

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-527

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-527
Proprietary Drug Name: Atrovent HFA Inhalation 21 mcg
Generic Name: Ipratropium Bromide
Indication: Maintenance treatment of bronchospasm associated with COPD.
Dosage Form: MDI
Strength: 21 µg per puff
Route of Administration: Oral Inhalation
Inhalation device: HFA Inhalation System (MDI)
Dosage and administration: **Adults (age 12 and older):** two inhalations four times a day. Patients may take additional inhalations as required; however, the total number of inhalations should not exceed 12 in 24 hours
Applicant: Boehringer Ingelheim, Inc.
Clinical Division: DPADP (HFD-570)
Submission Dates: December 10, 2002, March 28, 2003,
Reviewer: Sandra Suarez-Sharp, Ph.D.
Team Leader: Emmanuel O. Fadiran, Ph. D.

1. EXECUTIVE SUMMARY

Atrovent (ipratropium bromide) (IprBr) HFA inhalation aerosol has been developed by Boehringer Ingelheim, Inc., as a non-CFC alternative to Atrovent® CFC Inhalation System. Atrovent HFA inhalation aerosol is a metered-dose aerosol system (MDI). In support of this application, the sponsor has submitted the results of clinical safety and efficacy studies as well as the results of three pharmacokinetic studies. The clinical development program for this product consisted primarily of 11 studies conducted using the 1st and 2nd generation products. No pivotal clinical safety or efficacy studies were conducted with the to-be-marketed formulation (3rd generation product).

The PK studies (three) were conducted to assess for relative systemic exposure to IprBr delivered from atrovent HFA versus atrovent CFC. Studies U95-0343 and U96-0020 were phase I studies conducted in healthy volunteers using the 1st generation product of HFA and Study U01-3343 was conducted in COPD patients using the 3rd generation product (to-be-marketed product) of atrovent HFA. These studies showed that the systemic exposure (C_{max} and AUC for IprBr) following administration of atrovent HFA 1st generation product was significantly higher than that observed when delivered from atrovent CFC. However, the systemic exposure (C_{max} and AUC_t) of IprBr following administration of atrovent HFA using the 3rd generation product was lower (up to 26%) than that observed following administration of atrovent CFC. No pharmacokinetics studies were conducted with the second generation product.

1.1 COMMENTS TO THE MEDICAL OFFICER

- A PK study to link the systemic safety of the 1st, 2nd and 3rd of atrovent-HFA products to atrovent-CFC may not be needed. The rationale for this is that all the PK studies and the clinical trials were comparative studies between the HFA and CFC products. If the clinical trials conducted with the 1st and 2nd generation products it is shown same or better systemic safety for IprBr delivered from HFA formulation compared to the CFC formulation, then one can expect better systemic safety with the 3rd generation product, since the PK study using the 3rd generation product showed less IprBr systemic exposure when delivered from the HFA formulation.

1.2 RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceuticals / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-527 submitted on December 10, 2002. The NDA's Human Pharmacokinetics and Bioavailability Section is acceptable to OCPB. Please convey the labeling comments to the sponsor (see page 19).

Reviewer

Sandra Suarez-Sharp, Ph.D. _____

Office of Clinical Pharmacology and Biopharmaceuticals

Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader _____

cc

NDA 21-527 : Division File

HFD-870: Malinowski, Hunt

HFD-570: Fadiran, Purohit-Sheth, Chowdhury, Jafari, Suarez-Sharp

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3. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Atrovent (ipratropium bromide) (IprBr) HFA inhalation aerosol has been developed by Boehringer Ingelheim, Inc., as a non-CFC alternative to Atrovent® CFC Inhalation System.

Atrovent HFA inhalation aerosol is a metered-dose aerosol system (MDI). It is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. The usual starting dose of atrovent HFA Inhalation Aerosol is two inhalations four times a day.

In support of this application, the sponsor has submitted the results of clinical safety and efficacy studies as well as the results of three pharmacokinetic studies. The clinical development program for this product consisted primarily of 11 studies conducted using the 1st and 2nd generation products. No pivotal clinical safety or efficacy studies were conducted with the to-be-marketed formulation (3rd generation product). The container closure system for IprBr (IprBr) Inhalation Aerosol was optimized during development in order to improve its performance in the commercial phase. The most significant change was the change during the clinical development program (first generation to second generation). This change caused a shift of the aerodynamic particle size distribution towards smaller particles. The changes introduced after the completion of the pivotal clinical studies (second generation to third generation) were less significant and were made to improve the mechanical strength of the valve seals and overall robustness of the product.

The PK studies were conducted to assess the relative systemic exposure to IprBr delivered from atrovent HFA versus atrovent CFC. In addition, Studies U95-0343 and U96-0020 were Phase I studies conducted in healthy volunteers using the 1st generation product of HFA and study U01-3343 was conducted in COPD patients using the 3rd generation product (to-be-marketed product) of atrovent HFA. These studies showed that the systemic exposure (C_{max} and AUC_t for IprBr) following multiple administration of atrovent HFA 1st generation product was significantly higher (1.6- and 1.85-fold higher, respectively) than that observed when delivered from atrovent CFC (Table 1). However, the systemic exposure (C_{max} and AUC_t) of IprBr following multiple administration of atrovent HFA using the 3rd generation product was significantly lower (20% and 26%, respectively) than that observed following administration of atrovent CFC (Table 2). No pharmacokinetics studies were conducted with the second generation product. No significant age effect on the PK of the drug was observed following multiple administration of IprBr from either the HFA or CFC formulations.

A direct PK link between the 1st, 2nd and 3rd atrovent-HFA products and atrovent-CFC may not be needed. The rationale for this is that all the PK studies and the clinical trials were comparative studies between the HFA and CFC products. If in the results of the clinical trials conducted with the 1st and 2nd generation products it is demonstrated same or better systemic safety for IprBr delivered from HFA formulation compared to the CFC formulation, then one can expect better systemic safety with the 3rd generation product.

Table Q5.1 Arithmetic mean (SD) for the IprBr PK parameters (dose normalized to 160 µg) following multiple (Day 7) inhalation of IprBr -CFC, given at a dose of 40 mcg four times daily and IprBr -HFA (1st generation product), given at a dose of 80 mcg four times daily (data from study U95-0343)

Treatment	AUC _t (ng*hr/mL)	C _{max} (pg/mL)	Cumulative renal excretion (0.24h, % daily dose)*
IprBr -HFA	64.9 (22.8)	96.3 (45.9)	4.4 (3.3-6)
IprBr -CFC	35.1 (23.5)	60.3 (36.2)	2.9 (1.4-6.1)

*geometric mean

Table 2. Mean pharmacokinetic parameters for IprBr following single and multiple administration of atrovent HFA (3rd generation product) and atrovent CFC given at a dose of 84 µg daily for one week in COPD patients (data from Study U01-3343).

Parameter	IprBr HFA 84 µg	IprBr CFC 84 µg
Single Dose		
AUC _{0-6hr} (pg*hr/mL)	196.8	269.4
C _{max} (pg/mL)	58.9	92.7
Multiple dose		
AUC _{0-6hr} (pg*hr/mL)	265.1	359.5
C _{max} (pg/mL)	82.1	101.8
T _{max} (hrs)	0.27	0.45
C _{min} (pg/mL)	28.2	39.9
C _{ss} (pg/mL)	44.2	59.9
DF _{ss}	125.9	111.8

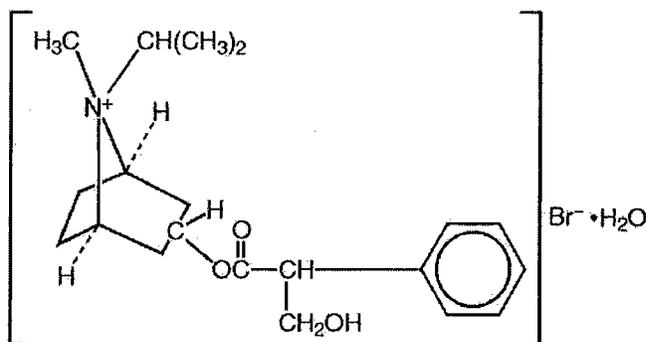
4. QUESTION BASED REVIEW

Q1. What are the general attributes of Atrovent-HFA?

Chemical name:

IprBr is an anticholinergic bronchodilator chemically described as 8-azoniabicyclo (3.2.1)-octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-,bromide, monohydrate (*endo,syn*)-,(±)-: a synthetic quaternary ammonium compound, chemically related to atropine.

Structural formula:



Molecular formula: C₂₀H₃₀BrNO₃•H₂O

Molecular weight: . 430.4

Solubility: IprBr is a white to off-white crystalline substance, freely soluble in water and methanol and sparingly soluble in ethanol and insoluble in lipophilic solvents such as ether, chloroform, and fluorocarbons.

FORMULATION

ATROVENT HFA Inhalation Aerosol is a pressurized metered-dose aerosol unit for oral inhalation that contains a solution of IprBr. The net weight is 12.9 grams; it yields 200

inhalations. Each actuation delivers 21.0 mcg of IprBr from the valve and ~ mcg from the mouthpiece. The excipients are HFA-134a (1,1,1,2-tetrafluoroethane) as propellant, purified water, dehydrated alcohol, and anhydrous citric acid. This product does not contain chlorofluorocarbons (CFCs) as a propellant or soya lecithin as an excipient (see Table Q1).

Table Q1. Quantitative composition of clinical batches of IprBr monohydrate (HFA-134a) inhalation aerosol

Ingredient	Function	Weight Percent (g/100 g)	Weight per Container (g)	Weight per Actuation Ex-Valve***	Weight per Actuation Ex-Mouthpiece (label claim)
Ipratropium Bromide Monohydrate (unmicronized)	Active Ingredient	/	/	21.00 µg	
Citric Acid, USP (anhydrous)		/	/	/	---
Purified Water, USP		/	/	/	---
Dehydrated Alcohol, USP *		/	/	/	---
1,1,1,2-tetrafluoroethane (HFA-134a)	Propellant	/	/	/	---
TOTAL		100.000	/	/	---

INDICATION (as per proposed label)

ATROVENT HFA (IprBr) Inhalation Aerosol is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.

DOSAGE AND ADMINISTRATION (as per proposed label)

The usual starting dose of ATROVENT HFA (IprBr) Inhalation Aerosol is two inhalations four times a day. Patients may take additional inhalations as required; however, the total number of inhalations should not exceed 12 in 24 hours.

Q2. What is known about the pharmacokinetics of IprBr?

The following information has been reported in NDA 19-085.

Most of an administered dose is swallowed as shown by fecal excretion studies. IprBr is not readily absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract as confirmed by blood level and renal excretion studies.

The half-life of elimination is about 2 hours after inhalation or intravenous administration. IprBr is minimally bound (0 to 9% *in vitro*) to plasma albumin and α_1 -acid glycoprotein. It is partially metabolized to inactive ester hydrolysis products. Following

intravenous administration, approximately one-half of the dose is excreted unchanged in the urine.

Special Populations

Renally Impaired Patients:

The pharmacokinetics of ATROVENT HFA Inhalation Aerosol have not been studied in patients with renal insufficiency.

Hepatically Impaired Patients:

The pharmacokinetics of ATROVENT HFA Inhalation Aerosol have not been studied in patients with hepatic insufficiency.

Drug Interactions

ATROVENT HFA Inhalation Aerosol has been used concomitantly with other drugs, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, commonly used in the treatment of chronic obstructive pulmonary disease. With the exception of albuterol, there are no formal studies fully evaluating the interaction effects of ATROVENT and these drugs with respect to effectiveness.

Anticholinergic agents: Although IprBr is minimally absorbed into the systemic circulation, there is some potential for an additive interaction with concomitantly used anticholinergic medications. Caution is therefore advised in the co-administration of ATROVENT Inhalation Aerosol with other anticholinergic-containing drugs.

Q3. Was the to-be-marketed formulation used in the pharmacokinetic studies?

The container closure system for IprBr Monohydrate (HFA-134a) Inhalation Aerosol was optimized during development in order to improve its performance in the commercial phase. The primary reasons for introducing changes during the clinical program were to lower the levels extractives and to improve the compatibility of the canister, valve spring and valve stem with the formulation. According to the sponsor, the changes introduced after the completion of the pivotal clinical studies (second generation to third generation) were less significant and were made to improve the mechanical strength of the valve seals and overall robustness of the product.

