CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-911

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA 20-911, Amendment 020
Drug/Drug Product: QVAR ™ (beclomethasone dipropionate HFA) inhalation aerosol
Sponsor: 3M Pharmaceuticals
Date of Submission: 2/28/00
Date of Review: 9/6/00
Reviewer: Young Moon Choi, Ph.D.
Type of Submission: Response to Action Letter dated 2/18/00

1. Background

Beclomethasone dipropionate (BDP), the active ingredient of QVAR ™, is a corticosteroid with antiinflammatory effect. In the body, BDP is readily hydrolyzed to 17-beclomethasone monopropionate (17-BMP), 21-beclomethasone monopropionate (21-BMP) and beclomethasone (BOH). Among these four moieties, 17-BMP showed higher corticosteroid receptor binding affinity than BDP. BOH and 21-BMP are not pharmacologically active.

Currently, at least two dosage forms for BDP, i.e., inhalation aerosol and nasal spray are marketed.

The sponsor has reformulated BDP with a nonozone-depleting propellant, hydrofluoroalkane-134a (HFA), for use in metered dose inhalers (MDIs). On 5/11/98, the sponsor submitted NDA 20-911 for this product, QVAR ™. The submission included the following information.

> Formulation: a pressurized, metered dose aerosol intended for oral inhalation. BDP in QVAR ™ is supplied in two strengths (40 and 80 µg per actuation; 50 and 100 µg from the valve, respectively) and two canister sizes (100 and 200 actuations) per strength.
>
> Indication: for maintenance treatment of asthma as prophylactic therapy in patients of age 12 years and older. QVAR ™ is also indicated for asthmatic patients who require systemic corticosteroid administration where adding QVAR ™ may reduce or eliminate the need for the systemic corticosteroid.
>
> Dosage regimen: The proposed dosage regimens are 40-160µg BID for mild to moderate asthma patients, and 240-320 µg BID for severe cases.

After the review, Clinical pharmacology and Biopharmaceutics reviewer (Dr. Chen) found following deficiencies:

(1) The sponsor measured the hydrolysis product of any BDP and metabolites present in the serum (total BOH), and there was no validated sensitive assay method to measure the most active metabolite, 17-BMP, in serum.
(2) There were no assessments of the equivalence between the two strengths at the same dose levels provided.

Accordingly, it was recommended that any additional pharmacokinetic studies would be expected to include a more specific assay than the one used in prior studies (Approvable letter dated 5/12/99).

In response to the above recommendation, the sponsor submitted summary results from an additional comparative pharmacokinetic study (1366-BRON) which used an analytical method to measure BDP, 17-BMP, 21-BMP, and B-OH individually in plasma. However, it appeared that only the summary results were not enough for complete evaluation. The full study report has been requested on 2/18/00, and the sponsor submitted the study report of 1366-BRON as a part of Amendment 20 to NDA 20-911 on 2/28/00.

By reviewing the present submission, the questions to be answered from a Clinical Pharmacology and Biopharmaceutics perspective are as follows:

- Is the analytical method appropriate?
- Are the two strengths at the same dose level equivalent?
- Is there dose proportionality within 100-400 µg dose?
- Does the total BOH in serum represent 17-BMP?

Q: Is the analytical method appropriate?

2. Analytical method

A — ; used to quantify BOH, 21-BMP, 17-BMP, and BDP in human plasma. The review is focused on the linearity, precision and accuracy, and specificity, extraction recovery, and stability.

2-1. Linearity (Attachment 1)

	Linearity (R)	LLOQ [a] (pg/ml)	UOQ [b] (pg/ml)	Observed Cmax (pg/ml)
BOH	—	—	—	
21-BMP	—	—	—	
17-BMP	—	—	—	
BDP	—	—	—	

[a] LLOQ represents lower limit of quantitation.
[b] UOQ represents upper limit of quantitation.

- **Reviewer's comment**: The observed maximum concentration of — pg/ml is out of the standard curve range. Total 5 out of 64 observed concentrations after 400 µg dosing appeared over — g/ml. It should be noted that 2 cases (— pg/ml) were included in the evaluation of AUC 0-inf. Considering the relatively small

deviation and the linearity of the standard curve, this reviewer is of the opinion that the data is acceptable.

2-2. Precision and Accuracy (Attachment 2)

Intraday precision and accuracy: The intraday precision and accuracy was determined by preparing 5 replicates at 3 concentration levels (LLOQ, ——— of calibration standards and assaying all samples in one analytical run.
The coefficient of variation at the 3 levels was less than 12 %. The relative error was from 10 – 11 %.

- **Reviewer's comment:** Data are acceptable.

Interday precision and accuracy: The interday precision and accuracy was calculated from QC samples. The first set of QC values from each of the first five days was used. The coefficient of variation at all the 3 concentrations of the 4 compounds ranged from 4.4 – 25.5 %, and the relative error was from –5.6 to 23.3 %.

- **Reviewer's Comment:** Interday precision and accuracy are out of acceptance criteria that is recommended in Draft Guidance for Industry: Bioanalytical Method Validation for Human Studies (12/99). The sponsor should improve the interday variation for the full validation of the assay. However considering the facts that a large part of the interday variation is attributed from one analysis out of 6 analyses, interday error and variation, although not optimal, is considered to be acceptable for the present study.

2-3. Specificity: Chromatograms were provided. A small peak is observed close to the 17-BMP-retention time. The peak is near the quantitation threshold and does not interfere with accurate quantitation in the calibration range.

2-4. Extraction recovery (Attachment 3)
Extraction recovery was determined at two concentrations (——— pg/ml).
Recovery is within — %.

