

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-457

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

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-457
Drug Substance	Albuterol Sulfate USP Inhalation Aerosol
Drug Product	Volare™ HFA Inhalation Aerosol
Strengths	90 µg of albuterol base per actuation
Route of Administration	MDI Oral Inhalation
Sponsor	IVAX Pharmaceuticals, Ireland
Type of submission	Original NDA
Date of submission	01/30/03
OCPB Division	DPE-II
Clinical Division	Pulmonary and Allergy Drug Products (HFD-570)
Reviewer	Shinja R. Kim, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D.

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1. EXECUTIVE SUMMARY

Volare™ (albuterol sulfate) is a selective β_2 -adrenergic receptor agonist, and it is indicated in adults and children 12 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease (2 inhalations every 4-6 hours) — . It is supplied in a pressurized aluminum canister with 200 actuations, 90 μ g albuterol per actuation.

One pharmacokinetic study (IXR-107-1-105) was conducted to support the NDA. The objective of this study was to compare the pharmacodynamics (e.g., ECG, glucose, potassium) and pharmacokinetics of Albuterol-HFA administered using a breath-operated (BOI, IVAX Pharmaceuticals, Ireland) and a metered-dose inhaler (MDI, IVAX Pharmaceuticals, Ireland) with an equivalent dose of Proventil® HFA MDI over a cumulative dose of 12 puffs (1080 mcg albuterol) in healthy volunteers. This study showed that there were no significant differences among the three products with respect to the PK or PD parameters.

1.1. Recommendation: The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Section 6, and found that NDA 21-457 is acceptable from a CPB standpoint provided that the sponsor agrees with the Agency's recommendation on the labeling.

Shinja R. Kim, Ph.D., DPE II

Emmanuel Fadiran, Ph.D., Team Leader

1.2. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The PK and PD data was obtained from the study IXR-107-1-105. This was a single-center, randomized, evaluator-blind, active-controlled, cumulative-dose crossover comparison study in 15 healthy subjects. Eligible subjects were randomized to receive 2 + 4 +6 actuations administered at 30 minutes intervals (180 + 360 + 540 mcg for a total treatment dose of 1080 mcg) of Albuterol-HFA-MDI, Albuterol-HFA-BOI, or Proventil HFA, with a minimum of 6 days between treatments. As shown in Table 1, the PK profiles are similar among these three products, although Albuterol-HFA-BOI was associated with slightly less total exposure, since 90% confidence intervals are within BE limit of 80-125%.

Pharmacodynamic parameters measured in this study include blood pressure, serum glucose and potassium, and ECG-derived QT and QTc intervals. All the changes in the pharmacodynamic parameters noted were expected based on the known pharmacological effects of albuterol drug substance.

Table 1. Comparison of Mean PK parameters for each product

Parameter	Least Square Mean (SE) ^a			Comparison ^c		
	(1) Alb-HFA- BOI	(2) Alb-HFA- MDI	(3) Proventil [®] HFA	1 vs. 2	1 vs. 3	2 vs. 3
AUC _t (pg/mL*hr)	24570.2 (1.03) ^b	26730.8 (1.03)	26905.3 (1.03)	0.92 (0.88-0.96) p = 0.0034	0.91 (0.87-0.95) p = 0.0018	0.99 (0.95-1.04) p = 0.8052
AUC _{inf} (pg/mL*hr)	25896.4 (1.03)	28425.8 (1.03)	28395.0 (1.03)	0.91 (0.87-0.95) p = 0.0016	0.91 (0.87-0.95) p = 0.0017	1.00 (0.96- 1.05) p = 0.9675
C _{max} (pg/mL)	3629.8 (1.06)	4072.9 (1.06)	3870.2 (1.06)	0.89 (0.82-0.97) p = 0.0247	0.94 (0.86-1.02) p = 0.1958	1.05 (0.97-1.14) p = 0.3001
T _{max} (hours)	1.444 (0.21)	1.850 (0.21)	1.674 (0.21)	P = 0.1368	P = 0.3919	P = 0.5122
T _{1/2} (hours)	5.8 (0.23)	6.2 (0.23)	5.9 (0.23)	P = 0.0856	P = 0.8105	P = 0.1345

^aLeast square mean (LSM) for each treatment (N = 15). ^bStandard Error

^cComparative data for the AUCs and C_{max} expressed as the ratio of the LSM, the 90% confidence limits of the LSM ratio, and the p value for the difference in LSM between the treatments. Significance was achieved if p<0.05.

Pharmacodynamics:

Blood pressure: Mean changes in both systolic and diastolic BP were comparable among products. The highest mean systolic BP increase was 4.5 to 7.5 mmHg at 15 minutes after the final (1080 µg) dose, and the mean between-treatment differences in systolic BP were less than 8 mmHg at all time points.

Serum Glucose: The changes in serum glucose from baseline were similar across products and no statistical significant differences (p <0.05) were found, with the exception of the 15-minute post-180-mcg and 540-mcg doses for Albuterol-HFA-MDI and Proventil[®] HFA. The greatest change in glucose from baseline (range: 13.5-18 mg/dL mean change) occurred at 15 and 30 minutes after the third dose (i.e., 1080 µg albuterol cumulative).

Serum Potassium: Potassium levels decreased after albuterol dosing. The maximum decrease occurred at 15 or 30 minutes (range: 0.57-0.79 mmol/L). The mean changes in potassium demonstrated no statistical differences across the three products.

Heart Rate: Mean change in HR (as derived from the ECG RR interval) occurred at 15 minutes after the last dose and remained mildly elevated at 4 hours post-third dose. There were no significant differences in heart rate across the three products.

