☛ statistical considerations:

- ✦ Two patient populations were analyzed; the intent-to-treat population (ITT) and the evaluable for efficacy population (efficacy population). The ITT population were all patients who received at least one dose of study medication. The efficacy population consisted of all patients who were considered compliant. In the ITT analysis, the patient's last recorded value was carried forward to each successive time point in the analysis. The ITT analysis was performed for the primary efficacy variable, other efficacy variables and all safety parameters while the efficacy population was evaluated for all efficacy analyses.

- ✦ For comparison of BDP-HFA and BDP-CFC, a 90% confidence interval for the mean difference between the two treatments was constructed. In terms of AM PEF, if the 90% confidence interval for the mean difference between active treatments was completely contained within the interval of ± 40 L/min the treatments were considered "equivalent".

- ✦ Survival curves for withdrawal due to asthma symptoms were compared using a log rank test. Estimates of the time without worsening of asthma symptoms were based on Kaplan-Meier estimates.

- ✦ Two post-hoc subgroup analyses were done for the primary efficacy parameter; patients taking vs patients not taking intranasal corticosteroids; patients taking vs patients not taking antihistamines.

- ✦ Patients could be included in the efficacy analysis even if they did not have a 15% or greater increase in AM PEF over the last 3 days of the oral corticosteroid treatment period if they had either: a 14% or greater improvement in AM PEF averaged over the last 3 days of the oral corticosteroid treatment period; or they had 10-13% improvement in AM

PEF averaged over the last 3 days of the oral corticosteroid treatment period and had a 15% or greater improvement in FEV-1 following the oral corticosteroid treatment period. There were 34 such patients, 15 in the BDP-HFA group and 19 in the BDP-CFC group.

- An unplanned analysis after unblinding was done for "equivalency testing" in regard to change in AM PEF from the end of the oral corticosteroid period to the end of the study using a ± 25 L/min interval, while "equivalency testing" was done using ± 0.2 L and ± 7.5% intervals for change for absolute and percent predicted change in FEV-1 from the end of the oral corticosteroid period to the end of the study. An interim analysis of pooled standard deviation in AM PEF was performed to determine if sample size calculations would provide sufficient numbers of patients to detect equivalence.

- The sponsor states that "the protocol had outlined that analysis of covariance, adjusting for the baseline mean response, would be used for all analysis of efficacy data" but that "assumptions of the analysis of covariance for parallelism were not met and therefore analysis of covariance was not performed."

STUDY RESULTS

- There were 11 patients who had major protocol violations and hence complete exclusion of their data from the efficacy analysis. This included 6 BDP-HFA patients and 4 BDP-CFC patients who had < 15% increase in AM PEF at the end of the oral corticosteroid period. Major protocol violations included inadequate period on or dose of inhaled corticosteroids prior to entry and non-compliance.

  There were 30 patients who had partial exclusion of data because of failure of the clinic spirometer to meet ATS criteria, use of protocol-excluded medications (2 BDP-CFC and 1 BDP-HFA patients) and non-compliance. One BDP-HFA patient

used inhaled Pulmicort 200 mcg bid during the entire study which was not discovered until after the analyses were completed. These protocol violations were approximately equally divided between the two study groups and did not influence the study results.

☛ There were 19 BDP-HFA patients excluded from the efficacy analysis, 15 for being undercompliant and 6 (as noted above) for major protocol violations, compared to 18 patients in the BDP-CFC group, 2 for being overcompliant, 12 for being undercompliant and 4 (as noted above) for major protocol violations.

☛ DEMOGRAPHICS: There were no significant baseline differences between the treatment groups in regard to gender, age, race, smoking history, duration of asthma, concomitant medications, pulmonary function, asthma symptom scores, nighttime sleep disturbance or beta agonist use (see table 4, p189, v1.92 below).

Table 4: Prestudy Demographic Characteristics and Habits (Patients Included in the Intent-to-treat Analysis)

		HFA-BDP 800 mcg (N = 116)	CFC-BDP 1500 mcg (N = 117)	P-value
Gender[a]	Female	63 (54.3%)	68 (58.1%)	0.426
	Male	53 (45.7%)	49 (41.9%)	
Age (years)[b]	Mean	40.5	40.1	0.827
	SD	13.34	14.12	
Race[a]	Caucasian	116(100.0%)	115 (98.3%)	0.782
	Afro-Caribbean	0 (0.0%)	1 (0.9%)	
	Asian	0 (0.0%)	1 (0.9%)	
Height (cm)[b]	Mean	166.8	167.3	0.729
	SD	9.77	9.43	
Weight (kg)[b]	Mean	72.68	72.79	0.961
	SD	13.518	16.625	
Tobacco Use[a]	None	71 (61.2%)	61 (52.1%)	0.139
	Current	20 (17.2%)	21 (17.9%)	
	Past	25 (21.6%)	35 (29.9%)	
Alcohol use[a]	None	34 (29.3%)	35 (29.9%)	0.608
	Current	78 (67.2%)	78 (66.7%)	
	Past	4 (3.4%)	4 (3.4%)	
Substance abuse[a]	None	116(100.0%)	117(100.0%)	1.000

[a] Based on a categorical linear model with treatment, center and treatment by center interaction terms in the model. Race was grouped as Caucasian versus non-Caucasian and smoking history, alcohol use and substance abuse were grouped as none versus current/past.

[b] Based on an ANOVA with treatment, center and treatment by center interaction terms in the model.

☛ EFFICACY FINDINGS:

PULMONARY FUNCTION TESTING

* AM PEF: Mean AM PEF increased substantially after treatment with prednisolone, and decreased minimally after institution of inhaled corticosteroids. There was no clinically significant difference between the response to 800 mcg/day of BDP-HFA and 1500 mcg/day of BDP-CFC (see figures below; fig2, p200, v1.192; fig4, p205, v1.192; and tables below; tab13, p201, v1.192; tab14, p203, v1.192; tab15, p204, v1.192). For the efficacy population, the curves over the 12 weeks of treatment were essentially superimposable.

A greater decrease in mean AM PEF was seen in female patients who received BDP-HFA than was seen in male patients. This distinction was not seen in the BDP-CFC group. The significance of this finding, if any, is unclear.

Patients with a smoking history, whether they received BDP-HFA (N = 45) or BDP-CFC (N = 56) had a greater mean decrease in AM PEF from the end of the oral corticosteriod treatment period throughout the study, although they also had lower mean AM PEF values at run-in and after treatment with oral corticosteroids (see pages 355-356, vol 1.192).

Patients who were concomitantly using intranasal corticosteroids had less of a decrease from the end of the oral corticosteroid treatment period throughout the study than those patients who were not using intranasal corticosteroids in the group that received BDP-HFA (6 patients using intranasal corticosteroids), while the reverse was true in the BDP-CFC group (4 patients using inhaled corticosteroids). The reason for this difference is not readily apparent, although the number of patients taking intranasal corticosteroids was very small (see pages 357-358, vol 1.192).

At most time points, there was a greater decrease in mean AM PEF in both groups over the 12 weeks of randomized treatment if the patient

was taking concomitant antihistamines, e.g. a 63% mean decrease in the BDP-HFA group after 12 weeks of treatment in those patients taking antihistamines (N = 7) compared to a 20% mean decrease in those patients not taking antihistamines. There were only 9 patients in the BDP-CFC group who were taking concomitant antihistamines and the mean decrease in AM PEF was 30% as compared to 23% in those not taking antihistamines. No conclusions can be drawn from these findings because of the small number of patients in each group that were taking antihistamines.

There was no clinically significant difference in change in mean PM PEF throughout the 12 weeks of randomized treatment between the BDP-HFA and the BDP-CFC groups.

Figure 2
Adjusted Mean Morning Peak Flow (L/min) and Standard Error by Study Week
(Patients Included in the Intent - to - treat Analysis).

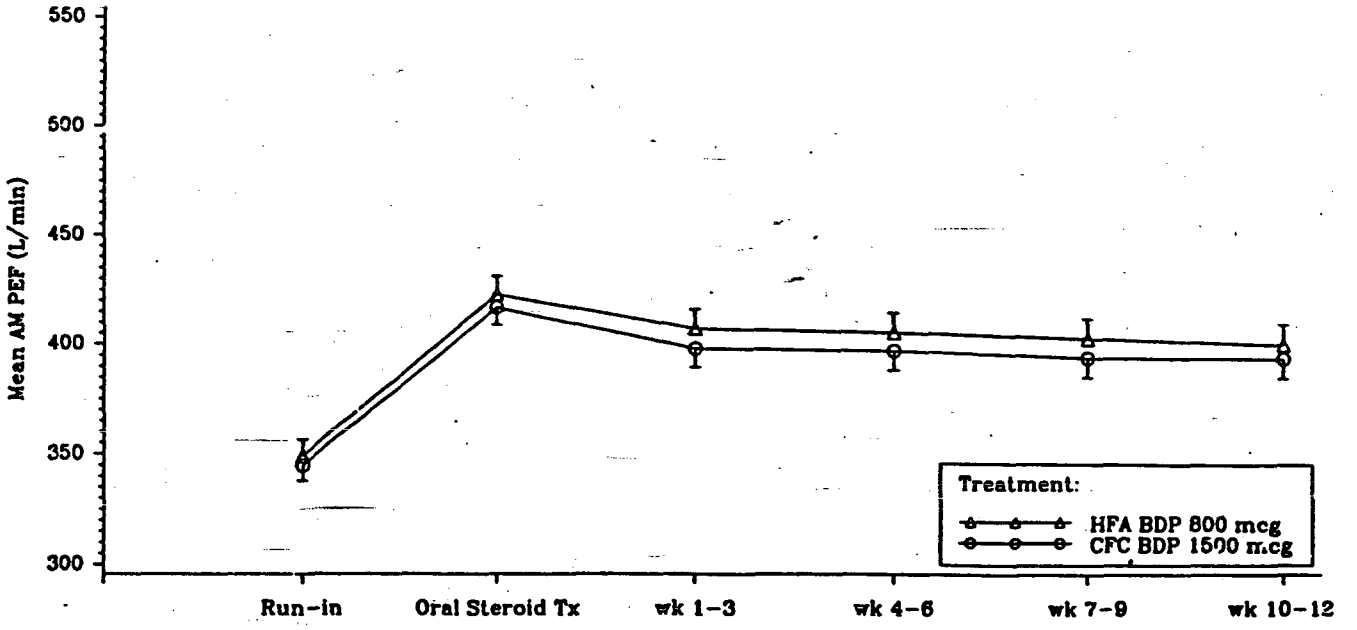


Table 13: Morning Peak Flow (L/min) Throughout Study [a] (Patients Included in the Intent-to-treat Analysis)

Study Week		HFA-BDP 800 mcg	CFC-BDP 1500 mcg
Run-in	Mean	349.1	344.9
	SE	7.42	6.97
	N	115	117
Oral Steroid Tx	Mean	423.0	417.1
	SE	8.46	7.95
	N	115	117
Weeks 1-3	Mean	407.6	398.3
	SE	8.81	8.26
	N	114	117
Weeks 4-6	Mean	406.1	397.6
	SE	9.19	8.65
	N	116	117
Weeks 7-9	Mean	403.6	394.8
	SE	9.31	8.76
	N	116	117
Weeks 10-12	Mean	401.4	395.1
	SE	9.53	8.97
	N	116	117

[a] Based on an ANOVA with treatment, center, and treatment by center interaction terms in the model.

Table 14: Change from Oral Steroid Treatment in Morning Peak Flow (L/min) [a] (Patients Included in the Intent-to-treat Analysis)

Study Week		HFA-BDP 800 mcg	CFC-BDP 1500 mcg
Run-in	Mean	349.1	344.9
	SE	7.42	6.97
	N	115	117
Oral Steroid Tx	Mean	423.0	417.1
	SE	8.46	7.95
	N	115	117
Change from Oral Steroid Tx at Weeks 1-3	Mean	-16.2	-18.8
	SE	3.75	3.52
	N	113	117
Change from Oral Steroid Tx at Weeks 4-6	Mean	-17.5	-19.4
	SE	4.80	4.51
	N	115	117
Change from Oral Steroid Tx at Weeks 7-9	Mean	-20.1	-22.2
	SE	5.37	5.05
	N	115	117
Change from Oral Steroid Tx at Weeks 10-12	Mean	-22.3	-21.9
	SE	5.37	5.05
	N	115	117

[a] Based on an ANOVA with treatment, center, treatment by center interaction terms in the model.

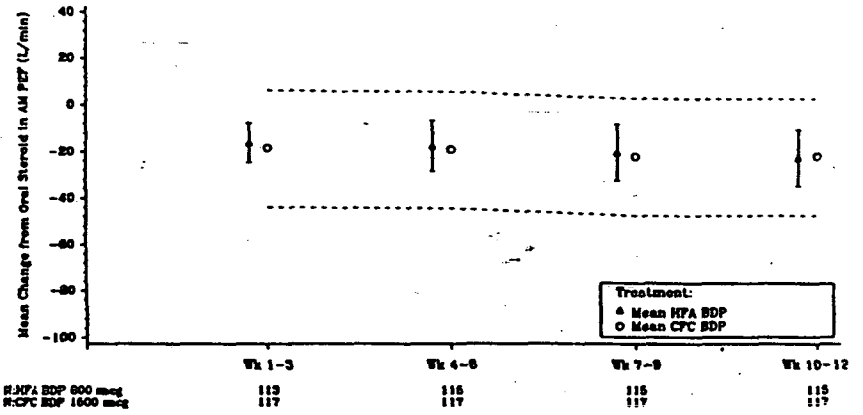
Table 15: Change from Oral Steroid Treatment in Morning Peak Flow (L/min) Equivalence of HFA-BDP 800 mcg Compared with CFC-BDP 1500 mcg (Patients Included in the Intent-to-treat Analysis)

Study Week	Mean Difference[a]	SE	90% C.I. of Difference	P-value for Equivalence[b]
Run-in	4.2	10.18	-12.63, 21.01	< 0.001
Oral Steroid Tx	6.0	11.61	-13.21, 25.17	0.002
Change from Oral Steroid Tx at Weeks 1-3	2.6	5.14	-5.92, 11.08	< 0.001
Change from Oral Steroid Tx at Weeks 4-6	1.9	6.59	-9.03, 12.75	< 0.001
Change from Oral Steroid Tx at Weeks 7-9	2.1	7.37	-10.03, 14.32	< 0.001
Change from Oral Steroid Tx at Weeks 10-12	-0.3	7.37	-12.50, 11.87	< 0.001

[a] Mean difference is the difference in the adjusted means based on an ANOVA with treatment, center, and treatment by center interaction terms in the model.

