- withdrawals: 3 patients withdrew because of adverse events; one patient receiving BDP placebo developed fever, headache and pharyngitis, one patient receiving 200 mcg/day of BDP-HFA developed fever and myalgia, and one patient receiving 400 mcg/day of BDP-HFA developed fever and headache. The data for these three patients was excluded from the data analysis, a decision made prior to breaking the randomization code.

- protocol violations: One patient had very low urine volumes on study day 13 and therefore day 14 urinary free-cortisol levels for this time frame were excluded from the analysis; the data for one patient with hypertension were excluded. One patient's cosyntropin value at screening was excluded because blood was drawn 20 minutes after injection of ACTH rather than 30 minutes.

- DEMOGRAPHICS: The significantly greater mean weight in the 200 mcg/day BDP-HFA group was driven by one 400 lb patient. There was a significant difference between the 800 mcg/day CFC group and the other treatment groups in regard to mean % predicted FEV-1. These differences were unlikely to have influenced the study results (see table 9, p90, v1.51 below). Most patients had a history of other allergic conditions.

Table 9: Demographic and Prestudy Characteristics (Patients Included in the Intent-to-treat Analysis)

		HFA-Placebo	HFA-BDP: 200 mcg	HFA-BDP: 400 mcg	HFA-BDP: 800 mcg	CFC-BDP: 800 mcg	P-value
Number of patients		9	9	9	8	8	
Sex[a]	Female	1 (11.1%)	1 (11.1%)	2 (22.2%)	2 (25.0%)	2 (25.0%)	0.901
	Male	8 (88.9%)	8 (88.9%)	7 (77.8%)	6 (75.0%)	6 (75.0%)	
Age (years)[b]	Mean	32.7	30.6	33.7	23.1	29.6	0.243
	SD	13.08	11.72	7.84	5.06	9.47	
Race[a]	Caucasian	5 (55.6%)	5 (55.6%)	5 (55.6%)	7 (87.5%)	7 (87.5%)	0.284
	Black	3 (33.3%)	4 (44.4%)	4 (44.4%)	1 (12.5%)	1 (12.5%)	
	Asian/Pac.	1 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Height (cm)[b]	Mean	178.6	181.2	174.4	175.9	179.1	0.620
	SD	9.50	11.50	7.07	11.74	8.37	
Weight (kg)[b]	Mean	98.69	109.49	83.79	80.51	80.40	0.053
	SD	30.091	32.964	11.085	19.218	17.377	
Body Mass Index (kg/m^2)[b]	Mean	30.49	33.13	27.64	26.05	24.93	0.058
	SD	7.156	7.833	3.987	6.452	4.469	
Tobacco use[a]	None	9(100.0%)	8 (88.9%)	7 (77.8%)	8(100.0%)	7 (87.5%)	0.637
	Past	0 (0.0%)	1 (11.1%)	2 (22.2%)	0 (0.0%)	1 (12.5%)	
Alcohol use[a]	None	2 (22.2%)	2 (22.2%)	2 (22.2%)	4 (50.0%)	3 (37.5%)	0.715
	Current	6 (66.7%)	5 (55.6%)	6 (66.7%)	3 (37.5%)	5 (62.5%)	
	Past	1 (11.1%)	2 (22.2%)	1 (11.1%)	1 (12.5%)	0 (0.0%)	
Substance abuse[a]	None	9(100.0%)	9(100.0%)	9(100.0%)	8(100.0%)	8(100.0%)	1.000
% Predicted FEV_1[b,c]	Mean	72.56	76.75	79.81	71.13	81.31	0.046
	SD	8.553	7.963	8.179	6.554	7.415	

[a] Based on a categorical linear model adjusting for treatment. Race was grouped as Caucasian versus non-Caucasian and Tobacco, Alcohol and Substance were grouped as none versus current/past.
[b] Based on an ANOVA model adjusting for treatment.
[c] Predicted FEV_1 was adjusted for race.

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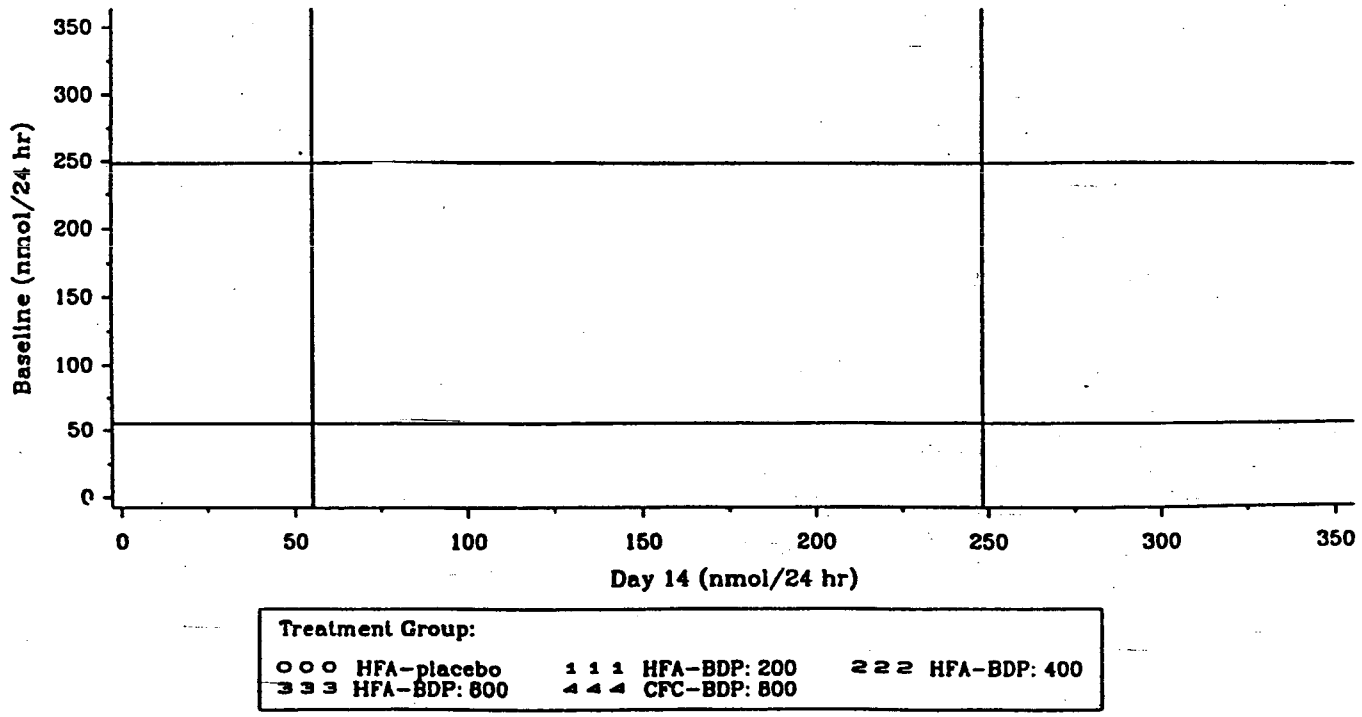
There was a statistically significant difference between the mean suppression of urinary free cortisol seen after administration of 400 and 800 mcg/day of BDP-HFA as well as 800 mcg/day of BDP-CFC as compared to placebo. While there was a decrease in mean urinary free cortisol in the BDP–HFA 200 mcg/day group and an increase in the HFA placebo group, this difference was not statistically significant (this might represent the "no effect" dose of BDP-HFA in terms of adrenal suppression). There was no statistically significant difference in change from baseline in mean urinary free cortisol between the 400 mcg/day BDP-HFA group, the 800 mcg/day BDP-HFA group and the 800 mcg/day BDP-CFC group.

One patient in the 800 mcg/day BDP-HFA group had a decrease in urinary free cortisol from 73 nmol/24 hours at baseline to 23 nmol/24 hours after 14 days of treatment (NRR = 55-248 nmol/24 hours) (see figure 2, p99, v1.51 below, plotting individual patient data)(this same patient had an abnormal ACTH stimulation test on day 15).

Figure 2
24–hr Urinary Free Cortisol
Plot of Individual Patient Data, Intent–to–Treat Analysis
Normal range of 55.2–248.4 nmol/24hr (20–90 ug/24hr) identified with vertical and horizontal lines



Aliquots of urine were obtained for the periods 8 PM to 7 AM, 7 AM to 9 AM and 9AM to 8 PM. The only statistically significant mean change from baseline was seen with the 800 mcg/day HFA and CFC groups, in terms of the 9AM to 8 PM sample. The major effect of BDP-HFA on endogenous cortisol excretion appeared to occur between 9 AM and 8 PM.

- Plasma cortisol levels: There was a significantly greater decrease in mean 7 AM plasma cortisol after 800 mcg/day of BDP-HFA (195 nmol/dL) than was seen in any other group (see fig14.3.4.2, p202, v1.51 below). In regard to the 9 AM plasma cortisol levels, there was no dose-response and no statistically significant difference between 400 or 800 mcg/day of BDP and placebo.

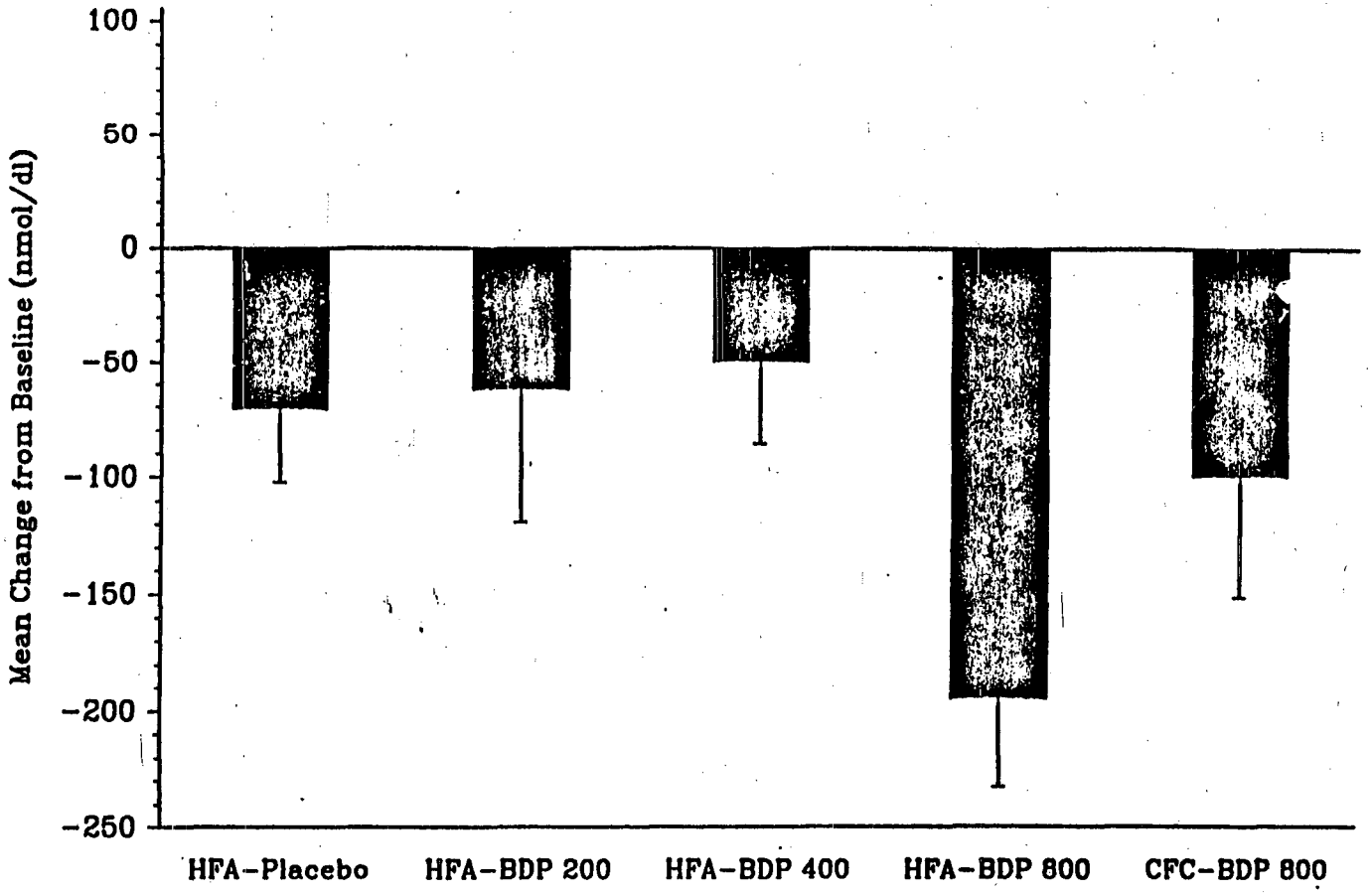
  There were 3 patients whose plasma cortisol level after 14 days of treatment was below the lower limit of the NRR. Two of these patients received 800 mcg/day of BDP-HFA and 1 received 800 mcg/day of BDP-CFC. The two BDP-HFA patients went from a baseline level of 113 nmol/L and 147 nmol/L to 27 nmol/L and 121 nmol/L, respectively, suggesting that in some patients at higher doses of BDP-HFA, not unexpectedly, an effect on the HPA axis can be seen.

