☛ periods of study:

* 10-12 day run-in period, during which AM and PM PEF, asthma symptoms, nighttime awakenings and inhaled beta agonist use were recorded and patients continued to take their usual asthma medications; the mean AM PEF during the last 5 days of the run-in period was considered the pre-prednisone baseline.

* 10-12 days on oral corticosteroids (30 mg/day of prednisone)

* 12 weeks of randomized treatment; clinic visits were every 3 weeks

☛ parameters evaluated:

EFFICACY: The primary efficacy variable was mean change in AM PEF from the end of the prednisone treatment period (the average of the AM PEF during the last 3 days of the prednisone treatment period) to the end of 12 weeks of randomized treatment, (weeks 10-12, i.e. an average of the last 3 weeks of AM PEF assessment).

* pulmonary function testing (FEV-1, FEF 25-75); performed at screening, at the end of the run-in period, at the end of the oral corticosteroid treatment period (day 1) and after 3, 6, 9, and 12 weeks of randomized treatment, with a 6 hour washout of inhaled beta agonists; baseline pulmonary function was obtained on day 1 after oral corticosteroid treatment for 10-12 days.

  The sponsor has defined "equivalence" in terms of mean change in AM PEF from baseline as the two products being within ± 7.5% using two one-sided testing (established post-hoc) and within ± 0.2 L;

* PEF: measured by patients in the AM upon awakening before taking study medication and in the PM before bed and before taking study medication was averaged over 3 week periods; baseline was the average of PEF values obtained during the last 3 days of prednisone treatment; PEF values were reported by patients at clinic visits every 3 weeks; Mini-Wright peak flow meter was used.

* asthma symptoms: assessed in the evening before the PM dose of study medication and reported at clinic visits every 3 weeks; wheezing, cough, chest tightness and shortness of breath were assessed using the following categorical scale:

  0 = none
  1 = mild, little or no discomfort
  2 = mild, annoying, little or no discomfort
  3 = moderate, discomfort, not affecting normal activities
  4 = severe, interfering at least once with normal activities
  5 = severe, not able to work/go to school/normally function

* nighttime sleep disturbance caused by asthma: assessed before taking AM dose of study medication, using the following categorical scale and reported at clinic visits every 3 weeks.

  0 = none
  1 = awakening once
  2 = awakening twice or more
  3 = awake most of night
  4 = so severe that patient did not sleep at all

The mean daily asthma symptom scores and sleep disturbance scores were computed over each 3 week period and analyzed by ANOVA, with 90% confidence intervals for the difference between the mean scores for patients receiving BDP-HFA and BDP-CFC. Symptom-free and sleep disturbance-free days were analyzed by ANOVA over each 3 week period.

* beta agonist use: was recorded by patients twice a day from the run-in period throughout the study and reported at clinic visits every 3 weeks; "use" of an inhaled beta agonist was considered to be anytime that inhaled beta agonists were required, regardless of the number of puffs used; beta agonist use was recorded in the morning upon awakening in terms of uses during the night and in the evening in regard to the number of uses during the day.

* quality of life (QOL) assessment: a questionnaire was completed by all patients prior to treatment with oral corticosteroids, just after treatment with oral corticosteroids, and after 12 weeks of randomized treatment. The mean change in score from the end of the prednisone treatment period to the end of 12 weeks of randomized treatment for each of the four domains (activity limitation, symptoms, emotional function, and exposure to environmental stimuli) and an overall score from the end of the prednisone treatment period to the end of the study were analyzed.

* time to withdrawal because of asthma symptoms: survival curves (survival being lack of worsening of asthma symptoms sufficiently to require withdrawal from the study) were compared using a log rank test and based on Kaplan-Meier estimates; criteria for withdrawal included > 20% fall in AM PEF from run-in baseline value (last 5 days of run-in period) on 2 consecutive days during the 12 weeks of randomized treatment, in conjunction on those days with a nighttime sleep disturbance score of ≥ 1 on one or both nights, OR with any asthma symptom score ≥ 3 on both days OR with any asthma symptom score of 5 on one day, OR with use of inhaled beta agonist > 4 times daily on both days.

* compliance: canisters were weighed; the patient was defined as compliant if the total number of puffs used during the study was ± 40% of predicted, i.e. within 60-140% of predicted. This is a very liberal definition of compliance.

SAFETY

* adverse events

* 12 lead ECGs: prior to the study and at the end of the study.

* vital signs: pulse rate and blood pressure were measured at baseline (study day 1) and weeks 3, 6, 9, and 12.

* laboratory tests: serum chemistries, hematology, urinalysis; measured at baseline (screening visit) and at the end of the study.

* plasma cortisol levels: at the end of the run-in period, on study day 1 (immediately after the oral corticosteroid period) and at the end of the study (last study day).

* serum osteocalcin levels: validated radioimmunoassay with antibodies to bovine osteocalcin was used; at the end of the run-in period, on study day 1 (immediately after the oral corticosteroid period) and at the end of the study (last study day) levels were obtained.

* assessment for candida infection: in patients who reported an oropharyngeal AE, and in whom the investigator noted lesions consistent with candida infection, mouth and/or throat cultures were obtained.

- data analysis:

  - two data sets were analyzed: the intent-to-treat (ITT) patient population, i.e. all patients who received at least one dose of study medication; and the evaluable for efficacy population (efficacy population), i.e. all patients who were considered compliant.

- For the ITT analysis, after randomization, data points were carried forward if there was a dropout or if there was missing data.

- An interim assessment of pooled standard deviation in AM PEF was done after 6 weeks to ensure sufficient numbers of patients for sample size calculations, which was felt to be adequate based on a standard deviation of 46 L/min change from the end of treatment with oral corticosteroids.

- For comparison of 400mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC, a 90% confidence interval for mean difference between the two treatments was constructed by the sponsor. The mean change in AM PEF demonstrated in patients who received BDP-HFA was considered "equivalent" to the mean change demonstrated in patients who received BDP-CFC if the 90% confidence interval for the mean difference between the two treatments was completely contained within ± 40 L/min. Subsequently, the protocol was modified so that efficacy "equivalence" was defined as a difference within ± 25L/min in AM PEF change from the end of treatment with oral corticosteroids to week 12 of randomized treatment for the 400 mcg/day BDP-HFA and the 800 mcg/day BDP-CFC groups. Based on this difference, an unplanned analysis was performed after unblinding. This unplanned analysis also used ± 0.2 L as the acceptable limits of difference for absolute FEV-1 and ± 7.5% as the acceptable limits of difference for percent predicted FEV-1.

- At the end of the study, an analysis was performed to determine if there was any difference in PEF between the two placebo groups. The sponsor states that because no difference was found, the data from the two placebo groups were pooled.

- Subset analysis was performed for patients who were and patients who were not taking inhaled corticosteroids at entry

into the study, as well as patients who were or were not using intranasal corticosteroids and antihistamines during the study.

- On the basis of data in the literature, the standard deviation for mean change in AM PEF from the prednisone treatment period to the end of the study was "assumed" to be "approximately" 126 L/min. Based on this assumption, it was estimated that 90 patients per active treatment group would be needed to ensure 90% power with alpha = 0.05.

- A difference of 60 L/min between active drug and placebo in terms of mean change in AM PEF from the end of treatment with oral corticosteroids to week 12 was considered clinically meaningful. It was determined that 90 patients would provide at least 80% power for determining if there was a clinically significant difference between active treatment and placebo in terms of mean change from baseline in AM PEF.

STUDY RESULTS

- ineligible patients: see table below listing reasons for ineligibility (tab2, p 164, 1.114); these are all legitimate reasons for not randomizing patients into the study.

Table 2: Number (%) of Patients Screened but Ineligible for Randomization by Primary Reason

Reason	
PEF not within 50.0% to 85.0% of Predicted	158 (33.7%)
PEF increase after prednisone treatment < 15%	121 (25.8%)
FEV_1 Reversibility < 15%	76 (16.2%)
Active signs and symptoms of asthma not present	29 (6.2%)
Adverse Event	15 (3.2%)
Violation of Inclusion/Exclusion criteria	12 (2.6%)
Withdrew consent	9 (1.9%)
Personal	7 (1.5%)
Laboratory abnormalities	5 (1.1%)
Not compliant with diary card entries	2 (0.4%)
Not compliant with prednisone tablets	2 (0.4%)
Pregnancy	1 (0.2%)
Abnormal ECG	1 (0.2%)
Non-compliance	1 (0.2%)
Could not perform PFTs	1 (0.2%)
Other	29 (6.2%)
Total	469

☛ withdrawals: the reasons for patient withdrawal prior to week 12 can be seen in the table below (tab 3, p165, v1.114); there were substantially more patients in the HFA placebo group who withdrew, primarily related to absence of active treatment (i.e. adverse events, fulfilling withdrawal criteria, inadequate response, noncompliance)

Table 3: Number (%) of Patients Who Withdrew Prior to Week 12 by Primary Reason and Treatment Group (Patients Included in the Intent-to-treat Analysis)

Reason	HFA-BDP 400 mcg (n= 113)	CFC-BDP 800 mcg (n= 117)	HFA-Placebo (n= 117)	Overall (n= 347)
Adverse event	7 (6.2%)	2 (1.7%)	18 (15.4%)	27 (7.8%)
Fulfilled withdrawal	1 (0.9%)	3 (2.6%)	10 (8.5%)	14 (4.0%)
Inadequate response	0 (0.0%)	1 (0.9%)	5 (4.3%)	6 (1.7%)
Personal	2 (1.8%)	2 (1.7%)	1 (0.9%)	5 (1.4%)
Entry criteria violated	1 (0.9%)	2 (1.7%)	1 (0.9%)	4 (1.2%)
Noncompliance	0 (0.0%)	0 (0.0%)	2 (1.7%)	2 (0.6%)
Withdraw consent	1 (0.9%)	1 (0.9%)	0 (0.0%)	2 (0.6%)
Pregnancy	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.3%)
Total	12 (10.6%)	12 (10.3%)	37 (31.6%)	61 (17.6%)

☛ protocol violations:

✱ There were 35 patients who had less than a 15% increase in AM PEF after oral corticosteroid treatment; 16 in the BDP-HFA group 13 in the placebo group and 6 in the BDP-CFC group; such patients could be included in the efficacy population analysis if they had either: 1) a 14% or greater improvement in AM PEF averaged over the last 3 days of the oral corticosteroid period; or 2) a 10-13% improvement in AM PEF averaged over the last 3 days of the oral corticosteroid period and had a 15% or greater improvement in FEV-1 following the oral corticosteroid treatment period.

- There were 11 patients who had major protocol violations; their data was completely excluded from the efficacy population analysis; this included 6 BDP-HFA patients, 3 BDP-CFC patients and 1 patient in the HFA placebo group who had less than a 15% increase in AM PEF after oral corticosteroid treatment, leaving 10 BDP-HFA, 12 placebo and 3 BDP-CFC patients in the analysis despite this violation, if they met the criteria specified above. The inclusion of these patients is appropriate based on the amount of improvement seen in pulmonary function during the last 3 days of the oral corticosteroid treatment period.

- There was a total of 20, 11, and 18 patients who were completely excluded from the efficacy population analysis in the BDP-HFA, BDP-CFC and placebo groups, respectively. Of the patients in the BDP-HFA group, 9 patients were over-compliant, 7 were under-compliant and 6 had major protocol violations. A similar degree of non-compliance was seen in the other two treatment groups.

- There was partial exclusion of data from the efficacy population analysis on 7 patients who had major protocol violations. Four of these patients received oral corticosteroids during the study (one BDP-CFC patient, 2 BDP-HFA patients and one HFA placebo patient)(one BDP-HFA and one placebo patient received parenteral corticosteroids); data on these patients was excluded from the time they first received these medications.

☛ <u>DEMOGRAPHICS</u>:

- more women received BDP, while more men received placebo; most patients were Caucasian (88-92%); most patients were never smokers (79-85%); most patients had a history of asthma for > 5 years (82-90%); most patients had allergies (86-92%); at entry into the study, 59% of the placebo group, 69% of the BDP-HFA group, and 61% of the BDP-CFC group

were not taking inhaled corticosteroids; all patients taking inhaled corticosteroids at entry into the study were receiving 200-400 mcg/day; 46% of patients had moderate asthma using the NAEPP Guidelines, while according to the sponsor, 33% had severe asthma (despite the fact that symptom severity was mild at baseline possibly related to the high use of inhaled beta agonists [3.4 times a day]) and 21% had mild persistent asthma. The patient group which received 400 mcg/day of BDP-HFA had a statistically significantly greater inhaled beta agonist use during the run-in period than the other two treatment groups. See table below for prestudy demographic characteristics (tab4, p170, v1.114)

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

Characteristic		HFA-BDP 400 mcg (n=113)	CFC-BDP 800 mcg (n=117)	HFA-Placebo (n= 117)	p-value
Sex[a]	Female	67 (59.3%)	63 (53.8%)	55 (47.0%)	0.190
	Male	46 (40.7%)	54 (46.2%)	62 (53.0%)	
Age (years)[b]	Mean	32.5	34.8	34.6	0.235
	SD	9.96	11.91	9.42	
Race[a]	White	102 (90.3%)	107 (91.5%)	103 (88.0%)	0.630
	Black	8 (7.1%)	7 (6.0%)	12 (10.3%)	
	American Indian	1 (0.9%)	0 (0.0%)	0 (0.0%)	
	Asian/Pac.	2 (1.8%)	3 (2.6%)	2 (1.7%)	
Height (cm)[b]	Mean	169.4	171.8	170.7	0.273
	SD	9.34	10.97	9.95	
Weight (kg)[b]	Mean	78.27	82.63	77.13	0.097
	SD	18.131	20.532	16.617	
Tobacco use[a]	None	96 (85.0%)	97 (82.9%)	92 (78.6%)	0.591
	Past	17 (15.0%)	20 (17.1%)	25 (21.4%)	
Alcohol use[a]	None	81 (71.7%)	76 (65.0%)	83 (70.9%)	0.326
	Current	28 (24.8%)	39 (33.3%)	28 (23.9%)	
	Past	4 (3.5%)	2 (1.7%)	6 (5.1%)	
Substance abuse[a]	None	111 (98.2%)	117(100.0%)	116 (99.1%)	0.824
	Past	2 (1.8%)	0 (0.0%)	1 (0.9%)	

[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-white and Tobacco, Alcohol 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.

