ADVERSE EVENTS

✦ adverse events: Of AEs that occurred in 3% or more of patients in either treatment group, those that occurred with a 2% or greater incidence in the BDP-HFA group than in the CFC group can be seen in the table below. AEs that occurred with both drug products but are consistent with a systemic corticosteroid effect included: depression, insomnia, dysmenorrhea, and purpura. There were also adverse events consistent with a local effect from the administration of an inhaled drug, i.e. dysphonia, other respiratory symptoms.

Adverse event	BDP-HFA	BDP-CFC
Fatigue	14 (4%)	1 (1%)
Abdominal pain	26 (7%)	4 (3%)
Strain	12 (3%)	1 (1%)
URIs	135 (38%)	43 (36%)
Sinusitis	64 (18%)	14 (12%)

✦ severe adverse events: There were 59 patients (17%) in the BDP-HFA group and 27 patients (23%) in the BDP-CFC group who experienced a severe AE. The most frequent severe AEs in the BDP-HFA group were headache (4%) and increased asthma symptoms (3)%. By contrast, 3% of the BDP-CFC group experienced headache, upper respiratory infection and increased asthma symptoms that was classified as severe. A dose-response trend was not seen for either BDP-HFA or BDP-CFC in terms of severe AEs, with most occurring at lower daily doses.

✦ adverse events possibly or probably related to the study drug: There were 59 patients (17%) in the BDP-HFA group who had an AE that was considered possibly or probably related to drug administration, as compared with 24 patients (20%) in the BDP-CFC group. There was a dose-response trend for both treatment groups for this type of AE. In the BDP-HFA group, the most frequent AEs considered possibly or probably related to the study drug were application site disorders (7%)(dysphonia, inhalation site sensation, inhalation taste

sensation) and respiratory system disorders (8%)(increased asthma symptoms, pharyngitis). By contrast, 6% and 13% of the BDP-CFC group had application site disorders (dysphonia, inhalation site sensation) and respiratory system disorders (bronchitis, pharyngitis), respectively, that were considered possibly or probably related to the study drug.

✦ <u>adverse events occurring in the 8 weeks after switch</u>: In the first 4 weeks after switching from BDP-CFC to BDP-HFA, there were more dysphonia, inhalation site sensation, inhalation taste and sinusitis in the group that received BDP-HFA (see table below, tab 12.2.2.5.A, p277, update).

Table 12.2.2.5.A: Summary of Respiratory and Application Site Adverse Events by Time on Study Drug Following the Switch from CFC to HFA: Number (%) of Patients With at Least One Report of an Adverse Event

[1 of 2 pages]

ADVERSE EVENT	TREATMENT	CFC-BDP Run-in No. (%)	Weeks 1-2 No. (%)	Weeks 3-4 No. (%)	Weeks 5-6 No. (%)	Weeks 7-8 No. (%)
No. of Patients at Risk[a]	HFA-BDP	354	354	349	343	336
	CFC-BDP	119	119	118	116	113
Acute Asthma Episode	HFA-BDP	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
	CFC-BDP	2 (1.7)	1 (0.8)	0 (0.0)	1 (0.9)	0 (0.0)
Bronchitis	HFA-BDP	3 (0.8)	5 (1.4)	8 (2.3)	9 (2.6)	6 (1.8)
	CFC-BDP	2 (1.7)	3 (2.5)	3 (2.5)	2 (1.8)	4 (3.5)
Coughing	HFA-BDP	0 (0.0)	1 (0.3)	1 (0.3)	3 (0.9)	2 (0.6)
	CFC-BDP	0 (0.0)	0 (0.0)	1 (0.8)	2 (1.7)	2 (1.8)
Expectoration	HFA-BDP	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
	CFC-BDP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Increased Asthma Symptoms	HFA-BDP	3 (0.8)	8 (2.3)	12 (3.4)	14 (4.1)	16 (4.8)
	CFC-BDP	1 (0.8)	5 (4.2)	4 (3.4)	3 (2.6)	3 (2.7)
Inhalation Administration-Dysphonia	HFA-BDP	2 (0.6)	5 (1.4)	6 (1.7)	6 (1.7)	4 (1.2)
	CFC-BDP	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Inhalation Administration-Increased Asthma Symptoms	HFA-BDP	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
	CFC-BDP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No. of Patients at Risk[a]	HFA-BDP	354	354	349	343	336
	CFC-BDP	119	119	118	116	113
Inhalation Site Sensation	HFA-BDP	0 (0.0)	4 (1.1)	5 (1.4)	4 (1.2)	2 (0.6)
	CFC-BDP	0 (0.0)	1 (0.8)	1 (0.8)	1 (0.9)	1 (0.9)
Inhalation Taste Sensation	HFA-BDP	0 (0.0)	5 (1.4)	4 (1.1)	3 (0.9)	4 (1.2)
	CFC-BDP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngitis	HFA-BDP	6 (1.7)	13 (3.7)	17 (4.9)	12 (3.5)	11 (3.3)
	CFC-BDP	3 (2.5)	8 (6.7)	7 (5.9)	6 (5.2)	2 (1.8)
Pleurisy	HFA-BDP	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
	CFC-BDP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory Disorder	HFA-BDP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
	CFC-BDP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis	HFA-BDP	13 (3.7)	23 (6.5)	27 (7.7)	20 (5.8)	24 (7.1)
	CFC-BDP	6 (5.0)	7 (5.9)	9 (7.6)	9 (7.8)	8 (7.1)
Sinusitis	HFA-BDP	1 (0.3)	9 (2.5)	15 (4.3)[b,c]	10 (2.9)	4 (1.2)
	CFC-BDP	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.9)
Upper Respiratory Tract Infection	HFA-BDP	11 (3.1)	21 (5.9)	29 (8.3)	29 (8.5)	20 (6.0)
	CFC-BDP	3 (2.5)	7 (5.9)	9 (7.6)	7 (6.0)[c]	9 (8.0)

[a] Number of patients at risk is the number of patients on study drug during the interval.
[b] P-value ≤0.05 (between-treatment comparison is based a blocked-Wilcoxon test, stratified by country).
[c] P-value ≤0.05 (between-treatment comparison of the change from run-in is based on a blocked-Wilcoxon test, stratified by country).

✦ <u>time to occurrence of first asthma exacerbation</u>: The time to occurrence of such events was slightly later in patients receiving BDP-HFA (see table below; tab 12.2.2.6.A, p279, update). There were 60 BDP-HFA patients (17%) and 27 BDP-CFC patients (23%) who had one or more asthma exacerbations (see tables below; tabs 12.2.4.A and B, p284, update).

Figure 12.2.2.6.A: Time to Onset of First Occurrence of Acute Asthma Episode or Increased Asthma Symptoms

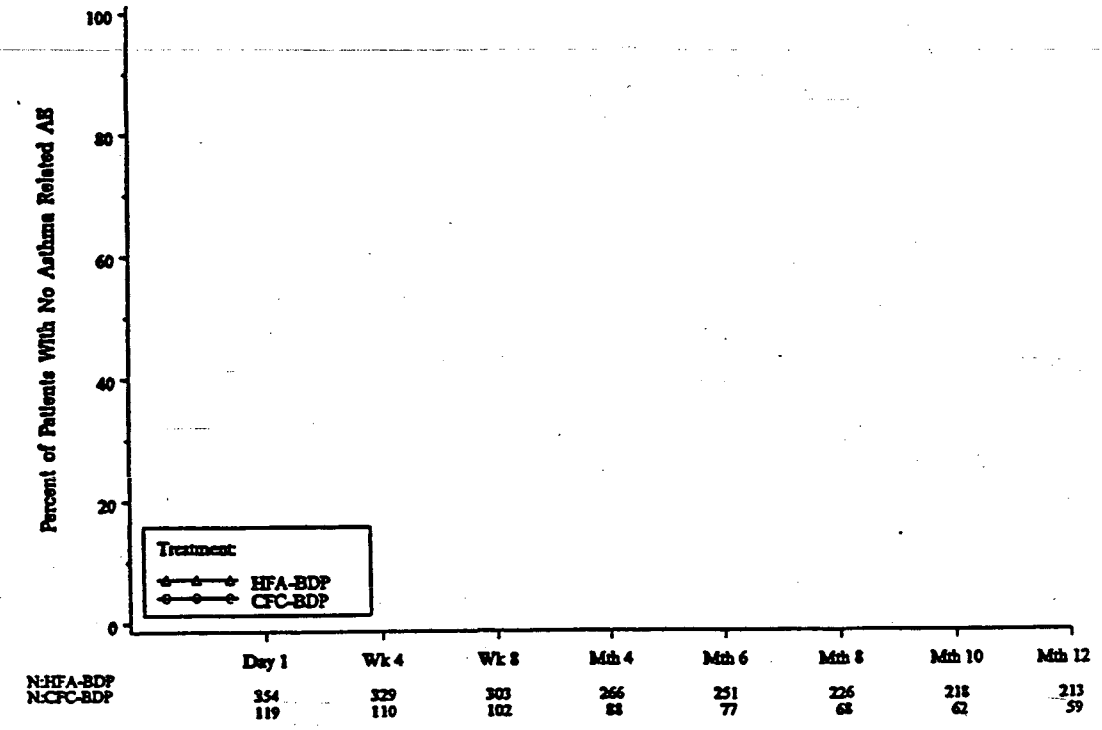


Table 12.2.4.A: Number (%) of Patients Who Experienced an Asthma Exacerbation by Initial Dose Groups of HFA-BDP

Number of Asthma Exacerbations	HFA-BDP ≤200 mcg N=182 No. (%)	HFA-BDP >200-400 mcg N=66 No. (%)	HFA-BDP >400-800 mcg N=106 No. (%)	Total N=354 No. (%)
0	157 (86.3)	47 (71.2)	90 (84.9)	294 (83.1)
1	20 (11.0)	10 (15.2)	11 (10.4)	41 (11.6)
2	4 (2.2)	7 (10.6)	2 (1.9)	13 (3.7)
3	0 (0.0)	1 (1.5)	3 (2.8)	4 (1.1)
4	1 (0.5)	1 (1.5)	0 (0.0)	2 (0.6)

Table 12.2.4.B: Number (%) of Patients Who Experienced an Asthma Exacerbation by Initial Dose Groups of CFC-BDP

Number of Asthma Exacerbations	CFA-BDP ≤500 mcg N=64 No. (%)	CFA-BDP >500-1000 mcg N=49 No. (%)	CFA-BDP >1000-1600 mcg N=6 No. (%)	Total N=119 No. (%)
0	53 (82.8)	35 (71.4)	4 (66.7)	92 (77.3)
1	8 (12.5)	9 (18.4)	2 (33.3)	19 (16.0)
2	1 (1.6)	2 (4.1)	0 (0.0)	3 (2.5)
3	1 (1.6)	2 (4.1)	0 (0.0)	3 (2.5)
4	1 (1.6)	1 (2.0)	0 (0.0)	2 (1.7)

- withdrawals due to adverse events: There were 6 BDP-HFA and 1 BDP-CFC patients who were withdrawn because of adverse events. The AEs causing withdrawal in the BDP-HFA group were rash, cerebrovascular disorder, abdominal pain, vomiting and asthenia, inhalation site sensation and edema associated with myalgia. The rash, vomiting, inhalation site sensation, and edema with myalgia were considered possibly/probably related to BDP-HFA and were considered mild-moderate in severity. There were also 7 patients from the BDP-HFA group who withdrew from the study because of asthma symptoms, as compared to none of the BDP-CFC group. Characteristics of these patients can be seen in the table below (tab 12.2.3.B, p283, update).

Table 12.2.3.B: Patients Withdrawn Due to Increased Asthma Symptoms

Center/ Patient ID	Age/ Sex	Race	Treatment and Dose at Time of Discontinuation	Reason for Withdrawal	Study Medication Start Date (dd/mm/yr)	Days on Study Drug Until Discontinuation
10/105	47/F	Caucasian	HFA-BDP 500 mcg/day	Asthma exacerbation requiring IV steroids	25/09/95	116
23/105	64/F	Caucasian	HFA-BDP 300 mcg/day	Pt. felt symptoms were worse than before	27/07/95	78
33/101	42/M	Caucasian	HFA-BDP 600 mcg/day	Cough and dyspnea	20/05/96	53
35/103	44/M	Caucasian	HFA-BDP 800 mcg/day	Asthma exacerbation	20/05/96	148
50/101	64/M	Caucasian	HFA-BDP 800 mcg/day	Asthma exacerbation x 2	27/03/96	280
52/101	59/M	Caucasian	HFA-BDP 600 mcg/day	Three exacerbations of asthma requiring oral steroids	16/04/96	49
54/201	46/F	Caucasian	HFA-BDP 600 mcg/day	Asthma exacerbation due to respiratory tract infection	20/03/96	31

- oropharyngeal candidiasis: There were no patients in either treatment group who had an oropharyngeal AE and candida growth exceeding normal flora.

