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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-911

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION
STABILITY STUDY

		Date:
NDA Number:	20-911	AUG 2 5 2000
Applicant:	3M Pharmaceuticals	
Name of Drug:	QVAR Inhalation Aerosol	
Statistical Reviewer:	Barbara Elashoff	
Chemistry Reviewer:	Alan Schroeder	
Documents Reviewed:	Electronic Data April 14, 2000; April 25, 2000	

Summary of Review

- The sponsor proposed a— -month expiration date for the 50 and 100 mcg strengths.

- The chemist requested a statistical review of the sponsor's stability data for the four different canister types:

  1. 50 mcg strength/100 actuations;
  2. 50 mcg strength/200 actuations;
  3. 100 mcg strength/100 actuations; and
  4. 100 strength/200 actuations.

- The data in this submission were unique in that the stability studies were carried out at two different manufacturing sites and in three different storage positions. Further, the number of months of stability data at each batch varied from 3 months to 36. Only batches with at least three datapoints were used in the analysis. Since data cannot be pooled across storage orientation, manufacturing site, or canister type (strength/ actuations), very few test parameters had the required three batches for each unique combination of storage orientation and manufacturing site. None of the four different canister types had enough data for all test parameters to make an overall determination of expiration date.

- The chemist requested a review of the individual acceptance criteria for particle size distribution and leakage rate. All batches passed the Level I test for both parameters.

Introduction

3M Pharmaceuticals has submitted stability data on four different cansiter types: 50 mcg/100 actuations, 50 mcg/200 actuations, 100 mcg/100 actuations and 100 mcg/200 actuations. The sponsor has proposed a – month expiration period for all canister types. The reviewing chemist has requested Division of Biometrics to perform a statistical review and evaluation of the sponsor's stability data (stored at the conditions of 25C/60%RH) for each of the following parameters in Table 1 using the specifications listed below:

Table 1: Factors Used to Estimate Expiration Dates Specifications

Test Factor	Minimum Specification	Maximum Specification
- Total		
Water -100 actuations -200 actuations		
Leakage Rate		

The reviewing chemist distinguished between the sponsor's specification for and the FDA's specification . The numbers in the table refer to the exact value of the maximum (or minimum) specification line that is plotted in the graphs (i.e., for). The earliest timepoint that a confidence interval crossed a specification line denotes the expiration date.

Sponsor's Analyses

The sponsor's analyses of the data incorporated the following:

- only used batches with at least 12 months of data and at least 5 timepoints;
- in cases where months 1 and 2 were recorded, deleted these timepoints from analysis;
- used log-transformed data for the analyses of the data.

This reviewer only used batches with at least 3 timepoints (regardless of the number of months), used all the data (did not delete Months 1 and 2) and used untransformed results.

The sponsor interpreted the data over time as being non-linear and thus used log-transformed data in the analyses. This reviewer plotted the data and found it to be fairly linear within batch. Taken as a whole, the 50/200 data do suggest a non-linear relationship (Figure 1). However, there is not enough data within batch to determine this. Further, the 100/200 data appear linear, even for Batch PD4300, which has 27 months of data (Figure 2).

Figure 1

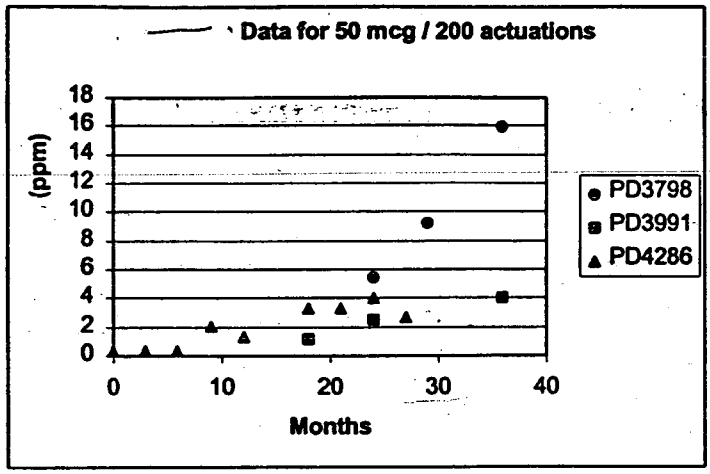
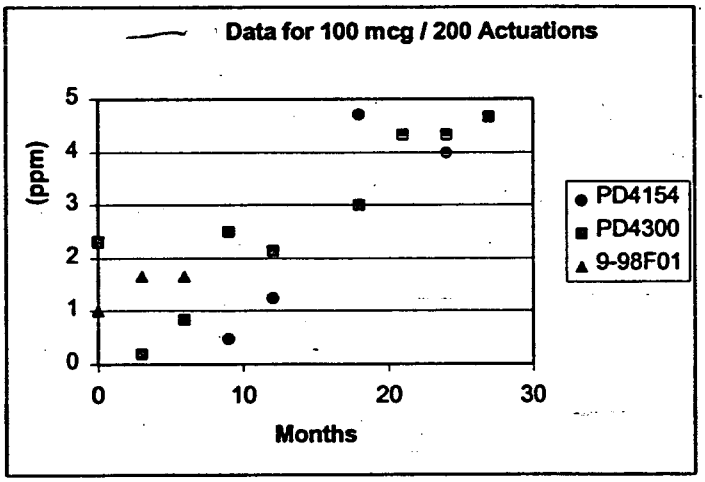


Figure 2



Reviewer's Analyses

The data in this submission were unique in that the stability studies were carried out at two different manufacturing sites and in three different storage positions. Further, the number of months of stability data at each batch varied from 3 months to 36. Only batches with at least three datapoints were used in the reviewer's analysis. Since data cannot be pooled across storage orientation, manufacturing site, or canister type (strength/ actuations), very few test parameters had the required three batches for each unique combination of storage orientation and manufacturing site. Figure 1 depicts the storage orientations, manufacturing sites and canister sites with at least 3 batches with at least 3 timepoints for each test parameter. None of the four different canister types had enough data for all test parameters to make an overall determination of expiration date.

Figure 1: Combinations of Storage Orientation, Site, Canister Type and Test Parameters that had at least 3 batches, with each batch having at least 3 timepoints

50 mcg - 100 actuations

	Inverted		Upright		Horizontal	
	CA	UK	CA	UK	CA	UK
Water content	X	X	X			
Total Impurities						
Individual Degradant:						
Leakage Rate						
PSD Plates 0-3						
PSD Plates 4-6						

50 mcg - 200 actuations

	Inverted		Upright		Horizontal	
	CA	UK	CA	UK	CA	UK
Water content	X	X		X		
Total Impurities						
Individual Degradant:						
	X					
Leakage Rate						
PSD Plates 0-3		X				
PSD Plates 4-6		X				

100 mcg - 100 actuations

	Inverted		Upright		Horizontal	
	CA	UK	CA	UK	CA	UK
Water content	X	X				
Total Impurities						
Individual Degradant:						
Leakage Rate		X				
PSD Plates 0-3		X				
PSD Plates 4-6		X				

100 mcg - 200 actuations

	Inverted		Upright		Horizontal	
	CA	UK	CA	UK	CA	UK
Water content	X	X				
Total Impurities		X				
Individual Degradant:		X				
		X				
Leakage Rate						
PSD Plates 0-3		X				
PSD Plates 4-6		X				

For the few test parameters that had at least 3 batches with at least 3 timepoints, the statistical procedures in the FDA Guidelines (February 1987) were applied. For all the parameters with upper limit specifications only, the estimated expiration dates were calculated from the specifications limit and the upper one-sided 95% confidence interval of the regression lines. For the Particle Size Distribution Plates 4-6 variable, the estimated expiration dates were calculated from the specifications limits and the upper and lower two-sided 95% confidence intervals of the regression lines. The estimated expiration dating periods for the four canister types are listed in Table 2.

Table 2: Summary Table of Expiration Dates
(Data were extrapolated 6 months beyond the range of available data using the batch with the longest amount of time on stability.)

Actuations	Strength	Test	Site	Position	Exp Date	Notes
100	50	Water	CA	Inverted	32	
100	50	Water	CA	Upright	35	
100	50	Water	UK	Inverted	28	
100	100	Leakage Rate	UK	Inverted	>42	1 batch had only 6 months of data
100	100	PDS 4-6	UK	Inverted	0	1 batch had only 3 months of data; all obs. >28
100	100	PSD 0-3	UK	Inverted	0	1 batch had only 3 months of data; all obs. >2
100	100	Water	CA	Inverted	29	
100	100	Water	UK	Inverted	28	
200	50	—	CA	Inverted	>42	
200	50	PDS 4-6	UK	Inverted	>30	1 batch had only 3 months of data
200	50	PSD 0-3	UK	Inverted	7	1 batch had only 3 months of data
200	50	Water	CA	Inverted	31	
200	50	Water	UK	Inverted	22	
200	50	Water	UK	Upright	30	
200	100	—	UK	Inverted	>32	1 batch had only 6 months of data
200	100	—	UK	Inverted	6	1 batch had only 6 months of data
200	100	PDS 4-6	UK	Inverted	0	1 batch had only 6 months of data; all obs. >30
200	100	PSD 0-3	UK	Inverted	>30	1 batch had only 6 months of data
200	100	Total Impurities	UK	Inverted	>30	1 batch had only 6 months of data
200	100	Water	CA	Inverted	32	
200	100	Water	UK	Inverted	33	1 batch had only 6 months of data

Note that in a few cases (PSD 0-3 and 4-6), all the observations were greater than the maximum specification limit.