[b] The p-value is from the two one-sided tests procedure for equivalence. Equivalence was defined as ±25 L/min from the adjusted CFC-BDP 1500 mcg mean.

Figure 4
Equivalence of HFA BDP 800 mcg and CFC BDP 1500 mcg for
Change from Oral Steroid Treatment in Mean Morning Peak Flow (L/min)
(Patients Included in the Intent-to-treat Analysis)



Dashed line is +/- 25 L/min from the CFC BDP mean.
The standard error bar around the HFA BDP mean is the standard error of the difference between HFA BDP and CFC BDP.

✱ FEV-1: Mean FEV-1 increased substantially after administration of oral corticosteroids and remained increased over baseline throughout the 12 weeks of randomized treatment with either 800 mcg/day of BDP-HFA or 1500 mcg/day of BDP-CFC. There was no clinically significant difference between the response after administration of BDP-HFA and BDP-CFC (see figures and table below; fig5, p208, v1.192; fig7, p213, v1.192; tab16, p211, v1.192) and no difference based on analysis of the ITT or the efficacy population.

Table 16: **Change from Oral Steroid Treatment in FEV_1 (L)[a] (Patients Included in the Intent-to-treat Analysis)**

Study Week		HFA-BDP 800 mcg	CFC-BDP 1500 mcg
Run-in	Mean	2.24	2.21
	SE	0.074	0.069
	N	115	117
Oral steroid Tx	Mean	2.45	2.51
	SE	0.079	0.074
	N	115	117
Change from oral steroid Tx at Week 3	Mean	0.07	-0.04
	SE	0.043	0.041
	N	113	115
Change from oral steroid Tx at Week 6	Mean	0.07	-0.02
	SE	0.050	0.047
	N	114	116
Change from oral steroid Tx at Week 9	Mean	0.04	-0.05
	SE	0.051	0.049
	N	114	116
Change from oral steroid Tx at Week 12	Mean	0.05	-0.04
	SE	0.048	0.046
	N	115	116

[a] Based on an ANOVA with treatment, center, treatment by center interaction terms in the model.

Figure 5
Adjusted Mean FEV1 (L) and Standard Error by Week
(Patients Included in the Intent-to-treat Analysis)

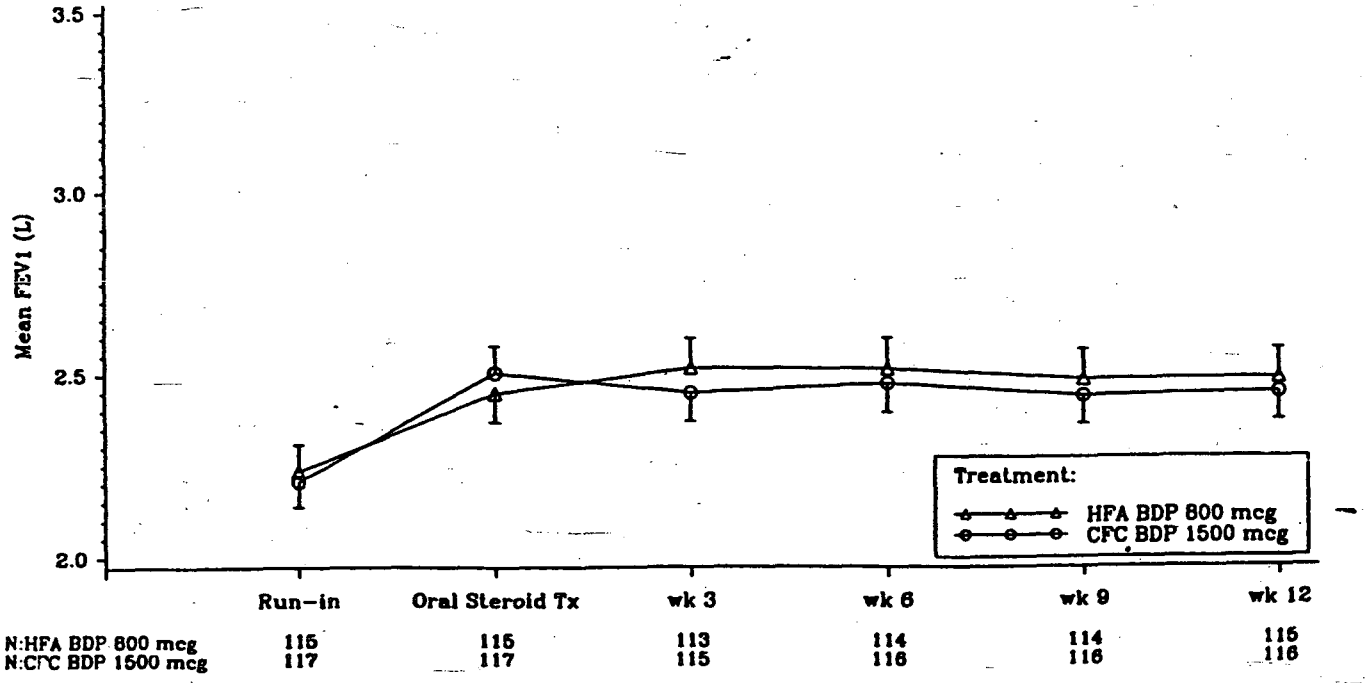
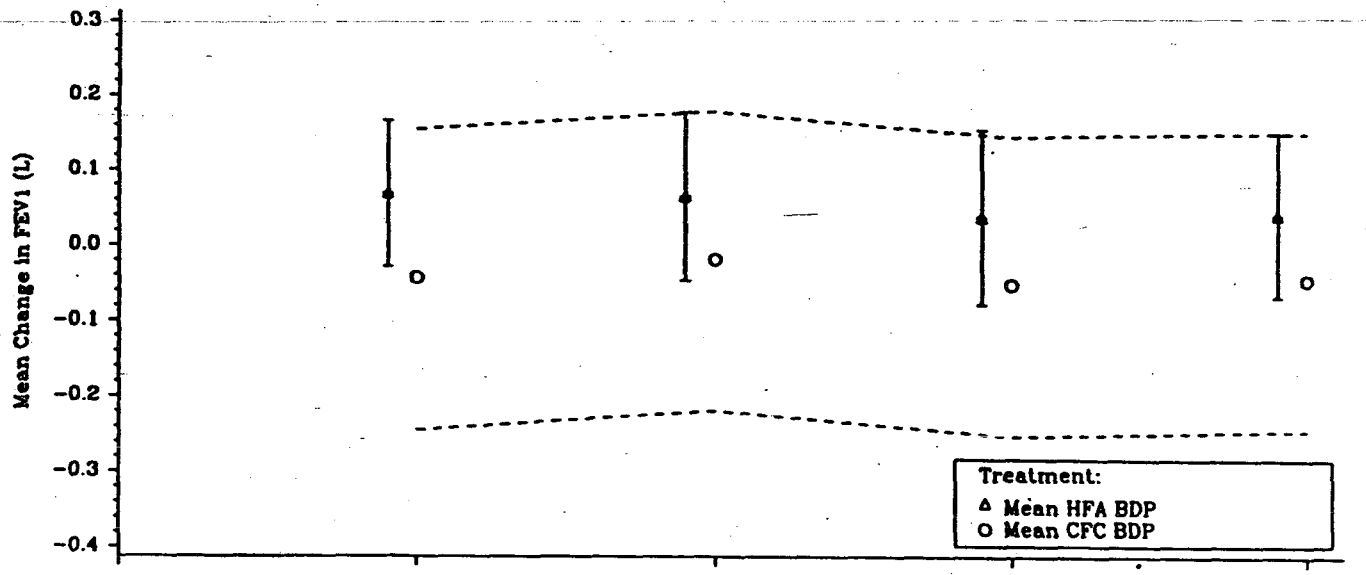


Figure 7
Equivalence of HFA BDP 800 mcg and CFC BDP 1500 mcg for
Change from Oral Steroid Treatment in FEV1 (L)
(Patients Included in the Intent-to-treat Analysis)

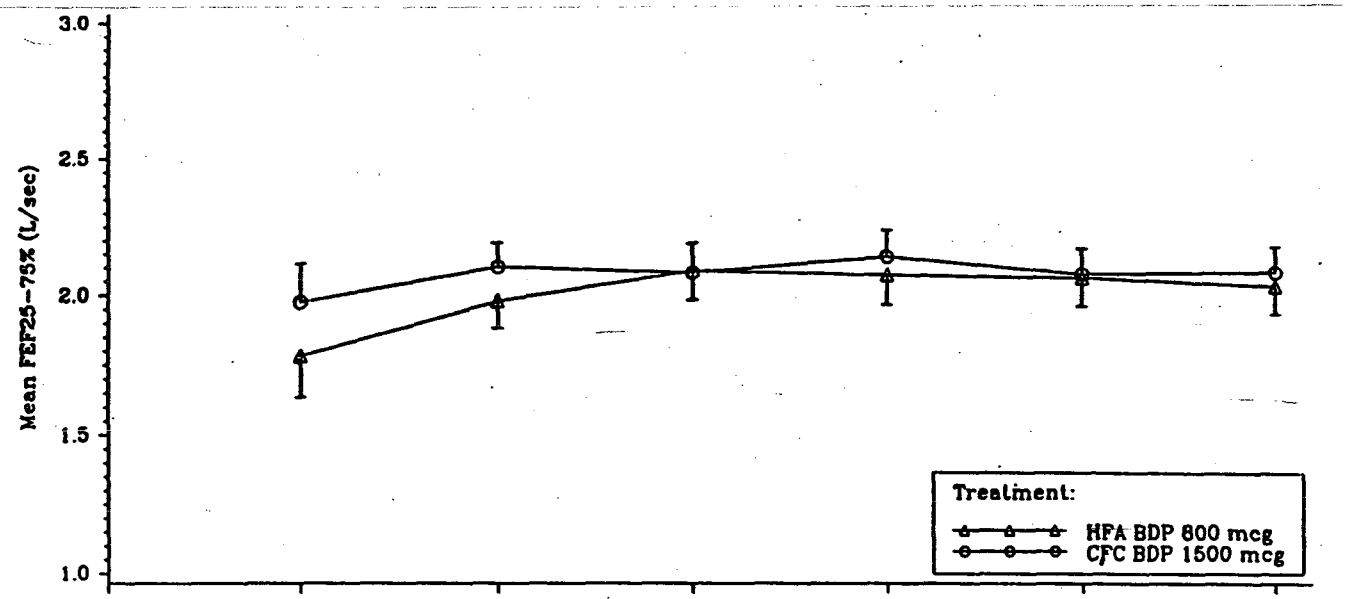


	wk 3	wk 6	wk 9	wk 12
N:HFA BDP 800 mcg	113	114	114	115
N:CFC BDP 1500 mcg	115	116	116	116

Dashed line is +/- 0.2 L from the CFC BDP mean.
The standard error bar around the HFA BDP mean is the standard error of the difference between HFA BDP and CFC BDP.

✱ **<u>FEF 25-75</u>: The increase in mean FEF 25-75 was less after treatment with oral corticosteroids than was seen for other pulmonary function parameters, but there was no decrease in mean FEF 25-75 after initiation of inhaled corticosteroids. There was no clinically significant difference between the group that received BDP-HFA and the group that received BDP-CFC in terms of mean FEF 25-75 over the 12 weeks of randomized treatment (see figure below; fig14.2.4.1.2, p399, v1.192).**

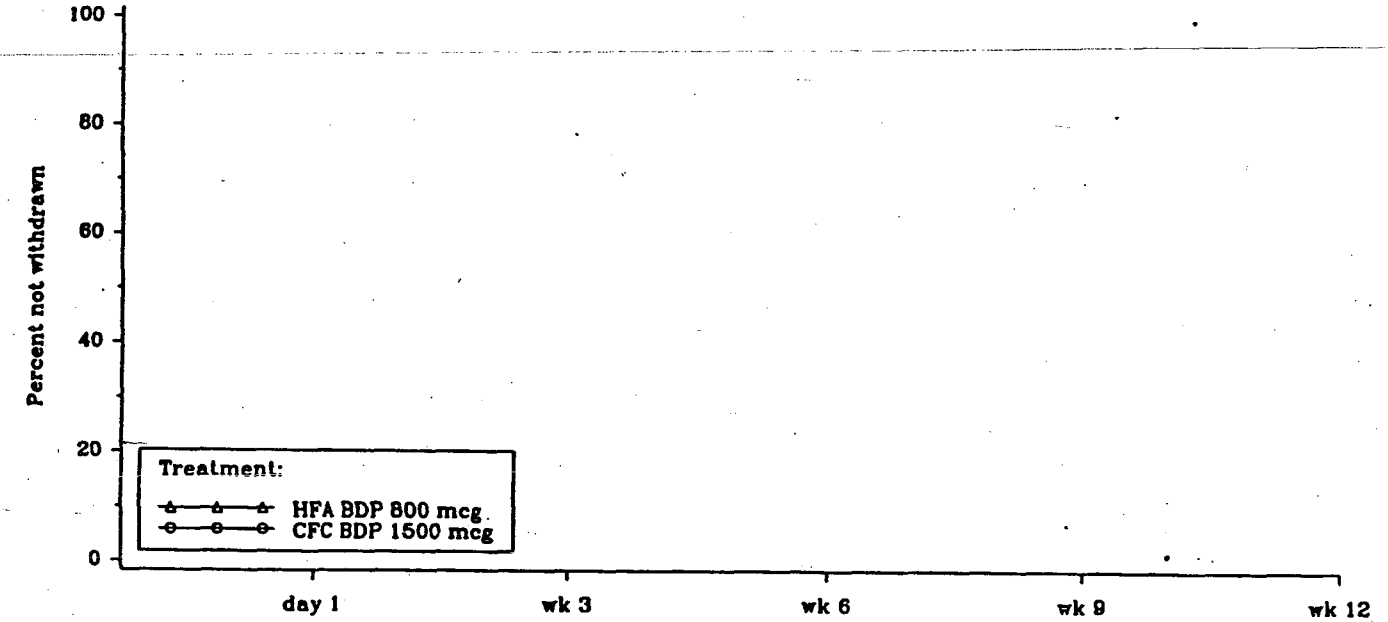
Figure 14.2.4.1.2
Adjusted Mean FEF25-75% (L/sec) and Standard Error by Week
(Patients Included in the Intent-to-treat Analysis)



	Run-in	Oral Steroid Tx	wk 3	wk 6	wk 9	wk 12
N:HFA BDP 800 mcg	116	113	113	114	114	115
N:CFC BDP 1500 mcg	117	117	116	116	116	116

TIME TO WITHDRAWAL BECAUSE OF ASTHMA SYMPTOMS:
There was no clinically significant difference between withdrawal rates due to exacerbation of asthma in the 800 mcg/day BDP-HFA group and the 1500 mcg/day BDP-CFC group (see figure below; fig8, p217, v1.192). There were 8 BDP-HFA patients withdrawn; 2 due to an asthma-related event that met withdrawal criteria (5 BDP-CFC patients fell into this category), 2 due to an asthma-related event that did not meet withdrawal criteria (2 BDP-CFC patients fell into this category), 1 who met withdrawal criteria but was withdrawn for another reason (2 BDP-CFC patients fell into this category), 1 patient met withdrawal criteria but was not withdrawn (1 BDP-CFC patient met this criteria) and 2 patients were withdrawn as having met withdrawal criteria but really did not meet this criteria (no BDP-CFC patients).