According to the sponsor, the most significant change was the change during the clinical development program (first generation to second generation) from a _____ stem. This change caused a shift of the aerodynamic particle size distribution towards smaller particles.

The proposed commercial product in its final container closure system has been used in the stability program and the product characterization studies.

Table Q3.1 summarizes the PK studies included in the present NDA submission and the type of formulation used in each study. There is no direct pharmacokinetic link between the 1st and 2nd or 3rd generation devices/formulation. In addition, studies conducted with the 1st generation device/product were conducted in healthy volunteers while the to-be-marketed formulation (3rd generation valve) used COPD patients. Clinical pivotal trials were conducted with the 1st and 2nd generation devices and no pivotal clinical trial was conducted with the 3rd generation product. Nevertheless, since in the PK study conducted in COPD patients (two-way crossover study) using the to-be-marketed HFA formulation and the already approved atrovent-CFC formulation was shown that the systemic exposure of IprBr from the HFA formulation is lower than that from the CFC formulation a direct link between the 1st, 2nd and 3rd devices may

not be needed. The rationale for this is that all the PK studies and the clinical trials were comparative studies between the HFA and CFC products. If the clinical trials conducted with the 1st and 2nd generation products show same systemic safety for IprBr delivered from either the CFC or HFA formulation, then one could expect better systemic safety with the 3rd generation product. This is because the PK studies conducted with the 3rd generation product showed lower systemic exposure with the HFA formulation while in the PK studies conducted with the 1st generation product the opposite was observed.

Table Q3.1. Formulations of IprBr used in the conduct of the PK studies submitted to NDA

U# (Study #)	Study Purpose	Number of Subjects	Where Conducted	HFA Formulation/ Batch No	Assay Method (LOQ)
U95-0343 (244.1401)	Tolerability and preliminary pharmacokinetics of ipratropium bromide HFA-MDI (4 x 80 µg) in comparison to ipratropium bromide CFC-MDI (4 x 40 µg) and placebo HFA-MDI after multiple inhalational administration over 7 days to healthy volunteers.	12 normal volunteers 6 males 6 females 24-46 years of age (mean = 34.5 yrs)	July 1994 – September 1994	1 st Generation Valve PD-1384	Ipratropium by radioreceptor assay (20 pg/mL)
U96-0020 (244.1402)	Pharmacokinetics after single inhalation of 40 and 80 µg ipratropium bromide HFA-MDI, placebo HFA-MDI, and 40 µg ipratropium bromide CFC-MDI in a crossover study in healthy volunteers.	12 normal volunteers 6 males 6 females 27-41 years of age (mean = 33.0 yrs)	December 1994 – January 1995	1 st Generation Valve PD-1383 PD-1384	Ipratropium by radioreceptor assay (20 pg/mL) HFA by GC/ (0.03 µg/mL)
U01-3343 (244.2480)	A double-blind, crossover, pharmacokinetic trial to determine the comparability of Atrovent pharmacokinetics after inhalation of Atrovent HFA for 7 days to the market standard, Atrovent CFC, and to obtain pharmacokinetic information on Atrovent in a COPD population.	30 COPD patients 21 males 9 females 48-79 years of age (mean = 63.7 yrs)	October 2000 – April 2001	3 rd Generation Valve PD-2041	Ipratropium by LC/MS/MS plasma (10 pg/mL) urine (0.10 ng/mL)

Q4. What is the dose-systemic exposure relationship of IprBr following inhalation using the HFA Inhaler System?

Study U96-0020 was a randomized, double blind, four-way crossover trial conducted in 12 healthy volunteers to obtain information on the PK of IprBr after single inhalation of 2 x 20 and 2 x 40 mcg IprBr HFA-MDI. It was also aimed to gain information on the comparative systemic exposure of IprBr when delivered from the HFA versus the CFC formulation.

Due to assay limitations (concentration below the limit of quantitation) the statistical analysis of PK parameters were not done. However, data from 24hrs urine collection was

available. Table Q4.1 summarizes the geometric mean values of the cumulative renal excretion data for IprBr. The 24 hours cumulative renal excretion of IprBr was 11.7% for the 40 mcg IprBr HFA-MDI dose and 13.1% for the 80 mcg IprBr HFA-MDI dose. These data suggests that there is an increase systemic exposure of IprBr delivered from the HFA formulation with increasing dose.

Table Q4.1. Geometric mean values of the cumulative renal excretion data for IprBr

Treatment	Geometric mean (mcg)
IprBr-HFA 40 mcg	4.66 (3.53-6.16)
IprBr-HFA 80 mcg	10.45 (7.54-14.48)

CONCLUSION

- There is a proportional increase in systemic exposure of IprBr delivered from the HFA formulation with increasing doses from 40 and 80 mcg.

Q5. How does the IprBr systemic exposure delivered from the HFA Inhaler System compare to that obtained using the CFC Inhalation System?

Three studies were conducted to assess for relative systemic exposure to IprBr delivered from atrovent HFA versus atrovent CFC. Studies U95-0343 and U96-0020 were phase I studies conducted in healthy volunteers using the 1st generation HFA product and Study U01-3343 was conducted in COPD patients using the 3rd generation product of atrovent HFA.

Study U95-0343 was a randomized, threefold cross-over placebo controlled study to assess the tolerability and preliminary pharmacokinetics of IprBr HFA-MDI (4x 80 mcg) in comparison to IprBr CFC-MDI (4 x 40 mcg) and placebo HFA-MDI after multiple inhalational administration over 7 days in 12 healthy volunteers. The following summarizes the findings from this study:

- Peak plasma concentrations after multiple administration of IprBr using the HFA-MDI device (mean=96.3 pg/mL, normalized to 160 mcg/dose) were significantly higher than those using the CFC-MDI device (mean 60.3 pg/mL) (n = 36).
- The AUC_t (from pre-dose and up to 60 min after the last of the 4 daily doses administration) of IprBr using the HFA-MDI device (arithmetic mean= 64.9 ng/mL•h, dose normalized to 160 mcg) was significantly higher than that using the CFC-MDI device (arithmetic mean= 35.1 ng*hr/mL) (Table Q5.1).
- No difference in C_{max} and AUC of IprBr values was found when comparing the treatment days 1, 3, and 7, indicating lack of accumulation of IprBr delivered from either the atrovent HFA or atrovent CFC products (Figure Q5.1 and Q5.2 respectively).
- Ninety percent confidence intervals (IprBr-HFA/ IprBr-CFC= 1.39, CI= 1.09-1.85) and the analysis of variance of the IprBr data derived from determinations in urine revealed again a significant difference between the 2 different Atrovent formulations.

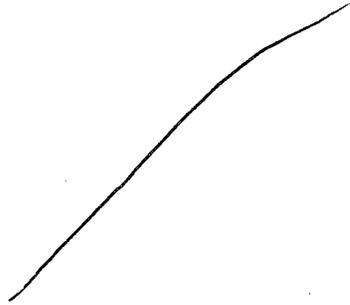


Figure Q5.1. Individual C_{max} values (dose normalized to 160 µg) for IprBr (IprBr) following multiple inhalation of IprBr -CFC, given at a dose of 40 µg four times daily and IprBr -HFA, given at a dose of 80 mcg four times daily.

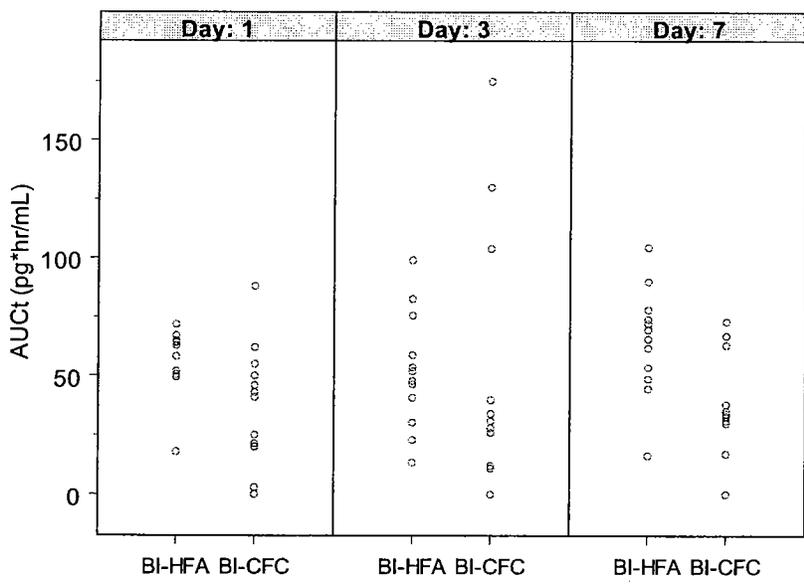


Figure Q5.2. Individual AUC values (dose normalized to 160 µg) for IprBr (IprBr) following multiple inhalation of IprBr -CFC, given at a dose of 40 µg four times daily and IprBr -HFA, given at a dose of 80 µg four times daily

Table Q5.1 Arithmetic mean (SD) for the IprBr PK parameters (dose normalized to 160 µg) following multiple (Day 7) inhalation of IprBr -CFC, given at a dose of 40 mcg four times daily and IprBr -HFA, given at a dose of 80 mcg four times daily

Treatment	AUC _t (ng*hr/mL)	C _{max} (pg/mL)	Cumulative renal excretion (0.24h, % daily dose)*
IprBr -HFA	64.9 (22.8)	96.3 (45.9)	4.4 (3.3-6)
IprBr -CFC	35.1 (23.5)	60.3 (36.2)	2.9 (1.4-6.1)

*geometric mean

Study U96-0020 was a randomized, double blind four-way crossover trial to determine the pharmacokinetics after single inhalation of 2 x 20 and 2 x 40 mcg IprBr HFA-MDI, placebo HFA-MDI and 2 x 20 mcg IprBr CFC-MDI in a crossover study in 12 healthy volunteers. The following conclusions were made from this study:

- The 24 hours cumulative renal excretion of IprBr (arithmetic means), for the two HFA-MDI strengths were significantly higher (1.2-fold and 1.3-fold higher for the 40 and 80 mcg, respectively) than that observed for CFC-MDI formulation (Table Q5.2 and Q5.3)
- Analysis of variance revealed no difference in the dose normalized renal excretion data of the 40 mcg (HFA-MDI) and the 80 mcg (HFA-MDI) formulation, suggesting no dose-dependent change in the bioavailability of IprBr
- The relative short half life calculated for the propellant HFA-134a suggest that this compound does not accumulate in the body (Figure Q5.3)

Table Q5.2. Arithmetic mean (SD) for the cumulative renal excretion data following inhalation of IprBr-CFC, given at a dose of 40 mcg and IprBr-HFA, given at a dose of 40 and 80 mcg

Treatment	mean (mcg)
IprBr -HFA 40 mcg	4.81 (1.15)
IprBr-HFA 80 mcg	10.94 (3.3)
IprBr -CFC 40 mcg	4.02 (1.11)

Table Q5.3. Ninety % confidence intervals for the ratio of geometric mean cumulative renal excretion among treatments (IprBr -HFA 80 mcg were dose normalized to 40 mcg)

Treatment	Point estimates		90% CI	
	Reported by sponsor	Calculated by this reviewer	Reported by sponsor	Calculated by this reviewer
IprBr-HFA 40 mcg/ IprBr-CFC 40 mcg	1.21	1.17	1.07-1.36	0.96-1.41
IprBr-HFA 80 mcg/ IprBr-CFC 40 mcg	1.12	1.27	1.19-1.52	1.04-1.54
IprBr-HFA 80 mcg/ IprBr-HFA 40 mcg		1.09		0.98-1.24

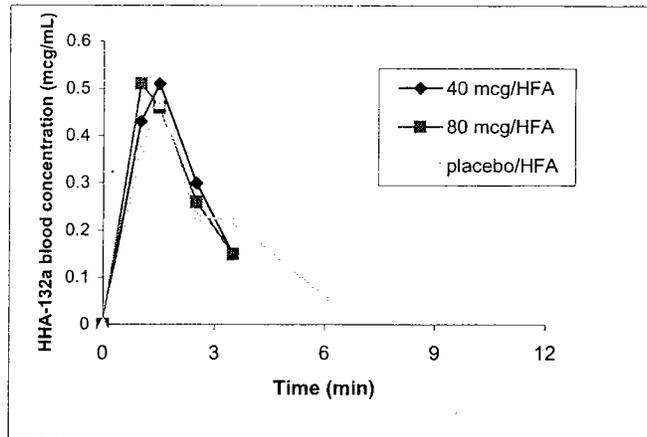


Figure Q5.3. Geometric means of HFA-134a concentrations in whole blood following administration of single dose of ipratropium HFA, given at a dose of 40 μg ($2 \times 20 \mu\text{g}/50 \mu\text{l}$) and single dose of ipratropium HFA, given at a dose of 80 μg ($2 \times 40 \mu\text{g}/50 \mu\text{l}$) and Placebo HFA