- ACTH stimulation:

  The criteria for an abnormal response to the rapid cosyntropin test were the following: 1) a pre-injection plasma cortisol < 138 nmol/L (< 5 mcg/dL); 2) an increment of < 193 nmol/L (< 7 mcg/dL); or a peak value of < 496.8 nmol/L (< 18 mcg/dL). If more than one of the criteria above were abnormal the response was considered abnormal.

  All of the treatment groups had comparable mean pre-injection plasma cortisol levels at screening and there were no individual patients with abnormal values, except for one patient in the 800

Figure 14.3.4.2
Change from Baseline in 7 AM Plasma Cortisol
Mean and Standard Error
(Patients Included in the Intent-to-treat Analysis)



** Indicates Significant Mean Difference from Placebo using Dunnett's test

mcg/day BDP-CFC group who had a screening value of 126 nmol/L. There was no statistically significant difference in the change from pre-injection plasma cortisol to cortisol levels measured 30 and 60 minutes after ACTH administration between the placebo group and any of the active treatment groups at screening.

Based on the criteria for incremental change, 7 patients had an abnormal response after 14 days of treatment; one 800 mcg/day BDP-CFC patient; one 800 mcg/day BDP-HFA patient; two 400 mcg/day BDP-HFA patients; and 3 HFA placebo patients (see figure 3, p105, v1.51; tables 14a, p107, v1.51and 14b. p107, v1.51 below)

Figure 3
Cosyntropin Stimulation Test, Increment Plasma Cortisol
Plot of Individual Patient Data
Normal response of increment > 193.2 nmol/L (7 ug/dL) identified with horizontal line

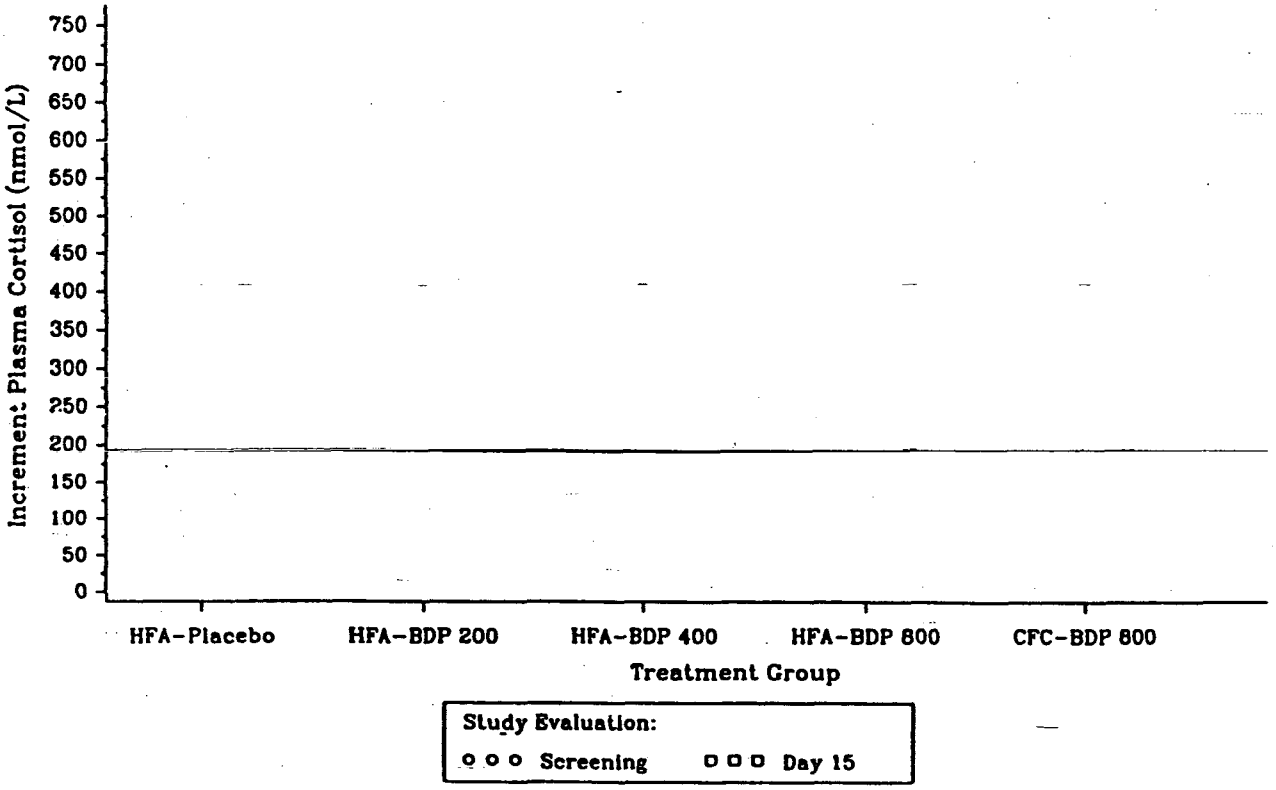


Table 14a: **Patients Who Did Not Meet Normal Pre-injection Cortisol, Increment and Peak Value Response Criteria for the Rapid Cosyntropin Test at Screening**

Treatment Group	Patient ID No.	Pre-injection Cortisol <138 nmol/L	Increment Value <193 nmol/L	Peak Value <496 nmol/L
HFA-placebo	001			
HFA-placebo	012			
HFA-BDP 200 mcg	033			
CFC-BDP 800 mcg	020			

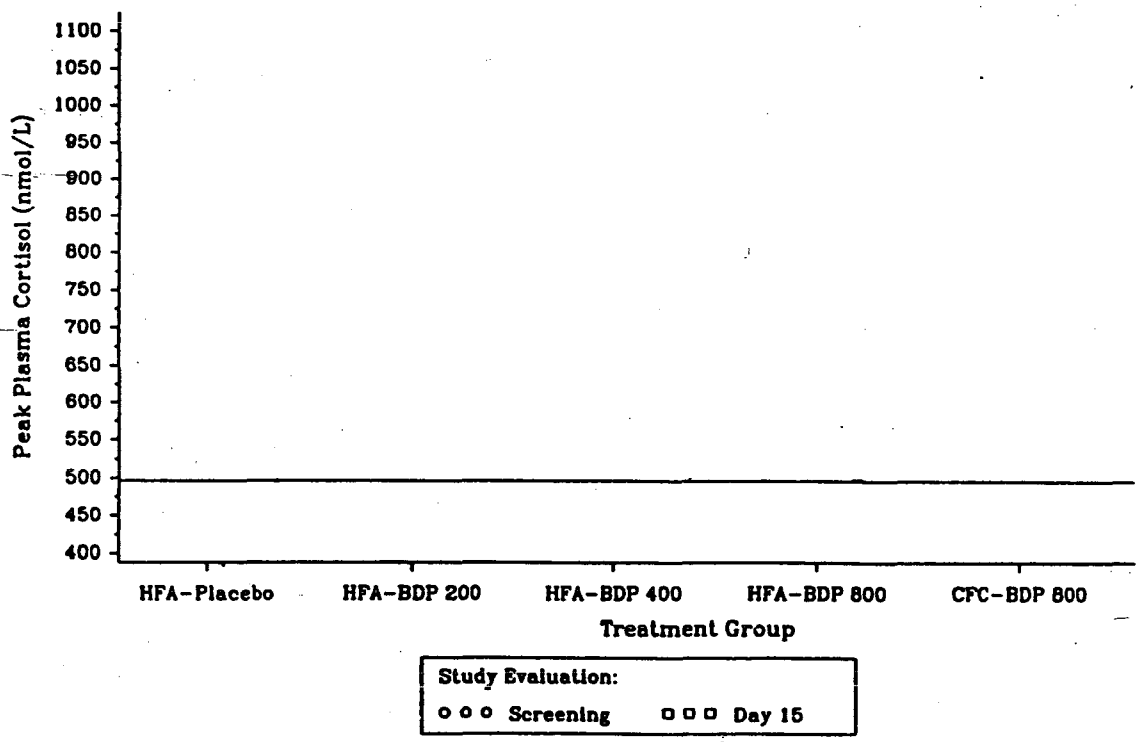
Table 14b: **Patients Who Did Not Meet Normal Pre-injection Cortisol, Increment and Peak Value Response Criteria for the Rapid Cosyntropin Test at Study Day 15**

Treatment Group	Patient ID No.	Pre-injection Cortisol <138 nmol/L	Increment Value <193 nmol/L	Peak Value <496 nmol/L
HFA-placebo	022			
	030			
	036			
HFA-BDP 400 mcg	025			
	026			
HFA-BDP 800 mcg	014			
	023			
	027			
CFC-BDP 800 mcg	024			
	034			

Note: Patient No. 027 is the only patient who does not meet two of the three criteria and therefore does not have a normal response to the cosyntropin test.

There were 2 patients who had abnormal peak cortisol values after ACTH stimulation, one 800 mcg/day BDP-HFA patient and one 800 mcg/day BDP-CFC patient. The BDP-HFA patient had a peak valule of 453 nmol/L but the patient's pre-injection plasma cortisol level was 44 nmol/L and there was an increment of 393 and 409 nmol/L at 30 and 60 minutes, respectively, after administration of ACTH (see figure 4, p109, v1.51 below)

Figure 4
Cosyntropin Stimulation Test, Peak Plasma Cortisol
Plot of Individual Patient Data
Normal response of peak > 496.8 nmol/L (18 ug/dL) identified with horizontal line



There were no "slow responders" at screening, "slow responders" being defined as an abnormal response at 30 minutes but a normal response at 60 minutes. There were, however, three patients who showed a "slow response" after treatment with 200 mcg/day BDP-HFA, 800 mcg/day BDP-HFA and 800 mcg/day BDP-CFC. In addition, there was one

800 mcg/day BDP-CFC patient who did not have a normal peak response at 30 or 60 minutes but had a normal incremental response at 60 minutes.

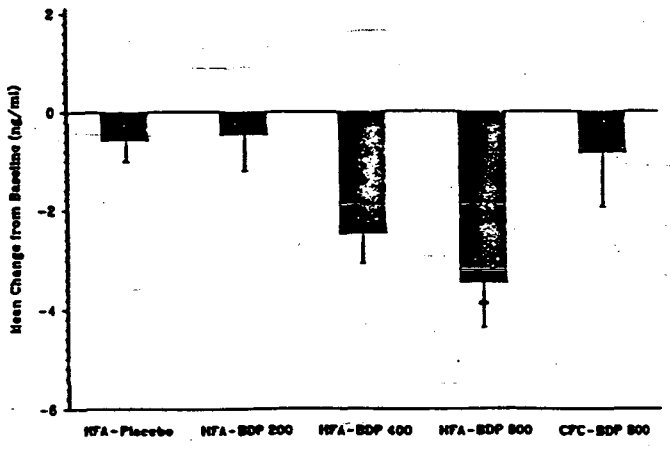
- serum osteocalcin levels: There were no statistically significant differences between any of the treatment groups after 14 days of treatment in regard to mean change from baseline in serum osteocalcin, except for the 800 mcg/day BDP-HFA group which had a mean decrease from baseline of 3.5 ng/ml that was statistically significantly different than the decrease seen in the placebo group (see table 15, p111, v1.51; figure 5, p112, v1.51 below).

Table 15: Serum Osteocalcin (ng/ml) (Patients Included in the Intent-to-treat Analysis)

		HFA-Placebo	HFA-BDP: 200 mcg	HFA-BDP: 400 mcg	HFA-BDP: 800 mcg	CFC-BDP: 800 mcg
Baseline	Mean	6.4	5.6	5.3	7.9	6.1
	SE	0.76	1.09	1.06	1.41	1.19
	N	9	9	8	8	8
Day 14	Mean	6.0	5.3	3.3	4.4	5.4
	SE	0.59	1.02	0.71	1.08	1.12
	N	8	8	8	8	7
Change from Baseline	Mean	-0.6	-0.5	-2.5	-3.5*	-0.9
	SE	0.43	0.74	0.59	0.91	1.09
	N	8	8	8	8	7

*Indicates significant mean difference from placebo using Dunnett's test

Figure 5
Change from Baseline in Osteocalcin
Mean and Standard Error
(Patients Included in the Intent-to-treat Analysis)



** Indicates Significant Mean Difference from Placebo using Dunnett's test

There were 5 patients who had serum osteocalcin levels below the lower limit of the NRR after 14 days of treatment; one patient who received 200 mcg/day of BDP-HFA, 2 patients who received 400 mcg/day of BDP-HFA, one patient who received 800 mcg/day of BDP-HFA and one patient who received 800 mcg/day of BDP-CFC. The clinical significance of these findings, if any, is unclear.