Figure 8
Time to Withdrawal Due to Asthma Symptoms
(Patients Included in the Intent-to-treat Analysis)

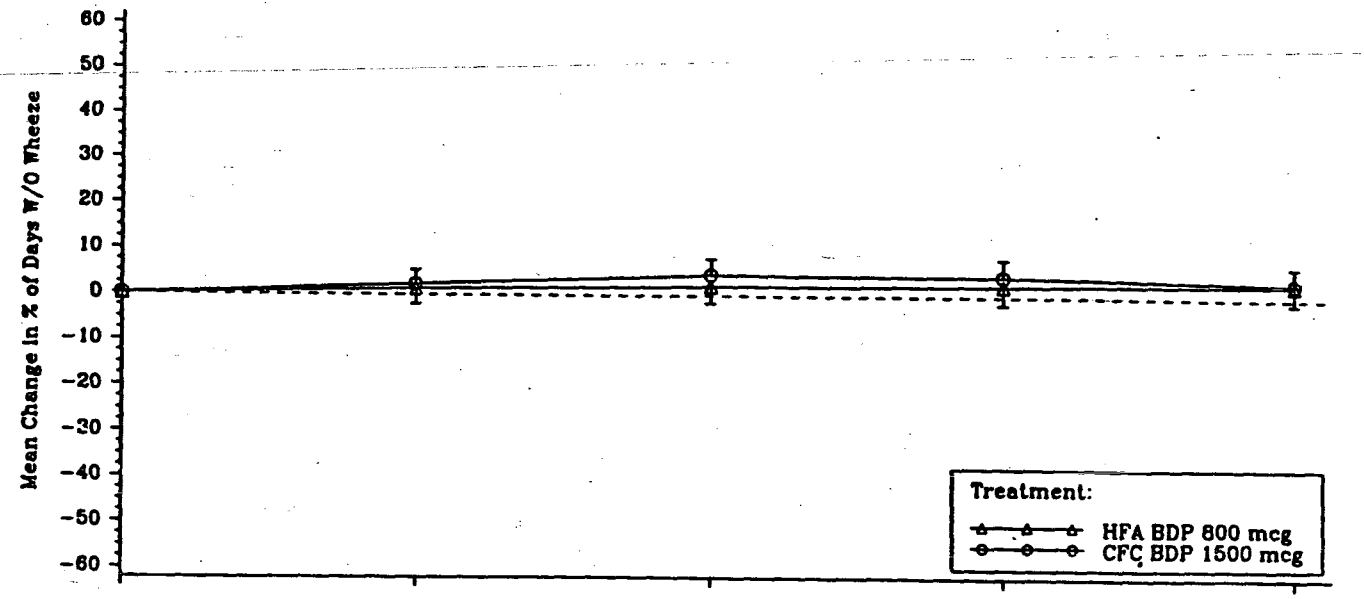


	day 1	wk 3	wk 6	wk 9	wk 12
N:HFA BDP 800 mcg	118	115	111	110	103
N:CFC BDP 1500 mcg	117	116	109	108	104

Overall between-treatment comparison of time to withdrawal due to asthma symptoms p= 0.327

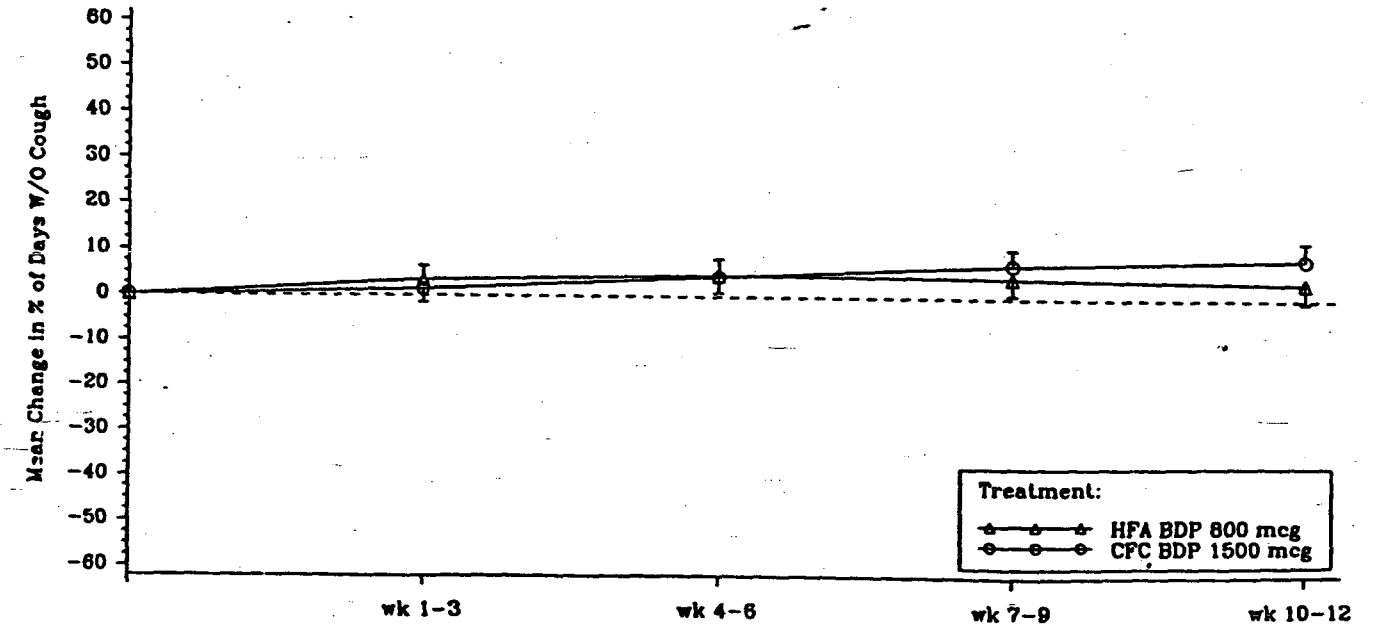
ASTHMA SYMPTOM SCORES: There was no clinically significant difference between the group that received 800 mcg/day of BDP-HFA and the group that received 1500 mcg/day of BDP-CFC and change from baseline was modest in terms of mean change in percent of days without wheezing (see figure below; fig9, p220, v1.192), mean change in wheeze score, mean change in percent of days without cough (see figure below; fig10, p224, v1.192), mean change in cough score, mean change in percent of days without shortness of breath (see figure below; fig 14.2.9.2.2, p33, v1.193), mean change in shortness of breath score, mean change in percent of days without chest tightness (see figure below; fig 14.2.10.2.2, p46, v1.193), or mean change in chest tightness score.

Figure 9
Adjusted Mean Change from Oral Steroid Treatment in Percent of Days Without Wheeze and Standard Error by Study Week
(Patients Included in the Intent-to-treat Analysis)



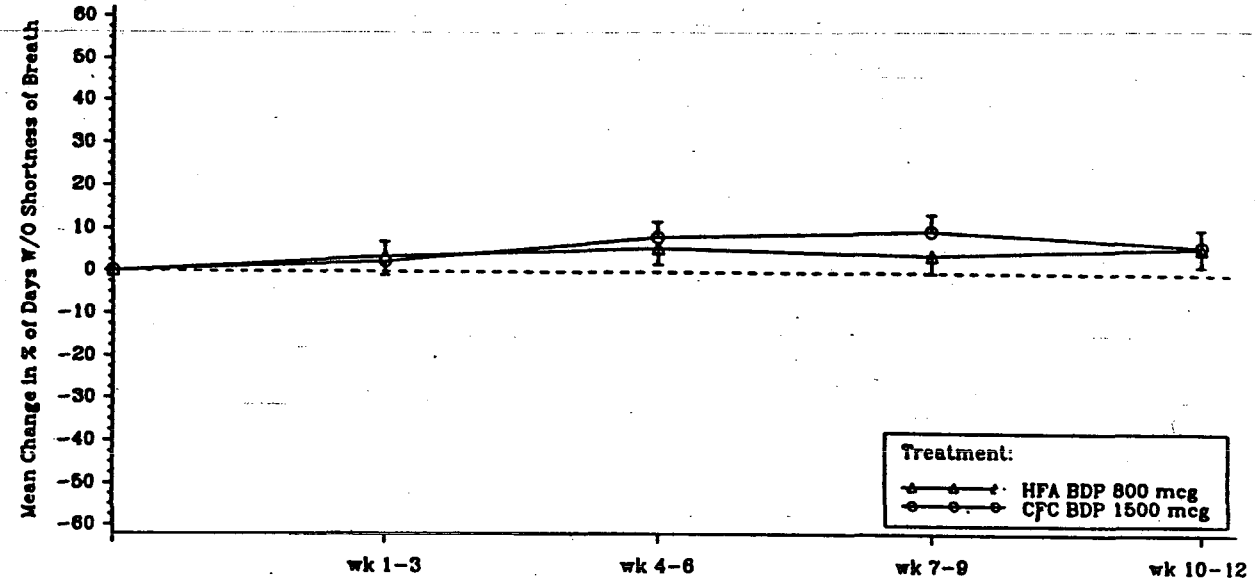
	wk 1-3	wk 4-6	wk 7-9	wk 10-12
N:HFA-BDP 800 mcg	113	114	114	114
N:CFC BDP 1500 mcg	117	117	117	117

Figure 10
Adjusted Mean Change from Oral Steroid Treatment in Percent of Days Without Cough and Standard Error by Study Week
(Patients Included in the Intent-to-treat Analysis)



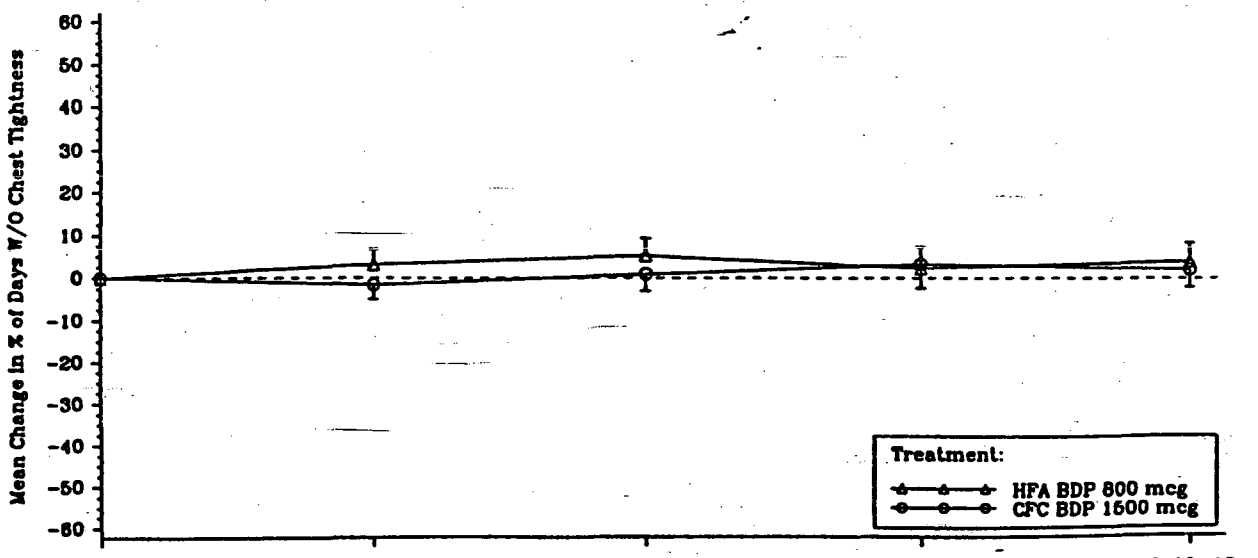
	wk 1-3	wk 4-6	wk 7-9	wk 10-12
N:HFA BDP 800 mcg	113	114	114	114
N:CFC BDP 1500 mcg	117	117	117	117

Figure 14.2.9.2.2
Adjusted Mean Change from Oral Steroid Treatment in Percent of Days Without Shortness of Breath and Standard Error by Study Week
(Patients Included in the Intent-to-treat Analysis)



	wk 1-3	wk 4-6	wk 7-9	wk 10-12
N:HFA BDP 800 mcg	113	114	114	114
N:CFC BDP 1500 mcg	117	117	117	117