* within 7 days of discontinuing study drug, there were 11 patients who used oral corticosteroids and 7 patients who used inhaled corticosteroids in the placebo group; from the BDP-HFA group, there were 3 patients who used oral corticosteroids (CS); and from the BDP-CFC group, there was one patient who used oral corticosteroids.

* <u>baseline pulmonary function</u>: at screening, mean actual values and percent predicted for FEV-1 and AM PEF, as well as mean percent reversibility for FEV-1 were comparable among the 3 treatment groups (see tab7, p175, v1.114 below); at the end of the run-in period, the mean actual values and percent predicted for FEV-1 and AM PEF were comparable among the 3 treatment groups; after the oral corticosteroid treatment period, there was a comparable response among the 3 treatment groups in terms of mean actual values and percent predicted for FEV-1 and AM PEF; there was a clinically significant improvement in all groups after administration of oral corticosteroids, based on improvement in lung function, as well as reduction in symptoms, sleep disturbance scores, and use of rescue medications.

Table 7: <u>Baseline Lung Function by Treatment Group[a] (Patients Included in the Intent-to-treat Analysis)</u>

		HFA-BDP 400 mcg (n=113)		CFC-BDP 800 mcg (n=117)		HFA- Placebo (n=117)		Overall p-value[b]	
		AM PEF	FEV_1	AM PEF	FEV_1	AM PEF	FEV_1	AM PEF	FEV_1
Screening Actual Values	Mean	380.1	2.36	389.7	2.40	386.0	2.41	0.704	0.871
	SD	72.11	0.697	80.20	0.674	84.13	0.711		
% Predicted	Mean	71.0	67.4	71.1	66.7	69.1	67.2	0.319	0.957
	SD	9.93	16.05	9.95	12.66	10.89	16.07		
% Reversibility to Beta-agonist	Mean		31.9		31.5		30.0		0.774
	SD		22.10		15.68		17.61		
Run-in[c] Actual Values	Mean	369.6	2.46	372.7	2.41	373.5	2.54	0.936	0.519
	SD	74.18	0.732	75.49	0.732	82.60	0.795		
% Predicted	Mean	68.9	70.2	68.1	67.3	66.6	70.3	0.296	0.303
	SD	10.03	16.32	9.17	14.19	10.23	16.97		
Oral Steroid Tx[d] Actual values	Mean	453.5	2.80	451.9	2.86	453.3	2.81	0.991	0.885
	SD	82.22	0.761	84.44	0.821	92.52	0.844		
% Predicted	Mean	84.7	80.1	82.6	79.7	81.1	78.0	0.085	0.631
	SD	11.12	16.01	10.18	14.84	11.56	17.75		
% Oral Steroid Response	Mean	23.7	17.0	21.9	21.4	22.3	14.3	0.419	0.179
	SD	9.59	25.46	10.14	23.38	9.45	31.09		

[a] AM PEF was recorded in L/min; FEV_1 was recorded as L.
[b] Based on an ANOVA with treatment, center and treatment-by-center interaction terms in the model.
[c] AM PEF is the average of the last 5 days of the run-in period; FEV_1 is the value taken at the clinic visit at the end of the run-in period.
[d] AM PEF is the average of the last 3 days of the oral steroid treatment period; FEV_1 is the value taken at the clinic visit at the end of the oral steroid treatment period.

✱ compliance evaluated at the end of the study for the efficacy population was 94% (BDP-HFA), 90% (BDP-CFC) and 98% (placebo).

☛ **EFFICACY FINDINGS:**

PULMONARY FUNCTION TESTING:

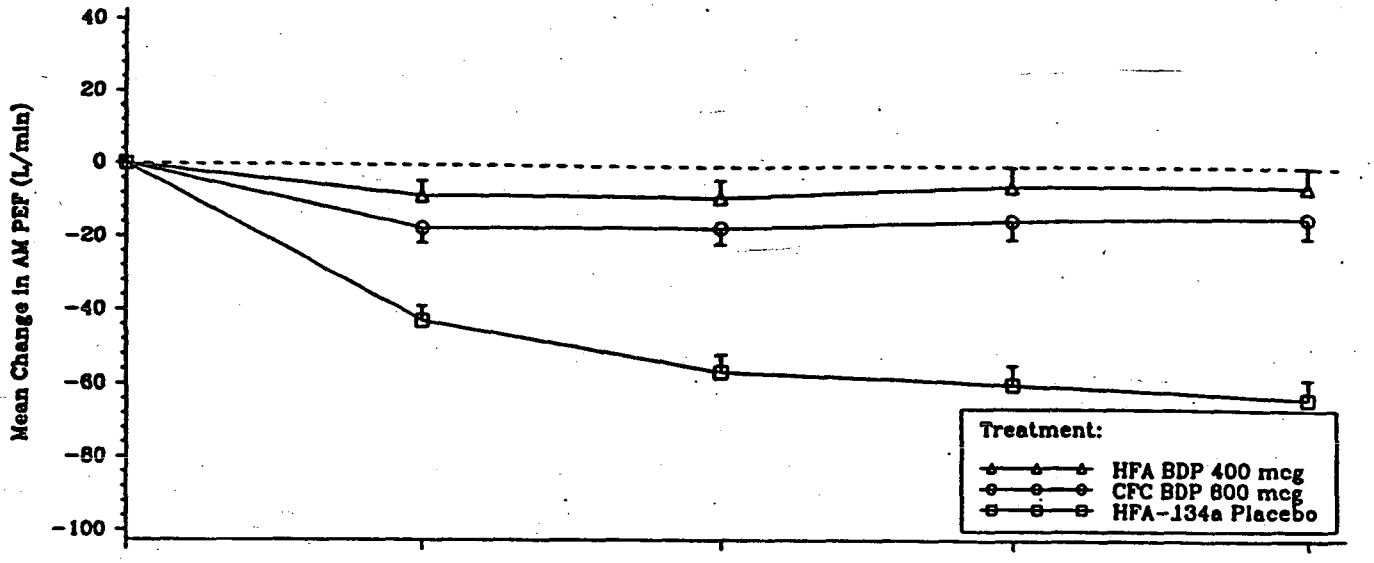
✱ AM PEF: see table and figure below (tab12, p182, v1.114, fig3, p181, v1.114);

Table 12: Change from Oral Steroid Treatment in Morning Peak Flow (L/min) Analysis: Comparisons with Placebo (Patients Included in the Intent-to-treat Analysis)

Study week		HFA-BDP 400 mcg	CFC-BDP 800 mcg	HFA-Placebo	Overall p-value[a]
Run-in	Mean	369.6	372.7	373.5	0.936
	SE	8.09	7.72	8.07	
	N	113	117	117	
Oral Steroid Tx	Mean	453.5	451.9	453.3	0.991
	SE	9.11	8.69	9.08	
	N	113	117	117	
Change from Oral Steroid Tx at Weeks 1-3	Mean	-8.4**	-17.3**	-42.7	<0.001
	SE	4.09	3.92	4.08	
	N	113	116	115	
Change from Oral Steroid Tx at Weeks 4-6	Mean	-8.4**	-17.0**	-56.6	<0.001
	SE	4.77	4.57	4.76	
	N	113	116	115	
Change from Oral Steroid Tx at Weeks 7-9	Mean	-5.5**	-15.0**	-59.8	<0.001
	SE	5.24	5.03	5.24	
	N	113	116	115	
Change from Oral Steroid Tx at Weeks 10-12	Mean	-5.3**	-14.0**	-63.4	<0.001
	SE	5.44	5.22	5.44	
	N	113	116	115	

[a] Based on an ANOVA with treatment, center, treatment-by-center interaction terms in the model. Comparisons of active treatments with placebo: ** p ≤0.003.

Figure 3
Comparisons With Placebo
Adjusted Mean Change from Oral Steroid Treatment in Morning Peak Flow (L/min)
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 400 mcg	113 **	113 **	113 **	113 **
N:CFC BDP 800 mcg	116 **	116 **	116 **	116 **
N:HFA-134a Placebo	115	115	115	115

P-values for comparisons of each active treatment with placebo: **: p<= 0.003; *: p<= 0.017; +: p<= 0.03.

The separation of response to 400 mcg/day BDP-HFA and 800 mcg/day BDP-CFC occurred during the first three weeks of treatment with essentially no further separation of effect throughout the 12 weeks of the study. During the first three weeks of treatment, there was less of a decrease in mean AM PEF in the group that received 400 mcg/day of BDP-HFA than in the group that received 800 mcg/day of BDP-CFC, suggesting that less than ½ the dose of BDP-HFA is needed to produce an effect comparable to a given dose of BDP-CFC.

An unplanned analysis was done, which revised the range of "equivalence" from ± 40 L/min (protocol-specified) to ± 25 L/min in terms of mean change from baseline in AM PEF following oral corticsteroids. This was done after unblinding the data. The 95% confidence interval of the difference in

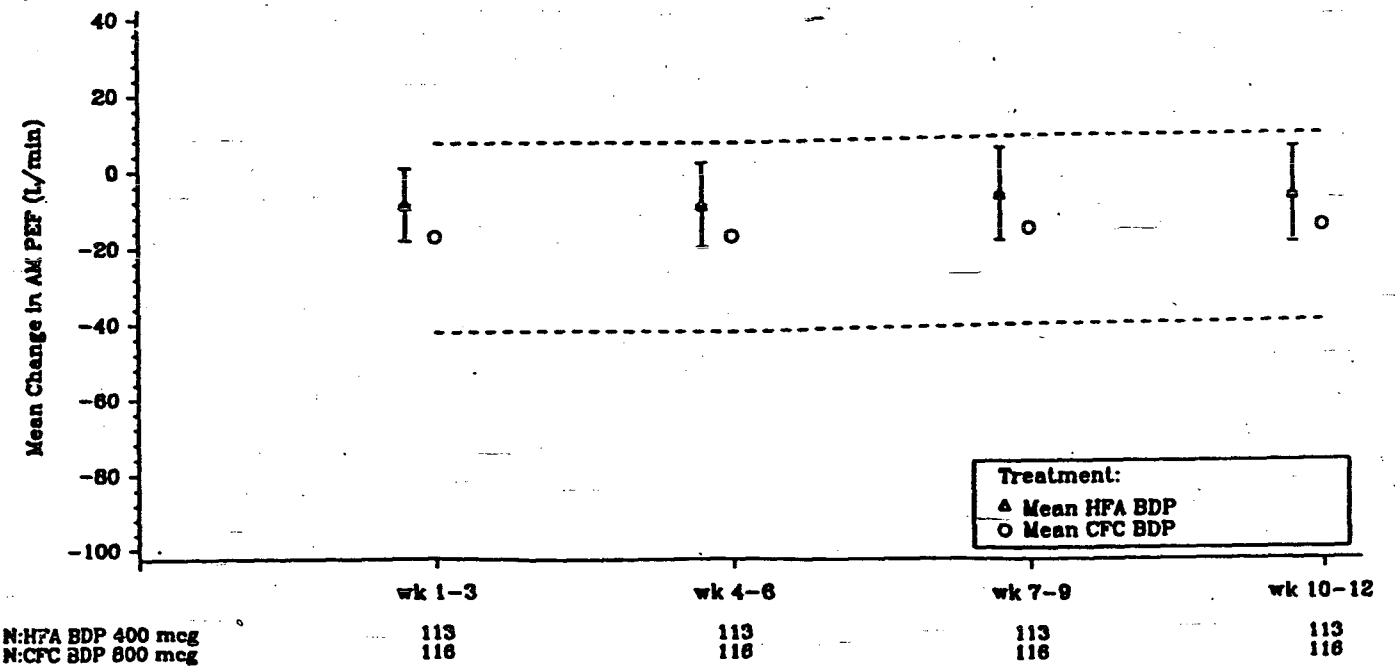
adjusted mean change from baseline in AM PEF between BDP-HFA 400 mcg/day and BDP-CFC 800 mcg/day (ITT analysis) falls within the ± 25 L/min criterion established by the sponsor for "equivalence" (see table and figure below; tab 13, p183, v1.114 and fig4, p184, v1.114).