2-5. Sample stability (Attachments 4-7)

— storage stability: Stability samples were stored in — Vials were — and analyzed at various time intervals.
Results for the — stability are within — % of the original mean values and indicate no evidence of degradation over a six-month period.

— stability:
Aliquots of the stability samples were ——— to determine the effect on analyte levels. Results for the — are within — % of the original mean values.

Room temperature stability (before extraction):

Room temperature stability study was performed by spiking a low and a high standard into blank plasma. Three aliquots of each spiked plasma samples were analyzed after being kept at room temperature for 1, 2, 4, 6, 8, 10, and 24 hours. Results for the 24-hour time point are within —% of the theoretical values.

Extracted sample stability at room temperature:
For extracted stability, two sets of test samples were prepared for each concentrations which consisted of a calibration curve and 3 replicates at —— pg/ml. All samples were prepared on the same day. To ensure that 2 sets are identical, all samples were pooled according to concentrations after being fully processed and were re-aliquoted into individual —— vials. One was run on the day of preparation while the other set was run after being held in —— vials at room temperature. Results from the extracted plasma stability samples are within —% of the target values. The results indicate that the extracted samples are stable at room temperature in fully processed state for at least — hours.

- **Reviewer's comment on the analysis:**

This reviewer is of the opinion that the analytical method performed in the present study, although not optimal, is acceptable for the quantitation of B-OH, 21-BMP, 17-BMP, and BDP in human plasma.
However, the sponsor needs to improve interday precision and accuracy for the full validation.

Q: Are the two strengths at the same dose level equivalent?

3. Review of the Study 1366-BRON

3-1. Design/ Procedure
The study was a single dose, Phase I, randomized, open label, 4-period crossover study in 32 patients (male 10; female 22; age 17 to 70 years old) with mild asthma. Patients received each of the following HFA-BDP treatments: 100 µg from the 50 µg/actuation inhaler, 100 µg from 100 µg/actuation strength, 400 µg from 50 µg/actuation inhaler, and 400 µg from 100 µg/actuation strength. (The dose mentioned here is based on amount delivered from valve.)
A predose blood sample was collected. After dosing, serial blood samples were drawn for over a 12-hour period (at 0.5, 1, 2, 4, 6, 9, and 12 hours after dosing).

The primary pharmacokinetic parameters were Cmax and AUC for 17-BMP: The evaluation included evaluation of partial AUC values (AUC0-2 and AUC 0-6), AUC to the last quantifiable time point (AUC0-t), and AUC extrapolated to infinity (AUC 0-inf). Secondary parameters included Tmax and t1/2.

Each pharmacokinetic variable was analyzed using an analysis of variance (ANOVA) model accounting for sequence, patients within sequence, and treatments. Inclusion of a

period effect or a first-order carry-over effect in the statistical model was not possible due to the inadvertent handling of the samples and hence continuation for an extra study day. AUC and Cmax were logarithmically transformed before analysis.
The 2-one sided test was used to assess the equivalence of the 50 μg/actuation and 100 μg/actuation formulation in the dose level of 100 and 400 μg. The 90% confidence intervals (CI) were provided for the geometric mean ratios of Cmax and AUC.

The dose proportionality was assessed by comparing ¼ of the 400 μg dose value with the 100 μg dose value for both strengths. The 90 % CI was provided for the adjusted geometric mean values (i.e., ¼ of Cmax and AUC after 400 μg dose) vs. 100 μg dose values.

Equivalence for the Cmax and AUC parameters was concluded if the 90% CI for the ratio was completely within an interval of 0.8 to 1.25.

Protocol Changes or Violations: There were three changes from the originally planned protocol.

(1) **Repeat study days**: Due to the inadvertent sample handling, four subjects (patient # 1,2and 5 for study day 2 and patient #7 for study day 4) were repeated. Because the extra study day for each of the patients was the fifth study day, it was not possible to include a period effect or a first-order carry-over effect in the statistical model.
   - **Reviewer's comment:** Considering 2-7 days of wash out period and 2.8 ± 0.59 hr of half-life of 17-BMP, the carry over effect is not expected. This reviewer is of the opinion that the current statistical analysis is acceptable.

(2) **AUC calculation**: Due to the low plasma levels after 100 μg dose, AUC was estimated up to 2 hours (AUC 0-2). Similarly, the AUC0-6, AUC 0-t, and AUC inf were estimated only for the 400 μg dose.
   - **Reviewer's comment:** This is acceptable since the equivalence is evaluable by the AUC 0-inf , which reflects whole plasma profile at the higher dose level.

(3) **Omitted Cmax value of Patient#1** due to the low plasma concentration level after 100 μg dose level.
   - **Reviewer's comment:** This is acceptable since still the equivalence can be estimated using rest of the data.

3-2. Results

3-2-1. Plasma concentrations (Attachment 8)
Issue of the predose plasma concentration of 17-BMP: Five patients in the 400 μg dose, 100 μg/actuation strength treatment period had quantifiable predose plasma concentrations. These predose values appeared to be random and no patient had a quantifiable predose value in more than 1 treatment period. Without knowing any reason, the sponsor's approach was to be conservative to estimate, i.e., no value was rejected and

all quantifiable predose levels were treated as valid data and included in the pharmacokinetic analysis.

- **Reviewer's comment:** It is noted that two patients (Subject 14 and 18) who had pre-dose concentrations were included in the estimation of AUC0-inf. To evaluate the impact of these predose concentrations to the present study result, this reviewer estimated and compared the AUC0-inf with or without predose concentration. It appeared that the contribution of the predose concentration to the total AUC was less than 1 %. It is thought that removing these data from the pharmacokinetic comparison would not have affected any of the pharmacokinetic conclusions. This reviewer accepts the sponsor's approach.