QT and QTc Intervals: This reviewer analyzed QT data using Fridericia (QTcF) as well as Bazett's (QTcB) correction methods (the sponsor used Bazett's method only). The **Mean** change from baseline in QTcB and QTcF is summarized in the table below:

PD Parameter	Dose	Timepoint	Proventil HFA	Alb-HFA-MDI	Alb-HFA-BOI
QTcB interval (msec)	180 mcg	15 min	2.1±18	5.3±20	-11.1±31
		540 mcg	15 min	12.5±21	16.8±26
	1080 mcg	15 min	28.9±20	25.3±27	5.0 ^a ±34
		30 min	33.3±41	23.4±25	1.7 ^b ±36
		1 hour	15.9±18	10.3±27	4.3±55
		2 hours	9.3±23	15.7±28	-4.6±39
		3 hours	8.5±19	6.6±23	-11.9 ^c ±36
		4 hours	6.0±17	5.6±23	-6.1±32
QTcF interval (msec)	180 mcg	15 min	-1.5±12	1.5±16	-13.9±31
		540 mcg	15 min	2.2±15	5.5±21
	1080 mcg	15 min	13.1±15	9.1±21	-6.8±32
		30 min	17.9±36	8.6±21	-10.1±34
		1 hour	3.7±15	-0.4±23	-4.7±23
		2 hours	2.3±16	7.1±22	-9.6±35
		3 hours	3.8±12	3.3±18	-14.3±33
		4 hours	2.8±14	2.4±18	-8.7±31

^ap=0.02, ^bp=0.02, ^cp=0.04; p value for the difference in least square mean between proventil and BOI

As shown in the table, there was high inter-individual variation. Analysis of QT outliers shows that QTcB changes of ≥30 msec from the baseline occurred 69 times (23 times based on QTcF) out of 414 time-point measurements. The individual (#308) with highest change of QTcB showed an increase of 152 msec (125.8 msec by QTcF) from a baseline one hour after the third dose of Albuterol-HFA-BOI.

In conclusion, this study showed that there were no significant differences between the three products for PK or PD parameters.

2. Question Based Review

2.1 General Attributes

2.1.1 What are the known pharmacokinetic characteristics of albuterol sulfate?

Information on pharmacokinetics of albuterol from currently marketed albuterol products is scanty. Albuterol is the official generic name in the United States, but the World Health Organization recommended name for the drug is salbutamol. Due to the insensitivity of the assay method, the clearance and elimination half-life of albuterol in plasma could not be determined. However, urinary excretion provided data indicating that albuterol has an elimination half-life of 3.8 hours. Approximately 72% of the inhaled dose is excreted within 24 hours in the urine, and consists of 28% as unchanged drug and 44% as metabolite. Note: this NDA showed improvement in assay sensitivity, resulting satisfactory PK parameter values including $t_{1/2}$.

2.2 Clinical Pharmacology

2.2.1. What is the bioavailability of albuterol from the Albuterol-HFA-MDI, Albuterol-HFA-BOI, and Proventil HFA in healthy adults?

The bioavailabilities of albuterol from these products are obtained from the study IXR-107-1-105. This was a single-center, randomized, evaluator-blind, active-controlled, three-treatment, cumulative-dose crossover comparison study in 15 healthy subjects. Eligible subjects were randomized to receive 2 + 4 + 6 actuations administered at 30 minutes intervals (180 + 360 + 540

µg for a total treatment dose of 1080 µg) of Albuterol-HFA-MDI, Albuterol-HFA-BOI, or Proventil HFA, with a minimum of 6 days between treatments. The results are shown in Figure 1 and Table 1.

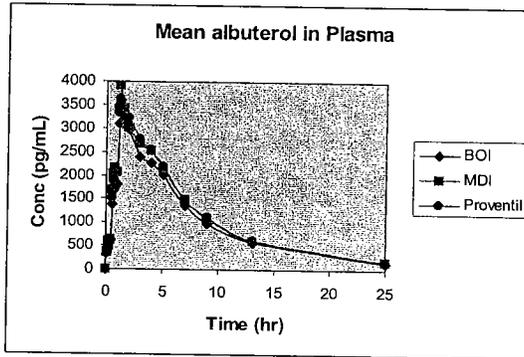
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T _{max} (hours)	1.444 (0.21)	1.850 (0.21)	1.674 (0.21)	P = 0.1368	P = 0.3919	P = 0.5122
T _{1/2} (hours)	5.8 (0.23)	6.2 (0.23)	5.9 (0.23)	P = 0.0856	P = 0.8105	P = 0.1345

^aLeast square mean (LSM) for each treatment (N = 15). ^bStandard Error

^cComparative data for the AUCs and C_{max} expressed as the ratio of the LSM, the 90% confidence limits of the LSM ratio, and the p value for the difference in LSM between the treatments. Significance was achieved if p<0.05.

Figure 1. Mean plasma albuterol concentration-time profiles by treatment (n = 15)



The 3 albuterol plasma curves in Figure 1 appear similar with the maximum mean concentration of albuterol occurring about 1.5-hr post-first dose or 30 min post-final dose for all 3 products. Comparison of the pharmacokinetic parameters for Albuterol-HFA-MDI and Proventil[®] HFA demonstrated no statistically significant differences. Significant differences were observed between Albuterol-HFA-BOI and Albuterol-HFA-MDI for AUC_t (p = 0.0034), AUC_{inf} (p = 0.0016) and C_{max} (p = 0.0247). Also, statistically significant differences were observed between Albuterol-HFA-BOI and Proventil-HFA-MDI for AUC_t (p = 0.0018) and AUC_{inf} (p = 0.0017). However, in all cases, the 90% CI for the ratio of mean PK parameters were within 80 - 125%,

indicating that these products are comparable. No significant differences were detected for t_{\max} and $t_{1/2}$ among these 3 products.

2.2.2 What are the characteristics of pharmacodynamic profiles (safety measurements) of albuterol from the Albuterol-HFA-MDI, Albuterol-HFA-BOI, and Proventil HFA in healthy adults?

Pharmacodynamic measures included blood pressure, serum glucose and potassium, and ECG-derived QT and QTc intervals. All the changes in the pharmacodynamic parameters noted were expected based on the known pharmacological effects of albuterol drug substance.