Table 13: Change from Oral Steroid Treatment in Morning Peak Flow (L/min) Analysis: Equivalence of HFA-BDP 400 mcg Compared with CFC-BDP 800 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	-3.1	11.19	-21.56, 15.35	0.026
Oral Steroid Tx	1.6	12.59	-19.22, 22.32	0.032
Change from Oral Steroid Tx at Weeks 1-3	8.9	5.66	-0.42, 18.26	0.002
Change from Oral Steroid Tx at Weeks 4-6	8.6	6.60	-2.33, 19.46	0.007
Change from Oral Steroid Tx at Weeks 7-9	9.5	7.26	-2.50, 21.47	0.017
Change from Oral Steroid Tx at Weeks 10-12	8.7	7.54	-3.72, 21.16	0.016

[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 800 mcg mean.

Figure 4
Equivalence of HFA BDP 400 mcg and CFC BDP 800 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.

Evaluation of the data using the efficacy population, as well as subgroups based on inhaled corticosteroid use prior to the study, use of intranasal corticosteroids or antihistamines or gender did not change the conclusions based on the sponsor's analysis. There was a wider separation of mean effect between 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC after 12 weeks of treatment in males as compared to females, but the same effect was seen in patients who used antihistamines or intranasal corticosteroids during the study, and did not change conclusions about the efficacy or comparability of these two drug products.

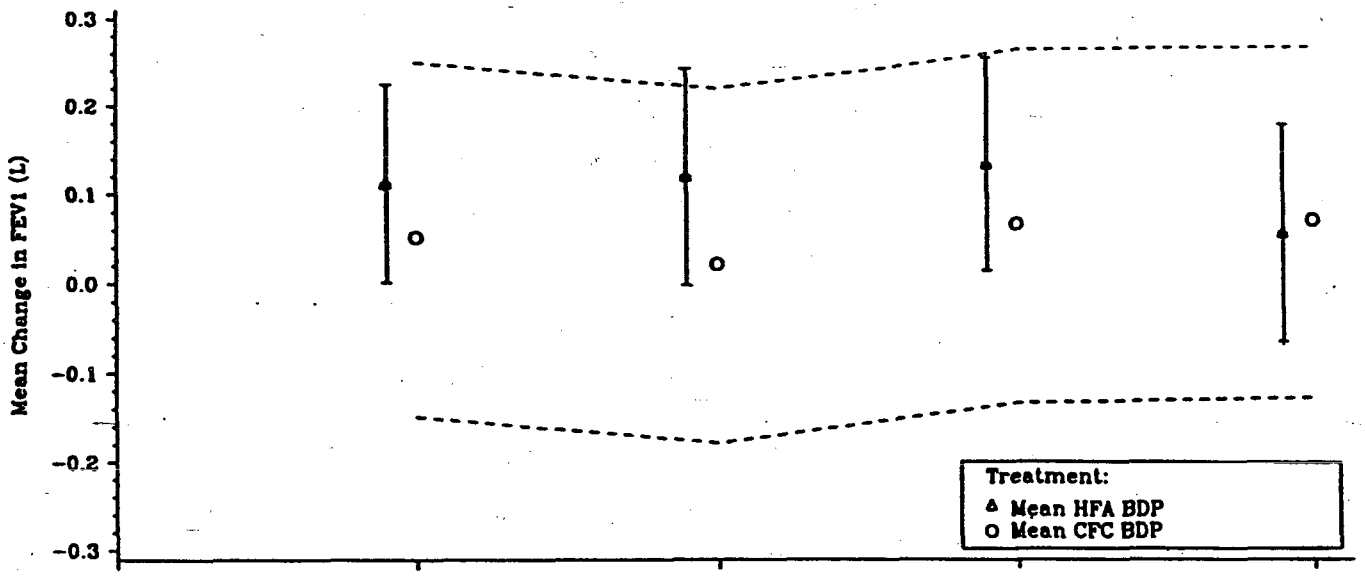
The method of analysis for used by the sponsor was not approved by the Division and is not acceptable for determining ". Most importantly, the study design was not appropriate for demostration of

The difference of 9 L/min between the two products after the first 3 weeks of treatment is not a clinically significant difference, and therefore, allows a conclusion that 400 mcg/day of BDP-HFA is "comparable" to 800 mcg/day of BDP-CFC, although not ". However, the difference of 26-34 L/min between BDP and placebo after the same time frame, is clinical significant and demonstrates the efficacy of BDP-HFA.

- PM PEF: The mean decrease in PM PEF was significantly smaller ($p \leq 0.003$) after administration of 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC than after administration of placebo. The baseline PM PEF was the average of the PM PEF values obtained during the last 5 days of the prednisone treatment period.

- FEV-1: Using the sponsor's analysis, less than a $\pm$ 20 L difference was defined as "equivalence". Based on this definition, "equivalence" of 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC was demonstrated (see figure below; fig 7, p192, v1.114).

Figure 7
Equivalence of HFA BDP 400 mcg and CFC BDP 800 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 400 mcg	111	113	113	113
N:CFC BDP 800 mcg	117	117	117	117

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.

Since the Division has not agreed that the sponsor's analysis can be used to demonstrate [redacted], the sponsor can not make a claim [redacted]

As indicated below, however, the response to 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC, based on mean change in FEV-1 from baseline was comparable.

After switching from oral corticosteroids to either 400 mcg/day of BDP-HFA or 800 mcg/day of BDP-CFC, there was a slight mean improvement in FEV-1, which was statistically significantly different than the placebo group, in whom there was a decrease in mean FEV-1 ($p \leq 0.003$). Improvement in mean FEV-1 was seen with either BDP drug product after 3

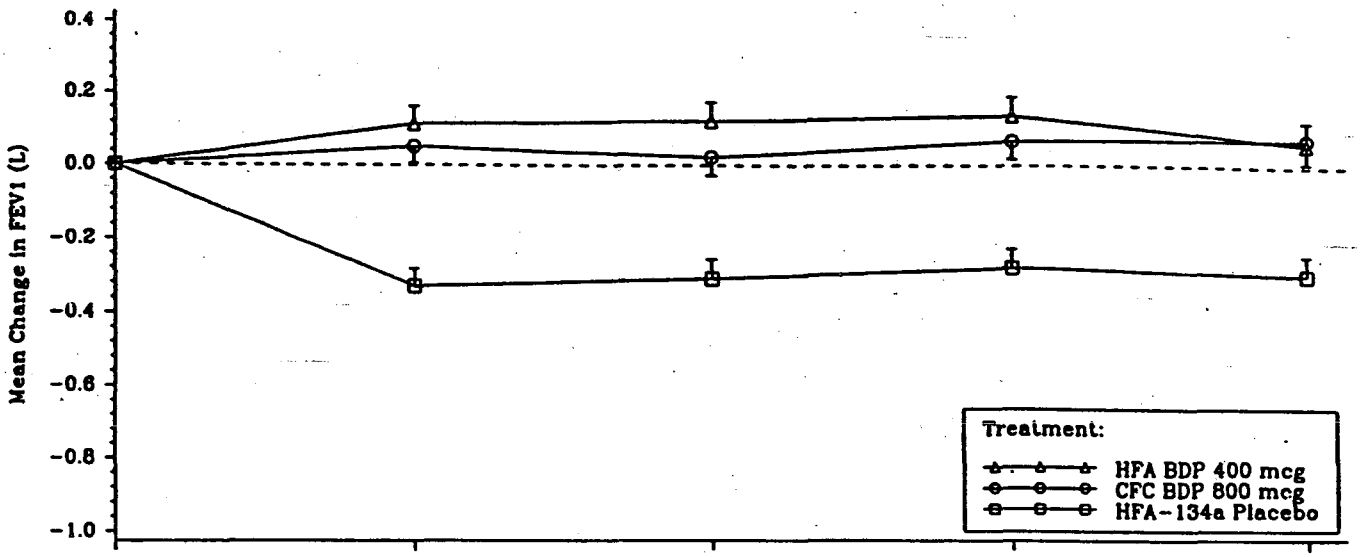
weeks of treatment and persisted during the 12 weeks of the study (see figure and table below; fig6, p189, v1.114, tab14, p190, v1.114). There was also a significant difference in the change in percent predicted FEV-1 between the groups that received BDP and the group that received placebo ($p \leq 0.003$).

Table 14: Change from Oral Steroid Treatment in FEV_1 (L): Comparisons with Placebo (Patients Included in the Intent-to-treat Analysis)

Study week		HFA-BDP 400 mcg	CFC-BDP 800 mcg	HFA-Placebo	Overall p-value[a]
Run-in	Mean	2.46	2.41	2.54	0.519
	SE	0.080	0.076	0.079	
	N	113	117	117	
Oral Steroid Tx	Mean	2.80	2.86	2.81	0.885
	SE	0.085	0.081	0.085	
	N	113	117	117	
Change from Oral Steroid Tx at Week 3	Mean	0.11**	0.05**	-0.33	< 0.001
	SE	0.048	0.045	0.048	
	N	111	117	116	
Change from Oral Steroid Tx at Week 6	Mean	0.12**	0.02**	-0.31	< 0.001
	SE	0.052	0.050	0.053	
	N	113	117	116	
Change from Oral Steroid Tx at Week 9	Mean	0.14**	0.07**	-0.28	< 0.001
	SE	0.052	0.049	0.052	
	N	113	117	116	
Change from Oral Steroid Tx at Week 12	Mean	0.06**	0.08**	-0.30	< 0.001
	SE	0.053	0.050	0.053	
	N	113	117	116	

[a] Based on an ANOVA with treatment, center, treatment-by-center interaction terms in the model.
Comparisons of active treatments with placebo: ** $p \leq 0.003$.

Figure 6
Comparisons With Placebo
Adjusted Mean Change from Oral Steroid Treatment in FEV1 (L)
and Standard Error by Week
(Patients Included in the Intent-to-treat Analysis)



	wk 3	wk 6	wk 9	wk 12
N:HFA BDP 400 mcg	111 **	113 **	113 **	113 **
N:CFC BDP 800 mcg	117 **	117 **	117 **	117 **
N:HFA-134a Placebo	116	116	116	116

P-values for comparisons of each active treatment with placebo: **: p<= 0.003; *: p<= 0.017; +: p<= 0.03.

Using the sponsor's ± 7.5% definition of "equivalence", based on 90% and 95% confidence intervals, respectively, the sponsor claims [redacted]

[redacted] Since the study was not adequately designed to assess [redacted] no such claim by the sponsor is appropriate.

* <u>FEF 25-75</u>: As would be expected, there was a significant mean decrease in FEF 25-75 in patients who had been on oral corticosteroids and who were then randomized to placebo (14-18% change). In contrast, there was an increase in FEF 25-75

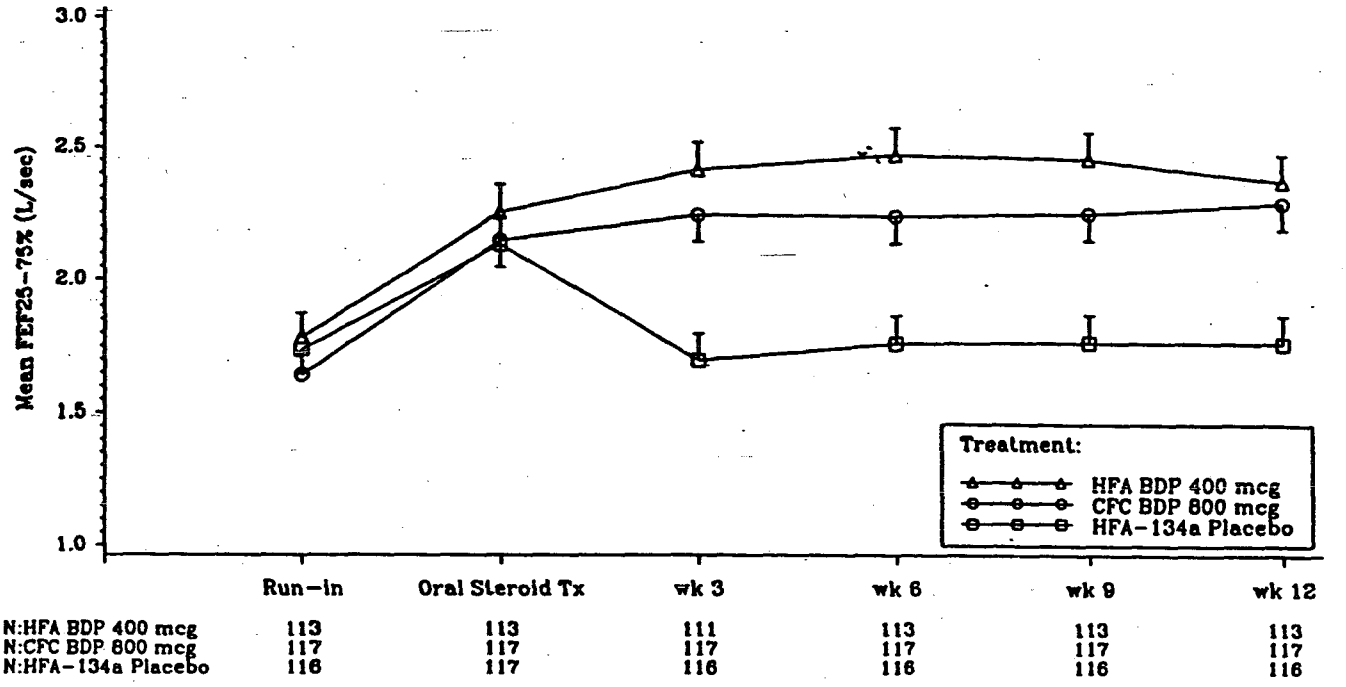
after administration of 800 mcg/day of BDP-CFC and an even greater increase in FEF 25-75 after administration of 400 mcg/day of BDP-HFA (approximately twice as great), through week 9 (see table and figure below; tab 14.2.4.2.1, p373, v1.114; fig 14.2.4.1.2, p372, v1.114).