- serious adverse events: There were 17 patients who received BDP-HFA and 8 patients who received BDP-CFC who had a serious AE, none of which were considered to be related to the study drug. One patient receiving 800 mcg/day of BDP-HFA developed dyspnea possibly related to weight gain and "changing hormone levels"

LABORATORY TESTS

- There were 12 patients who had abnormal LFTs at some point in the study. Two of these patients were withdrawn from the study with adenocarcinoma of the common bile duct and hepatitis. Abnormalities in bilirubin were attributed to Gilbert's Disease. Three patients in each treatment group had abnormally high liver enzymes at baseline and should not have been entered into the study. One patient on BDP-HFA developed elevation in liver enzymes only after 12 months of treatment, without any reason given and returned to normal in 10 days.

HPA AXIS EVALUATION

- Only in the BDP-CFC 1000-1600 mcg/day group was there a decrease in mean plasma cortisol levels, that was seen from month 8 onwards (see table below; tab 12.4.1.B, p297, update).

Table 12.4.1.B: Mean Percent Change from Baseline in Plasma Cortisol (nmol/L) by Study Visit and Initial Dose Groups

STUDY VISIT		HFA-BDP ≥200 mcg	HFA-BDP >200-400 mcg	HFA-BDP >400-800 mcg	CFC-BDP ≤500 mcg	CFC-BDP >500-1000 mcg	CFC-BDP >1000-1600 mcg
Baseline	Mean	444.8	440.6	393.0	410.3	425.1	484.1
	SE	19.71	25.15	17.93	25.16	34.16	143.58
	N	180	66	104	64	49	5
% Change from Baseline at Month 2	Mean	4.5	22.2	10.9	19.0	17.9	34.4
	SE	3.25	8.98	4.80	7.35	10.26	21.25
	N	158	59	81	58	43	5
% Change from Baseline at Month 4	Mean	10.9	20.8	17.0	8.0	4.4	43.7
	SE	4.48	10.93	5.71	5.40	6.53	19.56
	N	165	61	82	56	42	5
% Change from Baseline at Month 8	Mean	16.7	9.2	19.2	19.2	25.4	-9.5
	SE	6.53	6.14	8.29	11.30	12.48	24.75
	N	76	27	48	29	27	2
% Change from Baseline at Month 12	Mean	12.2	21.9	8.2	36.4	10.6	-21.2
	SE	4.87	12.82	6.97	14.33	8.16	7.43
	N	144	52	67	53	34	4
% Change from Baseline at Last Visit	Mean	8.8	19.4	3.9	40.9	8.1	-4.9
	SE	4.23	10.36	5.42	12.98	6.32	17.36
	N	176	65	94	62	47	5

There were no clinically significant differences at any time point in the percent of patients in the two treatment groups that had plasma cortisol levels outside the NRR (see table below; tab12.4.1.C, p298, update).

Table 12.4.1.C: Number (%) of Patients with Plasma Cortisol Levels Outside Normal Limits by Visit

STUDY VISIT	HFA-BDP				CFC-BDP			
	N	Below N (%)	Within N (%)	Above N (%)	N	Below N (%)	Within N (%)	Above N (%)
Baseline	350	15 (4.3)	288 (82.3)	47 (13.4)	118	3 (2.5)	96 (81.4)	19 (16.1)
Month 2	302	14 (4.6)	243 (80.5)	45 (14.9)	107	4 (3.7)	81 (75.7)	22 (20.6)
Month 4	311	14 (4.5)	244 (78.5)	53 (17.0)	104	6 (5.8)	85 (81.7)	13 (12.5)
Month 8	152	2 (1.3)	120 (79.0)	30 (19.7)	59	5 (8.5)	40 (67.8)	14 (23.7)
Month 12	266	16 (6.0)	209 (78.6)	41 (15.4)	92	3 (3.3)	77 (83.7)	12 (13.0)
Last Visit	339	18 (5.3)	268 (79.1)	53 (15.6)	115	4 (3.5)	94 (81.7)	17 (14.8)

✦ ACTH stimulation test:

✱ a normal response was defined as: 1) a pre-injection cortisol level of 138 nmol/L or greater; 2) an incremental value of 193 nmol/L or greater; and 3) a peak value of 496.8 nmol/L or greater. An abnormal response was defined as a failure to meet any 2 of these criteria. The mean pre-injection cortisol levels, as well as mean incremental increase, and mean peak cortisol values following ACTH administration can be seen in the table below.

✱ There was less of an mean cortisol incremental decrease in the BDP-HFA than in the BDP-CFC group. In fact, the change from baseline after treatment for 2 months was significantly different (p = 0.03), with the BDP-HFA group having a decrease of 10 nmol/L, as compared to the BDP-CFC group which had a decrease of 108 nmol/L. The BDP-HFA group also had a greater increase in mean peak cortisol, and there was a 73 nmol/L decrease seen in the BDP-CFC group after 12 months of treatment, compared to an increase of 3 nmol/L in the BDP-HFA group.

✱ The number of patients who had an abnormal cosyntropin response was greater in the BDP-HFA group, except at the last visit. Of these patients, 6 were receiving 500 mcg/day or less of BDP-HFA and the one patient was receiving 200 mcg/day. These differences were small and probably not clinically significant (see table below tab 12.4.2.A, p300, update).

ACTH (COSYNTROPIN) STIMULATION TESTING

MEAN PRE-INJECTION CORTISOL VALUES (nmol/L)

Parameter	BDP-HFA	BDP-CFC
Pre-study	442	507
Baseline	432	496
Month 2	463	612
Month 4	488	575
Month 12	462	510

MEAN INCREMENT CORTISOL VALUE (nmol/L)

Parameter	BDP-HFA	BDP-CFC
Pre-study	474	332
Baseline	445	422
Month 2	435 (- 10)	314 (- 108)
Month 4	417 (- 28)	370 (- 52)
Month 12	422 (- 23)	362 (- 60)

MEAN PEAK CORTISOL VALUE (nmol/L)

Parameter	BDP-HFA	BDP-CFC
Pre-study	922	847
Baseline	876	933
Month 2	898 (+ 22)	938 (+ 5)
Month 4	897 (+ 21)	945 (+ 12)
Month 12	879 (+ 3)	860 (- 73)

* **The only patient who had a consistently abnormal response also had an abnormal response at baseline (see table below; tab 12.4.2.B, p301, update). Only 4 patients who received 800 mcg/day of BDP-HFA had ACTH stimulation testing both prior to and following randomization, so that an analysis of this high dose BDP-HFA group could not be made.**

Table 12.4.2.A: Number of Patients[a] with an Abnormal[b] Response to Cosyntropin by Treatment

STUDY VISIT	HFA-BDP No. (%)	CFC-BDP No. (%)	P-value[c]
Baseline	3/138 (2.2)	0/45 (0.0)	1.000
Month 2	3/127 (2.4)	0/42 (0.0)	0.575
Month 4	3/128 (2.3)	0/43 (0.0)	0.573
Month 12	1/110 (0.9)	0/35 (0.0)	1.000
Last Visit	1/138 (0.7)	1/45 (2.2)	0.432

[a] Based on patients with tests at baseline and at least one visit after randomization to treatment.
[b] Patient did not meet two of the three criteria and therefore did not have a normal response to the rapid cosyntropin test.
[c] The p-value for the overall treatment comparison is based on a two-sided Fisher's Exact test.

Table 12.4.2.B: Patients With an Abnormal[a] Response to Cosyntropin (nmol/L) by Dose of HFA-BDP

Site/Pt. ID	Dose of HFA-BDP	Cosyntropin (nmol/L) Response by Visit					
		Values	Baseline	Month 2	Month 4	Month 12	Last Visit
7/101	200 mcg	Pre-injection	372.6	Visit <53 days	361.6	Test Not	361.6
		Increment	-85.6	after	499.5	Performed	499.5
		Peak	287.0	randomization[b]	861.1		861.1
7/110	200 mcg	Pre-injection	113.2	179.4	93.8	27.9	27.9
		Increment	361.5	469.2	455.4	513.1	513.1
		Peak	474.7	648.6	549.2	541.0	541.0
8/108	200 mcg	Pre-injection	289.8	300.8	27.9	245.6	245.6
		Increment	276.0	452.7	96.3	452.7	452.7
		Peak	565.8	753.5	124.2	698.3	698.3
11/104	200 mcg	Pre-injection	127.0	124.2	300.8	182.2	182.2
		Increment	198.7	207.0	190.5	182.1	182.1
		Peak	325.7	331.2	491.3	364.3	364.3
3/107	300 mcg	Pre-injection	416.8	436.1	491.3	529.9	529.9
		Increment	557.5	-96.6	505.1	347.8	347.8
		Peak	974.3	339.5	996.4	877.7	877.7
11/102	500 mcg	Pre-injection	314.6	292.6	33.1	529.9	529.9
		Increment	375.4	309.1	391.9	347.8	347.8
		Peak	690.0	601.7	425.0	877.7	877.7
28/102	600 mcg	Pre-injection	254.6	22.3	Visit >134 days	Patient	374.4
		Increment	748.2	272.5	after	discontinued	408.4
		Peak	1002.8	294.8	randomization[c]	prior to month 12	782.8

[a] Failure to meet two of three criteria required for normal response. The abnormal responses for each patient are presented in boldface type.
[b] This visit was outside the window (53 to 67 days) for month 2.
[c] This visit was outside the window (106 to 134 days) for month 4.

✦ serum osteocalcin: There were no clinically significant differences between the two groups in regard to the change from baseline in serum osteocalcin (see table below; tab 12.4.3.A, p304, update).

Table 12.4.3.A: Adjusted Mean Change From Baseline in Serum Osteocalcin (ng/mL) by Study Visit (Age ≥21 years)[a]

STUDY VISIT		HFA-BDP	CFC-BDP	95% C.I. of HFA-BDP - CFC-BDP	P-value
Baseline	Mean	1.99	1.96	-0.323 - 0.387	0.860
	SE	0.092	0.16		
	N	304	101		
Change from Baseline at Month 2	Mean	0.05	-0.00	-0.247 - 0.355	0.724
	SE	0.080	0.131		
	N	249	87		
Change from Baseline at Month 4	Mean	-0.09	-0.05	-0.360 - 0.277	0.799
	SE	0.082	0.140		
	N	259	87		
Change from Baseline at Month 8	Mean	-0.07	0.03	-0.605 - 0.399	
	SE	0.142	0.211		0.686
	N	125	50		
Change from Baseline at Month 12	Mean	-0.12	-0.14	-0.440 - 0.471	0.946
	SE	0.12	0.198		
	N	223	77		
Change from Baseline at Last Visit	Mean	-0.18	-0.22	-0.348 - 0.441	0.816
	SE	0.102	0.173		
	N	294	97		

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

✦ pregnancy: During the 12 months of the study, 8 patients became pregnant, 6 of whom were receiving BDP-HFA. The outcome for patients who became pregnant while taking BDP are noted below in the table (tab12.4.7.A, p307, update).

Table 12.4.7.A: Summary of Outcome for Patients Who Became Pregnant While Receiving Study Drug

Site/Pt. ID	Drug Start Date	Drug Stop Date	Randomized Drug/ Total Daily Dose	Total Exposure (mg)	Outcome
4/113	11/12/95	26/04/96	HFA-BDP 200 mcg	27.4	Normal pregnancy, labor, and delivery: 6.8 lb male; no infant abnormalities
4/123	13/03/96	03/02/97	HFA-BDP, 200 mcg	65.4	Normal pregnancy, labor, and delivery: 5.5 lb female; no infant abnormalities
15/106	12/02/96	13/06/96	HFA-BDP, 200 mcg	24.4	Pregnancy terminated - fetus had Dandy Walker Cyst syndrome (history of same in 1993).
16/107	20/09/95	08/01/96	HFA-BDP, 200 mcg	30.2	Miscarriage approx. 25/01/96
16/116	02/11/95	26/03/96	HFA-BDP, 200 mcg	29.0	Normal pregnancy, labor, and delivery: 8 lb female; no infant abnormalities
45/201	09/07/96	04/07/97	HFA-BDP, 800 mcg	288	Pregnancy terminated
13/103	02/08/95	24/02/96	CFC-BDP, 400 mcg	82.4	Gestational diabetes; nausea. C-section - 3.84 lb female; no infant abnormalities
56/103	14/06/96	10/12/96	CFC-BDP, 1000 mcg	179	Unknown

VITAL SIGNS: No significant changes were seen in vital signs in either the BDP-HFA or the BDP-CFC group.

ECGs: No significant changes were seen in ECGs in either treatment group.

☎ overall evaluation of efficacy and safety data and conclusions:

☛ The database from this study is adequate (n = 288) to support a claim for the safety of BDP-HFA. Only 110 BDP-HFA patients, receiving different doses and concentrations of the drug product, were evaluated in regard to response to cosyntropin, which an acceptable number. However, of the patients who received 800 mcg/day of BDP-HFA, only 5 were studied in response to ACTH stimulation, which is not adequate to support the safety of this dose in terms of adrenal effect. Although there are no safety concerns raised by any of the safety parameters evaluated, there were more patients in the BDP-HFA group who were withdrawn from the study because of adverse events and more patients in this group who had serious adverse events. Nevertheless, it is the lack of adequate data relating to the effect of the 800 mcg/day dose of BDP-HFA on the HPA axis, that makes it difficult to conclude that safety of BDP-HFA has been demonstrated in this study across the dose range proposed for the marketed product.

