of either patient population. The improvement in wheezing, using either percent of days without wheezing or mean change in wheeze score, and using either the ITT or the efficacy analysis, was not clinically significant.

◆ cough: The mean change from baseline in percent of days without cough and the mean change from baseline in cough can be seen in the tables and figures below (tab20, p116, v1.92; fig10, p117, v1.92; tab14.2.6.4, p287, v1.92; tab14.2.6.12, p295, v1.92; fig14.2.6.13, p296, v1.92; tab14.2.6.14, p297, v1.92)

Table 20: Adjusted Mean Change from Baseline in Percent of Days Without Cough (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	40.3	40.1	0.476
	SE	4.66	4.38	4.43	
	N	80	84	84	
Change from Baseline at Weeks 1-2	Mean	11.4	14.7	8.7	0.475
	SE	3.84	3.44	3.52	
	N	77	81	79	
Change from Baseline at Weeks 3-4	Mean	14.8	23.8*	7.7	0.038
	SE	4.89	4.39	4.48	
	N	77	81	80	
Change from Baseline at Weeks 5-6	Mean	15.8	31.1**	10.3	0.007
	SE	5.29	4.74	4.84	
	N	77	81	80	

[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 14.2.6.12
Adjusted Mean Change from Baseline in Cough 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	0.91	0.88	1.03	0.535
	SE	0.106	0.100	0.101	
	Median	0.7	0.8	0.7	
	Min				
	Max				
	N	80	84	84	
Change from Baseline at Weeks 1-2	Mean	-0.29	-0.29+	-0.07	0.044
	SE	0.075	0.067	0.069	
	Median	-0.1	-0.1	0.0	
	Min				
	Max				
	N	77	81	79	
Change from Baseline at Weeks 3-4	Mean	-0.37+	-0.41*	-0.06	0.013
	SE	0.101	0.090	0.092	
	Median	-0.2	-0.2	0.0	
	Min				
	Max				
	N	77	81	80	
Change from Baseline at Weeks 5-6	Mean	-0.43	-0.44	-0.13	0.057
	SE	0.112	0.100	0.102	
	Median	-0.3	-0.3	0.0	
	Min				
	Max				
	N	77	81	80	

a Based on an ANOVA with treatment, center, treatment by center interaction terms.
**: p <= 0.003; *: p <= 0.017; +: p <= 0.03.

There was a statistically significantly greater improvement from baseline in percent of days without cough in the BDP-100 group at 3-4 weeks and in mean change from baseline in cough score at 1-2 weeks using either the ITT or efficacy population. No statistically significant difference from the placebo group was seen in the BDP-50 group at any time point in terms of percent of days without cough, although a statistically significant difference from placebo was seen for mean change from baseline in cough score at 3-4 weeks and there was a strong trend favoring BDP-50 at all time points. The improvement in percent of days without cough and mean cough score seen after administration of 400 mcg/day of BDP as either the 50 mcg/puff or the 100 mcg/puff concentration was not clinically significant. Percent of days without cough was 40-47% during the run-in period and the cough score for each group during the run-in period was 0.88 to 1.03. Based on cough, the patient population evaluated had very mild asthma, with little room for clinically significant improvement from baseline.

◆ <u>shortness of breath</u>: The mean change from baseline in shortness of breath can be seen in the tables and figure below (tab14.2.7.13, p313, v1.92; tab14,2,7,15, p 315, v1.92; fig 14.2.7.14, p 314, v1.92)

Table 14.2.7.13
Adjusted Mean Change from Baseline in Shortness of Breath 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	1.11	0.95	1.17	0.379
	SE	0.124	0.116	0.118	
	Median	0.9	0.7	0.8	
	Min				
	Max				
	N	69	65	66	
Change from Baseline at Weeks 1-2	Mean	-0.36*	-0.40**	-0.05	0.001
	SE	0.098	0.071	0.074	
	Median	-0.3	-0.3	0.0	
	Min				
	Max				
	N	77	83	79	
Change from Baseline at Weeks 3-4	Mean	-0.57**	-0.52*	-0.14	0.002
	SE	0.100	0.089	0.092	
	Median	-0.4	-0.3	0.0	
	Min				
	Max				
	N	77	83	80	
Change from Baseline at Weeks 5-6	Mean	-0.50*	-0.50	-0.24	0.042
	SE	0.105	0.094	0.096	
	Median	-0.4	-0.4	-0.1	
	Min				
	Max				
	N	77	83	80	

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

◆ chest tightness: The mean change from baseline in percent of days without chest tightness and the mean change from baseline in chest tightness can be seen in the tables and figures below (tab 14.2.8.3, p321, v1.92; fig 14.2.8.4; tab 14.2.8.5, p323, v1.92; tab 14.2.8.13, p331, v1.92; fig 14.2.8.14, p332, v1.92; tab 14.2.8.15, p333, v1.92)

Table 14.2.8.3
Adjusted Mean Change from Baseline in Percent of Days Without Chest Tightness
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	61.7	59.6	67.1	0.636
	SE	4.48	4.19	4.27	
	Median	[illegible]	[illegible]	[illegible]	
	Min				
	Max				
	N	80	85	84	
Change from Baseline at Weeks 1-2	Mean	9.5*	7.8*	-4.8	0.005
	SE	3.51	3.13	3.34	
	Median	0.0	0.0	0.0	
	Min				
	Max				
	N	77	82	78	
Change from Baseline at Weeks 3-4	Mean	14.7*	13.0*	-1.5	0.004
	SE	4.02	3.57	3.67	
	Median	0.0	0.0	0.0	
	Min	-80.0	-71.4	-80.0	
	Max	100.0	100.0	100.0	
	N	77	82	80	
Change from Baseline at Weeks 5-6	Mean	15.9*	14.7*	1.8	0.029
	SE	4.43	3.94	4.05	
	Median	0.0	0.0	0.0	
	Min				
	Max				
	N	77	82	80	

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

Table 14.2.8.13
Adjusted Mean Change from Baseline in Chest Tightness 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	0.65	0.49	0.65	0.417
	SE	0.100	0.094	0.095	
	Median	0.4	0.1	0.1	
	Min				
	Max				
	N	80	85	84	
Change from Baseline at Weeks 1-2	Mean	-0.25**	-0.18**	0.11	< 0.001
	SE	0.063	0.056	0.058	
	Median	0.0	0.0	0.0	
	Min				
	Max				
	N	77	82	78	
Change from Baseline at Weeks 3-4	Mean	-0.22*	-0.24	-0.01	0.016
	SE	0.083	0.074	0.076	
	Median	-0.1	0.0	0.0	
	Min				
	Max				
	N	77	82	80	
Change from Baseline at Weeks 5-6	Mean	-0.34*	-0.24	-0.05	0.049
	SE	0.088	0.079	0.081	
	Median	-0.1	0.0	0.0	
	Min				
	Max				
	N	77	82	80	

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

✱ <u>sleep disturbance scores</u>: Sleep disturbance was evaluated by patients upon awakening in the morning and before taking the AM dose of study medication, using the following categorical scale:

0 = none
1 = awakened once or early because of asthma symptoms
2 = awakened twice or more with asthma symptoms
3 = awake most of night due to asthma symptoms
4 = patient did not fall asleep at all due to asthma symptoms

◆ During the run-in period, the average percentage of nights without sleep disturbance was 49% and the average sleep disturbance score was 0.7.

◆ The mean change from baseline in percent of nights without sleep disturbance and the mean change from baseline in sleep disturbance scores can be seen in the tables and figures below (tab21, p127, v1.92, fig11, p128, v1/92; tab 14.2.9.4, p340, v1.92; tab 14.2.9.12, p348, v1.92; fig 14.2.9.13, p349, v1.92; tab 14.2.9.14, p350, v1.92)

Table 21: <u>Adjusted Mean Change from Baseline in Mean Percent of Nights Without Sleep Disturbance (Patients Included in the Intent-to-treat Analysis)</u>

Study Week		HFA-BDP$_{84}$	HFA-BDP$_{168}$	HFA-Placebo	Overall P-value[a]
Baseline	Mean	47.9	50.1	51.0	0.888
	SE	4.66	4.36	4.44	
	N	80	85	83	
Change from Baseline at Weeks 1-2	Mean	15.1*	15.7*	0.0	0.008
	SE	4.32	3.84	3.97	
	N	77	82	78	
Change from Baseline at Weeks 3-4	Mean	23.1**	26.2**	0.6	<0.001
	SE	4.77	4.24	4.37	
	N	77	82	79	
Change from Baseline at Weeks 5-6	Mean	25.7**	29.8**	2.4	<0.001
	SE	5.22	4.65	4.79	
	N	77	82	79	

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

Table 14.2.9.12
Adjusted Mean Change from Baseline in Sleep Disturbance 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	0.75	0.71	0.73	0.961
	SE	0.065	0.079	0.081	
	Median	0.6	0.4	0.6	
	Min				
	Max				
	N	--	--	--	
Change from Baseline at Weeks 1-2	Mean	-0.25*	-0.35**	0.03	0.003
	SE	0.071	0.063	0.066	
	Median	-0.1	-0.1	0.0	
	Min				
	Max				
	N	77	82	78	
Change from Baseline at Weeks 3-4	Mean	-0.37**	-0.39**	0.02	< 0.001
	SE	0.062	0.073	0.075	
	Median	-0.1	-0.1	0.0	
	Min				
	Max				
	N	77	82	79	
Change from Baseline at Weeks 5-6	Mean	-0.41**	-0.48**	-0.06	< 0.001
	SE	0.091	0.081	0.083	
	Median	-0.1	-0.1	0.0	
	Min				
	Max				
	N	77	82	79	

a Based on an ANOVA with treatment, center, treatment by center interaction terms.
**: p <= 0.003; *: p <= 0.017; +: p <= 0.03.

✱ beta agonist use: beta agonist use was recorded by patients bid during the run-in period and during randomized treatment. The number of times that an inhaled beta agonist was used, not the number of inhalations was recorded.

◆ The average use of an inhaled beta agonist during the run-in period was 2.5 times in a 24 hour period.

◆ The mean daily change in inhaled beta agonist use can be seen in the tables and figure below (tab22, p131, v1.92; tab 14.2.10.6, p359, v1.92; fig12, p132, v1.92). The statistically significant difference seen between both active treatments and placebo was driven predominantly by the decreased nighttime use of inhaled beta agonists.

Table 22: Adjusted Mean Change from Baseline in Daily Beta-agonist Use (Patients Included in the Intent-to-treat Analysis)

Study Week		HFA-BDP$_{50}$	HFA-BDP$_{100}$	HFA-Placebo	Overall P-value[a]
Baseline	Mean	2.39	2.75	2.53	0.564
	SE	0.252	0.237	0.241	
	N	80	84	82	
Change from Baseline at Weeks 1-2	Mean	-0.85**	-1.04**	0.04	<0.001
	SE	0.203	0.182	0.187	
	N	76	81	78	
Change from Baseline at Weeks 3-4	Mean	-0.94*	-1.49**	-0.16	<0.001
	SE	0.225	0.201	0.206	
	N	76	81	79	
Change from Baseline at Weeks 5-6	Mean	-0.98+	-1.58**	-0.24	<0.001
	SE	0.241	0.216	0.220	
	N	76	81	79	

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

☎ **overall evaluation of improvement in secondary endpoints after treatment with 400 mcg/day of BDP-HFA compared to placebo:**

Change from baseline compared to placebo after 6 weeks treatment

	ITT	**mcg/puff**			**Efficacy Population**			
Parameter	**50**	**100**	**placebo**	**p-value**	**50**	**100**	**placebo**	**p-value**
% days without wheezing	S 3-4, 5-6 T 1-2 26%	S 5-6 T 1-2, 3-4 21%	5%	0.005	T 3-4, 5-6 27%	T 5-6 20%	10%	0.09
Mean change wheeze score	S -0.49	N -0.19	-0.06	0.007	S -0.51	T 3-4, 5-6 -0.21	-0.10	0.03
% days without cough	S 3-4 T 5-6 16%	S 1-2, 3-4 T 5-6 31%	10%	0.007	S 1-2, 3-4 T 5-6 16%	S 1-2, 3-4 T 5-6 31%	11%	0.03
Mean change cough score	S 3-4 T 5-6 -0.43	S 1-2, 3-4 T 5-6 -0.44	-0.13	0.06	S 1-2, 3-4 T 5-6 -0.48	S 1-2, 3-4 T 5-6 -0.47	-0.14	0.07
% days without dyspnea	T 1-2 S 3-4, 5-6 24%	S 31%	7%	< 0.001	S 3-4 T 1-2, 5-6 27%	S 3-4 T 1-2, 5-6 29%	14%	0.08
Mean change SOB score	S -0.58	S 1-2, 3-4 T 5-6 -0.50	-0.24	0.04	S 1-2, 3-4 T 5-6 -0.73	S 1-2, 3-4 T 5-6 -0.50	-0.33	0.07
% days without chest tight	S 16%	S 15%	2%	0.03	S 1-2, 3-4 T 5-6 15%	S 1-2, 3-4 T 5-6 16%	3%	0.08
Mean change chest tight	S -0.34	S 1-2 T 3-4, 5-6 -0.24	-0.05	0.05	S 1-2, 3-4 T 5-6 -0.35	S 1-2, 3-4 T 5-6 -0.28	-0.10	0.2
% nights with sleep disturbed	S 26%	S 30%	2%	< 0.001	S 1-2, 3-4 T 5-6 24%	S 33%	6%	0.002
Mean change sleep disturbed	S -0.41	S -0.40	none	< 0.001	S -0.42	S -0.46	-0.08	0.01
Mean daily change beta agonist use	S -0.98	S -1.58	-0.24	< 0.001	S 1-2, 3-4 T 5-6 -1.19	S -1.62	-0.47	0.01

☛ SAFETY FINDINGS

✱ exposure: The extent of exposure can be seen in the table below. The sponsor has assumed, perhaps correctly, perhaps not, that the safety of 400mcg/day using BDP-50 is the same as 400 mcg/day using BDP-100 and has combined both groups of patients receiving BDP, in terms of extent of exposure.

