/44, 36.4%).

The most frequently used concomitant medications other than anti-asthmatics were analgesics, anti-bacterials and antihistamines for systemic use, anti-inflammatory and anti-rheumatic products, cough and cold preparations, and nasal preparations, which included nasal steroids. The use of these drugs were comparable across treatment arms

6.4.2 Treatment Emergent Adverse Events (TEAEs)

The percentage of patients reporting at least one TEAE was similar among treatment groups: 88/8% in the HFA flunisolide group, 94.9% in the beclomethasone group, and 93.2 % in the cromolyn group. TEAEs reported by more than 20% of patients in the total HFA flunisolide group were headache, pharyngitis, viral infection, increased cough and sinusitis. TEAEs across treatment groups of $\geq 5\%$ incidence and having twice or more incidence reported in a parallel group are listed below:

- ◆ When comparing the 4-5 year old HFA flunisolide group with the 6-11 year old HFA flunisolide group, headache and pain were reported more frequently in the older population, compared with bacterial infection, diarrhea, epistaxis, laryngitis, ear pain and otitis media in the younger population. The differences in frequency and type of events specific to these age populations are not unexpected.
- ◆ When comparing the 6-11 year old HFA flunisolide treated patients to the other active control groups, more HFA flunisolide treated patients than beclomethasone treated patients reported asthma and bronchitis, whereas more beclomethasone treated patients than HFA flunisolide treated patients reported infection, bacterial infection, diarrhea, urticaria, and conjunctivitis.
- ◆ When comparing HFA flunisolide treated patients to cromolyn treated patients, more HFA flunisolide treated patients than cromolyn treated patients reported allergic reaction, vomiting, and pneumonia, whereas more cromolyn treated patients than HFA flunisolide treated patients reported eczema.

In assessing all TEAEs reported at $\geq 3\%$ and which occurred at a higher rate in the HFA flunisolide group as compared to either of the two active comparators included, viral infection, dyspepsia, vomiting, epistaxis, laryngitis, pneumonia, and otitis media. (table 6.4.2A; applicant's in-text table 21, vol. 4.10)

Table 6.4.2A TEAEs Reported at $\geq 3\%$ of Patients in any Treatment Group: Number (%) of Safety Patients

<i>Body System</i>	<i>HFA flunisolide (N=152)</i>	<i>Beclomethasone (N=39)</i>	<i>Cromolyn (N=44)</i>
One or more*	135 (88.8)	37 (94.9)	41 (93.2)
Body as a Whole	103 (67.8)	29 (74.4)	29 (65.9)
Abdominal Pain	15 (9.9)	6 (15.4)	8 (18.2)
Accidental Injury	15 (9.9)	6 (15.4)	4 (9.1)
Allergic Reaction	9 (5.9)	3 (7.7)	0
Fever	22 (14.5)	8 (20.5)	9 (20.5)
Flu syndrome	26 (17.1)	10 (25.6)	6 (13.6)
Headache	31 (20.4)	11 (28.2)	8 (18.2)
Infection	4 (2.6)	3 (7.7)	2 (4.6)
Infection bacterial	14 (9.2)	6 (15.4)	4 (9.1)
Malaise	0	2 (5.1)	1 (2.3)
Pain	12 (7.9)	3 (7.7)	5 (11.4)
Viral infection	44 (29.0)	11 (28.2)	8 (18.2)
Cardiovascular System	4 (2.6)	3 (7.7)	0
Migraine	2 (1.3)	2 (5.1)	0
Digestive System	35 (23.0)	8 (20.5)	9 (20.5)
Diarrhea	7 (4.6)	4 (10.3)	1 (2.3)
Dyspepsia	5 (3.3)	0	1 (2.3)
Gastroenteritis	4 (2.6)	1 (2.6)	2 (4.6)
Nausea	5 (3.3)	1 (2.6)	2 (4.6)
Tooth disorder	1 (0.7)	0	2 (4.6)
Vomiting	17 (11.2)	4 (10.3)	2 (4.6)
Musculoskeletal System	5 (3.3)	1 (2.6)	5 (11.4)
Leg cramps	0	0	2 (4.6)
Nervous System	11 (7.2)	3 (7.7)	0
Dizziness	1 (0.7)	2 (5.1)	0

(continued next page)

Table 6.4.2A TEAEs Reported at $\geq 3\%$ of Patients in any Treatment Group: Number (%) of Safety Patients (continued)

<i>Body System</i>	<i>HFA flunisolide (N=152)</i>	<i>Beclomethasone (N=39)</i>	<i>Cromolyn (N=44)</i>
Respiratory System	115 (75.7)	29 (74.4)	35 (79.6)
Asthma	12 (8.0)	1 (2.6)	4 (9.1)
Bronchitis	12 (8.0)	1 (2.6)	5 (11.4)
Cough increased	34 (22.4)	10 (25.6)	9 (20.5)
Epistaxis	6 (4.0)	1 (2.6)	1 (2.3)
Laryngitis	5 (3.3)	0	0
Lung disorder	4 (2.6)	0	2 (4.6)
Pharyngitis	82 (54.0)	23 (59.0)	25 (56.8)
Pneumonia	9 (5.9)	2 (5.1)	1 (2.3)
Rhinitis	25 (16.5)	9 (23.1)	8 (18.2)
Sinusitis	32 (21.1)	12 (30.8)	5 (11.4)
Skin and Appendages	20 (13.2)	13 (33.3)	7 (15.9)
Eczema	1 (0.7)	2 (5.1)	3 (6.8)
Pruritus	1 (0.7)	2 (5.1)	0
Rash	11 (7.2)	5 (12.8)	3 (6.8)
Skin disorder	3 (2.0)	2 (5.1)	0
Urticaria	4 (2.6)	4 (10.3)	0
Special Senses	15 (9.9)	9 (23.1)	9 (20.5)
Conjunctivitis	3 (2.0)	5 (12.8)	2 (4.6)
Ear pain	5 (3.3)	2 (5.1)	2 (4.6)
Otitis media	25 (16.5)	4 (10.3)	7 (15.9)
Urogenital System	3 (2.0)	2 (5.1)	0
Urinary tract infection	1 (0.7)	2 (5.1)	0

^a Patients are counted once within each body system.

^b "One or more" includes the number of patients who reported at least one TEAE in any treatment group.

Cross-reference: After-text Table 4.1

Severe TEAEs were comparable across treatment groups, but most frequently reported in the beclomethasone (17.9%, 7/39) and cromolyn (15.9%, 7/44) treated groups as compared with the HFA flunisolide treated group (12.5%, 19/152).

Overall, pharyngitis was the TEAE most frequently reported as severe across treatment groups (4 patients in the HFA flunisolide group, 1 patient in the beclomethasone group, and 2 patients in the cromolyn group). However, asthma was also reported as severe in 4 patients in the HFA flunisolide group, compared with 1 patient in the beclomethasone group and no patient in the cromolyn group. Among patients treated with HFA flunisolide, the 4-5 year old population had a similar AE severity profile as compared with the 6-11 year old group.

The HFA flunisolide group had most frequently reported study-drug TEAE relatedness. 16.4% (25/152) of HFA flunisolide treated patients had TEAEs reported as possibly related or related to study drug, compared with 10.3% (4/39) beclomethasone treated patients or 9.1% (4/44) cromolyn treated patients.

6.4.3 Treatment Discontinuation due to AEs

Premature treatment discontinuation rate due to one or more AEs were comparable but highest in the cromolyn group (5.9% (9/152) in the HFA flunisolide group, 2.6% (1/39) in the beclomethasone group and 6.8% (3/44) in the cromolyn group). The most common AE leading to discontinuation was asthma exacerbation reported in 4.0% (6/152) HFA flunisolide treated patients, 2.6% (1/39) beclomethasone treated patients, and 6.8% (3/44) cromolyn treated patients. Among the 9 patients who dropped out in the HFA flunisolide group, 1 patient was a 5 year old male, who experienced 2 episodes of asthma exacerbation. The first episode occurred on day 154 of study medication. The patient was hospitalized but continued on study medication. The second asthma exacerbation occurred on day 272 of study medication, which resolved after 3 days, but resulted a change in asthma controller medication (monteleukast added) and in discontinuation from the study (table 6.4.3A; applicant's in-text table 24, vol. 4.10).