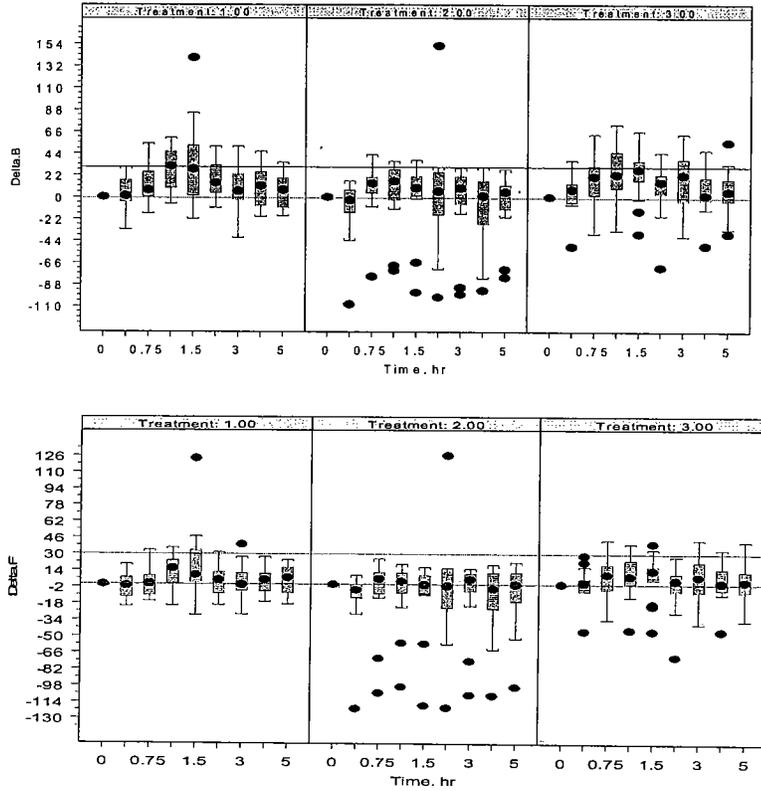
Blood Pressure: Mean changes in both systolic and diastolic BP were comparable among products. Systolic BP increased with treatment and returned to baseline or just below baseline, while diastolic BP initially decreased then rose to just above baseline then gradually decreased below baseline over the treatment period. The highest mean systolic BP increase was 4.5 to 7.5 mmHg at 15 minutes after the final (1080 mcg) dose, and the mean between-treatment differences in systolic BP were less than 8 mmHg at all time points. One subject (#9305) experienced an increase of 30 mmHg 15 minutes after the final dose of Albuterol-HFA-MDI. Ten subjects had a decrease in diastolic BP of 10 mmHg or more, and one subject (#314) experienced a decrease of 23 mmHg. The highest diastolic BP was 87 mmHg in two subjects (#306, three hours after third dose of Albuterol-HFA-BOI; #314, two hours after third dose of Albuterol-HFA-BOI).

Glucose and Potassium: Mean changes in serum glucose and potassium were comparable among products. Serum glucose levels increased and serum potassium decreased with treatment, then both returned to baseline over several hours. The mean increase in serum glucose was 15.4 to 18.0 mg/dL at 30 minutes after the third dose. The largest individual change (#302) was an increase of 35 mg/dL from a baseline of 91 mg/dL 30 minutes after the third dose of Albuterol-HFA-MDI. Two subjects had serum glucose levels of 129 mg/dL (#309, 15 minutes after the third dose of Albuterol-HFA-MDI; #311, 30 minutes after the third dose of Albuterol-HFA-BOI). The maximum decrease in serum potassium level was -0.57 to -0.79 mmol/L at 15-30 minutes after the third dose. The largest individual change (#313) was -1.6 mmol/L from a baseline of 4.6 mmol/L 30 minutes after the third dose of Albuterol-HFA-MDI. Nine subjects had potassium levels of <3.4 mmol/L, with the lowest recorded value of 2.9 mmol/L (#311, baseline 2.9 mmol/L) at 15 and 30 minutes after the third dose of Albuterol-HFA-MDI.

2.2.3. Does albuterol has the potential to prolong QT? Was there any dose-dependent increase in QT? How does the QT profile of test product (Albuterol-HFA-MDI or Albuterol-HFA-BOI) compare to that of the reference product (Proventil HFA MDI)?

ECG was obtained from the study IXR-107-1-105. This reviewer analyzed QT data using Fridericia (QTcF) as well as Bazett's (QTcB) correction method (the sponsor used Bazett's method only). The median changes of QTcB and QTcF after each treatment are presented in Figure 2, and the **Mean** change from baseline in QTcB and QTcF is summarized in Table 2. There was extremely high inter-subject variability in QTcB or QTcF; baseline QT was measured only once, which would contribute the variability (Table 2).

Figure 2. Median change of QTcB (upper) and QTcF (lower) from baseline



Note: Treatment 1, 2 and 3 refer to Proventil HFA, Albuterol HFA BOI and Albuterol HFA MDI, respectively.

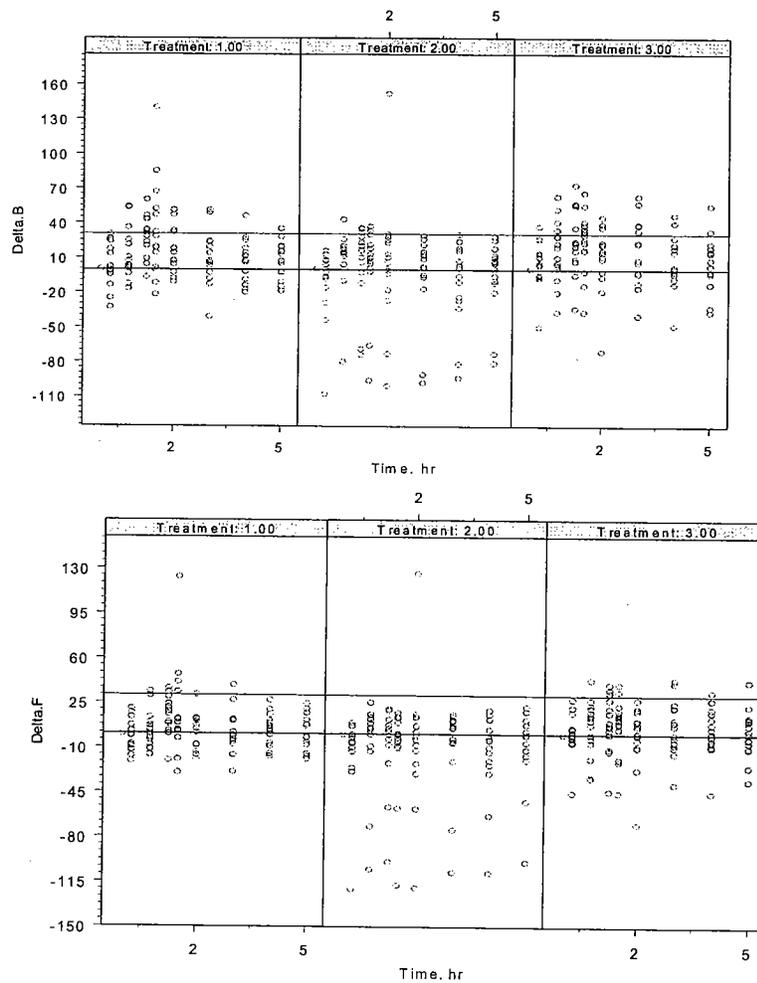
Table 2. Mean changes from baseline in QTcB and QTcF