Table 14.2.4.2.1
Adjusted Mean Change from Oral Steroid Treatment in $FEF_{25-75\%}$ (L/sec)
Comparisons with Placebo

(Patients Included in the Intent-to-treat Analysis)

Study week		HFA BDP 400 mcg	CFC BDP 800 mcg	HFA-134a Placebo	Overall P-value*
Run-in	Mean	1.79	1.65	1.74	0.518
	SE	0.091	0.087	0.091	
	Median	1.6	1.6	1.6	
	Min				
	Max				
	N	113	117	116	
Oral Steroid Tx	Mean	2.26	2.15	2.14	0.683
	SE	0.106	0.101	0.105	
	Median	2.1	2.1	2.0	
	Min				
	Max				
	N	113	117	117	
Change from Oral Steroid Tx at Week 3	Mean	0.18**	0.10**	-0.45	< 0.001
	SE	0.083	0.078	0.083	
	Median	0.1	0.1	-0.4	
	Min				
	Max				
	N	111	117	116	
Change from Oral Steroid Tx at Week 6	Mean	0.22**	0.09**	-0.39	< 0.001
	SE	0.085	0.081	0.085	
	Median	0.2	0.1	-0.2	
	Min				
	Max				
	N	113	117	116	
Change from Oral Steroid Tx at Week 9	Mean	0.21**	0.10**	-0.38	< 0.001
	SE	0.081	0.077	0.081	
	Median	0.2	0.1	-0.2	
	Min				
	Max				
	N	113	117	116	

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 400 mcg	113	113	111	113	113	113
N:CFC BDP 800 mcg	117	117	117	117	117	117
N:HFA-134a Placebo	116	117	116	116	116	116

Table 14.2.4.2.1
Adjusted Mean Change from Oral Steroid Treatment in $FEF_{25-75\%}$ (L/sec)
Comparisons with Placebo

(Patients Included in the Intent-to-treat Analysis)

Study week		HFA BDP 400 mcg	CFC BDP 800 mcg	HFA-134a Placebo	Overall P-value*
Change from Oral Steroid Tx at Week 12	Mean	0.13**	0.15**	-0.38	< 0.001
	SE	0.082	0.078	0.083	
	Median	0.2	0.2	-0.3	
	Min				
	Max				
	N	113	117	116	

*Based on an ANOVA with treatment, center, treatment by center interaction terms in the model.
Comparisons of active treatments with placebo: **: $p <= 0.003$; *: $p <= 0.017$; + <= 0.03.

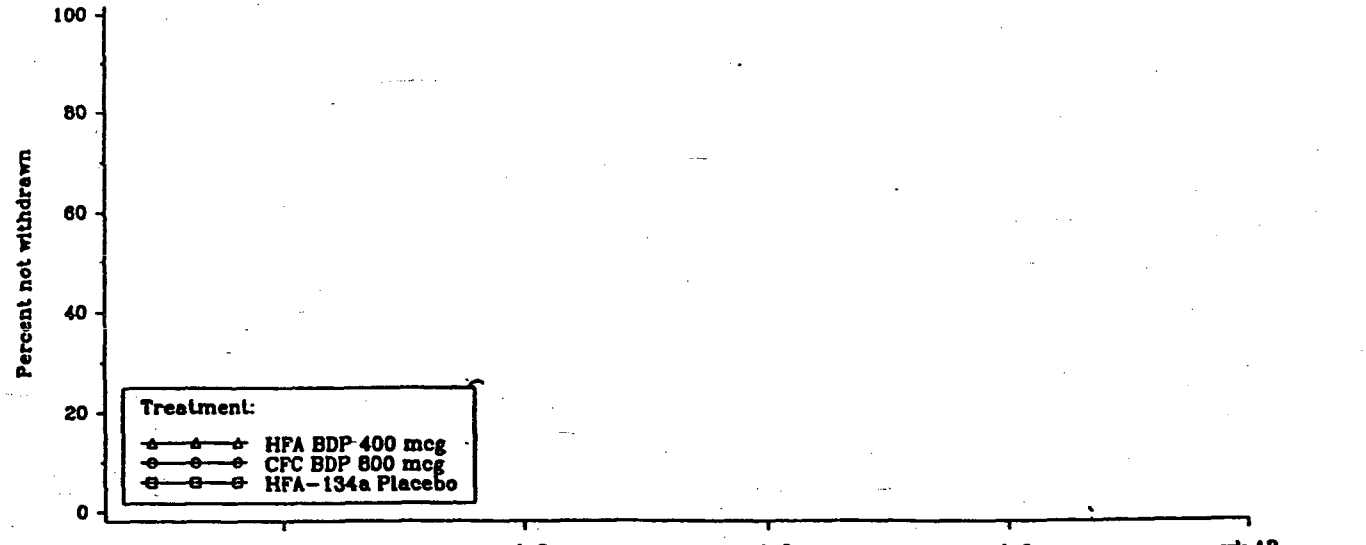
The difference in response between both BDP drug products and placebo was statistically significant ($p \leq 0.003$). The greater difference in response to 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC in terms of FEF 25-75, as compared to FEV-1 or AM PEF could reflect greater deposition of BDP-HFA in smaller airways due to smaller particle size of BDP-

HFA, as suggested by the sponsor. The baseline value was that value recorded at the clinic visit closest to the day of randomization and prior to the first dose of study drug.

OTHER EFFICACY PARAMETERS:

* time to withdrawal because of asthma symptoms: Not surprisingly, there were substantially fewer patients in the two active treatment groups who withdrew from the study because of asthma symptoms (see figure below; fig8, p196, v1.114). Only 5 patients (4%) in the BDP-HFA and 5 patients (4%) in the BDP-CFC were withdrawn due to asthma, compared with 33 (28%) in the placebo group, 31 by week 7 (note that 64% of the placebo patients who were withdrawn were on inhaled corticosteroids at entry, compared to 41%, 31% and 39% of the placebo, BDP-HFA and BDP-CFC groups, respectively, overall at entry).

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



Overall between-treatment comparison of time to withdrawal due to asthma symptoms p=<0.001

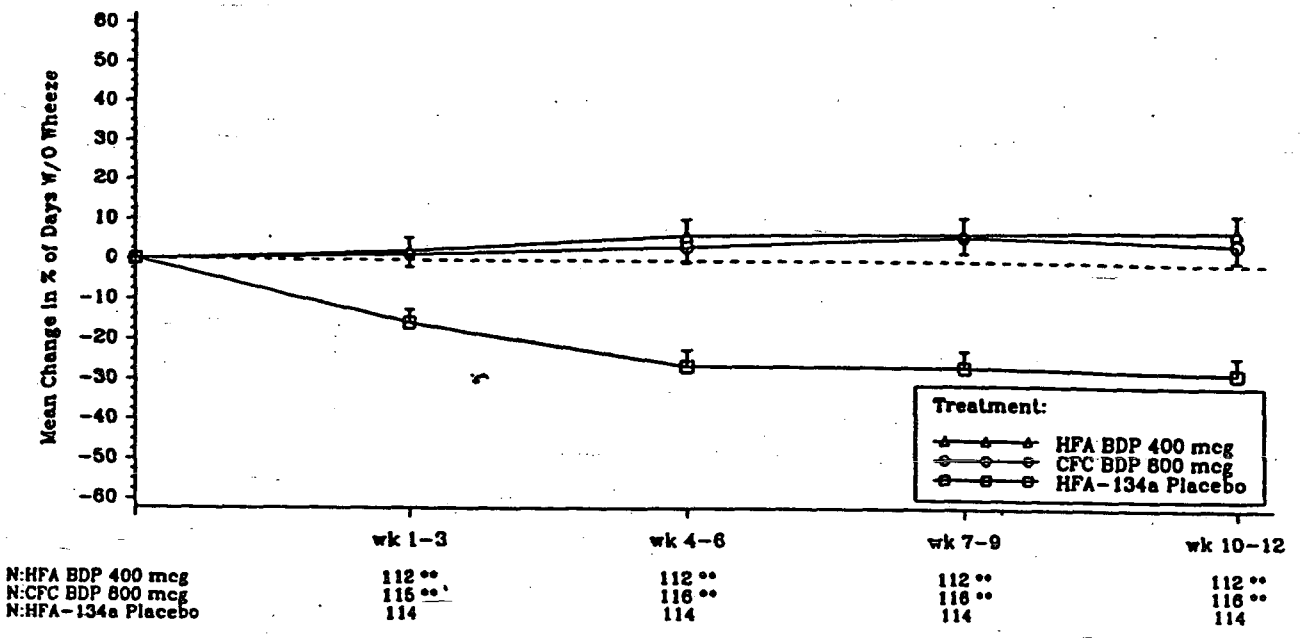
* **<u>days without wheezing</u>: The mean change in the percent of days without wheezing did not significantly change after switching from oral corticosteroids to inhaled BDP, but decreased significantly in the group which received HFA placebo ($p \leq 0.003$). The mean change in the percent of days without wheezing was comparable for the BDP groups throughout the study (see figure and table below; fig9; p199, v1.114; tab16, p200, v1.114)**

Table 16: **<u>Change from Oral Steroid Treatment in Percent of Days Without Wheeze: Comparisons with Placebo (Patients Included in the Intent-to-treat Analysis)</u>**

Study week		HFA-BDP 400 mcg	CFC-BDP 800 mcg	HFA-Placebo	Overall p-value*
Run-in	Mean	22.3	25.7	24.2	0.820
	SE	3.95	3.77	3.94	
	N	113	117	117	
Oral Steroid Tx	Mean	51.0	52.2	53.9	0.911
	SE	4.80	4.57	4.78	
	N	112	117	116	
Change from Oral Steroid Tx at Weeks 1-3	Mean	2.3**	1.4**	-15.6	< 0.001
	SE	3.31	3.17	3.30	
	N	112	115	114	
Change from Oral Steroid Tx at Weeks 4-6	Mean	6.4**	3.5**	-26.4	< 0.001
	SE	4.18	4.00	4.18	
	N	112	116	114	
Change from Oral Steroid Tx at Weeks 7-9	Mean	6.9**	6.2**	-26.6	< 0.001
	SE	4.22	4.03	4.21	
	N	112	116	114	
Change from Oral Steroid Tx at Weeks 10-12	Mean	8.4**	5.0**	-27.6	< 0.001
	SE	4.40	4.21	4.40	
	N	112	116	114	

*Based on an ANOVA with treatment, center, treatment-by-center interaction terms in the model. Comparisons of active treatments with placebo: ** $p \leq 0.003$.

Figure 9
Comparisons with Placebo
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 400 mcg	112 **	112 **	112 **	112 **
N:CFC BDP 800 mcg	115 **	116 **	116 **	116 **
N:HFA-134a Placebo	114	114	114	114

P-values for comparisons of each active treatment with placebo: **: p<= 0.003; *: p<= 0.017; +: p<= 0.03.