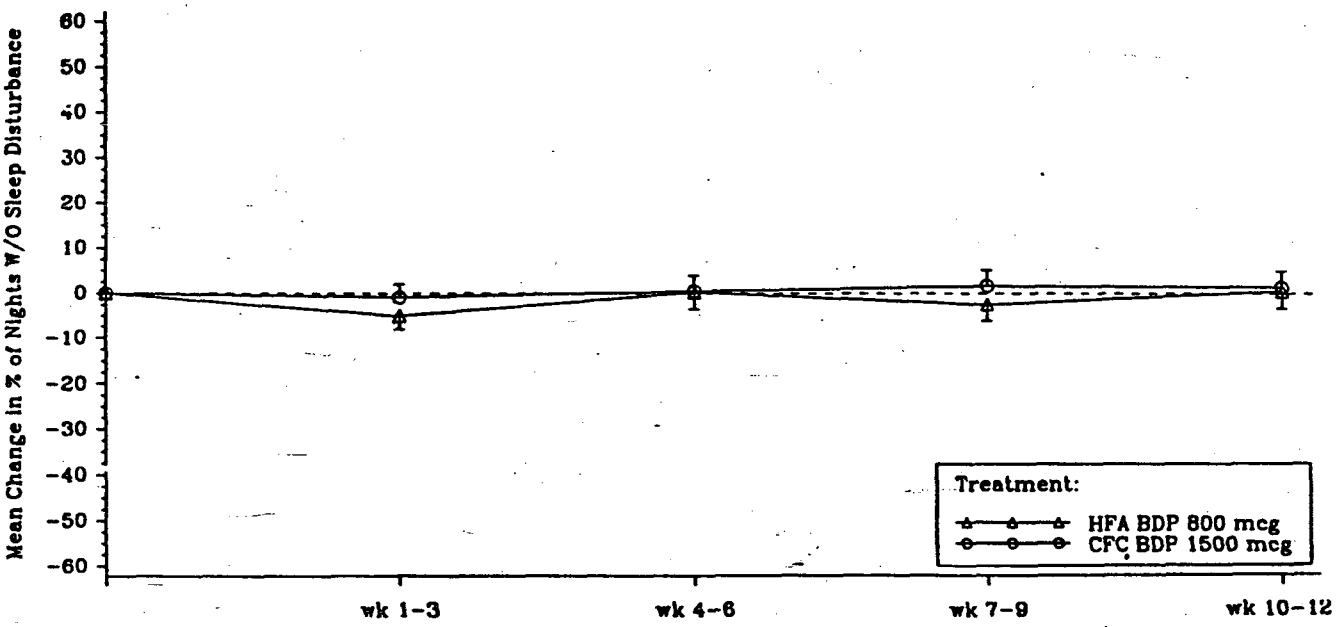
Figure 14.2.10.2.2
Adjusted Mean Change from Oral Steroid Treatment in Percent of Days Without Chest Tightness and Standard Error by Study Week
(Patients Included in the Intent-to-treat Analysis)



	wk 1-3	wk 4-6	wk 7-9	wk 10-12
N:HFA BDP 800 mcg	113	114	114	114
N:CFC BDP 1500 mcg	117	117	117	117

SLEEP DISTURBANCE SCORES: There was no clinically significant difference between the group that received 800 mcg/day of BDP-HFA and the group that received 1500 mcg/day of BDP-CFC in terms of mean change in percent of nights without sleep disturbance or sleep disturbance score (see figure below; fig11, p231, v1.192) and improvement was modest.

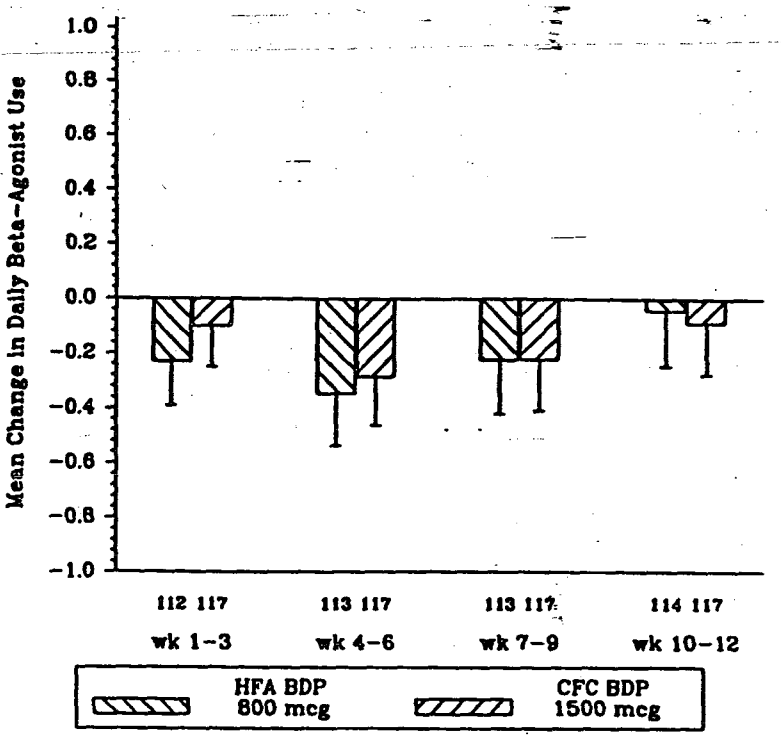
Figure 11
Adjusted Mean Change from Oral Steroid Treatment in Percent of Nights Without Sleep Disturbance and Standard Error by Study Week
(Patients Included in the Intent-to-treat Analysis)



	wk 1-3	wk 4-6	wk 7-9	wk 10-12
N:HFA BDP 800 mcg	112	114	114	114
N:CFC BDP 1600 mcg	117	117	117	117

INHALED BETA AGONIST USE: There was no clinically significant difference between the group that received 800 mcg/day of BDP-HFA and the group that received 1500 mcg/day of BDP-CFC in terms of mean change in daily, daytime or nighttime inhaled beta agonist use and the change seen was modest (see figure below; fig12, p235, v1.192).

Figure 12
Adjusted Mean Change from Oral Steroid Treatment in Daily Beta-Agonist Use and Standard Error by Study Week
(Patients Included in the Intent-to-treat Analysis)



☛ SAFETY FINDINGS:

✱ exposure: see table below; tab25, p251, v1.192.

Table 25: Extent of Exposure to Treatments Used in this Study

Days on Treatment	HFA-BDP 800 mcg (N=116)	CFC-BDP 1500 mcg (N=117)
> 14 Days	116	116
> 28 Days	114	112
> 42 Days	111	109
> 56 Days	111	108
> 70 Days	108	105
> 84 Days [a]	68	71
Mean Time on Treatment (days)	82.3	80.8
Median Time on Treatment (days)	85	85
Range of Treatment Time (days)	21-120	8-105

[a] Twelve HFA-BDP patients and 19 CFC-BDP patients were on study treatments ≥88 days.

✵ adverse events:

- total adverse events: There were 62 patients (53%) in the BDP-HFA group and 69 patients (59%) in the BDP-CFC group who reported an AE during this study.

- Based on AEs that occurred in 2% or greater of the patients in either treatment group, the table below includes those AEs that occurred with a frequency at least 2% greater in patients who received BDP-HFA than occurred in patients who received BDP-CFC. There were 7 patients in each group who reported abnormal taste, but 6 of the 7 BDP-CFC patients specifically attributed abnormal taste to the HFA placebo.

Adverse event	800 mcg/day BDP-HFA	1500 mcg/day BDP-CFC
Cough	3 (3%)	None p=0.1 *
Dysphonia	9 (8%)	4 (3%) p = 0.2
Inhalation site	10 (9%)	8 (7%) p = 0.6
Chest pain	2 (2%)	None p = 0.2
Stomatitis	3 (3%)	1 (1%) p =0.4
Viral infection	3 (3%)	1 (1%) p = 0.4
Conjunctivitis	4 (3%)	None p = 0.06

* the incidence of the adverse event was significantly different in the BDP-HFA and BDP-CFC groups if $p < 0.05$.

- severe adverse events: There were 3 severe AEs reported in the BDP-HFA group and 9 in the BDP-CFC group. The severe AEs in the BDP-HFA group were inhalation taste sensation, pharyngitis, and eczema. No severe pharyngitis was noted in the BDP-CFC group. There were 11 patients (9%) in each group that reported pharyngitis as an adverse event.

- adverse events considered possibly or probably related: There were 30 patients (26%) in the BDP-HFA group and 27 patients (23%) in the BDP-CFC group that had AEs considered possibly or probably related to the study drug. In the BDP-HFA group, the following AEs were considered probably related to study drug: cough (3), dysphonia (3), inhalation site sensation (4), taste (7), infection (3), and pharyngitis (1). In the BDP-HFA group, the following AEs were considered possibly related to the study drug: dysphonia (6), inhalation site sensation (6), weight increase (1), appetite increase (1), increased asthma symptoms (1), pharyngitis (3), rash (1) and purpura (2). Bruising was noted in three patients who received BDP-HFA, one associated with trauma, on physical examination.

- discontinuation due to adverse events: There were 4 BDP-HFA and 5 BDP-CFC patients who withdrew from the study due to an AE. There was one BDP-HFA patient who withdrew because of oral candidiasis, one BDP-HFA patient who withdrew because of increased asthma symptoms, one BDP-HFA patient who withdrew because of taste, chest pain and tremor, and one BDP-HFA patient who withdrew because of moderately severe eczema probably not related to study drug.

- serious adverse events: There was only one serious AE that occurred during randomized treatment with BDP-HFA, which was a tonsillectomy in a 32 year old woman on the first day of drug administration.

- oral candidiasis: One patient in the BDP-CFC group reported an oropharyngeal AE and had a mouth/throat culture that grew out candida in excess of that expected in the normal flora, compared to none in the BDP-HFA group.

* 12 lead ECGs: no significant changes on ECGs was seen after administration of either BDP-HFA or BDP-CFC.

* plasma cortisol: There were 4 BDP-HFA patients and 14 BDP-CFC patients who had a plasma cortisol level after 12 weeks of treatment that was below the lower limit of the NRR and who had a normal plasma cortisol level at the end of the run-in period. Whether the evaluation was done excluding or including patients who had taken oral contraceptives (the former through an unplanned post-hoc analysis), the mean increase in plasma cortisol after 12 weeks of treatment with BDP-HFA compared with the value obtained after the oral corticosteroid period was greater than the increase seen after administration of BDP-CFC (171 nmol/L increase in the BDP-HFA group and 119 nmol/L increase in the BDP-CFC group in the analysis excluding patients who had received estrogen during the study). This finding suggests, although a single plasma cortisol level is inadequate to assess HPA axis effect, that a dose of BDP-HFA that is approximately ½ a given dose of BDP-CFC may produce less systemic effect, while at the same time producing a comparable degree of effect in the bronchial passageways.

* serum osteocalcin: The sponsor notes that there were a large number of osteocalcin results missing at each time point. Based on the data that was available, there was no clinically significant difference in serum osteocalcin levels after administration of BDP-HFA or BDP-CFC.

* laboratory tests: Not unexpectedly, there were patients who received 800 mcg/day of BDP-HFA and patients who received 1500 mcg/day of BDP-CFC who developed an increase in non-fasting plasma glucose to a level above the upper limit of the NRR (NRR 3.8-6 nmol/L) with a normal value at baseline. Examples include 4.8 to 7.1, 5.2 to 7.3, 4.8 to 7.2 nmol/L after administration of BDP-HFA with even greater increases being seen after administration of BDP-CFC. There were 15 BDP-

HFA patients and 10 BDP-CFC patients who went from a low or normal value for plasma glucose to a value above the upper limit of the NRR. Mean changes in plasma glucose from baseline to the final visit were 0.6 and 1.10 nmol/L for BDP-HFA and BDP-CFC, respectively. There were no clinically significant differences between the two treatments for any of the laboratory tests obtained.

☞ <u>overall evaluation of efficacy and safety data and conclusions</u>:

☛ The sponsor has shown that 800 mcg/day of BDP-HFA at a concentration of 100 mcg/puff produces efficacy comparable to 1500 mcg/day of BDP-CFC at a concentration of 250 mcg/puff. This has been demonstrated, however, without a placebo control to validate the study data and using an active treatment control at a concentration that is not marketed in this country. Therefore, given these defects in the study, any demonstration of comparability is questionable, in terms of the clinical applicability of this finding.

☛ Cross-study comparison with study 1129 is not appropriate, given the active treatment control used in this study and the concentration of BDP-HFA used (100 mcg/puff whereas a 50 mcg/puff was used in study 1129), as well as other limitations on such comparisons. The potential for such differences to produce an unexpected response is highlighted by the finding that 800 mcg/day of BDP-HFA in this study was less effective, based on changes in FEF 25-75 and AM PEF, than 400 mcg/day of BDP-HFA in study 1129.

☛ The sponsor has not designed this study appropriately to demonstrate [redacted] of BDP-HFA and BDP-CFC. This study was also not appropriately designed to [redacted]

☛ Therefore, this study can not be used to support the efficacy [redacted] because the active treatment control at the concentration studied, is not marketed in this country. Nor can the sponsor claim [redacted] of 800 mcg/day of BDP-HFA and 1500 mcg/day of BDP-CFC.

☛ There were no concerns raised in regard to safety of a dose of 800 mcg/day of BDP-HFA at a concentration of 100 mcg/puff, based on the safety parameters evaluated in this study.

ABSTRACT

METHODS: Study 1163 was a block randomized, open label, multicenter (US, UK, Belgiumm Netherlands), parallel, repetitive dose, active treatment controlled study in 354 adolescent and adult patients (354 patients randomized to receive BDP-HFA, 119 to receive BDP-CFC) who had mild asthma receiving a stable dose of inhaled corticosteroids between 400 and 1600 mcg/day and who had normal adrenal function. After a 14 day run-in period on the dose of inhaled corticosteroid that they were currently taking, patients were randomized to continue on the same dose of BDP-CFC or switch to BDP-HFA at ½ the dose, using either a 50 or 100 mcg/puff concentration, for a period of 12 months. During the first 8 weeks of randomized treatment, patients were maintained on a stable dose of either BDP-HFA or BDP-CFC. After the first 8 weeks, patients were titrated to as low or high a dose as was needed to control their asthma. Parameters evaluated included AM and PM PEF, other pulmonary function testing, asthma symptoms, sleep disturbance scores, inhaled beta agonist use, and QOL assessments. From a safety perspective, adverse events were monitored, patients had assessment for oropharyngeal candidiasis, and laboratory tests, ECGs, vital signs and serum osteocalcin were evaluated. HPA axis assessment was made on the basis of change in plasma cortisol levels and ACTH stimulation testing.