PD Parameter	Dose	Timepoint	Proventil HFA	Alb-HFA-MDI	Alb-HFA-BOI
QTcB interval (msec)	180 mcg	15 min	2.1±18	5.3±20	-11.1±31
	540 mcg	15 min	12.5±21	16.8±26	3.9±37
	1080 mcg	15 min	28.9±20	25.3±27	5.0 ^a ±34
		30 min	33.3±41	23.4±25	1.7 ^b ±36
		1 hour	15.9±18	10.3±27	4.3±55
		2 hours	9.3±23	15.7±28	-4.6±39
		3 hours	8.5±19	6.6±23	-11.9 ^c ±36
		4 hours	6.0±17	5.6±23	-6.1±32
QTcF interval (msec)	180 mcg	15 min	-1.5±12	1.5±16	-13.9±31
	540 mcg	15 min	2.2±15	5.5±21	-6.1±35
	1080 mcg	15 min	13.1±15	9.1±21	-6.8±32
		30 min	17.9±36	8.6±21	-10.1±34
		1 hour	3.7±15	-0.4±23	-4.7±23
		2 hours	2.3±16	7.1±22	-9.6±35
		3 hours	3.8±12	3.3±18	-14.3±33
		4 hours	2.8±14	2.4±18	-8.7±31

^ap=0.02, ^bp=0.02, ^cp=0.04; p value for the difference in least square mean between proventil and BOI

Changes in QTcB or QTcF from baseline for each subject following the three products are shown in Figure 3. In analysis of QT outliers, QTcB changes of ≥ 30 msec from the baseline occurred 69 times (23 times based on QTcF) out of 414 time-point measurements. The largest individual (#308) change of QTcB was an increase of 152 msec (126 msec by QTcF) from a baseline one hour after the third dose of Albuterol-HFA-BOI. The 2nd largest individual (#304) change of QTcB was an increase of 140 msec (123 msec by QTcF) from a baseline 30 minute after the third dose of Proventil-HFA-MDI. Thus, it appears that the higher the plasma concentrations of albuterol the greater the QT interval prolongation.

Figure 3. Change of QTcB (upper) and QTcF (lower) from baseline: Individual data



Note: As RR interval (ECG derived) increased QT also increased. When QT was corrected by Fridericia or Bazett's method QT decreased as RR interval increased. However, QT was over corrected at elevated HR and under corrected at lower HR using Bazett's compared to that using Fridericia's method. Therefore, Fridericia's formula may be more correct in subjects with extreme heart rate values.

In overall conclusion, the study IXR-107-1-105 showed that there were no significant differences among the three products for PK or PD parameters.

2.3 Biopharmaceutics

2.3.1 Has the to-be-marketed product been adequately linked to the batches used in clinical trials?

The proposed-marketed product formula is identical to the batches used in all clinical studies used to support this NDA. The table below shows the components of the to-be marketed formulation in each can as well as the quantity in each lot.

Material	Function	QTY per Actuation (nominal values)	QTY per Can	QTY per batch
Albuterol sulfate USP (micronized) ¹	Active	-	-	-
alcohol	Excipient	-	-	-
Total suspension				
Propellant HFA 134a ²	Propellant	-	-	-
Total theoretical WT			8.5 g	-

²HFA- 134a (1,1,1,2-tetrafluoroethane)

2.3.2 What bioanalytical methods are used to assess concentrations of albuterol in plasma?

Analysis of albuterol was done by LC/MS/MS with mass spectrometric detection. Limit of quantifications for albuterol from plasma was 2 pg/mL, with linearity from 2 to 4000 pg/mL. Overall, the specificity, sensitivity, accuracy, precision, recovery, and stability of formoterol were satisfactory.

3. **Labeling Recommendations:** Underlined words are addition and the crossed out words are for deletion, as follows:



APPENDICES

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Protocol No. IXR-107-1-105

Study Type: Relative BA, PK/PD, 3-cumulative doses.

Title: Comparison of Extrapulmonary Effects and Pharmacokinetics of HFA-Propelled Albuterol Inhalation Aerosol (Norton Waterford) by Breath-Operated and Press-and-Breathe Inhalers When Compared to Proventil® HFA (Key Pharmaceuticals).

Investigator: _____

Objective: The objective of this study was to compare the extrapulmonary effects and pharmacokinetics of Albuterol-HFA, administered using a breath-operated (BOI) and a metered-dose inhaler (MDI) (Norton Waterford Ltd.) with an equivalent cumulative dose of Albuterol-HFA in a marketed formulation using an MDI (Proventil® HFA) in healthy volunteers.

Methodology: This investigation was a single-center, randomized, evaluator-blind, active-controlled, three-treatment, three-period, three-sequence, cumulative-dose, crossover comparison of Albuterol-HFA-MDI, Albuterol-HFA-BOI and Proventil® HFA in 16 subjects (15 completed). After screening, subjects were randomized to receive all three treatments a minimum of 6 days apart.

The three treatments were:

- Albuterol-HFA-MDI, Lot #AAW13A; MDI actuator: _____
- Albuterol-HFA-BOI, Lot #AAW13A; BOI actuator: _____ (main body assembly) and _____
- Proventil® HFA, Lot #GBD002A

The total albuterol dose per treatment was 1080 µg ex-actuator (albuterol 180 + 360 + 540 µg = 2 + 4 + 6 actuations). Each dose was administered 30 minutes apart.