☛ The sponsor has not provided appropriate data, based on the data from the first 8 weeks of the study, to conclude

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

SAFETY
s-1

Integrated Summary of Safety (ISS):

- 24 studies to assess safety; 20 included in ISS; only serious AEs were included in ISS from 4 ongoing studies (see tables below)(tab2A-F, p23-29, v1.271 and tab3A, p32,v1.271);

- 2293 patients:

  - 1403 received BDP-HFA
    - 125 received single doses
    - 184 received for 4 weeks or less
    - 740 received for 6-12 weeks
    - 354 received for 1 year
  - 337 received placebo HFA
  - 41 received oral BDP
  - 682 received BDP-CFC
  - 17 received placebo CFC

- key studies (6): 1081, 1083, 1192, 1129, 1130 and 1163 ☛ 1902 pts

- repetitive dose studies of 6-12 weeks: 5 studies;

  - BDP-HFA ☛ 740 patients
  - placebo HFA ☛ 289 patients
  - BDP-CFC ☛ 400 patients
  - BDP-HFA 50 mcg/puff concentration ☛ 353 patients
  - BDP-HFA 100 mcg/puff concentration ☛ 387 patients
    (see tab5.1.1.C, p79, v1.271 below)

  - subset: pooled studies (1081, 1192, 1129): recommended dose range, mild-severe asthma, HFA placebo and CFC-BDP controlled studies

- long term study of 12 months duration: study 1163; see tabs5.1.3.B and C, pgs83-84, v1.271 below in regard to dose and concentration related to duration of administration.

☛ supporting studies (14) ☛ 392 pts

✷ single dose studies: 6 studies; one study with healthy volunteers

✦ study 1006: assessment of bronchospasm

✷ repetitive dose studies of 4 weeks or less: 8 studies; two studies with healthy volunteers

✷ doses of 100-2800 mcg/day of BDP-HFA

Table 2.A: Single Dose Studies: 1069, 1070, 1075, 1152, 1191, 1006
[1 of 2 pages]

Protocol # Principal Investigator	Completion Status (Dates)	Location (No. sites)	Study Design	Treatment	Total Daily Dosage	No. Pts Randomized/ Treatment / Total	Treatment Duration	Age Range (Mean)	No. M/F (W/B/O)	Full Report/Data Listings Location	CRF Location
1069 W. Howland	Complete (4/94-10/94)	US (1)	Phase I, open-label, randomized, cross-over design	HFA-BDP$_{200}$ HFA-BDP$_{800}$ *Oral BDP* *0.2 mg* *0.5 mg* *1 mg* *2 mg* *5 mg*	200 mcg 800 mcg *0.2 mg* *0.5 mg* *1 mg* *2 mg* *5 mg*	20 20 *8* *8* *8* *9* *8* 41[a]	single dose	18-49 (27)	33/8 (36/5/0)	V1.24 p.1/ V1.25 p.349	V1.477 p.245
1070 J. Doane	Complete (10/93-1/94)	US (1)	Phase I, DB, randomized, cross-over design	HFA-BDP$_{50}$ HFA-BDP$_{800}$ HFA-BDP$_{1600}$	400 mcg 800 mcg 1600 mcg	13 14 14 15[a]	single dose	19-50 (33)	9/6 (13/2/0)	V1.27 p.1/ V1.28 p.270	none
1075 W. Howland	Complete (5/94-11/94)	US (1)	Phase I, open-label, randomized, cross-over design	HFA-BDP$_{50}$ CFC-BDP$_{50}$	200 mcg 400 mcg *400 mcg*	26 23 *24* 27[a]	single dose	19-49 (31)	20/7 (26/1/0)	V1.29 p.1/ V1.33 p.246	none
1152 R. Boudreau	Complete (12/94-5/95)	US (1)	Phase II, open-label, crossover design, pilot study	HFA-BDP$_{50}$ HFA-BDP$_{100}$ CFC-BDP$_{50}$ CFC-BDP$_{250}$	1 to 3 puffs	12 12 6 *12* 12[a]	single dose	25-50 (34)	12/0 (12/0/0)	V1.44 p.1/ V1.45 p.116	none
Protocol # Principal Investigator	**Completion Status (Dates)**	**Location (No. sites)**	**Study Design**	**Treatment**	**Total Daily Dosage**	**No. Pts Randomized/ Treatment / Total**	**Treatment Duration**	**Age Range (Mean)**	**No. M/F (W/B/O)**	**Full Report/Data Listings Location**	**CRF Location**
1191 R. Boudreau	Complete (11/95-12/95)	US (1)	Phase II, open-label, randomized, cross-over design	HFA-BDP$_{50}$	1 puff	16 16	single dose	18-52 (33)	5/11 (15/1/0)	V1.46 p.1/ V1.46 p.218	none
1006 J. Ayres	Complete (1/93-4/93)	UK (1)	Phase I, SB, randomized, cross-over design	HFA-BDP$_{250}$ CFC-BDP$_{250}$ HFA-Placebo CFC-Placebo	8 puffs of each treatment	16 *16* 17 17 18[a]	single dose	19-68 (47)	2/16 (16/1/1)	V1.50 p.1/ V1.50 p.81	none

M/F=Male/Female W/B/O= White/ Black/ Other DB=Double-blind SB=Single-blind

[a] Due to the crossover design and patient discontinuations, the number of patients randomized will not equal the total.

Table 2.B: **Multiple Dose Studies ≤ 4 weeks: 1162, 1025, 1063, 1064, 1084, 1155, 1211, 1030**

[1 of 2 pages]

Protocol # Principal Investigator	Completion Status (Dates)	Location (No. sites)	Study Design	Treatment	Total Daily Dosage	No. Pts Randomized/ Treatment / Total	Treatment Duration	Age Range (Mean)	No. M/F (W/B/O)	Full Report/ Data Listings Location	CRF Location
1162 R. Dockhorn	Complete (8/95-12/95)	US (1)	Phase II, dose-level blind, randomized, parallel design	HFA-BDP$_{80}$ *CFC-BDP$_{80}$* HFA-Placebo	200 mcg 400 mcg 800 mcg *800 mcg* 16 puffs	9 9 8 *8* 9 43	14 days	18-60 (30)	35/8 (29/13/1)	V1.51 p.1/ V1.54 p.191	V1.492 p.227
1025 J. Riddell	Complete (8/92-8/92)	UK (1)	Phase I, dose-level blind, randomized, parallel design	HFA-BDP$_{200}$ *CFC-BDP$_{200}$*	1200 mcg 2000 mcg 2800 mcg *1500 mcg* *2500 mcg* *3500 mcg*	7 8 7 *7* *7* *7* 43	10 days	19-52 (27)	43/0 (43/0/0)	V1.42 p.1/ V1.42 p.177	V1.477 p.1
1063 J. Riddell	Complete (3/93-3/93)	UK (1)	Phase I, dose-level blind, randomized, parallel design	HFA-BDP$_{80}$ *CFC-BDP$_{80}$*	1200 mcg 2000 mcg 2800 mcg *1200 mcg* *2000 mcg* *2800 mcg*	6 6 6 *6* *6* *6* 36	10 days	18-47 (27)	36/0 (36/0/0)	V1.43 p.1/ V1.43 p.132	none
1064 R. Dockhorn	Complete (7/93-8/93)	US (1)	Phase II, DB, randomized parallel design	HFA-BDP$_{80}$ HFA-BDP$_{800}$ HFA-Placebo	200 mcg 800 mcg 1600 mcg 8 puffs	6 9 6 6 27	14 days	18-58 (30)	22/5 (22/4/1)	V1.58 p.1/ V1.58 p.191	none

Protocol # Principal Investigator	Completion Status (Dates)	Location No. sites (Total/Active)[a]	Study Design	Treatment	Total Daily Dosage	No. Pts Randomized/ Treatment / Total	Treatment Duration	Age Range (Mean)	No. M/F (W/B/O)	Full Report/ Data Listings Location	CRF Location
1084 B. O'Connor	Complete (10/93-2/95)	UK (1)	Phase II, DB, randomized, parallel design	HFA-BDP$_{80}$ HFA-BDP$_{200}$ HFA-Placebo	300 mcg 1200 mcg 6 puffs	9 9 9 27	14 days	19-37 (26)	14/13 (26/1/0)	V1.60 p.1/ V1.60 p.274	none
1155 R. Ahrens	Complete (2/95-8/96)	US (1)	Phase II, DB, randomized, cross-over design	HFA-BDP$_{80}$ HFA-BDP$_{800}$	100 mcg 800 mcg	12 12 12	21 days	19-39 (27)	7/5 (12/0/0)	V1.62 p.1/ V1.67 p.399	V1.492
1211 R. Dockhorn	Complete (11/95-12/95)	US (1)	Phase I, open-label	HFA-Placebo	16 puffs	7 7	14 days	20-70 (40)	5/2 (5/2/0)	V1.42 p.1/ V1.47 p.147	none
1030 R. Diehl	Complete (2/93-11/93)	Denmark Norway (2/2)	Phase II, DB, DD, cross-over design	HFA-BDP$_{80}$ *CFC-BDP$_{80}$*	200mcg 300mcg 400mcg 500mcg 600mcg *200mcg* *300mcg* *400mcg* *500mcg* *600mcg*	6 11 34 11 5 *6* *12* *32* *11* *4* 68[b]	4 weeks	19-68 (49)	59/9 (68/0/0)	V1.262 p.1/ V1.263 p.1	V1.477 p.51

M/F=Male/Female W/B/O= White/ Black/Other DB=Double-blind DD=Double Dummy

[a] Total includes all sites which were sent study drug. Active includes only sites that screened patients.

[b] Due to the crossover design and patient discontinuations, the number of patients randomized will not equal the total. Refer to the individual Sponsor's Study report for details.

Table 2.C: Multiple Dose Studies of 6 or 12 Weeks: 1081, 1083, 1192, 1129, 1130

Protocol # Principal Investigator	Completion Status (Dates)	Location No. sites (Total/Active)*	Study Design	Treatment	Total Daily Dosage	No. Pts Randomized/ Treatment / Total	Treatment Duration	Age Range (Mean)	No. M/F (W/B/O)	Full Report/ Data Listings Location	CRF Location
1081 F. Hampel, — J. Guerin	Complete US (5/95-12/95) France (12/94-12/95)	US (21/20) France (22/11)	Phase III, modified-blind, randomized, parallel design	HFA-BDP 50 HFA-BDP 100 HFA-Placebo	100 mcg 200 mcg 2 or 4 puffs	91 92 87 270	6 weeks	18-74 (34)	117/153 (252/14/4)	VI.70 p.1/ VI.74 p.1	VI.478 p.1
1083 H. Matthys	Complete (11/94-9/95)	Germany, Poland, Slovakia (29/20)	Phase III, DB, DD, randomized, parallel design	HFA-BDP 50 HFA-BDP 100 HFA-Placebo	400 mcg 400 mcg 8 puffs	83 88 85 256	6 weeks	18-67 (40)	129/127 (254/0/2)	VI.92 p.1/ VI.95 p.181	VI.479 p.1
1192 W. Busse	Complete (2/96-12/96)	US (25/25)	Phase III, modified-blind, randomized, parallel design	HFA-BDP 50 *CFC-BDP 50*	100 mcg 400 mcg 800 mcg *100 mcg* *400 mcg* *800 mcg*	50 51 56 *59* *55* *52* 323	6 weeks	18-79 (37)	117/206 (283/39/1)	VI.156 p.1/ VI.162 p.41	VI.495 p.1
1129 G. Gross	Complete (7/94 - 6/95)	US (27/27)	Phase III, modified - blind, randomized, parallel design	HFA-BDP 50 *CFC-BDP 50* HFA-Placebo	400 mcg *800 mcg* 8 or 16 puffs	113 *117* 117 347	12 weeks	18-65 (34)	162/185 (312/27/8)	VI.114 p.1/ VI.118 p.1	VI.480 p.1
1130 R. Davies	Complete (7/94-11/95)	UK (37/31)	Phase III, DB, DD, randomized, parallel design	HFA-BDP 250 *CFC-BDP 250*	800 mcg *1500 mcg*	116 *117* 233	12 weeks	18-65 (40)	102/131 (231/1/1)	VI.192 p.1/ VI.196 p.1	VI.490 p.1

M/F=Male/Female W/B/O= White /Black /Other DB=Double-blind DD=Double-dummy

*Total includes all sites which were sent study drug. Active includes only sites that screened patients.

Table 2.D: Long Term Study: 1163

Protocol # Principal Investigator	Completion Status (Dates)	Location No. sites (Total/Active)*	Study Design	Treatment	Total Daily Dosage	No. Pts Randomized/ Treatment / Total	Treatment Duration	Age Range (Mean)	No. M/F (W/B/O)	Full Report/ Data Listings Location	CRF Location
1163[b] R. Cohen, —	Ongoing (6/95-currently ongoing)	US (25/24) UK (20/18) Belgium/ Netherlands (15/15)	Phase III, open-label, randomized, parallel design	HFA-BDP 50 HFA-BDP 100 *CFC-BDP 50* *CFC-BDP 100* *CFC-BDP 250*	1/2 previous CFC dose 200-800 mcg *Current CFC dose* *400-1600 mcg*	354 *119* 473	12 months	12-68 (40)	192/280 (441/20/11)	VI.221 p.1/ VI.225 p.36	VI.493 p.1

M/F=Male/Female W/B/O= White /Black /Other DB=Double-blind DD=Double-dummy

*Total includes all sites which were sent study drug. Active includes only sites that screened patients.