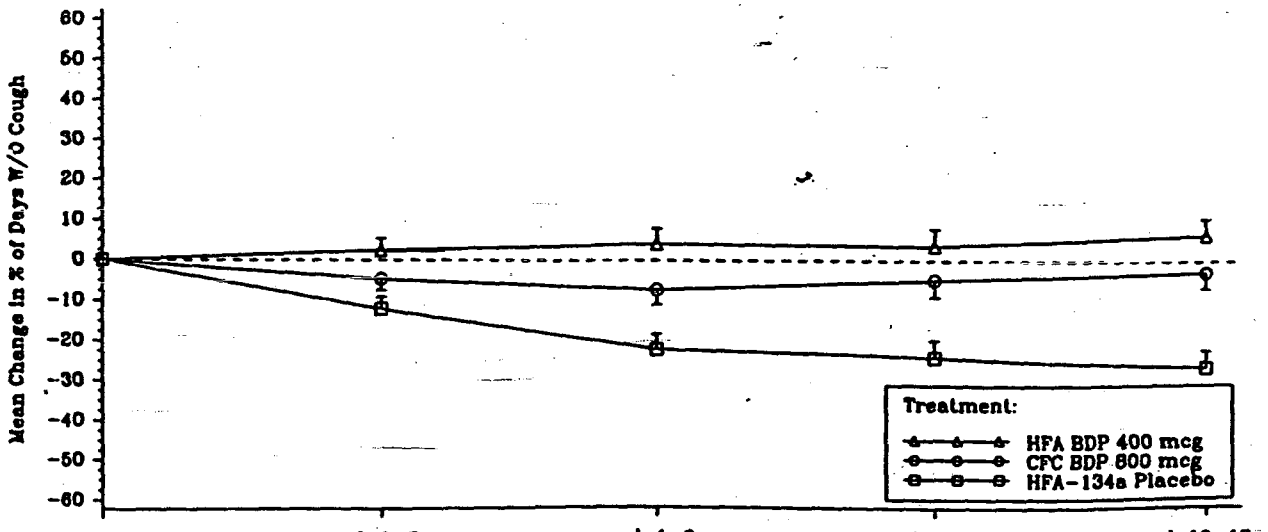
✱ <u>days with cough</u>: **The mean change in percent of days without cough was significantly less in the groups that received BDP than in the group that received HFA placebo. The response to 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC was not comparable, however. The group that received BDP-CFC had a slight decrease in mean percent of days without cough while the group that received BDP-HFA had a slight increase in this parameter, compared to a substantial decrease in the group that received placebo (see figure and table below; fig10, p203, v1.114; tab17, p204, v1.114).**

Table 17: **Change from Oral Steroid Treatment in Percent of Days Without Cough: Comparisons with Placebo (Patients Included in the Intent-to-treat Analysis)**

Study week		HFA-BDP 400 mcg	CFC-BDP 800 mcg	HFA-Placebo	Overall p-value*
Run-in	Mean	49.1	39.8	50.8	0.154
	SE	4.46	4.25	4.44	
	N	113	117	117	
Oral Steroid Tx	Mean	66.5	72.5	72.2	0.559
	SE	4.46	4.25	4.44	
	N	113	117	117	
Change from Oral Steroid Tx at Weeks 1-3	Mean	2.4**	-4.7	-12.2	0.002
	SE	2.94	2.82	2.93	
	N	113	115	115	
Change from Oral Steroid Tx at Weeks 4-6	Mean	4.0**	-7.3*	-22.2	<0.001
	SE	3.88	3.71	3.87	
	N	113	116	115	
Change from Oral Steroid Tx at Weeks 7-9	Mean	3.6**	-5.0**	-24.3	<0.001
	SE	4.32	4.14	4.32	
	N	113	116	115	
Change from Oral Steroid Tx at Weeks 10-12	Mean	6.4**	-2.9**	-26.8	<0.001
	SE	4.21	4.03	4.20	
	N	113	116	115	

* Based on an ANOVA with treatment, center, treatment-by-center interaction terms in the model.
Comparisons of active treatments with placebo: ** p ≤0.003, * p≤0.017.

Figure 10
Comparisons with Placebo
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 400 mcg	113 **	113 **	113 **	113 **
N:CFC BDP 800 mcg	116	116 *	116 **	116 **
N:HFA-134a Placebo	116	116	116	116

P-values for comparisons of each active treatment with placebo: **: p<= 0.003; *: p<= 0.017; +: p<= 0.03.

* <u>shortness of breath</u>: There was an increase in the mean percent of days without shortness of breath after administration of BDP (more after administration of BDP-HFA than after administration of BDP-CFC) and a significant decrease after administration of HFA placebo (see tables and figure below; tab 14.2.9.2.1, p408, v1.114; fig 14.2.9.2.2, p410, v1.114; tab 14.2.9.2.3, p411, v1.114). Mean asthma symptom scores showed the same pattern, i.e. minimal increase after administration of BDP-CFC, minimal decrease after administration of BDP-HFA, and significant increase after placebo).

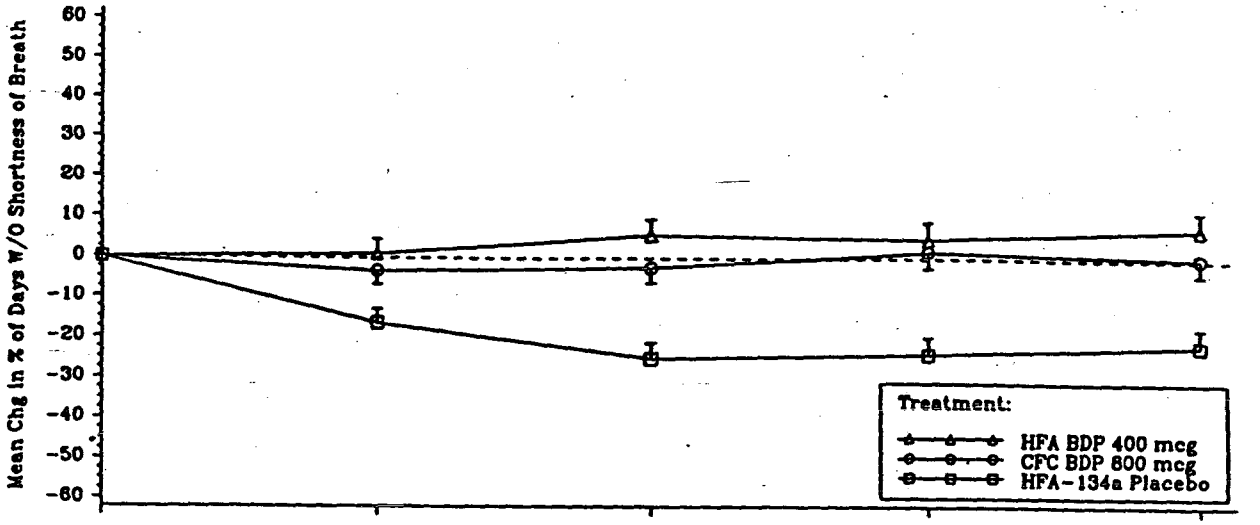
Table 14.2.9.2.1
Adjusted Mean Change from Oral Steroid Treatment in Percent of Days Without Shortness of Breath Comparisons with Placebo

(Patients Included in the Intent-to-treat Analysis)

Study week		HFA BDP 400 mcg	CFC BDP 800 mcg	HFA-134a Placebo	Overall P-value[a]
Run-in	Mean	17.4	19.2	18.1	0.922
	SE	3.35	3.20	3.34	
	Median	0.0	0.0	0.0	
	Min				
	Max				
	N	113	117	117	
Oral Steroid Tx	Mean	44.8	53.4	43.8	0.270
	SE	4.72	4.50	4.70	
	Median	33.3	66.7	33.3	
	Min				
	Max				
	N	113	117	117	
Change from Oral Steroid Tx at Weeks 1-3	Mean	0.9**	-3.4*	-16.5	0.002
	SE	3.54	3.40	3.54	
	Median	0.0	0.0	0.0	
	Min				
	Max				
	N	113	116	115	
Change from Oral Steroid Tx at Weeks 4-6	Mean	5.8**	-2.5**	-25.2	<0.001
	SE	3.93	3.76	3.92	
	Median	0.0	0.0	0.0	
	Min				
	Max				
	N	113	116	115	
Change from Oral Steroid Tx at Weeks 7-9	Mean	4.8**	1.7**	-24.1	<0.001
	SE	4.27	4.10	4.27	
	Median	0.0	0.0	0.0	
	Min				
	Max				
	N	113	116	115	
Change from Oral Steroid Tx at Weeks 10-12	Mean	7.7**	0.4**	-21.7	<0.001
	SE	4.40	4.21	4.39	
	Median	0.0	0.0	0.0	
	Min				
	Max				
	N	113	116	115	

[a] Based on an ANOVA with treatment, center, treatment by center interaction terms in the model.
Comparisons of active treatments with placebo: **: p <= 0.003; *: p <= 0.017; + <= 0.03.

Figure 14.2.9.2.2
Comparisons with Placebo
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 400 mcg	113 **	113 **	113 **	113 **
N:CFC BDP 800 mcg	116 *	116 **	116 **	116 **
N:HFA-134a Placebo	115	115	115	115

P-values for comparisons of each active treatment with placebo: **: p<= 0.003; *: p<= 0.017; +: p<= 0.03.

Table 14.2.9.2.3
Adjusted Mean Change from Oral Steroid Treatment in Percent of Days Without Shortness of Breath
HFA BDP 400 mcg Compared with CFC BDP 800 mcg

(Patients Included in the Intent-to-treat Analysis)

Study week	Mean difference [a]	S.E.	90% C.I. of Difference
Run-in	-1.8	4.63	-9.48, 5.80
Oral Steroid Tx	-8.5	6.52	-19.28, 2.24
Change from Oral Steroid Tx at Weeks 1-3	4.4	4.91	-3.73, 12.46
Change from Oral Steroid Tx at Weeks 4-6	8.2	5.44	-0.75, 17.19
Change from Oral Steroid Tx at Weeks 7-9	3.1	5.92	-6.65, 12.88
Change from Oral Steroid Tx at Weeks 10-12	7.3	6.09	-2.70, 17.38

[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.

✱ chest tightness: There was a slight mean increase in percent of days without chest tightness in the group that received BDP-HFA, a slight mean decrease in the group that received BDP-CFC and a significant decrease in the group that received HFA placebo (see tables and figure below; tab 14.2.10.2.1, p419, v1.114; tab14.2.10.2.1, p420, v1.114; fig 14.2.10.2.2, p421, v1.114). A similar pattern of change was noted in regard to symptom scores for chest tightness.

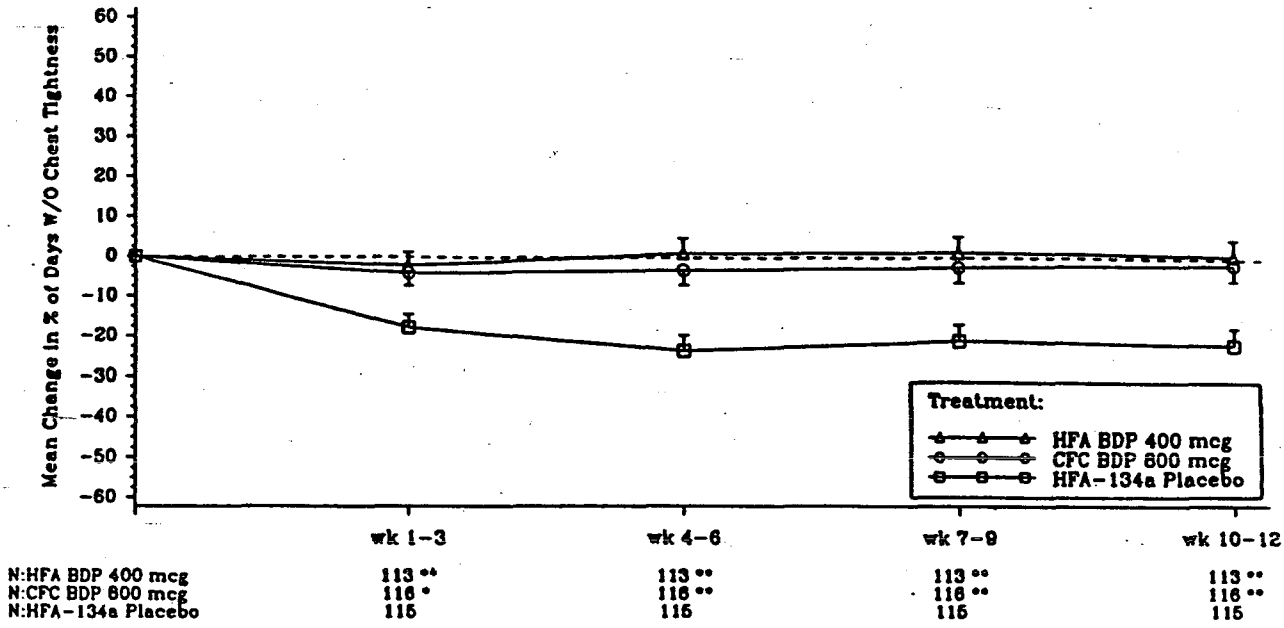
Table 14.2.10.2.1
Adjusted Mean Change from Oral Steroid Treatment in Percent of Days Without Chest Tightness
Comparisons with Placebo

(Patients Included in the Intent-to-treat Analysis)

Study week		HFA BDP 400 mcg	CFC BDP 800 mcg	HFA-134a Placebo	Overall P-value*
Run-in	Mean	21.2	28.6	21.8	0.239
	SE	3.55	3.39	3.54	
	Median	0.0	20.0	0.0	
	N	113	117	117	
Oral Steroid Tx	Mean	47.8	58.1	50.0	0.238
	SE	4.63	4.42	4.62	
	Median	66.7	66.7	66.7	
	N	113	117	117	
Change from Oral Steroid Tx at Weeks 1-3	Mean	-2.1**	-4.1*	-17.7	0.001
	SE	3.31	3.17	3.31	
	Median	0.0	0.0	0.0	
	N	113	116	115	
Change from Oral Steroid Tx at Weeks 4-6	Mean	1.0**	-3.2**	-23.5	<0.001
	SE	3.88	3.72	3.88	
	Median	0.0	0.0	0.0	
	N	113	116	115	
Change from Oral Steroid Tx at Weeks 7-9	Mean	1.3**	-2.5**	-21.0	<0.001
	SE	4.06	3.89	4.06	
	Median	0.0	0.0	0.0	
	N	113	116	115	
Change from Oral Steroid Tx at Weeks 10-12	Mean	0.8**	-1.6**	-21.8	<0.001
	SE	4.20	4.02	4.20	
	Median	0.0	0.0	0.0	
	N	113	116	115	

* Based on an ANOVA with treatment, center, treatment by center interaction terms in the model.
Comparisons of active treatments with placebo: **: p <= 0.003; *: p <= 0.017; + <= 0.03.