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Table 6.4.3A Adverse Events Resulting in Discontinuation of Treatment

<i>Adverse Event</i>	<i>No. (%) of Patients</i>		
	<i>HFA Flunisolide (N=152)</i>	<i>Beclomethasone (N=39)</i>	<i>Cromolyn (N=44)</i>
One or more ^a	9 (5.9)	1 (2.6)	3 (6.8)
Asthma	6 (4.0)	1 (2.6)	3 (6.8)
Migraine	1 (0.7)	0	0
Cough Increased	1 (0.7)	0	0
Dyspnea	1 (0.7)	0	0
Headache	1 (0.7)	0	0
Pharyngitis	1 (0.7)	0	0

^a "One or more" includes any patients for whom treatment was discontinued for one or more adverse events. Patients are counted once for "one or more" adverse events and once for each adverse event.

Cross-reference: After-text Table 4.4

6.5 Deaths and Serious Adverse Events (SAEs)

There were no deaths in this study.

- ◆ No patient in the beclomethasone group experienced a SAE
- ◆ Overall, asthma as an SAE was reported seven times in 6 HFA flunisolide treated patients. Pneumonia was reported separately in one patient; anxiety was reported separately in one patient; increased cough and dyspnea was reported concurrent to asthma in one patient, viral infection was reported concurrent to asthma in one patient; pharyngitis was reported concurrent to asthma in one patient.
- ◆ Four patients in the cromolyn group experienced an SAE: one patient with asthma, one patient with osteomyelitis and pyomyositis, one patient with pharyngitis who underwent T and A, and one patient with a musculoskeletal congenital anomaly who underwent surgical repair of pes planus.

6.6 Clinical Laboratory evaluations, U/A Vital Signs, ECG, PE and Lung Examination

Hematology test mean changes from screening at Week 26, 52 and end of study were comparable across treatment arms, and no clinically important trends observed. The incidence of abnormal hematology tests results were low (<3%) and comparable across treatment groups.

Mean changes from screening at Week 26, 52 and end of study for all chemistry parameters were comparable among all treatment groups and no clinically important trends were observed. Among potentially clinically significant chemistry test results, no clear trends were noted. Abnormal triglycerides and cholesterol were seen in 29.2% and 8.4% of HFA flunisolide patients, respectively, 25.9% and 11.4% of beclomethasone patients, respectively, and 34.4% and 10.3% cromolyn patients, respectively.

Urinalysis test result mean changes from screening at Week 26, 52 and end of study were small and comparable across treatment arms. Shifts from normal at screening to abnormal at the end of the study were observed in urine ketone (1 patient in the HFA flunisolide group; 1 patient in the beclomethasone group), urine protein (1 patient in the beclomethasone group), urine RBCs (3 patients in the HFA flunisolide group and urine WBCs (1 patient in the HFA flunisolide group, 2 patients in the beclomethasone group and 2 patients in the cromolyn group).

Vital signs mean changes from screening at week 26, 52 and end of study were comparable across treatment groups for all parameter and similar in the 4-5 year old patients as compared to the 6-11 year old patients. The incidence of PCS vital signs was low and also comparable across all treatment groups.

No patient had clinically significant abnormal ECGs at screening or at the end of the study.

Overall, the incidences of transitions from normal to abnormal in physical examinations were comparable across treatment groups and similar in the 4-5 year old patients as compared to the 6-11 year old patients. The body system with most frequent transitions from normal to abnormal was in the Eyes, Ears, Nose and Throat., which is not unexpected. These incidences were reported at the following rates: 29.7%, 43.8%, and 16.7% for HFA flunisolide, beclomethasone, and cromolyn groups, respectively. Results in the 4-5 year old population were similar to the 6-11 year old HFA population.

The incidences of lung exam abnormalities in treatment groups ranged from 0-13.9% at each post-baseline visit, but was not consistently higher in one group versus another.

6.7 Plasma Cortisol Levels after Cortrosyn Stimulation

HPA axis assessment did not include timed urinary cortisol, which is thought to be a more sensitive test. Cortrosyn stimulation tests were performed in 84 patients at 12 selected sites. Plasma cortisol levels showed an increase at 30 minutes and a further increase at 60 minutes post-cortrosyn, with similar post-cortrosyn increases across treatment groups, and between 4-5 year old patients and 6-11 year old HFA flunisolide treated patients. These test results should be interpreted with caution however, since the assessment was done following 250µg IV cortrosyn stimulation, and mild perturbations in HPA axis function may not be seen with this test. Additionally, total numbers of assessed patients were small. Of note, cromolyn treated patients experienced the highest change at 60 minutes post cortrosyn at week 52 and end of study (table 6.7A; applicant's in-text table 33). These results may be a small signal of glucocorticoid HPA axis effect in both the HFA flunisolide and beclomethasone groups, or a reflection of inadequate sample size.

Table 6.7A Cortrosyn Stimulation - Safety Population at Selected Sites

<i>Visit</i>	<i>HFA Flunisolide (N=61)</i>		<i>Beclomethasone (N=17)</i>		<i>Cromolyn (N=19)</i>	
	<i>N</i>	<i>Mean±SD</i>	<i>N</i>	<i>Mean±SD</i>	<i>N</i>	<i>Mean±SD</i>
BASELINE						
Pre-Cortrosyn	52	12.1±4.17	15	13.2±4.00	17	10.5±3.08
30 minutes post	51	21.8±5.10	15	23.8±3.65	18	20.2±4.16
Change at 30 min	51	9.75±4.67	15	10.6±3.94	17	9.59±5.04
60 minutes post	50	25.0±5.64	15	27.6±4.45	18	24.1±5.09
Change at 60 min	50	12.8±5.52	15	14.4±4.76	17	13.5±5.92
VISIT 8 (WEEK 52)						
Pre-Cortrosyn	40	11.7±4.19	14	12.5±5.71	10	11.7±3.62
30 minutes post	34	22.7±3.84	13	22.8±3.79	10	23.1±3.35
Change at 30 min	34	10.9±3.97	13	10.5±4.61	10	11.4±3.69
60 minutes post	34	25.8±4.27	13	26.2±4.62	10	26.4±3.31
Change at 60 min	34	13.9±4.62	13	13.9±5.52	10	14.7±4.47
END OF STUDY						
Pre-Cortrosyn	40	11.9±3.95	14	12.5±5.71	12	11.3±3.55
30 minutes post	34	22.9±3.19	13	22.8±3.79	12	22.6±3.37
Change at 30 min	34	10.9±3.97	13	10.5±4.61	12	11.3±3.86
60 minutes post	34	26.1±3.43	13	26.2±4.62	11	26.3±3.17
Change at 60 min	34	14.0±4.53	13	13.9±5.52	11	15.0±4.36

Cross-reference: After-text Table 4.12.1

The number and percentage of responders at baseline who became non-responders to Cortrosyn stimulation at the end of study was also similar across treatment groups, however, total numbers of assessed patients were small and interpretation of these data is difficult. It is notable, however, that no cromolyn treated patient experienced this shift from responder to non-responder, whereas this observation was made in one patient in the beclomethasone group (7.7%, 1/17) and one patient in the HFA flunisolide group (2.94%, 1/61). These data may be another small signal of glucocorticoid HPA axis effect of both HPA flunisolide and beclomethasone, or simply a reflection of inadequate sample size (Table 6.7B; applicant's in-text table 34, vol. 4.10).