Study U01-3343 was an open-label, crossover, pharmacokinetic study to determine the comparability of 84 mcg IprBr HFA-134a inhalation aerosol to 84 mcg ATROVENT CFC inhalation aerosol, in 29 patients with chronic obstructive pulmonary disease (COPD). The following conclusions were made from this study:

- The mean C_{max} and AUC_t of IprBr following single administration of atrovent HFA were 36 % and 27 % lower than those observed following administration of atrovent CFC. The lower limit of the ninety percent confidence intervals for the log-transformed PK parameters for the ratio IprBr -HFA/ IprBr -CFC was as low as 57 for the C_{max} and 60 for the AUC_t (Figures Q5.4 and Q5.5).
- The mean C_{max} and AUC_t of IprBr following multiple administration of atrovent HFA were 19 % and 26 % lower than those observed following administration of atrovent CFC. The lower limit of the ninety percent confidence intervals for the log-transformed PK parameters for the ratio IprBr -HFA/ IprBr -CFC was as low as 67.5 for the C_{max} and 63 for the AUC_t (Tables Q5.4 and Q5.5).
- There was a trend of lower (25 % lower) mean atrovent HFA amount excreted in urine compared to mean atrovent CFC, however the difference in means was not statistically significant (Figure Q5.6).
- There was a trend of higher C_{max} and $\text{AUC}_{0-6\text{hr}}$ values as the age of the patients increased. The mean C_{max} and $\text{AUC}_{0-6\text{hr}}$ for patients older than 65 years old receiving multiple dosing of IprBr -HFA were 16% and 6% higher, respectively than those observed for younger patients. Although the 90% CI for the log-transformed PK parameters were out of the BE goal post (C_{max} CI=0.85-1.43; AUC CI=0.81-1.33), these differences may not be clinically significant. Therefore, there is no age effect on the PK of atrovent-HFA after multiple administration.

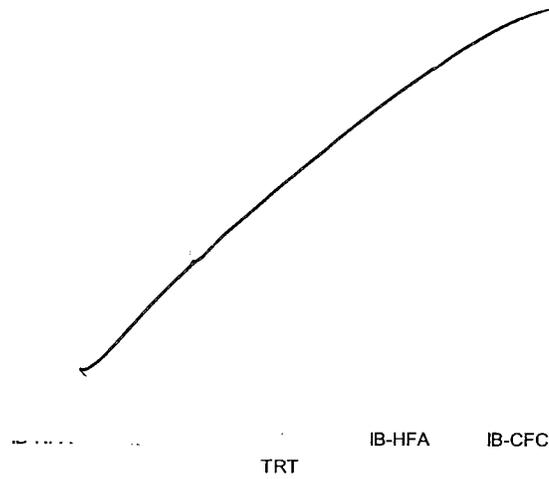


Figure Q5.4. Individual C_{max} (pg/mL) values for IprBr (IprBr) following single and multiple administration of atrovent HFA and atrovent CFC given at a dose of 84 µg q.i.d daily (336 µg/daily) for one week.

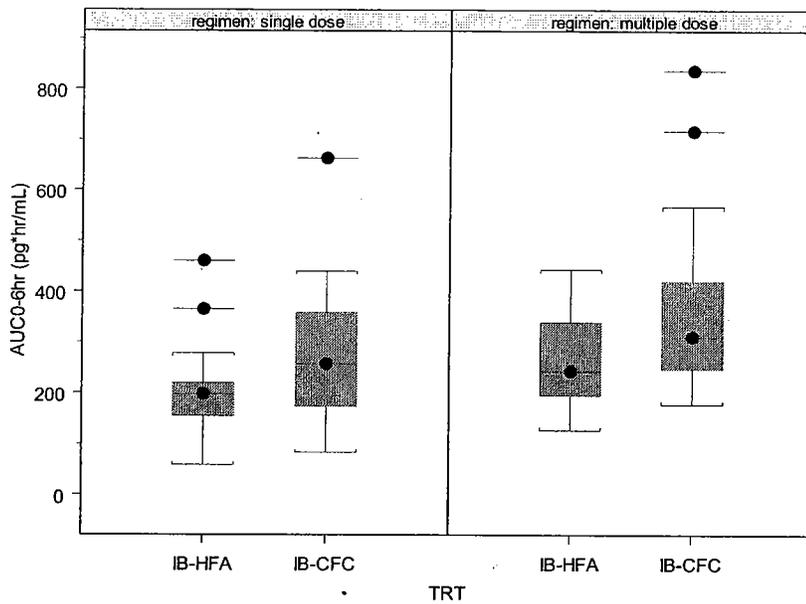


Figure Q5.5. Individual AUC_τ (pg*hr/mL)_τ values for IprBr (IprBr) following single and multiple administration of atrovent HFA and atrovent CFC given at a dose of 84 µg q.i.d daily (336 µg/daily) for one week.

Table Q5.4. Mean pharmacokinetic parameters for IprBr following single and multiple administration of the two treatments

Parameter	IprBr HFA 84 µg	IprBr CFC 84 µg
Single Dose		
AUC _{0-6hr} (pg*hr/mL)	196.8	269.4
Cmax (pg/mL)	58.9	92.7
Multiple dose		
AUC _{0-6hr} (pg*hr/mL)	265.1	359.5
Cmax (pg/mL)	82.1	101.8
Tmax (hrs)	0.27	0.45
Cmin (pg/mL)	28.2	39.9
Css (pg/mL)	44.2	59.9
DFss	125.9	111.8

Table Q5.5. Point estimates and 90% confidence intervals for the log-transformed PK parameters following single and multiple administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
Single dose			
IprBr -HFA/ IprBr -CFC	AUC _τ	74.5	60-92
	Cmax	70.8	57-88
Multiple dose			
IprBr -HFA/ IprBr -CFC	AUC _τ	74.7	63-88.6
	Cmax	80.5	67.5-96.1

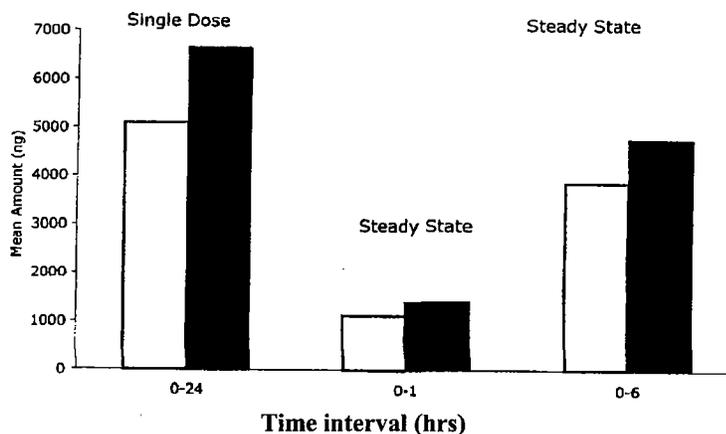


Figure Q5.6. Ipratropium mean amount (ng) excreted in the urine following administration of 84 mcg single dose inhalation or multiple administration for one week (QD) of either atrovent HFA or atrovent CFC (dark bars).

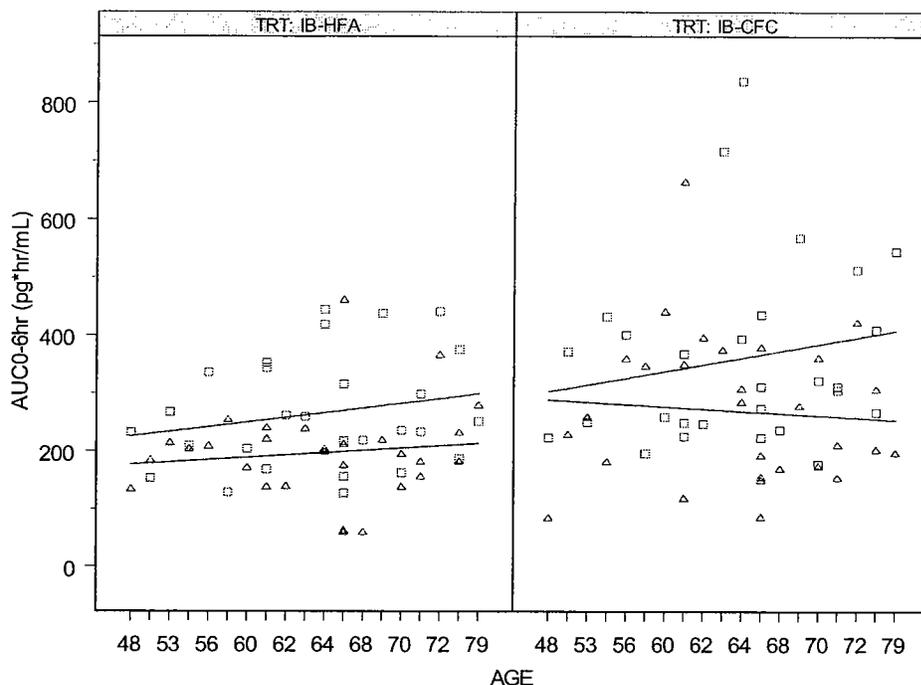


Figure Q5.7. AUC-AGE relationship following single (triangles) and multiple (squares) administration of atrovant HFA and atrovant CFC given at a dose of 84 μg q.i.d daily for one week.

OVERALL CONCLUSIONS

- The systemic exposure (C_{max} and AUC for IprBr) following administration of atrovant HFA 1st generation product was significantly higher than that observed when delivered from atrovant CFC.
- The systemic exposure (C_{max} and AUC_t) of IprBr following administration of atrovant HFA using the 3rd generation product was significantly lower (up to 26%) than that observed following administration of atrovant CFC.
- A direct PK link between the 1st, 2nd and 3rd atrovant-HFA products and atrovant-CFC may not be needed. The rationale for this is that all the PK studies and the clinical trials were comparative studies between the HFA and CFC products. If the clinical trials conducted with the 1st and 2nd generation products demonstrate same or better systemic safety for IprBr delivered from HFA formulation compared to the CFC formulation, then one can expect better systemic safety with the 3rd generation product.

Q6. Was the suitability of the analytical method supported by the submitted information?

The sponsor submitted all the appropriate information that supports that the analytical methods used in NDA 21-527 are accurate, precise, sensitive and specific. A summary of assay performance is shown in the Tables below:

Table Q6.1. Assay performance (In-study validation) for IprBr from study U01-3343

	Plasma	Urine
Method	LC-MS-MS	LC-MS-MS
Linearity	Satisfactory: Standard curve range from 0.01 to 5.0 ng/mL; $r^2=0.9993$	Satisfactory: Standard curve range from 0.1-100 ng/mL; $r^2=0.9994$
Accuracy	Satisfactory: %Bias: 1.67 at 25 pg/mL; -1.6% at 250 pg/mL; -3.1% at 4000 pg/mL.	Satisfactory: %Bias: 5.0 at 0.25 ng/mL; 5.6% at 5 ng/mL; 2.6% at 80 ng/mL.
Inter-day Precision	Satisfactory: %CV: 6.8 at 25 pg/mL; -3.4% at 250 pg/mL; 3.96% at 4000 pg/mL.	Satisfactory: % CV: 3.4 at 0.25 ng/mL; 3.5% at 5 ng/mL; 2.7% at 80 ng/mL.
Intra-day Precision	Satisfactory: %CV: 3.7 at 25 pg/mL; -1.4% at 250 pg/mL; 3.0% at 4000 pg/mL.	Satisfactory: % CV: 3.6 at 0.25 ng/mL; 3.7% at 5 ng/mL; 2.03% at 80 ng/mL.
Specificity	Satisfactory: Chromatograms submitted	Satisfactory: Chromatograms submitted

Table Q6.2. Assay performance (In-study validation) for IprBr and HFA-134a from study U96-0020