RESULTS: Baseline comparison of the treatment groups showed that there was a higher percentage of current smokers and males in the BDP-HFA group, and as a result of the latter, higher actual pulmonary function, although percent predicted FEV-1 and AM PEF were comparable between the two groups.

There was no greater deterioration of asthma in patients who received BDP-HFA after they were switched from BDP-CFC than in patients who remained on BDP-CFC during the first eight weeks of the study. Patients receiving BDP-HFA had a slightly greater improvement from baseline in mean AM PEF than did patients receiving BDP-CFC, except when measured after 8 weeks of treatment, while mean change

from baseline in FEV-1 as percent of predicted was slightly greater in the BDP-CFC group than in the BDP-HFA group after 8 weeks of treatment and throughout the rest of the study. These differences were not clinically significant. There was no clinically significant difference between the two groups in terms of other pulmonary function tests, asthma symptoms, beta agonist use or QOL.

Fatigue, abdominal pain, strain, URIs and sinusitis occurred significantly more frequently in the group that received BDP-HFA. The clinical significance of this finding, if any, is unclear. There were more severe adverse events in the BDP-CFC group, but the most frequent severe adverse events in the BDP-HFA group were headache and increased asthma symptoms. A dose-response trend was not seen for either treatment group in regard to severity of adverse events. More patients in the BDP-CFC group also had adverse events that were considered possibly or probably related to study drug. In the first 8 weeks after switching from BDP-CFC to BDP-HFA, more dysphonia, inhalation site sensation, inhalation taste and sinusitis were seen in the BDP-HFA group than in patients who remained on BDP-CFC. There were 6 BDP-HFA and 1 BDP-CFC patients who were withdrawn from the study because of an adverse event. Of the 6 BDP-HFA patients, rash, vomiting, inhalation site sensation and edema with myalgia were considered possibly/probably related to study drug. There were also 7 BDP-HFA patients who withdrew from the study because of asthma symptoms, which did not occur in any of the BDP-CFC patients. Serious adverse events were reported in 17 of the BDP-HFA and 8 of the BDP-CFC patients, although none of these was considered to be related to the study drug.

Only in the BDP-CFC group that received 1000-1600 mcg/day was there a decrease in mean plasma cortisol levels seen from month 8 until the conclusion of the study. There was no clinically significant difference at any time point in the percent of patients in the two treatment groups that had plasma cortisol levels outside the normal reference range. The number of patients who had an abnormal cosyntropin response was generally greater in the BDP-HFA group,

e.g. 3 BDP-HFA patients and no BDP-CFC patients after 2 months of treatment. These differences were small and probably not clinically significant. Less of a decrease in mean incremental cortisol levels and a greater mean peak cortisol level was seen in the BDP-HFA group at all time points after ACTH injection. There were no clinically significant differences between the two groups in terms of serum osteocalcin, laboratory tests, vital signs or ECGs.

DISCUSSION: The database from this study is adequate (n = 288) to support a claim for the safety of BDP-HFA over a dose range of 200 – 800 mcg/day. Adrenal function was evaluated in 110 patients which is adequate to support the safety of BDP-HFA at doses lower than 800 mcg/day in terms of adrenal effect, but not the safety of the 800 mcg/day dose, since only 5 patients at this dose range were evaluated in terms of effect on HPA axis. Although there are no safety concerns raised by any of the safety parameters evaluated, there were more patients in the BDP-HFA group who were withdrawn from the study because of adverse events and more patients in this group who had serious adverse events. Nevertheless, it is the lack of adequate data relating to the effect of the 800 mcg/day dose of BDP-HFA on the HPA axis, that makes it difficult to conclude that the safety of BDP-HFA has been demonstrated in this study across the entire dose range proposed for the marketed product. Moreover, the sponsor has not provided appropriate data, based on the data from the first 8 weeks of the study

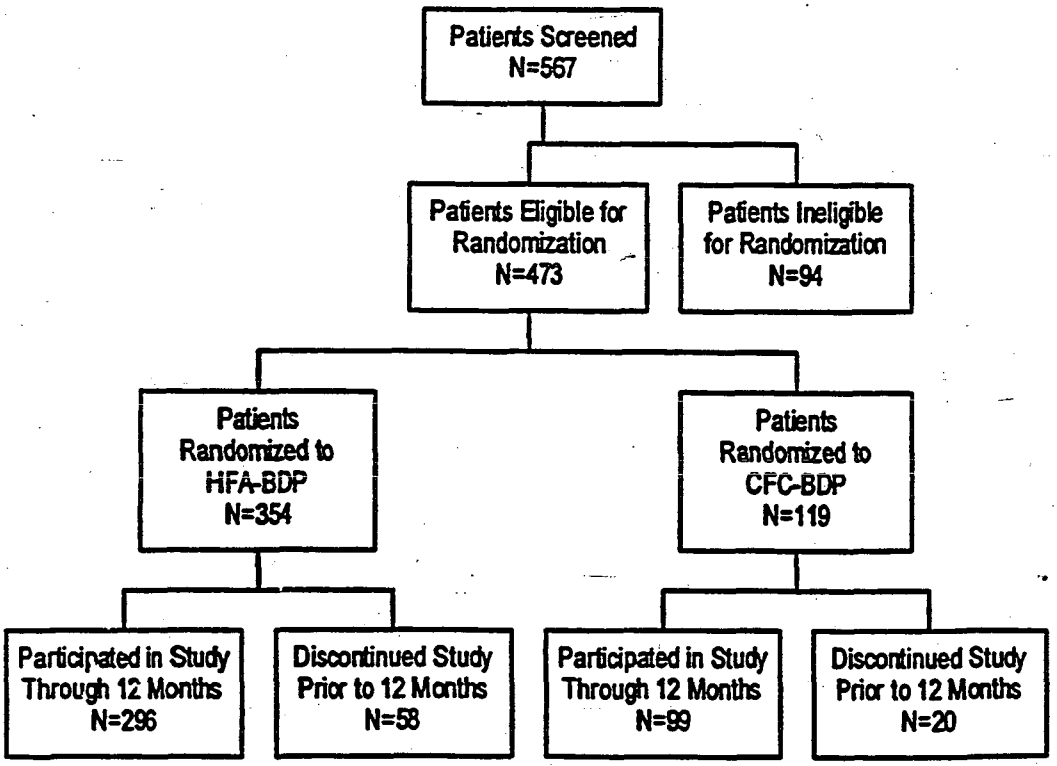
It is impossible to make any conclusions in this regard because of the wide array of doses of both BDP-HFA and BDP-CFC and the different concentrations of these two drug products.

☎ study 1163:

☛ The primary objective of this study was to compare the safety of BDP-HFA and BDP-CFC through 12 months of treatment. The secondary objective of this study was to determine if there was any change in efficacy or safety when patients were switched from previous treatment with BDP-CFC to BDP-HFA.

☛ number of patients: 567 patients screened; 473 patients enrolled; 354 patients randomized to BDP-HFA and 119 patients randomized to BDP-CFC (see flow chart below).

Figure 10.1.A: Disposition of Patients



94 patients were ineligible (see table below; tab 10.1.A, p202, update).

Table 10.1.A: **Number (%) of Patients Screened but Ineligible for Randomization by Reason**

Reason for Ineligibility	No. (%)
Violation of Incl/Excl Criteria	50 (53.2)
Withdrew Consent	13 (13.8)
FEV_1 <60% of Predicted at Screening	12 (12.8)
Laboratory Abnormalities	6 (6.4)
Personal	3 (3.2)
Difficulty Obtaining Lab Draw	2 (2.1)
Not Compliant with Diary Entry Cards	1 (1.1)
Pregnancy	1 (1.1)
Intercurrent Illness	1 (1.1)
Noncompliance	1 (1.1)
Inability to Perform PFTs	1 (1.1)
Failed to Return	1 (1.1)
Other	2 (2.1)
Total	94 (100.0)

A significantly greater percentage of patients received higher doses of BDP-CFC and BDP-HFA in the UK than in the US while the vast majority of patients who received lower doses of these drug products were in the US (see tables below; tab 10.1.C, p203, update; tab 10.1.D, p203, update). This reflects different approaches to patient management of asthma in these countries, as well as the maximum approved dose of BDP-CFC in the United States.

Table 10.1.D: **Number (%) of Patients Randomized to Each Dose Group of CFC-BDP by Country**

Country	≤500 mcg[a] No. (%)	>500 to 1000 mcg No. (%)	>1000 to 1600 mcg No. (%)	Overall No. (%)
US	56 (87.5)	17 (34.7)	0 (0.0)	73 (61.3)
NL/BE	8 (12.5)	12 (24.5)	1 (16.7)	21 (17.6)
UK	0 (0.0)	20 (40.8)	5 (83.3)	25 (21.0)
Total	64 (53.8)	49 (41.2)	6 (5.0)	119 (100.0)

[a] All patients in this dose group were randomized to 500 mcg total daily dose.

☛ age range: 12-68 years

☛ patient population:

- ✱ asthma of at least 6 months duration; on a stable dose of inhaled BDP-CFC between 400 and 1600 mcg/day for at least 2 weeks prior to the study; FEV-1 60% or greater without inhaled beta agonist for 6 hours; documented reversibility of 15% or more after an inhaled beta agonist, a course of inhaled or oral corticosteroids, or a positive methacholine or histamine challenge; using inhaled beta agonist on PRN basis.

- ✱ patients were allowed to use concomitant medications for asthma during the study; patients were withdrawn if: 1) they experienced > 4 exacerbations (> 3 days treatment with oral or IV corticosteroids, hospitalization, or urgent medical care) over the 12 weeks of the study; or 2) they experienced > 2 exacerbations over the first 2 months of the study;

- ✱ plasma cortisol level at baseline within 10% of the lower limits of the NRR; using < 400 mcg/day of intranasal corticosteroids.

☛ study design: open label, multicenter (US, UK, Belgium, Netherlands; a total of 38 sites), block randomized, parallel, repetitive dose, active treatment controlled study.

☛ drug administration:

✱ patients were required to discontinue use of spacers at the prestudy visit (about 18% were using a spacer at the prestudy visit);

✱ BDP-HFA at a dose of 200-800 mcg/day; BDP-CFC at a dose of 400-1600 mcg/day; BDP-HFA was administered as either a 50 mcg/puff or a 100 mcg/puff concentration dependent on the total daily dose; 2-5 puffs bid of BDP-HFA were used (see table below);

✱ each inhaler was primed twice before dispensing; patients were not to prime the inhalers after that; patients were to be kept on a stable dose of medication over the first 8 weeks of the study; after the first 8 weeks, patients could be titrated to a dose of BDP-HFA as low as 100 mcg/day.

Table 9.1.4.1.A: Dose Conversion Table for Patients Randomized to HFA-BDP Using CFC-BDP 50-mcg per Puff Inhaler During Run-in

CFC Total Daily Dose During Run-in (mcg)	HFA Total Daily Dose During Study (mcg)	Strength of HFA Inhaler (mcg per puff)	Dosing Regimen During Study (puffs bid)
400	200	50	2
600	300	50	3
800	400	100	2
1000	500	50	5

Table 9.1.4.1.B: Dose Conversion Table for Patients Randomized to HFA-BDP Using CFC-BDP 100-mcg per Puff Inhaler During Run-in

CFC Total Daily Dose During Run-in (mcg)	HFA Total Daily Dose During Study (mcg)	Strength of HFA Inhaler (mcg per puff)	Dosing Regimen During Study (puffs bid)
400	200	100	1
600	400	100	2
800	400	100	2
1200	600	100	3
1600	800	100	4

Table 9.1.4.1.C: Dose Conversion Table for Patients Randomized to HFA-BDP Using CFC-BDP 250-mcg per Puff Inhaler During Run-in

CFC Total Daily Dose During Run-in (mcg)	HFA Total Daily Dose During Study (mcg)	Strength of HFA Inhaler (mcg per puff)	Dosing Regimen During Study (puffs bid)
500	400	100	2
1000	600	100	3
1500	800	100	4

Table 9.1.4.1.D: Dosing Table for Patients Randomized to CFC-BDP Using a 100-mcg per Puff Inhaler During Run-in and During the Study

CFC Total Daily Dose During Run-in (mcg)	CFC Total Daily Dose During Study (mcg)	Dosing Regimen During Study (puffs bid)
400	400	2
800	800	4
1200	1200	6
1600	1600	8

The following BDP-CFC products were used.

* Beclovent 50 mcg/puff (lot #s 4ZpA201, 5ZPAA101)

* Becotide 50 mcg/puff (lot S1024MD)

* Becotide 100 mcg/puff (lot #s 10072904, S6704KA, 10065959, 10072883, 10072886)

* Becloforte 250 mcg/puff (lot #s 10072552, S5174MB, 10125138. 10125148, 10125156, 10170961, 10125202)

☛ periods of study:

✱ prestudy evaluation

✱ 14 day run-in period; during this period patients took the same dose and concentration (50, 100, or 250 mcg/puff) of BDP-CFC that they took prior to the study.

✱ 12 months of treatment; with either the dose of BDP-CFC that the patient was taking at the end of the run-in period or BDP-HFA at approximately ½ the dose of BDP-CFC they were taking at this time and at a concentration of either 50 or 100 mcg/puff; randomization was 3:1, i.e. for every patient who was continued on BDP-CFC, 3 patients were randomized to BDP-HFA; patients made a minimum of 8 visits to the clinic during this period of time on day 1 and after 1, 2, 4, 7, 8, 11, and 12 months of treatment.