[b]In study 1163, 473 patients were randomized. At this time, the case report form for one patient who withdrew immediately following randomization is not available. No data postrandomization are available for this patient. Therefore, all summaries for Study 1163 will be based on 472 patients.

Table 2.E: Ongoing IND Study: —

Protocol # Principal Investigator	Completion Status (Dates)	Location No. sites (Total/Active)*	Study Design	Treatment	Total Daily Dosage	No. Pts Randomized/ Treatment / Total	Treatment Duration	Age Range (Mean)	No. M/F (W/B/O)	Full Report/ Data Listings Location	CRF Location
— D. Tashkin	Ongoing (12/96-currently ongoing)	US (1)	Phase IIIb, DB, DD, randomized, parallel design	HFA-BDP 50 *CFC-BDP 50*	200mcg *200mcg*	[redacted]	4 weeks	[redacted]	[redacted]	[redacted]	[redacted]

M/F=Male/Female W/B/O= White /Black /Other DB=Double-blind DD=Double-dummy

*Total includes all sites which were sent study drug. Active includes only sites that screened patients.

Table 2.F: Ongoing Foreign non-IND Studies:

Protocol # Principal Investigator	Completion Status (Dates)	Location No. sites (Total/Active)*	Study Design	Treatment	Total Daily Dosage	No. Pts Randomized/ Treatment Total	Treatment Duration	Age Range (Mean)	No. M/F (W/B/O)	Full Report/ Data Listings Location	CRF Location
J. Garrett	Ongoing (1/95-currently ongoing)	Australia/ New Zealand (4/4)	Phase II, DB, DD, dose reduction, parallel design	HFA-BDP_{100} CFC-BDP_{100}	Dose reduce from 800-1200 mcg/day by 200 mcg every 3 weeks until loss of asthma control occurs		variable, dose reduction every 3 weeks				
H. Matthys	Ongoing (3/96-currently ongoing)	Germany (1)	Phase II, DB, DD, randomized, parallel design	HFA-BDP_{100} CFC-*Budesonide* $_{200}$	400 mcg 800 mcg		6 weeks				
A.J. Fairfax	Ongoing (7/97-currently ongoing)	UK & Ireland (30)	Phase IIIb, DB, DD, randomized, parallel design	HFA-BDP_{50} CFC-*Fluticasone* $_{25}$	400 mcg 400 mcg		6 weeks				

M/F=Male/Female W/B/O= White /Black /Other DB=Double-blind DD=Double-dummy
*Total includes all sites which were sent study drug. Active includes only sites that screened patients.

Table 3.A: Partitioning of the Integrated Safety Database

Analysis	Single Dose Studies	Multiple Dose Studies ≤ 4 weeks	Multiple Dose Studies 6 or 12 Weeks	Multiple Dose Studies Pooled For Labeling	Long Term Study
	1069, 1070, 1075, 1152, 1191, 1006	1162, 1025, 1063, 1064, 1084, 1155, 1211, 1030	1081, 1083, 1192, 1129, 1130	1081, 1192, 1129	1163
Extent of Exposure	P	P	P	P	I
Demographics and Baseline Characteristics	P	P	P	P	I
Baseline Lung Function	--	--	P	P	I
General Medical History	--	--	P	P	I
Drug Therapy History	--	--	P	P	I
Concomitant Medication	--	--	P	P	I
Acute Tolerance	I (1006)				
Adverse Events	P	P	P	P	I
Discontinuations	P	P	P	P	I
Candidiasis			P	P	I
24-Hour UFC					
• Mean % Change from Baseline		I (1025, 1063, 1162)			
• % of Patients Below the Reference Range		P (1025, 1063, 1162) I (1064)			
Morning Plasma Cortisol					
• Mean % Change from Baseline		I (1025, 1162)	I (1129, 1130)		I
• % of Patients Below the Reference Range		I (1025, 1162)	P (1129, 1130)		I
ACTH Stimulation Test		I (1162)			I
Serum Osteocalcin					
• Mean Change from Baseline		I (1064, 1162)	I (1129, 1130)		I
• % of Patients Below the Reference Range		I (1064, 1162)	P (1129, 1130)		I
24-Hour Urinary Hydroxyproline		I (1064)			
Clinical Laboratory Tests	--	P	P	P	I
Vital Signs	--	P	P	P	I
Physical Exams - Medical Review	--	--	I (1081, 1083, 1192, 1129, 1130)	I (1081, 1129, 1192)	I
ECGs - Medical Review	--	--	I (1083, 1129, 1130)	I (1129)	I

Note: I = Individual Study P = Pooled Studies -- = Data was collected, but analyses were not performed for this Integrated Summary of Safety.
Shaded areas indicate that the data was not collected for the corresponding group of studies.

Table 5.1.1.C: **1081, 1083, 1192, 1129, and 1130: Summary of Number (%) of Patients Exposed to HFA-BDP by Inhaler Strength and Duration of Exposure for the Multiple Dose Studies of 6 or 12 Weeks[a]**

Duration of Exposure	Inhaler Strength	HFA-BDP
Number (%) of Patients	Total	740 (100%)
	50 mcg	353 (48%)
	100 mcg	387 (52%)
<2 Weeks (1-14 days)	50 mcg	10 (1%)
	100 mcg	9 (1%)
2-4 Weeks (15-28 days)	50 mcg	5 (<1%)
	100 mcg	6 (<1%)
4-6 Weeks (29-42 days)	50 mcg	191 (26%)
	100 mcg	93 (13%)
6-8 Weeks (43-56 days)	50 mcg	41 (6%)
	100 mcg	164 (22%)
8-10 Weeks (57-70 days)	50 mcg	5 (<1%)
	100 mcg	6 (<1%)
10-12 Weeks (71-84 days)	50 mcg	56 (8%)
	100 mcg	40 (5%)
12-14 Weeks (85-98 days)	50 mcg	45 (6%)
	100 mcg	67 (9%)
14-18 Weeks (99-126 days)	50 mcg	0 (0%)
	100 mcg	2 (<1%)

[a] Percentages are based on the total number of patients randomized to HFA-BDP.

Table 5.1.3.B: **1163: Summary of Number of Patients Exposed to Study Treatment by Dose, Duration of Exposure and Sex for the Long Term Study**

Treatment Group	Total Daily Dose (mcg)	No. of Patients Exposed to Dose		Total No. of Exposures		Total No. of Weeks of Exposure		Median Weeks of Exposure	
		Female	Male	Female	Male	Female	Male	Female	Male
HFA-BDP	200	125	60	135	71	3280.0	1573.6	28.3	28.0
	300	30	12	30	14	585.4	214.1	27.9	17.3
	400	30	29	32	31	466.0	601.1	13	27.9
	500	7	1	7	1	107.8	11.7	11.6	11.7
	600	33	55	34	57	746.5	1341.8	28.2	28.6
	800	11	16	11	16	273.5	318.1	29.1	28.1
CFC-BDP	400	38	18	44	18	986.6	430.2	28.4	28.1
	500	6	3	8	3	153.5	88.4	28.5	30.1
	600	12	5	13	6	260.8	96.3	27.9	13.9
	800	7	3	9	3	131.4	63.2	16.3	20.1
	900	1	0	1	0	0.1	0	0.1	0
	1000	21	11	23	11	513.4	304.5	28.1	29.1
	1200	3	0	3	0	56.1	0	27.6	0
	1500	2	3	2	3	28.5	92.2	14.3	30.1
	1600	0	1	0	1	0	6.6	0	6.6
	2250[a]	1	0	1	0	0.4	0	0.4	0

[a] The protocol specified an upper dose limit of 1600 mcg. This dose of 2250 mcg was a departure from protocol.

Table 5.1.3.C: — Summary of Number (%) of Patients Exposed to HFA-BDP by Inhaler Strength and Duration of Exposure for the Long Term Study[a]

Duration of Exposure	Inhaler Strength	HFA-BDP
Number (%) of Patients	Total	354 (100%)
	Unknown[b]	18 (5%)
	50 mcg	207 (58%)
	100 mcg	129 (36%)
<2 Weeks (1 - 14 days)	50 mcg	1 (<1%)
	100 mcg	2 (<1%)
2-4 Weeks (15-28 days)	50 mcg	1 (<1%)
	100 mcg	4 (1%)
4-6 Weeks (29-42 days)	50 mcg	2 (<1%)
	100 mcg	4 (1%)
6-8 Weeks (43-56 days)	50 mcg	1 (<1%)
	100 mcg	3 (<1%)
8-10 Weeks (57-70 days)	50 mcg	1 (<1%)
	100 mcg	1 (<1%)
10-12 Weeks (71-84 days)	50 mcg	2 (<1%)
	100 mcg	0 (0%)
12-14 Weeks (85-98 days)	50 mcg	0 (0%)
	100 mcg	0 (0%)
14-18 Weeks (99-126 days)	50 mcg	5 (1%)
	100 mcg	0 (0%)
18-22 Weeks (127-154 days)	50 mcg	4 (1%)
	100 mcg	1 (<1%)
22-26 Weeks (155-182 days)	50 mcg	1 (<1%)
	100 mcg	1 (<1%)
26-30 Weeks (183-210 days)	50 mcg	149 (42%)
	100 mcg	75 (21%)
30-34 Weeks (211-238 days)	50 mcg	40 (11%)
	100 mcg	36 (10%)
34-38 Weeks (239-266 days)	50 mcg	0 (0%)
	100 mcg	2 (<1%)

[a] Percentages are based on the total number of patients randomized to HFA-BDP.
[b] Because of outstanding data queries, information regarding strength of inhaler is unknown for some patients at the time of this Integrated Summary of Safety.

O Study 1006: acute tolerance of BDP-HFA in patients receiving dry powder budesonide by inhalation in a four period crossover study. Each patient (N = 16) received 8 puffs of BDP-HFA 200 mcg/puff (1600 mcg), placebo HFA, BDP-CFC 250 mcg/puff (2000 mcg) and placebo CFC. Mean percentage change FEV-1 from baseline (pre-dose) was assessed 2, 10, 20, 40 and 60 minutes after drug administration. Cough counts were measured during and for one minute after drug administration.

Mean change in FEV-1 over the period of assessment was small, with a maximum fall of 4.3% 2 minutes after inhalation of placebo HFA. The mean fall in FEV-1 was significantly greater 2 and 10 minutes after administration of HFA placebo than after administration of BDP-HFA, BDP-CFC or CFC placebo. With this exception, mean change in FEV-1 was comparable for the treatment groups. Cough counts were high for all treatment groups, and generally comparable, although higher in the BDP-CFC and CFC placebo groups than in the BDP-HFA and HFA placebo groups (see tabs 7.A. and B. p110, v1.271 below).

CONCLUSION: BDP-HFA is no more likely to produce an irritative response in the airways than is BDP-CFC.

Table 7.A: 1006: Mean Percent Change from Pre-Dose in FEV_1 Over Time

Post-Dose Assessment Time in Minutes		HFA-BDP N=16	CFC-BDP N=16	HFA-Placebo N=16	CFC-Placebo N=16
2	Mean	-0.9	-1.0	-4.2	-1.3
	SE	1.7	1.7	1.7	1.7
10	Mean	-1.0	0.2	-4.3	-0.6
	SE	2.0	2.0	2.0	2.0
20	Mean	-0.5	-0.1	-0.2	-2.5
	SE	2.0	2.0	2.0	2.0
40	Mean	-0.8	-1.9	-1.9	-1.2
	SE	1.5	1.5	1.5	1.5
60	Mean	2.5	-1.0	-0.8	-0.7[a]
	SE	1.6	1.6	1.6	1.8

[a] Two CFC-placebo treated patients did not have an FEV_1 measured at 60 minutes post-dose, one due to investigator error (patient #110), the other due to cough (patient #113).

Table 7.B: 1006: Cough Counts

Cough Counts	HFA-BDP N=16	CFC-BDP N=16	HFA-Placebo N=16	CFC-Placebo N=16	P-value[a]
Mean [b]	5	8	4	8	0.061
SE	0.63	0.71	0.47	0.68	

[a] The p-value is based on the overall test of treatment from an ANOVA model for a four-period cross-over.
[b] In order to adjust for the transformation back from square roots to the original scale, an adjustment of $[S^2(n-1)]/n$ was added to the means.

☎ ADVERSE EVENTS

➸ single dose studies

BDP-HFA – 48%
BDP-CFC – 35%
HFA placebo – 24%
CFC placebo – 35%
Oral BDP – 56%

acute asthma episode

BDP-HFA – 22%
BDP-CFC – 15%
Oral BDP – 29%

Coughing

BDP-HFA – 2%
BDP-CXC – 4%
HFA placebo – 12%
CFC placebo – 24%
Oral BDP – none

➸ multiple dose studies 4 weeks or less

BDP-HFA – 45%
BDP-CFC – 38%
HFA placebo – 48%

inhalation administration-cough

BDP-HFA – 1%
BDP-CFC – none
HFA placebo – 13% *

* one study; severe asthmatics; 8 puffs bid X 14 days

→ studies of 6-12 weeks (table 8.3.1.A, p117, v1.271 on p s-10a)

BDP-HFA – 46%; 11% possibly/probably related
BDP-CFC – 59%; 16% possibly/probably related
HFA placebo – 51% 10% possibly/probably related

In regard to AEs occurring ≥ 3%, there was no greater incidence of any type of AE after administration of BDP-HFA than after administration of BDP-CFC and/or HFA placebo. The incidence of severe AEs was significantly less in the group which received BDP-HFA than the group which received HFA placebo ($p = 0.005$) and the BDP-CFC group ($p = 0.12$). The incidence of severe AEs was not dose-dependent.