✣ Ten patients had serum analyzed for beclomethasone; one patient received placebo, 2 patients received 200 mcg/day BDP-HFA, 2 patients received 400 mcg/day BDP-HFA, 2 patients received 800 mcg/day BDP-HFA, and 3 patients received 800 mcg/day BDP-CFC; beclomethasone levels were below the lowest limit of quantitation (< pg/ mL) for both patients receiving 200 mcg/d after the first dose and for one patient receiving this dose at steady state; the maximum individual concentrations at steady state for BDP-HFA were: 100 mcg bid = 14 pg/mL, 200 mcg bid = 41 pg/mL, and 400 mcg bid = 81 pg/mL; 400 mcg bid BDP-CFC = 48 pg/mL; mean <u>total</u> belcomethasone concentrations, Cmax and AUC can be seen in figures 6 and 7, pgs 116 and 118, v1.51 below.

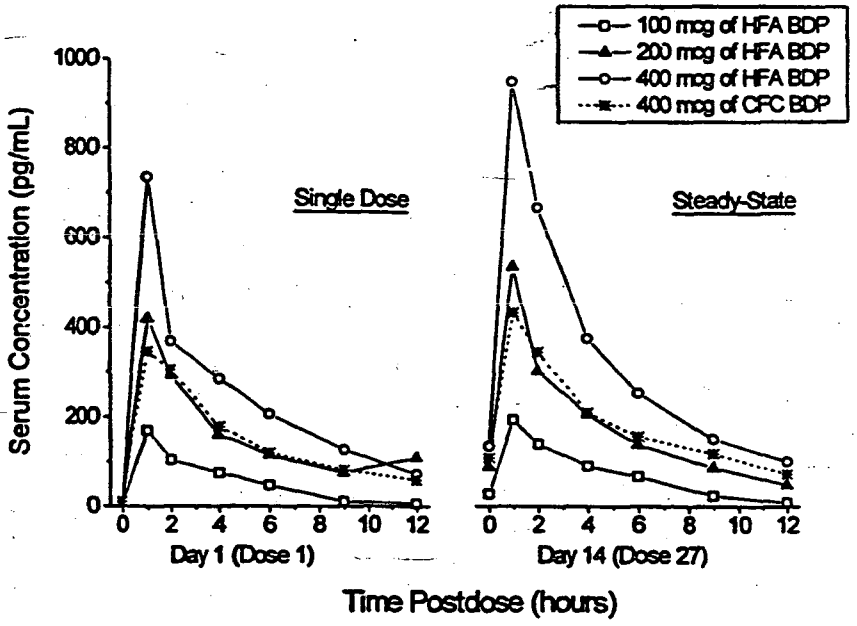


Figure 6: <u>Mean total-beclomethasone concentrations in patients receiving HFA-BDP or CFC-BDP every twelve hours for 14 days</u>

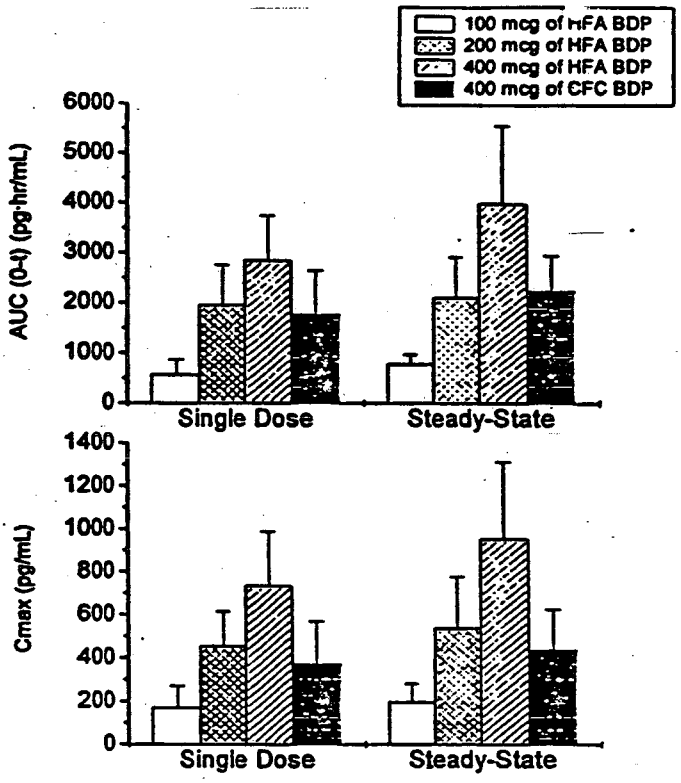


Figure 7. Mean total-BOH C_{max} and AUC in patients receiving HFA-BDP or CFC- BDP every twelve hours for 14 days

- Blood ethanol levels: none were detected in the pre-dose and 60 minutes post-dose samples; one sample had a low level of ethanol at 30 minutes post-dose in a patient who received 200 mcg bid; the clinical significance, if any, of this finding is unclear.

- Urinary TFA levels: none was detected.

- oropharyngeat candidiasis: There were 3 patients, 2 who received 400 mcg/day and 1 who received 800 mcg/day of BDP-HFA who had white plaques noted in the oropharynx but cultures did not show candida growth exceeding that expected normally in the oropharynx. Despite the culture findings, 3 patients receiving

BDP-HFA developed oropharyngeal candidiasis. It is not unexpected that some patients receiving inhaled corticosteroids will develop oropharyngeal candidiasis.

- adverse events: There were 4 patients who experienced at least one adverse event during the study; one placebo patient, one BDP-HFA 200 mcg/day patient, and 2 BDP-HFA 400 mcg/day patients. All AEs were considered mild. However, 3 patients were withdrawn from the study due to an AE; 1 placebo patient, one BDP-HFA 200 mcg/day and one 400 mcg/day BDP-HFA patient. All 3 patients had fever, associated with either pharyngitis, headache or myalgia and were considered probably not related to the study drug.

- vital signs: no clinically significant changes in vital signs were noted.

- laboratory tests: no clinically significant changes in laboratory tests were noted, with the exception of two patients who received 400 mcg/day of BDP-HFA and had elevated LFTs. One patient had a GGT of 146 U/L (NRR 10-61 U/L) and a SGPT of 77 U/L (NRR 6-43 U/L) on day 15 and the other patient had a GGT of 79 U/L, a SGPT of 65 U/L and a SGOT of 48 U/L (NRR 11-36 U/L) when withdrawn from the study because of headache and fever. It is unclear if these elevations were related to BDP-HFA administration.

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☞ Overall evaluation of safety data and conclusions:

☛ Based on individual patient 24 hour urinary free cortisol (UFC) levels, individual plasma cortisol levels and the response to ACTH stimulation, there was a suggestion that more adrenal suppression occurred after administration of 800 mcg/day of BDP-HFA for 14 days, than was seen after administration of the same dose of BDP-CFC over this period of time. This impression is based, however, on a small number of patients and a very small difference, i.e. one more patient who had a urinary free cortisol level below the lower limit of the NRR (1 patient), one more patient who had a plasma cortisol level below the lower limit of the NRR (2 patients) and one more patient who met the criteria for an abnormal ACTH stimulation test (1 patient)(see table below). On the other hand, there was less of a decrease in mean UFC after 800 mcg/d of BDP-HFA than after the same dose of BDP-CFC. Nevertheless, it can be assumed that some patients will develop adrenal suppression after administration of high doses of inhaled corticosteroids. Therefore, the labeling should reflect the fact that 800 mcg/day of BDP-HFA may cause adrenal suppression in some patients, and that use of this dose requires a careful benefit: risk assessment.

	BDP-HFA			BDP-CFC	
Parameter	200 mcg/d	400 mcg/d	800 mcg/d	800 mcg/d	placebo
Mean change from baseline 24 hour UFC	- 25	- 59	- 65	- 94	23
# pts UFC below lower limit of NRR after 14d	0	0	1	0	0
# pts with plasma cortisol level below NRR after 14 days	0	0	2	1	0
# pts with incremental ACTH change < 193 after 14 days	0	2	1	1	3
# pts with peak < 496 after 14 days after ACTH	0	0	1	1	0
# pts who met criteria for abnormal ACTH stimulation	0	0	1	0	0

In studies in normal volunteers (studies 1025 and 1063) BDP-HFA was administered over a range of 1200-2800 mcg/day for 10 days. Based on 24 hour urinary free cortisol levels, a these doses, there was a greater degree of adrenal suppression with BDP-HFA than with BDP-CFC. However, there were only 5-6 patients per treatment group in these studies.

- There was substantially greater mean <u>total</u> beclomethasone plasma levels, mean <u>total</u> beclomethasone Cmax and mean <u>total</u> beclomethasone AUC both after a single dose of 400 mcg of BDP-HFA and at steady state after administration of 400 mcg bid of BDP-HFA for 14 days than was seen after a single dose of 400 mcg of BDP-CFC or at steady state after administration of 400 mcg bid of BDP-CFC. These data are based on a very small number of patients but suggest that, despite the findings from in-vitro and lung deposition studies, there is more systemic availability of BDP-HFA than BDP-CFC.

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ABSTRACT

Study 1081 was a parallel, treatment-blinded, placebo-controlled, randomized, repetitive dose study in 270 adult patients (approximately 90 in each arm) who had mild to moderate asthma and were not receiving inhaled corticosteroids. Patients received either 100 mcg/day or 200 mcg/day of BDP-HFA at a concentration of 50 mcg/puff (1 or 2 puffs bid) in comparison with placebo for 6 weeks. The primary efficacy parameter was mean change in percent predicted FEV-1 from baseline and secondary efficacy parameters included FEF 25-75, AM and PM PEF, asthma symptoms, nighttime sleep disturbance, and beta agonist use. Safety was assessed by adverse events, vital signs and laboratory tests. Two study populations were analyzed; 1) an intent-to-treat population; and 2) an evaluable for efficacy population. The two placebo groups were combined for analysis.

There was a 14 day run-in period, following which patients were randomized to treatment. Baseline comparison of the treatment groups showed that they were comparable in terms of demographics, medication use, pulmonary function and other criteria.

There was a statistically significant improvement in mean percent change in FEV-1 in the groups that received 100 and 200 mcg/day of BDP-HFA in comparison with the group that received placebo after 6 weeks of treatment, as well as a trend favoring improvement in comparison with placebo after 2-4 weeks of treatment. A statistically significant improvement in other pulmonary function parameters was seen within 3-4 weeks after initiating treatment with BDP-HFA. A trend toward greater improvement of asthma symptoms, nights with sleep disturbance and beta agonist use after administration of BDP-HFA as compared with placebo was seen as early as 1-2 weeks after starting therapy, and for certain parameters (percent of nights without sleep in the group that received 200 mcg/day of BDP-HFA) a statistically significant difference from placebo was seen 1-2 weeks after starting treatment.

Abstract-2

The sponsor has demonstrated that doses of 100 mcg/day and 200 mcg/day of BDP-HFA, given as a 50 mcg/puff concentration, were efficacious over the 6 weeks of the study, compared with placebo. The minimum effective dose has not been established in this study. A dose-response trend was demonstrated but the data suggests that doses above 100 mcg/day of BDP-HFA are on the flat part of the dose-response curve in this patient population. Significant improvement in some parameters was demonstrated as early as 1-2 weeks after initiation of treatment with both doses of BDP-HFA. The percentage of patients who experienced a clinically significant improvement in pulmonary function was greater in the groups that received BDP-HFA. There was a clinically significant improvement in pulmonary function demonstrated after administration of both doses of BDP-HFA. Based on the parameters measured in this study, BDP-HFA appears to be safe. Platelet counts will be carefully evaluated in other studies with BDP-HFA to determine if there is a consistent pattern of a decrease in platelets after administration of this drug product.