Table 23: Extent of Exposure

Length Of Exposure	HFA-Placebo	Daily Dose 400 mcg HFA-BDP
Total Exposure	Number of Patients n=85	Number of Patients n=171
> 14 days	78	157
> 28 days	73	153
> 42 days	30	64
Unknown	2	2

Time on Treatment	HFA-Placebo	Daily Dose 400 mcg HFA-BDP
Mean number of days on drug	39.3	39.5
Median number of days on drug	42	42
Range of days on drug	2 - 50	2 - 49

Note: Patient 456 receiving HFA-placebo and patients 155 and 329 receiving 400 mcg HFA-BDP were lost to follow-up. Patient 240 receiving HFA-placebo withdrew consent. Therefore, the extent of exposure is not available for these patients.

✱ adverse events: There were significantly less patients ($p = 0.02$) who reported at least one AE in the BDP-50 group (8%) than in the BDP-100 group (19%) or the HFA-placebo group (24%). The only AE reported by ≥ 2% of patients where there was more than one more occurrence after administration of BDP-HFA than after administration of HFA placebo was upper respiratory infection (3% of the BDP-100 group and 1% of the HFA placebo group)(see table below: tab24, p142, v1.92). Therefore, there is no apparent concern about BDP-HFA at a dose of 400 mcg/day producing any significant AEs beyond those seen with placebo. Comparing the BDP-50 and the BDP-100 groups in regard to AEs reported by ≥ 2% of patients, there were some AEs where there was more than one more

occurrence after either administration of BDP-50 or BDP-100 – dysphonia, headache, pharyngitis, and upper respiratory infection occurring more frequently in the BDP-100 group and taste sensation occurring more frequently in the BDP-50 group. These differences are probably not of clinical significance. There was no significant difference between the treatment groups in terms of severe AEs or events that were probably or possibly related to the treatment. There were less patients in the BDP-50 and BDP-100 groups than in the placebo group who were withdrawn from the study due an AE.

Table 24: Summary Of All Clinical Adverse Events Reported By ≥ 2% Of Patients - Number (%) Of Patients With At Least One Report Of The Adverse Event. (Patients Included In The Intent-To-Treat-Analysis)

Adverse Event	HFA-BDP$_{50}$	HFA-BDP$_{100}$	HFA-Placebo	P-value*
Total Number Of Patients	63	66	65	
Number (%) Of Patients Reporting At Least One Adverse Event	7 (8%)	17 (19%)	20 (24%)	0.022
Application Site Disorders	3 (4%)	4 (5%)	4 (5%)	1.000
Inhalation Admin - Cough	0 (0%)	0 (0%)	2 (2%)	0.214
Inhalation Admin - Dysphonia	0 (0%)	2 (2%)	1 (1%)	0.775
Inhalation Site Sensation	1 (1%)	2 (2%)	1 (1%)	1.000
Inhalation Taste Sensation	2 (2%)	0 (0%)	1 (1%)	0.213
Body As A Whole - General Disorders	0 (0%)	2 (2%)	0 (0%)	0.331
Chest Pain	0 (0%)	1 (1%)	0 (0%)	1.000
Fever	0(0%)	1 (1%)	0 (0%)	1.000
Cent & Periph Nerv Syst Disorders	0 (0%)	3 (3%)	5 (6%)	0.045
Dizziness	0 (0%)	1 (1%)	0 (0%)	1.000
Headache	0 (0%)	2 (2%)	4 (5%)	0.127
Neuralgia	0 (0%)	0 (0%)	1 (1%)	0.656
Resistance Mechanism Disorders	1 (1%)	2 (2%)	5 (6%)	0.230
Infection Viral	1 (1%)	2 (2%)	4 (5%)	0.402
Otitis Media	0 (0%)	0 (0%)	1 (1%)	0.656
Respiratory System Disorders	4 (5%)	8 (9%)	11 (13%)	0.178
Acute Asthma Episode	0 (0%)	0 (0%)	1 (1%)	0.656
Bronchitis	1 (1%)	0 (0%)	2 (2%)	0.321
Coughing	1 (1%)	2 (2%)	1 (1%)	1.000
Increased Asthma Symptoms	1 (1%)	1 (1%)	0 (0%)	0.897
Laryngitis	0 (0%)	1 (1%)	0 (0%)	1.000
Pharyngitis	0 (0%)	2 (2%)	2 (2%)	0.551
Upper Resp Tract Infection	0 (0%)	3 (3%)	1 (1%)	0.328

* The p-value for the overall treatment comparison is based on a two-sided Fisher's Exact Test.

✱ laboratory tests: There were 8 patients in the BDP-100 group who developed a serum albumin level above the NRR after 6 weeks of treatment compared with none of the HFA placebo patients. There were significant changes in LFTs seen in all 3 treatment groups. One patient who received BDP-100 had an increase in SGPT from 18 to 61 IU/L (N = 7-39 IU/L). There were more patients, however, in the placebo group who had an increase in LFTs to above the upper limit of the NRR except for bilirubin where there were 3 BDP-50, 1 BDP-

100 and no placebo patients who developed levels above the upper limit of the NRR. In the BDP-100 group, the mean platelet level decreased from 242 at baseline to 230 after 6 weeks of treatment while the mean platelet count in the other two treatment groups increased. There were 1-2 patients in each treatment group who had a fall in platelet levels below the lower limit of the NRR.

* vital signs: no significant mean changes in pulse or blood pressure was noted after administration of BDP-HFA.

* 12 lead ECGs: there were no significant changes in ECGs after administration of BDP-HFA.

CONCLUSIONS:

1. 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 not taking inhaled corticosteroids.

2. It is not possible to assess comparability between BDP-HFA delivered as the 50 mcg/puff concentration and BDP-HFA delivered as the 100 mcg/puff concentration, because there was no dose-response built into this study, in order to detect differences if differences existed. The sponsor has tried to [illegible] but this is not acceptable. Asthma severity in this patient population was probably too mild to detect a difference in response to the two different concentrations of BDP-HFA evaluated, if a difference existed, at a dose of 400 mcg/day. 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.

3. No safety concerns were apparent on the basis of safety parameters monitored in this study.

ABSTRACT

METHODS: Study 1192 was a parallel, modified blind, double-dummy, active treatment controlled, multicenter, repetitive dose study in 323 adult patients (50-60 patients in each arm) who had mild-moderate asthma and were receiving inhaled corticosteroids. After a corticosteroid washout period, patients were randomized to receive either 100, 400, or 800 mcg of either BDP-HFA or BDP-CFC at a concentration of 50 mcg/puff (9 puffs bid) for 6 weeks. The primary efficacy variable was mean change in percent predicted FEV-1 from baseline after 6 weeks of treatment. Secondary efficacy parameters included other pulmonary function assessments (FVC, FEF 25-75, AM and PM PEF), asthma symptoms, sleep disturbance, inhaled beta agonist use and reversibility. Safety was assessed by adverse events, vital signs, assessment for candidiasis and laboratory tests. Two study populations were analyzed: 1) an intent-to-treat population; and 2) an evaluable for efficacy population.

There was a 7-14 day run-in period, following which patients entered a 28 day single-blind inhaled corticosteroid washout period, where the patient's inhaled corticosteroid was replaced with CFC placebo. Patients then entered a 6 week period of randomized treatment, during which they were evaluated in the clinic, with pulmonary function testing, 5 days out of every week. Baseline comparison of the treatment groups showed that they were comparable in terms of demographics, medication use, pulmonary function, and other criteria.

RESULTS: A minimal dose-response was seen after administration of BDP-HFA and BDP-CFC for 6 weeks, based on mean change from baseline in percent predicted FEV-1. The primary separation of effect between the three doses of each drug product occurred after the first week of treatment. Subsequent to the first week of treatment, there was a flattening of the dose-response curve. The difference in effect between the three doses of either drug product is of questionable clinical significance. Although there was a consistently greater effect seen after administration of a given dose of BDP-HFA than after administration of the same dose of BDP-CFC, these differences were small and of questionable clinical significance. There was a clinically significant

improvement in mean change from baseline in FEV-1 percent of predicted, percentage of patients with a 12% or greater, as well as 50% or greater improvement in FEV-1, mean percent change in FEF 25-75 from baseline, mean change from baseline in AM PEF, mean percent of wheeze-free days and mean change from baseline in inhaled beta agonist use after administration of 100, 400, and 800 mcg/day of BDP-HFA. There were no safety concerns raised by the data from this study.

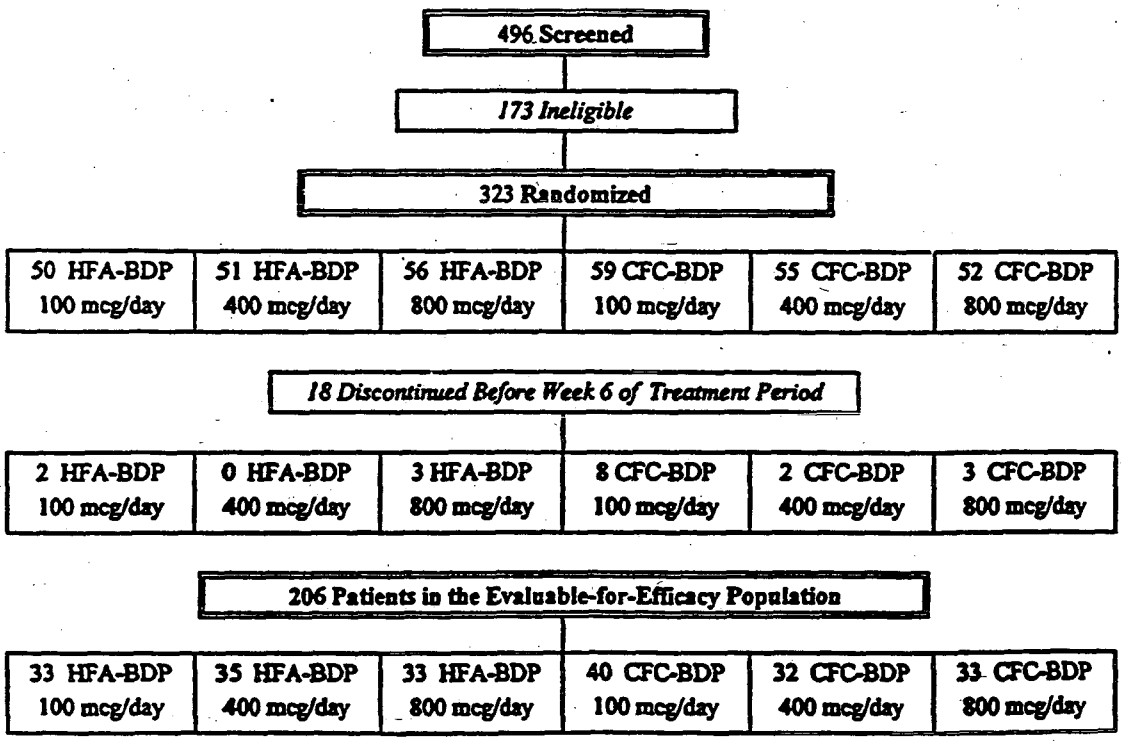
DISCUSSION: Based on the degree of improvement expected with an inhaled corticosteroid, the sponsor has adequately demonstrated a dose-response for BDP-HFA and BDP-CFC, across the dose range of BDP-HFA proposed for clinical use. Efficacy of BDP-HFA at doses between 100 and 800 mcg/day was demonstrated for most parameters. The significant improvement in FEF 25-75 after administration of 800 mcg/day of BDP-HFA suggests an effect of BDP-HFA on smaller airways, a finding that is consistent with lung deposition studies. Although no safety concerns were raised by this study, some adjustment may be required when patients are switched from BDP-CFC to BDP-HFA because of the greater incidence of AEs noted in this study with BDP-HFA at a dose of 800 mcg/day.