Increased asthma symptoms were reported by 8% of patients who received BDP-CFC as compared to only 3% of patients who received BDP-HFA. Of patients who received 100 mcg/day of BDP-CFC and BDP-HFA, the incidence of increased asthma symptoms was 14% and 2% respectively. This could reflect greater deposition of BDP-HFA in the lower respiratory tract as suggested by lung deposition studies with better control of asthma symptoms as a result.

Rhinitis symptoms were significantly greater in the BDP-CFC group (8%) than in the BDP-HFA group (5%) possibly due to greater systemic effect with BDp-HFA.

Dysphonia was less in the BDP-HFA group (< 1%) than in the BDP-CFC group (3%), possibly due to the smaller particle size of the BDP-HFA formulation with less deposition in the upper respiratory tract. There was more dysphonia, that was considered to be possibly/probably related to drug administration, seen in the BDP-HFA group than in the BDP-CFC group, but less possibly/probably related "inhalation site sensation" seen in the BDP-HFA group than in the BDP-CFC group. Less of both types of AEs was seen in patients who received HFA placebo.

Table 8.3.1.A: 1081, 1083, 1192, 1129, an 1130: Most Frequently Reported (≥3% in Any Treatment Group) or Statistically Significant Adverse Events in the Multiple Dose Studies of 6 or 12 Weeks

Adverse Events	HFA-BDP N=740	CFC-BDP N=400	HFA-Placebo N=289	Overall N=1429	Overall P-Value[a]
Number (%) of Patients Reporting at Least One Adverse Event	340 (46%)[b]	237 (59%)[d]	146 (51%)	723 (51%)	<0.001
Application Site Disorders	59 (8%)[b]	47 (12%)[d]	13 (4%)	119 (8%)	0.003
Inhalation Administration - Dysphonia	22 (3%)	11 (3%)	4 (1%)	37 (3%)	0.377
Inhalation Administration - Increased Asthma Symptoms	1 (<1%)[b]	5 (1%)	1 (<1%)	7 (<1%)	0.026
Inhalation Site Sensation	27 (4%)	23 (6%)[d]	5 (2%)	55 (4%)	0.022
Body as a Whole - General Disorders	46 (6%)	39 (10%)	16 (6%)	101 (7%)	0.052
Back Pain	10 (1%)	12 (3%)	4 (1%)	26 (2%)	0.132
Pain	13 (2%)	12 (3%)[d]	1 (<1%)	26 (2%)	0.028
Central & Peripheral Nervous System Disorders	101 (14%)	68 (17%)	38 (13%)	207 (14%)	0.250
Dysphonia	5 (<1%)[b]	11 (3%)	6 (2%)	22 (2%)	0.012
Headache	78 (11%)	48 (12%)	27 (9%)	153 (11%)	0.532
Gastro-Intestinal System Disorders	33 (4%)[b]	35 (9%)[d]	9 (3%)	77 (5%)	0.002
Nausea	7 (<1%)	8 (2%)[d]	0 (0%)	15 (1%)	0.037
Vomiting	2 (<1%)[b]	7 (2%)	2 (<1%)	11 (<1%)	0.014
Heart Rate & Rhythm Disorders	0 (0%)[b]	3 (<1%)	0 (0%)	3 (<1%)	0.030
Musculo-Skeletal System Disorders	20 (3%)	20 (5%)[d]	5 (2%)	45 (3%)	0.040
Myalgia	10 (1%)	10 (3%)	4 (1%)	24 (2%)	0.349
Psychiatric Disorders					
Depression	0 (0%)[b]	4 (1%)	0 (0%)	4 (<1%)	0.008
Resistance Mechanism Disorders	27 (4%)	19 (5%)	20 (7%)	66 (5%)	0.081
Infection Viral	13 (2%)[c]	6 (2%)[d]	13 (4%)	32 (2%)	0.024
Respiratory System Disorders	182 (25%)[bc]	147 (37%)	103 (36%)	432 (30%)	<0.001
Bronchitis	15 (2%)	13 (3%)	11 (4%)	39 (3%)	0.194
Increased Asthma Symptoms	24 (3%)[bc]	31 (8%)[d]	52 (18%)	107 (7%)	<0.001
Pharyngitis	59 (8%)[c]	40 (10%)[d]	12 (4%)	111 (8%)	0.014
Respiratory Disorder [illegible]	0 (0%)[b]	3 (<1%)	0 (0%)	3 (<1%)	0.030
Rhinitis	36 (5%)[bc]	33 (8%)	25 (9%)	94 (7%)	0.023
Sinusitis	18 (2%)	13 (3%)	5 (2%)	36 (3%)	0.443
URTI	68 (9%)	53 (13%)	33 (11%)	154 (11%)	0.098
Skin and Appendages Disorders	29 (4%)	20 (5%)	6 (2%)	55 (4%)	0.114

[a] The p-value for the overall comparison is based on the two-sided Fisher's Exact Test.
[b] The pairwise comparison between HFA-BDP and CFC-BDP was statistically significant ($p \le 0.05$) based on the two-sided Fisher's Exact Test.
[c] The pairwise comparison between HFA-BDP and HFA-placebo was statistically significant ($p \le 0.05$) based on the two-sided Fisher's Exact Test.
[d] The pairwise comparison between CFC-BDP and HFA-placebo was statistically significant ($p \le 0.05$) based on the two-sided Fisher's Exact Test.

Pharyngitis was reported by 8% of the patients who received BDP-HFA and 10% of the BDP-CFC patients as compared with 4% of the patients who received placebo HFA ($p = 0.03$ comparing placebo HFA and BDP-HFA). The highest incidence among patients who received BDP-HFA was in the group that received 800 mcg/day (15%). The highest incidence of pharyngitis in patients who received BDP-CFC was in the group that received 100 mcg/day (12%).

- Pooling of data from studies 1081, 1192, and 1129:

Sponsor's Rationale:

1) recommended dose range of 100-800 mcg/day;
2) patients with mild-severe asthma
3) performed primarily in US
4) BDP-CFC and placebo controls

NOTE: The reasons put forward by the sponsor for pooling the data from these studies is not compelling. BDP-CFC or placebo controls were used in studies 1083 and 1130 as well. Studies 1083 and 1130 also used doses within the recommended dose range and included patients with asthma. Perhaps the most compelling reasons for pooling the data are features of studies 1083 and 1130 themselves, namely study 1083 was done in Europe where AEs were apparently assessed differently and study 1130 used a non-FDA approved control, e.g. Becloforte at a 250 mcg/puff concentration. Another compelling reason, not mentioned by the sponsor, is that the 50 mcg/puff concentration was used in these three studies, whereas the 100 mcg/puff concentration was used in the other studies.

The sponsor contends that the lower incidence of dysphonia and gastrointestinal AEs noted in the BDP-HFA than in the BDP-CFC group, regardless of whether the data from all the 6-12 week studies is used or just the pooled data, can be explained on

the basis of the smaller particle size produced by delivery of BDP-HFA. This is a reasonable explanation for this finding.

Based on the pooled data, there was a significantly (this reviewer's definition of significant was a 2% or greater difference from placebo) higher percentage of patients who experienced "pain", headache, musculoskeletal system disorders, pharyngitis, sinusitis and skin and appendage disorders. The reason for this difference between the BDP-HFA and HFA placebo groups is unclear. There was a higher incidence of adverse events in patients who received higher doses of BDP-HFA (400 and 800 mcg/day) than in those who received lower doses (100 and 200 mcg/day), but the incidence in the high dose groups were comparable to the incidence seen in the HFA placebo group.

Based on the pooled data, the incidence of pharyngitis and headache were significantly higher in the group that received 800 mcg/day of BDP-HFA than in the group that received HFA placebo and the group which received 800 mcg/day of BDP-CFC. No dose-related trend was otherwise apparent. A statistically significant difference between males and females was seen for AEs overall, and specifically for CNS and PNS disorders, headaches, respiratory system disorders and rhinitis, with more females reporting these types of AEs.

- subset analysis: There was a consistently greater incidence of number of patients with at least one report of an AE, general disorders, CNS and PNS disorders, including headache, GE disorders, rhinitis, sinusitis, and URIs in patients with concomitant antihistamine use (31% of patients were taking antihistamines), regardless of treatment group. Intranasal corticosteroids were being used by 11% of patients without any significant increase in AEs.

NOTE: There was a statistically significantly greater frequency of AEs noted in patients receiving BDP-HFA when AEs for all the 6-12 week studies were considered. A similar trend was noted when only studies

1081, 1192 and 1129 were analyzed. In addition, there was a trend noted toward increased incidence of AEs and increased dose when only these studies were analyzed. The sponsor attributes an increased incidence of reactions at the inhalation site, as well as nausea, vomiting and increased asthma symptoms in patients who received BDP-CFC to different deposition patterns for BDP-CFC and BDP-HFA, as discussed above. This is a reasonable conclusion in regard to the AEs noted in these studies.

☛ study 1163: study of 12 months duration

✹ Based on all doses used for BDP-HFA and BDP-CFC, there was a greater incidence of application site adverse events, fatigue, headache, abdominal pain, vomiting, sinusitis, URIs and "strain" in patients who received BDP-HFA than patients who received BDP-CFC. The greater incidence of these AEs after administration of BDP-HFA was not clinically significant either in terms of the incidence or the difference from occurrence after administration of BDP-CFC. There was no dose- dependent trend for AEs after administration of BDP-HFA at doses of < 200 mcg to 800 mcg/day.

✹ Significantly more women than men developed gastritis, respiratory system disorders, increased asthma symptoms, pharyngitis and urinary system disorders in this study. The incidence of arthralgia, dysphonia and diarrhea was greater among men. The clinical relevance of these findings, if any, is unclear.

✹ The percentage of patients who were receiving antihistamines and reported an adverse event was higher (91%) than the percentage of patients who reported an adverse event and were not taking antihistamines (75%). This included a higher incidence of gastritis, increased asthma symptoms, rhinitis, sinusitis, URIs, GI disorders, female reproductive disorders, respiratory system disorders and skin and appendages disorders in patients who were taking antihistamines, irrespective of treatment. In terms of concomitant intranasal corticosteroid use, more CNS, PNS, and psychiatric disorders were seen in the BDP-HFA group if patients were receiving intranasal

corticosteroids. The reverse was seen in the group that received BDP-CFC.

☛ overall considerations based on entire safety database

✹ local topical effect: The incidence of application site adverse events was comparable or significantly lower in the BDP-HFA group as compared with placebo and/or active treatment controls and no dose-response was demonstrated.

✹ systemic effect: The incidence of adverse events was comparable to, or less than, that seen with BDP-CFC and/or placebo.

✦ candidiasis

NOTE: Spacer use was prohibited in the studies of 6-12 weeks duration. In the 12 month study, spacers were allowed only if the patient developed candidiasis or dysphonia.

Rinsing of the mouth was allowed but not required in all studies.

☛ None of the patients treated with BDP-HFA in the 6-12 week studies developed symptomatic oropharyngeal candidiasis. However, there were 5 patients who had visible oropharyngeal abnormalities after receiving BDP-HFA where definitive diagnosis could not be made because of laboratory error. The same number of patients who received BDP-CFC also developed such a finding. In the studies pooled for labeling purposes (see discussion above), 30% of patients receiving 800 mcg/day of BDP-HFA developed an oropharyngeal AE compared with 22% of patients who received 800 mcg/day of BDP-CFC and 12% of patients who received HFA placebo. None of the patients in the 12 month study developed symptomatic oropharyngeal candidiasis. Only one patient developed symptomatic oropharyngeal candidiasis after receiving BDP-CFC 1500 mcg/day.

- withdrawals due to adverse events (all studies)

  - 2%: BDP-HFA
    1%: BDP-CFC
    8%: HFA placebo

- serious adverse events

  - 1%: BDP-HFA
    1%: BDP-CFC
    0: HFA placebo

  - After review of the data submitted by the sponsor about the patients who experienced serious AEs, it does not appear that any of these AEs reported were related to administration of BDP-HFA.