Figure 14.2.10.2.2
Comparisons with Placebo
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 400 mcg	113 **	113 **	113 **	113 **
N:CFC BDP 600 mcg	116 *	116 **	116 **	116 **
N:HFA-134a Placebo	115	115	115	115

P-values for comparisons of each active treatment with placebo: **: p<= 0.003; *: p<= 0.017; +: p<= 0.03.

Table 14.2.10.2.3
Adjusted Mean Change from Oral Steroid Treatment in Percent of Days Without Chest Tightness
HFA BDP 400 mcg Compared with CFC BDP 800 mcg

(Patients Included in the Intent-to-treat Analysis)

Study week	Mean difference [1]	S.E.	90% C.I. of Difference
Run-in	-7.4	4.91	-15.49, 0.71
Oral Steroid Tx	-10.3	6.41	-20.82, 0.32
Change from Oral Steroid Tx at Weeks 1-3	2.0	4.58	-5.57, 9.55
Change from Oral Steroid Tx at Weeks 4-6	4.3	5.37	-4.59, 13.14
Change from Oral Steroid Tx at Weeks 7-9	3.8	5.62	-5.48, 13.07
Change from Oral Steroid Tx at Weeks 10-12	2.3	5.82	-7.25, 11.94

[1] 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.

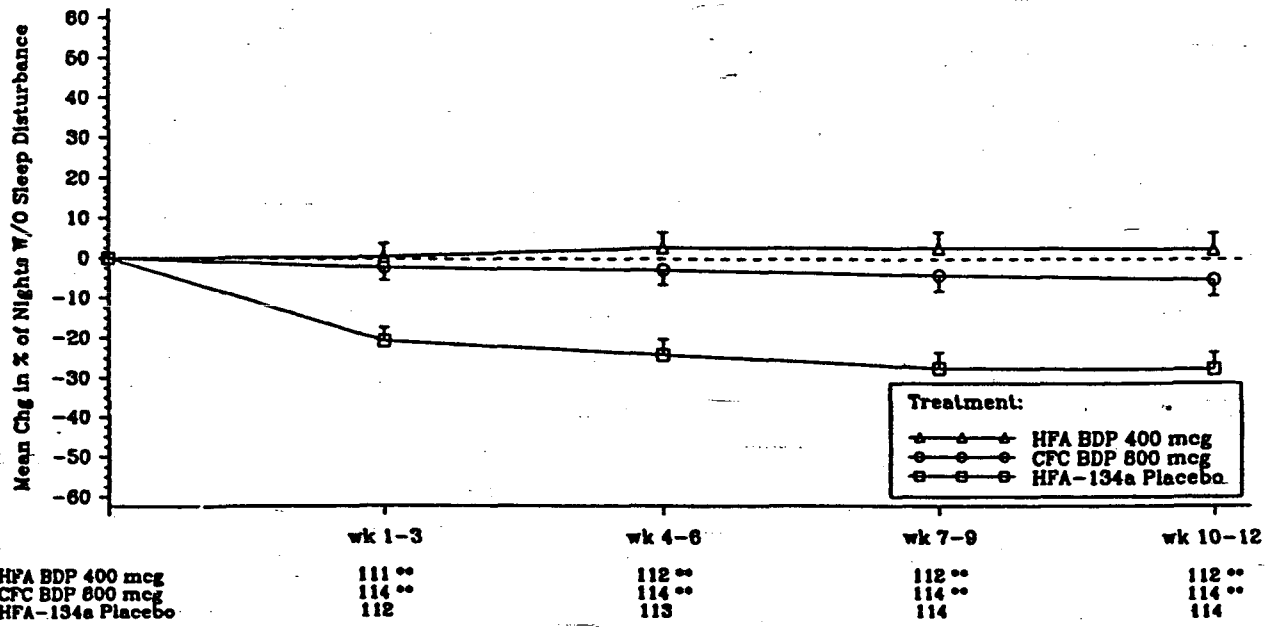
* sleep disturbance: **There was a slight mean increase in percent of nights without sleep disturbance in the BDP-HFA group, a slight mean decrease in the BDP-CFC group and a significant decrease in the HFA placebo group (see tables and figure below; tab18, p212, v1.114; tab 14.2.11.2.3, p434, v1.114; fig 11, p211, v1.114). A similar pattern of change was noted in regard to sleep disturbance scores.**

Table 18: Change from Oral Steroid Treatment in Percent of Nights without Sleep Disturbance: Comparisons with Placebo (Patients Included in the Intent-to-treat Analysis)

Study week		HFA-BDP 400 mcg	CFC-BDP 800 mcg	HFA-Placebo	Overall p-value*
Run-in	Mean	43.5	42.1	46.2	0.754
	SE	4.04	3.85	4.01	
	N	111	115	116	
Oral Steroid Tx	Mean	72.4	77.1	74.5	0.709
	SE	4.13	3.96	4.13	
	N	112	115	116	
Change from Oral Steroid Tx at Weeks 1-3	Mean	0.5**	-2.2**	-20.6	<0.001
	SE	3.32	3.20	3.36	
	N	111	114	112	
Change from Oral Steroid Tx at Weeks 4-6	Mean	2.8**	-2.8**	-24.1	<0.001
	SE	3.84	3.70	3.89	
	N	112	114	113	
Change from Oral Steroid Tx at Weeks 7-9	Mean	2.8**	-4.1**	-27.4	<0.001
	SE	3.99	3.86	4.00	
	N	112	114	114	
Change from Oral Steroid Tx at Weeks 10-12	Mean	2.5**	-5.2**	-27.6	<0.001
	SE	4.19	4.05	4.20	
	N	112	114	114	

* Based on an ANOVA with treatment, center, treatment-by-center interaction terms in the model.
Comparisons of active treatments with placebo: ** $p \leq 0.003$.

Figure 11
Comparisons with Placebo
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)



P-values for comparisons of each active treatment with placebo: **: p<= 0.003; *: p<= 0.017; +: p<= 0.03.

Table 14.2.11.2.3
Adjusted Mean Change from Oral Steroid Treatment in
Percent of Nights
without Sleep Disturbance:
HFA BDP 400 mcg Compared with CFC BDP 800 mcg

(Patients Included in the Intent-to-treat Analysis)

Study week	Mean difference *	S.E.	90% C.I. of Difference
Run-in	1.4	5.57	-7.77, 10.62
Oral Steroid Tx	-4.7	5.72	-14.17, 4.70
Change from Oral Steroid Tx at Weeks 1-3	2.7	4.61	-4.90, 10.32
Change from Oral Steroid Tx at Weeks 4-6	5.7	5.33	-3.14, 14.46
Change from Oral Steroid Tx at Weeks 7-9	6.9	5.55	-2.21, 16.11
Change from Oral Steroid Tx at Weeks 10-12	7.6	5.83	-2.00, 17.24

* 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.

✱ beta agonist use: There was a slight increase in mean daily beta agonist use after administration of BDP-HFA, a slight decrease after administration of BDP-CFC and a larger increase after administration of HFA placebo (see tables and figure below; tab19, p216, v1.114; tab 14.2.12.2.2, p445, v1.114; fig12, p215, v1.114). The difference between daily beta agonist use was driven by slightly greater nighttime use of inhaled beta agonists in the BDP-HFA group. These differences between BDP-HFA and BDP-CFC were not clinically significant, but were statistically significant ($p \leq 0.003$).

Table 19: Change from Oral Steroid Treatment in Daily Beta-agonist Use: Comparisons with Placebo (Patients Included in the Intent-to-treat Analysis)

Study week		HFA-BDP 400 mcg	CFC-BDP 800 mcg	HFA-Placebo	Overall p-value*
Run-in	Mean	3.83**	3.37	2.94	0.006
	SE	0.196	0.187	0.196	
	N	113	117	117	
Oral Steroid Tx	Mean	2.00	1.79	1.77	0.553
	SE	0.164	0.156	0.163	
	N	113	117	117	
Change from Oral Steroid Tx at Weeks 1-3	Mean	0.07**	-0.07**	0.87	<0.001
	SE	0.129	0.123	0.129	
	N	113	116	115	
Change from Oral Steroid Tx at Weeks 4-6	Mean	-0.00**	-0.02**	1.38	<0.001
	SE	0.152	0.146	0.152	
	N	113	116	115	
Change from Oral Steroid Tx at Weeks 7-9	Mean	0.13**	-0.05**	1.54	<0.001
	SE	0.176	0.169	0.176	
	N	113	116	115	
Change from Oral Steroid Tx at Weeks 10-12	Mean	0.15**	-0.03**	1.59	<0.001
	SE	0.191	0.183	0.191	
	N	113	116	115	

* Based on an ANOVA with treatment, center, treatment-by-center interaction terms in the model.
Comparisons of active treatments with placebo: ** $p \leq 0.003$.

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)

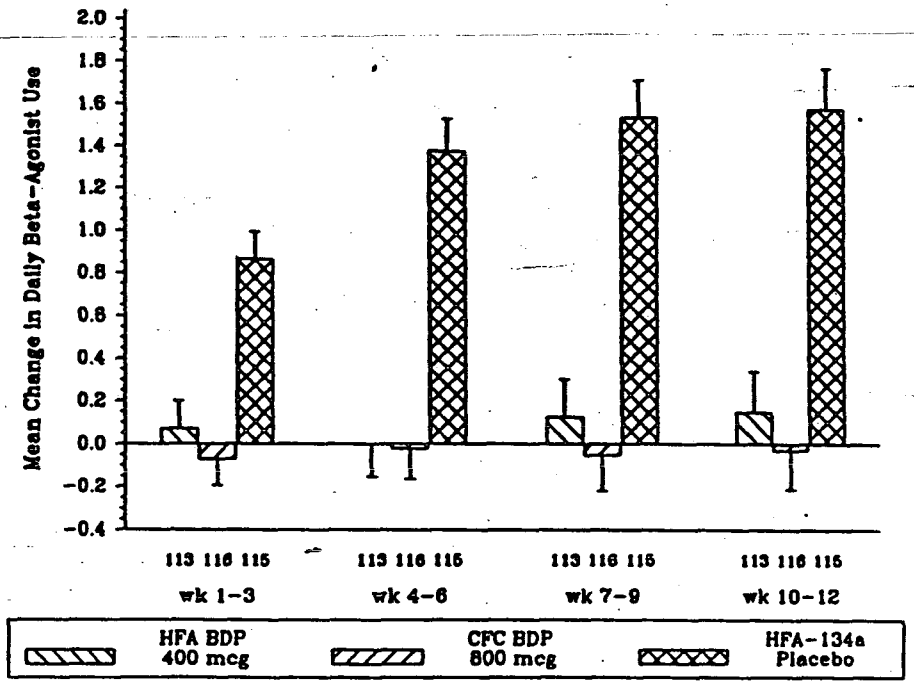


Table 14.2.12.2.2
Adjusted Mean Change from Oral Steroid Treatment in Daily Beta-agonist Use
HFA BDP 400 mcg Compared with CFC BDP 800 mcg

(Patients Included in the Intent-to-treat Analysis)

Study week	Mean difference *	S.E.	90% C.I. of Difference
Run-in	0.46	0.271	0.011, 0.906
Oral Steroid Tx	0.20	0.227	-0.170, 0.577
Change from Oral Steroid Tx at Weeks 1-3	0.14	0.178	-0.152, 0.437
Change from Oral Steroid Tx at Weeks 4-6	0.02	0.210	-0.329, 0.365
Change from Oral Steroid Tx at Weeks 7-9	0.18	0.244	-0.224, 0.581
Change from Oral Steroid Tx at Weeks 10-12	0.18	0.265	-0.259, 0.614

* 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.

* quality of life (QOL): Overall quality of life scores improved slightly after treatment with 400 mcg/day of BDP-HFA from the end of oral corticosteroid treatment to week 12 and to a greater degree from prior to treatment with oral corticosteroids to week 12. After administration of 800 mcg/day of BDP-CFC, there was a slight decrease in QOL from the end of the oral corticosteroid treatment and less of an increase from prior to

oral corticosteroid treatment to week 12. The difference in assessment between each of the BDP groups and the placebo group was statistically significant ($p \leq 0.003$)(see table below; tab 20, p220, v1.114), but of unclear clinical significance. The clinical instrument used was the Juniper-Guyatt asthma questionnaire evaluating 4 domains; activity limitations, symptoms, emotional function and exposure to environmental stimuli. The degree to which oral corticosteroids influenced the change in QOL from assessment prior to their administration to week 12 is a confounding factor that makes this analysis invalid.