☞ study 1192

- The primary objective of this study was to demonstrate a dose response with administration of 100 to 800 mcg/day of BDP-HFA in patients with asthma by comparing the dose-response curves of BDP-HFA and BDP-CFC across this dose range.

- number of patients: 496 patients were screened; 323 patients were randomized to treatment; 50, 51, and 56 (157) patients were randomized to receive 100, 400, and 800 mcg/day of BDP-HFA, respectively and 59, 55, and 52 (166) patients were randomized to receive 100, 400, and 800 mcg/day of BDP-CFC; 206 patients were included in the efficacy population (evaluable for efficacy population)(see flow chart below); the number of patients enrolled at each center ranged from 4 to 24.

Figure 10.1.A: Patient Disposition



PLACEBO	PROPELLANT	ADAPTER COLOR	DESIGNED TO
A	HFA-134a	white	match HFA-BDP
E	HFA-134a	pink	match CFC-BDP
D	CFC-11/12	white	match HFA-BDP
F	CFC-11/12	pink	match CFC-BDP

TREATMENT	TOTAL DAILY DOSE (ex-valve)	INHALER(S)	ADAPTER COLOR	REGIMEN
HFA-BDP_{50}	100 mcg	active	white	1 puff BID
		HFA-placebo (E)	pink	4 puffs BID
		HFA-placebo (E)	pink	4 puffs BID
HFA-BDP_{50}	400 mcg	HFA-placebo (E)	pink	1 puff BID
		active	white	4 puffs BID
		HFA-placebo (A)	white	4 puffs BID
HFA-BDP_{50}	800 mcg	HFA-placebo (E)	pink	1 puff BID
		active	white	4 puffs BID
		active	white	4 puffs BID
CFC-BDP_{50}	100 mcg	active	pink	1 puff BID
		CFC-Placebo (D)	white	4 puffs BID
		CFC-Placebo (D)	white	4 puffs BID
CFC-BDP_{50}	400 mcg	CFC-Placebo (D)	white	1 puff BID
		active	pink	4 puffs BID
		CFC-Placebo (F)	pink	4 puffs BID
CFC-BDP_{50}	800 mcg	CFC-Placebo (D)	white	1 puff BID
		active	pink	4 puffs BID
		active	pink	4 puffs BID

☛ periods of study:

✱ 7-14 day run-in period during which patients continued to use inhaled corticosteroids;

✱ the run-in period was followed by a 28 day single-blind inhaled corticosteroid washout period where the patient's inhaled corticosteroid was replaced with a CFC placebo without the patient's knowledge; patients returned to the clinic for evaluation at least 5 mornings of each week; loss of asthma control during this period of time was defined as a decrease of at least 10% in FEV-1 or a decrease of 20% or more in PEF on the same day as the lowest FEV-1 was measured, associated with an increase in the

total number of puffs of Maxair used on the day preceding the qualifying drop in FEV-1 by 2 or more compared with the highest total number of puffs used on any day during the last 7 days of the run-in period and the daily sum of the asthma symptom score and sleep disturbance score on the day preceding the qualifying drop in FEV-1 was higher than the highest daily sum of these scores during the last 7 days of the run-in period; asthma exacerbations during this period of time (FEV-1 < 40% predicted) could be treated with nebulized beta agonist and if the patient responded, the patient could stay in the study

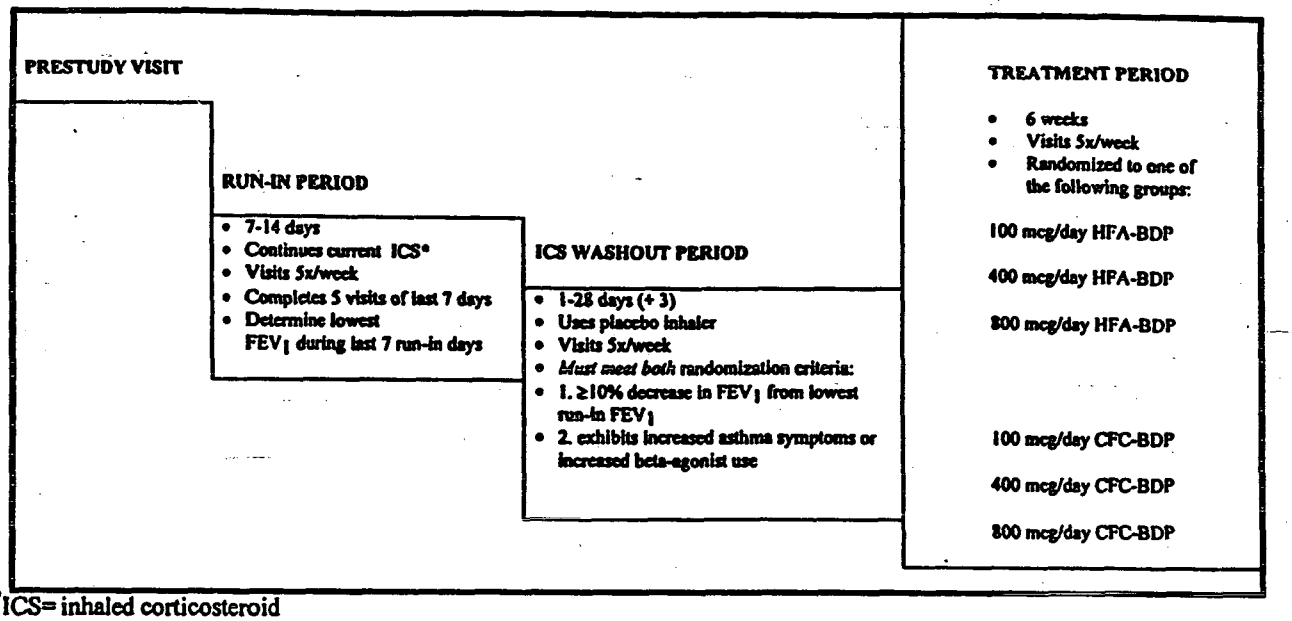
* following the corticosteroid washout period patients received 6 weeks of randomized treatment; during this period, patients could only be treated with two courses of nebulized beta agonist and one course of oral antibiotics; need for additional treatment resulted in the patient being withdrawn from the study.

☛ parameters evaluated:

EFFICACY

* the primary efficacy variable was percent of predicted FEV-1 change from baseline; FEV-1 was measured 5 times per week during the last week of the run-in period, 5 times per week during the inhaled corticosteroid washout period and 5 times per week during weeks 1, 2, 3, 4, 5, and 6 of treatment (see flow chart below); baseline was the value obtained at the end of the inhaled corticosteroid washout period (day 1); FEV-1 values were averaged over each weekly interval; a minimum of 3 days per week was required to calculate a weekly average.

Figure 9.1.A: **1192-BRON Dose-Response Study Design**



*ICS= inhaled corticosteroid

- FVC and FEF 25-75 were also measured at the time of FEV-1 assessment; PEF was measured in the AM upon arising and in the PM upon retiring;

- asthma symptoms and sleep disturbance: the highest daily value during the last 7 days of the run-in period was used as baseline; asthma symptoms and sleep disturbance scores were evaluated by patients during the run-in period, the corticosteroid washout period and during randomized treatment; asthma symptoms during the day were evaluated by patients when they took their PM dose of study drug; sleep disturbance caused by asthma was assessed by patients before taking their AM study drug.

- Inhaled beta-agonist use: the highest daily total number of puffs of Maxair during the last 7 days of the run-in period was used as baseline; during randomized treatment, the total number of puffs of Maxair use was recorded daily.

- reversibility: spirometry performed 30 minutes after 400 mcg of Maxair on study days 1, 8, 15, 22, 29, 36, and 43 or at the time of discontinuation was compared between doses and study drugs.

SAFETY

- assessment for candidiasis: if the patient complained of symptoms referable to the mouth or throat, examination of the oropharynx was done; if there were clinical signs of oral candidiasis, a swab was taken; if the results were positive for Candida albicans, the patient was withdrawn from the study.

- adverse events

- vital signs: prestudy, study day 1, and end of treatment visit; ITT population only was analyzed.

- laboratory values: ITT population only was analyzed; prestudy and end of treatment determinations

☛ data analysis:

- Two patient populations were analyzed, the intent-to-treat population (ITT) and the evaluable for efficacy population (efficacy population). The ITT population included all patients who received at least one dose of study medication; the primary analysis used the efficacy population which excluded those patients who were protocol violators or noncompliant. In regard to the primary efficacy variable, for the ITT analysis, if a patient had fewer than 3 values for a given week, the average was calculated using data from previous weeks until 3 non-missing data points were available. For the efficacy population analysis, if a patient had fewer than 3 values in a week, no average was computed.

☛ withdrawals: see table, tab 10.1.D, p87, v1.156) below.

Table 10.1.D: Number (%) of Patients Who Withdrew Prior to Week 6 by Primary Reason and Treatment

Reason	HFA-BDP (mcg/ day)			CFC-BDP (mcg/ day)			Overall (n=323)
	100 (n =50)	400 (n =51)	800 (n =56)	100 (n =59)	400 (n =55)	800 (n =52)	
Personal	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.1%)	1 (1.8%)	2 (3.8%)	6 (1.9%)
Adverse Event	1 (2.0%)	0 (0.0%)	0 (0.0%)	3 (5.1%)	0 (0.0%)	1 (1.9%)	5 (1.5%)
Inadequate response	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (1.8%)	0 (0.0%)	3 (0.9%)
Entry criteria violation	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Intercurrent disease	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Withdrew consent	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Total	2 (4.0%)	0 (0.0%)	3 (5.4%)	8 (13.6%)	2 (3.6%)	3 (5.8%)	18 (5.6%)

☛ protocol violations: There were 67 patients who had major protocol violations which resulted in complete exclusion of their data from the efficacy population analysis. In addition, 68 patients were excluded from this analysis because of noncompliance (31 received BDP-HFA and 37 received BDP-CFC (see table below; tab 11.1.A, p93, v1.156). The number of non-compliant patients was comparable in all the treatment groups, varying between 9 and 14 patients. Most patients who were overcompliant (9/10) received 100 mcg/day of either BDP-HFA or BDP-CFC, while patients who were undercompliant were evenly distributed between the groups which received the two higher doses of BDP-HFA and BDP-CFC. Compliance was generally good, probably in part because of frequent review with patients about medications (patients were evaluated 5 days in each week).

Table 11.1.A: Patients Completely Excluded From the Evaluable-for-Efficacy Analyses by Reason and Treatment Group

Treatment Groups	HFA-BDP mcg/day			CFC-BDP mcg/day			Total
	100 (n=50)	400 (n=51)	800 (n=56)	100 (n=59)	400 (n=55)	800 (n=52)	(n=323)
Major Protocol Departure	8	9	16	11	15	8	67
Study-Drug Noncompliance	9	10	12	10	13	14	68
Major Departure and Noncompliance*	0	3	5	2	5	3	18
Total	17	16	23	19	23	19	117

* These patients were counted in both the major protocol departure and study-drug noncompliance exclusion categories

* There were 16 patients who had less than 3 valid data points during the first week of treatment, three of whom withdrew from the study during week 1. The data from these patients was excluded from the efficacy population analysis.

* partial exclusion of data from the efficacy population analysis was done for patients who had spirometry performed after 12:30 PM, an inhaled beta agonist was used within 4 hours of spirometry or reversibility testing was done outside the time frame allocated. Two patients who took prednisone during the treatment period had data obtained after taking prednisone excluded from analysis. Decision to exclude this data was done before unblinding of study results.

* complete exclusion of data from the efficacy population analysis was done in 67 patients. These protocol violations were due to either failure to meet inclusion/exclusion criteria (inhaled corticosteroid not 400 mcg/day or more, patients took excluded medications, patients were not using inhaled beta agonist at screening, and/or patients had a disallowed prior medical condition) or failure to meet interim inclusion (lowest FEV-1 during run-in > 75% predicted, failure to continue inhaled corticosteroid during run-in, failure to demonstrate an increase in symptoms or beta agonist use at the end of the corticosteroid washout period, failure to show a 10% or greater decrease in FEV-1 from the lowest run-in value, and FEV-1 < 40% predicted at the end of the corticosteroid washout period). Decision to exclude this data was done before unblinding of the study results.