- HPA axis suppression

  - 24 hour urinary free cortisol

    - 4 studies: 2 in healthy volunteers (1025, 1063)(NRR = 60-250 nmol/24 hours); 2 in mild asthmatics not receiving corticosteroids (1064, 1162)(NRR study 1162 = 55-248 nmol/24 hours)(NRR study 1064 = 5-47 mcg/24 hours)

    - study 1162: parallel, dose-level blind study with 14 days of treatment with 200, 400, and 800 mcg/day of BDP-HFA, 800 mcg/day of BDP-CFC or HFA placebo in 40 sequestered patients (8 per treatment group). Two 24 hour urine collections were obtained prior to treatment and following treatment with averaging of the two collections at each time point. There was a statistically significant change from baseline in mean 24 hour urinary free cortisol in the groups that received 400 and 800 mcg/day of BDP-HFA and the group that received

800 mcg/day of BDP-CFC compared to placebo ($p \leq 0.05$). There was a dose-related decrease in mean 24 hour urinary free cortisol in the groups that received BDP compared with placebo (see table below; tab 11.1.1.A, p225, v1.271). The placebo group had a mean increase of 17% in 24 hour urinary free cortisol, whereas there was a 12% mean decrease in the group that received 200 mcg/day of BDP-HFA, a 24% decrease in the group that received 400 mcg/day of BDP-HFA and a 37% mean decrease in the group that received 800 mcg/day of BDP-HFA. By contrast, there was a 47% mean decrease in the group that received 800 mcg/day of BDP-CFC. There was no statistically significant difference between the mean decrease in mean 24 hour urinary free cortisol seen in the 800 mcg/day BDP-HFA and the 800 mcg/day BDP-CFC groups.

Table 11.1.1.A 1162: Mean 24-h Urinary Free Cortisol Excretion (nmol/24 hours) Values[a]

Visit		HFA-Placebo	HFA-BDP 200 mcg	HFA-BDP 400 mcg	HFA-BDP 800 mcg	CFC-BDP 800 mcg
Baseline[b]	Mean	157.1	172.6	198.4	172.9	192.8
	SE	9.90	20.97	18.02	27.54	10.43
	N	9	9	9	8	8
Day 14[c]	Mean	179.1	148.5	132.4	107.7	99.3
	SE	16.67	20.87	12.55	18.04	8.64
	N	8	8	8	8	8

[a] Reference range: 55 - 248 nmol/24 hours.
[b] The baseline values for each patient represent the mean of both study day -3 to -2 and -2 to -1.
[c] The day 14 values for each patient represent the mean of study days 12 to 13 and 13 to 14.

- study 1025: parallel, dose-level blind study comparing the mean percent change in 24 hour urinary free cortisol following 10 days of treatment with 1200, 2000, and 2800 mcg/day of BDP-HFA (200 mcg concentration) and 1500, 2500, and 3500 mcg/day of BDP-CFC (250 mcg concentration) in 38 normal healthy sequestered volunteers.

The NRR for 24 hour urinary free cortisol excretion in this study was 60-250 nmol/24 hours. There was a dose dependent change in mean 24 hour urinary free cortisol after administration of both BDP-HFA and BDP-CFC. The mean 24 hour urinary free cortisol level fell below the lower limit of the NRR after 10 days of treatment with 2000 and 2800 mcg/day of BDP-HFA and 3500 mcg/day of BDP-CFC. The decrease in 24 hour urinary free cortisol was comparable in the group that received 1200 mcg/day of BDP-HFA and the group that received 2500 mcg/day of BDP-CFC (see table below; tab11.1.2.A, p227, v1.271).

Table 11.1.2.A: 1025: Mean 24-h Urinary Free Cortisol Excretion (nmol/24 hours) Values[a]

Visit		HFA-BDP 1200 mcg	HFA-BDP 2000 mcg	HFA-BDP 2800 mcg	CFC-BDP 1500 mcg	CFC-BDP 2500 mcg	CFC-BDP 3500 mcg
Baseline	Mean	144.1	178.9	171.8	128.1	154.0	130.3
	SE	21.9	23.5	25.0	14.2	18.6	14.6
	N	7	6	6	6	7	6
Day 10	Mean	65.1	52.0	25.5	80.5	71.6	40.8
	SE	15.5	8.3	6.5	10.3	19.8	10.1
	N	7	6	6	6	7	6

[a] Reference range: 60 - 250 nmol/24 hours

- **study 1063: parallel, dose-level blind study comparing the mean percent change from baseline in 24 hour urinary free cortisol following 10 days of treatment with 1200, 2000, and 2800 mcg/day of BDP-HFA and BDP-CFC using a 50 mcg/puff concentration in sequestered healthy male volunteers.**

The 24 hour urinary free cortisol NRR in this study was 60-250 nmol/24 hours. A dose response trend was seen for both BDP-HFA and BDP-CFC. The decrease in mean 24 hour urinary free cortisol was comparable after 1200 mcg/day of BDP-HFA and after 2000 mcg/day of BDP-CFC, although somewhat greater in the BDP-CFC group (see table below; tab11.1.3.A, p229, v1.271)

Table 11.1.3.A 1063: Mean 24-h Urinary Free Cortisol Excretion (nmol/24 hours) Values[a]

Visit		HFA-BDP 1200 mcg	HFA-BDP 2000 mcg	HFA-BDP 2800 mcg	CFC-BDP 1200 mcg	CFC-BDP 2000 mcg	CFC-BDP 2800 mcg
Baseline	Mean	143.3	143.8	176.2	194.3	171.0	227.7
	SE	8.1	25.6	23.0	11.4	17.9	29.4
	N	6	6	6	6	6	6
Day 10	Mean	44.7	39.8	31.0	110.0	56.8	66.3
	SE	9.8	11.1	12.3	9.9	7.9	21.2
	N	6	6	6	6	6	6

[a] Reference range: 60 - 250 nmol/24 hours

- pooling of studies 1162, 1025, and 1063 in terms of percent of patients who were below the lower limit of the NRR in regard to 24 hour urinary free cortisol levels after treatment:

  - cross-study comparison of number of patients whose 24 hour urinary free cortisol level fell below the NRR after repetitive dose treatment in pooled studies:

BDP-HFA (mcg/day)				BDP-CFC (mcg/day)				
800	1200	2000	2800	1500	2000	2500	2800	3500
1/8	8/13	8/12	11/12	1/6	4/6	3/7	2/6	4/6

COMMENT: From a clinical standpoint, significantly more patients who received BDP-HFA at a given dose had a fall in 24 hour urinary free cortisol to a level below the NRR than patients who received a higher dose of BDP-CFC, e.g. 62% after receiving 1200 mcg/day of BDP-HFA compared to 43% after receiving 2500 mcg/day of BDP-CFC, recognizing that only small numbers of patients were studied. The one patient who fell below the NRR after 800 mcg/day of BDP-HFA had a level at baseline that was just above the lower limit of the NRR. Nevertheless, it appears clear that at higher doses of BDP-HFA, suppression of the HPA axis can occur.

- study 1064: double-blind, parallel study in sequestered patients with mild asthma who were not receiving corticosteroids. Patients were treated with 200, 800 or 1600 mcg/day of BDP-HFA or HFA placebo for 14 days. The — assay was not sufficiently sensitive below the NRR of 5-47 mcg/24 hours to allow analysis of percent change from baseline.

☛ number of patients with 24 hour urinary free cortisol levels below the NRR after 10 days of treatment with BDP-HFA *.

200 mcg/day	800 mcg/day	1600 mcg/day	HFA placebo
1/6	2/8	3/6	0/6

* 4 patients has baseline levels close to the lower limit of the NRR; 1 patient who received 200 mcg/day and 1 patient who received 800 mcg/day had a baseline value of 7 mcg while 2 patients who received 1600 mcg/day had a baseline value of 5 mcg.

COMMENT:Measurement of 24 hour urinary free cortisol has shown:

1. There was a dose-dependent suppression of mean 24 urinary free cortisol after administration of BDP-HFA for 14 days comparable to that seen after comparable doses of BDP-CFC.

2. The mean 24 hour urinary free cortisol fell below the lower limit of the NRR after 10 days of treatment with higher doses of BDP-HFA (2000-2800 mcg/day).

3. The percent of patients whose 24 hour urinary free cortisol fell below the lower limit of the NRR was greater after administration of BDP-HFA at doses > 800 mcg/day than after administration of BDP-CFC.

4. BDP-HFA, based on 24 hour urinary free cortisol levels, suppresses the HPA axis in a dose-dependent manner to a degree that is comparable to comparable doses of BDP-CFC.

☛ AM plasma cortisol :

✹ 5 studies: 1162 (138-690 nmol/L)
1025 (150-700 nmol/L)
1129 (166-828 nmol/L)
1130 (193-690 nmol/L)
1163 (110-828 nmol/L)

- parameters:
  - mean percentage change from baseline
  - percentage of patients with values below the lower limit of the NRR after treatment

- study 1162:
  - 200, 400, and 800 mcg/day BDP-HFA
    800 mcg/day BDP-CFC
    HFA placebo
  - 7 AM and 9 AM plasma cortisol at baseline and after 14 days of treatment
  - no significant difference between treatment with BDP or placebo was seen in terms of 9 AM plasma cortisol levels but there was a significantly greater decrease in 7 AM mean plasma cortisol level after administration of 800 mcg of BDP-HFA than after administration of 800 mcg of BDP-CFC or placebo (see tables below; tab11.2.1.A, p238, v1.271 and tab11.2.1.B, p239, v1.271)

Table 11.2.1.A: 1162: 0700 Hour Plasma Cortisol (nmol/L)[a]

		HFA-Placebo	HFA-BDP 200 mcg	HFA-BDP 400 mcg	HFA-BDP 800 mcg	CFC-BDP 800 mcg
Baseline[b]	Mean	485.0	383.1	443.7	434.6	466.3
	SE	16.37	36.73	26.21	55.22	44.05
	N	9	9	9	8	8
Day 14[c]	Mean	415.5	313.5	393.7	239.8	366.4
	SE	41.66	22.79	33.35	46.92	24.14
	N	8	8	8	8	8
% Change from Baseline	Mean	-15.4	2.5	-9.6	-47.5	-15.8
	SE	6.52	26.31	8.82	6.77	9.76
	N	8	8	8	8	8

[a] Reference range: 138 - 690 nmol/L.
[b] The baseline values for each patient represent the mean of Day -2 and -1 0700 hour plasma cortisol levels.
[c] The 'Day 14' values for each patient represent the mean of Day 13 and 14 0700 hour plasma cortisol levels.

Table 11.2.1.B: 1162: 0900 Hour Plasma Cortisol (nmol/L)[a]

		HFA-Placebo	HFA-BDP 200 mcg	HFA-BDP 400 mcg	HFA-BDP 800 mcg	CFC-BDP 800 mcg
Baseline[b]	Mean	319.3	262.2	338.5	266.3	330.5
	SE	29.78	32.81	39.76	39.71	53.35
	N	9	9	9	8	8
Day 14[c]	Mean	267.9	316.0	329.9	252.8	275.6
	SE	22.03	20.78	23.45	47.26	31.58
	N	8	8	8	8	8
% Change from Baseline	Mean	-9.9	40.1	16.2	-10.6	-10.2
	SE	6.67	34.46	15.70	11.57	11.52
	N	8	8	8	8	8

[a] Reference range: 138 - 690 nmol/L.
[b] The baseline values for each patient represent the mean of Day -2 and -1 0900 hour plasma cortisol levels.
[c] The 'Day 14' values for each patient represent the mean of Day 13 and 14 0900 hour plasma cortisol levels.

☛ **patients with AM plasma cortisol levels below the NRR after 14 days of treatment (see tables below; tabs 11.2.1.C and 11.2.1.D, p240, v1.271):**

Table 11.2.1.C: 1162: Patients Whose 0700 Hour Day 14 Plasma Cortisol Value Was Below the Reference Range[a]

ID Number	Treatment Group	Baseline (nmol/L)	Final (nmol/L)
23	800 mcg/day HFA-BDP	513.4	136.8
27	800 mcg/day HFA-BDP	81.3	27.3

[a] Reference Range: 138-690 nmol/L

Table 11.2.1.D: 1162: Patients Whose 0900 Hour Day 14 Plasma Cortisol Value Was Below the Reference Range[a]

ID Number	Treatment Group	Baseline (nmol/L)	Final (nmol/L)
18	800 mcg/day HFA-BDP	146.6	120.5
27	800 mcg/day HFA-BDP	112.5	27.3
20	800 mcg/day CFC-BDP	223.4	135.1

[a] Reference Range: 138-690 nmol/L

COMMENT: It is interesting to note that there was a significant decrease from baseline in mean AM plasma cortisol at 7 AM but not 9 AM after 14 days of treatment with 800 mcg/day of BDP-HFA. A similar effect was not seen with lower doses of BDP-HFA or after 800 mcg/day

of BDP-CFC. This was a small study with very small numbers of patients in each treatment group and AM plasma cortisol levels are not considered to be a reliable indicator of adrenal effect. Although the clinical relevance of this finding is, therefore, unclear, the potential for a dose of 800 mcg/day of BDP-HFA for 14 days to lower the 7 AM plasma cortisol level significantly in at least some patients in this study is clear.