Table 6.7B – Results of Cortrosyn Stimulation Tests. Safety Population

<i>Time Point</i>	<i>HFA flunisolide (N=61)</i>	<i>Beclomethasone (N=17)</i>	<i>Cromolyn (N=19)</i>
BASELINE			
Responder	47 (90.4)	15 (100)	16 (88.9)
Nonresponder ^b	5 (9.6)	0	2 (11.1)
VISIT 8 (52 WEEKS)			
Responder	31 (91.2)	12 (92.3)	10 (100)
Nonresponder	3 (8.8)	1 (7.7)	0
END OF STUDY			
Responder	32 (94.1)	12 (92.3)	11 (91.7)
Nonresponder	2 (5.9)	1 (7.7)	1 (8.3)
Change from responder at baseline to non-responder at end of study	1 (2.94)	1 (7.7)	0

^a Percentages are based on the number of patients tested for stimulation following cortrosyn administration.

^b Non-responder = a patient who does not have an increase in plasma cortisol ≥ 7 $\mu\text{g/dL}$ or does not have an absolute value ≥ 18 $\mu\text{g/dL}$ after cortrosyn injection.

6.8 Culture for Candida

Although all treatment groups were comparable at baseline for presence of yeast cells, the cromolyn group had the lowest incidence of positive fungal culture and smears at Visit 6, 8, and end of study, as well as the lowest change from baseline from no yeast cells to yeast cells present, whereas patients in the beclomethasone group had the highest incidence for those same parameters. The incidence of clinical thrush infection was reported in 4 HFA flunisolide patients (2.2%), whereas no patient in either active control group reported thrush infection. Thrush is not unexpected for this class of medication, especially in children who may not rinse their mouth well after dose administration. This will need to be addressed in the labeling.

6.9 Asthma exacerbations

The rate of asthma exacerbation was lowest in the beclomethasone group, (38.5%) as compared with HFA flunisolide (45.4%) and cromolyn (50%). In the HFA flunisolide group, the greatest incidence of first asthma exacerbation occurred between weeks 0-4, whereas this occurred between week 8-16 in both the beclomethasone group and cromolyn group (table 6.9A; applicant's in-text table 37, vol. 4.10).

Table 6.9A Cumulative Number (%) of Patients who Experienced their First Asthma Exacerbation during the Study – Safety Population

<i>Cumulative Dropout Rate</i>	<i>HFA Flunisolide (N=152)</i>	<i>Beclomethasone (N=39)</i>	<i>Cromolyn (N=41)</i>
Visit 2 (week 0)	0	0	0
Visit 3 (week 4)	3 (2.0)	0	3 (6.8)
Visit 4 (week 8)	4 (2.6)	0	3 (6.8)
Visit 5 (week 16)	4 (2.6)	0	4 (9.1)
Visit 6 (week 26)	7 (4.6)	0	5 (11.4)
Visit 7 (week 39)	9 (5.9)	0	5 (11.4)
Visit 7A (week 45)	9 (5.9)	0	5 (11.4)
Visit 8 (week 52)	9 (5.9)	0	5 (11.4)
Post Visit 8	9 (5.9)	1 (2.6)	6 (13.6)

Cross-reference: After-text Table 4.16

Among the three treatment groups, the drop-out rates due to asthma or insufficient therapeutic effect was highest in the cromolyn group (6/44, 13.6%) whereas 9/152 (5.9%) of HFA flunisolide patients and 1/39 beclomethasone patients dropped out.

Among patients who received HFA flunisolide, more patients experienced their first asthma exacerbation during the study treatment period following run-in with stable asthma in the 4-5 year old population than in the 6-11 year old HFA groups, particularly during the first 8 weeks of the study (37.9% in patients 4-5 years old and 20.3% in patients 6-11 years old at 8 weeks).

Overall, although unequal randomization and small numbers make interpretation of these differences difficult, there is a small signal, especially among 4-5 year old patients, that at the doses used in this study over one year, HFA flunisolide may be less effective than beclomethasone in controlling asthma, and perhaps more effective than cromolyn.

6.10 Growth

Although growth was evaluated in this study, study design was not adequate to allow for meaningful interpretation of the results. There was no assessment of Tanner staging at any point during the trial, calibration of the assessment tool (stadiometer) was not protocol specified, and the

manner in which physiologically improbable data points were handled were not protocol specified or described in the Final Study Report. Further, a descriptive comparison of growth velocities between girls and boys were also omitted, and there was some imbalance for sex among treatment arms. Therefore, study results indicating equal mean change in baseline height at week 52 in 6-11 year old patients for cromolyn and HFA flunisolide groups (6.2 cm/yr) vs. a mean change of 5.1 cm/yr in the beclomethasone group are not clearly interpretable (mean change from baseline in the 4-5 year old HFA flunisolide group was 5.8cm/yr. Table 6.10A; applicant's in-text table 39, vol. 4.10). Although data are limited, it is notable that greatest growth occurred in the cromolyn group at week 26 as compared with either HFA flunisolide or beclomethasone, but by week 52, very similar rates of growth were seen between the HFA flunisolide and cromolyn groups.

Table 6.10A Change from Baseline in Height (cm) – Safety Population

<i>Height (cm)</i>	<i>HFA Flunisolide 4 to 5 years (N=29)</i>	<i>HFA Flunisolide 6 to 11 years (N=123)</i>	<i>Beclomethasone (N=39)</i>	<i>Cromolyn (N=44)</i>
BASELINE (WEEK 0)				
N	28	117	39	39
Mean ± SD	111.2 ± 5.4	137.9 ± 10.3	137.6 ± 10.0	137.3 ± 11.8
VISIT 6 (WEEK 26)				
N	23	101	34	33
Mean ± SD	114.5 ± 5.1	140.6 ± 10.7	140.8 ± 9.9	140.5 ± 12.6
Change ± SD	3.1 ± 1.3	2.9 ± 1.7	2.6 ± 1.5	3.9 ± 2.2
VISIT 8 (WEEK 52)				
N	17	71	26	26
Mean ± SD	116.8 ± 4.7	144.0 ± 11.0	142.5 ± 10.6	144.0 ± 12.5
Change ± SD	5.8 ± 1.8	6.2 ± 2.9	5.1 ± 1.9	6.2 ± 2.3

Cross-reference: After-text Table 5.1

Similarly, growth velocity assessments between groups that the applicant reports as showing no statistically significant differences between HFA and cromolyn are not definitively meaningful, but are presented below (table 6.10B; applicant's in-text table 40, vol. 4.10).

Table 6.10B Growth Velocity – Safety Population

<i>Growth Velocity (cm/year)</i>	<i>HFA Flunisolide 4 to 5 years (N=29)</i>	<i>HFA Flunisolide 6 to 11 years (N=123)</i>	<i>Beclomethasone (N=39)</i>	<i>Cromolyn (N=44)</i>	<i>p-value^a</i>
Mean (n)	6.2 (23)	6.2 (102)	5.3 (36)	6.9 (34)	0.97
SD	2.08	2.57	1.87	2.93	
Median	6.2	5.8	5.5	6.2	
HFA flunisolide versus beclomethasone					0.90
HFA flunisolide versus cromolyn					0.94

^a P-value was based upon comparison among patients in the 6- to 11-year-old groups using the random coefficient model.

Cross-reference: After-text Table 5.2

6.11 REVIEWER'S COMMENTS ON SAFETY

Results for routine assessments of vital signs, physical and lung examination, and ECGs were comparable across all treatment groups and there were no clinically significant results or trends for these parameters. However, special safety concerns, growth and effects on the HPA axis, which are associated with the glucocorticoid class of drugs in children, were not addressed well in this study, secondary to inadequate study design.

Response to Cortrosyn stimulation was assessed by demonstrating increase in mean plasma cortisol levels at 30 and 60 minutes following 250 mcg IV injection. This study did not assess timed urinary cortisol excretion, which is thought to be a more sensitive assessment of HPA axis function. Although this study did not demonstrate an appreciable HPA axis effect within or between study groups, study design flaws that include insensitive HPA axis testing, 3:1:1 randomization without stratification based on prior history of steroid exposure, and small sample size in the active comparator arms, does not allow clear assessment for HFA flunisolide's effect on the HPA axis.