	Ipratropium in Plasma	Ipratropium in Urine	HFA-134a in Plasma
Method	Radioreceptor assay	Radioreceptor assay	Gas chromatograohy
Linearity	Satisfactory: Standard curve range from 20 to 5000 pg/mL;	Satisfactory: Standard curve range from 0-4 ng/mL	Satisfactory: Standard curve range from 0-12 mcg/mL; $r^2=0.999$
Accuracy	Satisfactory: %Bias: -5.4 at 100 pg/mL; 5.9% at 200 pg/mL; 5.6% at 1000 pg/mL.	Satisfactory: %Bias: 9.4 at 200 pg/mL; -0.9% at 800 pg/mL; 0.3% at 4000 pg/mL.	Satisfactory: %Bias: 5.9 at 0.08 mcg/mL; 3.9% at 1.56 mcg/mL; 2.1% at 6 mcg/mL.
Inter-day Precision	Satisfactory: CV %: 0 at 1000 pg/mL; 0.5% at 200 pg/mL; 5.6% at 1000 pg/mL	Satisfactory: CV %: 21.6 at 200 pg/mL; 5.7% at 800 pg/mL; 8.5% at 4000 pg/mL.	Satisfactory: CV %: 4.8 at 0.08 mcg/mL; 6.7% at 1.56 mcg/mL; 6.6% at 6 mcg/mL.
Intra-day Precision	Satisfactory: CV %: 16.2 at 1000 pg/mL; 11.2% at 200 pg/mL; 4.2% at 1000 pg/mL.	Satisfactory: CV %: 24.4 at 200 pg/mL; 16.2% at 800 pg/mL; 5.3% at 4000 pg/mL.	Satisfactory: CV %: 4.4 at 0.08 mcg/mL; 3.1% at 1.56 mcg/mL; 4.9% at 6 mcg/mL.
Specificity	Satisfactory: cross-reactivity determined	Satisfactory: cross-reactivity determined	Satisfactory: chromatograms submitted

Table Q6.3. Assay performance (In-study validation) for IprBr (study U95-0343)

	Plasma	Urine
Method	Radioreceptor assay	Radioreceptor assay
Linearity	Satisfactory: Standard curve range from 20 to 5000 pg/mL;	Satisfactory: Standard curve range from 8-200 ng/mL
Accuracy	Satisfactory: %Bias: 13.3 at 50 pg/mL; 2.2% at 200 pg/mL; -0.8% at 1000 pg/mL.	Satisfactory: %Bias: 9.8 at 2.0 ng/mL; 0% at 8 ng/mL; 2.7% at 40 ng/mL.
Inter-day Precision	Satisfactory: CV %: 27 at 50 pg/mL; 14.1% at 200 pg/mL; 13.2% at 1000 pg/mL	Satisfactory: CV %: 9.8 at 2.0 ng/mL; 0% at 8 ng/mL; 2.7% at 40 ng/mL.
Intra-day Precision	Satisfactory: CV %: 7.4 at 50 pg/mL; 0% at 200 pg/mL; 0% at 1000 pg/mL.	Satisfactory: CV %: at 2.0 ng/mL; 10.5% at 8 ng/mL; 10.8% at 40 ng/mL.
Specificity	Satisfactory: cross-reactivity determined	Satisfactory: cross-reactivity determined

GENERAL COMMENTS

- Ipratropium bromide pharmacokinetic results delivered from the CFC formulation were not consistent across studies. The AUC values (dose normalized) were much lower (4-fold) in study U95-0343 compared to study U01-3343. Provide an explanation for these unexpected results and submit cross-study validation data comparing bioanalytical assays.

Note: the sponsor has responded to this request and stated that there is no cross-validation data between bioanalytical assays.

**APPEARS THIS WAY
ON ORIGINAL**

13 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

6.2 Individual Reviews

"Pharmacokinetics after single inhalation of 2 x 20 and 2 x 40 mcg ipratropium bromide HFA-MDI, placebo HFA-MDI and 2 x 20 mcg ipratropium bromide CFC-MDI in a crossover study in healthy volunteers"

Study: U96-0020
Volume: 36
Date of Report: Oct 23, 1995
Dates of Trial: Dec 08, 1994- Jan 27, 1995

OBJECTIVE

- to obtain information about the pharmacokinetics after single inhalational administration of IprBr and HFA-134a in healthy young volunteers. To this purpose, blood samples were taken and urine samples collected. Additionally, safety and tolerability were assessed.

SUBJECTS

Twelve subjects (6 males and 6 females) were entered into the study and all completed the study. The demographic features were as follows:

	Female subjects (N = 6)	Male subjects (N = 6)	All subjects (N = 12)
Age (years)	33.5 (29 to 41)	29.5 (27 to 38)	33.0 (27 to 41)
Weight (kg)	61.5 (52 to 79)	79.0 (67 to 84)	68.0 (52 to 84)
Height (cm)	165.5 (155 to 176)	181.5 (173 to 193)	173.5 (155 to 193)
Weight in percent of normal weight (Broca)	-5.8 (-17.5 to 12.9)	-6.8 (-12.9 to 1.3)	-6.8 (-17.5 to 12.9)

STUDY DESIGN AND TREATMENT ADMINISTRATION

The study was a randomized, double blind four-way crossover trial. The pharmacokinetics of 40 µg and 80 µg IprBr HFA-MDI given as a single dose were compared with a single dose of 40 µg IprBr CFC-MDI. Subjects received the following treatments:

Treatment A: single dose of ipratropium CFC, given at a dose of 40 µg (2 x 20 µg)

Treatment B: single dose of ipratropium HFA, given at a dose of 40 µg (2 x 20 µg/50 µl)

Treatment C: single dose of ipratropium HFA, given at a dose of 80 µg (2 x 40 µg/50 µl)

Treatment D: Placebo HFA

There was a wash-out period of at least two days between treatments.

FORMULATION

The following formulations and batch numbers were used in this study.

Table 1. Ipratropium formulation used in this study

Study Drug/Strength	Batch Number
ipratropium CFC-MDI	PD-1385
ipratropium HFA-MDI 20 µg per puff	PD-1383
ipratropium HFA-MDI 40 µg per puff	PD-1384
Placebo HFA	PD-1382

PHARMACOKINETIC MEASUREMENTS

Blood and urine sampling

Blood samples to determine drug plasma levels were taken predose and at 5, 15 min and 1, 3 and 4 hours after administration. Blood samples for to determine HFA-134a plasma level were taken before drug administration on each study day as well as at 1, 1.5, 2.5, 3.5, 6, 10, 20, and 30 minutes after administration.

Urine was collected quantitatively during the 24 hours following the medication at the following time intervals: 0-4 hours; 4-8 hours and 8-24 hours. A urine void was collected prior to each 24-hours sampling interval.

Analytical Method

Plasma and urine samples for ipratropium determinations were analyzed by radioreceptor assay. The blood levels of HFA-134a were determined by — gas chromatography with — detection.

DATA ANALYSIS

Pharmacokinetic Analysis

Most IprBr concentrations in plasma were below the limit of quantitation, therefore, no calculations were performed.

The area under the plasma concentration-time curve (AUC) for HFA concentrations was estimated by using the trapezoidal rule between 0 to 30 min. No extrapolation was applied. The values for the peak plasma concentration (C_{max}) and the time to reach the peak plasma concentration (t_{max}) were taken directly from the original data.

Total renal excretion expressed as percentage of the daily dose was calculated by multiplication of the measured urine concentration [ng/ml] and the total urine volume [ml] of the fraction of each time interval, divided by the daily dose. The total daily renal excretion (0-24 h) of each volunteer was calculated as the sum of the renal excretion of the 3 individual urine fractions.

Statistical analysis

No statistical calculations were performed on the plasma concentration data of IprBr. Renal excretion data were described by geometric mean values and the geometric I-SD interval. Mean and SD were calculated from the log-transformed data. Geometric means of the HFA-134a concentrations in blood were calculated and plotted against the

time. Zero values were set to 0.001mcg/mL prior to log-transformation.

Analysis of variance of the log-transformed renal excretion data of IprBr (0-0.5 h and 0-24h-fractions) and of the log-transformed AUC (0-30 min) and Cmax data of the HFA-134a measurements in blood was performed separating the variabilities due to the factors ‘sex’, ‘subject (sex)’, ‘treatment’, ‘period’, and ‘treatment *sex’, followed by pairwise comparison of the least squares means for treatment groups.

Based on the renally excreted IprBr amount, the relative bioavailability of the two HFA-MDI-formulations compared to the CFC-MDI formulation was estimated by appropriate two-sided 90%-confidence intervals. This interval estimation was obtained through backtransformation (antilog) of the 90%-confidence interval for the difference of the least squares means: $lsmeans(HFA-MDI)-lsmeans(CFC-MDI)$, calculated for the logarithmically transformed cumulative renal excretion data.

SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

RESULTS

Analytical Method Pre-Study Validation

Limit of Quantitation:

Plasma: 20 pg/mL

Urine: 0.4 ng/mL

Precision and Accuracy:

% Bias and CV% were lower than 20% for all the quality control used.

In-Study Validation

Table 2 shows the in-study validation assay performance for IprBr in plasma and urine.

Table 2. Assay performance (In-study validation) for IprBr and HFA-134a

	Ipratropium in Plasma	Ipratropium in Urine	HFA-134a in Plasma
Linearity	Satisfactory: Standard curve range from 0 to 5000 pg/mL;	Satisfactory: Standard curve range from 0-4 ng/mL	Satisfactory: Standard curve range from 0-12 mcg/mL; $r^2=0.999$
Accuracy	Satisfactory: %Bias: -5.4 at 100 pg/mL; 5.9% at 200 pg/mL; 5.6% at 1000 pg/mL.	Satisfactory: %Bias: 9.4 at 200 pg/mL; -0.9% at 800 pg/mL; 0.3% at 4000 pg/mL.	Satisfactory: %Bias: 5.9 at 0.08 mcg/mL; 3.9% at 1.56 mcg/mL; 2.1% at 6 mcg/mL.
Inter-day Precision	Satisfactory: CV %: 0 at 1000 pg/mL; 0.5% at 200 pg/mL; 5.6% at 1000 pg/mL	Satisfactory: CV %: 21.6 at 200 pg/mL; 5.7% at 800 pg/mL; 8.5% at 4000 pg/mL.	Satisfactory: CV %: 4.8 at 0.08 mcg/mL; 6.7% at 1.56 mcg/mL; 6.6% at 6 mcg/mL.
Intra-day Precision	Satisfactory: CV %: 16.2 at 1000 pg/mL; 11.2% at 200 pg/mL; 4.2% at 1000 pg/mL.	Satisfactory: CV %: 24.4 at 200 pg/mL; 16.2% at 800 pg/mL; 5.3% at 4000 pg/mL.	Satisfactory: CV %: 4.4 at 0.08 mcg/mL; 3.1% at 1.56 mcg/mL; 4.9% at 6 mcg/mL.
Specificity	Satisfactory: cross-reactivity determined	Satisfactory: cross-reactivity determined	Satisfactory: chromatograms submitted

Pharmacokinetic Results

Only 80 out of 216 investigated plasma samples (HFA-MDI 2 x 20 mcg (A): 20, HFA-MDI 2 x 40 pig (B): 43, CFC-MDI 40 mcg (D): 17) contained IprBr concentrations greater than 20 mcg/mL (LOQ). In 29 out of the 80 plasma samples with measurable IprBr concentrations values exceeded 50 mcg/mL. Table 3 summarizes the geometric mean values of the cumulative renal excretion data for IprBr. Table 4 shows the analysis of variance of the logarithmically transformed and dose normalized cumulative renal excretion data. Table 5 shows the 90% confidence intervals for the geometric mean cumulative renal excretion between formulations. The 24 hours cumulative renal excretion of IprBr was 11.7% for the 40 mcg IprBr HFA-MDI dose, 13.1% for the 80 mcg IprBr HFA-MDI dose and 9.7% for the 40 mcg IprBr CFC-MDI. Regarding the 24 hours cumulative renal excretion of IprBr, the two HFA-MDI formulations differed significantly from the CFC-MDI formulation. Figure 1 shows the cumulative amount (mcg) of IprBr excreted unchanged over 24 hrs following single inhalation of IprBr_CFC 40 µg, IprBr_HFA 40 µg, and IprBr_HFA 80 µg. Figure 2 shows the geometric means of HFA-134a in blood following administration of the treatments. Table 6 shows the geometric mean values of the AUC and Cmax of HFA-134a in blood.