☛ DEMOGRAPHICS: There were no significant baseline differences between the treatment groups in regard to gender, age, race, smoking history, duration of asthma, concomitant rhinitis/sinusitis, concomitant medications, pulmonary function (prestudy, run-in, baseline; see table below; tab 11.2.4.A, p102, v1.156), asthma symptom scores, nighttime sleep disturbance or beta agonist use (see table below; tab11.2.5.A, p103, v1.156). The mean symptom scores were very low at baseline. Mean inhaled beta agonist use was

moderate. Although symptoms did not significantly increase during the corticosteriod washout period, there was an increase in use of inhaled beta agonists. The majority of patients in each treatment group were women. The majority of patients in each treatment group were Caucasian; 12% were African-American. Most patients were never smokers and the majority of patients had experienced asthma for > 5 years.

Table 11.2.4.A: Prestudy Lung Function by Treatment Group (Intent-to-Treat Analysis)

FEV$_1$ Parameters		HFA-BDP (mcg/day) 100	400	800	CFC-BDP (mcg/day) 100	400	800	Overall P-value[a]
Prestudy	Mean	2.29	2.30	2.32	2.36	2.30	2.40	0.929
Absolute Values (L)	SD	0.555	0.534	0.576	0.579	0.502	0.620	
	N	50	51	56	59	55	52	
% Predicted	Mean	64.77	66.02	64.87	65.42	64.42	66.16	0.842
	SD	7.061	7.557	8.654	7.569	7.603	7.618	
	N	50	51	56	59	55	52	
% Reversibility	Mean	25.78	25.00	26.62	24.78	28.57	23.29	0.667
Following	SD	17.328	14.118	18.388	13.738	16.388	12.055	
Beta-Agonist	N	48	51	55	59	55	50	
Run-in	Mean	2.17	2.22	2.21	2.30	2.21	2.26	0.883
Lowest Value (L)	SD	0.572	0.585	0.574	0.620	0.545	0.602	
	N	50	51	56	59	55	52	
% Predicted	Mean	67.81	68.32	68.57	69.54	66.83	68.77	0.810
	SD	9.037	9.482	10.780	10.181	10.238	7.979	
	N	50	51	56	59	55	52	
Baseline	Mean	1.85	1.85	1.86	1.93	1.85	1.92	0.911
Actual values (L)	SD	0.489	0.494	0.506	0.542	0.459	0.512	
	N	50	51	56	59	55	52	
% Predicted	Mean	52.28	53.06	52.11	53.56	51.56	53.01	0.865
	SD	7.990	8.522	9.951	9.001	8.800	7.984	
	N	50	51	56	59	55	52	
% Reversibility	Mean	42.19	44.89	47.50	38.50	45.71	43.94	0.372
	SD	21.249	20.229	25.458	21.133	21.032	23.087	
	N	50	50	56	58	55	51	

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

Table 11.2.5.A: Adjusted Mean Asthma Symptom Scores, Sleep Disturbance Scores and Beta-Agonist Use During the Baseline Period (Intent-to-Treat Analysis))

Baseline Symptom Scores		HFA-BDP (mcg/day)			CFC-BDP (mcg/day)			Overall
		100	400	800	100	400	800	p-value
Wheeze Score	Mean	1.88	1.63	1.38	1.67	1.54	1.74	0.218
	SD	1.037	1.013	1.038	1.079	1.076	0.933	
	N	50	51	56	59	55	52	
Cough Score	Mean	1.06	0.87	0.93	1.00	0.78	1.18	0.392
	SD	1.097	0.839	0.821	0.911	0.897	1.103	
	N	50	51	56	59	54	52	
Shortness of Breath Score	Mean	2.24	2.01	1.96	1.97	1.98	2.07	0.715
	SD	1.057	0.830	1.021	1.105	1.014	1.056	
	N	50	51	56	59	55	52	
Chest Tightness Score	Mean	2.16	2.12	1.96	1.95	1.79	1.89	0.520
	SD	1.055	0.907	1.140	1.091	1.020	1.137	
	N	50	51	56	59	55	52	
Sleep Disturbance Score	Mean	0.84	0.74	0.76	0.84	0.87	0.89	0.927
	SD	0.872	0.735	0.881	0.918	0.842	0.796	
	N	50	51	56	59	55	52	
Daily Beta-agonist (number of uses)	Mean	3.63	3.56	3.63	3.86	3.45	3.42	0.704
	SD	1.302	1.356	1.752	1.577	1.497	1.353	
	N	50	51	56	59	55	52	
Daily Beta-agonist (number of puffs)	Mean	7.06	6.88	6.59	6.87	6.45	6.53	0.886
	SD	2.796	2.833	3.156	2.682	2.743	2.713	
	N	50	51	56	59	55	52	

☛ EFFICACY FINDINGS:

PULMONARY FUNCTION TESTING:

✱ FEV-1 percent of predicted: see figures and table below; fig 11.4.1.1.1.A, p105, v1.156; fig 11.4.1.1.2.A, p106, v1.156; tab 11.4.1.1.2.A, p107, v1.156); Based on analysis using either the ITT or the efficacy population, there was a dose-response seen after the first week of treatment for both BDP-HFA and BDP-CFC, but no further dose-response between week 1 and week 4. Between 4-6 weeks of treatment with both products, a separation of effect was seen between the 400 mcg/day and the 800 mcg/day dose for both BDP-HFA and BDP-CFC, so that there was a statistically significant difference in mean change in percent predicted FEV-1 from baseline between the group which received 800 mcg/day of BDP-HFA and the group that

received 400 mcg/day of BDP-HFA after 6 weeks of treatment ($p = 0.04$), based on the ITT analysis. This difference was marginally significant ($p = 0.07$) using the efficacy population for analysis.

After 6 weeks of treatment, there was no significant difference between the mean change in percent predicted FEV-1 from baseline after administration of 400 mcg/day and 100 mcg/day of BDP-HFA. The dose-response seen at most time points, based on absolute differences in change from baseline FEV-1 as percent of predicted throughout the study was modest and of uncertain clinical significance.

Based on analysis of the ITT population, there was a greater mean change in FEV-1 as percent of predicted at each dose level after administration of BDP-HFA ($p = 0.06$), e.g. the mean change in FEV-1 from baseline was greater after administration of 800 mcg/day of BDP-HFA than after administration of 800 mcg/day of BDP-CFC. In fact, the improvement in FEV-1 after 400 mcg/day of BDP-HFA was comparable to the improvement after 800 mcg/day of BDP-CFC, while the improvement in FEV-1 was greater after 100 mcg/day of BDP-HFA than after 400 mcg/day of BDP-CFC. The same general pattern of response was seen when the efficacy population was analyzed.

Using a regression analysis of change from baseline in percent predicted FEV-1 versus the log of the total daily dose and a parallel line bioassay methodology to quantify the "relative airway availability" of BDP-HFA compared to BDP-CFC over a dose range of 100 to 800 mcg/day, the "relative airway availability" was estimated by the sponsor to be 2.6 after 6 weeks of treatment, i.e. that a dose approximately 2.6 times greater of BDP-CFC was needed to produce a response equivalent to a given dose of BDP-HFA (see figure below; fig 11.4.1.1.2.B, p108, v1.156). However, the 95% CI around this estimate was large (1.1, 11.6). Although the validity of this type

of analysis can be questioned, it is clear that less BDP-HFA is needed to produce a comparable change in FEV-1 compared to BDP-CFC.

The major change from baseline in mean percent predicted FEV-1 occurs after one week of treatment with all doses of BDP-HFA and BDP-CFC, with very little additional improvement in the subsequent 5 weeks.

Table 11.4.1.1.2.A: **Adjusted Mean Change From Baseline in FEV_1 as Percent of Predicted by Study Week (Intent-to-Treat Analysis)**

Study Week		HFA-BDP (mcg/day)			CFC-BDP (mcg/day)		
		100	400	800	100	400	800
Baseline (L)	Mean	52.28	53.06	52.11	53.56	51.56	53.01
	SE	1.264	1.235	1.186	1.163	1.222	1.234
	N	50	51	56	59	55	52
Change from Baseline at Week 1	Mean	14.35	16.24	18.14	12.49	13.73	16.60
	SE	1.325	1.283	1.186	1.207	1.261	1.293
	N	46	48	56	55	52	50
Change from Baseline at Week 2	Mean	17.19	18.77	20.90	13.11	15.44	18.66
	SE	1.336	1.305	1.254	1.263	1.296	1.305
	N	50	51	56	57	54	52
Change from Baseline at Week 3	Mean	17.98	19.53	22.19	14.79	16.77	20.08
	SE	1.464	1.431	1.374	1.384	1.420	1.430
	N	50	51	56	57	54	52
Change from Baseline at Week 4	Mean	17.32	19.89	22.68	14.88	16.95	20.17
	SE	1.489	1.455	1.397	1.407	1.444	1.454
	N	50	51	56	57	54	52
Change from Baseline at Week 5	Mean	16.70	18.46	23.86	15.05	17.15	21.40
	SE	1.557	1.521	1.461	1.471	1.510	1.520
	N	50	51	56	57	54	52
Change from Baseline at Week 6	Mean	18.12	19.39	23.78	14.93	17.71	21.48
	SE	1.606	1.568	1.507	1.518	1.557	1.568
	N	50	51	56	57	54	52

Figure 11.4.1.1.1.A: **Adjusted Mean FEV_1 as Percent of Predicted by Week (Intent-to-Treat Analysis)**

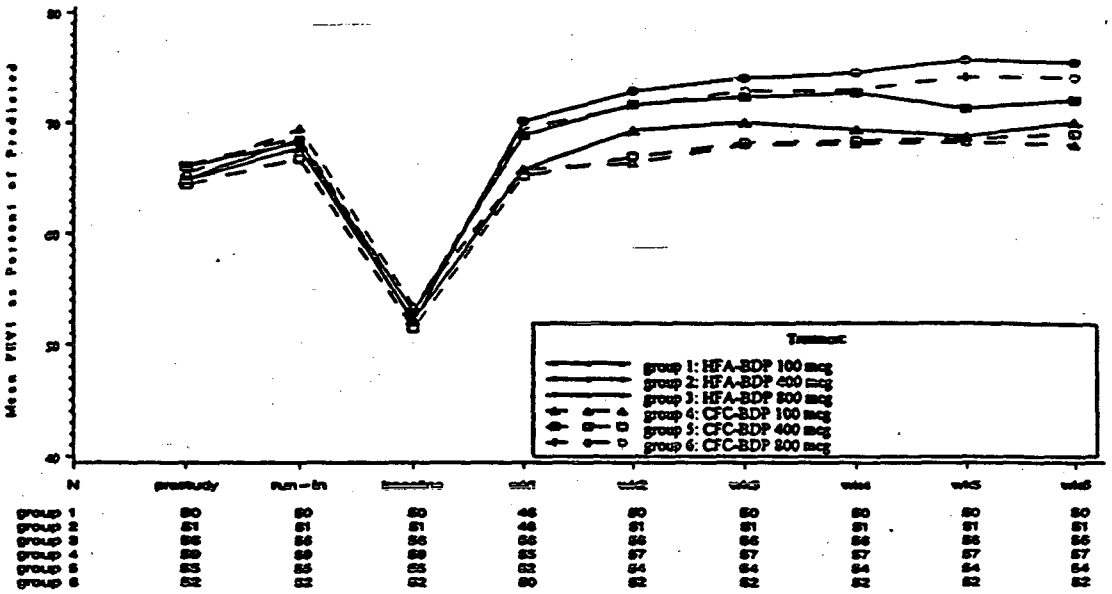
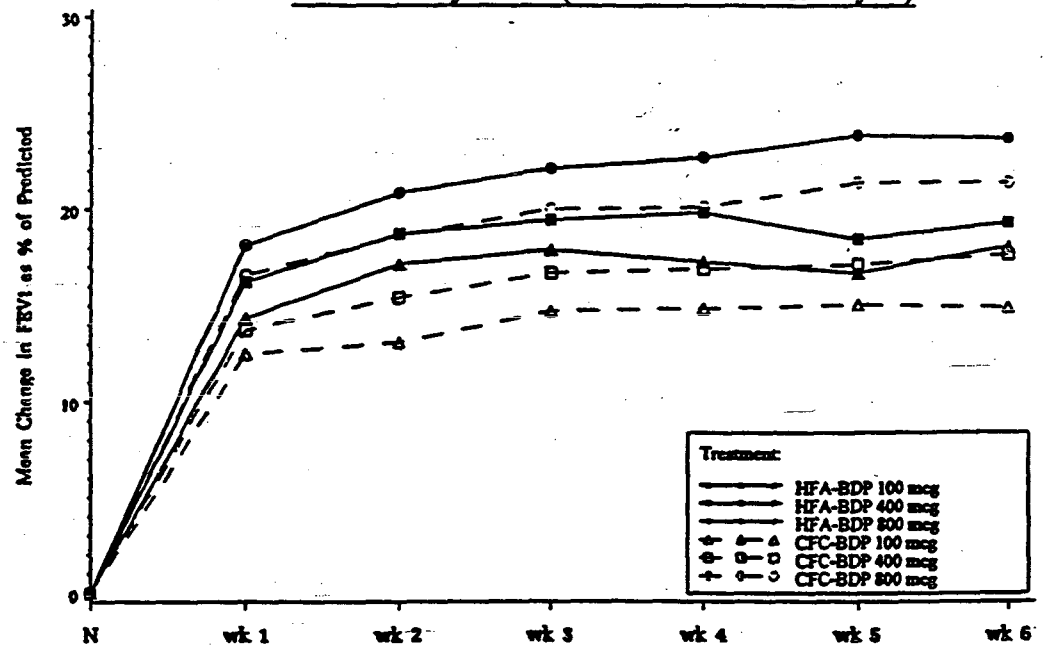
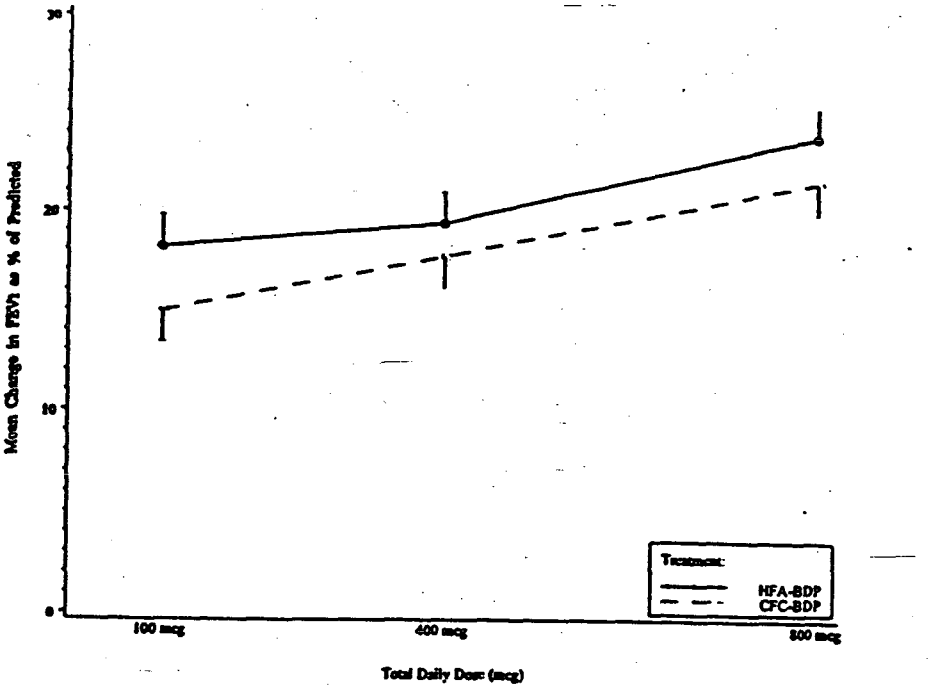