Although growth was evaluated in this study, study design was not adequate to allow interpretation of the results. There was no assessment of Tanner staging at any point during the trial, calibration of the assessment tool (stadiometer) was not protocol specified, and the manner in which physiologically improbable data points were handled were not protocol specified or described in the Final Study Report. Further, there was some imbalance for sex among treatment arms, and a descriptive comparison of growth velocities between girls and boys was also omitted.

Overall TEAE frequency was comparable, but slightly lower for patients treated with HFA flunisolide (88.8%) compared with patients treated with beclomethasone (94.9%) or cromolyn (93.2%). Pharyngitis, viral infection, headache, increased cough, and sinusitis were the most frequent TEAEs reported at >20% of patients in the HFA flunisolide group, and were reported at comparable rates in the other active treatment groups.

No patient died in this study. SAEs were reported for 8 (5.3%) patients, including asthma in six patients in the HFA flunisolide group. Four SAEs were reported in the cromolyn group. It is notable that no patient in the beclomethasone group experienced an SAE.

Local adverse events including laryngitis (in 5/152 HFA flunisolide patients), voice alteration (in 2/152 HFA flunisolide patients), glossitis (in 1/152 HFA flunisolide patients), oral moniliasis (in 4/152 HFA flunisolide patients), dry mouth (in 2/152 HFA flunisolide patients) were observed, but seen in no patient treated with either cromolyn or beclomethasone in this trial. Epistaxis occurred at almost twice the rate seen in either the cromolyn or beclomethasone groups, however, this rate was driven by the high rate seen in the under 6 year old subset, which were ages not represented by the cromolyn or beclomethasone group.

Patient discontinuation due to AEs occurred at a higher rate in the HFA flunisolide group (9 patients, 5.9%) as compared to patients treated with beclomethasone (1 patient, 2.6%), but at a slightly lower rate than cromolyn (3 patients, 6.8%). The AE most frequently resulting in discontinuation in the HFA flunisolide group was asthma (6/142, (4%) and it was the only AE cited for discontinued patients in both beclomethasone (1/39, 2.6%) and cromolyn (3/44, 6.8%) treatment groups).

Similar percentages of patients experienced asthma exacerbation over 52 weeks across treatment groups, with the highest rate seen in the cromolyn group (22/44, 50%), followed by HFA flunisolide (69/152, 45.4%) and beclomethasone (15/39, 38.5%) treatment groups. The greatest incidence of first asthma exacerbation in the HFA flunisolide treatment group occurred in the first 4 weeks of the trial, whereas this occurred between week 8-16 in the beclomethasone and cromolyn groups. Among patients who received HFA flunisolide, asthma exacerbation was more frequent in the 4-5 year old subset than in the 6-11 year old groups, particularly during the first eight weeks of the study. This may be a signal that HFA flunisolide may be less effective in maintaining asthma control at tested dose regimens over one year, either as a result of drug activity differences with the active comparator, or because of compliance differences, especially in the 4-5 year old subset.

In conclusion, over a 1-year course of treatment, HFA flunisolide appeared to be safe in children 6-11 years of age with mild asthma, as assessed by general clinical and laboratory tests. This study does not provide adequate data to clearly determine one-year HFA flunisolide effects on the control of mild asthma in the 4-5 year old population. Further, this study does not provide adequate data to clearly determine the effects one-year effects of HFA flunisolide on growth or the HPA axis in the 6-11 year old population. Other long-term glucocorticoid class effects were not addressed in this study (effects on bone density and development of cataracts and glaucoma). Consideration of these other long-term effects may be considered for phase 4 commitment studies.

EFFICACY RESULTS AND REVIEWER'S COMMENTS ON EFFICACY

Demographic data for the ITT population was similar to the safety population. At both screening and baseline, no significant differences were observed in any efficacy parameter across treatment groups. The goal of the treatment phase of this study was to maintain the pulmonary function recorded at the baseline visit.

Pulmonary function in 4-11 year old patients as measured by percent predicted FEV₁ (not assessed in 4-5 year old patients), PEF_R, prn albuterol use, asthma symptoms, and number of nocturnal awakenings due to asthma requiring albuterol over the 52 week was generally well maintained in the beclomethasone and cromolyn groups. However, in the 6-11 year old HFA flunisolide group, % predicted FEV₁ declined very slightly from baseline at the end of the study (-0.5% ± 13.7), but without decline in AM PEF_R, and without increase in mean daily prn albuterol use, or asthma symptom score. This decline was not seen in either the beclomethasone or cromolyn groups. This very slight decline without other signals of HFA flunisolide loss of efficacy at the end of the study has no clear clinical relevance, however, it is noted there was no placebo group in this study and the trial was not powered to assess efficacy (Table 6.11; applicant's in-text table 41, vol.4.10).

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Table 6.12 Efficacy Parameters – Safety Population

Parameter/ Visit	HFA Flunisolide		Beclomethasone		Cromolyn	
	N	Mean±SD	N	Mean±SD	N	Mean±SD
PERCENT PREDICTED FEV₁^a (%)						
Baseline	125	89.3±12.2	39	89.6±13.6	41	91.0±12.9
Change at 26 weeks	108	-0.7±13.7	36	2.3±12.1	33	-0.1±16.5
Change at 52 weeks	80	1.5±12.7	30	2.0±9.9	27	2.3±17.3
End of Study	125	-0.5±13.7	39	0.5±10.5	41	0.8±16.9
AM PEAK EXPIRATORY FLOW RATE (L/MIN)						
Baseline	144	223±68.7	39	239±56.3	41	250±66.3
Change at 26 weeks	125	12.5±44.6	35	14.4±35.0	32	14.8±39.5
Change at 52 weeks	94	26.3±41.8	28	26.4±27.6	25	25.3±48.3
End of Study	144	18.3±43.3	39	18.3±35.7	41	10.5±50.9
DAILY PRN ALBUTEROL USE (PUFFS/DAY)						
Baseline	144	1.7±1.7	39	1.3±1.2	41	1.2±1.3
Change at 26 weeks	125	-0.24±1.8	35	-0.03±1.4	32	-0.52±1.4
Change at 52 weeks	94	-0.45±1.6	28	-0.23±1.4	25	-0.65±1.3
End of Study	143	-0.33±1.8	39	-0.08±1.5	41	-0.21±1.6
DAILY ASTHMA SYMPTOM SCORES						
Baseline	144	0.66±0.55	39	0.80±0.57	41	0.64±0.62
Change at 26 weeks	125	-0.16±0.61	35	-0.25±0.50	32	-0.17±0.50
Change at 52 weeks	94	-0.21±0.61	29	-0.42±0.52	26	-0.30±0.43
End of Study	143	-0.11±0.61	39	-0.40±0.50	41	-0.15±0.60
NOCTURNAL AWAKENINGS (NUMBER/NIGHT) DUE TO ASTHMA REQUIRING ALBUTEROL						
Baseline	141	0.06±0.15	38	0.08±0.24	41	0.03±0.07
Change at 26 weeks	123	-0.01±0.17	35	-0.02±0.20	32	0.01±0.09
Change at 52 weeks	93	-0.02±0.17	29	-0.02±0.15	26	-0.02±0.08
End of Study	141	0.03±0.21	38	-0.05±0.19	41	0.07±0.32

^a Includes all 6- to 11-year-old safety patients and those 4- to 5-year-old patients who had FEV₁ data available.
Cross-reference: After-text Tables 6.1 through 6.6.

In conclusion, this study does not suggest loss of pulmonary function in 4-11 year old mild asthmatic patients treated with HFA flunisolide. However, an increased rate of asthma exacerbation was seen in the 4-5 year old HFA flunisolide population compared with the 6-11 year old HFA flunisolide population. This study had insufficient power to assess long-term efficacy and no placebo control. A larger comparative study powered to an efficacy endpoint would be necessary to clarify these issues further.