The estimated expiration dating periods in this review are based on data extrapolation beyond the range of storage time actually observed, which is valid under the assumption that the pattern of deterioration does not change significantly over the extrapolation period. The standard policy is to extrapolate only 6 months beyond the range of available data. Usually, all three batches in the analysis have the same number of months of data. In some of the cases in this submission, one of the batches had as little as 3 or 6 months of data (see Table 2 above), significantly fewer months than the other batches (— months). The greater the extrapolation period beyond the observed data, the less accurate the estimate of the line is. It is unclear what can be inferred from the cases in which one batch has significantly fewer months of data than the others.

Table 3 below depicts the same information as Table 2, in a different format.

Table 3: Summary Table of Expiration Dates
(Data were extrapolated 6 months beyond the range of available data using the batch with the longest amount of time on stability.)

50 mcg - 100 actuations

	Inverted		Upright		Horizontal	
	CA	UK	CA	UK	CA	UK
Water content	32	28	35			
Total Impurities						
Individual Degradant: —						
—						
Leakage Rate						
PSD Plates 0-3						
PSD Plates 4-6						

50 mcg - 200 actuations

	Inverted		Upright		Horizontal	
	CA	UK	CA	UK	CA	UK
Water content	31	22		30		
Total Impurities						
Individual Degradant: —						
—	>42					
Leakage Rate						
PSD Plates 0-3		7				
PSD Plates 4-6		38				

100 mcg - 100 actuations

	Inverted		Upright		Horizontal	
	CA	UK	CA	UK	CA	UK
Water content	29	28				
Total Impurities						
Individual Degradant: —						
—						
Leakage Rate		>42				
PSD Plates 0-3		0				
PSD Plates 4-6		0				

100 mcg - 200 actuations

	Inverted		Upright		Horizontal	
	CA	UK	CA	UK	CA	UK
Water content	32	33				
Total Impurities		>30				
Individual Degradant: —		6				
—		>32				
Leakage Rate						
PSD Plates 0-3		>30				
PSD Plates 4-6		6				

Individual Acceptance Criteria

The chemist requested a review of the individual acceptance criteria for particle size distribution (plates 0-3 and 4-6) and leakage rate. All batches passed the level 1 test for the particle size distribution parameter, with the following comments:

- UK Batch PD4333 Inverted, Month 6: 100 mcg/100 actuation: sampled n=4 instead of n=5
- UK Batch 9-98F01 Initial, Month 0: 100 mcg/200 actuation: sampled n=6 instead of n=5
- UK Batch PD10267 Inverted, Month 2: 100 mcg/100 actuation: sampled n=10 instead of n=5 (the first 5 canisters passed the Level 1 test)
- CA Batch PD10118 Initial, Month 0: 50 mcg/200 actuation: sampled n=6 instead of n=5
- CA Batch PD4284 Inverted, Month 22: 100 mcg/200 actuation: sampled n=10 instead of n=5 (the first 5 canisters passed the Level 1 test)
- CA Batch PD4375 Inverted, Month 22: 100 mcg/100 actuation: sampled n=10 instead of n=5 (the first 5 canisters passed the Level 1 test)

All batches passed the level 1 test for leakage rate as well, with the following comment:

- UK Batch 10267 Inverted, Month 1: 100 mcg/100 actuation: sampled n=13 instead of n=12

Conclusions

The estimated expiration dating periods in this review are based on data extrapolation beyond the range of storage time actually observed, which is valid under the assumption that the pattern of deterioration does not change significantly over the extrapolation period. The proposed — month expiration date for the four canisters is not supported by the data the sponsor submitted. Very few test parameters had the required three batches for each unique combination of storage orientation and manufacturing site. None of the four different canister types had enough data for all test parameters to make an overall determination of expiration date.

/S/

Barbara Elashoff

/S/ 8/25/2000

Concur: Dr. Lin

8/25/2000

cc:
Orig. NDA
HFD-570 / Division File
HFD-570 / SBarnes, ASchroeder, GPoochikian, Y-YChiu, RNicklas
HFD-715 / Division File, BElashoff, SWilson, KLin

INTEROFFICE MEMO

TO: NDA 20911

FROM: C. Joseph Sun, Ph. D., Pharmacologist/Toxicologist Team Leader (HFD-570)

DATE: May 10, 1999 May 10, 1999

The NDA has been filed under the provisions of 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The new preclinical studied submitted in the present application include bridging toxicology and reproductive toxicology studies to support an HFA-134 formulation.

I concur with pharmacologist's recommendation that pharmacology and toxicology of beclomethasone dipropionate (BDP) have been adequately studied and the drug is approvable form a preclinical standpoint.

BDP is a synthetic corticosteroid with anti-inflammatory activity.

Chronic toxicity studies were performed in rats (subcutaneous) and dogs (intramuscular). Systemic toxicity revealed in both species is typical glucocorticoid activity evidenced by changes in thymus and adrenal and lymphoid depletion. Local toxicity investigated in dogs and rats (up to 6 months in duration by inhalation/intranasal route) found only limited typical systemic toxicity in adrenal gland but without any local toxicity in respiratory tree.

Impairment of fertility was indicated by inhibition of the estrous cycle in dogs following oral administration but was not observed by the inhalation route.

Mutagenic studies have not been performed in the currently marketing products.

BDP demonstrated no carcinogenic potential in a 95-week rat study (82 weeks by oral route and 13 weeks by inhalation route).

BDP, like other corticoids, produced teratogenicity and embryotoxicity in the mouse and rabbit by subcutaneous route but not by inhalation route.

The bridging inhalation toxicity studies in rats (3 months) and dogs (one year) using the HFA-134 formulation revealed no unusual systemic and local toxicity. Although no teratogenicity was found in the rat bridging inhalation teratology study, finding of drug-related adrenal toxicity in fetuses following BDP/HFA-134 formulation suggest the infant born of mother receiving BDP/HFA-134 during pregnancy should be observed for adrenal toxicity and this should be indicated in the labeling.

The proposed labeling needs to be updated with the above-mentioned findings.

There is no outstanding preclinical issue.

CC: Orig NDA 20911
HFD-570/Division
HFD-570/Sun
HFD-570/Barnes

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA #:	20-911 Date: MAY 11 1999
Applicant:	3M Pharmaceuticals
Name of Drug:	QVAR™, Beclomethasone Dipropionate in Propellant HFA-134a, Inhalation Aerosol
Indication:	Maintenance treatment of asthma as prophylactic therapy, and for asthma patients who require systemic corticosteroid treatment to reduce or eliminate the need for systemic corticosteroids
Documents Reviewed:	11-May, 1998. Vols. 1.1 – 1.2, and 1.276 – 1.476 10-September, 1998, Amendment 2, 4-month Safety Update
Statistical Reviewer:	Stephen E. Wilson, Dr. P.H.
Medical Input:	Richard Nicklas, M.D. (HFD-570)
Key Words:	comparability, equivalence, switch, dose-response, Jonckheere's test for linear trend

The sponsor has submitted the results from six controlled trials (Studies 1081, 1083, 1192, 1129, 1130 and 1163) designed to demonstrate the efficacy and safety of **QVAR™**, Beclomethasone Dipropionate in Propellant HFA-134a (HFA- BDP), Inhalation Aerosol for the maintenance and treatment of asthma as prophylactic therapy, and for asthma patients who require inhaled corticosteriod (ICS) treatment to reduce or eliminate the need for systemic corticosteroids. The trial results submitted represent the sponsor's efforts to develop and conduct a CFC "switch" program, as described in the Points to Consider for the "Clinical Development Programs for MDI and DPI Drug Products" issued by the Division of Oncology and Pulmonary Drug Products, September 19, 1994. (Sponsor tables and figures describing these six trials are included with this report in Attachment A.1. - 4.)