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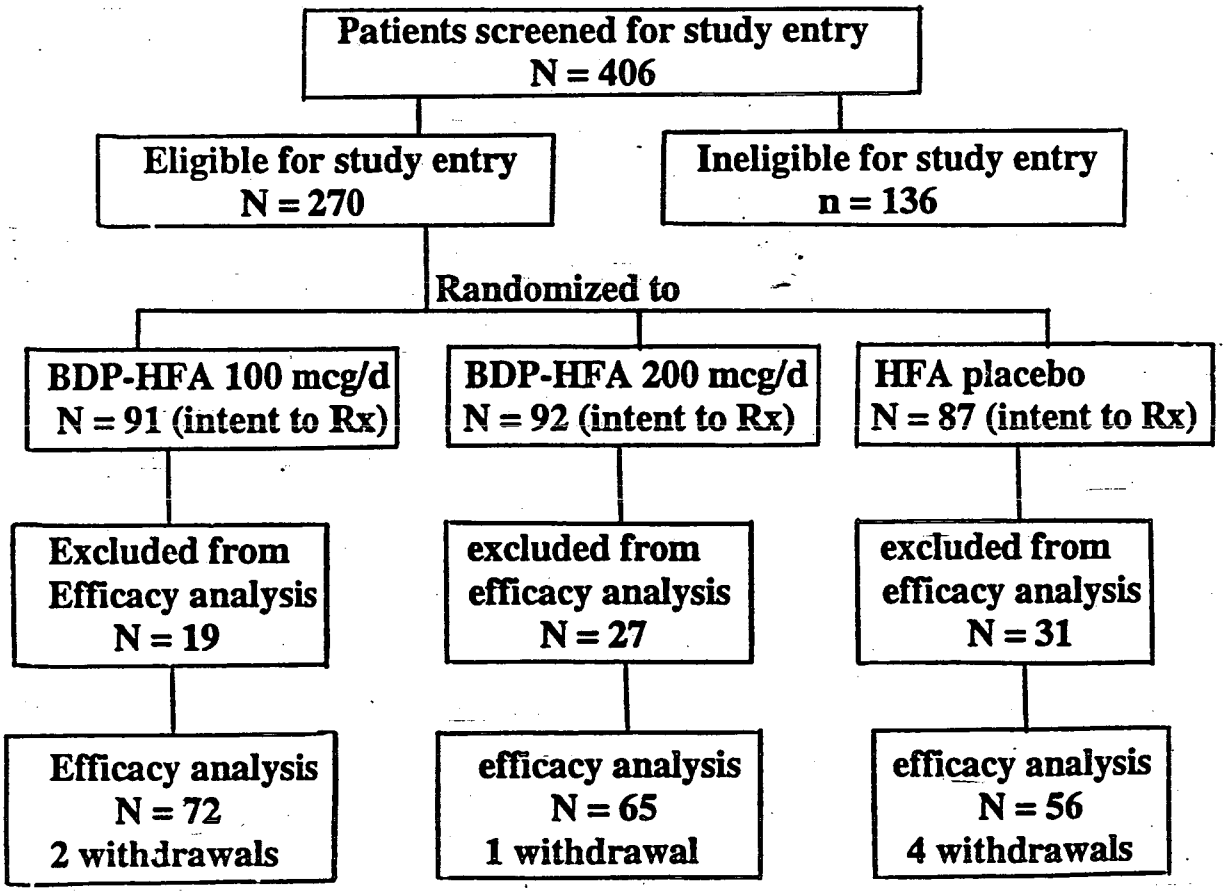
DESCRIPTION OF SPECIFIC STUDIES

☎ Study 1081

number of patients: A total of 270 patients were randomized to treatment. There were 91 patients randomized to treatment with 100 mcg/day of BDP-HFA, 92 patients randomized to treatment with 200 mcg/day of BDP-HFA, and 87 randomized to treatment with placebo. The one French center randomized 32 patients and the US centers randomized 238 patients. Of these, 193 patients were considered acceptable for efficacy analysis (see flow chart below). There were 4 patients who withdrew from the study because of AEs, one patient receiving 100 mcg/day BDP-HFA, one patient receiving 200 mcg BDP-HFA and 2 patients receiving HFA placebo.



- age range: 18-74 years; mean age of patients who received BDP-HFA 100 mcg/day, 200 mcg/day, and HFA placebo was 32, 38, and 34 years, respectively.

- study design: parallel, modified blind, randomized, multicenter, placebo-controlled, repetitive dose study. Patients and investigators were blinded to active treatment or placebo but not to the number of puffs of BDP-HFA or placebo;

- patient population: mild-moderate asthma not receiving corticosteroids; FEV-1 65-85% of predicted; 15% reversibility with a beta agonist; all but one patient was using a short-acting inhaled beta agonist prior to entry into study.

- drug administration: 100 mcg/day of BDP-HFA (1 puff of 50 mcg/puff concentration bid), 200 mcg/day of BDP-HFA (2 puffs of 50 mcg/puff concentration bid) or HFA placebo for 6 weeks.

- periods of study: 6 weeks of randomized treatment; 14 day run-in period, during which patients continued to take inhaled beta agonist PRN, PEF was measured bid, asthma symptom and sleep disturbance scores were kept.

- parameters evaluated: The primary efficacy parameter was percent predicted FEV-1 at weeks 2, 4, and 6. Other efficacy parameters included AM/PM PEFR, FEF25-75, beta agonist use, asthma symptom scores and nighttime sleep disturbance scores. Safety parameters included AEs, vital signs, and laboratory tests.

- data analysis: There were two study populations analyzed: the intent-to-treat (ITT) population; and the evaluable for efficacy analysis (efficacy population or efficacy analysis). Most of the patients excluded from the efficacy analysis were excluded because of non-compliance (n = 70 out of 77 excluded). There were an additional 11 patients who were partially excluded from the efficacy analysis that was felt to affect a specific outcome or specific period of time for a specific outcome.

☛ patient withdrawals: see table below (tab4, p115, v1.70). There was no consistent pattern in terms of time of withdrawal. The number of patients in each treatment group that were withdrawn for each category were comparable. The study results were not influenced by the patient withdrawals in this study.

Table 4: Number (%) of Patients Who Withdrew Prior to Week 6 by Reason and Treatment (Patients Included in the Intent-to-treat Analysis)

Reason	HFA-BDP 100 mcg (n= 91)	HFA-BDP 200 mcg (n= 92)	HFA-placebo (n= 87)	Overall (n=270)
Lost to follow-up	1 (1.1%)	2 (2.2%)	3 (3.4%)	6 (2.2%)
Adverse event	1 (1.1%)	1 (1.1%)	2 (2.3%)	4 (1.5%)
Personal	1 (1.1%)	1 (1.1%)	1 (1.1%)	3 (1.1%)
Inadequate response	0 (0.0%)	0 (0.0%)	2 (2.3%)	2 (0.7%)
Noncompliance	1 (1.1%)	1 (1.1%)	0 (0.0%)	2 (0.7%)
Total	4 (4.4%)	5 (5.4%)	8 (9.2%)	17 (6.3%)

☛ protocol violations:

✱ exclusion from the efficacy analysis because of major protocol violations: 10 patients evenly divided among the treatment groups

- ◆ 5 – FEV-1 outside specified range (41%, 55%, 58%, 105%, 106%)
- ◆ 1 – participated in another investigational drug study
- ◆ 3 – took prohibited medication
- ◆ 1 – 74 years of age; 65 years the upper limit for inclusion

✱ partial exclusion for the period of time when the violation occurred and/or for subsequent periods; or for the specific parameter affected by the violation; 11 patients; these patients were evenly divided among the treatment groups.

✱ The protocol violations noted above were acceptably handled and did not influence the study results.

☛ <u>baseline demographic characteristics</u>:

*** see table below (tab6, p121, v1.70); these demographic characteristics was either not significantly different between the treatment groups or where there was a significant difference (alcohol use), would not have influenced the study results.**

Table 6: <u>Prestudy Demographic Characteristics and Habits (Patients Included in the Intent-to-treat Analysis)</u>

Characteristic		HFA BDP 100 mcg (N=91)	HFA BDP 200 mcg (N=92)	HFA placebo (N=87)	P-value
Gender[a]	Female	52 (57.1%)	56 (60.9%)	45 (51.7%)	0.543
	Male	39 (42.9%)	36 (39.1%)	42 (48.3%)	
Age (years)[b]	Mean	32.2	35.8	32.6	0.091
	SD	10.22	12.14	12.29	
Race[a]	Caucasian	86 (94.5%)	86 (93.5%)	80 (92.0%)	0.886
	Afro-Caribbean	4 (4.4%)	4 (4.3%)	6 (6.9%)	
	Asian	0 (0.0%)	1 (1.1%)	1 (1.1%)	
	Oriental	1 (1.1%)	1 (1.1%)	0 (0.0%)	
Height (cm)[b]	Mean	169.8	168.4	170.3	0.400
	SD	9.56	9.37	9.74	
Weight (kg)[b]	Mean	75.09	75.34	77.42	0.667
	SD	18.518	17.664	19.346	
Tobacco use[a]	None	69 (75.8%)	68 (73.9%)	67 (77.0%)	0.969
	Past	22 (24.2%)	24 (26.1%)	20 (23.0%)	
Alcohol use[a]	None	48 (52.7%)	59 (64.1%)	58 (66.7%)	0.043
	Current	40 (44.0%)	30 (32.6%)	26 (29.9%)	
	Past	3 (3.3%)	3 (3.3%)	3 (3.4%)	
Substance abuse[a]	None	90 (98.9%)	92(100.0%)	87(100.0%)	1.000
	Past	1 (1.1%)	0 (0.0%)	0 (0.0%)	

[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 tobacco use, 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.

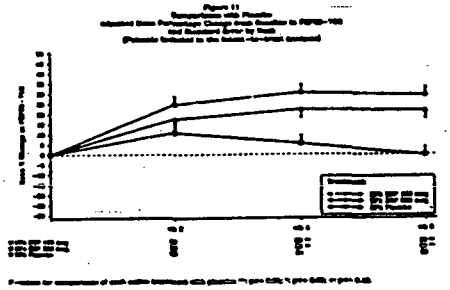
- **PM PEF: PEF was measured before retiring in the evening and before taking study medication. Inhaled beta agonists were not to be taken within 4 hours of measuring PEF. Based on the ITT population, there was a 25 and 26 L/min mean improvement after administration of BDP-HFA 100 mcg/day and BDP-HFA 200 mcg/day for 6 weeks, respectively, as compared to a 6 L/min improvement in the group which received placebo. This magnitude of effect was not seen when the efficacy population was used for analysis and no statistically significant difference was seen between the three treatment groups.**

- **FEF 25-75%: The improvement in FEF 25-75 after 6 weeks of treatment with BDP-HFA at a dose of 100 mcg/day or 200 mcg/day was significantly greater than the improvement seen after administration of placebo, regardless of whether the ITT or efficacy population was used for analysis (see table and figure below (tab20, p153, v1.70; fig11, p154, v1.70).**

Table 20: Adjusted Mean Percent Change from Baseline in $FEF_{25-75\%}$: Comparison with Placebo (Patients Included in the Intent-to-Treat Population)

Study week		HFA BDP 100 mcg	HFA BDP 200 mcg	HFA Placebo	Overall P-value[a]
Baseline	Mean	2.15	2.13	2.30	
	SE	0.096	0.096	0.099	
	N	90	91	86	
Change from Baseline at Week 2	Mean	17.55	24.64	10.83	0.066
	SE	4.087	4.098	4.245	
	N	88	88	83	
Change from Baseline at Week 4	Mean	22.26**	30.48**	5.38	<0.001
	SE	3.985	4.010	4.103	
	N	89	89	84	
Change from Baseline at Week 6	Mean	21.81**	29.21**	-0.34	<0.001
	SE	4.081	4.156	4.237	
	N	90	89	85	

[a] Based on an ANOVA with treatment, center, treatment by center interaction terms in the model.
Comparisons of active treatments with placebo: ** $p \leq 0.01$; * $p \leq 0.05$; + $p \leq 0.10$.



- overall evaluation of improvement in pulmonary function after 6 weeks of treatment with BDP-HFA:

	ITT				Efficacy Population			
parameter	100 mcg/day	200 mcg/day	placebo	p val	100 mcg/day	200 mcg/day	placebo	p val
Mean change FEV-1	S 0.24 L	S 0.29 L	0	Less than 0.001	S 0.24 L	S 0.31 L	0.03L	Less than 0.001
Mean % change FEV-1	S 6.7%	S 8.6%	0.4%	Less than 0.001	S 6.6%	S 9.5%	-0.9%	Less than 0.001
% change responders	--	--	--		T 35%	T 38%	17%	
Mean change AM PEF	S 30L/min	S 34L/min	5L/ min	Less than 0.001	S 29%	S 41%	2L/ min	Less than 0.001
Mean change PM PEF	S 23L/min	S 22L/min	6L/ min	0.03	N 22L/min	N 23L/min	9L/ min	0.17
Mean change FEF 25-75	S 0.38L/sc	S 0.40L/sc	0	Less than 0.001	S 0.38L/sc	S 0.54L/sc	-0.1L/ sec	Less than 0.001
Mean % change FEF 25-75	S 22%	S 29%	-0.3%	Less than 0.001	S 22%	S 34%	-3%	Less than 0.001

S = statistically significant difference from placebo ($p \leq 0.05$)
T = definite trend favoring BDP-HFA over placebo
N = no statistically significance or trend compared with placebo
-- = no data given

☛ mean change from baseline in percent of days without asthma symptoms at study weeks 5-6 compared with placebo: see table below (tab22. p157, v1.70)

✱ Asthma symptoms (wheezing, cough, shortness of breath and chest tightness) which occurred during the day were recorded using a categorical scale (see below) each evening prior to taking the study drug.

0 = none
1 = present, little or no discomfort
2 = mild, annoying, little or no discomfort
3 = moderate, discomfort, not affecting daily activities
4 = severe, interfere at least once with daily activities
5 = so severe that not able to go to school/work or able to carry out other daily activities

Table 22: Adjusted Mean Change from Baseline in Percent of Days without Asthma Symptoms Compared with Placebo at Study Weeks 5-6 (Patients in the Intent-to-Treat Analysis)[a]

% of Days without Asthma Symptom: Change from Baseline	HFA BDP 100 mcg	HFA BDP 200 mcg	HFA-Placebo
Wheeze			
Baseline	28.1	35.0	27.5
Change from Baseline	20.7	22.2	12.7
Cough			
Baseline	46.7	54.1	55.9
Change from Baseline	15.3	13.7	3.5
Shortness of Breath			
Baseline	27.2	21.4	32.1
Change from Baseline	17.6	23.5*	8.6
Chest Tightness			
Baseline	33.6	29.0	34.3
Change from Baseline	13.6	19.2	8.6

[a]Based on an ANOVA with treatment, center, treatment by center interaction terms.
**: $p \leq 0.01$; *: $p \leq 0.05$; +: $p \leq 0.10$.