7.0 INTEGRATED SUMMARY OF SAFETY (vol 1.87 et seq and 4.21 et seq)

This review is based on the ISS submitted by the sponsor in their original April 27, 2000 HFA flunisolide NDA submission. Integrated safety information from 2 twelve week, double-blind, fixed-dose, placebo controlled studies, ANC-MD-01 conducted in adolescent and adult asthmatic patients, and ANC-MD-03 conducted in pediatric asthmatic patients 4-11 years of age are presented. Integrated safety information from 2 open label, flexible-dose, active-controlled one-year studies, ANC-MD-02 in adolescent and adult asthmatics and ANC-MD-04 in pediatric asthmatics are also presented. Since study designs and populations are different across studies (refer to review of individual study reports), this information is presented as individual studies, but in some cases these data are pooled together for 12-week trial ISS assessments, as well as pooled together for 1-year trial ISS assessments. It should be appreciated, however, that this pooling combines adult and pediatric populations.

Safety information from 103 subjects who received at least one dose of active study medication in the five pharmacokinetic studies is included in this ISS. A summary of a literature search conducted by Forest Laboratories on January 21, 2000 was also submitted and a review of post-marketing ADRs in the AERS database was performed by OPDRA, for all flunisolide containing approved drugs used in the USA. Results of this literature search and OPDRA review is briefly summarized.

The ISS is organized as follows: patient exposure, demographics, SAEs, dropouts, common TEAEs assessed by pattern, dose response, age and gender, and race, abnormal labs and EKGs, and HPA-axis effects, summary of safety information from PK studies, and summary of post-marketing ADRs for drugs containing flunisolide. Effects on growth (ANC-MD-04), serum osteocalcin (Anc-MD-01) and first dose tolerability (ANC-MD-01) were assessed in single studies, addressed in the individual study reports and will not be again reported here. CRFs were reviewed for SAEs and adverse events dropouts.

7.1 Patient Exposure

Table 7.1A Enumeration of Patients in Completed Clinical Studies

	Treatment Group				Total
	Placebo	HFA flunisolide	CFC flunisolide	Other Active Control	
ANC-MD-01	104	288	277	NA	669
ANC-MD-03	116	231	236	NA	583
ANC-MD-02	NA	162	NA	53	215
ANC-MD-04	NA	152	NA	83	235
total	220	833	513	136	1702

519 adult and pediatric asthmatic patients were exposed to HFA flunisolide in the 2 twelve week, double-blind, fixed dose, placebo controlled studies. A total of 1252 patients were randomized: 669 patients in ANC-MD-01 and 583 patients in Study ANC-MD-03. The mean duration of exposure across both studies was 69.4 days for placebo, 76.7, 78.2, and 80.5 days for Flunisolide HFA Inhaler System 85 mcg, 170 mcg, and 340 mcg bid, respectively. Lower mean exposure to placebo can be attributed to the higher treatment discontinuation rate secondary to asthma or insufficient treatment effect seen in that group (applicant's in-text tables 6 and 13- vol. 1.87)

314 adult and pediatric patients received HFA flunisolide in the one-year, open-label, flexible dose trials. Of the 162 randomized adult and adolescent patients who received HFA flunisolide treatment for a mean duration of 279 ± 127 days in Study ANC-MD-02, 100 completed the study. Of the 152 randomized pediatric patients who received HFA flunisolide for a mean duration of 295 ± 120 days in Study ANC-MD-04, 106 completed the study. The overall median duration of treatment among patients in both studies was comparable: patients who received HFA flunisolide was 360 days, compared with 364 days in the beclomethasone group and 361 in the cromolyn group. (applicant's in-text tables 4 and 12, vol. 4.21).

7.2 Patient Demographics

Across all treatment groups and across all 4 trials, mean age of patients was 22.4 years \pm 17.0, with age range of 3 years -78 years. Of those patients exposed to HFA flunisolide across all 4 trials, 46.1% were 4-11 years of age, 7.4% of patients were 12-17 years of age, 45.5% were 18-56 years of age, and 1.0% were \geq 65 years of age. Similar percentages of patients age 4-11, 12-17, 18-56 and \geq 65 were randomized to placebo or other active control drugs.

Among HFA flunisolide exposed patients, 53.8% were male and 46.2% were female, 79% were Caucasian, 13.2% were Black, 5.5% were Hispanic, and 2.3 % were Other. No important differences in race demographics were observed across placebo, HFA flunisolide, or other active control groups.

Mean asthma history among HFA flunisolide exposed patients was 12.3 years, and 80% reported never smoking (smoking history determined in ANC-MD-01 and ANC-MD-02, only). Similar results were reported across placebo, HFA flunisolide and other active control groups.

The distribution of patients by race and gender was similar across treatment groups in the double-blind studies and in the open label long-term studies. However, a larger percentage of Black patients (ranging from 15%-15.8% among the three treatment groups) were randomized in the double-blind studies than in the open label long-term studies (10.5% and 9.6% in the HFA flunisolide and active control groups, respectively). There were no important differences in the mean duration of asthma (10.5-10.9 years in the long term studies and 11.0-13.2 years in the short term studies) or important differences in smoking histories between the double blind and open-label studies.

7.3 Deaths, Serious Adverse Events (SAEs) and Adverse Events Dropouts (ADOs)

7.3.1 Deaths

There were no deaths among any enrolled patient in these 4 studies. One death was recorded in a patient who did not meet screening criteria in study ANC-MD-04 and had not been randomized to receive study medication.

7.3.2 Serious Adverse Events (SAEs)

Incidence of SAEs was low across all four studies and no consistent dose related or gender differences were observed. A total of 34/1702 enrolled patients reported a serious adverse event (SAE) in these four studies (Table 7.3.2A; applicant's in text table 15, vol. 1.87): 3 patients in the run-in phase and 32 patients in the treatment phase. Among patients treated in the 12-week double blind studies (Table 7.3.2B; applicant's in-text table 16, vol. 1.87), 14/1252 patients experienced SAEs, with the highest percentage in the placebo group, as compared to the pooled HFA flunisolide group and pooled CFC flunisolide group (1.8% vs. 1.0% in each of the pooled HFA and CFC flunisolide groups.) The most commonly reported SAE was asthma. The only SAEs reported by more than one patient in any treatment group was infection (reported in 2 CFC flunisolide patients, 0 HFA flunisolide patient) and asthma (3 (0.6%) HFA flunisolide patients vs. 1 (0.2%) CFC flunisolide patient). Of the five patients who reported SAEs in the HFA flunisolide group, 3/519 (0.6%) were female and 2/519 (0.4%) were male. Four of these patients were enrolled in the adult/adolescent and 1 patient was enrolled in the pediatric study.

In the long-term safety studies (Table 7.3.2C; applicant's in-text table 17, vol. 1.87), 17/450 patients experienced SAEs during the treatment phase. The overall incidence of SAEs was similar in the pooled HFA flunisolide and active control groups (3.5% vs. 4.4%, respectively). Exacerbation of asthma was the most commonly reported single event and was the only SAE reported by more than one patient in any treatment group. Of 11/314 patients who reported SAEs in the HFA flunisolide group, 2.8% (4/142) were female and 4.1% (7/172) were male. 8/11 of these patients were enrolled in the pediatric trial. 6/11 of these pediatric patients had exacerbations of asthma.

Table 7.3.2A Serious Adverse Events during the Phase III Clinical Studies: number (%) of patients

<i>Study Number</i>	<i>Run-in Phase</i>	<i>Treatment Phase</i>		
		<i>Placebo</i>	<i>HFA flunisolide</i>	<i>Active control^a</i>
		N = 220	N = 833	N = 649
ANC-MD-01	1	1 (0.5)	4 (0.5)	2 (0.3)
ANC-MD-03	1	3 (1.4)	1 (0.1)	3 (0.5)
ANC-MD-02	0	NA	3 (0.4)	2 (0.3)
ANC-MD-04	1	NA	8 (1.0)	4 (0.6)

^a: Active control was CFC flunisolide in Studies ANC-MD-01 and ANC-MD-03; beclomethasone in Study ANC-MD-02; and beclomethasone and cromolyn in Study ANC-MD-04.