The plasma profiles of 17 BMP are attached. (Attachment 8).

Concentrations of BDP were not quantifiable in any of the patients given the 100μg dose and in about half the patients given 400 μg. Accordingly, only Cmax and Tmax were evaluated.

Concentrations of 21-BMP were not quantifiable in the plasma at any time during all treatments except for 3 patients.

Concentrations of BOH were not quantifiable in most of the patients given a 100 μg dose. However, concentrations of BOH were measurable in all patients given the 400 μg dose. The Plasma profile is attached (Attachment 9).

3-2-2. Pharmacokinetic parameters

Following tables summarize the pharmacokinetic parameters.

Pharmacokinetic parameters of 17-BMP

Dose/ strength (μg)/ (μg/actuation)	Pharmacokinetic parameter						
	Cmax	Tmax	AUC0-2	AUC0-6	AUC0-t	AUC0-inf	T1/2
	Pg/ml	h	pg·h/ml	pg·h/ml	pg·h/ml	pg·h/ml	h
100/50	370±138	0.9±0.68	459±175				
100/100	364±167	0.9±0.74	496±188				
400/50	1432±400	0.7±0.41	1999±614	4034±1101	4336±1517	5183±1298	2.7±0.79
400/100	1419±475	0.7±0.33	1997±650	3848±1230	4348±1595	4985±1334	2.8±0.59

Pharmacokinetic parameters of BDP following 400 μg dose

Test product		Pharmacokinetic parameter	
Dose (μg)	Strength (μg/actuation)	Cmax (pg/ml)	Tmax (h)
100 (n=32)	50	NA	NA
100 (n=32)	100	NA	NA
400 (n=18)	50	76± 23	0.6±0.35
400 (n=16)	100	88±31	0.5±0.02

NA represents that the values could not be calculated as there were no quantifiable plasma concentrations at any time point.

Pharmacokinetic parameters of BOH following 100 and 400 μg doses of BDP

Test product		Pharmacokinetic parameter			
Dose (μg)	Strength (μg/actuation)	Cmax (pg/ml)	Tmax (h) (h)	AUC0-t (pg·h/ml)	T1/2 (h)
100	50	20±26.5	4±1.5	77±112	NA
100	100	14±3.2	5±1.3	56±49.6	NA
400	50	40±9.7	5±1.7	311±49.6	7.0±3.6
400	100	42±10.6	4±1.9	322±98.3	6.1±1.45

NA represents that the values could not be calculated as there were no quantifiable plasma concentrations at any time point.

Q: Are the two strengths at the same dose level equivalent?

3-2-3. Bioequivalence test between two strengths (using 17-BMP data).

The result of equivalence assessment of 50 μg / actuation vs. 100 μg / actuation formulation are summarized in the following table.

Parameter	Dose 100 μg (C.I)	Dose 400 μg (C.I)
Cmax	BE (0.82, 1.11)	BE (0.81, 1.11)
AUC 0-2	Not BE (0.89, 1.28)	BE (0.83, 1.17)
AUC 0-6	Data not available	Not BE (0.77, 1.03)
AUC 0-t	Data not available	BE (0.81, 1.22)
AUC 0-inf	Data not available	BE (0.82, 1.13)

C.I. indicates confidence interval of the ratio of the geometric mean.
BE represents that the confidence interval of the ratio of the geometric mean values are within 0.8 – 1.25.

- **Reviewer's comment:** Cmax and AUC inf after 400 μg dose are considered as key parameters in determining equivalence, since these were obtained from complete plasma profiles. Based on these results, this reviewer is of the opinion that the two strengths (50 and 100 μg / actuation) formulation at 400 μg dose level are bioequivalent.

Q: Are there dose proportionality within 100-400 μg dose?

3-2-4. Bioequivalence test for dose proportionality

The results of equivalence assessment of 100 μg dose vs. 400 μg dose are summarized in the following table.

Parameter	50 µg/actuation formulation (C.I.)	100 µg /actuation formulation (C.I.)
Cmax	BE (0.84, 1.14)	BE (0.84, 1.14)
AUC 0-2	Not BE (0.91, 1.30)	BE (0.83, 1.20)

C.I. indicates confidence interval of the ratio of the geometric mean.
BE represents that the confidence interval of the ratio of the geometric mean values are within 0.8 – 1.25.

- **Reviewer's comment:** Dose proportionality was observed for both strengths in terms of Cmax and for 100 µg /actuation strength for AUC 0-2. The 90 % CI for the dose proportionality analysis with the 50 µg /actuation exceeds 1.25. However, considering the CI of 0.91 – 1.30, this reviewer agrees with the sponsor's opinion that there is not enough statistical power to conclude strict dose proportionality with this strength.

Does the total BOH in serum represent 17-BMP?

3-2-5. Comparison of AUC 0-t of 17-BMP and total BOH
One of the purposes of conducting Study 1366-BRON was to confirm the results of another bioequivalence trial, Study 1194-BRON, which used an assay that measured total B-OH. The rationale for using the total-BOH assay in Study 1194-BRON was that this assay measured primarily 17-BMP and was an acceptable surrogate for 17-BMP (which could not be assayed separately at that time).

This assumption was confirmed in Study 1366-BRON by observing that 17-BMP AUC0-t was 90 % or more of the total AUC, i.e., the sum of AUC0-t of 17-BMP, BOH, BDP, and 21-BMP in plasma. This value is obtained by calculating the individual AUC 0-t values for each analyte and converting them to beclomethasone equivalents for comparison.

- **Reviewer's comment:** It is ideal to analyze 17-BMP and total-BOH from each analyte and then compare the AUC values. However, considering assay sensitivities (10, 50, 75, and 50 for BOH, BDP, 17-BMP, and 21-BMP, respectively), this reviewer agrees with the sponsor's approach and concludes that the total BOH in serum primarily represents 17-BMP in terms of total exposure.