The statistical review and evaluation of NDA 20-911 focuses on four of these controlled trials (Studies 1081, 1083, 1092 and 1129):

Study 1081: A 6 Week Comparison of a Daily Dose of 100 mcg and 200 mcg of HFA-134a Beclomethasone Dipropionate with Placebo in Subjects with Mild to Moderate Reversible Obstructive Airways Disease;

Study 1083: Six-Week Trial to Demonstrate Equivalent Efficacy of Two Dose Strengths of HFA-134a Beclomethasone Dipropionate in Subjects With Reversible Obstructive Airway Disease;

Study 1129: Comparison of 400 mcg HFA-134a Beclomethasone Dipropionate (HFA-BDP), 800 mcg CFC-11/12 Beclomethasone Dipropionate (CFC-BDP), and Placebo (HFA-Placebo) in Patients with Asthma; and

Study 1192: Dose Response Comparison of HFA-134a Beclomethasone Dipropionate with CFC-11/12 Beclomethasone Dipropionate in Patients with Asthma.

(Attachment B 1. - 4.) describes study design features of each of these four trials, abstracted from the sponsor's protocols).

In consultation with the medical reviewer for this application, the remaining two studies -- Studies 1130 and 1163 -- were not included in this review. Study 1130 was a comparison of a high dose (800 mcg) of HFA-BDP and an unapproved, high dose (1500 mcg) of CFC-BDP in asthmatic subjects. Study 1163 was a 12-month, open-label, safety and efficacy study of HFA-BDP in which subjects were switched from CFC-BDP to HFA-BDP and individually titrated to maintenance doses.

Background and Overview

This reviewer has concluded that the sponsor's submission, describing the four reviewed studies, represents generally good statistical practice in clinical trials design, analysis and reporting. The statistical approach was, with few exceptions, consistent across studies. ANOVA with terms for treatment, center and treatment-by-center interaction was used to test differences between products. In an attempt to demonstrate comparability the sponsor predefined "equivalence" boundaries and used a two one-sided test approach. The two primary lung function, efficacy endpoints (mean change from baseline in AM PEFR in Studies 1083 and 1129, and mean change from baseline in FEV_1 as percent predicted in Studies 1081 and 1192) were well described in the protocols. In addition, analyses for the studies (with the exception of Study 1192, discussed below) were pre-defined and results consistently presented in the study reports and appendices. Additional details concerning design, conduct and analysis are included in following sections that provide detailed descriptions of the studies and comments regarding review issues (Note: results presented in this review, unless otherwise stated, are for the sponsor defined intent-to-treat populations).

Likewise, it appears that exclusion and inclusion criteria were successfully implemented and that baseline values were well-balanced across treatment groups in each of the four trials. Withdrawal rates for each of the studies were relatively modest given the condition of the patients studied, ranging from 5.6% for Study 1192 (a 12-week dose-ranging, switch study that did not include a placebo) to 17.6% for Study 1129 (a 12-week study with a 31.6% placebo drop-out rate). Compliance, as measured by limits placed on pre-specified canister weighing procedures and measurement of the use of concomitant medications appear to be within reasonable limits in each of the four studies. In general, conclusions based on secondary efficacy variables (described as "confirmatory efficacy measures" by the sponsor)

tend to agree with analyses using the primary variables. In conclusion, with a few exceptions, these trials appear to well conducted and reported.

In a switch program, the sponsor is required to present data describing the "comparability" of the innovator to the currently marketed product. As an important part of a switch program, the Division (the Division of Pulmonary Drug Products or DPDP) recommends that sponsors conduct a double-blind, randomized, 12 week dose-ranging, safety and efficacy study with three treatment arms -- CFC active, non-CFC active and non-CFC placebo formulations -- with at least two doses of each of the active formulations covering a range that is capable of demonstrating comparable, differential responses. Complicating this assessment of the comparability of CFC-BDP and HFA-BDP formulations, the application does not include a study using this design. However, the sponsor maintains that the trial results submitted with the application provide sufficient evidence to make a judgement concerning the comparability of the products.

An initial step in evaluating a switch-oriented study is to determine, based on pre-defined design and analytical criteria, whether or not the active treatments are statistically superior to placebo. If both of the active treatments "beat" placebo (evidence that the trial confirms the efficacy of the active treatments), then a "comparability" assessment can be made. If a placebo is not practical in studying a given population, then a low dose treatment group can be used for these statistical comparisons. However, the decision as to whether or not two treatments are "comparable" is not strictly based on statistical test procedures -- assessment of comparability is based on review and assessment of all of the relevant evidence submitted in an application.

Given the complexity of determining appropriate doses for inhalation products, the Division recommends that the dose-ranging study include more than one dose of the active treatment over a comparable range of activity -- it is not sufficient to measure the effect of a single dose of the CFC and the non-CFC product and to judge the two products comparable at all prescribed doses. The Division needs data to provide guidance for the range of patients who will be substituting the non-CFC product for their CFC inhaler -- single dose comparisons do not provide sufficient information.

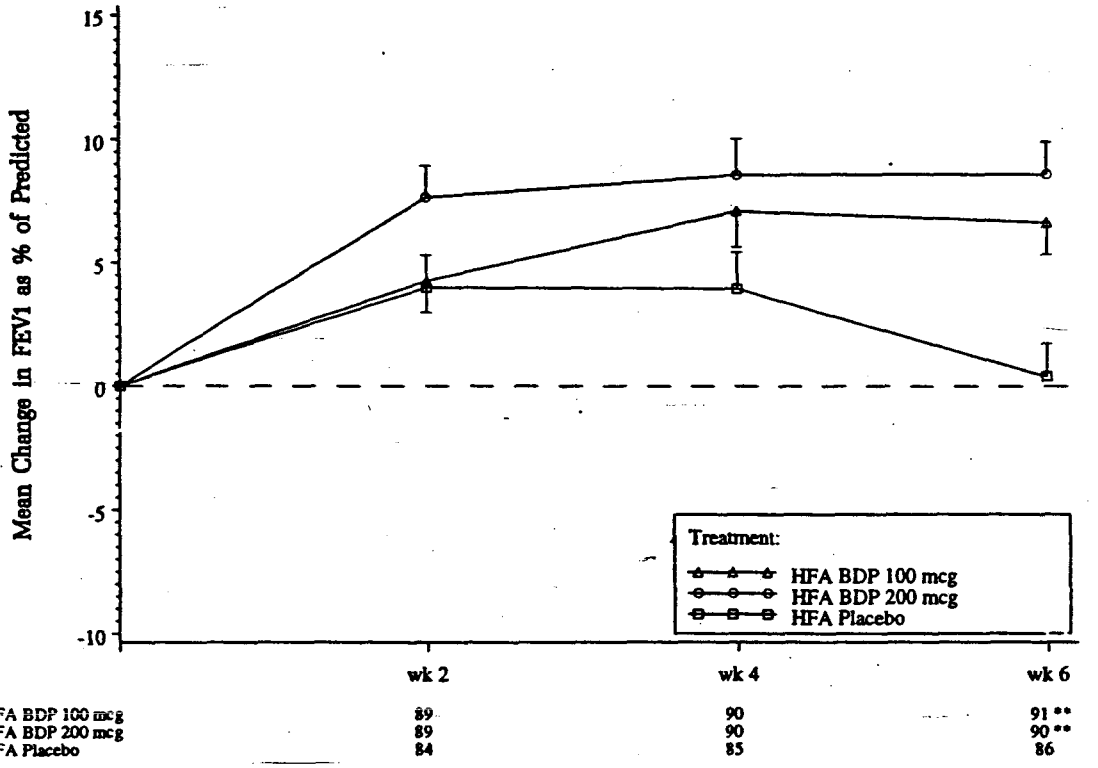
As this submission does not include a single study with all of the recommended design features, it is important to piece together the relevant information from different trials to determine whether or not, as the sponsor contends, there is sufficient information to make a comparability assessment. As cross-study comparisons are inherently complex as differences in design, study conditions, conduct, patient populations, timing, etc. independently condition the conclusions and influence the estimates of each study, this assessment is difficult.

Study 1081

Results from Study 1081 (displayed in Figure 1 and Table 1), a comparison of 100mcg HFA-BDP_{50}, 200mcg HFA-BDP_{50} and HFA placebo, clearly demonstrated that both of the tested doses of active drug were statistically superior to placebo in treating asthma.

Reviewer Comment. The designed doubling of doses in this study did not statistically differentiate the activity of the treatment over the low, limited range of doses tested (i.e., the results for the 100mcg HFA-BDP_{50} treatment group were not statistically different from those for the 200mcg HFA-BDP_{50} treatment group.)

Figure 1 **Study 1081: Comparisons with Placebo for Adjusted Mean (SE) Change from Baseline in FEV_1 as Percent of Predicted by Week (Patients Included in the Intent-to-Treat Analysis)**



Source: NDA 20911, Vol. 2, p. 109, Figure 3.8.3.1.1.A.