Table 20: Change in Asthma Quality-of-Life Scores from the End of Oral Steroid Treatment to Week 12 (Patients Included in the Intent-to-treat Analysis)

		HFA-BDP 400 mcg	CFC-BDP 800 mcg	HFA-Placebo	90% C.I.[a]	Overall p-value[b]
Overall Quality-of-life score	Mean	0.13**	-0.03**	-0.81	-0.090, 0.414	< 0.001
	SE	0.109	0.107	0.110		
	N	110	111	108		
Symptoms	Mean	0.12**	-0.04**	-0.98	-0.125, 0.440	< 0.001
	SE	0.122	0.120	0.124		
	N	110	111	108		
Emotions	Mean	0.17**	-0.09**	-0.93	-0.055, 0.593	< 0.001
	SE	0.140	0.137	0.142		
	N	110	111	108		
Environment	Mean	0.04**	-0.02**	-0.49	-0.167, 0.292	< 0.001
	SE	0.099	0.097	0.100		
Activity Limitations	Mean	0.16**	0.01**	-0.68	-0.103, 0.409	< 0.001
	SE	0.111	0.108	0.112		
	N	110	111	108		

[a] 90% confidence interval for the difference between adjusted mean change for HFA-BDP 400 mcg and CFC-BDP 800 mcg treated patients.
[b] Based on an ANOVA with treatment, center, and treatment-by-center interaction terms in the model. Comparisons of active treatments to placebo: ** $p \leq 0.003$.

☛ SAFETY FINDINGS

EXPOSURE: see table below (tab25, p232, v1.114)

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

Duration of Exposure	HFA-BDP (N=113)	CFC-BDP (N=117)	HFA-Placebo (N=117)
> 14 days	113	115	108
> 28 days	111	113	98
> 42 days	107	111	90
> 56 days	106	107	83
> 70 days	101	107	80
> 84 days	45	45	33
Mean Time on Treatment (days)	80.7	79.8	67.3
Median Time on Treatment (days)	84.0	84.0	83.0
Range of Treatment Time (days)	21-96	1-98	4-107

ADVERSE EVENTS

✦ Overall, there were reports of AEs in 65% of the BDP-HFA group (73 patients), 64% of the BDP-CFC group (75 patients) and 74% of the placebo group (87 patients).

✦ AEs reported by > 2% of patients in any treatment group: There was > 1 more report in the BDP-HFA group than in the placebo group for the following AEs:

- ☛ dry mouth (2 patients BDP-HFA, none BDP-CFC/placebo)
- ☛ pain (4 BDP-HFA, 1 BDP-CFC, 1 placebo)
- ☛ rigors (chills) (2 BDP-HFA, none BDP-CFC, none placebo)
- ☛ headache (16 BDP-HFA, 20 BDP-CFC, 12 placebo)
- ☛ nausea (2 BDP-HFA, 2 BDP-CFC, none placebo)
- ☛ otitis media (3 BDP-HFA, 1 BDP-CFC, none placebo)
- ☛ sinusitis (7 BDP-HFA, 5 BDP-CFC, 3 placebo)
- ☛ URI (31 BDP-HFA, 25 BDP-CFC, 23 placebo)

COMMENT: These are generally small and insignificant differences between BDP-HFA and placebo. It could be argued that the HFA product has more of an irritative effect on the

upper respiratory tract, assuming that the reports of otitis, sinustits, and URI are not all related to infection and that headaches were consistent with sinus inflammation. However, this assumption can not be made based on the data available, including the case report forms. There is also no reason to believe that the HFA product is more likely to make patients susceptible to the development of local infection.

- ✦ severe adverse events: There were 9 severe AEs in the BDP-HFA group, 8 severe AEs in the BDP-CFC group and 20 severe AEs in the HFA placebo group. Severe AEs in patients who received BDP-HFA were dry mouth, headache, increased asthma symptoms (3), pharyngitis, rhinitis, sinusitis, URI.

- ✦ pharyngitis: There were 11 patients in the BDP-HFA group (10%), 8 patients in the BDP-CFC group (7%) and 10 patients in the HFA placebo group (9%) who developed pharyngitis.

- ✦ possibly/probably related AEs: There were 11 (9.7%) AEs in the BDP-HFA group that were considered possibly/probably related to the study drug, as compared to 23 (19.7%) in the BDP-CFC group and 18 (15.4%) in the HFA placebo group.

- ✦ study discontinuations due to AEs: There were 7 discontinuations due to an AE in the BDP-HFA group (6.2%), 2 in the BDP-CFC group (1.7%) and 18 in the HFA placebo group (15.4%). All of the discontinuations in the placebo group were due to respiratory AEs. There were 3 BDP-HFA and 1 BDP-CFC patients who were withdrawn for non-respiratory-related AEs; numbness of teeth, dry throat, and lightheadedness in the HFA group and headaches in the CFC group.

- ✦ oropharyngeal candidiasis: Patients with oropharyngeal AEs with oropharyngeal lesions on physical exam had cultures of the mouth/throat performed. None of these cultures showed levels

of candida growth that exceeded the amount expected in normal flora, according to the sponsor.

VITAL SIGNS: No significant changes were seen in blood pressure or pulse rate after administration of BDP-HFA for 12 weeks.

ECGs: No significant changes were seen in ECGs after administration of BDP-HFA for 12 weeks.

PLASMA CORTISOL: Because patients were allowed to use oral contraceptives in the study and use of oral contraceptives could affect plasma cortisol levels, a post-hoc unplanned analysis was performed, excluding patients who had used oral contraceptives. The results of this analysis were consistent with the analysis of the ITT population. After 12 weeks of treatment, there were 5 patients (3 had low plasma cortisol levels at the end of run-in) in the BDP-HFA group, 3 patients (1 had a low plasma cortisol level at the end of run-in) in the BDP-CFC group and 8 patients (1 had low a plasma cortisol level at the end of run-in) in the HFA placebo group who had plasma cortisol levels below the lower limit of the NRR. The mean decrease in plasma cortisol level (nmol/L) was greater after oral corticosteroid treatment in the BDP-CFC and HFA placebo groups, 297 and 298 respectively, than in the BDP-HFA group, 245 nmol/L. This suggests that, at the time of randomization, a greater systemic corticosteroid effect was possible in the BDP-CFC group than in the BDP-HFA group, but does not indicate any expected difference between these drug products in terms of local effect. After treatment with 400 mcg/day of BDP-HFA for 12 weeks, the mean increase in plasma cortisol was 260 nmol/L for the ITT population, which was comparable to mean increases of 250 nmol/L and 257 nmol/L, seen respectively in the 800 mcg/day BDP-CFC and HFA placebo groups, using the ITT population. Excluding patients on oral contraceptives, mean change in plasma cortisol level was 191, 206, and 184 nmol/L in the BDP-HFA, BDP-CFC and HFA placebo groups.

SERUM OSTEOCALCIN: There were no clinically significant differences in regard to the mean change in serum osteocalcin from day 1 to the final visit between any of the three treatment groups (see table below; tab27, p236, v1.114)

Table 27: Serum Osteocalcin (ng/mL) by Treatment Group at Each Assessment Period [a] (Patients Included in the Intent-to-treat Analysis)

Study week		HFA-BDP 400 mcg	CFC-BDP 800 mcg	HFA-Placebo
Prior to oral steroid Tx	Mean	3.0	3.2	2.9
	SE	0.16	0.15	0.16
	N	111	114	114
Day 1 (prior to study Tx)	Mean	2.0	2.0	1.9
	SE	0.13	0.13	0.13
	N	112	113	114
Final visit	Mean	2.5	2.8	2.8
	SE	0.16	0.15	0.16
	N	111	114	110

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

LABORATORY TESTS: There were more patients in the BDP-HFA group who had a normal SGPT at baseline and a SGPT above the upper limit of the NRR after treatment (9) than in the BDP-CFC group (4) or in the HFA placebo group (4). None of the increases in SGPT seen in the BDP-HFA group, however, was inconsistent with the degree of change seen in the other two treatment groups nor was the level significantly greater than was seen in patients prior to drug administration. No clinically significant mean or individual patient changes were seen in any laboratory test after treatment with BDP-HFA.

☛ overall evaluation of efficacy and safety data and conclusions:

☛ A dose of 400 mcg/day (200 mcg bid) of BDP-HFA at a concentration of 50 mcg/puff was demonstrated to be efficacious, when compared to placebo. The degree of effectiveness produced by a burst of oral corticosteroids was maintained in adult patients with mild-moderate asthma, both with and without a history of inhaled corticosteroid use, when 400 mcg/day of BDP-HFA was administered over a period of 12 weeks.

☛ [redacted] of 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC was not demonstrated, since the study was not designed to demonstrate [redacted]. Although [redacted] was not demonstrated, comparability of 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC was demonstrated. Although the effectiveness of 400 mcg/day of BDP-HFA was consistently slightly greater, across a range of parameters, than 800 mcg/day of BDP-CFC, this difference was not clinically significant. The comparability of 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC is not inconsistent with the in-vitro data showing that BDP-HFA has a smaller particle size than BDP-CFC and that there is greater deposition in the lung of BDP-HFA than BDP-CFC. However, there is approximately 10 times more deposition of the BDP-HFA product in the lung which is not consistent with the fact that ½ a given dose of BDP-CFC given as BDP-HFA produced a comparable effect. This inconsistency probably reflects the unreliability and questionable clinical relevance of data from [redacted] studies.

☛ The comparability of 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC (the maximum daily recommended dose of the approved CFC product) is not adequate by itself to support [redacted]

(note that patients were actually switched from BDP-CFC to BDP-HFA in study 1163 but that study is flawed as well).

On the other hand, lines of survival in patients receiving the HFA and CFC products are essentially superimposable over the 12 weeks of the study. This strongly suggests but does not conclusively demonstrate, in conjunction with the other parameters evaluated, that a patient might be safely switched from 800 mcg/day of BDP-CFC to 400 mcg/day of BDP-HFA without concern about whether such a change would result in less control of the patient's asthma.

☛ From the standpoint of practical use of BDP-HFA, the findings in this study do not demonstrate that a high dose of BDP-HFA (400 mcg/day) is [redacted]" in the way that it is usually defined,

☛ There was no concern about the safety of 400 mcg/day of BDP-HFA delivered as the 50 mcg/puff concentration raised, based on the safety parameters evaluated in this study.

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ABSTRACT

METHODS: Study 1130 was a randomized, parallel, active treatment controlled, double-blind, double-dummy, repetitive dose, multi-center study conducted in the UK in 233 adult patients (116 in one arm and 117 in the other arm), who had mild-moderate asthma receiving inhaled corticosteroids at a dose of > 400 mcg/day. After a 10-12 day run-in period on their usual asthma medications, patients entered a 7-13 day period on 30 mg of prednisolone/day, following which they were randomized to receive 800 mcg/day of BDP-HFA (100 mcg/puff concentration)(4 puffs bid) or 1500 mcg/day of BDP-CFC (250 mcg/puff concentration)(3 puffs bid) for 12 weeks. The primary efficacy variable was mean change in AM PEF from the end of the oral corticosteroid treatment period to an average of the last 3 weeks of randomized treatment. Secondary efficacy parameters included other pulmonary function assessments (FEV-1, FEF 25-75, PM PEF), asthma symptoms, nighttime sleep disturbance caused by asthma, beta agonist use, and time to withdrawal because of asthma exacerbation. Safety was assessed by adverse events, vital signs, assessment for candidiasis, plasma cortisol levels, serum osteocalcin levels and laboratory tests. Two study populations were analyzed: 1) an intent-to-treat population; and 2) an evaluable for efficacy population.

RESULTS: Baseline comparison of the treatment groups showed that they were comparable in terms of demographics, medication use, pulmonary function, and other criteria. Mean AM PEF increased substantially after treatment with prednisolone, and decreased minimally after institution of treatment with inhaled BDP. There was no clinically significant difference between the response to 800 mcg/day of BDP-HFA and 1500 mcg/day of BDP-CFC throughout the 12 weeks of randomized treatment. The comparability [redacted] of 800 mcg/day of BDP-HFA and 1500 mcg/day of BDP-CFC was supported by other parameters, including PM PEF, FEV-1, FEF 25-75, time to withdrawal because of asthma symptoms, asthma symptoms, nighttime sleep disturbance because of asthma and inhaled beta agonist use. Differences in adverse events and other safety parameters between the group that received 800 mcg/day of BDP-HFA and the group that

received 1500 mcg/day of BDP-CFC were minimal and not clinically significant.

DISCUSSION: Although there was no placebo control in this study and despite the concentrations used, the comparability of the response to 800 mcg/day of BDP-HFA (at a concentration of 100 mcg/puff) and 1500 mcg/day (at a concentration of 250 mcg/puff) of BDP-CFC, strongly suggests (but does not prove; see discussion below) that a dose of 800 mcg/day of BDP-HFA at a concentration of 100 mcg/puff is effective.

The sponsor has attempted by cross-study comparison with study 1129, in which a placebo control was used but a concentration of 50 mcg/puff of BDP-HFA was also used, to argue that a dose-response was seen across studies, thereby validating the results of this study. However, in addition to potential differences related to the concentration of BDP-HFA and the active treatment employed, the differences in response in these two studies is highlighted by the fact that 800 mcg/day of BDP-HFA in study 1130 was less effective, based on change in FEF 25-75 and AM PEF, than 400 mcg/day of BDP-HFA in study 1129.