Figure 11.4.1.1.2.A: **Adjusted Mean Change From Baseline in FEV_1 as Percent of Predicted by Week (Intent-to-Treat Analysis)**



HFA-BDP 100 mcg	46	50	50	50	50	50
HFA-BDP 400 mcg	48	51	51	51	51	51
HFA-BDP 800 mcg	56	56	56	56	56	56
CFC-BDP 100 mcg	55	57	57	57	57	57
CFC-BDP 400 mcg	52	54	54	54	54	54
CFC-BDP 800 mcg	50	52	52	52	52	52

1192: Adjusted Mean (SE) Change from Baseline in FEV_1 as a Percent of Predicted by Dose Level at Week 6
(Patients Included in the Intent-to-Treat Analysis)



* absolute mean change from baseline in FEV-1: the changes noted were consistent with those noted for change in mean percent predicted FEV-1 from baseline. No different conclusions can be drawn from analysis of absolute mean change from baseline in FEV-1 using either the ITT or the efficacy population.

* mean AUC change from baseline for percent predicted FEV-1: A greater mean change was seen with BDP-HFA than BDP-CFC after administration of each of the three doses and a dose-response was seen for both products, using the ITT analysis. Using the efficacy population for analysis, a greater mean change from baseline was seen after administration of 400 mcg/day of BDP-CFC than after administration of 400 mcg/day of BDP-HFA, and there was only minimal dose-response between 400 and 800 mcg/day of both drug products.

* mean percent change from baseline in FEF 25-75 (ITT analysis): The same pattern of change was seen when the data was analyzed in terms of mean change in FEF 25-75 as was seen when the data was analyzed based on mean change in FEV-1, except that a significantly greater amount of improvement was seen after administration of 800 mcg BDP-HFA compared with that seen after administration of 800 mcg BDP-CFC. The 99% mean change from baseline in FEF 25-75 after 6 weeks of treatment with 800 mcg/day of BDP-HFA was impressive and may reflect a significant effect of BDP-HFA on smaller airways due to smaller particle size. A dose-response was seen for both products ($p = 0.001$ and $p = 0.01$ for BDP-HFA and BDP-CFC, respectively) most notably between 400 mcg/day and 800 mcg/day doses. Using the sponsor's method of analysis, the estimate of increased airway availability with BDP-HFA compared with BDP-CFC for percentage change from baseline in FEF 25-75 was 3.2, but the 95% CI was very large (1.3,15.8).

A consistently greater mean improvement from baseline was seen with a given dose of BDP-HFA than with the same dose of BDP-CFC. In fact, approximately the same degree of improvement was seen after administration of BDP-HFA with ½ the dose of BDP-CFC. The sponsor's estimate of the airway availability for BDP-HFA was 3.2 compared to BDP-CFC, which suggests that more than twice the amount of drug for a given dose BDP was being delivered to the lower airway when delivered with HFA propellant as when delivered with CFC propellant (see figures and tables below; fig 11.4.1.2.1.A, p115, v1.156; fig 11.4.1.2.1.B, p118, v1.156; tab 11.4.1.2.1.A, p116, v1.156; tab 11.4.1.2.1.B, p117, v1.156;)

Table 11.4.1.2.1.A: Adjusted Mean Percentage Change From Baseline $FEF_{25-75\%}$ by Study Week (Intent-to-Treat Analysis)

Study Week	Stat.	HFA-BDP (mcg/day)			CFC-BDP (mcg/day)		
		100	400	800	100	400	800
Baseline (L/s)	Mean	1.16	1.16	1.22	1.23	1.22	1.32
	SE	0.071	0.069	0.067	0.065	0.069	0.069
	N	50	51	56	59	55	52
% Change from Baseline at Week 1	Mean	41.75	53.44	73.99	38.14	36.85	53.90
	SE	6.597	6.388	5.909	6.012	6.281	6.442
	N	46	48	56	55	52	50
% Change from Baseline at Week 2	Mean	57.31	66.73	90.46	37.93	44.05	62.59
	SE	7.251	7.083	6.805	6.853	7.033	7.081
	N	50	51	56	57	54	52
% Change from Baseline at Week 3	Mean	57.74	68.16	95.25	43.68	49.85	67.13
	SE	8.229	8.038	7.722	7.777	7.981	8.035
	N	50	51	56	57	54	52
% Change from Baseline at Week 4	Mean	56.55	71.76	93.05	44.98	49.43	69.05
	SE	7.903	7.720	7.417	7.470	7.665	7.717
	N	50	51	56	57	54	52
% Change from Baseline at Week 5	Mean	57.22	65.36	96.04	47.97	50.74	74.76
	SE	8.324	8.131	7.811	7.867	8.073	8.128
	N	50	51	56	57	54	52
% Change from Baseline at Week 6	Mean	60.43	69.51	98.91	45.63	52.85	76.69
	SE	8.946	8.739	8.395	8.455	8.677	8.736
	N	50	51	56	57	54	52

Figure 11.4.1.2.1.A: Adjusted Mean Percentage Change From Baseline $FEF_{25-75\%}$ by Week (Intent-to-Treat Analysis)

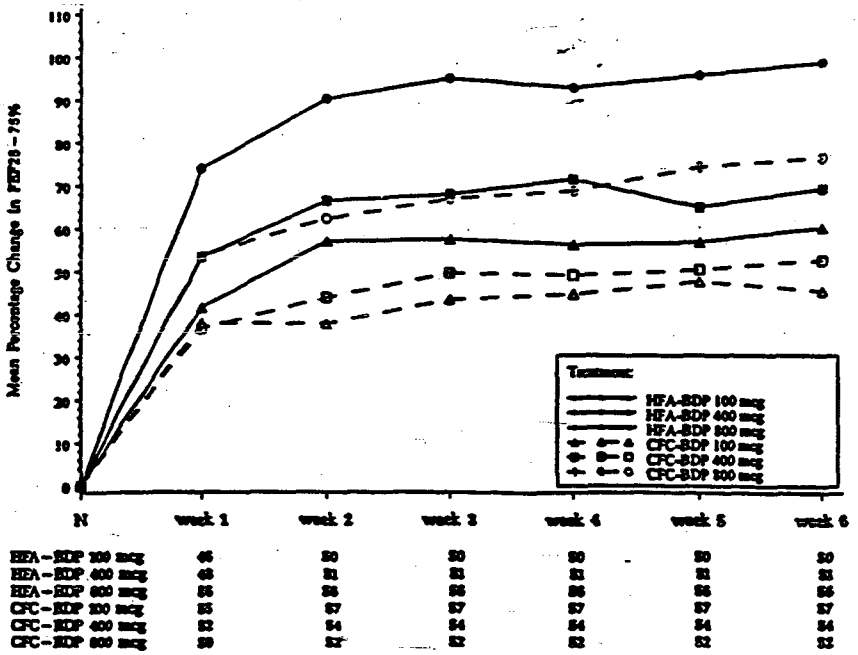


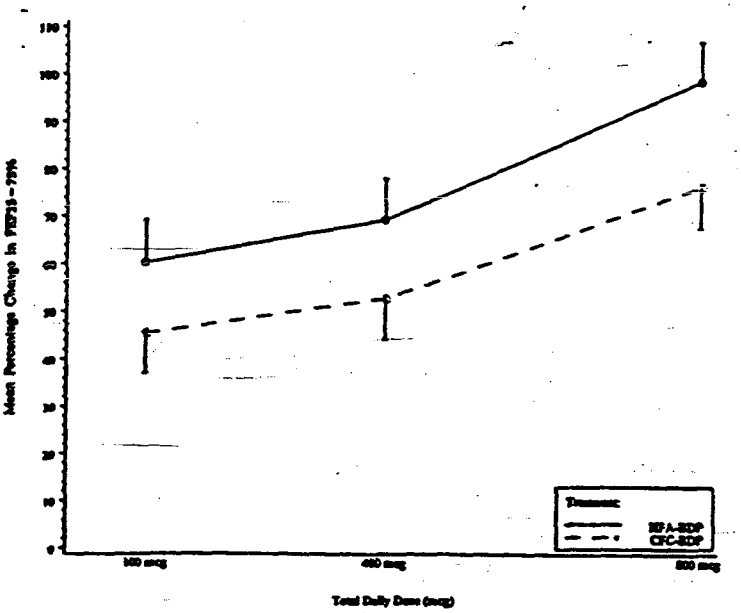
Table 11.4.1.2.1.B: **Analysis of Variance Results of the Percentage Change From Baseline in $FEF_{25-75\%}$ at Week 6 (Intent-to-Treat Analysis)**

-	Week 6 Summary Statistics	100 mcg/day	400 mcg/day	800 mcg/day
HFA-BDP	N	50	51	56
	Mean ± SE	60.43 ± 8.946	69.51 ± 8.739	98.91 ± 8.395
CFC-BDP	N	57	54	52
	Mean ± SE	45.63 ± 8.455	52.85 ± 8.677	76.69 ± 8.736

Anova Model	P-value
Product Effect	0.012
Dose Effect	<0.001
Product by Dose Interaction	0.905
HFA-BDP Treatment Comparisons	
Linear Trend	0.001
100 mcg/day versus average of 400 and 800 mcg/day	0.029
400 mcg/day versus 800 mcg/day	0.016
CFC-BDP Treatment Comparisons	
Linear Trend	0.010
100 mcg/day versus average of 400 and 800 mcg/day	0.068
400 mcg/day versus 800 mcg/day	0.054

P-values are based on an analysis of variance using a model that adjusts for product, dose, pooled center and their interaction terms

Figure 11.4.1.2.1.B: **Adjusted Mean Percentage Change From Baseline in $FEF_{25-75\%}$ and Standard Error by Dose Level at Week 6 (Intent-to-Treat Analysis**



* **mean percent change from baseline in FVC: The improvement in mean FVC was essentially the same for all doses of both BDP-HFA and BDP-CFC throughout the 6 weeks of study without any clinically significant difference between the response of any dose of either product , although there was a slight dose-response trend between 400 and 800 mcg/day of BDP-HFA, based on analysis of the ITT population (see figures 14.2.3.2, p396, v1.156 and 14.2.3.4, p399, v1.156 below)**