Table 1 **Study 1081. Adjusted Mean Change from Baseline in FEV_1 as Percent of Predicted: Comparisons with Placebo (Patients Included in the Intent-to-Treat Analysis)**

Study Week		HFA Placebo	HFA BDP 100 mcg	HFA BDP 200 mcg
Baseline	Mean	77.1	75.3.	75.5
	SE	0.83	0.80	0.81
	N	87	91	92
Change from Baseline at Weeks 1-2	Mean	4.0	4.3	7.7
	SE	1.32	1.28	1.29
	N	84	89	89
Change from Baseline at Weeks 3-4	Mean	4.0	7.1	8.6
	SE	1.50	1.46	1.47
	N	85	90	90
Change from Baseline at Weeks 5-6	Mean	0.4	6.7**	8.6**
	SE	1.34	1.30	1.32
	N	86	91	90

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

b. Comparisons of active treatments with placebo: ** $p \leq 0.01$; * $p \leq 0.05$; + $p \leq 0.10$

Source: NDA 20911, Vol. 276, p. 168, Table 13

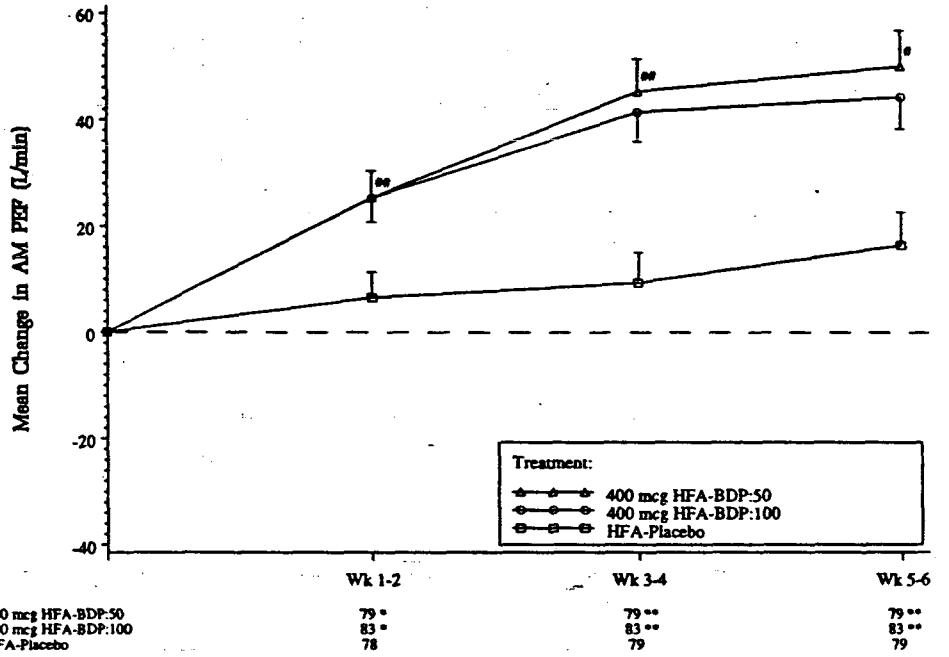
Study 1083

In Study 1083, the sponsor compared equal doses (400mcg) of two formulations (HFA-BDP_{50} and HFA-BDP_{100}) to demonstrate equivalence. Validating the study, both formulations at the 400mcg dose were statistically better than placebo in improving AM-PEFR, and were not statistically different from one another. The sponsor attempted to pre-specify equivalence boundaries in using a two one-sided test procedure to demonstrate equivalence. In the protocol ± 40 L/min was described as the pre-specified limits. However, after the study was completed the sponsor used ± 25 L/min *post hoc* boundaries. The results for the two HFA-BDP products fell within these limits for the study's primary endpoint [Adjusted Mean Change from Baseline in Morning Peak Flow (L/min),Weeks 5-6] and the sponsor uses this result to support an equivalence claim.

Review comment: In applying a two one-sided test paradigm to decide if two products are equivalent, it is necessary to preset acceptable boundaries. There was no agreement as to what difference in the products constituted an acceptable boundary. The sponsor's pre-specified ± 40 L/min pre-specified limits are clearly too wide and the post hoc *± 25 L/min are still too liberal to serve as acceptance boundaries. Similar to the recommended requirements for the CFC-HFA switch program, a comparability assessment of two formulations of an inhaled corticosteriod should be based on more than one dose level of each product. The sponsor has not provided these data.*

Other data collected in Study 1083 potentially counter the sponsor's equivalence claim. In addition to the results for the primary variable (Percent Change from Baseline in AM PEFR -- Figure 2 and Table 2), the results for Change from Baseline in FEV_1 as Percent of Predicted are presented below in Figure 3. The results for FEV_1 appear to indicate a potential diminution in efficacy by the sixth week of the trial. Though this decrease is not evident in the primary variable (which averages daily AM PEFR scores over the fifth and sixth weeks of the study) it might possibly merit additional investigation.

Figure 2 **Study 1083: Comparisons with Placebo for Adjusted Mean (SE) Change from Baseline in Morning Peak Flow (L/min) by Study Week (Patients Included in the Intent-to-Treat Analysis)**



	Wk 1-2	Wk 3-4	Wk 5-6
N:400 mcg HFA-BDP:50	79 *	79 **	79 **
N:400 mcg HFA-BDP:100	83 *	83 **	83 **
N:HFA-Placebo	78	79	79

P-values for comparisons of each active treatment with placebo: **: <= 0.003; *: p<= 0.017; +: p<= 0.03.
Source: NDA 20911, Vol. 2, p. 111, Figure 3.8.3.1.2.B.

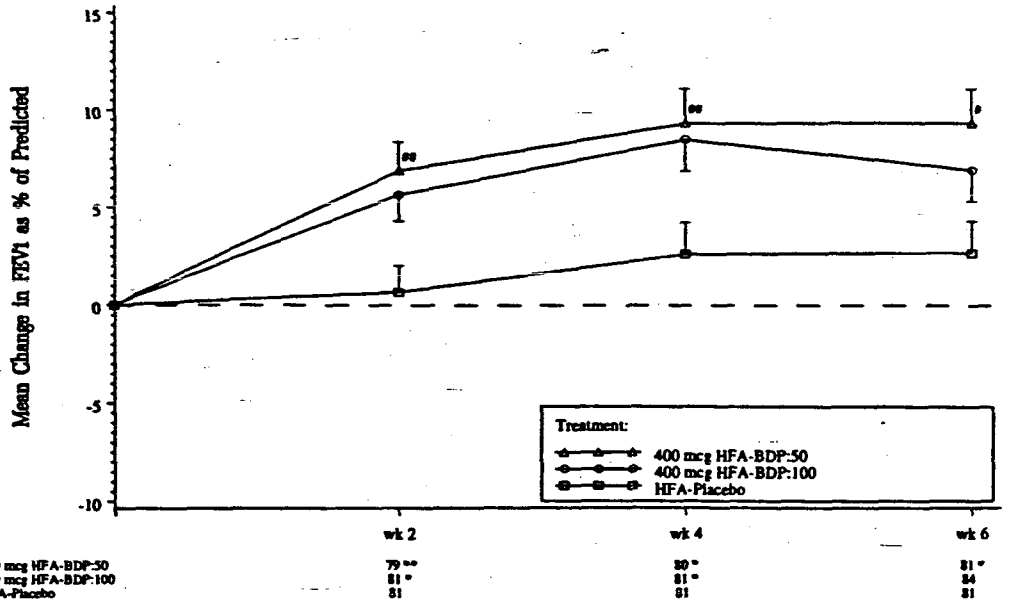
Table 2 **Study 1083 Adjusted Mean Change from Baseline in Morning Peak Flow (L/min): Comparisons with Placebo (Patients Included in the Intent-to-Treat Analysis)**

Study week	HFA-Placebo	HFA-BDP$_{50}$ 400 mcg	HFA-BDP$_{100}$ 400 mcg
Baseline (L/min)	350.1	374.1	362.4
	8.23	8.51	8.04
	83	82	86
Change from Baseline at Weeks 1-2	6.6	25.4*	25.3*
	4.75	5.10	4.57
	78	79	83
Change from Baseline at Weeks 3-4	9.4	45.4**	41.5**
	5.68	6.12	5.49
	79	79	83
Change from Baseline at Weeks 5-6	16.5	50.2**	44.4**
	6.24	6.72	6.03
	79	79	83

Comparisons of active treatments with placebo:** : $p \leq 0.003$; * : $p \leq 0.017$; +: $p \leq 0.03$ (Bonferroni Adjustment).

Source: NDA 20911, Vol. 2, p. 110, Table 3.8.3.1.2.A.