4. Recommendation:
The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation 2, has completed the review of the submission to NDA 20-911 (Amendment 20) dated 2/18/00. The following were found:

- The analytical method used in the present study is acceptable. However, the sponsor needs to improve interday precision and accuracy for full validation.
- The two strengths, i.e., 50 µg/actuation and 100 µg/actuation, are equivalent at the same dose level.
- The results support the dose proportionality between 100 and 400 µg dose level.
- The results of the present study support the assumption that the total BOH measured by the assay used in the early study (Study 1194-BRON) is primarily 17-BMP when total exposure is assessed.

The following 'Labeling comments' and 'Comments to the sponsor' should be forwarded to the sponsor.

5. Labeling comments

5-1. The label under 'Absorption' : Add peak levels and [redacted] of 17-BMP achieved with QVAR at a recommended dose or doses.

5-2. The label under 'Absorption': Describe the dose proportionality and bioequivalence between two strengths obtained from the study 1366- BRON using 17-BMP.

5-3. Under 'Excretion': Change the subtitle 'Excretion' to 'Elimination' and add values of elimination half-life of 17-BMP after inhalation of QVAR.

5-4. The label under 'Special Populations' under the section of 'Pharmacokinetics' should read as following:

> **Special Populations**: Formal pharmacokinetic studies using QVAR were not conducted in any special populations.

5-5. Following is the Agency's labeling recommendation:

Pharmacokinetics

DRAFT

Absorption:

Draft

Metabolism:

Lung slices can metabolize BDP rapidly to 17-BMP and more slowly to BOH. 17-BMP is the most active metabolite.

Distribution: There is no evidence of tissue storage of BDP or its metabolites.

Elimination: Major route of elimination of the inhaled BDP appears to be metabolism. More than 90 % of the inhaled BDP was found as 17-BMP in the systemic circulation. The mean elimination half- life of 17-BMP was 2.8 hour. Irrespective of the route of administration (injection, oral or inhalation), BDP and its metabolites are mainly excreted in the feces. Less than 10 % of BDP and its metabolites are excreted in the urine.

Special Populations: Formal pharmacokinetic studies using QVAR were not conducted in any special populations.

6. Comment to the sponsor

For full validation of assay in future, the sponsor needs to improve the interday precision and accuracy.

9/7/00

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

S
9/8/00

Venkata Ramana Uppoor, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC:

HFD-570	Div., Barnes
HFD-870	Hunt, Huang, Choi, Uppoor
CDR	Attn: Barbara Murphy (1x)

Attachment 1. Linearity
Attachment 2. Intra-day and interday precision and accuracy
Attachment 3. Extraction recovery
Attachment 4. stability
Attachment 5. stability
Attachment 6. Room Temperature stability
Attachment 7. Extracted sample stability at room temperature
Attachment 8. Mean plasma concentrations of 17-BMP
Attachment 9. Mean plasma concentrations of BOH
Attachment 10. Sponsor proposed label

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pages of trade

secret and/or

confidential

commercial

information

16 pages redacted from this section of the approval package consisted of draft labeling

MAY 3 1999

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-911
Beclomethasone Dipropionate
Inhalation Aerosol (40 and 80 μg/actuation)

SUBMISSION DATE:
05/11/98 (Serial N-000)

BRAND NAME: QVAR

SPONSOR: 3M Pharmaceuticals

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Original NDA Submission

Code: 3S

TITLE: "Review of Human Pharmacokinetics and Bioavailability Section"

BACKGROUND:

Beclomethasone dipropionate (BDP) is a white to creamy white, odorless powder with a molecular formula of $C_{28}H_{37}ClO_7$ and a molecular weight of 521.1. It is slightly soluble in water, very soluble in chloroform and freely soluble in acetone and in alcohol. BDP is an anti-inflammatory agent (not a new molecular entity) and is currently approved and marketed as inhalation aerosol and nasal spray dosage forms.

The pharmacologic activities of BDP and its metabolites have been reported in the literature. Results of *in vitro* affinity studies to corticosteroid receptor using animal and/or human cell tissues show that as compared to a standard corticosteroid (as 1.0), **1)** a metabolite, 17-beclomethasone monopropionate (17-BMP), is the most abundant and the most pharmacologically active species (≈ 10) in the body, **2)** BDP is less potent (<1), and **3)** other metabolites, 21-beclomethasone monopropionate (21-BMP) and beclomethasone (BOH) are not pharmacologically active.

SYNOPSIS:

On 05/11/98, 3M submitted an original NDA 20-911 for QVAR (non-CFC — BDP) inhalation aerosol. QVAR drug product has a mean particle size of 1 to 1.2 microns for the emitted aerosol spray. Each unit contains a solution of BDP in propellant HFA-134a and ethanol. There is no need for a surfactant. It is supplied in two strengths (40 and 80 μg per actuation; 50 and 100 μg from the valve, respectively) and two canister sizes (100 and 200 actuations) per strength.

QVAR is a pressurized, metered-dose aerosol intended for oral inhalation only to patients 12 years of age and older. It is indicated for the maintenance treatment of asthma as prophylactic therapy. The dosing regimens to be recommended are **1)** for mild to moderate asthma patients: 40 to 160 μg BID (total daily dose of 80 to 320 μg)

and 2) for severe cases, 240 to 320 μg BID (total daily dose of 480 to 640 μg). It is NOT indicated for the relief of acute bronchospasm. QVAR is also indicated for asthmatic patients who require systemic corticosteroid administration where adding QVAR may reduce or eliminate the need for the systemic corticosteroids. For the proposed steps of replacement from CFC-BDP to HFA-BDP or elimination of systemic corticosteroids, please see the package insert (PI) in Attachment 1 for details.