Figure 14.2.3.2
Adjusted Mean FVC (L)
by Week
(Patients Included in the Intent-to-treat Analysis)

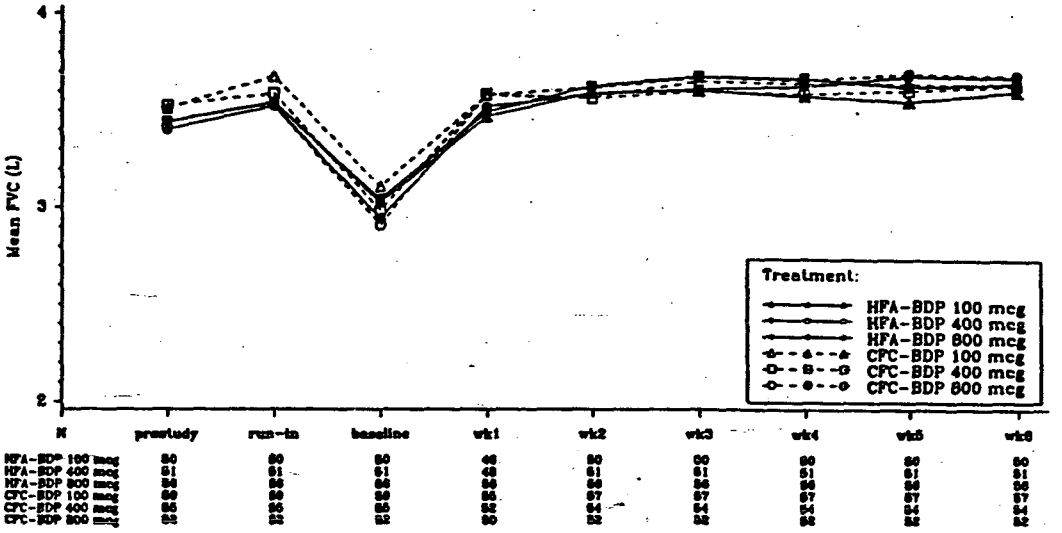
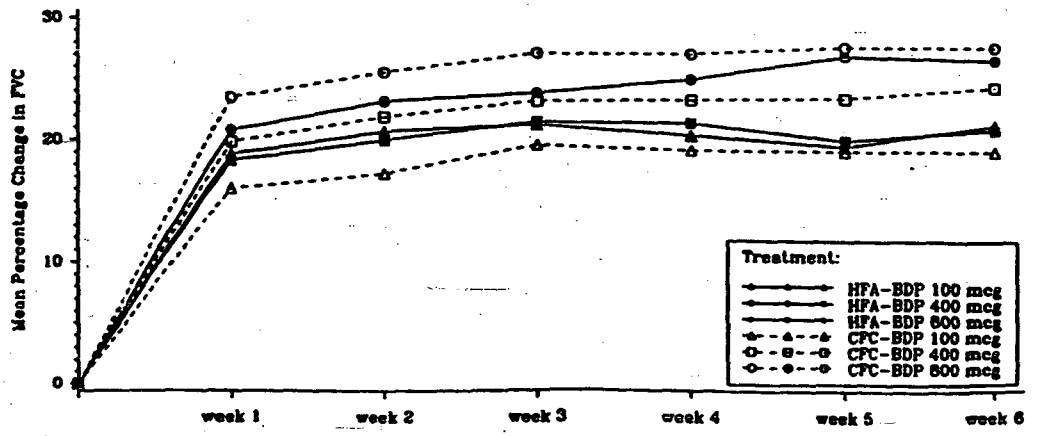


Figure 14.2.3.4
Adjusted Mean Percentage Change from Baseline in FVC
by Week
(Patients Included in the Intent-to-treat Analysis)



	week 1	week 2	week 3	week 4	week 5	week 6
N:HFA-BDP 100 mcg	46	50	50	50	50	50
N:HFA-BDP 400 mcg	48	51	51	51	51	51
N:HFA-BDP 800 mcg	56	56	56	56	56	56
N:CFC-BDP 100 mcg	55	57	57	57	57	57
N:CFC-BDP 400 mcg	62	64	64	64	64	64
N:CFC-BDP 800 mcg	50	52	52	52	52	52

* **mean AM PEF change from baseline: AM PEF was measured upon awakening in the morning. As with other pulmonary function parameters, there was a significant improvement in mean AM PEF after administration of both BDP-HFA and BDP-CFC, which was accomplished mainly after one week of treatment. While there was significantly more improvement after administration of 800 mcg/day of BDP-HFA as compared with the same dose of BDP-CFC, the response to 400 mcg/day of BDP-HFA was comparable to the response to 400 mcg/day of BDP-CFC (see figures below; fig 5.2.4.A, p119, v1.269; fig 11.4.1.5.1.B, p127, v1.156; tab11.4.1.5.1.A, p126, v1.156)**

Figure 5.2.4.A: 1192: Adjusted Mean Change from Baseline in Morning Peak Flow (L/min) by Week (Patients Included in the Intent-to-Treat Analysis)

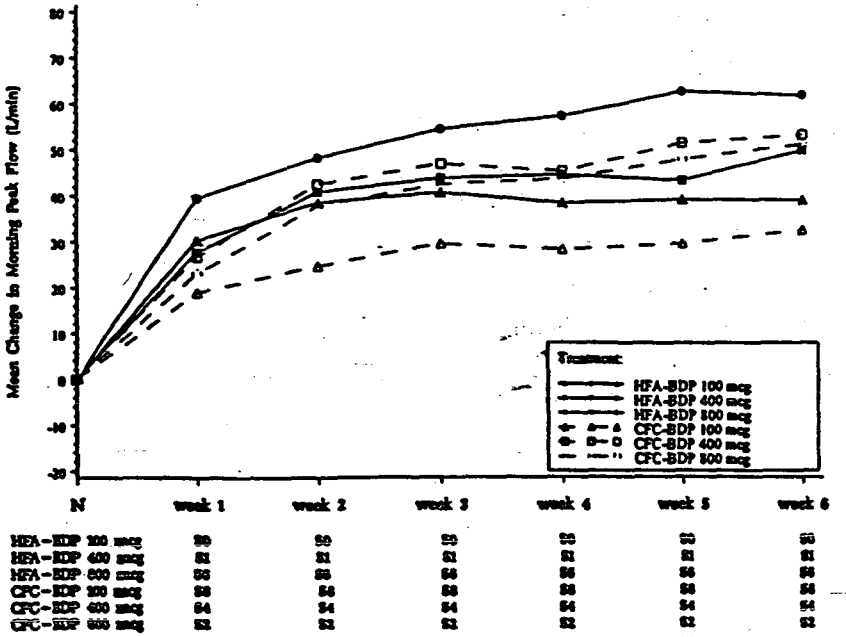


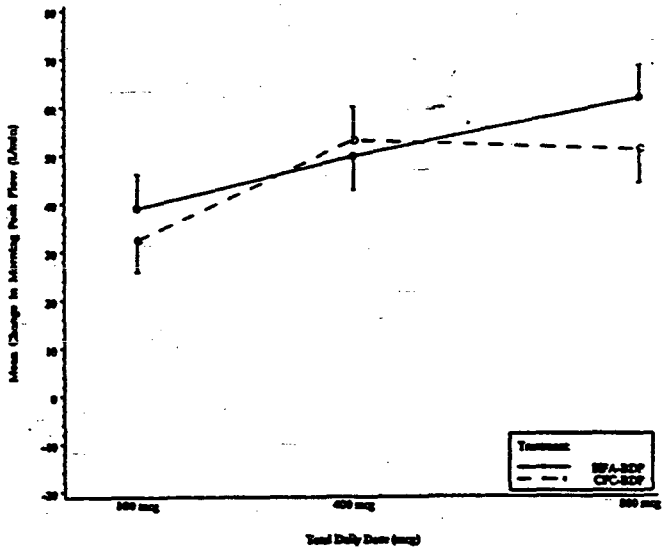
Table 11.4.1.5.1.A: **Analysis of Variance Results for the Change From Baseline in Morning Peak Flow at Week 6 (Intent-to-Treat Analysis)**

	Week 6 Summary Statistics	100 mcg/day	400 mcg/day	800 mcg/day
HFA-BDP	N	50	51	56
	Mean ± SE (L/min)	39.07 ± 7.148	49.85 ± 6.982	61.86 ± 6.708
CFC-BDP	N	58	54	52
	Mean ± SE (L/min)	32.50 ± 6.650	53.20 ± 6.933	51.20 ± 6.980

Anova Model	P-value
Product Effect	0.413
Dose Effect	0.008
Product by Dose Interaction	0.582
HFA-BDP Treatment Comparisons	
Linear Trend	0.021
100 mcg/day versus average of 400 and 800 mcg/day	0.053
400 mcg/day versus 800 mcg/day	0.216
CFC-BDP Treatment Comparisons	
Linear Trend	0.070
100 mcg/day versus average of 400 and 800 mcg/day	0.018
400 mcg/day versus 800 mcg/day	0.839

P-values are based on an analysis of variance using a model that adjusts for product, dose, pooled center and their interaction terms

Figure 11.4.1.5.1.B: **Adjusted Mean Change in Morning Peak Flow and Standard Error by Dose Level at Week 6 (Intent-to-Treat Analysis)**



* mean PM PEF change from baseline: PM PEF was measured upon retiring in the evening. No dose-response was demonstrated for either BDP-HFA or BDP-CFC based on either ITT or efficacy population analysis.

* individual patient improvement in FEV-1: The percent of patients who had a ≥ 12% improvement in FEV-1 and the percent of patients who had a ≥ 50% improvement in FEV-1 after 6 weeks of treatment with either BDP-HFA or BDP-CFC ("responders") can be seen in the table below (tab 5.2.2.2.A, p111, v1.269). There were a consistently greater percentage of patients who had a ≥ 12% improvement in FEV-1 from baseline as well as a consistently greater percentage of patients who had a ≥ 50% improvement in FEV-1 from baseline after receiving a given dose of BDP-HFA, as compared to the same dose given as BDP-CFC. The only exception to this trend was the percentage of patients who had a ≥ 12% improvement after 800 mcg/day of BDP-CFC, which was greater than the percentage of patients who had such an improvement after 800 mcg/day of BDP-HFA. It should be noted that mean data relating to change in pulmonary function which supports the sponsor's contention that only ½ the dose of BDP-CFC is needed to produce a comparable effect when administering BDP-HFA, can not be extrapolated to individual patient response.

Table 5.2.2.2.A: Percent of Patients with at Least a 12% or 50% Change from Baseline in FEV_1 at Week 6 (Patients Included in the Intent-to-Treat Analysis)

	Study 1192					
Response	HFA-BDP 100 mcg	HFA-BDP 400 mcg	HFA-BDP 800 mcg	CFC-BDP 100 mcg	CFC-BDP 400 mcg	CFC-BDP 800 mcg
≥12%	46/50 92.0%	49/51 96.1%	54/56 96.4%	45/57 78.9%	48/54 88.9%	51/52 98.1%
≥ 50%	14/50 28.0%	13/51 25.5%	25/56 44.6%	9/57 15.8%	11/54 20.4%	17/52 32.7%

✱ reversibility: mean percent reversibility varied between 43-47% in the BDP-HFA groups at baseline and between 39-46% in the BDP-CFC groups at baseline. After treatment for 6 weeks, mean reversibility was 18, 20, and 15% in the 100, 400, and 800 mcg/day BDP-HFA groups, respectively and 16, 23, and 13% in the 100, 400, and 800 mcg/day BDP-CFC groups, respectively, using the ITT analysis. No dose-response was seen in regard to this parameter and no significant difference was noted between the two drug products at any dose level.

OTHER EFFICACY PARAMETERS

✱ symptom scores: patients evaluated symptoms daily during the run-in period, the inhaled corticosteroid washout period, and during treatment. Asthma symptoms (wheezing, cough, shortness of breath and chest tightness) during the day were evaluated by patients when they took their evening dose of study drug, using a categorical scale as shown below.

0 = none
1 = present 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

◆ wheeze: The mean change in percent of days without wheezing by week can be seen in figure 11.4.1.7.1.1.A (p129, v1.156) below, and analysis of this data is presented in the table 11.4.1.7.1.1.A (p130, v1.156) and figure 11.4.1.7.1.1.B (p131, v1.156) below. There was no consistent dose-response demonstrated for either BDP-HFA or BDP-CFC, using either the ITT or the efficacy population for analysis. A greater amount of improvement was seen after administration of 400 mcg/day of BDP-CFC than after administration of 400

mcg/day of BDP-HFA or 800 mcg/day of BDP-CFC. Improvement, as was seen with pulmonary function, occurred primarily after the first week of treatment. There was no significant difference between drug products or across dose levels for either drug product in regard to mean change from baseline in wheeze score.