✱ The data from the first 8 weeks of the 12 month treatment period were compared to data from the run-in period, to determine if there was any change in efficacy or safety when patients were switched from BDP-CFC to BDP-HFA.

☛ parameters evaluated: see flow chart below

Table 9.5.1.3.A: Flow Chart of Safety and Efficacy Measures

PROCEDURE	Prestudy[a]	Study Day 1[a]	Month 1[b]	Month 2[a]	Month 4[a]	Month 7[b]	Month 8[a]	Month 11[b]	Month 12[a]
Informed Consent	X								
Incl/Excl Checklist	X	X							
PFTs[c,d]	X	X		X	X		X		X
Physical Examination	X								X
Pulse Rate, Blood Pressure[d]	X	X		X	X		X		X
12-Lead ECG	X								X
History of Drug Therapy	X	X							
Plasma Cortisol[e]	X	X		X	X		X		X
Serum Osteocalcin[e]		X		X	X		X		X
Hematology Panel[e]	X	X		X	X		X		X
Chemistry Panel[e]	X	X		X	X		X		X
Pregnancy Test[f]	X								X
Urinalysis	X								X
Inhaler Technique	X	X	X	X	X	X	X	X	
PEF Technique	X	X	X			X		X	
Issue Diary Card	X	X	X			X		X	
Collect Diary Card		X	X	X			X		X
Issue Study Medication	X	X		X	X	X	X	X	
Collect Study Medication		X		X	X	X	X	X	X
Concomitant Med. Review			X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X
QOL Questionnaire		X		X	X		X		X
Rapid Cosyntropin[g]	X	X		X	X				X

[a] These visits took place between 0700 and 1000 hours.
[b] These visits took place at any time during the day.
[c] PFTs were performed prior to 1200 hours.
[d] These procedures required a 10-minute rest period prior to start.
[e] These procedures required a 30-minute rest period prior to start.
[f] Serum test in US and UK; urine test in Belgium and The Netherlands.
[g] This test was performed at subset of study sites.

EFFICACY

- AM and PM PEF: during run-in and during the first 2 months of treatment and during study months 7-8 and 11-12; Mini Wright peak flow meter was used; measurements were made upon arising in the morning and before retiring in evening; baseline was the mean AM PEF over the last 7 days of the run-in period; mean AM PEF was computed for each month.

- other pulmonary function tests (FEV-1, FEF 25-75, FVC); during run-in and on study day 1, and after 2, 4, 8 and 12 months of treatment; change from baseline in percent predicted FEV-1; baseline FEV-1 was the value obtained closest to randomization.

- asthma symptoms: during run-in, during the first 2 months of treatment and during study months 7-8 and 11-12; recorded in the evening at the same time as measurement of PEF; wheezing, cough, chest tightness, and shortness of breath were assessed with the following categorical scale:

  0 = none
  1 = mild, little or no discomfort
  2 = mild, annoying, little or no discomfort
  3 = moderate, discomfort, not affecting daily activities
  4 = severe, interfered at least once a day with activities
  5 = severe, could not go to work or carry out activities

- sleep disturbance scores: during run-in, during the first 2 months of treatment and during study months 7-8 and 11-12; recorded in the morning at the same time as measurement of PEF; the following categorical scale was used to assess sleep disturbance:

  0 = none
  1 = awakening once or early
  2 = awakening twice or more
  3 = awake most of night
  4 = could not fall asleep at all

- inhaled beta agonist use: during run-in, during the first 2 months of treatment and during study months 7-8 and 11-12; patients recorded the number of puffs used twice over a 24 hour period.

- quality of life assessments: at baseline, on study day 1 and after 2, 4, 8 and 12 months of treatment; Juniper's QOL questionnaire was used.

SAFETY: The primary safety outcome variable was incidence of adverse events.

- adverse events

- assessment for oropharyngeal candidiasis

- asthma exacerbations; defined as need for urgent care, > 3 days of systemic corticosteroids or hospitalization; if there was no improvement after 2 weeks of treatment with systemic corticosteroids, the patient was withdrawn from the study; if the patient had > 2 exacerbations during the first 2 months of randomized treatment or > 4 exacerbations during the 12 month period of treatment, the patient was withdrawn from the study.

- laboratory tests: at baseline (study day 1) and after 2, 4, 8 and 12 months of treatment; hematology, chemistries, and urinalysis (urinalysis was only performed at baseline and after 12 months treatment.

- vital signs: at baseline (study day 1) and after 2, 4, 8 and 12 months of treatment.

- ECGs: at baseline (prestudy) and after 12 months of treatment.

- serum ostecalcin: at baseline and on study day 1 and after 2, 4, 8 and 12 months of treatment.

- ✦ plasma cortisol: at baseline and on study day 1(baseline) and after 2, 4, 8 and 12 months of treatment.

- ✦ ACTH stimulation: at 25 sites; the rapid cosyntropin test was used; done at prestudy and on study day 1, and after 2, 4 and 12 months of treatment; increment and peak values were determined; the increment value was defined as the largest increase in plasma cortisol concentration observed at 30 or 60 minutes after injection; the peak value was defined as the maximum plasma cortisol level obtained 30 or 60 minutes after injection.

☛ compliance: inhalers were weighed following run-in, on study day 1, and after 2, 8, and 12 months of treatment; patients were considered to be compliant if the weight of the inhaler was within 60-140% of the predicted weight; predicted and actual inhaler canister weights were converted to number of doses administered using mean shot weights.

☛ statistical considerations:

- ✦ There was only one population analyzed, the intent-to-treat population defined as all patients who were randomized and received study drug. The last post-randomization response was carried forward if the patient dropped out or there was missing data.

- ✦ The participating centers were grouped according to countries, with Belgium and The Netherlands being grouped together, i.e. there were 3 "countries", the US, the UK and Belgium/The Netherlands.

- ✦ In the safety analysis, the analysis was stratified according to "country", which adjusted the overall association between treatment and occurrence of adverse events based on sample size and association observed in each "country".

- ✦ All tests were performed at the two-sided 0.05 alpha level.

- ✦ Subgroup analysis included gender, age, intranasal corticosteroid use, antihistamine use, and smoking status.

STUDY RESULTS

☛ **DEMOGRAPHICS: There was a higher percentage of current smokers in the BDP-HFA than in the BDP-CFC group, 7.6% and 5.9% respectively. There was also a higher percentage of males in the BDP-HFA group (43%) than in the BDP-CFC group (34%) (see table below; tab 11.2.1.A, p117, v1.221)**

Table 11.2.1.A: Prestudy Demographic Characteristics, Habits and Asthma/Allergy Profile by Treatment

Characteristic, Habits, Asthma/Allergy Profile		HFA-BDP No. (%) N=354	CFC-BDP No. (%) N=119	P-value
Sex [a]	Female	202 (57.1)	79 (66.4)	0.005
	Male	152 (42.9)	40 (33.6)	
Age (years) [b]	Mean	39.9	39.8	0.971
	SD	14.05	14.08	
Race [a]	Caucasian	330 (93.2)	112 (94.1)	0.450
	Afro-Caribbean	18 (5.1)	2 (1.7)	
	Asian	5 (1.4)	4 (3.4)	
	American Indian	0 (0.0)	1 (0.8)	
	Asian/Pac	1 (0.3)	0 (0.0)	
Height (cm) [b]	Mean	170.6	166.7	0.001
	SD	10.19	9.38	
Weight (kg) [b]	Mean	75.70	74.10	0.449
	SD	17.499	15.982	
Tobacco use [a]	None	227 (64.1)	76 (63.9)	0.909
	Current	27 (7.6)	8 (6.7)	
	Past	100 (28.2)	35 (29.4)	
Alcohol abuse [a]	None	349 (98.6)	117 (98.3)	0.368
	Current	0 (0.0)	1 (0.8)	
	Past	5 (1.4)	1 (0.8)	
Substance abuse [a]	None	348 (98.3)	118 (99.2)	0.952
	Past	6 (1.7)	1 (0.8)	
Duration of asthma [a]	Unknown	1 (0.3)	0 (0.0)	0.989
	<1 Year	4 (1.1)	1 (0.8)	
	1-5 Years	90 (25.5)	30 (25.2)	
	>5 Years	259 (73.4)	88 (73.9)	
Allergies [a]	No	91 (25.7)	35 (29.4)	0.498
	Yes	263 (74.3)	84 (70.6)	
Intent to rinse and spit after treatment [a]				
	No	135 (38.1)	41 (34.5)	0.326
	Yes	219 (61.9)	78 (65.5)	

[a] P-value based on categorical linear model with treatment, country, and treatment-by-country interaction terms in the model. Race was grouped as white vs nonwhite; tobacco use and alcohol and substance abuse were grouped as none vs current/past. Allergies were no vs yes, and duration of asthma as less than 1 year, between 1 to 5 years, and more than 5 years.

[b] P-value based on an ANOVA with treatment, country, and treatment-by-country interaction terms in the model.

Demographic data by initial dose groups for each treatment were tabulated but not analyzed. Upon review of the data certain trends were noted:

Prior to the prestudy visit, all patients had been using an inhaled corticosteroid for at least 3 months. More patients who were randomized into the BDP-CFC group had used oral corticosteroids (2.5%) than patients who were randomized into the BDP-HFA group (0.3%). During the study, there were more patients who used oral corticosteroids in the BDP-CFC group (23%) than in the BDP-HFA group (21%) as well as intranasal corticosteroids, 22% and 18% in the BDP-HFA and BDP-CFC groups, respectively. There were 4 BDP-HFA and 1 BDP-CFC patients who received parenteral corticosteroids. These differences were relatively small and did not, in all probability, bias the study results in any way. Differences in actual pulmonary function at baseline was, according to the sponsor, due to the fact that there were a larger number of males in the BDP-HFA group. This is a reasonable explanation. Percent predicted FEV-1 and AM PEF were comparable between the two groups (see table below; tab 11.2.5.A, p125, v1.221).

Table 11.2.5.A: Baseline Lung Function by Treatment[a]

		HFA-BDP		CFC-BDP		P-value[b]	
		AM PEF	FEV_1	AM PEF	FEV_1	AM PEF	FEV_1
Screening							
Actual Values	Mean	-	2.84	-	2.64	-	0.036
	SD	-	0.812	-	0.673		
	N	-	354	-	118		
% Predicted	Mean	-	83.1	-	83.30	-	0.876
	SD	-	15.29	-	14.13		
	N	-	354	-	118		
Baseline[c]							
Actual Values	Mean	417.4	2.84	390.5	2.73	0.038	0.259
	SD	110.59	0.810	95.48	0.797		
	N	350	353	117	118		
% Predicted	Mean	76.2	83.3	75.7	85.7	0.786	0.227
	SD	16.01	16.19	15.66	15.60		
	N	350	353	117	118		

[a] Morning PEF was recorded in L/min; FEV_1 was recorded as L.
[b] Based on an ANOVA with treatment, country, and treatment-by-country interaction terms in the model.
[c] Morning PEF is the average of the last 7 days of the run-in period; FEV_1 is the value taken at the clinic visit at the end of the run-in period.

Mean scores for all asthma symptoms and nighttime sleep disturbance were very low at baseline, compatible with the a patient population that had mild asthma on appropriate therapeutic regimens.

Table 11.2.6.A: Baseline Asthma Symptoms, Sleep Disturbance Scores, and Beta-Agonist Use by Treatment[a]

Parameter Measured		HFA-BDP	CFC-BDP	P-value
% of Days w/o Wheeze	Mean	66.00	58.42	0.106
	SD	37.839	38.370	
	N	344	116	
Mean Wheeze Score	Mean	0.50	0.68	0.044
	SD	0.690	0.732	
	N	344	116	
% of Days w/o Cough	Mean	65.49	66.83	0.778
	SD	36.968	39.195	
	N	345	114	
Mean Cough Score	Mean	0.55	0.54	0.974
	SD	0.701	0.708	
	N	345	114	
% of Days w/o Shortness of Breath	Mean	57.74	57.82	0.988
	SD	40.760	40.307	
	N	345	115	
Mean Shortness of Breath Score	Mean	0.72	0.77	0.628
	SD	0.830	0.878	
	N	345	115	
% of Days w/o Chest Tightness	Mean	60.76	53.11	0.121
	SD	38.613	41.325	
	N	346	115	
Mean Chest Tightness Score	Mean	0.62	0.83	0.027
	SD	0.723	0.890	
	N	346	115	
% of Nights w/o Sleep Disturbance	Mean	76.57	69.68	0.083
	SD	31.790	34.638	
	N	350	117	
Mean Sleep Disturbance Score	Mean	0.31	0.38	0.178
	SD	0.465	0.481	
	N	350	117	
Mean Daily Beta-Agonist Use	Mean	1.28	1.68	0.526
	SD	1.450	1.736	
	N	24	8	
Mean Daily Beta-Agonist Puffs	Mean	2.81	3.23	0.287
	SD	3.088	3.142	
	N	279	93	

[a] Based on an ANOVA with treatment, country, and treatment-by-country interaction terms in the model.

During the first 2 months of randomized treatment, 83% of the BDP-HFA group and 84% of the BDP-CFC group were compliant; during months 11-12, 82% and 83% of the BDP-HFA and the BDP-CFC groups were compliant, respectively.