Nine human pharmacokinetic (PK)/bioavailability (Bio) studies were conducted and submitted to support the approval of this product. Three were pivotal (Attachment 2 for details). The validated assay method used during the Phase -1 PK studies was either for serum BOH levels or for total serum levels of BOH after hydrolysis of serum BDP, 17- or 21-BMP to BOH levels. Both strengths (50 and 100 μg) of the canister for 200 actuations were employed in the human PK/Bio and clinical trials. The 50 and 100 μg formulations tested clinically are the same as the to-be-marketed formulations.

TABLE OF CONTENTS: Page

I. SUMMARY OF HUMAN PK/BIO SECTION:

1. Lung Deposition and Distribution of Radiolabeled HFA-BDP vs. CFC-BDP:

A pilot open-label, crossover study (No. 1152) was conducted in 12 male healthy volunteers (18-55 years old) to assess the deposition of single doses of radiolabeled HFA-BDP_{50}, HFA-BDP_{100}, and CFC-BDP_{50} (plus a not currently marketed CFC-BDP_{250} formulation in the US) using a standard press-and-breathe (P&B) MDI. Another open-label, crossover, but pivotal study (No. 1191) was conducted in 16 (5M+11F) patients with asthma (18-52 years old) using standard P&B MDI and Autohaler devices to assess the deposition of single doses of radiolabeled HFA-BDP_{50}. The results of the studies provided basic information on the deposition of these two products (**Table 1**).

Table 1. The Results of Ex-Actuator Lung Deposition

Treatment	% Deposited (Mean ± SD)[a]				
	Oropharynx	Lungs	Mediastinum	Abdomen	Exhaled
No. 1152[b]					
HFA-BDP_{50} (n=3)	29.3 ± 15.0	50.9 ± 11.7	0.67 ± 0.83	1.10 ± 1.91	18.0 ± 2.9
HFA-BDP_{100} (n=3)	27.2 ± 18.4	59.7 ± 13.6	0.33 ± 0.58	1.87 ± 1.69	10.9 ± 3.6
CFC-BDP_{50} (n=3)	78.5 ± 31.2	3.90 ± 3.58	1.03 ± 1.79	15.2 ± 26.4	1.30 ± 0.95
CFC-BDP_{250} (n=4)	84.3 ± 14.5	6.70 ± 2.58	1.58 ± 2.29	5.8 ± 10.6	1.68 ± 1.25
No. 1191[b,c]					
HFA-BDP_{50} (n=16)	30.5 ± 8.9	56.4 ± 8.8	1.53 ± 0.76	2.58 ± 3.59	9.01 ± 4.30

[a]. Mean ± standard deviation (SD) of the % deposited as the total radiolabeled dose using technetium-99m.

[b]. A 10-second breath hold technique was employed.

[c]. Only the mean PK values obtained from the standard P&B MDI presented for comparison since no major differences were found between the P&B and Autohaler actuators ($p>0.05$).

Conclusions:

No major differences in deposition pattern were seen **1)** between the HFA-BDP_{50} and HFA-BDP_{100} strengths, **2)** between volunteers and patients given single doses of HFA-BDP_{50}, and **3)** between the P&B MDI and Autohaler devices. However, asthmatic patients in Study No. 1191 appeared to have more central deposition and exhaled less in the air than the volunteers in Study No. 1152.

HFA-BDP had much less deposition in the oropharynx region (≈30%) as compared to ≈80% for CFC-BDP and much more in the lung region (50-60% vs. 4-7% for CFC-BDP) and in the exhaled air (10-20% vs. 1-2% for CFC-BDP). The above differences are seemingly consistent with the fact that HFA-BDP has finer particle size distribution indicating that asthma control may be achieved with lower doses of HFA-BDP than with CFC-BDP.

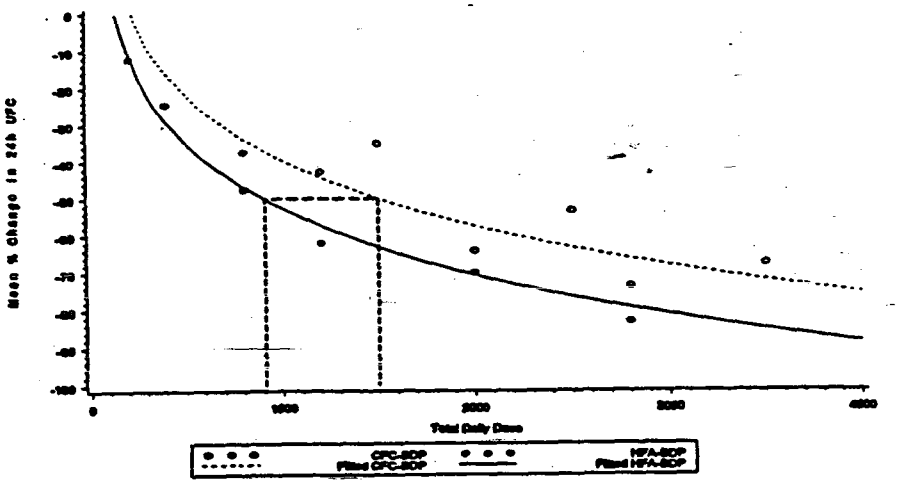
2. Effects of Multiple Doses of HFA-BDP on 24-Hour Urinary Free Cortisol Excretion