Criteria for evaluation:

PK: C_{max} , t_{max} , AUC_t , AUC_{inf} , and $t_{1/2}$.

Blood samples were collected at

- 12-hrs and immediately prior to the first dose,
- 5, 10, 15, and 29 min following the completion of the last actuation of the 2- and 4-actuation doses.
- 5, 10, 15, 30 and 45 min, and 1, 2, 3, 4, 6, 8, 12, and 24 hrs following the completion of the last actuation of the 6-actuation dose.

Pharmacodynamics:

- *Serum potassium and glucose* - prior to the first dose, 15 min following the completion of the last actuation of the 2- and 4-actuation doses. 15 and 30 min, and 1, 2, 3, and 4 hrs following the completion of the last actuation of the 6-actuation dose.
- *ECG (R-R, QT and QTc intervals)* - prior to the first dose, 15 min following the completion of the last actuation of the 2- and 4-actuation doses. 15 and 30 min, and 1, 2, 3, and 4 hrs following the completion of the last actuation of the 6-actuation dose. Heart rate was calculated as, $HR = (60 \times 1000) / RR$ (msec) bpm.

Analytical Methodology:

Assay method: LCMS/MS

Assay Sensitivity: Linearity over the range of 2 and 4000 pg/mL.

Accuracy and Precision: Intra- and inter- assay precision and accuracy did not exceed 15% for QC controls.

Statistical methods:

- For the safety (PD) parameters of primary interest, t-tests derived from the mixed effects model with fixed effects for the treatment sequence, period and treatment group and random effect of subject-within-sequence were used. Analyses comparing the three albuterol formulations were done separately for post-dose 1 (180 mcg), 2 (360 mcg) and 3 (540 mcg). Results were declared statistically significant at the 0.05 significance level.
- The mixed effect model was used for comparisons of pharmacokinetic parameters, and also comparing mean changes from baseline in the QT and QTcB (by Bassett’s correction method) intervals. For the AUCs and C_{max}, the logarithmic transformation was used.

Results

Pharmacokinetics

The mean plasma albuterol concentration profiles and the results of the statistical analysis for PK parameters are presented in Figure 1 and Table 1, respectively.

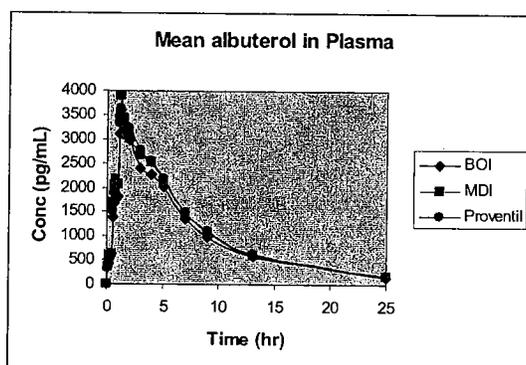
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C _{max} (pg/mL)	3629.8 (1.06)	4072.9 (1.06)	3870.2 (1.06)	0.89 (0.82-0.97) p = 0.0247	0.94 (0.86-1.02) p = 0.1958	1.05 (0.97-1.14) p = 0.3001
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^cComparative data for the AUCs and C_{max} expressed as the ratio of the LSM, the 90% confidence limits of the LSM ratio, and the p value for the difference in LSM between the treatments. Significance was achieved if p<0.05.

Figure 1. Mean plasma albuterol concentration profiles by treatment (n = 15)



The 3 albuterol plasma curves in Figure 1 are similar with the maximum mean concentration of albuterol occurring about 1-hr post-first dose or 15 min post-final dose for all 3 products. Comparison of the pharmacokinetic parameters for Albuterol-HFA-MDI and Proventil[®] HFA demonstrated no statistically significant differences. Significant differences were observed between Albuterol-HFA-BOI and Albuterol-HFA-MDI with respect to AUC_t ($p = 0.0034$), AUC_{inf} ($p = 0.0016$) and C_{max} ($p = 0.0247$). However, in all cases, the 90% CI for the ratio of means were within 80 - 125%, indicating that the two products can be considered comparable. No significant differences were detected between Albuterol-HFA-BOI and Albuterol-HFA-MDI with respect to t_{max} ($p = 0.1368$) and $t_{1/2}$ ($p = 0.0856$).

Pharmacodynamics

Pharmacodynamic measures included systolic and diastolic blood pressure, serum glucose and potassium, and ECG-derived QT and QTc intervals. All pharmacodynamic parameters noted were expected based on the known physiologic effects of albuterol drug substance.

Blood pressure: Mean changes in both systolic and diastolic BP were comparable among products. Systolic BP rose with treatment and returned to baseline or just below baseline, while diastolic BP initially decreased then rose to just above baseline then gradually lowered below baseline over the treatment period. The highest mean systolic BP increase was 4.5 to 7.5 mmHg at 15 minutes after the final (1080 mcg) dose, and the mean between-treatment differences in systolic BP were less than 8 mmHg at all time points. One subject (#9305) experienced an increase of 30 mmHg 15 minutes after the final dose of Albuterol-HFA-MDI. The highest systolic BP was 146 mmHg. Ten subjects had a decrease in diastolic BP of 10 mmHg or more, and one subject (#314) experienced a decrease of 23 mmHg. The highest diastolic BP was 87 mmHg in two subjects (#306, three hours after third dose of Albuterol-HFA-BOI; #314, two hours after third dose of Albuterol-HFA-BOI).

Serum Glucose: The changes in serum glucose from baseline were similar across products (Figure 2) and no significant differences were found, with the exception of the 15-minute post-180-mcg and 540-mcg doses for Albuterol-HFA-MDI and Proventil[®] HFA (Table 3). The greatest change in glucose from baseline (range: 13.5-18 mg/dL mean change) occurred at 15 and 30 minutes after the third dose (i.e., 1080 mcg albuterol cumulative).