☛ **EFFICACY FINDINGS:**

PULMONARY FUNCTION TESTING

✱ **AM PEF: The 95% confidence interval of the differences in adjusted mean change from baseline comparing the treatment groups were all within ± 17 L/min when evaluated every 2 weeks (see table below; tab 11.4.1.1.A, p130, v1.221).**

Table 11.4.1.1.A: Adjusted Mean Change from Baseline in Morning Peak Flow (L/min) by Study Time Periods

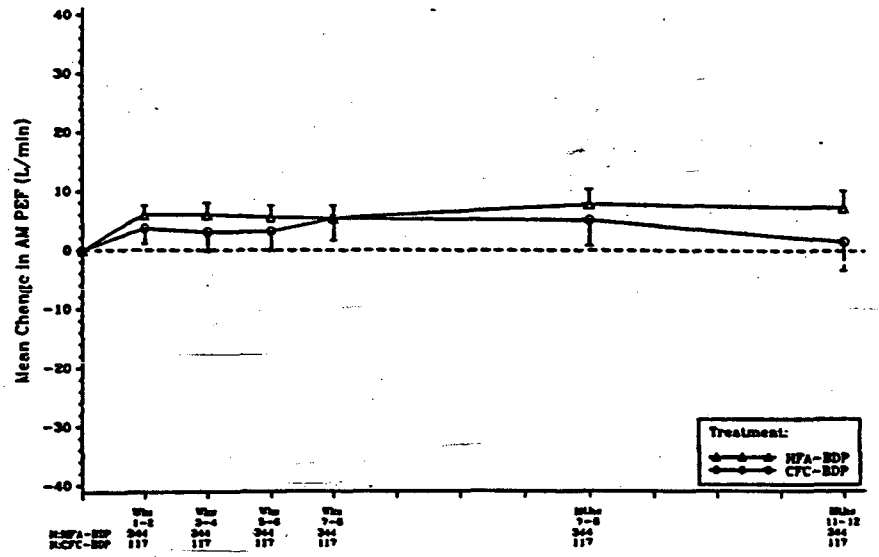
STUDY TIME PERIOD		HFA-BDP	CFC-BDP	95% C.I. of HFA-BDP to CFC-BDP	P-value
Baseline	Mean	417.4	388.7	3.42 to 53.93	0.026
	SE	6.44	11.12		
	N	350	118		
Change from Baseline at Weeks 1-2	Mean	6.1	3.7	-3.63 to 8.36	0.439
	SE	1.54	2.63		
	N	344	117		
Change from Baseline at Weeks 3-4 (Month 1)	Mean	6.0	3.1	-4.69 to 10.62	0.447
	SE	1.97	3.36		
	N	344	117		
Change from Baseline at Weeks 5-6	Mean	5.6	3.2	-5.21 to 10.02	0.536
	SE	1.96	3.34		
	N	344	117		
Change from Baseline at Weeks 7-8 (Month 2)	Mean	5.4	5.4	-8.55 to 8.57	0.998
	SE	2.20	3.76		
	N	344	117		
Change from Baseline at Months 7-8	Mean	7.8	5.1	-7.25 to 12.60	0.596
	SE	2.56	4.36		
	N	344	117		
Change from Baseline at Months 11-12	Mean	7.4	1.5	-5.33 to 17.02	0.305
	SE	2.88	4.90		
	N	344	117		

[a] Based on an ANOVA with treatment, country, and treatment-by-country interaction terms in the model.

Table 11.4.1.1.B: Mean Change from Baseline in Morning Peak Flow (L/min) by Study Time Period and Initial Dose Groups

STUDY TIME PERIOD		HFA-BDP ≤200 mcg	HFA-BDP >200-400 mcg	HFA-BDP >400-800 mcg	CFC-BDP ≤500 mcg	CFC-BDP >500-1000 mcg	CFC-BDP >1000-1600 mcg
Baseline	Mean	380.3	395.4	431.9	390.4	373.0	382.4
	SE	8.26	13.36	10.27	12.03	14.26	27.60
	N	180	65	105	64	48	6
Change from Baseline at Weeks 1-2	Mean	8.2	0.7	6.7	7.1	0.8	3.2
	SE	1.92	2.81	2.23	3.66	2.68	8.89
	N	178	65	101	63	48	6
Change from Baseline at Weeks 3-4 (Month 1)	Mean	5.5	2.0	7.0	7.6	-2.2	6.1
	SE	2.47	3.96	2.99	4.00	3.81	6.66
	N	178	65	101	63	48	6
Change from Baseline at Weeks 5-6	Mean	7.4	4.5	5.3	7.9	-5.1	7.0
	SE	2.23	3.94	3.26	3.98	4.39	6.50
	N	178	65	101	63	48	6
Change from Baseline at Weeks 7-8 (Month 2)	Mean	8.4	4.6	4.5	11.5	-3.3	12.8
	SE	2.52	4.28	3.58	5.02	4.52	6.83
	N	178	65	101	63	48	6
Change from Baseline at Months 7-8	Mean	16.1	7.5	4.3	12.5	0.4	6.3
	SE	3.12	4.97	4.43	4.70	4.68	9.97
	N	178	65	101	63	48	6
Change from Baseline at Months 11-12	Mean	17.0	13.1	1.8	10.2	-2.5	15.7
	SE	4.08	5.01	4.11	4.86	4.79	18.14
	N	178	65	101	63	48	6

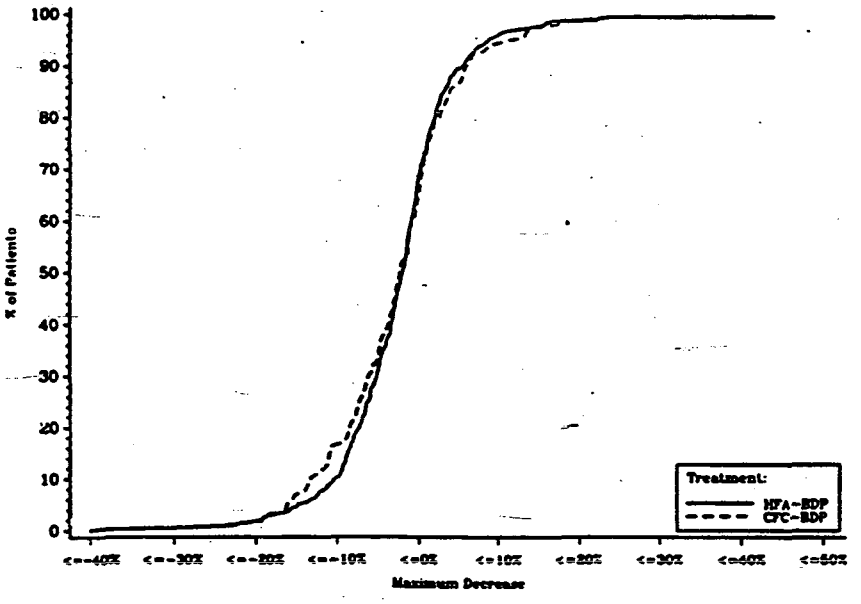
Figure 11.4.1.1.A: Adjusted Mean Change from Baseline in Morning Peak Flow (L/min) and Standard Error by Study Time Period[a]



[a] No statistical differences were seen between treatment groups.

It was important to determine if there was significant deterioration of asthma in patients who were switched from BDP-CFC to BDP-HFA at ½ the dose, compared to the patients who were continued on BDP-CFC after the run-in period. Based on the percent of patients with a maximum decrease in AM PEF, there was no greater deterioration of asthma in patients who received BDP-HFA than in patients who received BDP-CFC after 8 weeks of treatment (see figure and table below; fig 11.4.1.1.B, p134, v1.221; tab 11.4.1.1.C, p134, v1.221)

Figure 11.4.1.1.B: **Cumulative Percent of Patients with Maximum Decrease[a] in Morning PEF During the First 8 Weeks Following Randomization**



[a] Based on biweekly (every 2 weeks) average

Table 11.4.1.1.C: **Percent of Patients with Maximum Decrease[a] in AM PEF by Treatment**

MAXIMUM DECREASE	HFA-BDP (%)	CFC-BDP (%)
≤-30%	0.5	0.0
≤-20%	1.8	1.6
≤-10%	10.3	16.6

[a] Interpolated from empirical distributions.

Subgroup analyses for gender and intranasal corticosteroid use showed no significant differences between the two treatment groups.

In regard to antihistamine use, a significant treatment by subgroup interaction was found with patients in the BDP-CFC group having a larger increase from baseline in mean AM PEF if they were taking antihistamines concomitantly throughout the treatment period, whereas this effect was not seen in the BDP-HFA group until months 7-8. The clinical significance of this finding, if any, is unclear.

In both treatment groups, patients who were current or past smokers had a significantly larger increase from baseline in mean AM PEF than nonsmokers, although this effect was less pronounced after 7-8 months of treatment than earlier. The clinical significance of this finding is also unclear.

Patients 55 years of age and older showed smaller increases in AM PEF than younger patients in both treatment groups until 11-12 months of treatment when older patients receiving BDP-CFC had larger increases in AM PEF than younger patients, while the reverse was true in the BDP-HFA group. Because of the small number of patients in the group that was 55 years and older (n = 17), the clinical relevance of this finding, if any, is unclear.

* PM PEF: There were no significant differences between the two treatment groups at any time point.

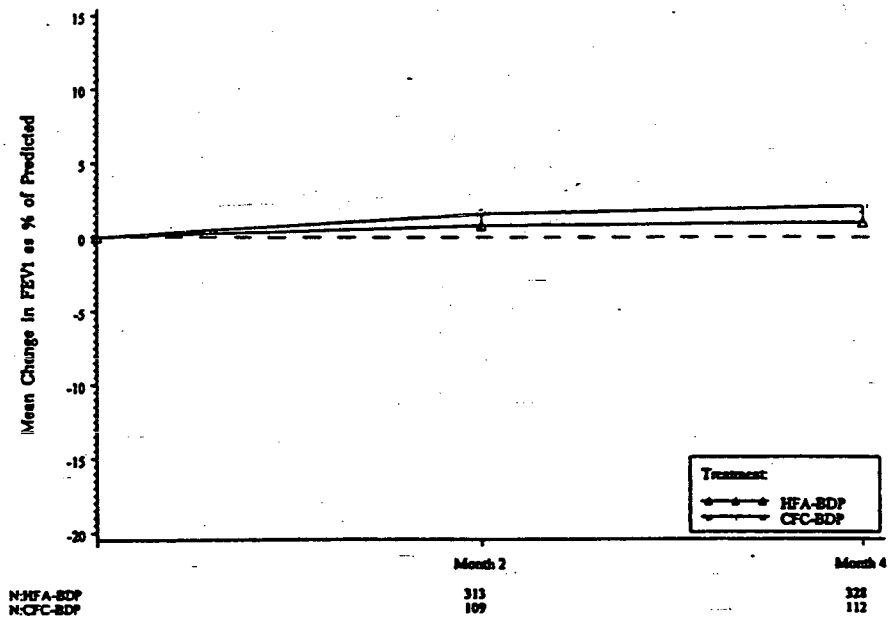
* FEV-1: The absolute mean increase in mean FEV-1 from baseline was 40 mL after 2 and 4 months of BDP-HFA administration. There was a 40 mL increase in mean FEV-1 from baseline after 2 months and a 60 mL increase after 4 months in the BDP-CFC group. There was also a slightly greater improvement in mean percent predicted FEV-1 in the group that received BDP-CFC than the group that received BDP-HFA over the first 4 months of treatment (see tables and figure below; tab 11.4.1.3.A, p137, v1.221, tab 11.4.1.3.B, p139, v1.221, fig 11.4.1.3.A, p138, v1.221)

Table 11.4.1.3.A: Adjusted Mean Change from Baseline in FEV_1 as Percent of Predicted by Study Visit[a]

Study Visit		HFA-BDP	CFC-BDP	95% C.I. of HFA-BDP to CFC-BDP	Overall P-value
Baseline (% Predicted)	Mean	83.3	85.7	-6.25 to 1.49	0.227
	SE	0.99	1.71		
	N	353	118		
Change from Baseline at Month 2	Mean	0.8	1.6	-3.45 to 1.92	0.575
	SE	0.70	1.17		
	N	313	109		
Change from Baseline at Month 4	Mean	1.0	2.1	-3.65 to 1.48	0.405
	SE	0.67	1.12		
	N	328	112		

[a] Based on an ANOVA with treatment, country, and treatment-by-country interaction terms in the model.

Figure 11.4.1.3.A: Adjusted Mean Change from Baseline in FEV_1 as Percent of Predicted and Standard Error by Study Visit[a]



[a] No statistical differences were seen between treatment groups.

Table 11.4.1.3.B: Mean Change from Baseline in FEV_1 as Percent of Predicted by Study Visit and Initial Dose Groups

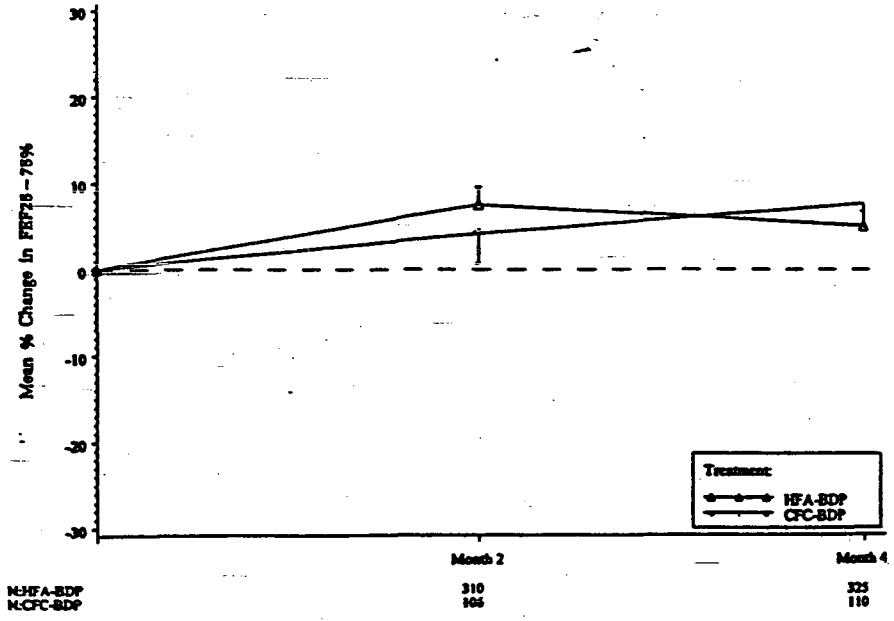
Study Visit		HFA-BDP ≤200 mcg[a]	HFA-BDP >200 - 400 mcg	HFA-BDP >400-800 mcg	CFC-BDP ≤500 mcg[b]	CFC-BDP >500-1000 mcg	CFC-BDP >1000-1600 mcg
Baseline (% Predicted)	Mean	85.90	84.4	81.1	86.8	84.4	81.7
	SE	1.16	1.90	1.67	1.81	2.46	6.66
	N	183	65	105	64	48	6
Change from Baseline at Month 2	Mean	1.6	0.3	0.9	-1.6	3.3	-2.0
	SE	0.67	1.39	1.22	1.21	2.44	3.99
	N	169	60	84	61	42	6
Change from Baseline at Month 4	Mean	0.7	-1.1	1.7	1.5	2.7	-1.1
	SE	0.66	1.63	1.15	1.17	1.69	3.23
	N	175	63	90	62	44	6

[a] All patients in this dose group were randomized to 200 mcg TDD.