☛ mean change from baseline in asthma symptom scores at study weeks 5-6 compared with placebo: see table below (tab23, p157, v1.70)

Table 23: Adjusted Mean Change from Baseline in Asthma Symptoms Scores Compared with Placebo at Study Weeks 5-6 (Patients in the Intent-to-Treat Analysis)[a]

Asthma Symptom	HFA-BDP 100 mcg	HFA-BDP 200 mcg	HFA-Placebo
Wheeze			
Baseline	1.36	1.22	1.22
Change from Baseline	-0.57**	-0.49+	-0.20
Cough			
Baseline	0.95	0.80	0.71
Change from Baseline	-0.38*	-0.32+	-0.04
Shortness of Breath			
Baseline	1.47	1.52	1.30
Change from Baseline	-0.49+	-0.56*	-0.23
Chest Tightness			
Baseline	1.34	1.31	1.21
Change from Baseline	-0.42	-0.39	-0.20

[a]Based on an ANOVA with treatment, center, treatment by center interaction terms.
**: $p \leq 0.01$; *: $p \leq 0.05$; +: $p \leq 0.10$.

✱ A change of 0.2-0.4 in symptom scores over placebo response is of very questionable clinical significance. Therefore, change in symptom scores in this study can not be used to support any claim for efficacy after administration of 100 mcg/day or 200 mcg/day of BDP-HFA.

☛ mean change from baseline in percent of nights without sleep disturbance at study weeks 5-6 compared with placebo: see table below (tab26, p172, v1.70)

Table 26: **Adjusted Mean Change from Baseline in Percent of Nights without Sleep Disturbance: Comparisons with Placebo (Patients Included in the Intent-to-treat Analysis)**

Study week		HFA BDP 100 mcg	HFA BDP 200 mcg	HFA Placebo	Overall P-value[a]
Baseline	Mean	43.7	50.5	53.1	0.306
	SE	4.39	4.39	4.52	
	N	89	90	86	
Change from Baseline at Weeks 1-2	Mean	15.1	20.3**	6.3	0.012
	SE	3.27	3.32	3.36	
	N	88	87	84	
Change from Baseline at Weeks 3-4	Mean	18.5+	24.8**	8.2	0.005
	SE	3.48	3.56	3.59	
	N	89	87	85	
Change from Baseline at Weeks 5-6	Mean	21.4*	25.2**	8.2	0.005
	SE	3.71	3.80	3.84	
	N	89	87	85	

[a] Based on an ANOVA with treatment, center, treatment by center interaction terms in the model. Comparisons of active treatments with placebo: ** $p \leq 0.01$; * $p \leq 0.05$; + $p \leq 0.10$.

- mean change from baseline in sleep disturbance compared with placebo: A greater reduction in sleep disturbance scores was seen after administration of BDP-HFA 100 mcg/day than after administration of BDP-HFA 200 mcg/day, with a statistically significant difference from placebo being shown after the 100 mcg/day dose using both the ITT and efficacy populations and after the 200 mcg/day dose using the efficacy population (with a strong trend favoring BDP-HFA 200 mcg/day using the ITT population)

Sleep disturbance caused by asthma recorded upon awakening in the AM and before taking AM dose of study drug, using the following categorical scale.

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

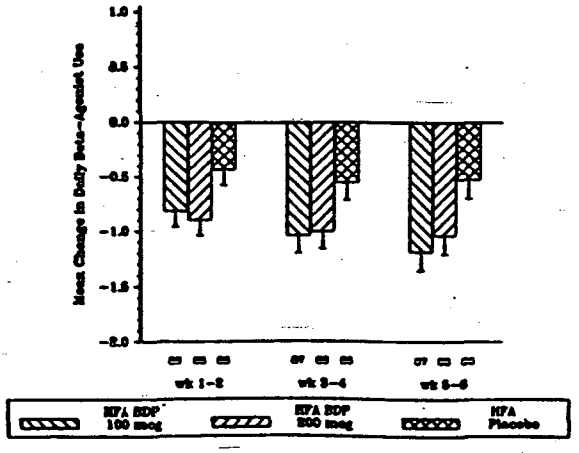
☛ Mean change from baseline in daily beta agonist use compared with placebo: see table below (tab27, p176, v1.70): patients recorded beta agonist use bid; patients used their usual beta agonist; number of uses were recorded NOT number of puffs.

Table 27: Adjusted Mean Change from Baseline in Daily Beta-agonist Use: Comparisons with Placebo (Patients Included in the Intent-to-treat Analysis)

Study week		HFA BDP 100 mcg	HFA BDP 200 mcg	HFA Placebo	Overall P-value[a]
Baseline	Mean	3.13	3.01	2.77	0.420
	SE	0.197	0.194	0.198	
	N	87	90	87	
Change from Baseline at Weeks 1-2	Mean	-0.81	-0.89	-0.43	0.053
	SE	0.143	0.142	0.143	
	N	86	88	85	
Change from Baseline at Weeks 3-4	Mean	-1.03	-1.00	-0.56	0.061
	SE	0.157	0.158	0.159	
	N	87	88	86	
Change from Baseline at Weeks 5-6	Mean	-1.19*	-1.04+	-0.53	0.019
	SE	0.171	0.172	0.173	
	N	87	88	86	

[a] Based on an ANOVA with treatment, center, treatment by center interaction terms in the model.
Comparisons of active treatments with placebo: ** $p \leq 0.01$; * $p \leq 0.05$; + $p \leq 0.10$.

Figure 15
Adjusted Mean Change from Baseline in Daily Beta-Agonist Use and Standard Error by Study Week
(Patients Included in the Intent-to-treat Analysis)



* **The differences noted in beta agonist daytime and nighttime use between the active treatments and placebo were not clinically significant (see tables below;tab 14.2.11.2.1, p423, v1.70, tab 14.2.12.2.1, p431, v1.70) . Therefore, despite the fact that statistical significance compared to placebo was reached at weeks 5-6, except for nighttime beta agonist use in the 200 mcg/day BDP-HFA group, a reduction in beta agonist use in this study can not be used to support the efficacy of 100 and 200 mcg/day of BDP-HFA.**

Table 14.2.12.2.1
Adjusted Mean Change from Baseline in Nighttime Beta-agonist Use
Comparisons with Placebo
(Patients Included in the Intent-to-treat Analysis)

Study week		HFA BDP 100 mcg	HFA BDP 200 mcg	HFA Placebo	Overall P-value
Baseline	Mean	0.91	0.72	0.71	0.190
	SE	0.066	0.066	0.069	
	Median	0.7	0.5	0.6	
	Min				
	Max				
	N	89	90	86	
Change from Baseline at Weeks 1-2	Mean	-0.32	-0.39	-0.11	0.063
	SE	0.066	0.067	0.068	
	Median	-0.3	-0.1	-0.1	
	Min				
	Max				
	N	88	87	84	
Change from Baseline at Weeks 3-4	Mean	-0.38	-0.26	-0.18	0.134
	SE	0.070	0.072	0.072	
	Median	-0.3	-0.2	-0.0	
	Min				
	Max				
	N	89	87	85	
Change from Baseline at Weeks 5-6	Mean	-0.44*	-0.23	-0.14	0.017
	SE	0.073	0.075	0.076	
	Median	-0.3	-0.2	0.0	
	Min				
	Max				
	N	89	87	85	

a Based on an ANOVA with treatment, center, and treatment by center interaction terms in the model.
Comparisons of active treatments with placebo: ** p<= 0.01; * p<= 0.05; + p<= 0.1.

Table 14.2.11.2.1
Adjusted Mean Change from Baseline in Daytime Beta-agonist Use
Comparisons with Placebo
(Patients Included in the Intent-to-treat Analysis)

Study week		HFA BDP 100 mcg	HFA BDP 200 mcg	HFA Placebo	Overall P-value a
Baseline	Mean	2.24	2.27	2.06	0.234
	SE	0.143	0.140	0.143	
	Median	2.0	2.3	2.0	
	Min				
	Max				
	N	87	91	87	
Change from Baseline at Weeks 1-2	Mean	-0.48	-0.61	-0.32	0.093
	SE	0.093	0.092	0.093	
	Median	-0.4	-0.6	-0.4	
	Min				
	Max				
	N	86	89	83	
Change from Baseline at Weeks 3-4	Mean	-0.61+	-0.76*	-0.35	0.025
	SE	0.105	0.104	0.105	
	Median	-0.6	-0.7	-0.3	
	Min				
	Max				
	N	87	89	86	
Change from Baseline at Weeks 5-6	Mean	-0.75*	-0.88*	-0.35	0.015
	SE	0.110	0.110	0.119	
	Median	-0.6	-0.7	-0.4	
	Min				
	Max				
	N	87	89	86	

a Based on an ANOVA with treatment, center, and treatment by center interaction terms in the model.
Comparisons of active treatments with placebo: ** p<= 0.01; * p<= 0.05; + p<= 0.1.

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☎ overall evaluation of improvement in secondary endpoints after 6 weeks of treatment with BDP-HFA compared to placebo:

	ITT				Efficacy Population			
Parameter	100 mcg/day	200 mcg/day	placebo	p value	100 mcg/day	200 mcg/day	placebo	p value
Mean % days without wheeze	T 21%	T 22%	13%	>0.10	T 23%	T 26%	26%	0.4
Mean % days without cough	T 15%	T 14%	4%	>0.10	T 21%	T 15%	9%	0.2
Mean % days without SOB	T 18%	S 24%	9%	<0.05	T 22%	T 26%	10%	0.1
Mean % days without chest tightness	T 14%	T 19%	9%	>0.10	T 18%	T 22%	11%	0.3
Mean change wheeze	S -0.6	T -0.5	-0.2	<0.05	T -0.6	T -0.6	-0.2	0.05
Mean change cough	S -0.4	T -0.3	-0.04	<0.05	S -0.5	T -0.3	-0.08	0.05
Mean change SOB	T -0.5	S -0.6	-0.2	<0.05	S -0.6	S -0.6	-0.2	0.02
Mean change chest tightness	T -0.4	T -0.4	-0.2	>0.10	T -0.5	T -0.5	-0.2	0.2
Mean change % nights	S 21%	T 25%	8%	<0.01	S 25%	S 30%	5%	Less than 0.001
Mean change sleep	S -0.4	T -0.3	-0.2	0.04	S -0.5	S -0.4	-0.1	0.004
Mean change beta agonist	S -1.2	T -1.0	-0.5	0.02	T -1.4	T -1.2	-0.7	0.07

- overall evaluation of improvement in secondary endpoints after 6 weeks of treatment with BDP-HFA, compared to placebo (cont):

	ITT				Efficacy Population			
Parameter	100 mcg/day	200 mcg/day	placebo	p value	100 mcg/day	200 mcg/day	placebo	p value
Mean change day beta agonist	S -0.75	S -0.80	-0.35	0.02	T -0.88	T -0.89	-0.48	0.12
Mean change night beta agonist	S -0.44	T -0.23	-0.14	0.02	S -0.52	T -0. 30	-0.17	0.04

S = statistically significant difference from placebo ($p \leq 0.05$)
T = definite trend favoring BDP-HFA over placebo

Change = change from baseline

Mean change asthma symptoms was based on a categorical scale of 0-5

Mean change % nights = mean change in % of nights without sleep disturbance

Mean change beta agonist = mean change in beta agonist use

Mean change day beta agonist = mean change in daytime beta agonist use

Mean change night beta agonist = mean change in nighttime beta agonist use

☞ safety evaluation: The number of patients who received BDP-HFA and the length of time that they received this drug product can be seen in the table below (tab28, p184, v1.70)

Table 28: Extent of Exposure

DURATION OF EXPOSURE	HFA-BDP 100 mcg (N=91)	HFA-BDP 200 mcg (N=92)	HFA-Placebo (N=87)
> 14 days	91	90	85
> 28 days	88	90	83
> 42 days	65	67	45
> 56 Days	1	3	1
> 70 Days	0	1	0
> 84 Days	0	1	0

☞ Adverse Events: Adverse events were reported by 47%, 51% and 45% of patients receiving 100 mcg/day BDP-HFA, 200 mcg/day BDP-HFA, and HFA placebo, respectively. Adverse events reported by ≥ 2% of patients (ITT analysis) where there was more than one greater number of reports in one or both of the BDP-HFA groups compared with placebo can be seen in the table below.