Furthermore, the sponsor has not designed the study appropriately to demonstrate [redacted]" of BDP-HFA and BDP-CFC, although from a clinical standpoint, the response to 800 mcg/day of BDP-HFA and 1500 mcg/day of BDP-CFC is comparable across the range of outcome variables that were evaluated. The study was also not appropriately designed to [redacted]

Therefore, this study can not be used to support the efficacy [redacted] active treatment control used, nor to claim [redacted]' of 800 mcg/day of BDP-HFA and 1500 mcg/day of BDP-CFC, because the study was not designed to demonstrate [redacted]' of the two products.

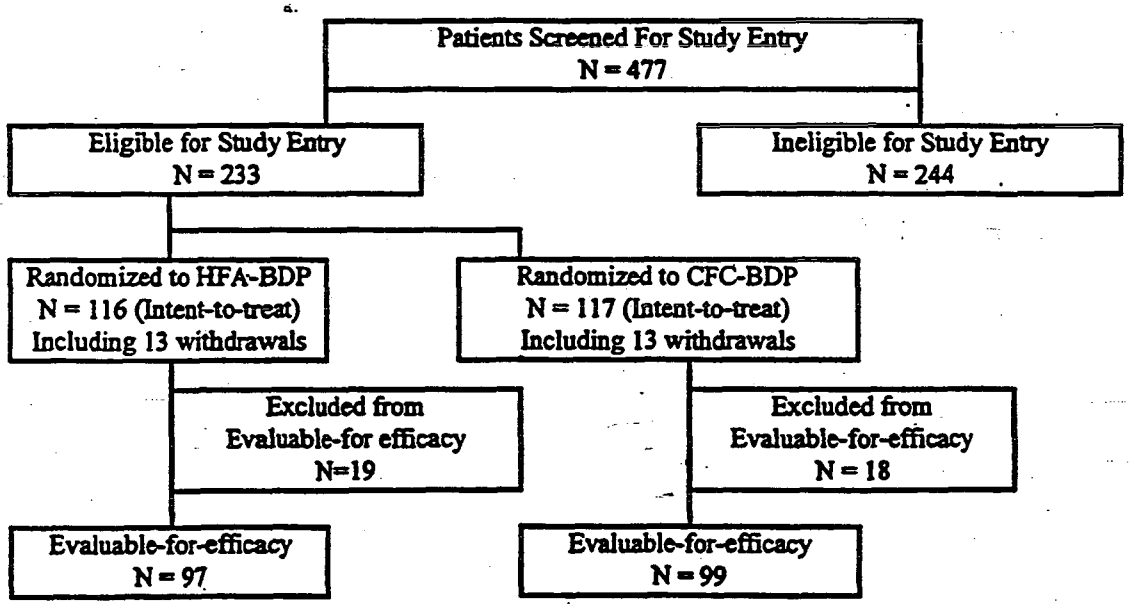
There were no concerns raised in regard to the safety of a dose of 800 mcg/day of BDP-HFA, based on the safety parameters evaluated in this study.

☎ study 1130

☛ The primary objective of this study was to determine if 800 mcg/day of BDP-HFA was "equivalent" in efficacy to 1500 mcg/day of BDP-CFC. The secondary objective was to assess the safety of 800 mcg/day of BDP-HFA.

☛ number of patients: 477 patients were screened; 233 patients were randomized (116 to BDP-HFA and 117 to BDP-CFC); 207 completed 12 weeks of evaluation (see flow chart below; fig1, p182, v1.192).

Figure 1: PATIENT DISPOSITION-1130-BRON



The reasons for ineligibility of patients can be seen in the table below; tab2, p183, v1.192).

Table 2: Number (%) of Patients Screened but Ineligible for Randomization by Reason

Reason	
PEF increase after prednisolone treatment < 15%	81 (33.2%)
PEF not within 50.0% to 85.0% of predicted	60 (24.6%)
FEV_1 reversibility <15%	49 (20.1%)
Active signs and symptoms of asthma not present	13 (5.3%)
Adverse event	10 (4.1%)
Violation of Inclusion/Exclusion criteria	9 (3.7%)
Withdrew consent	7 (2.9%)
Not compliant with diary card entries	3 (1.2%)
Laboratory abnormalities	2 (0.8%)
Not compliant with prednisolone tablets	1 (0.4%)
Pregnancy	1 (0.4%)
Other	8 (3.3%)
Total	244

The reasons for withdrawal of patients prior to the end of the study can be see in the table below; tab3, p184, v1.192).

Table 3: Number (%) of Patients Who Withdrew Prior to Week 12 by Primary Reason and Treatment (Patients Included in the Intent-to-treat Analysis)

Reason	HFA-BDP 800 mcg (N = 116)	CFC-BDP 1500 mcg (N = 117)	Overall (N = 233)
Fulfilled withdrawal criteria	3 (2.6%)	3 (2.6%)	6 (2.6%)
Adverse event	2 (1.7%)	3 (2.6%)	5 (2.1%)
Entry criteria violated	3 (2.6%)	2 (1.7%)	5 (2.1%)
Noncompliance	3 (2.6%)	1 (0.9%)	4 (1.7%)
Protocol violator	1 (0.9%)	1 (0.9%)	2 (0.9%)
Personal	0 (0.0%)	1 (0.9%)	1 (0.4%)
Inadequate response	0 (0.0%)	1 (0.9%)	1 (0.4%)
Withdrew consent	0 (0.0%)	1 (0.9%)	1 (0.4%)
Intercurrent disease	1 (0.9%)	0 (0.0%)	1 (0.4%)
Total	13 (11.2%)	13 (11.1%)	26 (11.2%)

☛ age range: 18-65 years

☛ patient population:

✦ asthma, moderate; symptom scores during run-in (see scoring system below) were consistent with mild asthma but there was a mean of approximately 4 uses/day of inhaled beta agonist during the run-in period and pulmonary function was consistent with moderate asthma.

✦ symptomatic; defined over the last 5 days of the run-in period as:

- ✱ sleep disturbance score of 1 or more on 1 or more nights OR
- ✱ daily asthma symptom score of 2 or more on 3 or more days for wheeze, cough, shortness of breath, and/or chest tightness OR
- ✱ use of inhaled beta agonist average of at least twice daily.

✦ AM PEF 50-85% predicted without inhaled beta agonists for 6 hours; reversibility ≥ 15% FEV-1 after 200-400 mcg of albuterol (see table below; tab9, p194, v1.192).

✦ on inhaled corticosteroids > 400mcg/day for at least 4 weeks of beclomethasone or budesonide (see table below; tab8, p192, v1.192); on inhaled beta agonists PRN for rescue;

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✦ demonstration of ≥ 15% improvement in AM PEF after oral corticosteroids (average of last 3 days of oral corticosteroid treatment compared with average of last 5 days of run-in period)(corticosteroid-responders).

Table 9: **Baseline Lung Function[a] (Patients Included in the Intent-to-treat Analysis)**

		HFA-BDP 800 mcg		CFC-BDP 1500 mcg		Overall P-value[b]	
		AM PEF	FEV_1	AM PEF	FEV_1	AM PEF	FEV_1
Screening Actual Values	Mean	365.3	2.08	364.1	2.16	0.902	0.413
	SD	75.38	0.698	76.23	0.668		
% Predicted	Mean	68.4	64.9	69.4	67.1	0.489	0.257
	SD	9.74	15.62	10.77	13.87		
% Reversibility to Beta-agonist	Mean		29.0		30.2		0.572
	SD		15.10		15.37		
Run-in[c] Actual Values	Mean	349.1	2.24	344.9	2.21	0.681	0.777
	SD	75.52	0.718	74.86	0.734		
% Predicted	Mean	65.4	70.3	65.7	68.8	0.869	0.549
	SD	10.91	19.06	10.41	17.32		
Oral Steroid Tx[d] Actual values	Mean	423.0	2.45	417.1	2.51	0.607	0.604
	SD	83.12	0.740	89.58	0.811		
% Predicted	Mean	79.4	76.5	79.4	77.7	0.975	0.593
	SD	12.05	16.82	12.24	16.95		
% Oral Steroid Response	Mean	21.9	12.2	21.6	17.9	0.814	0.274
	SD	8.77	21.21	11.44	47.00		

[a] Morning PEF was recorded in L/min; FEV_1 was recorded as L.
[b] Based on an ANOVA with treatment, center and treatment by center interaction terms in the model.
[c] Morning PEF is the average of the last 5 days of the run-in period; FEV_1 is the value taken at the clinic visit at the end of the run-in period.
[d] Morning PEF is the average of the last 3 days of the oral steroid treatment period; FEV_1 is the value taken at the clinic visit at the end of the oral steroid treatment period.

- study design: randomized, parallel, active treatment controlled, double-blind, double-dummy, repetitive dose, multicenter study (31 centers in the UK)

- drug administration: spacers not allowed; rinsing mouth after use was optional depending on what the patient had done previously (29% of the BDP-HFA group and 28% of the BDP-CFC group rinsed their mouth after use of inhaled corticosteroids).

  - 800 mcg/day BDP-HFA (100 mcg/puff)(4 puffs bid)(lot # A13846)

- 1500 mcg/day BDP-CFC (250 mcg/puff)(3 puffs bid)(lot #s S4614CA, S5084LA, and S5265AC)

- placebo used for double-dummy: HFA placebo (lot #s CT940324 and CT931212) and CFC placebo

☛ periods of study:

- 10-12 day run-in period with patient on usual medications

- 7-13 days on 30 mg of prednisolone

- 12 weeks of randomized treatment

☛ parameters evaluated:

EFFICACY

- AM and PM PEF: in morning upon awakening and evening before retiring and before taking medication; using a Mini-Wright peak flow meter; the primary efficacy variable was mean change in AM PEF from the end of the oral corticosteroid treatment period to weeks 10-12; equivalence was defined as ± 25 L/min; baseline AM PEF was defined as the average of the AM PEF taken over the last 3 days of the prednisolone treatment period; baseline AM PEF was compared to the average of the AM PEF measurements over the last 3 weeks of the study (weeks 10-12); baseline PM PEF was the average of the values obtained during the last 5 days of the prednisolone treatment period.

- asthma symptoms: in evening before taking medication; wheezing, cough, chest tightness and shortness of breath were scored using the following categorical scoring:

0 = none
1 = present, no discomfort
2 = mild, annoying, little or no discomfort
3 = moderate, discomfort, not affecting normal activities
4 = severe, interfering at least once with activities
5 = severe, could not work/got to school/do activities

- nighttime sleep disturbance: in morning before taking medication; assessed using the following categorical scale:

0 = none
1 = awakening once or early waking
2 = awakening twice or more
3 = awake most of night
4 = no sleep at all

- beta agonist use: recorded in AM and PM; use was defined as any time beta agonists were required, not the number of puffs.

- spirometry: FEV-1, FEF 25-75; prestudy, end of run-in period, after oral corticosteroids and every 3 weeks during randomized treatment; there was a 6 hour washout of inhaled beta agonists; absolute and percent change from baseline was calculated for each three week period of randomized treatment.

- time to withdrawal because of asthma: withdrawal criteria were a fall in AM PEF of $\geq 20\%$ from the run-in baseline value (average of the last 5 days of the run-in period) on 2 consecutive days AND:

  * the patient's nighttime sleep disturbance score was ≥ 1 on both nights AND/OR;

  * any asthma symptom score was ≥ 3 on both days AND/OR;

  * any asthma symptom score was 5 on one day AND/OR;

  * inhaled beta agonists were used > 4 times/day on both days.

SAFETY

- ✦ adverse events
- ✦ vital signs; on entry and after 12 weeks of treatment.
- ✦ ECGs; on entry into the study and after 12 weeks of treatment.
- ✦ laboratory tests: hematology, chemistries and urinalysis; end of run-in period, end of oral corticosteroid period, and the end of the study.
- ✦ plasma cortisol levels: end of run-in period, after oral corticosteroids and after 12 weeks of randomized treatment.
- ✦ serum osteocalcin levels: end of run-in period, after oral corticosteroids and after 12 weeks of randomized treatment
- ✦ oropharyngeal candidiasis: an oropharyngeal adverse event prompted examination by the investigator and if lesions were seen, mouth/throat cultures were taken.

☛ compliance: canister weight was converted to number of doses administered; a patient was considered compliant if the calculated overall total number of puffs was ± 40% of predicted, i.e. within 60-140% of predicted; reviewing diary cards; 12 missed diary card entries over any 3 week period was defined as non-compliance.

Compliance, as assessed by canister weights at the conclusion of the study, was 83% in the ITT population and 87% in the efficacy population (see below for description of population analyses). In the BDP-HFA group, there was 83% and 76% compliance in the efficacy and the ITT population, respectively, while there was 86% and 82% compliance in the efficacy population and the ITT population, respectively for the group that received BDP-CFC. Compliance was better in the BDP-CFC than in the BDP-HFA population, but not sufficiently to have influenced the study results.