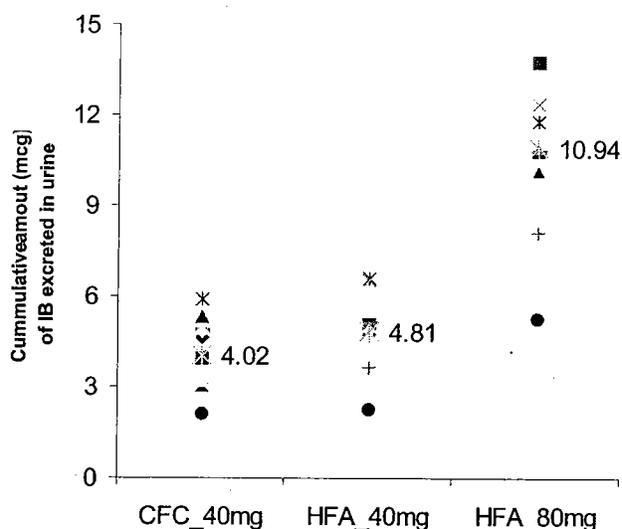


Figure 1. Cumulative amount (mcg) of IprBr excreted unchanged over 24 hrs following single inhalation of IprBr_CFC 40 µg, IprBr_HFA 40 µg, and IprBr_HFA 80 µg.

Table 3. Arithmetic mean (SD) for the cumulative renal excretion data following inhalation of IprBr-CFC, given at a dose of 40 mcg and IprBr-HFA, given at a dose of 40 and 80 mcg

Treatment	mean (mcg)
IprBr -HFA 40 mcg	4.81 (1.15)
IprBr-HFA 80 mcg	10.94 (3.3)
IprBr -CFC 40 mcg	4.02 (1.11)

Table 4. Analysis of variance of the logarithmically transformed cumulative renal excretion data

Source of variation	p-values
	Renal excretion data
Subject	0.0003
Treatment	0.0017
Period	0.17
sex	0.53
sex*treatment	0.54

Table 5. Ninety % confidence intervals for the ratio of geometric mean cumulative renal excretion among treatments (IprBr -HFA 80 mcg were dose normalized to 40 mcg)

Treatment	Point estimates		90% CI	
	Reported by sponsor	Calculated by this reviewer	Reported by sponsor	Calculated by this reviewer
IprBr-HFA 40 mcg/ IprBr-CFC 40 mcg	1.21	1.17	1.07-1.36	0.96-1.41
IprBr-HFA 80 mcg/ IprBr-CFC 40 mcg	1.12	1.27	1.19-1.52	1.04-1.54
IprBr-HFA 80 mcg/ IprBr-HFA 40 mcg		1.09		0.98-1.24

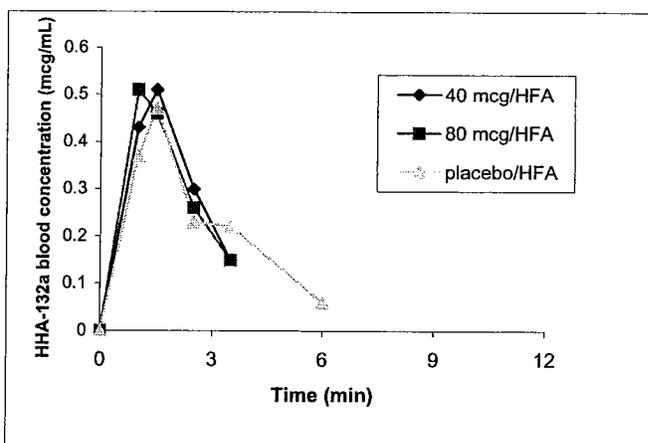


Figure 2. Geometric means of HFA-134a concentrations if whole blood following administration of single dose of single dose of ipratropium HFA, given at a dose of 40 µg (2 x 20 µg/50 µl) single dose of ipratropium HFA, given at a dose of 80 µg (2 x 40 µg/50 µl) and Placebo HFA

Table 6. geometric mean (geometric 1-SD interval) for the HFA-134a PK parameters following inhalation of IprBr-HFA, given at a dose of 40 and 80 mcg and placebo

Treatment	AUC _{0-30min} (mcg*hr/mL)	T1/2* (min)	Cmax (mcg/mL)
IprBr-HFA 40mcg	1.47 (0.91-2.37)	1.3	0.46 (0.23-0.92)
IprBr-HFA 80 mcg	1.49 (0.94-2.36)	1.3	0.48 (0.23-1.03)
Placebo	1.37 (0.8-2.34)	1.6	0.42 (0.22-0.8)

*determined from geometric mean blood concentration

CONCLUSIONS

-
- The 24 hours cumulative renal excretion of IprBr (arithmetic means), for the two HFA-MDI strengths were significantly higher (1.2-fold and 1.3-fold higher for the 40 and 80 mcg, respectively) than that observed for CFC-MDI formulation (Table Q5.2 and Q5.3)
- Analysis of variance revealed no difference in the dose normalized renal excretion data of the 40 mcg (HFA-MDI) and the 80 mcg (HFA-MDI) formulation, suggesting no dose-dependent change in the bioavailability of IprBr
- The relative short half life calculated for the propellant HFA-134a suggests that this compound is not accumulated in the body.

**APPEARS THIS WAY
ON ORIGINAL**

"Tolerability and preliminary pharmacokinetics of IprBr HFA-MDI (4x 80 mcg) in comparison to IprBr CFC-MDI (4 x 40 mcg) and placebo HFA-MDI after multiple inhalational administration over 7 days by healthy volunteers."

Study: U95-0343
Volume: 36
Date of Report: March 15, 1995
Dates of Trial: July 19, 1994- September 9, 1994

OBJECTIVE

- to obtain information about the safety and tolerability of IprBr HFA-MDI after multiple inhalational administration to healthy volunteers. In addition, a comparison with the conventional IprBr CPC-MDI as well as with placebo HFA-MDI was to be performed.

SUBJECTS

Twelve subjects (6 males and 6 females) were entered into the study and all completed the study. The demographic features are as follows:

	Female subjects (N = 6)	Male subjects (N = 6)	All subjects (N = 12)
Age (years)	36.0 (24 to 46)	33.5 (28 to 41)	34.5 (24 to 46)
Weight (kg)	62.5 (50 to 69)	78.0 (68 to 100)	68.5 (50 to 100)
Height (cm)	164.0 (156 to 168)	172.5 (169 to 193)	168.5 (156 to 193)
Weight in percent of normal weight (Broca)	-3.7 (-13.8 to 9.5)	2.7 (-2.8 to 8.3)	-1.5 (-13.8 to 9.5)

STUDY DESIGN AND TREATMENT ADMINISTRATION

The trial was a randomized, three period cross-over placebo controlled study to test the effects of multiple inhalational doses of ipratropium CFC and HFA. The test substances were given by inhalation for 7 days, the last dose being given in the evening of day 7. The time interval between the consecutive drug administrations was 4 h on each test day. There was a wash-out period of at least 7 days between each course of treatment. Subjects were randomized to the following treatments:

Treatment A: ipratropium CFC, given at a dose of 40 mcg four times daily

Treatment B: ipratropium HFA, given at a dose of 80 mcg four times daily

Treatment C: Placebo HFA given four times daily

FORMULATION

The following formulations and batch numbers were used in this study.

Table 1. Ipratropium formulation used in this study

Study Drug/Strength	Batch Number
ipratropium CFC-MDI	PD-1384
ipratropium HFA-MDI	PD-1385
Placebo HFA	PD-1382

PHARMACOKINETIC MEASUREMENTS

Blood and urine sampling

Blood samples to determine drug plasma levels were taken before the morning dose on days 1, 3 and 7, before and at 5, 15 min and 1 hour after the 4th dose on days 1, 3 and 7.

Urine was collected quantitatively during the 24 hours following the morning medication on days 1, 3 and 7 at the following time intervals: 0-4 hours; 4-8 hours and 8-24 hours. A urine void was collected prior to each 24-hours sampling interval.

Analytical Method

Plasma and urine samples for ipratropium determinations were analyzed by radioreceptor assay.

DATA ANALYSIS

Pharmacokinetic Analysis

Ipratropium concentrations determined in the plasma samples on days 1, 3, and 7 taken before the fourth of the daily doses (0 min/4th = 720 min) up to 60 min after the fourth dose (60 min/4th = 780 min) were used for pharmacokinetic calculations.

The area under the plasma concentration-time curve (AUC) was estimated by using the trapezoidal rule between 720 min and 780 min (4 data points). No extrapolation was applied. The values for the peak plasma concentration (C_{max}) and the time to reach the peak plasma concentration (t_{max}) were taken directly from the original data.

Total renal excretion expressed as percentage of the daily dose was calculated by multiplication of the measured urine concentration [ng/ml] and the total urine volume [ml] of the fraction of each time interval, divided by the daily dose. The total daily renal excretion (0-24 h) of each volunteer was calculated as the sum of the renal excretion of the 3 individual urine fractions.

Statistical analysis

Plasma concentration data (i.e. C_{max} and AUC) and renal excretion data were described by geometric mean values and the geometric 1-SD interval.

All plasma data of the HFA-MDI group were normalized to the dose of the CFC-MDI group (i.e. values were divided by 2). To allow log-transformation zero values were set to 1. Analysis of variance of the log-transformed data was performed separating the variabilities due to the factors "subject", "treatment", "period", "subject* treatment", "day", "subject* day", "treatment* day", and "period* day".

Based on the renally excreted IprBr fraction of the dose the relative bioavailability of the two MDI-formulations was estimated by an appropriate two-sided 90%-confidence interval. This interval estimation was obtained through backtransformation (antilog) of the 90%-confidence interval for the difference of the

least squares means. The statistical calculations were performed with the SAS software version 6.08 (SAS Institute Inc., Cary, NC, USA) on an HP-Vectra PC.

SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

RESULTS

Analytical Method Pre-Study Validation

Recovery:

Limit of Quantitation:

Plasma: 20 pg/mL

Urine: 0.8 ng/mL

Stability

No relevant degradation of IprBr in plasma during the 5-week period was observed. Ipratropium bromide was susceptible to repeated freeze-thawing.

The sample stability in urine was investigated in 3 different urine samples of a volunteer. After 24 hours at room temperature (2nd determination) a moderate decrease was only observed for the sample 3 for which a pH of 7.7 was measured. It is known that IprBr undergoes slow hydrolysis at alkaline pH. Therefore, adjustment of the urine pH to 4 - 6 is necessary.

A significant loss was found after the first thawing (100 pg/mL sample) or after the second thawing (500 pg/mL sample). Therefore, repeated thawing and freezing of IprBr-containing plasma samples should be avoided. In plasma samples left for 3 days at room temperature a significant loss of IprBr (-30%) was observed. However, the stock solution of IprBr in water (pH 4-5, acidified with HCl) was stable for 2 months.

Precision and Accuracy:

% Bias and CV% were lower than 20% for all the quality control used.

In-Study Validation

Table 2 shows the in-study validation assay performance for IprBr in plasma and urine.

Table 2. Assay performance (In-study validation) for IprBr

	Plasma	Urine
Linearity	Satisfactory: Standard curve range from 0 to 5000 pg/mL;	Satisfactory: Standard curve range from 0-200 ng/mL
Accuracy	Satisfactory: %Bias: 13.3 at 50 pg/mL; 2.2% at 200 pg/mL; -0.8% at 1000 pg/mL.	Satisfactory: %Bias: 9.8 at 2.0 ng/mL; 0% at 8 ng/mL; 2.7% at 40 ng/mL.
Inter-day Precision	Satisfactory: CV %: 27 at 50 pg/mL; 14.1% at 200 pg/mL; 13.2% at 1000 pg/mL	Satisfactory: CV %: 9.8 at 2.0 ng/mL; 0% at 8 ng/mL; 2.7% at 40 ng/mL.
Intra-day Precision	Satisfactory: CV %: 7.4 at 50 pg/mL; 0% at 200 pg/mL; 0% at 1000 pg/mL.	Satisfactory: CV %: at 2.0 ng/mL; 10.5% at 8 ng/mL; 10.8% at 40 ng/mL.
Specificity	Satisfactory: cross-reactivity determined	Satisfactory: cross-reactivity determined

Pharmacokinetic Results

Figures 1 and 2 show the individual dose normalized AUC and Cmax for IprBr after administration of the treatments as a function of time (Days 1, 3 and 7). Figure 3 shows the individual cumulative amount (μg) (normalized to 160 μg) of IprBr excreted exchanged in urine over 24hrs of collection on Days 1, 3, and 7 following inhalation of IprBr-CFC 40 μg QID (160 μg daily) and IprBr-HFA 80 μg QID (360 μg daily). Table 3 summarizes the geometric mean values of the Cmax and AUC (dose normalized) as a function of treatment. Table 4 shows the analysis of variance of the logarithmically transformed and dose normalized AUC, Cmax and cumulative renal excretion data. For interpretation of the results of this study, the renal excretion data may be considered to be more robust than the plasma data due to the less critical analytical determination (less problems with detectability) and because the 24-hour renal excretion is the result of 4 individual inhalational administrations, rather than only 1 administration (evening dose) which is mainly responsible for the plasma level data.