Adrenal function as the paradigm of systemic corticosteroid effects was assessed in the following studies. Multiple BID dosing (10 days) of **1)** HFA-BDP_{50} plus a not-to-be-marketed formulation HFA-BDP_{200} were given in the range of 1200 to 2800 µg/day and **2)** CFC-BDP_{50} and CFC-BDP_{250} were given in

the range of 1200 up to 3500 µg/day to a total of 74 male healthy volunteers (Study Nos. 1025 and 1063). Multiple BID dosing (14 days) of **1)** HFA-BDP_{50} was given in the doses of 200, 400, and 800 µg/day, **2)** HFA-BDP_{200} was given in the doses of 800 and 1600 µg/day, and **3)** CFC-BDP_{50} was given in the dose of 800 µg/day to 64 male and female asthmatic patients enrolled in the small clinical/PK studies (Nos. 1162 and 1064). The 24-hr urinary free cortisol levels (UFC_{24}) as the primary safety endpoints were obtained from the above studies and % decrease in UFC_{24} from baseline was calculated from each study. Due to assay sensitivity, no data on % decrease in UFC_{24} from the study No. 1064 were presented.

For the proposed dose range of 100 to 800 µg/day, study results obtained from No. 1162 (Phase II, randomized, parallel-design study) show that **1)** HFA-BDP_{50} given 200 µg/day had no significant effects (-12%) on the UFC_{24} when compared to placebo (+17%) and **2)** statistically significant decrease in % of UFC_{24} was found as doses of BDP increased, i.e., a mean of -25%, -37%, and -47% were obtained from 400 µg/day (HFA-BDP_{50}), 800 µg/day (HFA-BDP_{50}), and 800 µg/day (CFC-BDP_{50}), respectively. In general, the larger the dose of either BDP product, the more subjects in a group fell below the reference range. The results of pooled study data are shown in **Figure 1**.

Figure 1: Regression of Dose-Response Curves Based On Pooled Study Data



According to the dose-response curves (by regression using the pooled study data), the sponsor reported that the dose required to cause a 50% change (decrease) from baseline UFC_{24} was estimated to be 900 µg/day for HFA-BDP (filled circles) and 1500 µg/day for CFC-BDP (open circles).

Conclusions:

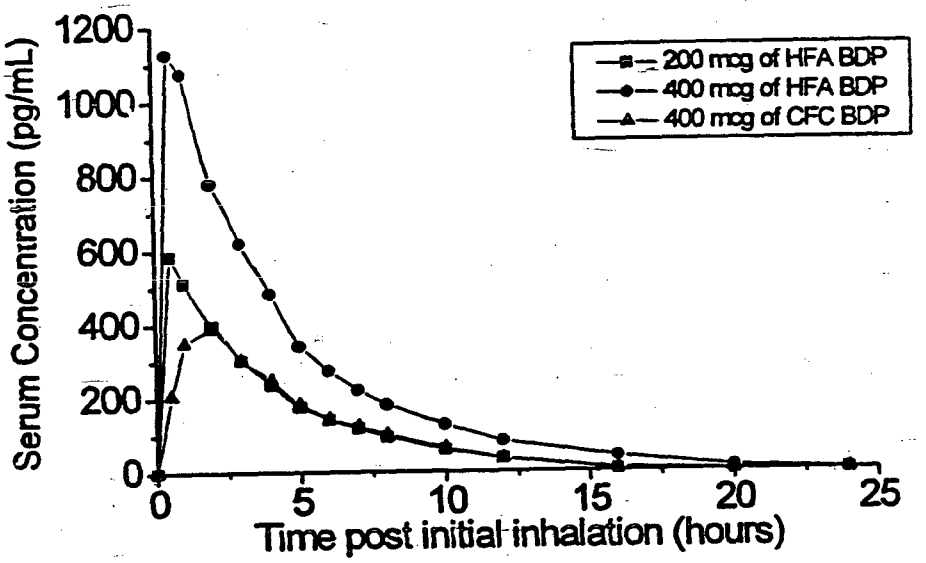
The pooled study data showed a nice dose-adrenal suppression (safety) relationship between the doses tested and the % change from baseline UFC_{24}. This data indicates greater adrenal suppression with the same dose of HFA BDP products compared to CFC-BDP products. However, the mean data points being deviated from the regression line (across the pooled study data) were observed which could be due to interstudy comparisons, i.e., different formulations and populations and/or different study designs employed.

3. Assessment of BDP PK Based on Beclomethasone (BOH)

The validated —— assay method that measured the total serum BOH levels after hydrolysis of serum BDP, 17- or 21-BMP to BOH levels as well as the one that measured only the serum BOH levels were used in the pivotal and supportive PK studies.

For the single-dose, dose-proportionality studies (Nos. 1069, 1070, and 1075), the dose ranges investigated were **1)** 200 and 400 µg doses using HFA-BDP_{50} and **2)** 200 and 800 µg doses using HFA-BDP_{100} plus single doses of 1600 µg using HFA-BDP_{200} and 400 µg dose using CFC-BDP_{50}. The study results obtained from the pivotal study No. 1075 for 200 and 400 µg doses using HFA-BDP_{50} and 400 µg dose using CFC-BDP_{50} dosing are shown below in **Figure 2**.

Figure 2: Serum Total BOH Levels obtained from Study No. 1075



For the pivotal multiple-dose study No. 1162, dose ranges studied were 200, 400, and 800 µg/day using BID dosing of HFA-BDP_{50}. The study was conducted to assess their relative bioavailability as compared to the dose of 400 µg/day using CFC-BDP_{50}.

As compared to CFC-BDP, HFA-BDP had a 2-fold higher mean peak (C_{max}) serum total BOH level and a 2-fold larger mean area under the serum total BOH curve (AUC_{0-t}) as shown in **Table 2**. From Study No. 1162, the accumulation ratio based on serum total BOH levels was estimated to be around 1.1-1.4 for HFA-BDP_{50} and 1.7 for CFC-BDP_{50}.