- study 1025:

  - 1200-2800 mcg/day BDP-HFA
    1500-3500 mcg/day BDP-CFC

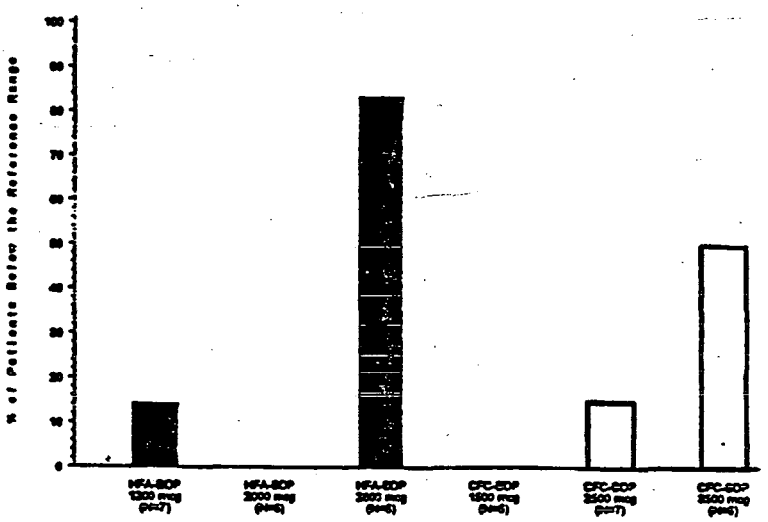
  - 8 AM plasma cortisol levels daily over 10 days of treatment

  - mean percent change in 8 AM plasma cortisol levels as well as number of patients with an 8 AM plasma cortisol level below the NRR after 10 days of treatment is consistent with the ability of high doses of BDP-HFA for 10 days to produce an effect on adrenal function (see table and figure below; tab 11.2.2.A, p241, v1.271 and fig11.2.2.A, p242, v1.271)

Table 11.2.2.A: 1025: 0800 Hour Baseline and Day 10 Plasma Cortisol Levels (nmol/L) and Mean Percent Change After 10 Days of Dosing

Response		HFA-BDP			CFC-BDP		
		1200 mcg	2000 mcg	2800 mcg	1500 mcg	2500 mcg	3500 mcg
Baseline	Mean	480.5	495.9	523.7	542.4	491.2	482.6
	SE	17.7	41.6	31.4	25.6	28.7	66.8
	N	7	6	6	6	7	6
Study day 10	Mean	299.9	338.5	75.7	333.7	313.7	179.8
	SE	41.6	31.1	32.3	26.7	54.1	46.6
	N	7	6	6	6	7	6
% Change from Baseline	Mean	-37.3	-28.6	-86.9	-38.0	-35.3	-65.5
	SE	9.0	10.2	4.7	5.3	9.7	5.7
	N	7	6	6	6	7	6

Figure 11.2.2.A: 1025: Percent of Patients Whose Morning Plasma Cortisol Level Was Below the Reference Range at Day 10



COMMENT: There was no placebo control in this study and the number of patients evaluated was small. Cross-study comparison with study 1162, however, suggests that the decrease in mean plasma cortisol levels after administration of 1200 and 2000 mcg/day of BDP-HFA for 10 days was greater than would have been expected after administration of placebo over this period of time. It is interesting to note that no dose response was seen between 1200 and 2000 mcg/day of BDP-HFA (or for that matter between 1500 and 2500 mcg of BDP-CFC). However, a dose of 2800 mcg of BDP-HFA produced a significant mean decrease in 8 AM plasma cortisol from baseline after 10 days of treatment (a greater mean decrease than was seen after 3500 mcg/day of BDP-CFC), a finding supported by the number of individual patients who had an 8 AM plasma cortisol level below the NRR after 10 days of treatment with 2800 mcg/day of BDP-HFA (which was also greater than the number seen after 3500 mcg/day of BDP-CFC). Consistent with the unreliability of single AM plasma cortisol measurements, the percentage of patients having an AM plasma cortisol level below the NRR was less in this study after administration of 1200 and 2000 mcg/day for 10 days than was seen

after administration of 800 mcg/day for 14 days in study 1162. It is clear from this study that high doses of BDP-HFA can significantly decrease adrenal function as measured by AM plasma cortisol levels.

✹ study 1129:

- ☛ patients not on corticosteroids or receiving up to 400 mcg/day BDP-CFC
- ☛ 8-9 AM plasma cortisol at end of 14 days run-in before oral corticosteroids (baseline), after oral corticosteroids and after 12 weeks of treatment with BDP-HFA 400 mcg/day, BDP-CFC 800 mcg/day or placebo.
- ☛ The administration of 400 mcg/day of BDP-HFA for 12 weeks had no significant effect on AM plasma cortisol levels (see table below; tab11.2.3.A, p243, v1.271).

Table 11.2.3.A: 1129: Adjusted Means at Each Assessment Period for Plasma Cortisol Levels (nmol/L)[a] Comparisons with Placebo

Study week		HFA-BDP 400 mcg	CFC-BDP 800 mcg	HFA-Placebo	Overall P-value[b]
Run-in Period (Prior to Oral Steroid Treatment)	Mean	457.6	469.7	477.0	0.853
	SE	24.46	23.33	24.62	
	N	112	116	116	
Study Day 1 (After Oral Steroid Treatment)	Mean	213.2	172.8	179.1	0.156
	SE	16.08	15.36	16.02	
	N	113	116	117	
Week 12[c]	Mean	483.7	430.2	452.1	0.382
	SE	27.33	27.42	29.81	
	N	100	102	80	
% Change from the Run-in Period at Week 12	Mean	9.7	0.1	1.9	0.257
	SE	4.36	4.35	4.81	
	N	99	102	79	

[a] Reference range for females 165.6-828 nmol/L, males 138-496.8 nmol/L.
[b] Based on an ANOVA with treatment, center, and treatment by center interaction terms in the model.
[c] Included patients who had received at least 78 days of treatment.

✹ study 1130:

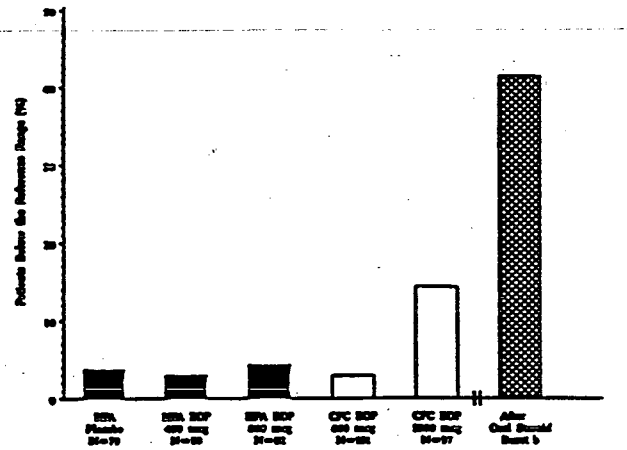
- ☛ patients were receiving 400-800 mcg/day BDP-CFC prior to the study.
- ☛ 8-9 AM plasma cortisol levels were measured at the end of a 14 day run-in (prior to oral corticosteroids), on study day 1 (after oral corticosteroids) and after 12 weeks of treatment with 800 mcg/day of BDP-HFA or 1500 mcg/day of BDP-CFC.
- ☛ There was a greater decrease in plasma cortisol level after administration of BDP-CFC for 12 weeks than after the administration of BDP-HFA for the same period of time (see table below; tab11.2.4.A, p244, v1.271)(NOTE: in contrast to the table, there was a 1% decrease in plasma cortisol in the BDP-HFA group and a 10% decrease in the BDP-CFC group).
- ☛ Combining results from studies 1129 and 1130, the percent of patients who had a plasma cortisol level below the NRR after 12 weeks of treatment can be seen below compared with the percent of patients who had such a level after oral corticosteroid treatment (fig11.2.5.A, p245, v1.271).

Table 11.2.4.A: 1130: Adjusted Means at Each Assessment Period for Plasma Cortisol Levels (nmol/L) [a,b]

Study Week		HFA-BDP 800 mcg	CFC-BDP 1500 mcg
Run-in Period (Prior to Oral Steroid Treatment)	Mean	565.1	560.7
	SE	31.93	29.74
	N	102	109
Study Day 1 (After Oral Steroid Treatment)	Mean	327.6	340.1
	SE	25.37	24.03
	N	109	110
Week 12[c]	Mean	494.7	477.0
	SE	29.83	28.28
	N	104	105
% Change from the Run-in Period at Week 12	Mean	5.5	-0.3
	SE	6.81	6.47
	N	92	99

[a] Reference range 193 - 690 nmol/L
[b] Based on an ANOVA with treatment, center, and treatment by center interaction terms in the model.
[c] Included patients who had received at least 78 days of treatment.

Figure 11.2.5.A: 1129 and 1130: Percent of Patients Whose Plasma Cortisol Level Was Below the Reference Range at Week 12[a]



[a] Included patients who had received at least 78 days of treatment and had an end of run-in, end of oral steroid treatment, and end of study treatment plasma cortisol measure.
[b] Oral steroid burst was given before patients were randomized to study treatment.

✺ study 1163:

- ☛ patients were receiving 400-1600 mcg/day prior to the study. After a 2 week run-in, they were randomized to their current dose of BDP-CFC or ½ their current dose of BDP-CFC as BDP-HFA. Plasma cortisol levels were drawn prior to treatment and after 2, 4, 8 and 12 months of treatment.

- ☛ percent of patients with plasma cortisol level below the NRR after treatment for 2 and 4 months:

	2 months	4 months
BDP-HFA	5%	5%
BDP-CFC	4%	6%

COMMENT: Plasma cortisol levels are not considered a reliably consistent indicator of adrenal function. Nevertheless, the data suggest that in some patients, suppression of adrenal function, based on plasma cortisol levels, may occur after administration of 800 mcg/day of BDP-HFA for 14 days. Clearly, higher doses (2800 mcg/day) of BDP-HFA for as short a period as 10 days may produce suppression of adrenal function, based on plasma cortisol levels, in

some patients. A dose of 400 mcg/day of BDP-HFA, on the other hand, did not produce a significant effect on mean plasma cortisol levels and the percentage of patients with a level below the NRR did not significantly increase.

☛ ACTH stimulation:

✹ rapid ACTH stimulation test; studies 1162 and 1163

✹ normal : plasma cortisol prior to ACTH injection = ≥ 5 mcg/dL
increase or decrease = ≥ 7 mcg/dL
peak = ≥ 18 mcg/dL

✹ study 1162:

✧ ACTH stimulation at baseline and after 14 days treatment

✧ there was no indication of adrenal suppression at any dose (200, 400 or 800 mcg/day of BDP-HFA) in terms of mean change or individual patient change after administration of ACTH.

✹ study 1163:

✧ rapid ACTH stimulation test at baseline and after 2, 4, and 12 months of treatment

✧ As can be seen in the table below (tab 11.3.2.B, p254, v1.271), there were 2 patients (8/108 and 11/102) who had a normal baseline ACTH stimulation test and an abnormal test after 4 months of treatment with BDP-HFA (COMMENT: there is limited amount of data at the highest dose, i.e. 800 mcg/day; in addition, there is no placebo control for comparison; the plasma cortisol levels prior to ACTH infusion after 4 months of treatment with BDP-HFA were substantially lower than those seen prior to ACTH infusion in patients who had an

abnormal ACTH stimulation test at baseline; the data is consistent with data generated in regard to other parameters of adrenal function over shorter periods of time, i.e. that in some patients, even lower doses of BDP-HFA when administered for longer periods of time can produce adrenal suppression.)

Table 11.3.2.B: 1163: Patients With an Abnormal[a] Response to Cosyntropin by Dose of HFA-BDP

Patient ID	Dose of HFA-BDP	Values	Baseline	Month 2	Month 4	Last Visit
3/107	300 mcg	Pre-injection	416.8	436.1	491.3	491.3
		Increment	557.5	-96.6	505.1	505.1
		Peak	974.3	339.5	996.4	996.4
7/101	200 mcg	Pre-injection	372.6	Visit <53 days	361.6	361.6
		Increment	-85.6	after	499.5	499.5
		Peak	287.0	randomization[b]	861.1	861.1
7/110	200 mcg	Pre-injection	113.2	179.4	93.8	93.8
		Increment	361.5	469.2	455.4	455.4
		Peak	474.7	648.6	549.2	549.2
8/108	200 mcg	Pre-injection	289.8	300.8	27.9	27.9
		Increment	276.0	452.7	96.3	96.3
		Peak	565.8	753.5	124.2	124.2
11/102	500 mcg	Pre-injection	314.6	292.6	33.1	33.1
		Increment	375.4	309.1	391.9	391.9
		Peak	690.0	601.7	425.0	425.0
11/104	200 mcg	Pre-injection	127.0	124.2	300.8	300.8
		Increment	198.7	207.0	190.5	190.5
		Peak	325.7	331.2	491.3	491.3
28/102	600 mcg	Pre-injection	254.6	22.3	Visit >134 days	374.4
		Increment	748.2	272.5	after	408.4
		Peak	1002.8	294.8	randomization[c]	782.8

[a] Failure to meet two of three criteria required for a normal response. Results in bold indicate an abnormal response.
[b] This visit was outside the window (53-67 days) for Month 2.
[c] This visit was outside the window (106-134 days) for Month 4.

- Bone Metabolism:
  - bone formation (serum osteocalcin)
    - study 1064:
      - double-blind, parallel, placebo-controlled (HFA placebo), repetitive dose study; 26 pts; 200 (6 pts), 800

(9 pts) and 1600 mcg/day (6 pts) of BDP-HFA; 14 days; osteocalcin levels obtained at baseline and after 14 days of treatment.