Figure 2. Mean change from baseline in serum glucose

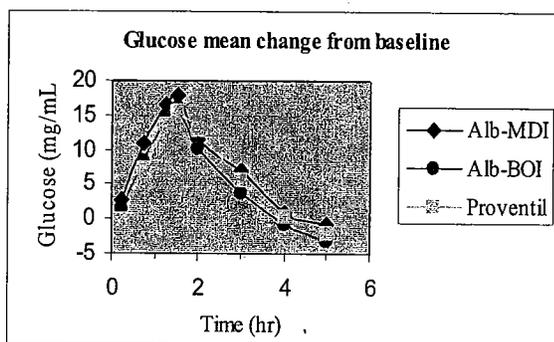


Table 3. Mean changes from baseline in serum glucose (mg/dL)

DOSE / TIME	TREATMENT LEAST SQUARE MEANS (SE) ^b			COMPARISONS (P VALUE) ^c	
	(1) Alb-HFA-BOI	(2) Alb-HFA-MDI	(3) Proventil [®] HFA	(1) vs. (3)	(2) vs. (3)
180 mcg/15 min ^d	1.40 (1.09)	2.73 (1.09)	-0.27 (1.09)	0.1641	0.0160
540 mcg/15 min ^d	8.33 (1.47)	11.07 (1.47)	7.27 (1.47)	0.5135	0.0261
1080 mcg/15 min ^d	14.67 (2.12)	16.47 (2.12)	13.53 (2.12)	0.5066	0.0932
30 min	16.07 (2.04)	18.00 (2.04)	15.40 (2.04)	0.7050	0.1476
1 hr	10.20 (1.88)	11.52 (1.92)	12.73 (1.88)	0.1437	0.4867
2 hr	3.87 (1.69)	6.93 (1.69)	5.60 (1.69)	0.2592	0.3830
3 hr	-0.73 (1.84)	0.87 (1.84)	0.33 (1.84)	0.5417	0.7596
4 hr	-3.07 (1.56)	-0.73 (1.56)	-2.00 (1.56)	0.5573	0.4864

^a Source: Tables 14A.3.4.1 and 14A.3.4.2.

^b Least square mean for each treatment (N = 15).

^c P value for the difference in least square mean between the treatments compared. Significance was achieved if p<0.05.

^d Each dose (2 + 4 + 6 actuations) was administered every 30 minutes to achieve the total 1080-mcg dose. Initial measurements were made 15 minutes after each dose.

Serum Potassium: Potassium levels decreased after albuterol dosing (Figure3 and Table 4). The maximum decrease occurred at 15 or 30 minutes (range: 0.57-0.79 mmol/L). The mean changes in potassium demonstrated no statistical differences across the three products.

Figure 3. Mean change from baseline in serum Potassium

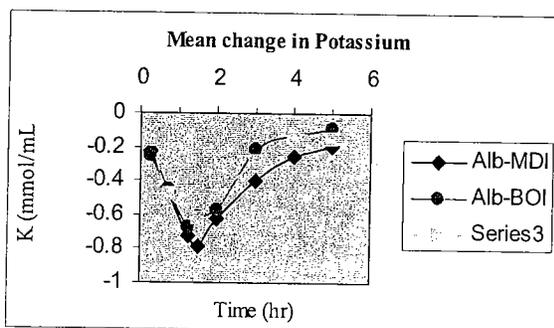


Table 4. Mean changes from baseline in serum potassium (mmol/L)

DOSE / TIME	TREATMENT LEAST SQUARE MEANS (SE) ^b			COMPARISONS (P VALUE) ^c	
	(1) Alb-HFA-BOI	(2) Alb-HFA-MDI	(3) Proventil [®] HFA	(1) vs. (3)	(2) vs. (3)
180 mcg/15 min ^d	-0.25 (0.07)	-0.22 (0.07)	-0.16 (0.07)	0.3373	0.5352
540 mcg/15 min ^d	-0.45 (0.10)	-0.47 (0.10)	-0.48 (0.10)	0.8409	0.9599
1080 mcg/15 min ^d	-0.67 (0.08)	-0.72 (0.07)	-0.57 (0.07)	0.2895	0.1192
30 min	-0.61 (0.08)	-0.79 (0.08)	-0.62 (0.08)	0.9432	0.0836
1 hr	-0.57 (0.07)	-0.62 (0.07)	-0.49 (0.07)	0.3187	0.1338
2 hr	-0.21 (0.09)	-0.40 (0.09)	-0.29 (0.09)	0.5354	0.4099
3 hr	-0.13 (0.10)	-0.26 (0.10)	-0.13 (0.10)	0.9624	0.3493
4 hr	-0.09 (0.08)	-0.19 (0.08)	-0.15 (0.08)	0.5426	0.6354

^a Source: Tables 14A.3.3.1 and 14A.3.3.2.

^b Least square mean for each treatment (N = 15).

^c P value for the difference in least square mean between the treatments compared. Significance was achieved if p<0.05.

^d Each dose (2 + 4 + 6 actuations) was administered every 30 minutes to achieve the total 1080-mcg dose. Initial measurements were made 15 minutes after each dose.

Heart Rate

Mean heart rate (as derived from the ECG RR interval) peaked at 15 minutes after the last dose and remained mildly elevated at 4 hours post-third dose (Table 6). There were no significant differences in heart rate across the three products.

Table 6. Mean changes from baseline in Heart Rate (bpm)

DOSE / TIME	TREATMENT LEAST SQUARE MEANS (SE) ^b			COMPARISONS (P VALUE) ^c	
	(1) Alb-HFA-BOI	(2) Alb-HFA-MDI	(3) Proventil [®] HFA	(1) vs. (3)	(2) vs. (3)
180 mcg/15 min ^d	2.23 (1.44)	3.46 (1.44)	3.18 (1.44)	0.6129	0.8761
540 mcg/15 min ^d	9.31 (2.01)	10.82 (2.01)	9.71 (2.01)	0.8528	0.6144
1080 mcg/15 min ^d	11.62 (2.15)	15.71 (2.15)	15.19 (2.15)	0.1908	0.8438
30 min	11.36 (2.15)	14.43 (2.15)	14.63 (2.15)	0.1644	0.9290
1 hr	8.35 (1.57)	10.67 (1.57)	11.66 (1.57)	0.0827	0.5947
2 hr	4.68 (2.10)	7.99 (2.10)	6.49 (2.10)	0.4269	0.5107
3 hr	2.07 (1.78)	2.57 (1.78)	4.57 (1.78)	0.1968	0.2990
4 hr	2.26 (1.47)	2.97 (1.47)	3.11 (1.47)	0.6509	0.9432

^a Source: Tables 14A.3.7.1 and 14A.3.7.2.