**APPEARS THIS WAY
ON ORIGINAL**

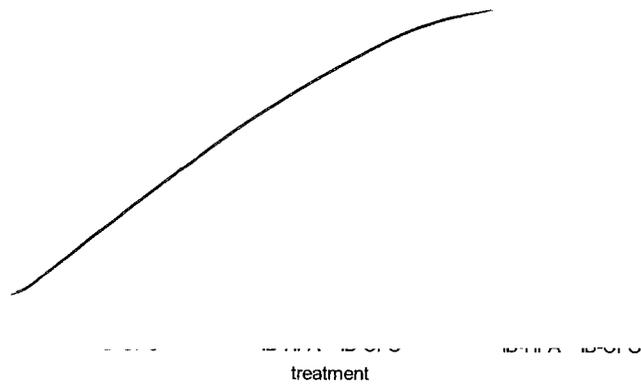


Figure 1. Individual C_{max} values (dose normalized) for IprBr (IprBr) following multiple inhalation of IprBr-CFC, given at a dose of 40 mcg four times daily and IprBr-HFA, given at a dose of 80 mcg four times daily

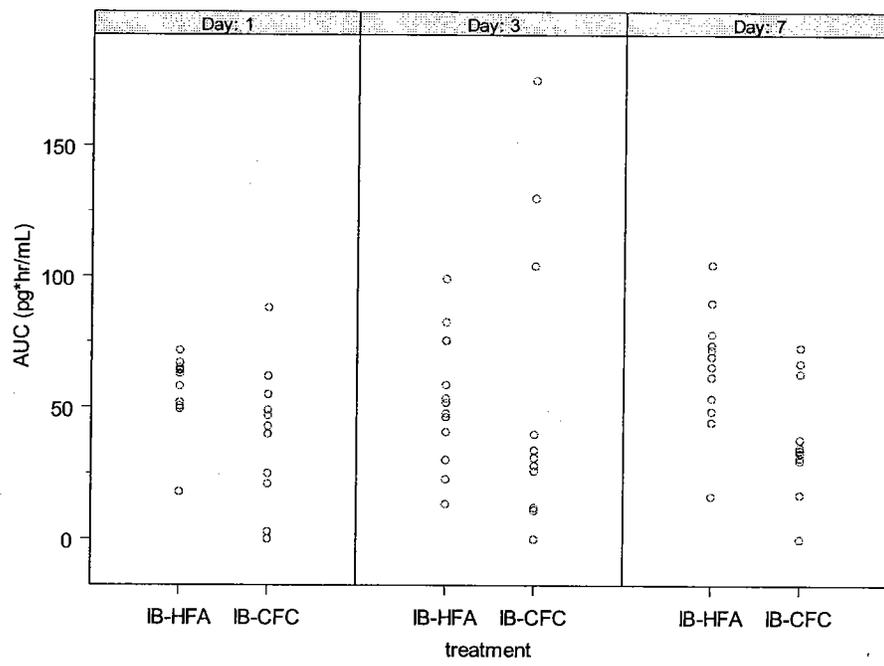


Figure 2. Individual AUC values (pg*hr/mL) (dose normalized to 160 µg) for IprBr (IprBr) following multiple inhalation of IprBr-CFC, given at a dose of 40 µg four times daily and IprBr-HFA, given at a dose of 80 µg four times daily

Table Q5.1 Arithmetic mean (SD) for the IprBr PK parameters (dose normalized to 160 µg) following multiple (Day 7) inhalation of IprBr -CFC, given at a dose of 40 mcg four times daily and IprBr -HFA, given at a dose of 80 mcg four times daily

Treatment	AUC τ (ng*hr/mL)	Cmax (pg/mL)	Cumulative renal excretion (0.24h, % daily dose)*
IprBr -HFA	64.9 (22.8)	96.3 (45.9)	4.4 (3.3-6)
IprBr -CFC	35.1 (23.5)	60.3 (36.2)	2.9 (1.4-6.1)

*geometric mean

Table 4. Analysis of variance of the logarithmically transformed and dose normalized AUC, Cmax and cumulative renal excretion data

Source of variation	p-values		
	AUC τ	Cmax	Renal excretion data
Subject	0.18	0.06	0.27
Treatment	0.0088	0.02	0.04
Period	0.84	0.86	0.43
Subject*treatment	0.07	0.43	0.001
Subject*day	0.18	0.39	0.06
Treatment*day	0.78	0.55	0.25

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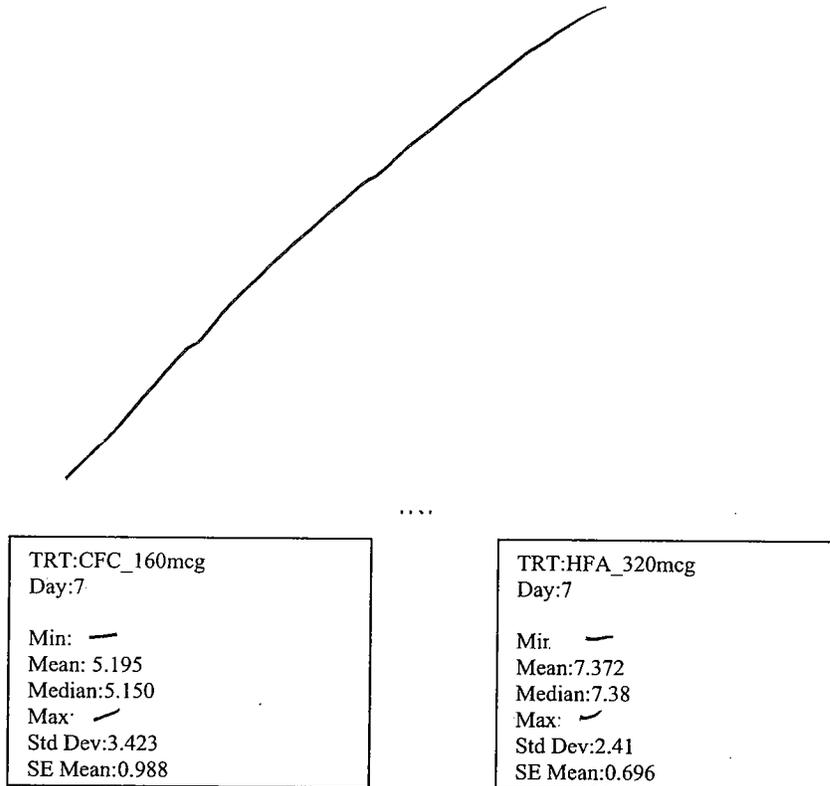


Figure 3. Individual cumulative amount (μg) (normalized to 160 μg) of IprBr excreted exchanged in urine over 24hrs of collection on Days 1, 3, and 7 following inhalation of IprBr-CFC 40 μg QID (160 μg daily) and IprBr-HFA 80 μg QID (360 μg daily).

CONCLUSION

- Peak plasma concentrations after administration of IprBr using the HFA-MDI device (74 pg/mL , normalized to 40 mcg/dose) were significantly higher than those using the CFC-MDI device (38 pg/mL (geometric means; $n = 36$)).
- AUC_{τ} (from pre-dose and up to 60 min after the last of the 4 daily doses administration) of IprBr using the HFA-MDI device (geometric mean=53 $\text{pg/mL}\cdot\text{h}$, dose normalized to 40 mcg) was significantly higher than that using the CFC-MDI device (geometric mean= 22 $\text{pg}\cdot\text{hr/mL}$).
- No difference in C_{max} and AUC values was found when comparing the treatment days 1, 3, and 7, indicating lack of accumulation.
- The cumulative amount (μg) (normalized to 160 mcg) of IprBr excreted exchanged in urine over 24hrs of collection on Day 7 following inhalation of IprBr-HFA 80 μg QID (360 μg daily) was 1.42-fold higher than that after IprBr-CFC 40 μg QID (160 μg daily)

- Ninety percent confidence intervals (IprBr-HFA/ IprBr-CFC= 1.39, CI= 1.09-1.85) and the analysis of variance of the IprBr data derived from determinations in urine again revealed a significant difference between the 2 different Atrovent formulations.

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An Open-Label, Crossover, Pharmacokinetic Trial to Determine the Comparability of 84 mcg IprBr HFA-134a Inhalation Aerosol to 84 µg ATROVENT CFC Inhalation Aerosol, in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Study: U01-3343
 Volume: 40
 Date of Report: November 19,
 Dates of Trial: October 27, 2000- April 9, 2001

OBJECTIVE

- The objective of this study was to compare the pharmacokinetic systemic exposure of 84 µg IprBr HFA-134a inhalation aerosol and 84 mcg ATROVENT® CFC Inhalation Aerosol following a single dose and at steady state after 1 week of 84 µg q.i.d. dosing in patients with COPD.

SUBJECTS

A total of 36 patients were screened for this trial. Thirty patients were randomized to receive the treatment and 29 patients completed the trial. The demographic features are as follows:

	Center 1	Center 2	Total
Number of Patients	16 (100.0)	14 (100.0)	30 (100.0)
Sex			
Male	10 (62.5)	11 (78.6)	21 (70.0)
Female	6 (37.5)	3 (21.4)	9 (30.0)
Age Class			
41-50	1 (6.3)	1 (7.1)	2 (6.7)
51-60	2 (12.5)	5 (35.7)	7 (23.3)
61-70	9 (56.3)	6 (42.9)	15 (50.0)
71-80	4 (25.0)	2 (14.3)	6 (20.0)
Age			
N	16	14	30
Mean	65.9	61.2	63.7
SD	7.3	6.7	7.3
Min	48	50	48
Median	66	61	64
Max	79	72	79
Weight (lb)			
N	16	14	30
Mean	172.06	195.36	182.93
SD	40.78	37.09	40.21
Min	124.0	135.0	124.0
Median	157.5	198.5	181.5
Max	260.0	261.0	261.0
Height (in)			
N	16	14	30
Mean	67.6	68.8	68.1
SD	3.8	4.4	4.1
Min	60.0	63.0	60.0
Median	69.0	68.0	68.5
Max	75	76	76
Race			
Black	1 (6.3)	4 (28.6)	5 (16.7)
White	15 (93.8)	10 (71.4)	25 (83.3)

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a two-treatment, open-label, randomized, crossover trial to determine the pharmacokinetic systemic exposure comparability of 84 µg IprBr HFA-134a

inhalation aerosol and 84 mcg ATROVENT® CFC Inhalation Aerosol in patients with COPD. Subjects were randomized to the following treatments:

Treatment A: Atrovent CFC inhalation aerosol, given at a dose of 84 µg (4 puffs, 21 mcg each) QD for 1 week

Treatment B: ipratropium HFA inhalation aerosol, given at a dose of 84 µg (4 puffs, 21 mcg each) QD for 1 week

Patients were instructed to take the study medication as four puffs four times daily for each of the one-week intervals between Visits 2 and 3 and Visits 4 and 5. There was a washout period of 3-7 days between Visits 3 and 4.

FORMULATION

The following formulations and batch numbers were used in this study.

Table 1. Ipratropium formulation used in this study

Study Drug/Strength	Batch Number	Expiration Date
IprBr inhalation aerosol 0.021 mcg TTV, 10 mL	PD-2050	03/02
IprBr monohydrate (HFA-134a) inhalation aerosol 0.021 mcg TTV, 10 mL	PD-2041	07/01
Placebo inhalation aerosol (used for training only)	PD-1845	03/01

PHARMACOKINETIC MEASUREMENTS

Blood and urine sampling

Blood samples to determine drug plasma levels were taken at Visits 2, 3, 4, and 5, at the time points specified in the protocol (0, 5, 15, 30, 60 minutes and 2, 4, and 6 hours after each inhalation).