Figure 3 **Study 1083: Comparisons with Placebo for Adjusted Mean (SE) Change from Baseline in FEV_1 as Percent of Predicted by Week (Patients Included in the Intent-to-Treat Analysis)**

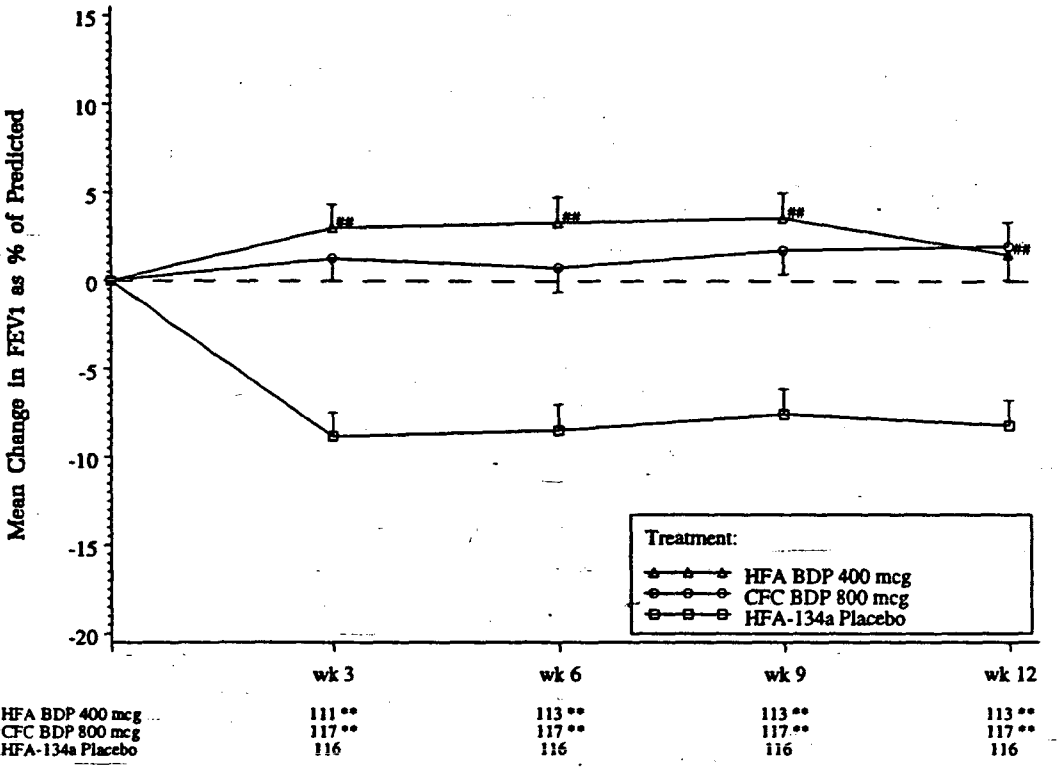


Source: NDA 20911, Vol. 2, p. 109, Figure 3.8.3.1.1.B.

Study 1129

Study 1129 tested a HFA-BDP_{50} 400mcg treatment against CFC-BDP 800mcg and HFA-BDP placebo. A combination of steroid naïve (63%) and oral steroid using patients were given a run-in, stabilizing dose of prednisone, and then randomized to one of the three groups. The measured AM PEFR (Figure 4 and Table 3) for the placebo patients declined, while the two active treatment groups maintained a high level of lung function. The two active treatments were statistically superior to placebo for the pre-specified endpoint (and statistically indistinguishable from one another).

Figure 4 **Study 1129: Comparisons with Placebo: Adjusted Mean (SE) Change from Oral Steroid Treatment in FEV1 as Percent of Predicted by Week (Patients Included in the Intent-to-Treat Analysis)**



Source: NDA 20911, Vol. 2, p. 130, Figure 3.8.3.3.1.A.

Table 3 **Study 1129. Adjusted Mean Change from Oral Steroid Treatment in FEV_1 as a Percent of Predicted Analysis[a] (Patients Included in the Intent-to-Treat Analysis)**

Study week		HFA-Placebo	HFA-BDP 400 mcg	CFC-BDP 800 mcg
Run-in (% predicted)	Mean	70.3	70.2	67.3
	SE	1.64	1.65	1.57
	N	117	113	117
Oral Steroid Tx (% predicted)	Mean	78.0	80.1	79.7
	SE	1.68	1.69	1.61
	N	117	113	117
Change from Oral Steroid Tx at Week 3	Mean	-8.8	3.0**	1.3**
	SE	1.32	1.32	1.25
	N	116	111	117
Change from Oral Steroid Tx at Week 6	Mean	-8.5	3.3**	0.8**
	SE	1.46	1.45	1.39
	N	116	113	117
Change from Oral Steroid Tx at Week 9	Mean	-7.5	3.6**	1.8**
	SE	1.44	1.43	1.37
	N	116	113	117
Change from Oral Steroid Tx at Week 12	Mean	-8.2	1.5**	2.0**
	SE	1.44	1.43	1.37
	N	116	113	117

[a] Based on an ANOVA with treatment, center, treatment by center interaction terms in the model.
Study 1129: Comparisons of active treatments with placebo: **: $p \leq 0.003$; *: $p \leq 0.017$; +: $p \leq 0.03$.

Source: NDA 20911, Vol. 2, p. 129, Table 3.8.3.3.1.A.

Reviewer Comment: If the doses selected for the active treatments wre too high for the population studied, the results from this trial could not provide a good measure of the comparability of the two active treatments. If both groups were maintained on doses that were higher than required (i.e., one or both were being overdosed), then this study design could not demonstrate a difference between the products -- the design favored a finding of no difference.

Study 1192

In Study 1192 ICS subjects were randomized to one of six treatment groups ($HFA\text{-}BDP_{50}$ – 100mcg, 400mcg, 800mcg: $CFC\text{-}BDP_{50}$ – 100mcg, 400mcg, 800mcg) after a washout period. There were no placebo groups in this dose response study. As a 12 week trial comparing a range of doses of both CFC and non-CFC formulations, the results from this study constitute a major portion of the sponsor's evidence regarding comparability of the CFC and HFA products.

Reported results (displayed in Figure 6 and Table 4, below) for the primary variable (Change from Baseline in FEV1 as Percent of Predicted) indicate that both formulations exhibited dose ordering over the doses tested, and that the *post hoc* statistical tests submitted by the

sponsor reflect significant dose trends, demonstrating some relationship between improvements in efficacy with increasing doses.

As there were no placebo treatments, to validate the study it is important to determine whether or not different doses of each product in the study were statistically different from one another. In testing contrasts between doses (Figure 5) the sponsor reported a significant pre-defined difference ($\alpha \leq 0.05$ -- unadjusted for multiple.comparisons) for Change from Baseline in FEV1 as Percent of Predicted at Week 6 HFA-BDP_{50} 400mcg vs. 800mcg.

Reviewer Comments. The tested comparison between 400mcg and 800mcg of the HFA-BDP and CFC-BDP products was pre-specified in the protocol. As this was the comparison of interest in defining the sample size for the study, it is apparent that the sponsor was interested in testing dose levels of a given product -- perhaps, to determine whether the trial included a large enough difference to be useful in describing the comparability of the products. The results were significant for the HFA-BDP product ($p = 0.044$), but not for the CFC-BDP product ($p=0.090$). The study report does not appear to include 100mcg vs. 400mcg or 800mcg test results or the planned tests of "comparable" doses. To demonstrate that this study was capable of detecting differences in doses (conforming to the expectations for a comparability study) the sponsor should test the 100mcg vs. 800mcg contrasts for both products using an adjustment for multiple comparisons.