^b Least square mean for each treatment.

^c P value for the difference in least square mean between the treatments compared. Significance was achieved if p<0.05.

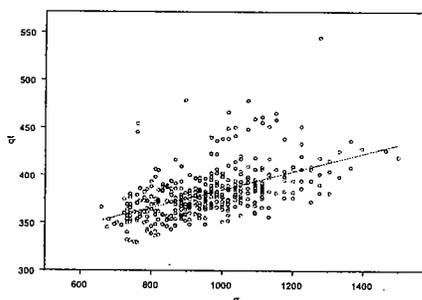
^d Each dose (2 + 4 + 6 actuations) was administered every 30 minutes to achieve the total 1080-mcg dose. Initial measurements were made 15 minutes after each dose.

Thirteen out of the 16 randomized subjects had post-treatment increases in heart rate of at least 15 bpm. Also, one subject (No. 309) had decreases exceeding 15 bpm (maximum decrease, 17.9 bpm) following treatment with Albuterol-HFA-BOI; the subject's baseline value was 67 bpm.

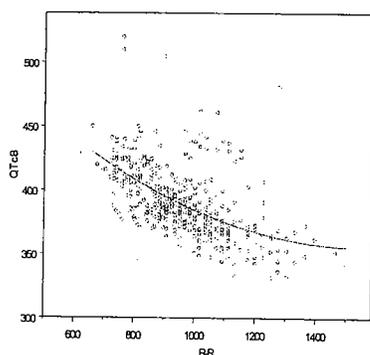
The largest individual post-treatment change in heart rate was an increase of 43.0 bpm that occurred in Subject No. 9305 30 minutes following the third dose of Proventil HFA; the subject's baseline was 47.9 bpm. The post-dose value achieved at this time point (90.9 bpm) was also the highest observed in the study.

QT and QTc Intervals: This reviewer analyzed QT data using Fridericia (QTcF) as well as Bazett's (QTcB) correction method (the sponsor used Bazett's method only). As RR interval increased QT also increased (A), while QTcB (B) or QTcF(C) decreased as RR interval increased. The slope of B is steeper than that of C: *i.e.*, QT was over corrected at elevated HR and under corrected at lower heart rate using Bazett's compared to that using Fridericia's method. Therefore, Fridericia's formula may be more correct in subjects with extreme heart rate values.

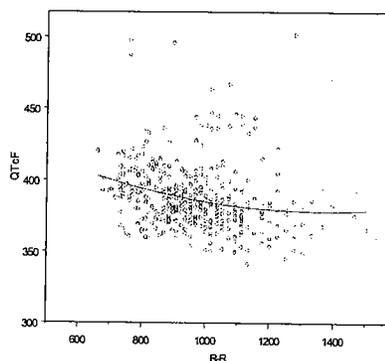
A: QT vs. RR



B: QTcB vs. RR

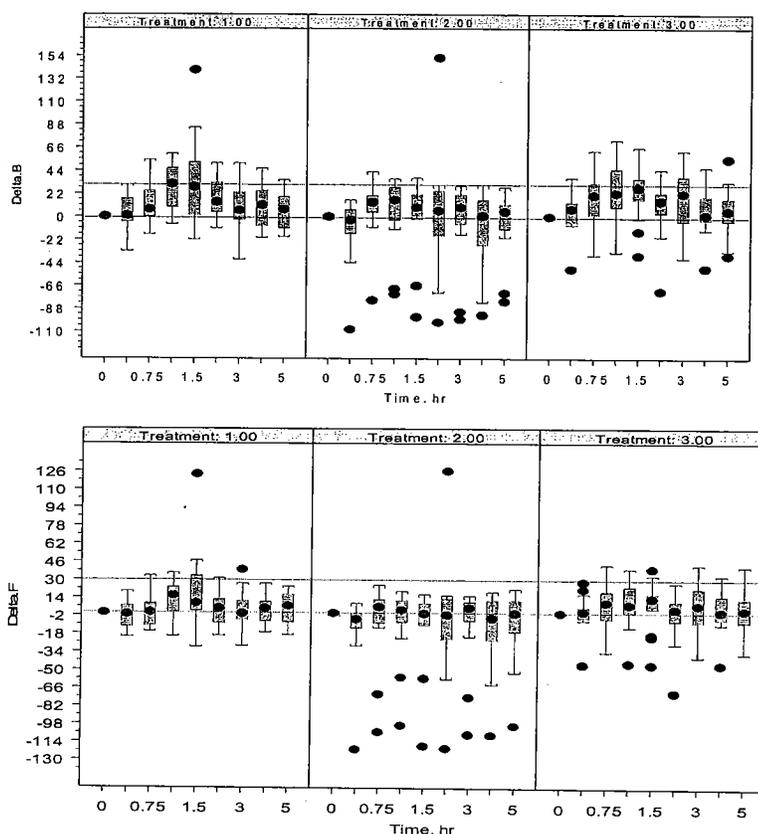


C: QTcF vs. RR



The effect of the treatments on QTcB and QTcF is summarized in Tables 5, and in Figure 5. The mean QTc peaked around 15-30 minutes after the final dose (1080 mcg). Albuterol-HFA-BOI started at a slightly higher baseline HR. Albuterol-HFA-BOI raised the heart rate less and had more negative effect on QT interval than the other two products, producing a very small net increase in QTc (+5.00) 15 minutes after the third (1080 mcg) dose. In contrast, the maximum change in QTc for Albuterol-HFA and Proventil HFA was 25.4 to 33.3 msec at 15-30 minutes after the third dose. However, there were no statistically significant differences in the changes in QT between Albuterol-HFA-MDI and Albuterol-HFA-BOI versus Proventil HFA except for QTc at 15 and 30 minutes and 3 hours after the third dose for Albuterol-HFA-BOI *versus* Proventil HFA, but the difference were small and not considered clinically important (Table 5, QTcB).