Figure 11.4.1.7.1.1.A: Adjusted Mean Percent of Days Without Wheeze by Week (Intent-to-Treat Analysis)

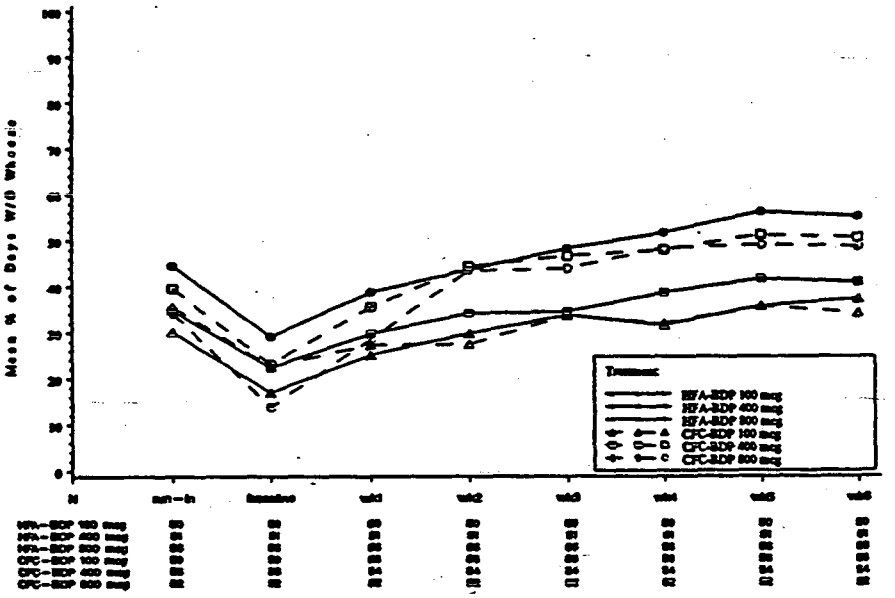


Figure 11.4.1.7.1.1.B: Adjusted Mean Percent of Days Without Wheeze and Standard Error by Dose Level at Week 6 (Intent-to-Treat Analysis)

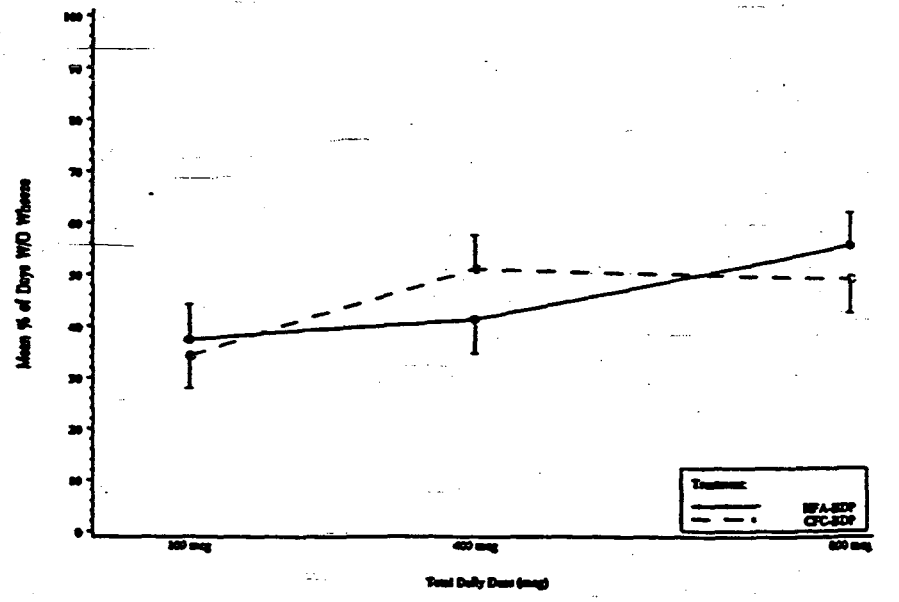


Table 11.4.1.7.1.1.A: Analysis of Variance Results for the Percent of Days Without Wheeze at Week 6 (Intent-to-Treat Analysis)

	Week 6 Summary Statistics	100 mcg/day	400 mcg/day	800 mcg/day
HFA-BDP	N	50	51	56
	Mean ± SE	37.40 ± 6.775	41.04 ± 6.618	55.36 ± 6.358
CFC-BDP	N	58	54	52
	Mean ± SE	34.29 ± 6.303	50.79 ± 6.571	48.83 ± 6.616
Anova Model			P-value	
Product Effect			0.994	
Dose Effect			0.044	
Product by Dose Interaction			0.426	
HFA-BDP Treatment Comparisons				
Linear Trend			0.048	
100 mcg/day versus average of 400 and 800 mcg/day			0.188	
400 mcg/day versus 800 mcg/day			0.120	
CFC-BDP Treatment Comparisons				
Linear Trend			0.138	
100 mcg/day versus average of 400 and 800 mcg/day			0.049	
400 mcg/day versus 800 mcg/day			0.833	
P-values are based on an analysis of variance using a model that adjusts for product, dose, pooled center and their interaction terms				

- cough: There was no consistently significant difference between BDP-HFA and BDP-CFC at any dose level and no consistently significant difference between doses of either drug product, using either the ITT population or the efficacy population, in regard to mean percent of days without cough or change in cough score.

- shortness of breath: There was no consistently significant difference between BDP-HFA and BDP-CFC at any dose level and no consistently significant difference between doses of either drug product, using either the ITT population or the efficacy population, in regard to mean percent of days without shortness of breath or change in shortness of breath score, compared to baseline.

- chest tightness: There was no consistently significant difference between BDP-HFA and BDP-CFC at any dose level and no consistently significant difference between doses of either drug product, using either the ITT population or the efficacy population, in regard to mean percent of days without chest tightness or change in chest tightness, compared to baseline.

- **sleep disturbance: There was no consistently significant difference between BDP-HFA and BDP-CFC at any dose level and no consistently significant difference between doses of either drug product, using either the ITT or the efficacy population, in regard to mean percent of days without sleep disturbance or change in sleep disturbance scores.**

- **beta agonist use: A linear dose-response was seen for BDP-CFC (p = 0.04), but not for BDP-HFA (p = 0.07), in terms of mean change in beta agonist use, using the ITT analysis, as well as the efficacy population analysis (p = 0.02 for both analyses). There was clinically significantly less use of inhaled beta agonists with all doses of both drug products, most notably with 800 mcg/day of BDP-HFA (see tables and figures below; tab 11.4.1.12.1.1.A, p141, v1.156; fig 5.2.6.A, p125, v1.269; fig 11.4.1.12.1.1.B, p 142, v1.156)**

Figure 5.2.6.A: 1192: Adjusted Mean Change from Baseline in Beta-Agonist Use by Week (Patients Included in the Intent-to-Treat Analysis)

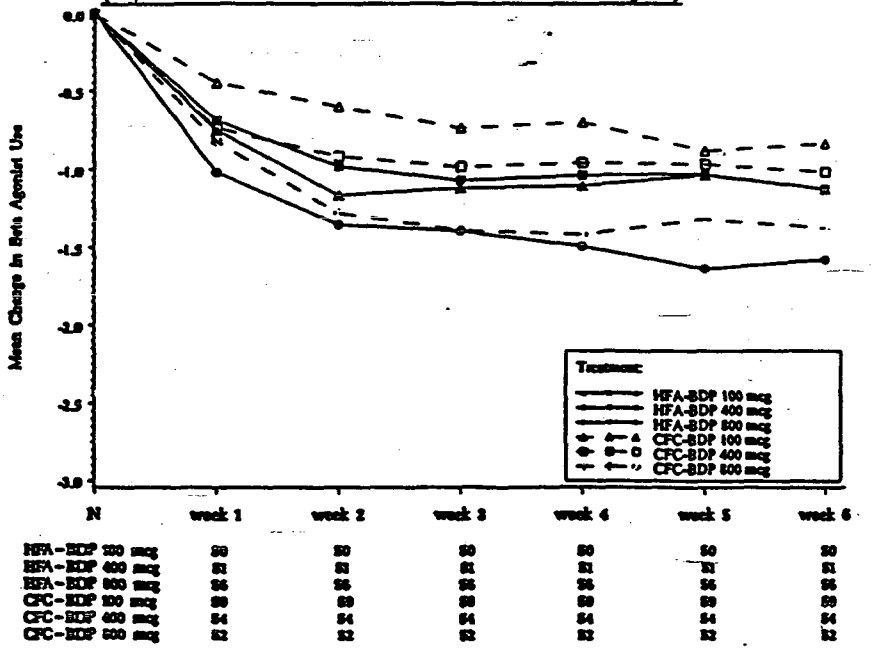


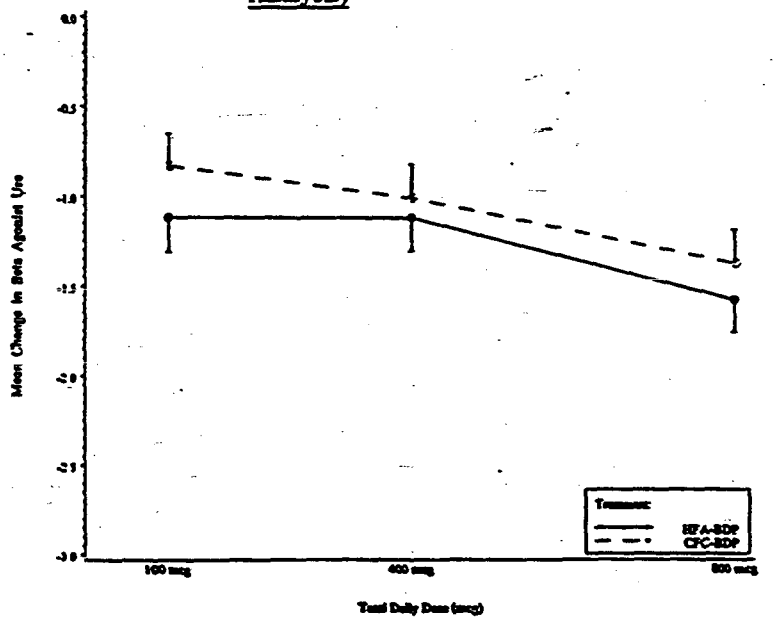
Table 11.4.1.12.1.1.A: Analysis of Variance Results for the Change From Baseline in the Number of Total Daily Beta-Agonist Uses at Week 6 (Intent-to-Treat Analysis)

	Week 6 Summary Statistics	100 mcg/day	400 mcg/day	800 mcg/day
HFA-BDP	N	50	51	56
	Mean ± SE	-1.12 ± 0.193	-1.12 ± 0.188	-1.57 ± 0.181
CFC-BDP	N	59	54	52
	Mean ± SE	-0.83 ± 0.177	-1.01 ± 0.187	-1.37 ± 0.188

Anova Model	P-value
Product Effect	0.185
Dose Effect	0.017
Product by Dose Interaction	0.891
HFA-BDP Treatment Comparisons	
Linear Trend	0.072
100 mcg/day versus average of 400 and 800 mcg/day	0.328
400 mcg/day versus 800 mcg/day	0.083
CFC-BDP Treatment Comparisons	
Linear Trend	0.036
100 mcg/day versus average of 400 and 800 mcg/day	0.105
400 mcg/day versus 800 mcg/day	0.176

P-values are based on an analysis of variance using a model that adjusts for product, dose, pooled center and their interaction terms

Figure 11.4.1.12.1.1.B: Adjusted Mean Change in Total Daily Beta-Agonist Uses and Standard Error by Dose Level at Week 6 (Intent-to-Treat Analysis)



☛ SAFETY FINDINGS

✱ exposure: There were 323 patients who had been randomized to study drug who were included in the safety evaluation. The vast majority of these patients were exposed for 29-42 days with the mean for all treatment groups being about 40 days.