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Table 7.3.2B Serious Adverse Events in Studies ANC-MD-01 and ANC-MD-03: number and (%) of patients

<i>COSTART Preferred Term</i>	<i>Placebo (N=220)</i>	<i>HFA Flunisolide (N=519)</i>	<i>CFC Flunisolide (N=513)</i>
ONE OR MORE	4 (1.8)	5 (1.0)	5 (1.0)
BODY AS A WHOLE	1 (0.5)	2 (0.4)	3 (0.6)
Abdominal Pain	0	0	1 (0.2)
Accidental Injury	0	0	1 (0.2)
Cellulitis	0	1 (0.2)	0
Chest Pain	0	1 (0.2)	0
Cyst	0	0	1 (0.2)
Infection	0	0	2 (0.4)
Viral Infection	1 (0.5)	0	0
CARDIOVASCULAR SYSTEM	0	1 (0.2)	0
Angina Pectoris	0	1 (0.2)	0
DIGESTIVE SYSTEM	1 (0.5)	0	0
Intestinal Obstruction	1 (0.5)	0	0
Nausea	1 (0.5)	0	0
Vomiting	1 (0.5)	0	0
NERVOUS SYSTEM	0	1 (0.2)	0
Paralysis	0	1 (0.2)	0
RESPIRATORY SYSTEM	2 (0.9)	3 (0.6)	1 (0.2)
Asthma	2 (0.9)	3 (0.6)	1 (0.2)
Hypoxia	1 (0.5)	0	0
SKIN AND APPENDAGES	0	1 (0.2)	0
Herpes Zoster	0	1 (0.2)	0
SPECIAL SENSES	0	0	1 (0.2)
Ear Pain	0	0	1 (0.2)
Otitis Media	0	0	1 (0.2)

^a "One or more" includes any patients with one or more SAEs. Patients were counted once for "One or more" category and once for each adverse event preferred term.

Cross reference: After-text Table 5a, ISS

Table 7.3.2C Serious Adverse Events in Studies ANC-MD-02 and ANC-.MD-04: number and (%) of patients

<i>COSTART Preferred Term</i>	<i>HFA Flunisolide (N=314)</i>	<i>Beclomethasone (N=92)</i>	<i>Cromolyn (N=44)</i>
ONE OR MORE	11 (3.5)	2 (2.2)	4 (9.1)
BODY AS A WHOLE	1 (0.3)	0	1 (2.3)
Infection	0	0	1 (2.3)
Viral Infection	1 (0.3)	0	0
CARDIOVASCULAR SYSTEM	0	1 (1.1)	0
Migraine	0	1 (1.1)	0
DIGESTIVE SYSTEM	1 (0.3)	0	0
Gastrointestinal Disorder	1 (0.3)	0	0
Gastrointestinal Hemorrhage	1 (0.3)	0	0
MUSCULOSKELETAL SYSTEM	0	0	2 (4.5)
Musculoskeletal Congenital Anomaly	0	0	1 (2.3)
Osteomyelitis	0	0	1 (2.3)
NERVOUS SYSTEM	1 (0.3)	0	0
Anxiety	1 (0.3)	0	0
RESPIRATORY SYSTEM	9 (2.9)	1 (1.1)	2 (4.5)
Asthma	8 (2.5)	1 (1.1)	1 (2.3)
Cough Increased	1 (0.3)	0	0
Dyspnea	1 (0.3)	0	0
Pharyngitis	1 (0.3)	0	1 (2.3)
Pneumonia	1 (0.3)	0	0

^a "One or more" includes any patients with one or more SAEs. Patients were counted once for "One or more" category and once for each adverse event preferred term resulting in discontinuation of treatment.

Cross-reference: After-text Table 5b, ISS

7.3.4 Adverse Event Dropouts (ADOs)

Across the four studies, 145/1702 enrolled patients discontinued from the study due to an adverse event (Table 7.3.4A; applicant's in-text table 18). The rate of discontinuation was higher in the placebo group as compared to the HFA flunisolide group, however, the rate of discontinuation in the one-year active controlled trials was lowest in the active controlled group. In the 2 double-blind treatment phase of the 12-week placebo-controlled trials, 118/1252 discontinued due to AEs. One person discontinued due to pregnancy. This was not considered an AE by the applicant and not included in tables of treatment emergent adverse events (TEAEs), but it is not clear whether there is any effect of HFA flunisolide on oral contraceptives efficacy.. Of 117/1252 (9.3%) in the 2 double-blind trials who discontinued due to TEAEs, the largest percentage was in the placebo group (15.5%), which was approximately twice the percentage of patients who discontinued in either pooled HFA or pooled CFC groups. The most commonly reported AE resulting in discontinuation was asthma (14.5%, 5.4%, and 6.6% in the placebo group, pooled HFA and pooled CFC flunisolide groups, respectively). All other TEAEs resulting in discontinuation occurred in less than 1% of patients in any of the treatment groups, with the exception of pharyngitis. Pharyngitis occurred in 1.6%, 1.3% and 0.9% in the pooled CFC flunisolide, HFA flunisolide and placebo groups, respectively. (table 7.3.4B; applicant's in-text table 19, vol. 1.87)

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Table 7.3.4B TEAEs Resulting in Discontinuation of Treatment (Studies ANC-MD-01 and ANC-MD-03)

<i>Adverse Event</i>	<i>Number (%) of Patients</i>		
	<i>Placebo (n=220)</i>	<i>HFA Flunisolide Pooled (n=519)</i>	<i>CFC Flunisolide Pooled (n=513)</i>
ONE OR MORE^A	34 (15.5)	39 (7.5)	44 (8.6)
BODY AS WHOLE	2 (0.9)	4 (0.8)	4 (0.8)
Allergic reaction	0	2 (0.4)	0
Asthenia	1 (0.5)	0	0
Chest pain	0	0	1 (0.2)
Chills	0	0	1 (0.2)
Fever	0	2 (0.4)	0
Headache	0	0	1 (0.2)
Viral infection	1 (0.5)	1 (0.2)	3 (0.6)
CARDIOVASCULAR	0	1 (0.2)	0
Syncope	0	1 (0.2)	0
DIGESTIVE	1 (0.5)	0	2 (0.4)
Flatulence	0	0	1 (0.2)
Intestinal obstruction	1 (0.5)	0	0
Nausea	1 (0.5)	0	0
Oral moniliasis	0	0	1 (0.2)
Vomiting	1 (0.5)	0	0
METABOLIC AND NUTRITIONAL DISORDERS	0	0	1 (0.2)
Dehydration	0	0	1 (0.2)
NERVOUS	0	0	1 (0.2)
Somnolence	0	0	1 (0.2)
RESPIRATORY	33 (15.0)	36 (6.9)	40 (7.8)
Asthma	31 (14.1)	28 (5.4)	34 (6.6)
Bronchitis	1 (0.5)	1 (0.2)	1 (0.2)
Cough increased	1 (0.5)	2 (0.4)	1 (0.2)
Hypoxia	1 (0.5)	0	0
Laryngitis	0	1 (0.2)	0
Lung disorder	0	0	3 (0.6)
Pharyngitis	2 (0.9)	7 (1.3)	8 (1.6)
Pneumonia	0	0	1 (0.2)
Rhinitis	0	1 (0.2)	1 (0.2)
Sinusitis	1 (0.5)	2 (0.4)	1 (0.2)
SKIN AND APPENDAGES	0	1 (0.2)	2 (0.4)
Rash	0	1 (0.2)	1 (0.2)
Urticaria	0	0	1 (0.2)

^a "One or more" includes any patients for whom one or more TEAEs resulted in discontinuation of treatment. Patients were counted once for "One or more" category and once for each TEAE preferred term resulting in discontinuation of treatment.