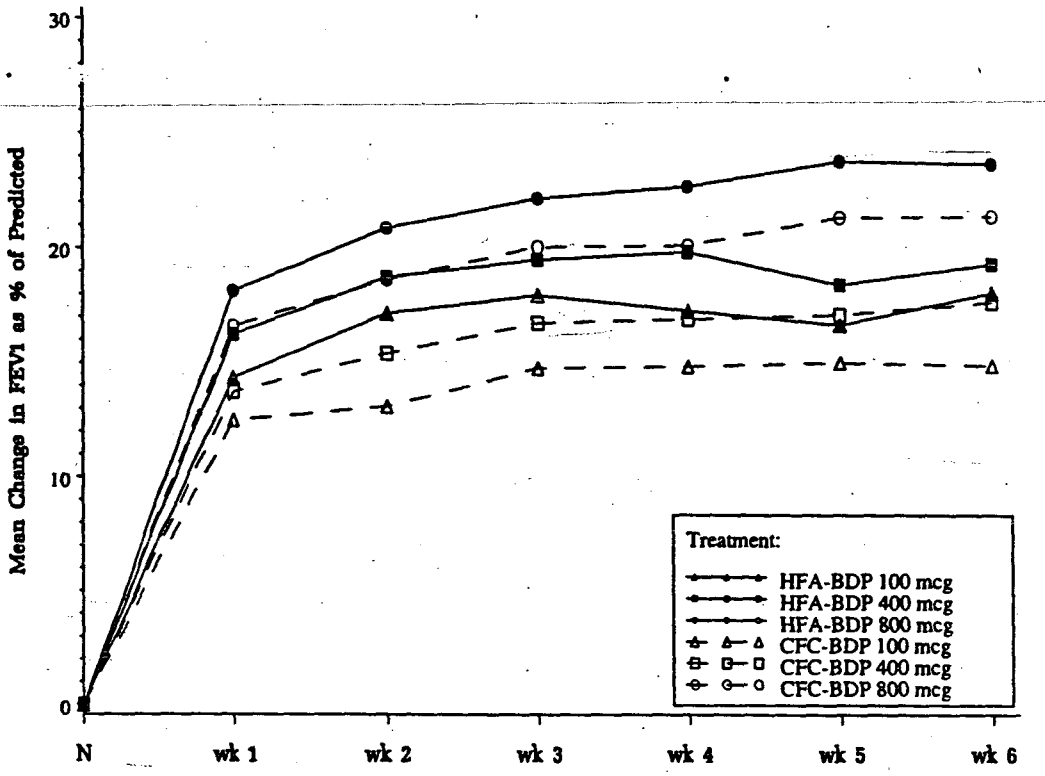
Figure 5 **Study 1192. Analysis of Variance Results for the Change from Baseline in FEV_1 as a Percent of Predicted at Week 6 (Patients Included in the Intent-to-Treat Analysis)**

ANOVA Model	P-value
Product Effect	0.061
Dose Effect	<0.001
Product by Dose Interaction	0.888
HFA-BDP Treatment Comparisons	
Linear Trend	0.009
100 mcg/day versus average of 400 and 800 mcg/day	0.075
400 mcg/day versus 800 mcg/day	0.044
CFC-BDP Treatment Comparisons	
Linear Trend	0.003
100 mcg/day versus average of 400 and 800 mcg/day	0.014
400 mcg/day versus 800 mcg/day	0.090

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

Source: NDA 20911, Vol. 2, p. 119, Table 3.8.3.2.1.B.

Figure 6 **Study 1192. Adjusted Mean Change From Baseline in FEV1 as Percent of Predicted by Week (Intent-to-Treat Analysis)**



	N	wk 1	wk 2	wk 3	wk 4	wk 5	wk 6
HFA-BDP 100 mcg	46	50	50	50	50	50	50
HFA-BDP 400 mcg	48	51	51	51	51	51	51
HFA-BDP 800 mcg	56	56	56	56	56	56	56
CFC-BDP 100 mcg	55	57	57	57	57	57	57
CFC-BDP 400 mcg	52	54	54	54	54	54	54
CFC-BDP 800 mcg	50	52	52	52	52	52	52

Source: *NDA 20911, Vol. 2, p. 118, Figure 3.8.3.2.1.A.*

Table 4 **Study 1192. Adjusted Mean Change from Baseline in FEV_1 as a Percent Predicted by Study Week (Patients Included in the Intent-to-Treat Analysis)[a]**

Study Week		HFA-BDP 100 mcg	HFA-BDP 400 mcg	HFA-BDP 800 mcg	CFC-BDP 100 mcg	CFC-BDP 400 mcg	CFC-BDP 800 mcg
Baseline (% predicted)	Mean	52.3	53.1	52.1	53.6	51.6	53.0
	SE	1.26	1.24	1.19	1.16	1.22	1.23
	N	50	51	56	59	55	52
Change from Baseline at Week 1	Mean	14.4	16.2	18.1	12.5	13.7	16.6
	SE	1.33	1.28	1.19	1.21	1.26	1.29
	N	46	48	56	55	52	50
Change from Baseline at Week 2	Mean	17.2	18.8	20.9	13.1	15.4	18.7
	SE	1.34	1.31	1.25	1.26	1.30	1.31
	N	50	51	56	57	54	52
Change from Baseline at Week 3	Mean	18.0	19.5	22.2	14.8	16.8	20.1
	SE	1.46	1.43	1.37	1.38	1.42	1.43
	N	50	51	56	57	54	52
Change from Baseline at Week 4	Mean	17.3	19.9	22.7	14.9	17.0	20.2
	SE	1.49	1.46	1.40	1.41	1.44	1.45
	N	50	51	56	57	54	52
Change from Baseline at Week 5	Mean	16.7	18.5	23.9	15.1	17.2	21.4
	SE	1.56	1.52	1.46	1.47	1.51	1.52
	N	50	51	56	57	54	52
Change from Baseline at Week 6	Mean	18.1	19.4	23.8	14.9	17.7	21.5
	SE	1.61	1.57	1.51	1.52	1.56	1.57
	N	50	51	56	57	54	52

[a] Based on ANOVA with product (HFA-BDP or CFC-BDP), dose (100, 400, or 800 mcg), center and all their interaction terms in the model.
Source: NDA 20911, Vol. 2, p. 117, Table 3.8.3.2.1.A.

Reviewer Comments. *In reviewing these results to make a determination of dose comparability, it is difficult to make strong conclusions concerning the observed relationship between the dose responses to CFC and HFA products. The sponsor maintains that there is an approximate 2 to 1 relationship in dosage strength, that is, due to differences in particle size and lung deposition, a patient requires only about one half of the dose of the HFA product to equal the efficacy of the CFC product.*

A visual inspection of the mean values for the primary variable (Adjusted Mean Change From Baseline in FEV1 as Percent of Predicted) at the end of the trial indicates that the dose relationship between the two products varied widely over the doses studied. For example, in contrast to the sponsor's hypothesized dose relationship, the 400mcg product was noticeably less effective than the 800mcg CFC treatment, while the 400 mcg CFC treatment was comparable to the 100mcg HFA-BDP_{50} (indicative of a 4 to 1 response ratio). Comparisons of this type demonstrate that the relationship between the doses of the two products varied with

dose level and that it is difficult to use a simplistic model to describe appropriate "switch" doses based on these trial data alone.

The sponsor presented a post hoc *analysis for Study 1192, choosing a "more informative model...that contained terms for product (HFA-BDP or CFC-BDP), dose, pooled center, and their interactions." This change in the analysis after an examination of the data is not appropriate in a confirmatory trial. Though there appears to be evidence that these data demonstrate dose ordering over the dose ranges tested, the sponsor should also present the planned analysis.*

In addition to this post hoc *change in the statistical model, the sponsor also chose to change plans regarding the study population used in the analysis. The original protocol states that the "evaluable" population will be used in the primary analysis, but the submission reports the analysis of the intent-to-treat population as the primary analysis. As the intent-to-treat population is a more appropriate population for this analysis, it is difficult to criticize this* post hoc *change. However, it is interesting to note that the results of the analysis for evaluable patients varied from those for the intent-to-treat population. For example, in the analysis of the evaluable population (Mean Change from Baseline in FEV_1 as a Percent Predicted), the 400mcg HFA and CFC treatment groups appear to be nearly identical (18.50 vs. 18.30). This sensitivity of the results to the selection of the population is another indication that it is difficult to assess switch doses based on these study data.*

Attempts to model these data to characterize dose response relationships are imprecise and subject to the reliance on unproved assumptions. The sponsor describes one such effort estimating that "relative airway availability" was "2.6, with a 95% CI of 1.1 to 11.6." Even if the assumptions used in developing this model could be shown to reflect reality with some confidence, it would be difficult to use such a potentially broad ranging estimate in describing dosing recommendations.

HFA-BDP_{50} and HFA-BDP_{100} Formulations as Stand-Alone Products

Given, as discussed above, that there is insufficient dosing information to make a confident determination as to whether the HFA and CFC products are comparable, it is useful to examine whether there is enough data to recommend that the HFA-BDP_{50} and HFA-BDP_{100} formulations can be approved as "stand-alone" products. Figure 7, below, provides a brief summary of the statistical test results for each formulation from the four studies.

Review Comments. These trials provide strong evidence that the HFA-BDP_{50} formulation effectively treats asthma. Statistically significant differences favoring doses of the test formulation were observed in relevant comparisons in each of the four studies. The sponsor has demonstrated that HFA-BDP_{50} product is superior to placebo at 100mcg, 200mcg and 400mcg strengths, and that the 800mcg dose was superior to the 400mcg strength in a dose response study of severe asthmatics (1192).

However, with the possible exception of the 400mcg strength, the sponsor has not independently replicated (in any two of the four studies reviewed) the findings for a given dose/formulation combination. The assessment of replicability (in a strict sense) for the

400mcg strength is complicated by the differences in the study designs of Studies 1083 and 1129, described above.