On Day 1 of each treatment (Visits 2 and 4) total urine was collected over a 24-hour period following drug administration in two separate aliquots: a Void 15 minutes prior to administration, and a 0-24 hour sample after drug administration. On Day 8 of each treatment (Visits 3 and 5) three separate aliquots of urine were collected: a Void 15 minutes prior to drug administration, 0-1 hour after administration, and 1-6 hours after administration.

Analytical Method

Plasma and urine samples for ipratropium determinations were analyzed by LC/MS/MS assay.

DATA ANALYSIS

Pharmacokinetic Analysis

Plasma data was analyzed using non-compartmental pharmacokinetic analysis using WinNonlin 3.1 software. Total amount excreted in the specified urine collection interval was calculated by multiplying the volume of urine collected by the concentration of IprBr in that interval.

Statistical analysis

- Comparability at Steady State (Visits 3 and 5) was assessed by:

- (a) the amount of unchanged ipratropium excreted in the urine within the first hour after inhalation (Ae0-1)
- (b) the amount of unchanged ipratropium excreted in the urine over the entire 6 hour dosing interval (Ae0-6)

- Comparability after Single Doses (Visits 2 and 4) was assessed by the amount of unchanged ipratropium excreted in the 24-hour urine sample after inhalation (Ae0-24).

The 95% confidence intervals for the difference in means (test and reference) were estimated.

The secondary assessments of comparability of systemic exposure were performed using the following pharmacokinetic parameters obtained from the concentration of ipratropium in the plasma samples.

- Comparability at Steady State (Visits 3 and 5) was assessed by
 - (a) Area under the plasma ipratropium concentration-time curve from time zero to time τ over the 6-hr dosing interval (AUC0- τ), where τ is the dosing interval.
 - (b) Peak plasma ipratropium concentration (C_{max,ss}) and the time to peak plasma ipratropium concentration (T_{max,ss}), obtained directly from the data without interpolation, after the last dose is administered.
 - (c) Plasma ipratropium concentrations at the beginning and end of each dosing interval (C_{min,ss}).
 - (d) Average drug concentration (C_{ss}), where $C_{ss} = AUC_{0-\tau} / \tau$.
 - (e) Degree of fluctuation (DF_{ss}), where $DF_{ss} = 100\% * (C_{max,ss} - C_{min,ss} / C_{ss})$
- Comparability after Single Doses (Visits 2 and 4) was assessed by
 - (a) Area under the plasma ipratropium concentration-time curve from time 0 to 6 hours.
 - (b) Peak plasma ipratropium concentration from 0 to 6 hours.

SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

RESULTS

Analytical Method Pre-Study Validation

Recovery in Plasma

The mean recovery was 66.7% for QC1 with a coefficient of variation of 7.22% and 53.3% for QC3 with a coefficient of variation of 4.66%.

The recovery of the internal standard was 53.5% with a coefficient of variation of 6.44% for QC1 and 43.8% with a coefficient of variation of 7.13% for QC3.

Recovery in Urine

The mean recovery was 72.3% for QC1 with a coefficient of variation of 8.71%

and 73.8% for QC3 with a coefficient of variation of 2.17%.

Recovery of the internal standard for the QC pools was evaluated in a similar manner. The recovery of the internal standard was 44.7% with a coefficient of variation of 7.44% for QC1 and **50.2%** with a coefficient of variation of 3.15% for Oct Data are presented in Tables SA through 5B.

Limit of Quantitation:

Plasma: 0.01 ng/mL

Urine: 0.1 ng/mL

Stability

Freeze/thaw Stability in Plasma

Freeze/thaw stability was evaluated at the low and high drug concentrations by analyzing quality control samples subjected to three freeze/thaw cycles. The mean concentration for the quality control samples was within 1.95% of theoretical following the third freeze/thaw cycle.

Freeze/thaw Stability in Urine

Freeze/thaw stability was evaluated at the low and high drug concentrations by analyzing quality control samples subjected to three freeze/thaw cycles. The mean concentration for the quality control samples was within 7.84% of theoretical following the third freeze/thaw cycle.

Precision and Accuracy in Plasma and Urine:

% Bias and CV% were lower than 20% for all the quality control used.

In-Study Validation

Table 2 shows the in-study validation assay performance for IprBr in plasma and urine.

Table 2. Assay performance (In-study validation) for IprBr

	Plasma	Urine
Linearity	Satisfactory: Standard curve range from 0.01 to 5.0 ng/mL; $r^2=0.9993$	Satisfactory: Standard curve range from 0.1-100 ng/mL; $r^2=0.9994$
Accuracy	Satisfactory: %Bias: 1.67 at 25 pg/mL; -1.6% at 250 pg/mL; -3.1% at 4000 pg/mL.	Satisfactory: %Bias: 5.0 at 0.25 ng/mL; 5.6% at 5 ng/mL; 2.6% at 80 ng/mL.
Inter-day Precision	Satisfactory: %CV: 6.8 at 25 pg/mL; -3.4% at 250 pg/mL; 3.96% at 4000 pg/mL.	Satisfactory: % CV: 3.4 at 0.25 ng/mL; 3.5% at 5 ng/mL; 2.7% at 80 ng/mL.
Intra-day Precision	Satisfactory: %CV: 3.7 at 25 pg/mL; -1.4% at 250 pg/mL; 3.0% at 4000 pg/mL.	Satisfactory: % CV: 3.6 at 0.25 ng/mL; 3.7% at 5 ng/mL; 2.03% at 80 ng/mL.
Specificity	Satisfactory: Chromatograms submitted	Satisfactory: Chromatograms submitted

Pharmacokinetic Results

Figures 1 shows the mean plasma concentration-time profiles for IprBr following single and multiple administration of IprBr-HFA 84 mcg or Atrovent CFC 84 μg q.i.d for one week. Figures 2 and 3 show the individual C_{max} (pg/mL) and AUC_{0-6hr} values, respectively, for IprBr (IprBr) following single and multiple administration of atrovent HFA and atrovent CFC given at a dose of 84 μg q.i.d daily for one week. The mean pharmacokinetic parameters for IprBr following administration of the two treatments are summarized in Table 3. Table 4 shows the 90% confidence intervals for the ratio of the log transformed C_{max} and AUC_t between IprBr-HFA and IprBr-CFC. Figure 4 shows the IprBr mean amounts excreted in the urine following 84 μg q.i.d for one week for either Atrovent HFA or atrovent CFC. Table 5 shows the analysis of variance for urine IprBr amounts excreted following single and multiple administration of the treatments. Figures 5 and 6 summarize the C_{max} -AGE and AUC-AGE relationship, respectively following single and multiple administration of atrovent HFA and atrovent CFC given at a dose of 84 μg q.i.d daily for one week

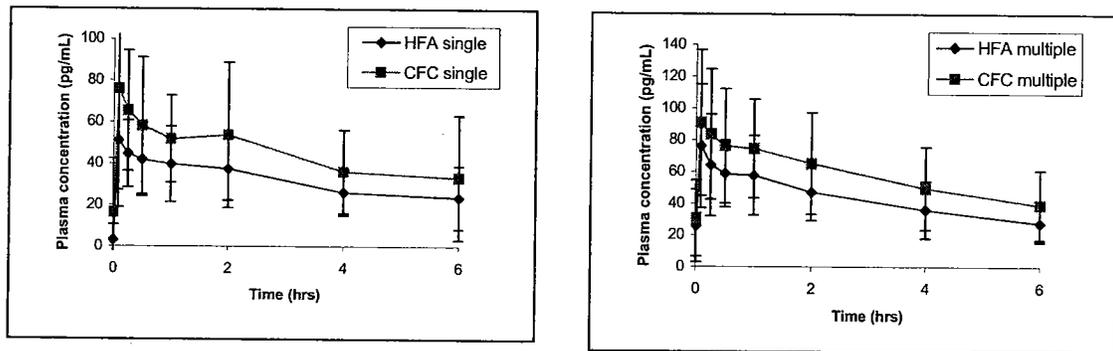


Figure 1. Mean plasma concentration-time profiles for IprBr following single (left panel) and multiple (right panel) administration of IprBr-HFA or Atrovent CFC 84 μg q.i.d for one week. Bars represent SD.

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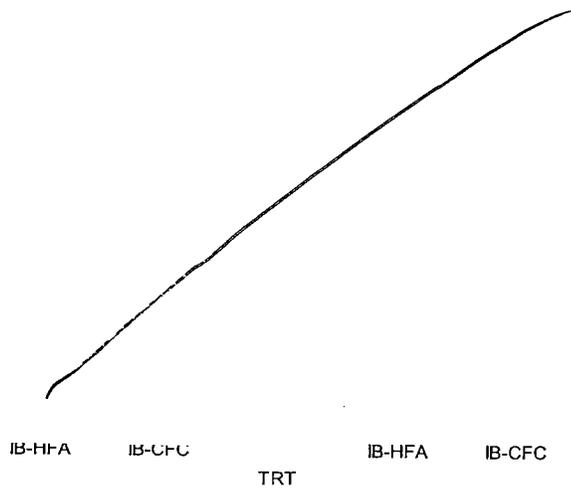


Figure 2. Individual C_{max} (pg/mL) values for IprBr following single (84 µg) and multiple administration of atrovent HFA and atrovent CFC given at a dose of 84 µg q.i.d daily (336 µg/daily) for one week.

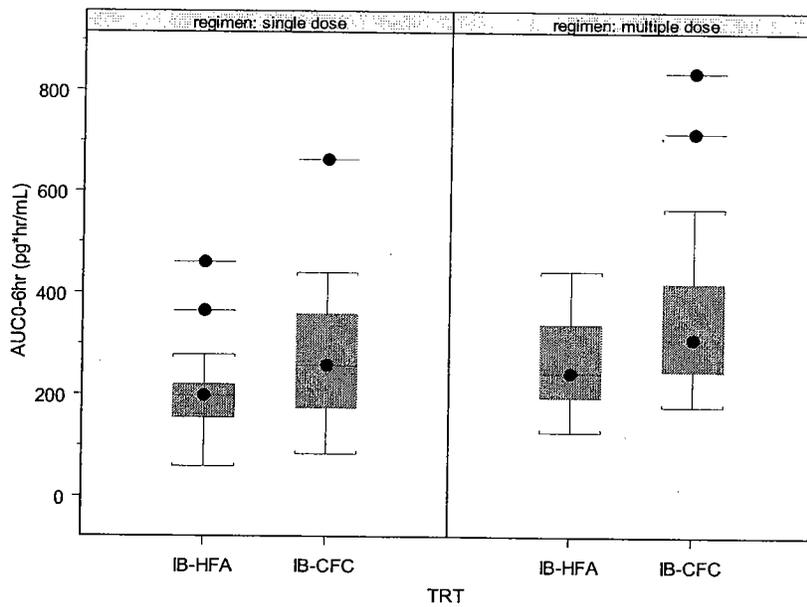


Figure 3. Individual AUC_τ (pg*hr/mL)_τ values for IprBr following single (84 µg) and multiple administration of atrovent HFA and atrovent CFC given at a dose of 84 µg daily q.i.d daily (336 µg/daily) for one week.

Table 3. Mean pharmacokinetic parameters for IprBr following single and multiple administration of the two treatments

Parameter	IprBr HFA 84 µg q.i.d	IprBr CFC 84 µg q.i.d
Single Dose		
AUC _{0-6hr} (pg*hr/mL)	196.8	269.4
Cmax (pg/mL)	58.9	92.7
Multiple dose		
AUC _{0-6hr} (pg*hr/mL)	265.1	359.5
Cmax (pg/mL)	82.1	101.8
Tmax (hrs)	0.27	0.45
Cmin (pg/mL)	28.2	39.9
Css (pg/mL)	44.2	59.9
DFss	125.9	111.8

Table 4. Point estimates and 90% confidence intervals for the log-transformed PK parameters following single and multiple administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
Single dose			
IprBr-HFA/IprBr-CFC	AUC _τ	74.5	60-92
	Cmax	70.8	57-88
Multiple dose			
IprBr-HFA/IprBr-CFC	AUC _τ	74.7	63-88.6
	Cmax	80.5	67.5-96.1

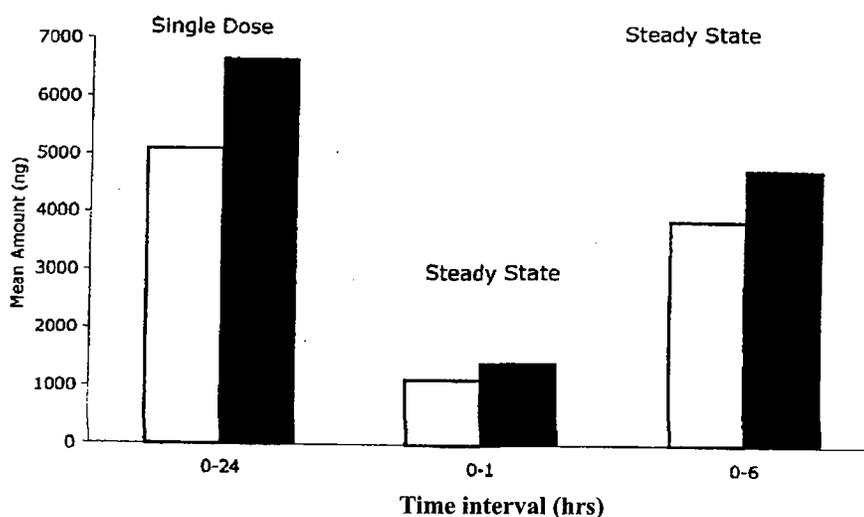


Figure 4. Ipratropium mean amount (ng) excreted in the urine following administration of 84 µg single dose inhalation or multiple administration for one week (QD) of either atrovent HFA or atrovent CFC.