Cross-reference: After-text Table 6a, ISS

In the 2 long term studies enrolling 450 patients, 27 patients discontinued due to TEAEs: 6.7% (21/314) in the HFA flunisolide group and 4.4% (6/136) in the active control groups. Among patients receiving HFA flunisolide, asthma (9 patients), taste perversion (5 patients) and pharyngitis (2 patients) were the only TEAEs resulting in patient discontinuation that occurred in more than one patient. (Table 7.3.4C; applicant's in-text table 20, vol.1.87)

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Table 7.3.4C TEAEs Resulting in Discontinuation of Treatment (Studies ANC-MD-02 and ANC-MD-04)

<i>COSTART Preferred Term</i>	<i>HFA Flunisolide (N=314)</i>	<i>Beclomethasone (N=92)</i>	<i>Cromolyn (N=44)</i>
ONE OR MORE	20 (6.4)	3 (3.3)	3 (6.8)
BODY AS WHOLE	1 (0.3)	0	0
Headache	1 (0.3)	0	0
CARDIOVASCULAR SYSTEM	2 (0.6)	0	0
Electrocardiogram Abnormal	1 (0.3)	0	0
Migraine	1 (0.3)	0	0
Palpitation	1 (0.3)	0	0
DIGESTIVE SYSTEM	1 (0.3)	0	0
Nausea	1 (0.3)	0	0
MUSCULOSKELETAL SYSTEM	1 (0.3)	1 (1.1)	0
Arthritis	0	1 (1.1)	0
Bursitis	1 (0.3)	0	0
NERVOUS SYSTEM	1 (0.3)	0	0
Dizziness	1 (0.3)	0	0
RESPIRATORY SYSTEM	12 (3.8)	2 (2.2)	3 (6.8)
Asthma	9 (2.9)	2 (2.2)	3 (6.8)
Cough Increased	1 (0.3)	0	0
Dyspnea	1 (0.3)	0	0
Laryngitis	1 (0.3)	0	0
Pharyngitis	2 (0.6)	0	0
Voice Alteration	1 (0.3)	0	0
SPECIAL SENSES	5 (1.6)	0	0
Taste Perversion	4 (1.3)	0	0
Vitreous Disorder	1 (0.3)	0	0

^a "One or more" includes any patients for whom one or more TEAEs resulted in discontinuation of treatment. Patients were counted once for "One or more" category and once for each TEAE preferred term resulting in discontinuation of treatment.

Cross-reference: After-text Table 6b, ISS

7.4 TEAEs

In the 12 week placebo controlled studies, asthma was the TEAE reported most frequently overall, and was seen most frequently in the placebo group (17.3%) than by the pooled HFA (7.5%) or CFC (9.9%) flunisolide groups. Other more frequently reported TEAEs (>10%) included headache, pharyngitis and rhinitis. The most frequently reported TEAE in the HFA group was pharyngitis, which may be attributable to local adverse steroid effect.

Many other TEAEs in the HFA flunisolide group in the 12 week trials, some of which occurred at a higher rate in the HFA flunisolide group as compared with the placebo group, and may be attributed to local and systemic glucocorticoid class effect of drug administration or withdrawal. Overall, TEAEs occurred at similar rates as compared with the CFC flunisolide group. Selected TEAEs of special interest which occurred at or greater than 0.5% and occurred at higher rates over placebo (except for asthma) are listed in Table 7.4A.

Table 7.4A Selected TEAE Incidence in Studies ANC-MD-01 and ANC-MD-03

	Placebo N = 220 Number (%)	HFA Flunisolide N = 519 Number (%)	CFC Flunisolide N = 513 Number (%)	Total N = 1252 Number (%)
Asthma	38 (17.3)	39 (7.5)	51 (9.9)	128 (10.2)
Pharyngitis	29 (13.2)	88 (17.0)	76 (14.8)	193 (15.4)
Rhinitis	22 (10.0)	55 (10.6)	50 (9.7)	127 (10.1)
Allergic reaction	5 (2.3)	23 (4.4)	25 (4.9)	53 (4.2)
Abdominal pain	5 (2.3)	13 (2.5)	16 (3.1)	34 (2.7)
Dyspepsia	3 (1.4)	15 (2.9)	12 (2.3)	30 (2.4)
Diarrhea	3 (1.4)	11 (2.1)	9 (1.8)	23 (1.8)
Nausea	3 (1.4)	10 (1.9)	13 (2.5)	26 (2.1)
Ecchymosis	1 (0.5)	3 (0.6)	1 (0.2)	5 (0.4)
Bacterial infection	2 (0.9)	10 (1.9)	6 (1.2)	18 (1.4)
Urinary tract infection	1 (0.5)	8 (1.5)	2 (0.4)	11 (0.9)
Stomatitis	1 (0.5)	3 (0.6)	4 (0.8)	8 (0.6)
Oral moniliasis	2 (0.9)	6 (1.2)	3 (0.6)	11 (0.9)
Voice alteration	1 (0.5)	4 (0.8)	4 (0.8)	9 (0.7)
Laryngitis	0	5 (1.0)	0	5 (0.4)
Taste perversion	1 (0.5)	8 (1.5)	4 (0.8)	13 (1.0)
Insomnia	1 (0.5)	5 (1.0)	3 (0.6)	9 (0.7)
Dizziness	1 (0.5)	7 (1.3)	9 (1.8)	17 (1.4)
Accidental injury	5 (2.3)	19 (3.7)	23 (4.5)	47 (3.8)
Myalgia	1 (0.5)	7 (1.3)	2 (0.4)	10 (0.8)

TEAEs in the HFA flunisolide group that occurred at > 3% of patients in any dose group and that were greater than in the placebo group are listed in Table 7.4B, from applicant's in-text table 23, vol.1.87). With the exception of UTI and dyspepsia, no dose related increases were observed in the HFA flunisolide group.

Table 7.4B TEAEs with frequency > 3% and Greater than Placebo in ANC-MD-01 and ANC-MD-03

	<i>Placebo</i> (N=220)	<i>HFA flunisolide</i>		
		<i>85 µg bid</i> (N=189)	<i>170 µg bid</i> (N=217)	<i>340 µg bid</i> (N=113)
BODY AS WHOLE				
Accidental Injury	5 (2.3)	7 (3.7)	8 (3.7)	4 (3.5)
Allergic Reaction	5 (2.3)	8 (4.2)	10 (4.6)	5 (4.4)
Back Pain	5 (2.3)	1 (0.5)	7 (3.2)	2 (1.8)
Fever	11 (5.0)	13 (6.9)	8 (3.7)	1 (0.9)
Headache	28 (12.7)	17 (9.0)	30 (13.8)	10 (8.8)
Infection Bacterial	2 (0.9)	7 (3.7)	2 (0.9)	1 (0.9)
Pain	8 (3.6)	5 (2.6)	10 (4.6)	2 (1.8)
DIGESTIVE SYSTEM				
Dyspepsia	3 (1.4)	4 (2.1)	7 (3.2)	4 (3.5)
Vomiting	9 (4.1)	8 (4.2)	10 (4.6)	0
RESPIRATORY SYSTEM				
Cough Increased	17 (7.7)	16 (8.5)	12 (5.5)	2 (1.8)
Epistaxis	2 (0.9)	6 (3.2)	2 (0.9)	0
Pharyngitis	29 (13.2)	33 (17.5)	36 (16.6)	19 (16.8)
Rhinitis	22 (10.0)	17 (9.0)	34 (15.7)	4 (3.5)
Sinusitis	12 (5.5)	14 (7.4)	9 (4.1)	10 (8.8)
SKIN AND APPENDAGES				
Rash	7 (3.2)	5 (2.6)	8 (3.7)	2 (1.8)
UROGENITAL SYSTEM				
Urinary Tract Infection	1 (0.5)	2 (1.1)	2 (0.9)	4 (3.5)

Cross-reference: After-text Table 7b, ISS

In the adult/adolescent population in the 2 twelve week trials, there was no age-related trend of adverse events. However, relatively small numbers of patients in >65 years of age (n=10) or 12-17 years of age (n=47) who received HFA flunisolide or placebo limits interpretability of drug or dose related effects in these sub-populations. In the pediatric population, no consistent differences of any specific TEAE were noted between the 4-5 year old sub-population and the 6-11 year old age group. However, the small numbers of 4-5 year old patients (n=39) limits interpretability of the results for any HFA flunisolide dose or drug related trends in that sub-population as compared to placebo, as well. Comparing the adult (>12 years) with the pediatric ((4-11 years) populations, there were no important differences in the incidences and distribution of TEAEs. Pharyngitis was the most frequently reported TEAE in all age groups, except in the 4-5 and >65 year old subsets.