Figure 7 Statistically significant comparisons ($\alpha \leq 0.05$) for tested HFA-BDP Formulations

Study	Formulation Tested				
	HFA-BDP_{50}				HFA-BDP_{100}
	100mcg	200mcg	400mcg	800mcg	400mcg
1081[1]	*	*			
1083[2]			*		*
1129[3]			*		
1192[4]				*	

1. Primary, pre-specified comparisons with placebo. Primary endpoint -- improvement in percent predicted FEV_1. Adjusted for multiple comparisons. Steroid naïve population at baseline.
2. Primary, pre-specified comparisons with placebo. Primary endpoint -- improvement in AM PEFR. Adjusted for multiple comparisons. Steroid naïve population at baseline.
3. Primary, pre-specified comparison with placebo. Primary endpoint -- decline in AM PEFR. Adjusted for multiple comparisons. Mixed, steroid naïve (63%) and inhaled steroid dependent population at baseline.
4. Comparison with 400mcg dose. Primary endpoint -- improvement in percent predicted FEV_1. Inhaled steroid dependent population at baseline. No adjustment for multiple comparisons. (Note: This result is based on a *post hoc* analysis presented by the sponsor to study test dose trends).

Data from a Disqualified Investigator: Dr. Edwards

Study 1129 included 13 patients (3.7% of the study population) from Dr Edwards, a disqualified investigator. In a submission dated September 10, 1998 the sponsor provided a sensitivity reanalysis of the data for this study.

Review Comment. It does not appear that the exclusion of Dr. Edwards data changes the conclusions of this study. If any of the results of Study 1129 are included in the label for the product, the sponsor should insure that these data do not include the results from Dr. Edwards.

Conclusions

- The sponsor has submitted the results from four well-controlled studies (1081, 1083, 1129 and 1192) statistically demonstrating that **QVAR™** at doses ranging from 100mcg to 800mcg improves (or maintains) lung function in a variety of asthmatic patient populations.

- Studies 1081, 1083 demonstrated that doses ranging from 100mcg to 400mcg HFA-BDP are more effective than placebo in improving lung function in asthmatic patients.

- Study 1129 demonstrated that 400mcg HFA-BDP was more effective than placebo in maintaining a high level of lung function after run-in treatment with a high dose of an oral corticosteroid.

- Study 1192 provided statistical evidence that 800mcg HFA-BDP is superior to 400mcg HFA-BDP.

- Only one HFA-BDP dose -- 400mcg -- has statistically demonstrated superiority to a control in two independent studies.

- There is not enough information to compare doses of CFC BDP and HFA BDP products. Study 1192 was the only trial to include more than one dose of both HFA-BDP and CFC-BDP products. The sponsor maintains that the HFA-BDP dose should be halved to equal the efficacy of the CFC-BDP product. However, the results from Study 1192 do not provide support for this assertion. In this study 100mcg of the HFA-BDP product appears to be comparable to 400mcg of the CFC-BDP product, while 400mcg of the HFA-BDP product was clearly less efficacious than the 800mcg CFC-BDP.

- In Study 1192 the sponsor changed the planned analysis after examining the data. This is not appropriate in a confirmatory trial. The sponsor should be requested to submit the results of the planned analysis.

- Only limited clinical trials data are available to describe the equivalence of the 50mcg and 100mcg HFA-BDP formulations. The results of only one study at one dose (400mcg) were submitted to demonstrate that the 50mcg and 100mcg formulations of the HFA-BDP product are "equivalent." In assessing "equivalence" the sponsor has relied on two one-sided tests against *post hoc* boundaries. There is insufficient clinical trial data to make a confident determination of equivalence for an inhaled product.

Attachment A.1. Controlled Clinical Trial Characteristics

Study Characteristics	Study 1081	Study 1083	Study 1129	Study 1192
Treatment Duration[a]	6 weeks	6 weeks	12 weeks	6 weeks
Placebo Controlled[b]	X	X	X	
CFC-BDP Comparison[c]			X	X
Patient Population[d]	Steroid naive[e] Mild/Moderate	Steroid naive Mild/Moderate	Symptomatic Steroid naive/inhaled steroid users Moderate/moderately severe	Symptomatic Inhaled steroid dependent Moderately severe
Dose of HFA-BDP Studied[f]	100, 200 mcg/day	400 mcg/day	400 mcg/day	100, 400, 800 mcg/day
HFA-BDP Strength[g]	50 mcg	50, 100 mcg	50 mcg	50 mcg
Clinical Practice Relevance	Symptomatic steroid naive patients in need of ICS therapy	Symptomatic steroid naive patients in need of ICS therapy	Symptomatic steroid naive patients and ICS users in need of oral steroid burst	N/A (designed to establish a dose response)

[a] The onset of clinical improvement with inhaled corticosteroids is quite rapid, with a plateau generally seen by 3-4 weeks. Six weeks is a sufficient duration to assess comparative effects of HFA-BDP versus placebo or versus CFC-BDP in improving or maintaining lung function.[10-14]

[b] A placebo comparison was not done in studies in which all patients were inhaled steroid dependent at entry.

[c] The CFC-BDP comparison was Beclovent® in study 1129 and Vanceril® in study 1192.

[d] Patients with a range of asthma severities were included in the program (Expert Panel Report II, Guidelines for the Diagnosis and Management of Asthma[3])

[e] Steroid naive = not receiving inhaled steroids at study entry; "washout time" varied.

[f] Doses were selected to be most appropriate for the patient population recruited for each study.

[g] Study 1083 [this is in the original table, but does not appear to be correct] was the pivotal study evaluating dose strength proportionality. Dose proportionality is also supported by pharmaceutics and pharmacokinetic data.

Source: NDA 20-911, Vol. 2, p.97, Table 3.8.3.A:

Attachment A.2. **HFA-BDP Clinical Program (Controlled Clinical Trials)**

Study No. Location	Study Dates	Treatment	Total Daily Dosage	No. Pts. Randomized /Treatment / Total	Treatment Duration	Age Range (Mean)	No. M/F (W/B/O)
PLACEBO CONTROLLED:							
1081 Multicenter United States & France	Complete US: (5/95-12/95) France: (12/94-12/95)	**HFA-BDP $_{50}$** HFA-placebo	**100 mcg** **200 mcg** 0 mcg (1 or 2 puffs BID)	**91** **92** 87 270	6 weeks	18-74 (34)	117/153 (252/14/4)
1083 Multicenter Germany, Poland & Slovakia	Complete (11/94-9/95)	**HFA-BDP $_{50}$** **HFA-BDP $_{100}$** HFA-placebo	**400 mcg** **400 mcg** 0 mcg (4 puffs BID)	**83** **88** 85 256	6 weeks	18-67 (40)	129/127 (254/0/2)
1129 Multicenter United States	Complete (7/94-6/95)	**HFA-BDP $_{50}$** *CFC-BDP $_{50}$* HFA-placebo	**400 mcg** *800 mcg* 0 mcg (4 or 8 puffs BID)	**113** *117* 117 347	12 weeks	18-65 (34)	162/185 (312/27/8)
DOSE COMPARISON CONCURRENT CONTROLLED:							
1192 Multicenter United States	Complete (2/96-12/96)	**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)

M/F=Male/Female **W/B/O=White/Black/Other**

Source: NDA 20911, Vol. 2, p. 101-102, Table 3.8.3B:

Attachment A.3. Important Design Features

1081	Minimum Effective Dose	Run-In ++++++++ 14-day	—————— ..... 6-Weeks Treatment	HFA-BDP$_{50}$ HFA-BDP$_{50}$ HFA-Placebo	100 mcg/day 200 mcg/day	N=91 N=92 N=87
1083	Dose Strength Equivalence	Run-In ++++++++ 14-day	—————— ..... 6 weeks Treatment	HFA-BDP$_{50}$ HFA-BDP$_{100}$ HFA-Placebo	400 mcg/day 400 mcg/day	N=83 N=88 N=85
1129	Mid-Dose Equivalent Asthma Control with CFC-BDP	Run-In ++++++++ 10-12 day	Oral Steroid —————— ..... 7-12 day 12-Weeks Treatment	HFA-BDP$_{50}$ CFC-BDP$_{50}$ HFA-Placebo	400 mcg/day 800 mcg/day	N=113 N=117 N=117
1192	Dose Response Direct CFC Comparability	Run-In ++++++++ 7-14 day	Placebo —————— ICS* Washout —————— —————— . up to 28 day 6-Weeks Treatment	HFA-BDP$_{50}$ HFA-BDP$_{50}$ HFA-BDP$_{50}$ CFC-BDP$_{50}$ CFC-BDP$_{50}$ CFC-BDP$_{50}$	100 mcg/day 400 mcg/day 800 mcg/day 100 mcg/day 400 mcg/day 800 mcg/day	N=50 N=51 N=56 N=59 N=55 N=52

Source: NDA 20911, Vol. 2, p. 104, Table 3.8.3.C:

Attachment A. 4 Percent of Patients Classified by Asthma Severity Based on Screening FEV_1 (STEPS Based on NAEP Guidelines)

	Study 1081 (N = 270)	Study 1083 (N = 256)	Study 1129 (N = 347)	Study 1192 (N = 323)
STEP 2 Mild Persistent ≥ 80 % predicted	75 (27.8%)	61 (23.8%)	75 (21.6%)	0
STEP 3 Moderate Persistent 60-80 % predicted	187 (69.3%)	124 (48.4%)	159 (45.8%)	228 (70.6%)
STEP 4 Severe Persistent ≤60 % predicted	8 (3.0%)	71 (27.7%)	113 (32.6%)	95 (29.4%)

Source: NDA 20911, Vol. 2, p. 106, Table 3.8.3.D.