Adverse event	100 mcg/day	200 mcg/day	placebo
Dysphonia	5 (5%)	2 (2%)	1 (1%)
Inhalation site	3 (3%)	2 (2%)	1 (1%)
Allergy reaction	3 (3%)	1 (1%)	0
Headache	11 (12%)	18 (20%)	11 (13%)
Nausea	0	2 (2%)	0
Myalgia	2 (2%)	4 (4%)	1 (1%)
Insomnia	1 (1%)	2 (2%)	0
Dysmenorrhea	4 (4%)	2 (2%)	1 (1%)
Laryngitis	0	2 (2%)	0
Pharyngitis	7 (8%)	6 (7%)	0
Sinusitis	4 (4%)	0	2 (2%)

- ✱ There were four patients in each treatment group who were categorized as having a severe adverse event. In the 100 mcg/day BDP-HFA group, these included headache, abdominal pain, dysmenorrhea, and rhinitis; in the 200 mcg/day BDP-HFA group, abdominal pain, nausea, and dyspepsia leading to cholestectomy, headache, malignant breast neoplasm, and urticaria; in the HFA placebo group, headache (2), rhinitis and sinusitis. These events were either seen in the placebo group as well as in the BDP-HFA groups or were unrelated to the study drug. There were 9.9%, 7.6% and 5.7% of patients in the 100 mcg/day, 200 mcg/day and HFA placebo groups, respectively, who had an adverse event that was considered possibly or probably related to the study drug. There were 2 patients, both in the 200 mcg/day group, who had a serious adverse event (cholecystectomy and malignant breast neoplasm) , which was unrelated to the study drug.

☛ laboratory studies: There were no abnormal laboratory tests that could be related to administration of the study drug. There were 2 patients who received 200 mcg/day of BDP-HFA who had follow-up for an elevated GGT and one patient who received 200 mcg/day of BDP-HFA who had follow-up for anemia and abnormal lymphocytes.

In addition, there was a suggestion that BDP-HFA might have an effect on platelets and the potential for this effect will need to be carefully considered when evaluating laboratory data from other studies with BDP-HFA. There was a slight decrease in mean platelet levels after 6 weeks of treatment with BDP-HFA, from 272,000 to 264,000 after 100 mcg/day and from 271,000 to 266,000 after 200 mcg/day, as compared to a mean increase after placebo from 259,000 to 264,000.

☛ vital signs: There were no clinically significant changes in vital signs in any of the treatment groups.

CONCLUSIONS:

1. Doses of 100 mcg/day and 200 mcg/day of BDP-HFA given to patients with mild to moderate asthma who were not receiving inhaled corticosteroids for 6 weeks at a concentration of 50 mcg/puff were efficacious when compared to placebo. This does not mean that 100 mcg/day is the minimum effective dose of BDP-HFA, since lower doses were not studied.

2. Based on change from baseline in mean percent predicted FEV-1 and some secondary efficacy parameters, a dose-response trend was demonstrated, although efficacy after administration of 200 mcg/day of BDP-HFA for six weeks was not dramatically greater than efficacy shown after administration of 100 mcg/day of BDP-HFA over the same period of time, i.e. above a dose of 100 mcg/day the response was on the flat part of the dose-response curve for this very mild patient population.

3. The onset of significant improvement was seen after the administration of BDP-HFA, in terms of most parameters, within 2-4 weeks. A statistically significant improvement in the primary efficacy parameter, mean percent improvement in FEV-1 from baseline, was seen after administration for 6 weeks, although a strong trend in this direction was seen for the 200 mcg/day dose after 2 weeks of treatment.

4. The improvement seen in pulmonary function was clinically significant.

5. No immediate effect of BDP-HFA was demonstrated when pulmonary function was measured for 12 hours after a dose of BDP-HFA when patients had received the drug for 6 weeks.

6. There were a significantly greater number of individual patients evaluated as percent of responders, who had a clinically significant response to both 100 mcg/day and 200 mcg/day of BDP-HFA.

7. No safety concerns were raised by the data generated in this study.

ABSTRACT

METHODS: Study 1083 was a parallel, double-blind, double-dummy, placebo-controlled, multicenter, repetitive dose study in 256 adult patients (~ 85 patients in each arm) who had mild-moderate asthma and were not receiving inhaled corticosteroids. After a 2 week run-in period, patients were randomized to receive 400 mcg/day of BDP-HFA as the 50 mcg/puff concentration or the 100 mcg/puff concentration or HFA placebo for 6 weeks. The primary efficacy variable was mean change in AM PEF from baseline after 6 weeks of treatment. Secondary efficacy parameters included FEV-1, FEF 25-75, PM PEF, asthma symptoms, sleep disturbance, and beta agonist use. Safety was assessed by adverse events, vital signs, laboratory tests, and 12 lead ECGs. Two patient 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. There was a 50 L/min improvement in mean AM PEF in the group that received the 50 mcg/puff concentration and a 44 L/min improvement in the group that received the 100 mcg/puff concentration, compared to a 17 L/min improvement in the HFA placebo group. Greater improvement in mean FEV-1 was seen in the group that received the 50 mcg/puff concentration. In general, there was a clinically significant, and in most cases a statistically significant, improvement from baseline in all pulmonary function parameters after receiving 400 mcg/day of BDP-HFA either as the 50 mcg/puff or the 100 mcg/puff concentration, as compared with placebo. For most parameters, a greater effect was seen with the 50 mcg/puff concentration than the 100 mcg/puff concentration. Onset of effectiveness was generally seen as early as weeks 1-2 in terms of asthma symptoms, sleep disturbance and beta agonist use. "Equivalence" of the 50 mcg/puff and the 100 mcg/puff concentrations was demonstrated, based on the sponsor's criteria (see discussion below). Significantly less adverse events were seen in the 50 mcg/puff group as compared to the 100 mcg/puff group. No

significant changes were noted in either treatment group in terms of laboratory tests, vital signs or ECGs.

DISCUSSION: A dose of 400 mcg/day of BDP-HFA, whether given as the 50 mcg/puff concentration or the 100 mcg/puff concentration, produced a significantly greater improvement in pulmonary function than did placebo ($p < 0.05$) in adults with mild-moderate asthma who were not using inhaled corticosteroids. Mean improvement was generally greater in patients who received the 50 mcg/puff concentration than in patients who received the 100 mcg/puff concentration, although the differences were not great.

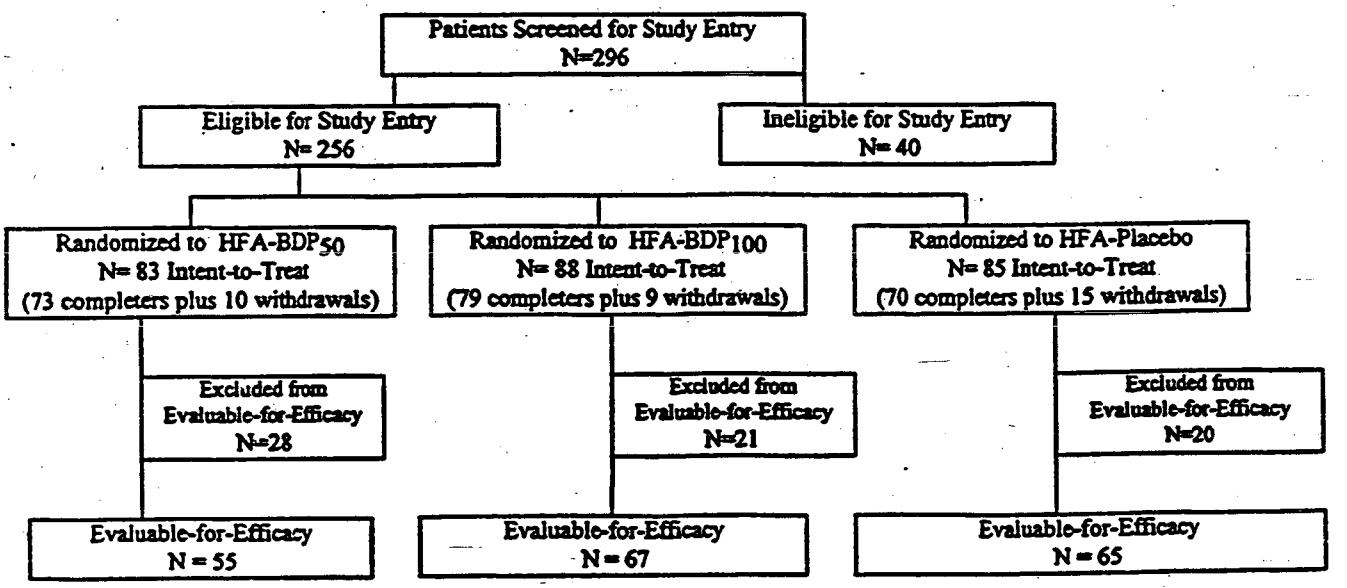
It is not possible to assess comparability ("equivalence") of the two concentrations because there was no dose-response built into the study, so that differences, if they existed, could be detected. Since this is the only study that attempted to demonstrate comparability of the 50 mcg/puff and the 100 mcg/puff concentrations, the approvability of the 100 mcg/puff concentration will depend upon the ability of this concentration to stand alone. This was the only acceptable study that studied the 100 mcg/puff concentration in 88 mild-moderate asthmatic patients not receiving inhaled corticosteroids. Because of the relatively small number of patients who received this concentration, the lack of any data to link other doses of the 100 mcg/puff concentration to the 50 mcg/puff concentration, and the lack of any data in patients receiving inhaled corticosteroids, it is unlikely that the data from this study will be adequate on its own to support the approvability of the 100 mcg/puff concentration of BDP-HFA.

☎ study 1083

☛ The primary objective of this study was to determine whether 400 mcg/day of BDP-HFA delivered as the 50 mcg/puff concentration produced comparable efficacy to 400 mcg/day of BDP-HFA delivered as the 100 mcg/puff concentration. The secondary objective was determine if 400 mcg/day of BDP-HFA was efficacious, compared with placebo in terms of change in AM PEF.

☛ number of patients: 256 patients randomized (83 received 400 mcg/day with 50 mcg/puff concentration, 88 received 400 mcg/day with 100 mcg/puff concentration and 85 received HFA placebo); 187 patients were included in the evaluable for efficacy analysis (see data analysis below)(55 received 400 mcg/day with 50 mcg/puff concentration, 67 received 400 mcg/day with 100 mcg/puff concentration and 65 received HFA placebo)(see flow chart below).

PATIENT DISPOSITION



- age range: 18-67 years

- study design: parallel, double-blind, double-dummy, placebo-controlled, multicenter, repetitive dose study done in Europe (note: the study was administered and monitored by —— —— Germany on behalf of 3M; 20 sites randomized patients, 9 in Germany, 9 in Poland and 2 in Slovakia)

- patient population: stable mild-moderate asthma, not receiving inhaled or other forms of corticosteroids for 3 weeks; AM PEF 50-80% predicted during 14 day run-in period; using inhaled beta agonists on a PRN basis; non-smokers

- drug administration: 400 mcg/day delivered as either 50 mcg/puff (batch numbers 94C01 and 94J01) or 100 mcg/puff concentration (batch numbers 94D01 and 94J01), 4 puffs bid and 2 puffs bid, respectively; HFA placebo (batch numbers CT940324 and CT950110) was given as 4 puffs bid; use of spacers was prohibited; inhalers were weighed to assess compliance by converting to number of doses administered using mean shot weights; patients were considered compliant if inhaled use during the study was 60-140% of predicted; inhalers were primed twice by investigators prior to the first dose of study drug but patients were instructed not to prime inhalers during the study

- periods of study: 6 weeks of randomized treatment following a 2 week run-in period; during the run-in period, patients continued to use their own inhaled beta agonist PRN; AM and PM PEF was measured during the run-in period, as were asthma symptoms and sleep disturbance

- parameters evaluated: FEV-1 and FEF 25-75 were measured at screening, on day 1 prior to drug administration and after 2, 4, and 6 weeks of treatment; baseline was pulmonary function done on study day 1, prior to randomization; AM/PM PEF, asthma symptoms, sleep disturbance and beta agonist use were also evaluated; safety parameters included adverse events, vital signs, laboratory tests, and

12 lead ECGs; change from baseline in vital signs was calculated at weeks 2, 4, and 6; laboratory tests were obtained at screening and after 6 weeks of drug administration; the primary efficacy variable was AM PEF; mean change from baseline (the last 7 days of the run-in period provided there were at least 5 valid days of assessment data) in AM PEF was compared among treatment groups at weeks 1-2, 3-4, and 5-6 (the daily PEF was averaged over each 2 week period, provided there were at least 10 days worth of valid assessment data.

☛ data analysis:

- ✷ "equivalence" for change from baseline in FEV-1 percent of predicted was defined as the percent of predicted FEV-1 produced by administration of 400 mcg/day of BDP-HFA 50 mcg/puff and 400 mcg/day BDP-HFA 100 mcg/puff being within ± 7.5% using two one-sided testing; the definition of "equivalence" for change from baseline in FEV-1 was ± 0.2 L and for change from baseline in AM and PM PEF ± 25 L/min (note: the definition of "equivalence" was not agreed to by the Division and in some parts of the protocol the sponsor refers to a 40 L/min difference in AM PEF between 400 mcg/day of BDP-HFA 50 mcg/puff and 400 mcg/day of BDP-HFA 100 mcg/puff).