Table 5. Analysis of variance for urine IprBr amounts excreted (ng) following single and multiple administration of the treatments

Parameter	Adjusted Means ^a		Mean difference	Standard error of the difference	95% Confidence Interval (lower, upper)	p-value
	IprBr HFA 84 µg	IprBr CFC 84 µg				
Single-dose (n=29) (V2 or V4)						
Ae 0-24	5088.7	6639.3	-1550.6	1043.4	(-3691.7, +590.5)	0.1488
Steady state (n=28) (V3 or V5)						
Ae 0-1	1113.8	1414.2	-300.5	203.4	(-717.9, +116.9)	0.1516
Ae 0-6	3858.0	4771.9	-913.9	446.7	(-1830.5, +2.7)	0.0514

^a Terms in the ANOVA are patient, treatment, and period
Source Data: Appendix 16.3.3, Pharmacokinetic STATDOC

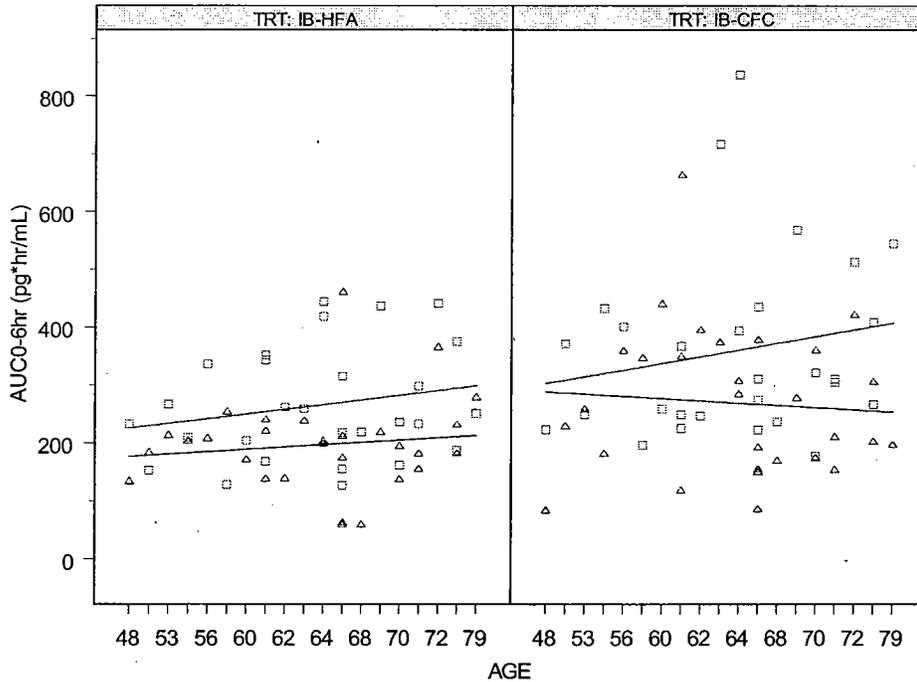


Figure 5. AUC-AGE relationship following single (triangles) and multiple (squares) administration of atrovent HFA and atrovent CFC given at a dose of 84 µg q.i.d daily for one week.

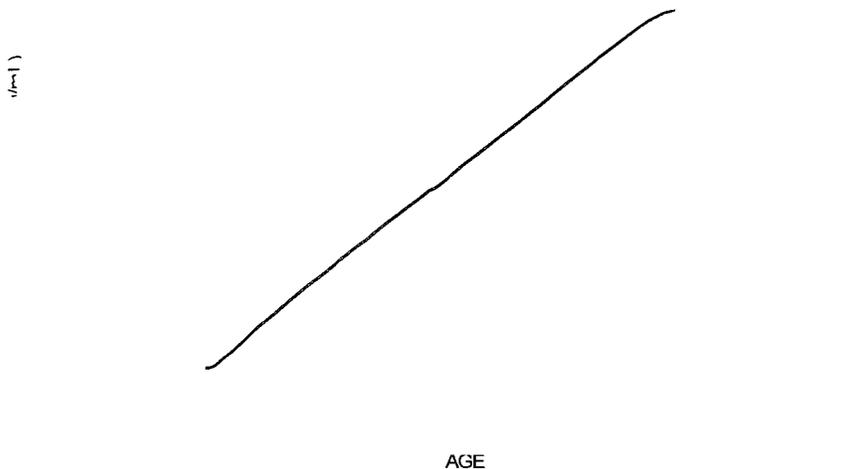


Figure 6. Cmax-AGE relationship following single (triangles) and multiple (squares) administration of atrovent HFA and atrovent CFC given at a dose of 84 µg q.i.d daily for one week

CONCLUSIONS

- The mean Cmax and AUCt of IprBr following single administration of atrovent HFA were 36 % and 27 % lower than those observed following administration of atrovent CFC. The lower limit of the ninety percent confidence intervals for the log-transformed PK parameters for the ratio IprBr -HFA/ IprBr -CFC was as low as 57 for the Cmax and 60 for the AUCt.
- The mean Cmax and AUCt of IprBr following multiple administration of atrovent HFA were 19 % and 26 % lower than those observed following administration of atrovent CFC. The lower limit of the ninety percent confidence intervals for the log-transformed PK parameters for the ratio IprBr -HFA/ IprBr -CFC was as low as 67.5 for the Cmax and 63 for the AUCt.
- There was a trend of lower (25 % lower) mean atrovent HFA amount excreted in urine compared to mean atrovent CFC, however the difference in means was not statistically significant.
- There was a trend of higher Cmax and AUC0-6hr values as the age of the patients increased. The mean Cmax and AUC0-6hr for patients older than 65 years old receiving multiple dosing of IprBr-HFA were 16% and 6% higher, respectively than those observed for younger patients. Although the 90% CI for the log-transformed PK parameters were out of the BE goal post (Cmax CI=0.85-1.43; AUC CI=0.81-1.33), these differences may not be clinically significant. Therefore, there is no age effect on the PK of atrovent-HFA after multiple administration.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-527	Brand Name	Atrovent HFA
OCPB Division (I, II, III)	II	Generic Name	Ipratropium bromide
Medical Division	DPADP	Drug Class	Anticholinergic
OCPB Reviewer	Sandra Suarez-Sharp	Indication(s)	Prevention of bronchospasm
OCPB Team Leader	Emmanuel Fadiran	Dosage Form	Inhalation solution
PM Reviewer		Dosing Regimen	2 inhalations (21 mcg/ actuation) 4x a day, not to exceed 12 inhalations/day
Date of Submission	December 10, 2002	Route of Administration	Oral inhalation
Estimated Due Date of OCPB Review	April, 2002	Sponsor	Boehringer Ingelheim
PDUFA Due Date	October 9, 2003	Priority Classification	Standard
Division Due Date	September 25, 2003		

3 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1	1	
multiple dose:	x	1	1	
Patients-				
single dose:				
multiple dose:	x	1	1	
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	x	1		
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	X	2		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	3	3		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. 1. The sponsor is highly recommended to provide a pharmacokinetic link between the to-be-marketed formulation and the formulations used in the pharmacokinetic and clinical trials. 2. Ipratropium bromide pharmacokinetic results delivered from the CFC formulation were not consistent across studies. The AUC values (dose normalized) were much lower (4-fold) in study U95-0343 compared to study U01-3343. Provide an explanation for these unexpected results and submit cross-study validation data comparing bioanalytical assays.		
QBR questions (key issues to be considered)		<ul style="list-style-type: none"> Question 1: Dose-proportionality Question 2: Systemic exposure of CFC vs. HFA formulations of Atrovent in healthy volunteers and COPD patients See QBR portion of the review		
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-527 (SE5-011), HFD-870 (Electronic Entry or Lee), HFD-570 (Jafari), HFD-870 (Fadiran, Hunt, Malinowski), CDR (B. Murphy)

NDA 21-527

OBJECTIVES:

- Compare systemic exposure of IprBr delivered from the Atrovent HFA vs the CFC formulation in healthy volunteers
- Determine dose-proportionality after single inhalation of 40 and 80 mcg of IB from the HFA formulation
- Compare systemic exposure of IprBr delivered from the Atrovent HFA vs the CFC formulation in COPD patients

U# (Study #)	Study Purpose	Number of Subjects	Where Conducted	HFA Formulation/ Batch No	Assay Method (LOQ)
U95-0343 (244.1401)	Tolerability and preliminary pharmacokinetics of ipratropium bromide HFA-MDI (4 x 80 µg) in comparison to ipratropium bromide CFC-MDI (4 x 40 µg) and placebo HFA-MDI after multiple inhalational administration over 7 days to healthy volunteers.	12 normal volunteers 6 males 6 females 24-46 years of age (mean = 34.5 yrs)	July 1994 – September 1994	1 st Generation Valve PD-1384	Ipratropium by radioreceptor assay (20 pg/mL)
U96-0020 (244.1402)	Pharmacokinetics after single inhalation of 40 and 80 µg ipratropium bromide HFA-MDI, placebo HFA-MDI, and 40 µg ipratropium bromide CFC-MDI in a crossover study in healthy volunteers.	12 normal volunteers 6 males 6 females 27-41 years of age (mean = 33.0 yrs)	December 1994 – January 1995	1 st Generation Valve PD-1383 PD-1384	Ipratropium by radioreceptor assay (20 pg/mL) HFA by GC/ (0.03 µg/mL)
U01-3343 (244.2480)	A double-blind, crossover, pharmacokinetic trial to determine the comparability of Atrovent pharmacokinetics after inhalation of Atrovent HFA for 7 days to the market standard, Atrovent CFC, and to obtain pharmacokinetic information on Atrovent in a COPD population.	30 COPD patients 21 males 9 females 48-79 years of age (mean = 63.7 yrs)	October 2000 – April 2001	3 rd Generation Valve PD-2041	Ipratropium by LC/MS/MS plasma (10 pg/mL) urine (0.10 ng/mL)

PK STUDIES SUBMITTED TO NDA 21-527

Study number	Tabular listing/PK summary	Analytical method	PK parameters	Statistical analysis
U95-0343 (Trial 244.1401)	√	<ul style="list-style-type: none">radioreceptor assayPre-study and In-study validation data	Individual and average PK parameters in plasma and urine.	<ul style="list-style-type: none">90% CI of the point estimates of PK parameters.95% CI for the point estimates of PD parameters.
U96-0020 (Trial 244.1402)	√	<ul style="list-style-type: none">radioreceptor assay and gas chromatography methodPre-study and In-study validation data	Individual and average PK parameters in urine and plasma.	<ul style="list-style-type: none">90% CI of the point estimates of PK parameters.
U01-3343 (Trial 244.2480)	√	<ul style="list-style-type: none">LC/MS/MS: Plasma conc.In-study and pre-study validation data	Individual and average PK parameters in urine and plasma.	<ul style="list-style-type: none">90% CI of the point estimates of PK parameters.

CONCLUSION: Submission is filable

COMMENTS TO SPONSOR:

1. The sponsor is highly recommended to provide a pharmacokinetic link between the to-be-marketed formulation and the formulations used in the pharmacokinetic and clinical trials.

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sandra Suarez
9/24/03 11:32:43 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
9/24/03 02:36:43 PM
BIOPHARMACEUTICS
I concur