[b] All patients in this dose group were randomized to 500 mcg TDD.

✱ FEF 25-75: No statistically significant differences were seen between the two treatment groups after 2 and 4 months of treatment in terms of FEF 25-75 (see figure below; fig 11.4.1.4.A, p140, v1.221)

Figure 11.4.1.4.A: Adjusted Mean Percent Change from Baseline in $FEF_{25\%-75\%}$ and Standard Error by Study Visit[a]



[a] No statistical differences were seen between treatment groups.

* **FVC: A greater degree of mean percent improvement from baseline in FVC was seen in the BDP-CFC group, 3.53%, compared to 0.63% in the BDP-HFA group after 2 weeks and 3.46%, compared to 0.91% in the BDP-HFA group after 4 weeks. These differences are of questionable clinical significance.**

ASTHMA SYMPTOMS

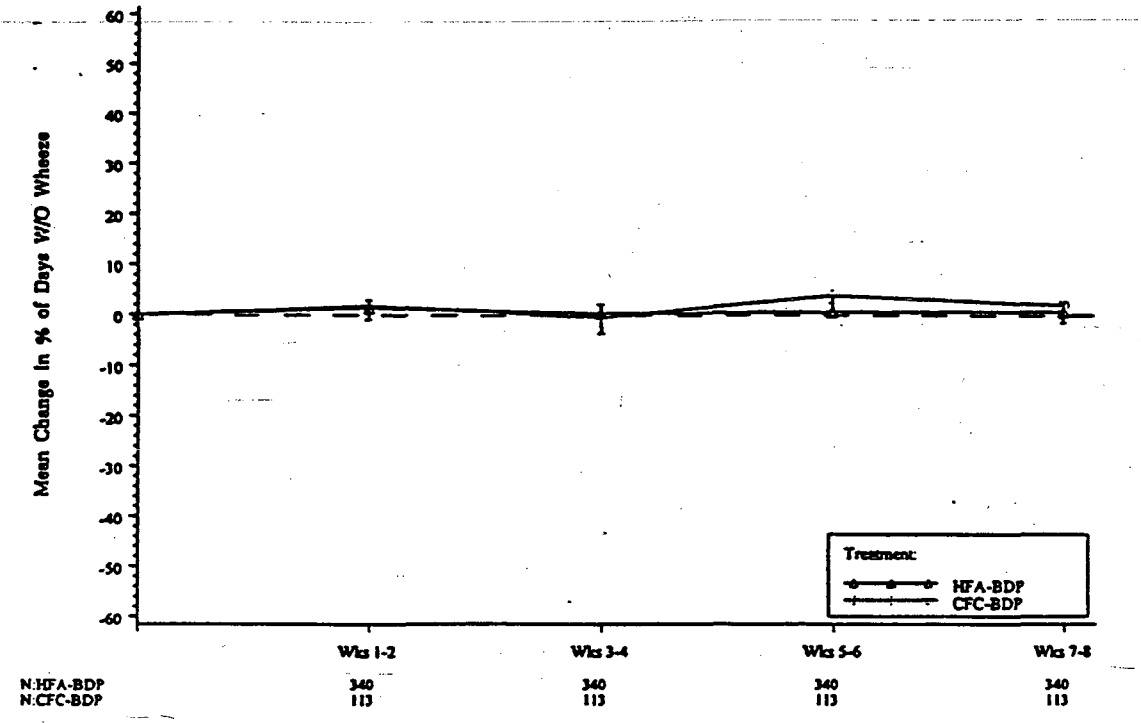
* **percent of days without wheezing: After 8 weeks of treatment, the mean improvement from baseline in percent days without wheezing was greater in the group that received BDP-CFC, but the difference was not clinically significant (see table below; tab 11.4.1.6.A, p142, v1.221)**

Table 11.4.1.6.A: Adjusted Mean Change from Baseline in Percent of Days Without Wheeze by Study Time Period[a]

Study Time Period		HFA-BDP	CFC-BDP	95% C.I. of HFA-BDP to CFC-BDP	P-value
Baseline (% of Days)	Mean	66.0	58.4	-1.61 to 16.77	0.106
	SE	2.34	4.05		
	N	344	116		
Change from Baseline at Weeks 1-2	Mean	1.5	1.9	-6.57 to 5.78	0.901
	SE	1.56	2.73		
	N	340	113		
Change from Baseline at Weeks 3-4	Mean	0.5	-0.4	-6.44 to 8.08	0.824
	SE	1.83	3.21		
	N	340	113		
Change from Baseline at Weeks 5-6	Mean	0.7	4.0	-10.48 to 3.95	0.374
	SE	1.82	3.19		
	N	340	113		
Change from Baseline at Weeks 7-8	Mean	0.8	2.1	-9.36 to 6.65	0.739
	SE	2.02	3.54		
	N	340	113		

[a] Based on an ANOVA with treatment, country, and treatment-by-country interaction terms in the model.

Figure 11.4.1.6.A: Adjusted Mean Change from Baseline in Percent of Days Without Wheeze and Standard Error by Study Time Period[a]



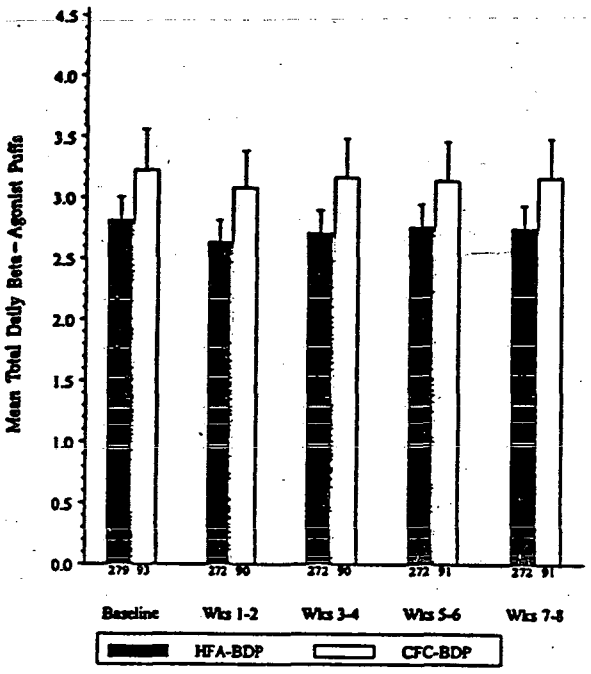
[a] No statistical differences were seen between treatment groups.

* percent of days without cough, chest tightness, dyspnea: There were no clinically significant differences between the treatment groups in regard to any of these symptoms after 8 weeks of drug administration.

* percent of nights without sleep disturbance: There were no clinically significant differences between the treatment groups after 8 weeks of drug administration in terms of percent of nights without sleep disturbance.

* beta agonist use: There was no clinically significant difference between the two treatment groups in regard to beta agonist use (see figure below; fig 11.4.1.11.A, p146, v1.221).

Figure 11.4.1.11.A: Adjusted Mean (SE) Total Daily Beta-Agonist Puffs by Study Time Period



✱ quality of life assessment: There was no clinically significant difference between the change in QOL seen after administration of BDP-HFA and BDP-CFC (see table below; tab 11.4.1.12.A, p147, v1.221).

Table 11.4.1.12.A: Adjusted Mean Change from Baseline in Overall Asthma Quality of Life Score by Study Visit[a]

Study Visit		HFA-BDP	CFC-BDP	95% C.I. of HFA-BDP to CFC-BDP	Overall P-value
Baseline	Mean	5.39	5.34	-0.173 to 0.270	0.670
	SE	0.056	0.098		
	N	347	115		
Change from Baseline at Month 2	Mean	0.18	0.09	-0.077 to 0.269	0.277
	SE	0.045	0.076		
	N	306	106		
Change from Baseline at Month 4	Mean	0.26	0.16	-0.089 to 0.292	0.296
	SE	0.050	0.083		
	N	322	111		

[a] Based on an ANOVA with treatment, country, and treatment-by-country interaction terms in the model.

☛ SAFETY FINDINGS: Data from this study was not included in the ISS.

EXPOSURE

✦ extent of exposure: The same percentage of patients in each group (81%) were exposed to drug for at least 11 months (see table below; tab12.1.A, p267, update)

Table 12.1.A: Number (%) of Patients by Time on Study Drug

DAYS OF TREATMENT EXPOSURE	HFA BDP N=354 No. (%)	CFC BDP N=119 No. (%)	OVERALL N=473 No. (%)
≤14	354 (100.0)	119 (100.0)	473 (100.0)
>14 - 28	349 (98.6)	118 (99.2)	467 (98.7)
>28 - 42	343 (96.9)	116 (97.5)	459 (97.0)
>42 - 56	336 (94.9)	113 (95.0)	449 (94.9)
>56 - 97	331 (93.5)	112 (94.1)	443 (93.7)
>Month 3 (>97 days)	324 (91.5)	110 (92.4)	434 (91.8)
>Month 4 (>134 days)	317 (89.5)	109 (91.6)	426 (90.1)
>Month 5 (>162 days)	311 (87.9)	108 (90.8)	419 (88.6)
>Month 6 (>192 days)	310 (87.6)	106 (89.1)	416 (87.9)
>Month 7 (>224 days)	307 (86.7)	104 (87.4)	411 (86.9)
>Month 8 (>254 days)	304 (85.9)	101 (84.9)	405 (85.6)
>Month 9 (>283 days)	301 (85.0)	100 (84.0)	401 (84.8)
>Month 10 (>313 days)	299 (84.5)	99 (83.2)	398 (84.1)
>Month 11 (>344 days)	288 (81.4)	96 (80.7)	384 (81.2)
>Month 12 (>375 days)	18 (5.1)	6 (5.0)	24 (5.1)
Mean (SD)	324.0 (100.2)	326.5 (96.7)	324.6 (99.2)

The BDP-CFC group received 400-2250 mcg/day while the BDP-HFA group received 200-1600 mcg/day. The majority of patients were within the range specified in the protocol for both treatment groups (see table below; tab12.1.B, p268, update).

Table 12.1.B: Patient Exposure to Study Drug by Total Daily Dose

Treatment Group	Total Daily Dose (mcg)	No. of Pts Exposed to Dose	Total No. of Exposures	Total Weeks of Exposure	Median Weeks of Exposure
HFA-BDP[a]	200	184	212	8151.6	51.6
	300	43	47	1325.5	22.7
	400	66	79	2051.8	19.7
	500	8	8	229.3	31.6
	600	93	98	3558.3	50.9
	800	31	33	1064.7	43.0
	900	2	2	1.4	0.7
	1200	3	4	19.4	3.1
	1600	2	3	2.3	1.1
CFC-BDP	400	57	68	2353.3	46.5
	500	9	11	422.8	52.1
	600	18	23	583.5	27.9
	800	14	17	403.4	19.4
	900	1	1	0.1	0.1
	1000	34	36	1436.9	51.4
	1200	3	3	101.2	49.1
	1500	5	5	208.4	52.0
	1600	2	2	22.9	11.5
	2250	1	1	0.4	0.4

[a] There were six patients in the HFA-BDP treatment group who had short exposures to CFC-BDP during the study; these exposures are not included in this table.

Comparable percentages of patients in each treatment group had their dose of BDP increased over the 12 months of the study, 10% of the BDP-HFA group and 9% of the BDP-CFC group. Not unexpectedly, the majority were patients receiving lower doses (see table below; tab 12.1.C, p269, update).

Table 12.1.C: Summary of Dose Changes by Treatment, Dose, and Time on Study

Treatment	Initial Dose (mcg/day)	N[a]	Dose at End of Day 1 to Month 2 Interval Compared with Initial Dose			Dose at End of Treatment or Month 12 Compared with Initial Dose		
			Decreased No. (%)	Same No. (%)	Increased No. (%)	Decreased No. (%)	Same No. (%)	Increased No. (%)
HFA-BDP	200	182	0 (0.0)	169 (92.9)	13 (7.1)	0 (0.0)	164 (90.1)	18 (9.9)
	300	31	0 (0.0)	29 (93.5)	2 (6.5)	1 (3.2)	22 (71.0)	8 (25.8)
	400	35	0 (0.0)	32 (91.4)	3 (8.6)	1 (2.9)	30 (85.7)	4 (11.4)
	500	2	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)
	600	84	3 (3.6)	79 (94.0)	2 (2.4)	3 (3.6)	77 (91.7)	4 (4.8)
	800	20	0 (0.0)	20 (100.0)	0 (0.0)	2 (10.0)	17 (85.0)	1 (5.0)
	Overall	354	3 (0.8)	331 (93.5)	20 (5.6)	7 (2.0)	312 (88.1)	35 (9.9)
CFC-BDP	400	56	0 (0.0)	53 (94.6)	3 (5.4)	0 (0.0)	48 (85.7)	8 (14.3)
	500	8	0 (0.0)	8 (100.0)	0 (0.0)	0 (0.0)	8 (100.0)	0 (0.0)
	600	13	0 (0.0)	12 (92.3)	1 (7.7)	0 (0.0)	12 (92.3)	1 (7.7)
	800	5	0 (0.0)	4 (80.0)	1 (20.0)	0 (0.0)	3 (60.0)	2 (40.0)
	1000	31	0 (0.0)	31 (100.0)	0 (0.0)	1 (3.2)	30 (96.8)	0 (0.0)
	1200	2	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)
	1500	4	0 (0.0)	4 (100.0)	0 (0.0)	0 (0.0)	4 (100.0)	0 (0.0)
	Overall	119	0 (0.0)	114 (95.8)	5 (4.2)	1 (0.8)	107 (89.9)	11 (9.2)

[a] Number of patients who started on this dose