- ✷ Two patient populations were analyzed: 1) the intent-to-treat population (ITT population)(all patients who received at least one dose of study medication); and 2) the evaluable-for-efficacy population (efficacy population)(patients who completed the 6 weeks of the study or up to the point of withdrawal and were considered compliant); in the ITT analysis, for patients who did not complete the 6 weeks of treatment, the last value obtained was carried forward to each successive timepoint.

STUDY RESULTS

- withdrawals: The same number of patients in each treatment group withdrew from the study during the first 2 weeks (see tab 16, p108, v1.92 below). There were 5 patients in the HFA placebo group, 2 patients in the BDP-HFA 50 mcg/puff group and 1 patient in the BDP-HFA 100 mcg/puff group who withdrew due to an adverse event (see table below; tab4, p74, v1.92). The two patients in the BDP-HFA 50 mcg/puff group were withdrawn because of severe inhalation sensation and cough, which were listed as possibly related to the study drug. The one patient in the BDP-HFA 100 mcg/puff group was withdrawn because of moderate chest pain, severe headache and hypertension and insomnia which were felt to be probably related to study drug. The five HFA placebo patients were withdrawn because of moderate cough, and moderate increased asthma symptoms (4). The number of patients who were withdrawn from the study for noncompliance and protocol departure, when considered together, were comparable between treatment groups.

Table 4: Number (%) of Patients Who Withdrew Prior to Week 6 by Reason and Treatment (Patients Included in the Intent-to-treat Analysis)

Reason	HFA-BDP$_{50}$ (n = 83)	HFA-BDP$_{100}$ (n = 88)	HFA-Placebo (n = 85)	Overall (n = 256)
Adverse event	2 (2.4%)	1 (1.1%)	5 (5.9%)	8 (3.1%)
Noncompliance	3 (3.6%)	2 (2.3%)	3 (3.5%)	8 (3.1%)
Lost to Follow-Up	2 (2.4%)	3 (3.4%)	1 (1.2%)	6 (2.3%)
Withdraw consent	1 (1.2%)	0 (0.0%)	3 (3.5%)	4 (1.6%)
Study site withdrawn	1 (1.2%)	1 (1.1%)	2 (2.4%)	4 (1.6%)
Protocol departure	0 (0.0%)	2 (2.3%)	0 (0.0%)	2 (0.8%)
Inadequate response	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (0.4%)
Pregnancy	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Total	10 (12.0%)	9 (10.2%)	15 (17.6%)	34 (13.3%)

Table 16: Number (%) of Patients Who Withdrew Prior to Week 6 by Center and Treatment (Patients Included in the Intent-to-treat Analysis)

Study Week	HFA-BDP$_{50}$ (n = 83)	HFA-BDP$_{100}$ (n = 88)	HFA-Placebo (n = 85)	Overall (n = 256)
Weeks 0-1	5 (6.0%)	5 (5.7%)	3 (3.5%)	13 (5.1%)
Weeks 1-2	2 (2.4%)	2 (2.3%)	4 (4.7%)	8 (3.1%)
Weeks 2-3	2 (2.4%)	1 (1.1%)	1 (1.2%)	4 (1.6%)
Weeks 3-4	1 (1.2%)	0 (0.0%)	4 (4.7%)	5 (2.0%)
Weeks 4-5	0 (0.0%)	0 (0.0%)	2 (2.4%)	2 (0.8%)
Weeks 5-6	0 (0.0%)	1 (1.1%)	1 (1.2%)	2 (0.8%)
Total	10 (12.0%)	9 (10.2%)	15 (17.6%)	34 (13.3%)

- protocol violations: There were 5 patients who had major protocol violations requiring exclusion of their data from the efficacy population analysis. These included incomplete diary card data and unsatisfactory PFTs due to technical problems, failure to demonstrate 15% reversal of FEV-1, use of an antibiotic for a respiratory infection, too long a time period between the run-in period and day 1, and re-randomization by error after the patient was lost to followup. Of these patients, 4 received BDP-HFA 100 mcg/puff and 1 received BDP-HFA 50 mcg/puff. The 5 patients who received BDP-HFA and were non-compliant were also excluded from the efficacy population analysis. A decision to exclude patients from the efficacy population analysis was made prior to unblinding of the study. There were 27 BDP-HFA 50 mcg/puff patients, 16 BDP-HFA 100 mcg/puff patients, and 20 HFA placebo patients who were excluded from the efficacy population analysis because of noncompliance.

- DEMOGRAPHICS: There were no significant differences in age, gender, ethnic background, asthma symptom scores, sleep disturbance scores, beta agonist use or concomitant medication use between the three treatment groups at baseline. There were no clinically significant differences between the treatment groups in terms of pulmonary function at baseline, although the AM PEF was consistently higher in the active treatment groups than in the placebo group at baseline and throughout the study, in both the ITT and the efficacy populations (see table below; tab8, p83, v1.92).

Table 8: Screening and Baseline Lung Function [a] (Patients Included in the Intent-to-treat Analysis)

Parameter		HFA-BDP$_{50}$		HFA-BDP$_{100}$		HFA-Placebo		Overall P-value [b]	
		AM PEF	FEV$_1$	AM PEF	FEV$_1$	AM PEF	FEV$_1$	AM PEF	FEV$_1$
Screening Actual Values	Mean	378.6	2.51	362.9	2.33	359.2	2.24	0.199	0.068
	SD	69.02	0.773	80.95	0.795	66.94	0.713		
	N	83	83	88	88	85	85		
% Predicted	Mean	68.4	71.0	65.4	67.3	67.5	69.8	0.069	0.318
	SD	8.18	16.40	8.78	16.50	8.58	14.94		
	N	83	83	88	88	85	85		
% Reversibility to Beta-agonist	Mean		30.5		29.2		29.4		0.912
	SD		17.55		15.97		22.77		
	N		83		88		85		
Baseline [c] Actual Values	Mean	374.1	2.66	362.4	2.47	350.1	2.44	0.131	0.191
	SD	75.28	0.840	81.10	0.905	71.69	0.791		
	N	82	83	86	88	83	85		
% Predicted	Mean	67.4	75.4	65.4	71.3	65.6	75.7	0.356	0.236
	SD	9.40	17.91	9.75	19.90	9.18	16.31		
	N	82	83	86	88	83	85		

[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 7 days of the run-in period, with at least 5 valid assessments; FEV$_1$ is the value taken at the clinic visit at the end of the run-in period.

☛ EFFICACY FINDINGS:

PULMONARY FUNCTION TESTING: PFTs in the clinic were done in the AM within 2 hours of the time of the morning at which screening PFTs were done, withholding inhaled beta agonists for 6 hours.

✱ AM PEF: change from baseline in L/min: There was a 50 L/min improvement in the 400 mcg/day 50 mcg/puff group, a 44 L/min improvement in the 400 mcg/day 100 mcg/puff group and a 17 L/min improvement in the HFA-placebo group after 5-6 weeks of treatment, based on analysis of the ITT population (see table and figure below; tab11, p88, v1.92; fig2, p87, v1.92).

Table 11: Adjusted Mean Change from Baseline in Morning Peak Flow (L/min) (Patients Included in the Intent-to-treat Analysis)

Study Week		HFA-BDP$_{50}$	HFA-BDP$_{100}$	HFA-Placebo	Overall P-value [a]
Baseline	Mean	374.1	362.4	350.1	0.131
	SE	8.51	8.04	8.23	
	N	82	86	83	
Change from Baseline at Weeks 1-2	Mean	25.4*	25.3*	6.6	0.007
	SE	5.10	4.57	4.75	
	N	79	83	78	
Change from Baseline at Weeks 3-4	Mean	45.4**	41.5**	9.4	< 0.001
	SE	6.12	5.49	5.68	
	N	79	83	79	
Change from Baseline at Weeks 5-6	Mean	50.2**	44.4**	16.5	< 0.001
	SE	6.72	6.03	6.24	
	N	79	83	79	

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

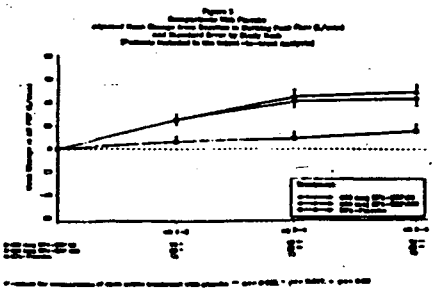
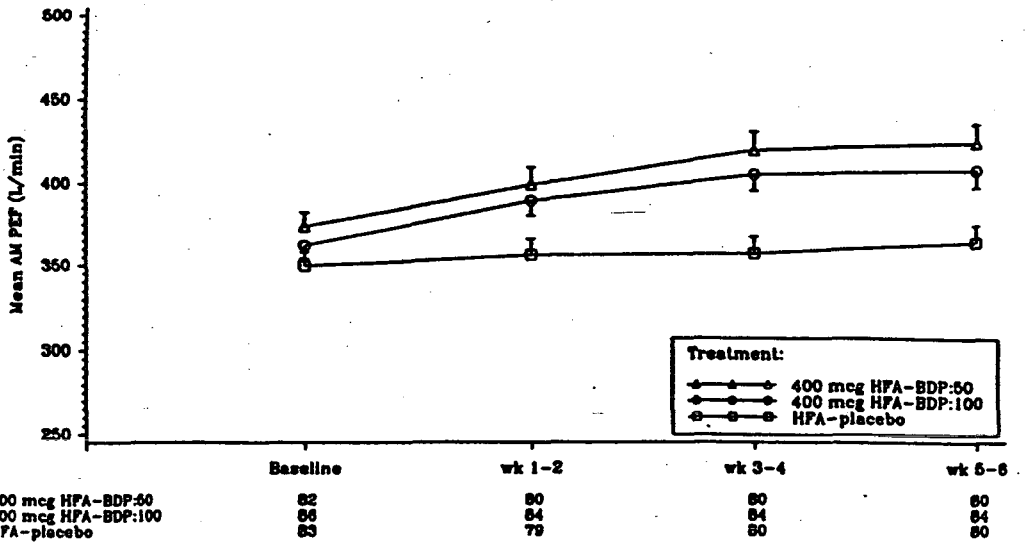


Figure 2
Adjusted Mean Morning Peak Flow (L/min) and Standard Error by Study Week
(Patients Included in the Intent-to-treat Analysis).



	Baseline	wk 1-2	wk 3-4	wk 5-6
N:400 mcg HFA-BDP:50	82	80	80	80
N:400 mcg HFA-BDP:100	86	84	84	84
N:HFA-placebo	83	79	80	80

The improvement in mean AM PEF after administration of BDP-HFA is clinically significantly greater than the improvement seen after administration of placebo and the improvement with BDP-HFA 50 mcg/puff (BDP-50) and 100 mcg/puff (BDP-100) is comparable, although a greater mean change from baseline was noted 3-4 and 5-6 weeks after initiation of treatment in patients who received BDP-50 than in patients who received BDP-100.

A comparison between the mean change from baseline in AM PEF for BDP-50 and BDP-100 at evaluation time points in the study can be seen in the table and figure below (tab12, p91, v1.92 and fig4, p92, v1.92). No significant difference was noted when the data was analyzed using the efficacy population. The 90% confidence interval of the difference in adjusted mean change from baseline in AM PEF between the group that received BDP-50 and the group that received BDP-100 fell within the sponsor's post-hoc criterion for "equivalence" (i.e. ± 25 L/min) at all time points.

Table 12: **Adjusted Mean Change from Baseline in Morning Peak Flow (L/min) HFA-BDP$_{50}$ Compared with HFA-BDP$_{100}$ (Patients Included in the Intent-to-treat Analysis)**

Study Week	Mean difference[a] (HFA-BDP$_{50}$ - HFA-BDP$_{100}$)	S.E.	90% C.I. of Difference	P-value for Equivalence[b]
Baseline	11.6	11.70	-7.71, 30.96	0.127
Change from Baseline at Weeks 1-2	0.1	6.84	-11.23, 11.39	< 0.001
Change from Baseline at Weeks 3-4	3.9	8.22	-9.67, 17.50	0.006
Change from Baseline at Weeks 5-6	5.8	9.03	-9.15, 20.69	0.017

[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 the mean difference being no more than ±25 L/min.

✱ PM PEF: A comparison of the mean change from baseline in mean PM PEF between BDP-50, BDP-100, and HFA placebo can be seen the tables and figures below, based on analysis of the ITT population (tab 14.2.2.5, p227, v1.92, tab 14.2.2.7, p229, v1.92, fig 14.2.2.6, p228, v1.92, fig 14.2.2.8, p230, v1.92). As noted in regard to the data for AM PEF, a clinically and statistically greater degree of improvement was seen with BDP-50 and BDP-100 than HFA placebo, and the improvement with BDP-50 and BDP-100 was comparable. The same results were obtained when the data was analyzed using the efficacy population.