- There was a dose-related decrease in serum osteocalcin (see table 11.4.1.1.A, p237, v1.271 below)

Table 11.4.1.1.A: 1064: Adjusted Mean Change From Baseline in Serum Osteocalcin Concentrations (ng/mL)[a]

Osteocalcin		HFA-Placebo	HFA-BDP 200 mcg	HFA-BDP 800 mcg	HFA-BDP 1600 mcg	P-value[b]
Baseline	Mean	14.3	14.0	16.0	18.8	0.557
	SE	2.18	1.83	2.72	2.30	
	N	6	6	9	6	
Mean Change at Day 14	Mean	-0.67	-2.01	-2.81	-5.74	0.098
	SE	1.35	1.35	1.16	1.38	
	N	6	6	8	6	

[a] The reference range was 5.1 - 23 ng/mL.
[b] The p-value was the overall between-treatment comparison using an analysis of covariance, where the baseline value was the covariate.

- between group analysis of mean change from baseline showed no statistically significant difference; it is not clear if a clinically significant difference was demonstrated.

- none of the individual patient osteocalcin levels fell below the lower limit of the NRR (ng/ml) after 14 days of treatment.

✺ study 1162:

- dose-level blind, parallel, placebo-controlled (HFA placebo), repetitive dose study; 43 pts; 200 and 400, mcg/day BDP-HFA and 800 mcg/day BDP-CFC; osteocalcin levels after 14 days of treatment

- There was a dose related decrease in serum osteocalcin(see table 11.4.1.2.A; p238, v1.271 below).

Table 11.4.1.2.A: 1162: Mean Serum Osteocalcin Concentrations and Change from Baseline[a] (ng/mL)

Study Visit		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[b]	-0.9[c]
	SE	0.43	0.74	0.59	0.91	1.09
	N	8	8	8	8	7

[a] Reference range 1.8 - 7.7 ng/mL
[b] Indicates significant mean difference from placebo ($p \leq 0.05$) using Dunnett's test.
[c] A significant difference was found between the HFA-BDP and CFC-BDP 800 mcg groups. 95% CI for the difference (HFA-BDP - CFC-BDP) was -4.89, -0.37.

- **There a statistically significantly greater decrease in serum osteocalcin after 800 mcg/day of BDP-HFA than after either 800 mcg/day of BDP-CFC or HFA-placebo ($p \leq 0.05$).**

- **There were 5 patients in the study who had serum osteocalcin levels below the lower limit of the NRR ( )after 14 days of treatment, 1 patient who received 200 mcg/day, 2 patients who received 400 mcg/day, 1 patient who received 800 mcg/day of BDP-HFA and 1 patient who received 800 mcg/day of BDP-CFC.**

study 1129:

- **12 week, parallel, modified blind, HFA-placebo-controlled study in 347 adult asthmatics who received either placebo, 400 mcg/day BDP-HFA or 800 mcg/day BDP-CFC; osteocalcin levels were obtained at the end of the run-in period (prior to treatment with oral corticosteroids), on study day 1 (after 7-12 days of treatment with oral corticosteroids) and after 12 weeks of treatment.**

- **There was no statistically significant difference between placebo and either active treatment in terms of change in**

serum osteocalcin from run-in after 12 weeks of treatment (see table 11.4.1.3.A, p239, v1.271 below).

Table 11.4.1.3.A 1129: Adjusted Mean Serum Osteocalcin Concentrations (ng/mL) by Treatment Group at Each Assessment Period

Study Visit		HFA-Placebo	HFA-BDP 400 mcg	CFC-BDP 800 mcg	Overall P-Value[a]
Run-in Period (Prior to Oral Steroid Treatment)	Mean	2.9	3.0	3.2	0.279
	SE	0.16	0.16	0.15	
	N	114	111	114	
Study Day 1 (After Oral Steroid Treatment)	Mean	1.9	2.0	2.0	0.840
	SE	0.13	0.13	0.13	
	N	114	112	113	
Week 12	Mean	3.0	2.5	2.8	0.146
	SE	0.18	0.16	0.16	
	N	80	100	102	
Change from Run-in Period at Week 12	Mean	-0.1	-0.5	-0.4	0.091
	SE	0.14	0.13	0.13	
	N	77	99	100	

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

- There were 5 HFA-placebo patients, 18 patients who received 400 mcg/day of BDP-HFA and 11 patients who received 800 mcg/day of BDP-CFC who had serum osteocalcin values below the NRR after 12 weeks of treatment, which were not also below the NRR at baseline (see fig 11.4.1.5.A, p242, v1.271 below)

- study 1130:

  - 12 week, parallel, double-blind, active treatment controlled study in 233 adult asthmatics who received either 800 mcg/day of BDP-HFA or 1500 mcg/day of BDP-CFC. Serum osteocalcin levels were obtained at the end of the run-in period (prior to oral corticosteroid treatment), on study day 1 (after oral corticosteroid treatment) and after 12 weeks of treatment.

  - There was neither a statistically significant nor a clinically significant change from baseline (end of run-in period) in

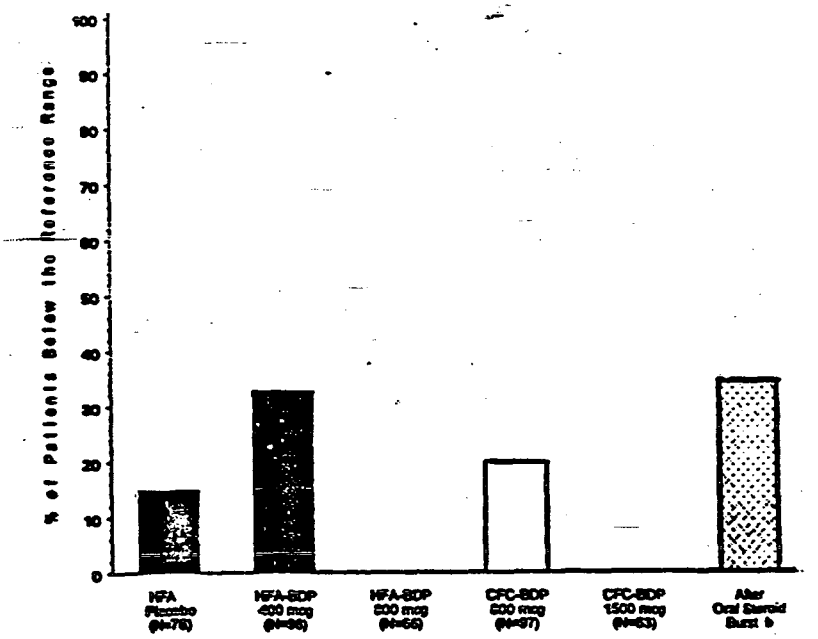
serum osteocalcin after 12 weeks of treatment with either 800 mcg/day of BDP-HFA or 1500 mcg/day of BDP-CFC (see table 11.4.1.4.A, p240, v1.271 below)

Table 11.4.1.4.A: 1130: Adjusted Means at Each Assessment Period for Serum Osteocalcin Concentrations (ng/mL) [a]

Study Week		HFA-BDP 800 mcg	CFC-BDP 1500 mcg
Run-in Period (Prior to Oral Steroid Treatment)	Mean	3.9	4.4
	SE	0.22	0.21
	N	93	98
Study Day 1 (After Oral Steroid Treatment)	Mean	2.7	2.9
	SE	0.16	0.15
	N	99	93
Week 12[c]	Mean	3.9	4.3
	SE	0.21	0.21
	N	91	86
Change from Run-in Period at Week 12	Mean	0.1	0.0
	SE	0.27	0.25
	N	71	73

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

Figure 11.4.1.5.A: 1129 and 1130: Percent of Patients Whose Serum Osteocalcin Concentration was Below the Reference Range at Week 12 [a]



[a] Included patients who had received at least 78 days of treatment and had an end of run-in, end of oral steroid treatment, and end of study treatment osteocalcin measure.

[b] Oral steroid burst was given before patients were randomized to study treatment.

✹ study 1163:

✦ 12 month, parallel, open study in 472 adult asthmatics; patients entered the study receiving 400-1600 mcg/day of BDP-CFC and were continued during the study on this dose or ½ the dose as BDP-HFA.

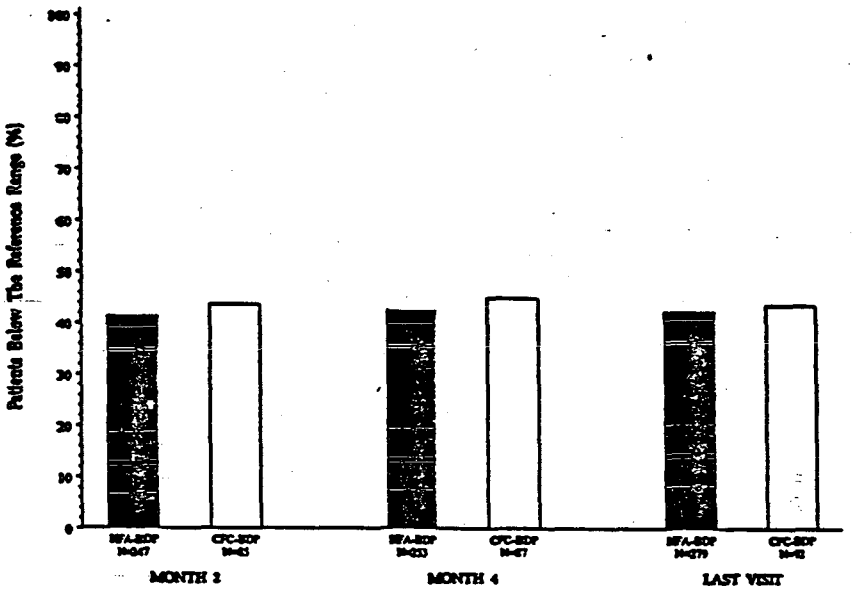
✦ There are no definitive conclusions about the effect of BDP-HFA on bone metabolism that can be drawn from the data obtained in this study. Based on mean change from baseline, there is a very slight, probably clinically insignificant, decrease in serum osteocalcin in patients receiving BDP-HFA and BDP-CFC (see table 11.4.1.6.A, p243, v1.271 below). On the other hand, over 40% of patients in both groups had serum osteocalcin levels below the lower limit of the NRR after 2 months of treatment (see figure 11.4.1.6.A below). Because these patients were receiving inhaled corticosteroids, in some cases, high dose inhaled corticosteroids, at entry into the study and received variable amounts of inhaled corticosteroids in an open fashion throughout the study, little clinical importance can be attached to the data from this study, other than the general impression that inhaled corticosteroids whether administered as the HFA or the CFC product will produce a decrease in serum osteocalcin that is of unknown clinical significance.

Table 11.4.1.6.A: 1163: Adjusted Means and Mean Change from Baseline in Serum Osteocalcin Concentrations (ng/mL) for Patients ≥ 21 Years of Age

Study Visit		HFA-BDP	CFC-BDP	P-Value[a]
Baseline	Mean	2.01	1.98	0.882
	SE	0.092	0.157	
	N	302	100	
Month 2	Mean	2.07	1.99	
	SE	0.094	0.154	—
	N	256	88	
Month 4	Mean	1.91	1.86	
	SE	0.093	0.159	—
	N	263	89	
Last Visit	Mean	1.96	1.89	
	SE	0.088	0.150	—
	N	290	95	
Change from Baseline at Month 2	Mean	0.02	0.04	0.913
	SE	0.080	0.132	
	N	247	84	
Change from Baseline at Month 4	Mean	-0.05	0.02	0.638
	SE	0.081	0.137	
	N	253	86	
Change from Baseline at Last Visit	Mean	-0.06	0.04	0.521
	SE	0.077	0.131	
	N	279	91	

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

Figure 11.4.1.6.A: **1163: Percent of Patients ≥ 21 Years of Age Whose Serum Osteocalcin Concentration was Below the Reference Range**



Cross-study Comparison of Decrease in Serum Osteocalcin

Dose of BDP	2 weeks	12 weeks
BDP-HFA		
200 mcg	2/0.5 ng/ml	----------
400 mcg	2.5 ng/ml	0.5 ng/ml
800 mcg	2.8/3.5 ng/ml	None
1600 mcg	5.7 ng/ml	----------
CFC-HFA		
800 mcg/ml	1 ng/ml	0.4 ng/ml
1500 mcg	-------	None

COMMENTS: The data suggest that there is an effect of BDP, whether delivered with the CFC or the HFA propellant, on serum osteocalcin and that this effect is dose-related. There is also a suggestion based on the data submitted from the studies of longer duration, that with continued administration, there is less of a decrease in serum osteocalcin. However, because of the difference in study design, the small number of patients in the studies of shorter duration, the wide variation in dose in the one year study, and the uncertain clinical significance of the changes seen in serum osteocalcin, no definitive statement can be made about the effect of BDP-HFA on bone metabolism, based on the serum osteocalcin values obtained in these studies.

- laboratory values: no significant changes were seen after administration of either BDP-HFA or BDP-CFC.

- Vital signs: no significant changes were seen after administration of either BDP-HFA or BDP-CFC.

- ECGs: no significant changes were seen after administration of either BDP-HFA or BDP-CFC.

CONCLUSIONS: The 50 mcg/puff concentration of BDP-HFA is safe based on the data provided by the sponsor, including evaluation of the HPA axis, over the dose range proposed for administration. There is inadequate data on the 100 mcg/puff concentration, particularly in regard to the effect on the HPA axis, to conclude that this concentration is safe over the dose range proposed for adminstration.