Conclusions:

A much faster (and greater) absorption of HFA-BDP_{50} from lungs as compared to CFC-BDP_{50} could be reflected by the much shorter mean time to peak (T_{max}) for serum total BOH levels observed from the 400 µg dose, i.e., a mean of 0.8 ± 0.5 hr for HFA-BDP_{50} as compared to 2.0 ± 0.5 hr for CFC-BDP_{50} (Study No. 1075).

Table 2. Comparison of Mean PK Parameters Obtained From Study Nos. 1075 (Single Dose) and 1162 (Multiple Dose) Based on Total BOH Levels

Dose	C_{max} [a] (pg/ml)			AUC_{0-t} [a] (pg-hr/ml)		
	No.1075	No.1162 (BID Dosing)		No.1075	No.1162 (BID Dosing)	
		Dose 1	Dose 27		Dose 1	Dose 27
HFA-BDP 100 µg	—	170 ± 101	197 ± 84	—	571 ± 303	792 ± 180.
HFA-BDP 200 µg	590 ± 200.	455 ± 159	539 ± 238	2239 ± 634	1958 ± 799	2113 ± 804
HFA-BDP 400 µg	1191± 385	736 ± 252	933 ± 359	4962 ± 1039	2854 ± 898	3999 ± 1562
CFC-BDP 400 µg	410 ± 177	374 ± 196	439 ± 188	2092 ± 1051	1782 ± 867	2256 ± 701

[a]. Based on total BOH levels in serum.

Both HFA-BDP_{50} (in a dose of 400 µg) and HFA-BDP_{100} (in a dose of 800 µg) were tested in an early single-dose PK study No. 1070, however, only the serum BOH levels were measured and no UFC_{24} was collected in this study. The mean AUC_{0-t} and C_{max} values for the 800 and 400 µg doses were 801 (— %) and 450 (— %) µg-hr/ml and 99 (— %) and 57 (— %) pg/ml, respectively. The dose-normalized mean AUC_{0-t} and C_{max} values between the 800 and 400 µg doses show comparable ratios, 0.89 and 0.87, respectively.

Comments:

A 2-fold increase in mean C_{max} and AUC_{0-t} for HFA-BDP_{50} as compared to CFC-BDP_{50} based on serum total BOH levels (**Table 2**) or dose-proportionality information based on serum BOH levels (the end metabolic species) could only be considered as supportive information and could not be used to address the

rate and extent of absorption or the dose-proportionality in PK of BDP. Furthermore, since a non-specific assay method was used, no assessment can be made on the comparability of the two strengths (50 and 100 μg).

4. Absorption and Metabolism PK of Ethanol and HFA-134a

In the pivotal Study No. 1162, blood samples were collected at predose, at 0.5 and 1 hr post morning doses on Days 1 and 14 to analyze for ethanol in whole blood. Only one out of 248 samples showed ethanol level of 1.72 μg/ml which was close to the detection limit of 1 μg/ml.

Blood levels of propellant HFA-134a and the possible metabolite, trifluoroacetic acid (TFA), were analyzed in Study No. 1075. Urinary levels of propellant HFA-134a and TFA were also analyzed in Study No. 1162. A rapid absorption and clearance of HFA-134a in humans was observed. HFA-134a was found to be minimally metabolized to TFA in humans and the amount of TFA in daily urine only represents <0.006% of the dose. The results are consistent to that obtained from Study No. 1211.

Conclusion:

No accumulation of ethanol or HFA-134a or their metabolites was found.

5. Assays:

Not until in the late drug development process was a more sensitive assay method explored and several patients' serum levels of BDP and its metabolites, 17-BMP, 21-BMP, and BOH were analyzed (after two years of sample storage). However, the sponsor was not able to validate the above assay method.

The validated — assay method used at beginning in most of the PK studies was, therefore, for serum total BOH levels after hydrolysis of serum BDP, 17- or 21-BMP to BOH levels at 3M St. Paul, MN. The above method was validated in the Report No. 9196.16. The standard curves were prepared between — pg/ml (n=4) with intraday precision CV% ranged from — % (at — pg/ml) and % accuracy ranged from — (at — pg/ml) to — %. Quality control data also showed that between — pg/ml (n=3), the interday precision CV% ranged from — % and % accuracy ranged from — %.

The same — assay method (Report No. 9196.4) was also used to determine the serum BOH levels at earlier stage of clinical development. The standard curves were prepared between — pg/ml (n=3) with intraday precision CV% ranged from — and % accuracy ranged from —% (at — pg/ml) to — %. Quality control data also showed that between — pg/ml

(n=3), the interday precision CV% ranged from —— (at —pg/ml) and % accuracy ranged from —% (at — pg/ml) to —%. Both assays were reviewed and found acceptable.

An RIA method was used to determine the UFC_{24}. The above method was validated in a project code No. ——. The standard curves were prepared between —— µg/dl (n=8) with precision CV% ranged from —— % and % accuracy ranged from — (at — µg/dl) to —— %. Quality control data also showed that between —— µg/dl (n=3), the interday precision CV% ranged from % (at — µg/dl) and % accuracy ranged from —— %. The above assay method was also reviewed and found acceptable.

RECOMMENDATION:

3M's original NDA 20-911 for QVAR (BDP 50 and 100 µg per actuation) that was submitted on 05/11/98 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB is of the opinion that the human PK/Bio section is less than ideal due to **1)** no validated sensitive assay method being used to measure the most abundant active metabolite, 17-BMP in serum and **2)** there were no assessments on the equivalence between the HFA-BDP_{50} and HFA-BDP_{100} at the same dose levels provided. The following General Comment and Labeling Comments as appropriate need to be conveyed to the sponsor ASAP.