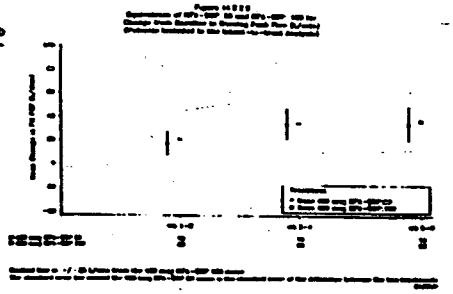
Table 14.2.2.5
Adjusted Mean Change from Baseline in Evening Peak Flow (L/min)
Comparisons with Placebo
(Patients Included in the Intent-to-treat Analysis)

Study week		HFA-BDP 50	HFA-BDP 100	HFA Placebo	Overall P-value a
Baseline	Mean	388.1	374.7	375.2	0.493
	SE	9.09	8.59	8.78	
	Median	366.4	376.6	366.4	
	Min				
	Max				
	N	82	90	84	
Change from Baseline at Weeks 1-2	Mean	17.9*	20.3*	3.3	0.011
	SE	4.61	4.13	4.29	
	Median	15.7	18.6	1.4	
	Min				
	Max				
	N	79	83	79	
Change from Baseline at Weeks 3-4	Mean	25.8**	26.1**	6.6	< 0.001
	SE	5.93	5.31	5.49	
	Median	23.7	25.0	1.8	
	Min				
	Max				
	N	79	83	80	
Change from Baseline at Weeks 5-6	Mean	27.2*	29.6**	11.2	0.001
	SE	6.52	5.84	6.04	
	Median	24.6	33.1	18.1	
	Min				
	Max				
	N	79	83	80	

a based on an ANOVA with treatment, center, treatment by center interaction terms.
**: p <= 0.003; *: p <= 0.017; .: p <= 0.05.

Table 14.2.2.7
Adjusted Mean Change from Baseline in Evening Peak Flow (L/min)
HFA-BDP: 50 Compared with HFA-BDP: 100
(Patients Included in the Intent-to-treat Analysis)

Study week	HFA-BDP: 50 - HFA-BDP: 100 Mean difference a	S.E.	90% C.I. of Difference		P-value for Equivalence b
Baseline	13.4	12.51	-7.31 ,	34.02	0.017
Change from Baseline at Weeks 1-2	-2.3	6.19	-12.55 ,	7.89	< 0.001
Change from Baseline at Weeks 3-4	-0.3	7.96	-13.45 ,	12.84	< 0.001
Change from Baseline at Weeks 5-6	-2.4	8.75	-16.89 ,	12.02	< 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 in the protocol as +/- 25 L/min from the adjusted HFA-BDP: 100 mean for the purpose of sample size calculation.

✱ FEV-1: As can be seen in the table and figure below (tab13, p97. V1.92, fig6, p98, v1.92) the mean improvement from baseline in FEV-1 was statistically greater than placebo at all evaluation times in the group that received BDP-50 but only for 4 weeks in the group that received BDP-100 based on the ITT population.

Table 13: Adjusted Mean Change from Baseline in FEV_1 (L) (Patients Included in the Intent-to-treat Analysis)

Study Week		HFA-BDP_{50}	HFA-BDP_{100}	HFA-Placebo	Overall P-value[a]
Baseline	Mean	2.66	2.47	2.44	0.191
	SE	0.094	0.089	0.091	
	N	83	88	85	
Change from Baseline at Week 2	Mean	0.26**	0.21*	0.03	0.003
	SE	0.053	0.048	0.048	
	N	79	81	81	
Change from Baseline at Week 4	Mean	0.33*	0.31*	0.09	0.005
	SE	0.061	0.056	0.056	
	N	80	81	81	
Change from Baseline at Week 6	Mean	0.35**	0.24	0.09	0.010
	SE	0.061	0.055	0.057	
	N	81	84	81	

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

Comparability was not demonstrated, using the sponsor's analytical approach, at week 6 between BDP-50 and BDP-100 based on the ITT population (see table and figure below; tab14, p100, v1.92, fig7, p101, v1.92) nor at any time point, based on the efficacy population, despite the fact that that the change

from baseline in FEV-1 was comparable in the two populations (see figure 14.2.3.9, p243, v1.92 below). There was a 9.4, 7 and 2.7 mean change from baseline in FEV-1 percent of predicted for the BDP-50, BDP-100 and HFA placebo groups, respectively, after 6 weeks of treatment based on the ITT population. The changes were not significantly different based on analysis of the efficacy population. Greater improvement in mean FEV-1 from baseline was seen in the group that received 400 mcg/day of BDP-50 than in the group that received 400 mcg/day of BDP-100 after 6 weeks of treatment.

Table 14: Adjusted Mean Change from Baseline in FEV_1 (L) HFA-BDP_{50} Compared with HFA-BDP_{100} (Patients Included in the Intent-to-treat Analysis)

Study Week	Mean difference[a] (HFA-BDP_{50} - HFA-BDP_{100})	S.E.	90% C.I. of Difference	P-value for Equivalence[b]
Baseline	0.19	0.129	0.027, 0.400	0.458
Change from Baseline at Week 2	0.04	0.072	-0.076, 0.160	0.014
Change from Baseline at Week 4	0.03	0.083	-0.109, 0.164	0.019
Change from Baseline at Week 6	0.10	0.083	-0.034, 0.239	0.119

[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 ± 0.2 L from the adjusted HFA-BDP_{100} mean.

* FEF 25-75: Using the ITT population, there was a statistically significantly greater improvement from baseline in mean FEF 25-75 after administration of BDP-50 and BDP-100 than after administration of placebo at week 2, week 4 and week 6 (see table and figure below; tab15, p104, v1.92, fig8, p105, v1.92). Using the efficacy population, the mean improvement in FEF 25-75 after 6 weeks of treatment with BDP-100 was not statistically different than the improvement seen after placebo. Mean percent improvement from baseline in FEF 25-75 was statistically significantly greater at all time points after administration of BDP-50 but not week 6 (ITT population) or

weeks 4 and 6 (efficacy population) after administration of BDP-100. After 6 weeks of treatment, more improvement was seen after administration of 400 mcg/day of BDP-50 than after administration of 400 mcg/day of BDP-100, although based on the sponsor's analysis, there was no statistically significant difference between improvement in FEF 25-75 after administration of 400 mcg/day as the 50 mcg/puff or the 100 mcg/puff concentration (table 14.2.4.6, p257, v1.92 below)

Table 15: Adjusted Mean Change from Baseline in $FEF_{25-75\%}$ (L/sec) (Patients Included in the Intent-to-treat Analysis)

Study Week		HFA-BDP$_{50}$	HFA-BDP$_{100}$	HFA-Placebo	Overall P-value[a]
Baseline	Mean	2.28	1.79	2.00	0.009
	SE	0.115	0.109	0.112	
	N	80	84	81	
Change from Baseline at Week 2	Mean	0.37**	0.36**	-0.02	< 0.001
	SE	0.083	0.076	0.076	
	N	76	78	78	
Change from Baseline at Week 4	Mean	0.47**	0.46**	0.05	< 0.001
	SE	0.093	0.086	0.086	
	N	77	78	78	
Change from Baseline at Week 6	Mean	0.61**	0.41*	0.06	< 0.001
	SE	0.102	0.094	0.095	
	N	78	81	78	

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

Table 14.2.4.6
Adjusted Mean Change from Baseline in FEF25-75% (L/sec)
HFA-BDP: 50 Compared with HFA-BDP: 100
(Patients Included in the Intent-to-treat Analysis)

Study week	HFA-BDP: 50 - HFA-BDP: 100 Mean difference a	S.E.	90% C.I. of Difference	
Baseline	0.49	0.158	0.227 ,	0.750
Change from Baseline at Week 2	0.01	0.112	-0.176 ,	0.194
Change from Baseline at Week 4	0.01	0.127	-0.204 ,	0.215
Change from Baseline at Week 6	0.20	0.139	-0.033 ,	0.425

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.

- **overall evaluation of improvement in pulmonary function after treatment with BDP-HFA 400 mcg/day:**

	ITT population				efficacy population			
parameter	50 mcg/puff	100 mcg/puff	placebo	p value	50 mcg/puff	100 mcg/puff	placebo	p value
Mean change AM PEF	S 50l/min	S 44L/min	17L/min	<0.001	S 53 L/min	S 48 L/min	14 L/min	< 0.001
Mean change PM PEF	S 37 L/min	S 40 L/min	11 L/min	0.001	S 43 l/min	S 40 L/min	5 L/min	< 0.001
Mean change FEV-1	S 0.35L	S wks 2,4 T wk 6 0.24L	0.09L	0.01	S 0.35L	S wks 2,4 T wk 6 0.24 L	0.09L	0.01
Mean % change FEV-1	S 9.4%	S wks 2,4 T wk 6 7%	2.7%	0.02	S wks 2,4 T wk 6 11%	S wk 4 T wks 2,6 6%	3.4%	0.08
Mean change FEF 25-75	S 0.61 L/sec	S 0.41 L/sec	0.06L/sec	<0.001	S 0.61 L/sec	S wks 2,4 T wk 6 0.41 L/sec	0.11 L/sec	0.02
Mean % change FEF 25-75	S 41%	S wks 2,4 T wk 6 31%	9%	0.01	S 45%	S wk 2 T wks 4,6 28%	9%	0.04

S = statistically significant at $p < 0.05$
T = strong trend favoring BDP over placebo

APPEARS THIS WAY
ON ORIGINAL

OTHER EFFICACY PARAMETERS

✱ symptom scores: Asthma symptoms (wheezing, cough, shortness of breath and chest tightness) which occurred during the day were evaluated by patients each evening prior to drug administration using a categorical scale as shown below. The mean daily symptom scores were evaluated for each 2 week period, i.e. weeks 1-2, weeks 3-4 and weeks 5-6.

0 = none
1 = present but causing little or no discomfort
2 = mild, annoying, causing little or no discomfort
3 = moderate, causing discomfort, not affecting activities
4 = severe, interfere at least once/day with activities
5 = severe, interferes with work, school, daily activities

The mean baseline symptom scores for the 4 asthma symptoms evaluated were between 0.5 and 1 and the percent of days without wheezing during the run-in period was approximately 50% for all treatment groups. Based on these scores, the patient population studied had extremely mild asthma without substantial room for improvement.

◆ wheeze: The mean change from baseline in percent of days without wheezing and the mean change from baseline in wheezing can be seen in the tables and figures below (tab19, p111, v1.92; tab14.2.5.4, p270, v1.92; tab14.2.5.12, p279, v1.92; tab14.2.5.14, p280, v1.92; fig9, p112, v1.92; fig14.2.5.13, p279, v1.92).

Table 19: **Adjusted Mean Change from Baseline in Percent of Days Without Wheeze (Patients Included in the Intent-to-treat Analysis)**

Study Week		HFA-BDP$_{50}$	HFA-BDP$_{100}$	HFA-Placebo	Overall P-value[a]
Baseline	Mean	47.0	50.6	53.4	0.652
	SE	5.01	4.69	4.77	
	N	80	85	84	
Change from Baseline at Weeks 1-2	Mean	15.1	7.2	3.2	0.050
	SE	3.57	3.17	3.31	
	N	76	82	77	
Change from Baseline at Weeks 3-4	Mean	25.5**	15.1	5.7	0.005
	SE	4.45	3.94	4.05	
	N	76	82	80	
Change from Baseline at Weeks 5-6	Mean	25.5**	21.0*	4.6	0.005
	SE	5.02	4.45	4.57	
	N	76	82	80	

[a] Based on an ANOVA with treatment, center, treatment by center interaction terms in the model.
Comparison of active treatments with placebo: **: $p \leq 0.003$; *: $p \leq 0.017$; +: $p \leq 0.05$.

Table 14.2.5.12
Adjusted Mean Change from Baseline in Wheeze Score
Comparisons with Placebo
(Patients Included in the Intent-to-treat Analysis)

Study week		HFA-BDP 50	HFA-BDP 100	HFA Placebo	Overall P-value a
Baseline	Mean	0.85	0.68	0.77	0.456
	SE	0.101	0.095	0.096	
	Median	0.7	0.6	0.5	
	Min				
	Max				
	N	80	85	84	
Change from Baseline at Weeks 1-2	Mean	-0.29**	-0.10	0.00	0.006
	SE	0.067	0.060	0.062	
	Median	-0.1	0.0	0.0	
	Min				
	Max				
	N	76	82	77	
Change from Baseline at Weeks 3-4	Mean	-0.46**	-0.19	-0.10	0.004
	SE	0.083	0.074	0.076	
	Median	-0.1	0.0	0.0	
	Min				
	Max				
	N	76	82	80	
Change from Baseline at Weeks 5-6	Mean	-0.49**	-0.19	-0.06	0.007
	SE	0.100	0.089	0.091	
	Median	-0.2	-0.0	0.0	
	Min				
	Max				
	N	76	82	80	

a Based on an ANOVA with treatment, center, treatment by center interaction terms.
**: p <= 0.003; *: p <= 0.017; +: p <= 0.05.

Consistently greater improvement in wheezing was seen in the group which received BDP-50 as compared to the group which received BDP-100, using either the ITT or the efficacy population. A trend favoring BDP over placebo was seen as early as weeks 1-2, and a statistically significant improvement compared to placebo was seen with a dose of 400 mcg/day of BDP-50 after 3-4 weeks and 400 mcg/day of BDP-100 after 5-6 weeks, based on analysis