Figure 5. Median change of QTcB (upper) and QTcF (lower) from baseline



Note: Treatment 1, 2 and 3 refer to Proventil HFA, Albuterol HFA BOI and Albuterol HFA MDI, respectively

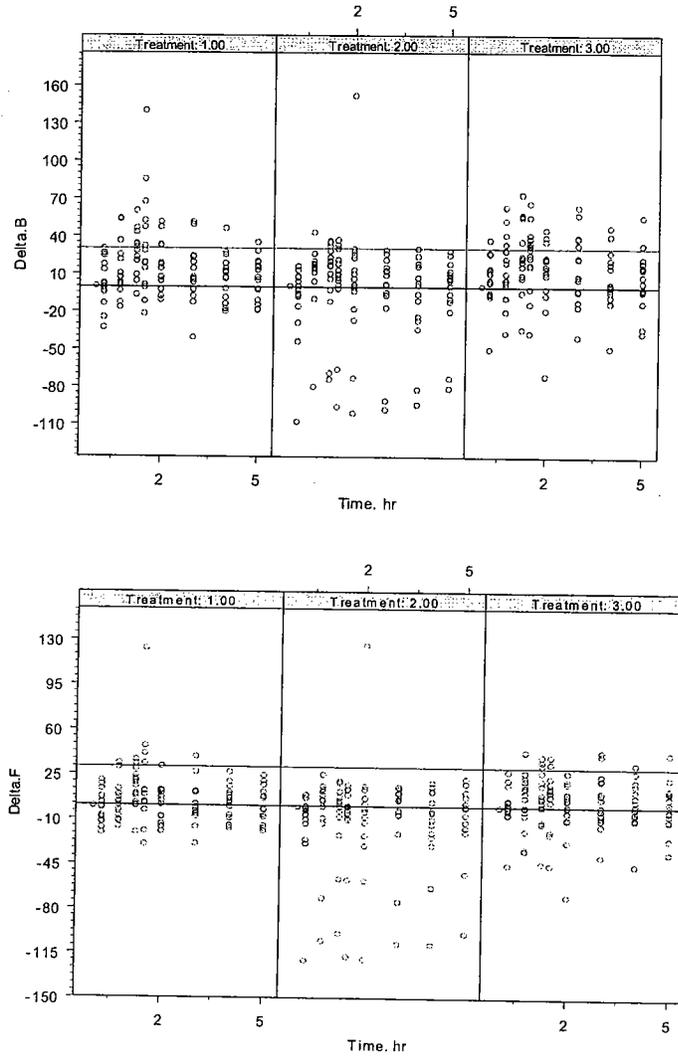
Table 5. Mean changes from baseline in QTcB and QTcF

PD Parameter	Dose	Timepoint	Proventil HFA	Alb-HFA-MDI	Alb-HFA-BOI
QTcB interval (msec)	180 mcg 540 mcg 1080 mcg	15 min	2.1±18	5.3±20	-11.1±31
		15 min	12.5±21	16.8±26	3.9±37
		15 min	28.9±20	25.3±27	5.0 ^a ±34
		30 min	33.3±41	23.4±25	1.7 ^b ±36
		1 hour	15.9±18	10.3±27	4.3±55
		2 hours	9.3±23	15.7±28	-4.6±39
		3 hours	8.5±19	6.6±23	-11.9 ^c ±36
QTcF interval (msec)	180 mcg 540 mcg 1080 mcg	15 min	-1.5±12	1.5±16	-13.9±31
		15 min	2.2±15	5.5±21	-6.1±35
		15 min	13.1±15	9.1±21	-6.8±32
		30 min	17.9±36	8.6±21	-10.1±34
		1 hour	3.7±15	-0.4±23	-4.7±23
		2 hours	2.3±16	7.1±22	-9.6±35
		3 hours	3.8±12	3.3±18	-14.3±33
4 hours	2.8±14	2.4±18	-8.7±31		

^ap=0.02, ^bp=0.02, ^cp=0.04; p value for the difference in least square mean between proventil and BOI

Changes in QTcB and QTcF from the baseline for all subjects after each treatment are shown in Figure 6. QTcB changes of ≥ 30 msec from baseline occurred 69 times (23 times based on QTcF) out of 414 time-point measurements. The largest change in QTcB interval, an increase of 152 msec (125.8 msec by QTcF), occurred in Subject No. 308, 1 hour following treatment with the third dose of Albuterol-HFA-BOI.

Figure 6. Change of QTcB (upper) and QTcF (lower) from baseline: Individual data



CONCLUSIONS: No significant differences among the three products were noted for PK or PD parameters.

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission			
	Information		Information
NDA Number	21-457	Brand Name	Volare™ HFA
OCBP Division (I, II, III)	DPE-II	Generic Name	Albuterol sulfate
Medical Division	HFD-570	Drug Class	Beta ₂ -adrenergic agonist
OCBP Reviewer	Shinja Kim	Indication(s)	Treatment or prevention of bronchospasm with reversible obstructive air way disease in adults and children ≤ 12 years of age
OCBP Team Leader	Emmanuel Fadiran	Dosage Form	Metered dose inhaler (MDI)
		Dosing Regimen	2 inhalation q4-6h.
Date of Submission	01/30/03	Route of Administration	Oral Inhalation
Estimated Due Date of OCPB Review	8/30/03	Sponsor	IVAX Pharmaceuticals
PDUFA Due Date	10/30/03	Priority Classification	S
Division Due Date	9/30/03		

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) -				
<i>Healthy Volunteers-</i>				
single dose:	x	1		Cumulative doses; physiological parameters (HR, BP, QT, glucose, etc.) were also assessed
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
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:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
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		1		PK information obtained only from IXR-107-1-105
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	x			
Comments sent to firm ?				
QBR questions (key issues to be considered)	<ul style="list-style-type: none"> • Is formulation used in the bio-studies identical to the to-be-marketed formulation? • Is PK profiles following Albuterol HFA-MDI and HFA-BOI similar to the referenced Proventil HFA? • Were the analytical procedures used to determine drug concentrations in this NDA acceptable? 			

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this page is the manifestation of the electronic signature.**

/s/

Shinja Kim
10/21/03 01:29:29 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
10/24/03 01:46:31 PM
BIOPHARMACEUTICS
I concur