GENERAL COMMENT: [Needs to be sent to the sponsor if additional study(ies) is/are needed prior to its approval]

In the Human Pharmacokinetics and Bioavailability Section of this NDA, dose-proportionality between 400 µg (using HFA-BDP_{50}) and 800 µg (using HFA-BDP_{100}) based on serum BOH levels (the end metabolic species) was reported in Study No. 1070. There were no assessments of equivalence between the two strengths, HFA-BDP_{50} and HFA-BDP_{100}. Furthermore, a 2-fold increase in mean C_{max} and AUC_{0-t} for HFA-BDP_{50} as compared to CFC-BDP_{50} based on serum total BOH levels was reported in Study No. 1162. The above information could only be considered as supportive information and could not be used to address the dose-proportionality or the rate and extent of absorption of BDP *in vivo*.

Therefore, it is recommended that **1)** a more sensitive and specific assay method for determining serum beclomethasone dipropionate (BDP) levels and its active metabolic species, i.e., 17-beclomethasone monopropionate (17-BMP) be developed, **2)** the assessment of equivalency between the two strengths, HFA-BDP_{50} and HFA-BDP_{100} at a measurable dose level be conducted, and **3)** the study results be submitted to the

Agency for review prior to the approval of the HFA-BDP_{100} strength unless the two strengths were adequately tested in clinical trials.

According to the in-house information known to the Agency, a very sensitive and specific assay method for BDP and 17-BMP is now available. Therefore, it is recommended that a sensitive and specific assay method for at least serum BDP and 17-BMP levels be developed and used for future PK studies.

PRELIMINARY LABELING COMMENTS (Need to be sent to the sponsor)

1. It was previously agreed upon in a pre-NDA meeting with the Agency that the pharmacokinetic (PK) data based on serum BOH and/or total BOH levels (after *in vitro* hydrolysis of serum BDP, 17-BMP, or 21-BMP to BOH) could be submitted since at that time, there was no validated sensitive assay method available to measure serum levels of each of the above species. The PK data submitted based on serum BOH and/or total BOH levels, however, could only be viewed as supportive data and therefore, the above data could not be used to attest the PK of BDP products or support their labeling.

2. The following is the Agency's version for the Pharmacokinetics subsection under the CLINICAL PHARMACOLOGY section. It is recommended that the above subsection be modified as suggested.

   a. The second sentence in the first paragraph under Pharmacokinetics subsection was either ambiguous or not supported by the study No. 1121 (annotation No. 7) or by study No. 1069 based on serum BOH levels:

Draft

   Therefore, it should be modified as follows:

   "The bioavailability information on beclomethasone dipropionate after inhaled administration is not available".

   b. The second paragraph should be modified as follows:

Draft

c. The third paragraph should be modified as follows:

Draft

3. The following is the Agency's version for the Pharmacodynamics subsection under the CLINICAL PHARMACOLOGY section. It is recommended that the above subsection be modified as suggested.

Draft

4. Under the Dosage and Administration Section, it is currently stated (line 402) that

Draft

The above paragraph is misleading since it does not clearly state that this is based on the results of *in vitro* testing and it is also misplaced since this is the Dosage and Administration Section. Therefore, the above paragraph should be revised to include the phrase of "in vitro testing" and should be relocated.

CPB Briefing on 04/30/99: Drs. M.L. Chen, R. Uppoor, D.J. Chatterjee, and T.M. Chen

/S/

04/15/99 05/03/99
Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by R. Uppoor, Ph.D. RU 04/19/99

FT initialed by R. Uppoor, Ph.D. /S/ 05/03/99

cc: NDA 20-911, HFD-570 (Nicklas, Barnes), HFD-870 (M.L. Chen, R. Uppoor, T.M. Chen), CDR (B. Murphy).

17 pages redacted from this section of the approval package consisted of draft labeling

Table 6.1.A: Clinical Pharmacology Program: Pharmacokinetics, Deposition, and Pharmacodynamics

[1 of 3 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
PHARMACOKINETICS											
1069 W. Howland	Complete (4/94-10/94)	US (1)	Phase I, open-label, randomized, cross-over design	HFA-BDP_{100} *Oral BDP*	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_{100} HFA-BDP_{200}	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

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

[a] 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 6.1.A: Clinical Pharmacology Program: Pharmacokinetics, Deposition, and Pharmacodynamics

[2 of 3 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_{50} *CFC-BDP_{50}* 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)	V1.35 p.1/ V1.38 p.191	V1.492 p.227
SPECIAL											
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)	V1.47 p.1/ V1.47 p.147	none
LUNG DEPOSITION											
1152 R. Boudreau	Complete (12/94-5/95)	US (1)	Phase II, open-label, cross-over 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
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

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

a 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 6.1.A: Clinical Pharmacology Program: Pharmacokinetics, Deposition, and Pharmacodynamics

[3 of 3 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
PHARMACODYNAMICS											
1025 J. Riddell	Complete (8/92-8/92)	UK (1)	Phase I, dose-level blind, randomized, parallel design	HFA-BDP_{200} *CFC-BDP_{250}*	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 p1
1063 J. Riddell	Complete (3/93-3/93)	UK (1)	Phase I, dose-level blind, randomized, parallel design	HFA-BDP_{50} *CFC-BDP_{50}*	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
1162 R. Dockhorn	Complete (8/95-12/95)	US (1)	Phase II, dose-level blind, randomized, parallel design	HFA-BDP_{50} *CFC-BDP_{50}* 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)	V1.35 p.1/ V1. 8 p.191	V1.492 p.227

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

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pages of trade secret and/or confidential commercial information