✱ adverse events:

◆ total adverse events: at higher doses, there was slightly greater frequency of AEs in patients receiving BDP-HFA than in patients receiving BDP-CFC (see table below). This is not a clinically significant difference. There were no patients who developed oropharyngeal candidiasis based on visible lesions and culture of candida from the mouth/throat.

mcg/d	HFA	CFC
100	54%	58%
400	57%	55%
800	63%	56%

◆ asthmatic adverse events: Increased asthma symptoms (> one day of asthma symptoms) were more frequent in patients who received BDP-CFC, especially the 100 mcg/day dose (see table below). The clinical significance of this finding, if any, is unclear, although the 100 mcg/day dose of BDP-CFC was probably inadequate to control asthma in some patients who had previously received a dose of at least 400 mcg/day. Acute asthma (one day or less of asthma symptoms) and/or increased asthma symptoms were most prevalent in patients who received 100 mcg/day of BDP-CFC (10 patients compared to 2 patients who received 100 mcg/day of BDP-HFA). Patients were required to have been receiving 400 mcg/day of inhaled corticosteroid for entry into the study and then enter a corticosteroid withdrawal

phase where a fall in pulmonary function and worsening of symptoms was necessary for randomization. After randomization, 2 of the 6 treatment groups (100 mcg/day of BDP-HFA or BDP-CFC) received daily doses of inhaled corticosteroids that was less than they had previously received. Some degree of asthma worsening is, therefore, not unexpected.

propellant	acute asthma	increased asthma	both
BDP-HFA 100	1	2	0
BDP-HFA 400	0	0	1
BDP-HFA 800	2	0	0
BDP-CFC 100	3	7	1
BDP-CFC 400	0	3	0
BDP-CFC 800	1	3	0

- pharyngitis: At higher doses, more episodes of pharnygitis occurred in patients receiving BDP-HFA than in patients receiving BDP-CFC (see table below). This suggests that BDP-HFA has more of an irritative effect on the upper airways than does the CFC formulation. If so, the formulation could be more of an irritant or there could be more deposition of this drug product in the upper airway. In terms of the latter, lung deposition studies suggest that less of the HFA formulation is deposited in the upper airways.

propellant	100 mcg/d	400 mcg/d	800 mcg/d
HFA	4%	10%	27%
CFC	12%	9%	17%

- Based on AEs that occurred in 3% or greater of the patients in any treatment group, the table below includes those AEs that occurred more commonly in patients who received BDP-HFA than in patients who received BDP-CFC. With the exception of headache, the differences

- between the two formulations are small, not associated with a dose-response and unlikely to be of clinical significance. Headache, on the other hand occurred in a significant number of patients (but not unexpectedly high numbers for a clinical study), a greater number of patients receiving BDP-HFA and was associated with a dose-response. The clinical significance of this finding, if any, is unclear, although sinus headaches could be caused by irritation from the drug product.

	BDP-HFA			BDP-CFC		
Adverse event	100	400	800	100	400	800
"allergy"	6%	2%	None	2%	None	2%
Headache	12%	20%	25%	14%	11%	15%
Earache	None	2%	4%	None	None	None
Epistaxis	None	4%	None	None	None	None
Dysmenorr	2%	8%	None	None	None	2%
Coughing	4%	2%	5%	3%	4%	None
Abrasion	None	2%	4%	None	None	None

- severe adverse events: severe AEs in the BDP-HFA group included otitis media, rhinitis, URI, inhalation site sensation, leg cramps, arthralgia, salivary duct obstruction and laceration. There were more severe AEs in the BDP-CFC group than in the BDP-HFA group (see table below). The only serious AE occurred in a patient who received 100 mcg/day of BDP-CFC who was hospitalized with streptococcal pharyngitis, diffuse gastritis, and an upper GI bleed.

propellant	100 mcg/d	400 mcg/d	800 mcg/d
HFA	4	0	4
CFC	8	4	3

- adverse events possibly or probably related: At higher doses, there were more AEs considered to be possibly or probably related to BDP-HFA than to BDP-CFC (see

table below). The only specific AE that was more frequent in the BDP-HFA group was pharyngitis, which was seen in 1 BDP-HFA 400 mcg/day and 3 BDP-HFA 800 mcg/day patients, as compared to no patients who received BDP-CFC. Mild vertigo, that was considered possibly but unlikely related to BDP-HFA 800 mcg/day, was experienced by one patient intermittently for 22 days and resolved while the patient was being continued on the study drug.

dose (mcg/d)	HFA	CFC
100	10%	15%
400	8%	7%
800	13%	4%

◆ discontinuations due to adverse events: an AE as the primary cause for withdrawal from the study was seen in two BDP-HFA and 4 BDP-CFC patients. The two BDP-HFA patients had sinusitis and exacerbation of asthma and were receiving 100 mcg/day.

✱ laboratory tests: There were no clinically significant changes in laboratory tests in any patients who received BDP-HFA. In cases where there was a change in a laboratory parameter from normal to above the upper limit of the NRR or below the lower limit of the NRR after administration of BDP-HFA, similar changes were seen after administration of BDP-CFC or at baseline.

✱ vital signs: There were no clinically significant changes in vital signs in any patients who received BDP-HFA. In cases where there was a change in vital signs to above or below the normal reference range after administration of BDP-HFA, such a change was also seen after administration of BDP-CFC or the finding was seen at baseline.

- overall evaluation of efficacy and safety data and conclusions:

  - A minimal dose-response was seen after administration of BDP-HFA and BDP-CFC for 6 weeks, based on mean change from baseline in percent predicted FEV-1. The primary separation of effect between the three doses occurred after the first week of treatment, which is not unexpected given the design of the study. Subsequent to the first week of treatment, there was a flattening of the dose-response curve, and the difference in effect between the three doses of either drug product is of questionable clinical significance. Nevertheless, given the degree of improvement anticipated with an inhaled corticosteroid, the sponsor has adequately demonstrated a dose-response for BDP-HFA and BDP-CFC, across the dose range of BDP-HFA proposed for clinical use.

  - Although there was a consistently greater effect seen after administration of a given dose of BDP-HFA than after administration of the same dose of BDP-CFC, these differences were small and of questionable clinical significance. Nevertheless, some adjustment may be required when patients are switched from BDP-CFC to BDP-HFA because of the greater incidence of AEs with 800 mcg/day of BDP-HFA.

  - There was a clinically significant improvement in mean change from baseline in FEV-1 percent of predicted, percentage of patients with a 12% or greater improvement in FEV-1 (a majority of patients in all treatment groups) and 50% or greater improvement in FEV-1 (32% of all BDP-HFA treated patients), mean percent change in FEF 25-75 from baseline (99% improvement after 6 weeks treatment with 800 mcg/day of BDP-HFA), mean change from baseline in AM PEF, mean percent of wheeze-fee days and mean change from baseline in inhaled beta agonist use after administration of 100, 400, and 800 mcg/day of BDP-HFA.

  - No safety concerns about BDP-HFA were raised by the data from this study.

ABSTRACT

METHODS: Study 1129 was a parallel, modified blind, placebo-controlled (HFA placebo), multicenter, repetitive dose study in 347 adult patients (113-117 patients in each arm) who had mild-moderate asthma, many but not all of whom were receiving inhaled corticosteroids. After a 10-12 day period on 30 mg/day of prednisone, patients were randomized to receive 400 mcg/day of BDP-HFA (4 puffs bid), 800 mcg/day of BDP-CFC (8 puffs bid)(Beclovent) or HFA placebo for 12 weeks. Active drug was administered at a 50 mcg/puff concentration. The primary efficacy variable was mean change in AM PEF from the end of the prednisone treatment period to the end of 12 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, QOL assessment, and time to withdrawal because of asthma symptoms. 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.

There was a 10-12 day run-in period, following which patients were given 30 mg/day of prednisone for 10-12 days, off inhaled corticosteroids. Patients were then entered into a 12 week period of randomized treatment, during which they were evaluated in the clinic every 3 weeks. Baseline comparison of the treatment groups showed that they were comparable in terms of demographics, medication use, pulmonary function, and other criteria.

RESULTS: 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, over a period of 12 weeks. The separation of response between 400 mcg/day and 800 mcg/day occurred during the

first three weeks of treatment with essentially no further separation of effect throughout the 12 weeks of the study. While not unexpectedly, there was a small decrease in AM PEF after switching to 400 mcg/day of BDP-HFA or 800 mcg/day of BDP-CFC (slightly more with BDP-CFC), there was a statistically significant difference in decline of AM PEF after administration of either active treatment and administration of placebo. The same pattern of change was seen in regard to most other parameters evaluated. Differences in AEs and other safety parameters between BDP-HFA and placebo were minimal and not clinically significant.

DISCUSSION: BDP-HFA at a dose of 400 mcg/day and a concentration of 50 mcg/puff is efficacious when mild-moderate asthmatics are treated over a 12 week period.

The primary objective of this study, however, was to show that 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC were ——
This was not accomplished, since the study was not designed to demonstrate —— . The effectiveness of 400 mcg/day of BDP-HFA was consistently slightly greater, across a range of outcome variables, than 800 mcg/day of BDP-CFC, but this difference was not clinically significant.

The data obtained after administration of 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC is not inconsistent with 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 similar effect. This inconsistency probably reflects the unreliability and questionable clinical relevance of data from —— studies.

There was no concern about the safety of 400 mcg/day of BDP-HFA, based on the safety parameters evaluated in this study.

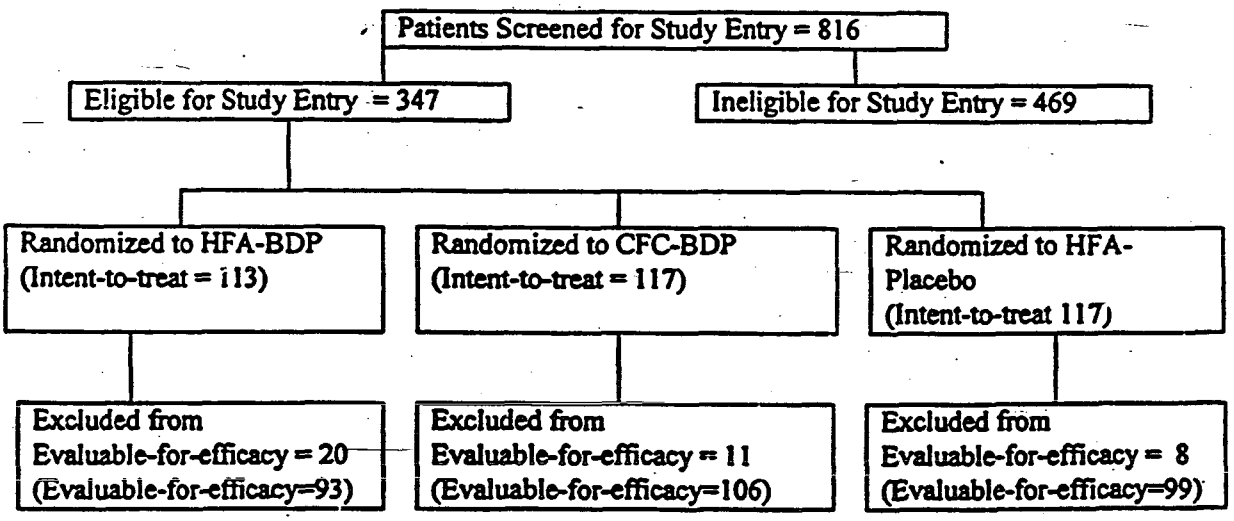
APPEARS THIS WAY
ON ORIGINAL

☎ study 1129

☛ The primary objective of this study was to determine if "equivalent" efficacy was demonstrated by 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC. Other objectives were to demonstrate that BDP was more effective than placebo in controlling asthma and assess the safety of BDP-HFA.

☛ number of patients: 816 patients were screened; 347 patients were randomized to treatment (113 received 400 mcg/day of BDP-HFA; 117 received 800 mcg/day of BDP-CFC; 117 received HFA placebo; 49 patients were excluded from the evaluable for efficacy analysis (efficacy population analysis), thereby leaving 298 patients in the efficacy analysis (see flow chart below); the number of patients at each center varied from 3 to 22; 61 (18%) of patients withdrew from the study prior to week 12, the majority in the placebo group.

Figure 1: PATIENT DISPOSITION-1129-BRON



☛ age range: 18-65 years of age

☛ patient population:

✱ "moderate-severe" symptomatic asthma of at least 3 months prior to admission to the study; AM PEF 50-85% predicted at

pre-prednisone baseline; use of inhaled beta agonists on a PRN basis; reversibility of 15% or more after 400 mcg of Maxair MDI.

- either no inhaled corticosteroids for at least 4 weeks or no more than 400 mcg/day of BDP-CFC at entry into study;

- demonstrated improvement after oral corticosteroids (at least a 15% improvement in AM PEF at least once during the last 3 days of oral corticosteroid treatment compared to the last 5 days of the run-in period); signs and symptoms of asthma during the last 5 days of the run-in period and a sleep disturbance score of 1 or more on 1 or more nights OR a daily asthma symptom score of 2 or more on 3 or more days for one or more symptoms AND/OR use of inhaled beta agonist on the average of at least twice daily.

- current non-smokers

☛ study design: parallel, modified blind, placebo-controlled (HFA placebo), multicenter (27 center) study; patients knew that they were receiving either 4 or 8 puffs bid but did not know whether it was active drug or placebo

☛ drug administration: use of spacers was not allowed during the study

- 400 mcg/day of BDP-HFA 50 mcg/puff concentration (4 puffs bid)(lot 3600)

- 800 mcg/day of BDP-CFC 50 mcg/puff concentration (8 puffs bid)(Beclovent)(lot 94-019)

- HFA placebo in MDI adapter identical in appearance to BDP-HFA MDI (4 puffs bid)(lot 940324) or HFA placebo in MDI adapter identical in appearance to BDP-CFC (8 puffs bid)(lot 940401)