Neither the overall incidence of TEAEs nor the incidence of individual TEAEs appeared gender related (n male = 406; n female = 333), either within the HFA flunisolide treatment groups or by comparison to placebo treatment in the two 12 week trials.

Within the White (n=562) and Black (n=112) patient populations in the 2 twelve week trials, the overall incidence of TEAEs was generally similar between HFA flunisolide and placebo groups. Black patients reported fewer individual TEAEs, which was especially apparent within the respiratory system. TEAEs did not appear to be dose related in either subpopulation. Too few Hispanic and Other patients were enrolled to make assessment of TEAEs by race.

TEAE incidences in the two 1-year studies, ANC-MD-02 and ANC-MD-04 were similar in the HFA flunisolide groups and control groups (beclomethasone or cromolyn). The highest TEAE incidences occurred in the Body as a Whole, Respiratory, and Digestive systems. It should be noted that these two studies differed in the age population enrolled and the active controls used (ANC-MD-02 did not randomize patients to cromolyn).

In ANC-MD-02 and ANC-MD-04, TEAEs reported by at least 10% of patients in the HFA flunisolide group and listed in order of frequency in the HFA flunisolide group were: pharyngitis, viral infection, headache, sinusitis, increased cough, rhinitis, pain, accidental injury, and otitis media. These more frequent TEAEs occurred at higher rates in the control groups than in the HFA flunisolide group, except for accidental injury and otitis media. Accidental injury also occurred at a higher rate in the HFA flunisolide group as compared to placebo in the 2 twelve week trials. TEAEs that occurred in <10% of the population, at a rate greater or equal to 5% in either group and were twice or more as frequent in the HFA flunisolide group as in the control group were allergic reaction (5.1% in the HFA flunisolide group vs. 2.2% in the combined control group) and dyspepsia (5.7% in the HFA flunisolide group vs. 2.2% in the combined control group). It is notable that allergic reaction and dyspepsia both occurred at higher rates in the HFA flunisolide group than in the placebo group in the 2 twelve week studies, although in both of those shorter term trials, the rate of those TEAEs were very similar to CFC flunisolide.

The following TEAEs were reported at increased rates (>1 patient) in the HFA flunisolide group (n=314) as compared to the combined (n=136) control groups in Studies ANC-MD-02 and ANC-MD 04: asthma, increased cough, dyspnea, accidental injury, allergic reaction, asthenia, myalgia, chest pain, neck pain, viral infection, dyspepsia, gastroenteritis, vomiting, stomatitis, leukopenia, ecchymosis, edema, anxiety, dizziness, dry mouth, insomnia, electrocardiogram abnormal, abnormal LFTs, vomiting, lymphadenopathy, epistaxis, laryngitis, voice alteration, eczema, herpes zoster, otitis externa, otitis media, cystitis, kidney calculus, urine abnormality, unintended pregnancy, vaginitis, and taste perversion. Overall, the reported TEAE rates as consistent with the population, disease and drug class; these increased rates were small in magnitude and are difficult to interpret because unequal randomization and small sample size.

In these long term studies, TEAE incidence rates in the 6-11 year old population were compared to the >18 year old subgroup, among patients who received HFA flunisolide with TEAEs>5% and twice or more incidence in either age group, since these populations represented 81% of HFA flunisolide treated patients. Minimal differences in event rates were noted between 4-5 year old and 6-11 year old subsets, or between 12-17 and >18 year old subsets. In adult patients, dyspepsia and myalgia were more commonly reported compared with pediatric patients who reported abdominal pain, fever, bacterial infection, vomiting, increased cough, rash and otitis media. Additionally, age-related trends were seen. Viral infection and pharyngitis appeared to decrease with increasing age whereas pain appeared to increase with increasing age. The applicant attributes these differences to the patient's age and natural course of disease rather than drug treatment. Overall this reviewer concurs about underlying epidemiological, age-related differences in disease rates, however, host immunity has been shown to be affected by the glucocorticoid class, and HFA flunisolide's potential effects on immunity may play a larger role in children. However, for these TEAEs, age related incidence and trend comparisons in the combined control group were similar to those in the HFA flunisolide group.

In these 2 one-year studies, TEAEs generally showed a similar pattern of distribution between males and females. However, among events that occurred at >5% incidence in either gender and at an incidence at twice or greater than the other gender, abdominal pain, and allergic reaction were more often reported by females whereas asthma and rash were more often reported by males. No notable differences were observed between HFA flunisolide and combined control groups.

In Studies ANC-MD-02 and ANC-MD-04, TEAEs showed a generally similar pattern of TEAE incidence between white and non-white patients. However, among events that occurred at >5% incidence in either whites or non-whites and at an incidence at twice or greater than the other race, accidental injury, bacterial infection, and pain were reported more frequently by white patients, whereas, rash was more frequently reported by non-white patients. No important differences were observed between HFA flunisolide and the combined control groups.

7.5 Abnormal Laboratory Assessments and Abnormal ECGs

Overall, a review of the laboratory assessments in all four studies did not show any significant alterations, with the exception of one adult HFA flunisolide-treated patient who developed an elevation in AST 10 times the upper limit of normal, and one pediatric patient treated with HFA flunisolide who had normal glucose at screening and had a value of 20 mg/dL at the end of the study. The elevated AST was considered by the investigator to be due to concomitant ibuprofen administration taken post-operatively after foot surgery. In follow-up testing LFTs returned to normal. No explanation for the low blood glucose or follow-up information was given, but hypoglycemia is an unlikely TEAE for this drug class. Otherwise, aberrations of questionable clinical importance were seen in serum chemistry and hematology, and U/A data. Shifts from normal values at screening to values on study that were higher or lower than the normal range were occasionally reported in all studies, however, no trends were observed in those parameters as compared to placebo or active comparator groups.

Among patients in the 2 twelve week studies, there were no important differences between treatment groups in the number of patients with abnormal ECGs, nor were there any clinically important changes noted between screening and week twelve visits. None of the patients in the one-year pediatric study had clinically important abnormal ECGs. In the adult one-year long-term study, there were two patients (1.2%) in the HFA flunisolide group with clinically significant changes in ECG results at the end of the study. One patient was reported to have prolonged QTc, however, the value reported (433ms) is not considered abnormally prolonged in women. The other patient was reported to have possible pre-excitation syndrome.

7.6 HPA-Axis Assessments

Study design flaws limits interpretability in both pediatric studies. Further, the more sensitive test for assessing HPA-axis effects of a drug, urinary cortisol, was performed in only the adult/adolescent 12-week and 1-year trials. Urinary cortisol excretion showed only minimal changes or increased either as absolute cortisol excretion or cortisol corrected for urinary creatinine over the course of the study among all study groups in both adult/adolescent trials. As compared to placebo, there was no clear relationship between HFA flunisolide dose and urinary cortisol excretion. However, the percentages of patients who changed from responder to non-responder following Cortrosyn stimulation were slightly higher in the HFA flunisolide group (9.1% vs. 7.4%) in ANC-MD-02. Pre and post cortrosyn stimulation cortisol levels were similar among HFA and CFC treatment groups and placebo in the 12-week pediatric study (ANC-MD-03). Among patients in the 1-year pediatric trial (ANC-MD-04, the percentage of responders at baseline who became non-responders at the end of the study included 1 (2.94%) patient in the HFA flunisolide group, 1 (7.7%) patient in the beclomethasone group, and zero patients in the cromolyn group. Please refer to individual study reports for a more detailed review of the individual study findings.