Attachment B.1.

Study 1081
A 6 Week Comparison of a Daily Dose of 100 mcg and 200 mcg of HFA-134a Beclomethasone Dipropionate$_{50}$ with Placebo in Subjects with Mild to Moderate Reversible Obstructive Airways Disease
Objective:
"The two primary objectives of this study were 1) to test whether a total daily dose of 100 mcg of Beclomethasone Dipropionate (BDP) formulated in HFA-134a (HFA) propellant was more efficacious than placebo, and 2) to test whether a total daily dose of 200 mcg BDP formulated HFA-propellant was more efficacious than placebo. The secondary objective was to assess the safety of HFA-BDP."
Planned Analysis
Primary Efficacy Variable(s) Mean change from baseline in percent predicted FEV_1 at the end of the study **Secondary Efficacy Variables** AM PEFR, PM PEFR, $FEF_{25-75\%}$,asthma symptom scores, sleep disturbance and use of beta-agonists. **Sample Size Justification** Change in percent predicted FEV_1: difference between placebo and active treatment - 10%, standard deviation - 16%, two-sided alpha = 0.025 with 90% power. 72 subjects per active treatment with 36 for each placebo arm "...for the comparison of each active treatment versus its matching placebo in the event that the assumption of homogeneity of the placebo responses is not met." **Primary Hypotheses** 1. Ho: mean change from baseline of percent predicted normal FEV_1 of HFA-134A BDP 100 mcg/day = placebo treated subjects 2. Ho: mean change from baseline of percent predicted normal FEV_1 of HFA-134A BDP 200 mcg/day = placebo treated subjects **Analytical Methodology** ANOVA with terms for country, center within country, treatment group, treatment by country interaction, and treatment by center within country interaction. (as modified in protocol amendment). **Datasets to be Analyzed** Intent-to-treat (with LOCF) and "evaluable" **Special Features:** Determination of whether or not placebo-treated subjects can be combined based non primary response.

Attachment B.2.

Study 1083
Six-Week Trial to Demonstrate Equivalent Efficacy of Two Dose Strengths of HFA-134a Beclomethasone Dipropionate in Subjects With Reversible Obstructive Airway Disease
Objectives:
The primary objective of this study was to tests whether 400 mcg of HFA-134a Beclomethasone Dipropionate (HFA-BDP) delivered as four actuations twice daily from a 50mcg/actuation (ex-valve) inhaler provided equivalent efficacy in improving asthma control as 400mcg HFA-BDP delivered as two actuations twice daily from 100 mcg/actuation inhaler (ex-valve) in patients with asthma. The secondary objective was to test whether each strength of HFA BDP was more efficacious than placebo in improving asthma control based on changes in AM PEF over 6 weeks of treatment.
Planned Analysis
Primary Efficacy Variable Mean change from run-in of morning peak expiratory flow rate (AM PEFR) at the end of the trial (Weeks 5-6, last 14 days of recordings). **Secondary Efficacy Variables** PM PEFR, $FEF_{25-75\%}$, asthma symptom scores, sleep disturbance and use of beta-agonists. **Primary Hypotheses** The mean change from run-in of AM PEFR of subjects treated with HFA-134a BDP 400 mcg/day using the 50 mcg strength product is unequal by more than ± 25 L/min (change from protocol-specified ± 40 L/min) to that of the subjects treated with HFA-134a BDP 400 mcg/day using the 100 mcg product. ("The rejection will imply equivalence of the 2 active treatments.") **Sample Size Justification** Based on pilot: standard deviation is assumed to be approximately 75 L/min. With two one-sided procedure -- 60 subjects per active will provide 80% power with alpha=0.05. **Analytical Methodology** ANOVA with terms for treatment, center and treatment-by-center interaction. To maintain overall alpha level of 0.05 "treatment contrasts were considered significant if $p<0.017$ (Bonferroni adjustment)". **Datasets to be Analyzed** Intent-to-treat (with LOCF) -- primary and safety -- and subjects who complete all six weeks and are compliant **Special Features:** Interim analysis to assess variance for sample size adjustment.

Attachment B.3.

Study 1129
Comparison of 400 mcg HFA-134a Beclomethasone Dipropionate (HFA-BDP), 800 mcg CFC-11/12 Beclomethasone Dipropionate (CFC-BDP), and Placebo (HFA-Placebo) in Patients with Asthma
Objectives:
Primary: to test whether 400 mcg HFA-BDP provided equivalent efficacy in controlling asthma as 800 mcg CFC-BDP in patients with symptomatic, moderately severe asthma. Secondary: to test whether both BDP formulations were more effective in controlling asthma than placebo and to assess safety of HFA-BDP.
Planned Analysis
Primary Efficacy Variable Mean change from run-in of morning peak expiratory flow rate (AM PEFR) at the end of the trial (Weeks 10-12, mean of last 21 days of recordings). **Secondary Efficacy Variables** AM FEV1, PM PEFR, $FEF_{25-75\%}$, asthma symptom scores, sleep disturbance, use of beta-agonists and time to withdrawal due to worsening of asthma. **Primary Hypotheses** The mean change from baseline of AM PEFR of subjects treated with HFA-134a BDP 400 mcg/day using the 50 mcg strength product is unequal by more than ± 40 L/min to that of the subjects treated with CFC 11/12 800 mcg/day. ("The two one-sided tests were performed to obtain the p-value for the test of the null hypothesis of no equivalence.") In addition: treatment mean changes from baseline are equal/differ from pooled placebo. **Sample Size Justification** Based on literature: standard deviation is assumed to be approximately 126 L/min. With two one-sided procedure -- 90 subjects per active will provide 90% power with alpha=0.05. **Analytical Methodology** ANOVA with terms for treatment, center and treatment-by-center interaction. **Datasets to be Analyzed** Primary Intent-to-treat (with LOCF) and subjects who complete all six weeks and are compliant (evaluable) **Special Design/Analytical Features:** Interim analysis to assess variance for sample size adjustment. Proposed analyses of subgroups for steroid naïve vs. steroid users.

Attachment B.4.

Study 1192
Dose Response Comparison of HFA-134a Blecomethasone Dipropionate with CFC-11/12 Beclomethasone Dipropionate in Patients with Asthma
Objectives:
Primary: To demonstrate increasing improvement in symptomatic asthmatic patients ... with increasing doses (100, 400 and 800 mcg/day dose ex-valve) of beclomethasone dipropionate, formulated in hydrofluouroalkane-134a (HFA-BDP).
Planned Analysis
Primary Efficacy Variable Mean change from baseline in percent predicted normal FEV_1 at Week 6 (average of last five days of the study) **Secondary Efficacy Variables** AM and PM PEF, $FEF_{25-75\%}$, FVC, reversibility following beta-agonist use, asthma symptom scores, sleep disturbance scores and use of beta-agonists. **Primary Hypotheses** A test for linear trend among the HFA-134a BDP doses using Jonckheere's test. Comparisons between each of the dose levels of HFA-134a BDP and the comparable dose of CFC-11/12 (with 95% confidence intervals) . **Sample Size Justification** 30 patients per dose level will ensure 80% power to detect a difference betweent he 400 and 800 mcg/day HFA-134a BDP groups of 7.5% in percent of predicted normal FEV1 assuming a standard deviation of 10% (alph=0.05). **Analytical Methodology** Jonckheere's test for linear trend, followed by ANOVA "of the ranked data" to assess effects of center and center by treatment interaction. ANOVA model will include terms for treatment, center and treatment-by-center interaction. • Datasets to be Analyzed Evaluable (primary) and Intent-to-treat (with LOCF). **Special Design/Analytical Features:** Plans for Analysis "Windows" to handle missing values.

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Concur: Dr. Nevius SEW 5/11/99

cc:
Archival NDA 20-911
HFD-570
HFD-570/Dr. Jenkins
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