

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCES
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA: 21-527/N000
Drug Name: Atrovent (Ipratropium Bromide) HFA 21 mcg Inhalation Aerosol
Indication: Chronic Obstructive Pulmonary Disease (COPD)
Applicant: Boehringer Ingelheim
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1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Ipratropium Bromide CFC is an anticholinergic bronchodilator approved for COPD. It was shown to improve FEV₁ AUC_{0-6 hours} compared to placebo. The present submission is for Ipratropium Bromide HFA.

There are some chemistry issues that might affect the conclusions made in this evaluation of the submission. Studies 244.1405 and 224.2543 were conducted with a device denoted as a 1st generation device. Study 244.1408 was started with the 1st generation device and then switched to a slightly different device called a 2nd generation device. The sponsor wants to market a slightly different device called a 3rd generation device. Study 244.2498 used the 3rd generation device. The sponsor has not provided adequate bridging studies for these devices. The chemistry reviewer is of the opinion that the difference between the 1st generation and the 3rd generation devices in the cascade impactor stages fractions is fairly large. These chemistry differences might make the interpretation of the results of these studies problematic.

If the chemistry issues can be resolved, Ipratropium Bromide HFA is approvable from a statistical perspective. Ipratropium Bromide was significantly different from placebo in FEV₁ AUC₀₋₆ above test-day baseline and Peak FEV₁ above test-day baseline in Studies 244.2498 and 244.1405. There might be slight differences between the CFC and HFA formulations in efficacy, but only sporadic significant differences were seen in the four studies comparing the HFA and CFC formulations with inconsistent numeric superiority seen in FEV₁ AUC₀₋₆ above test-day baseline or Peak FEV₁ above test-day baseline.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

This review discusses one single dose, placebo and active-controlled, crossover study; one 12-week active and placebo controlled study, and two active controlled studies in patients with COPD.

1.3 STATISTICAL ISSUES AND FINDINGS

This reviewer was able to duplicate the sponsor's analyses from the datafiles provided. There are no statistical issues with the sponsor's conclusions.

2. INTRODUCTION

2.1 OVERVIEW

Ipratropium Bromide CFC is an anticholinergic bronchodilator approved for COPD. It was shown to improve FEV₁ AUC_{0-6 hours} compared to placebo. The safety and efficacy of Atrovent CFC have been well characterized. The present submission is for Ipratropium

Bromide HFA. Since CFC products have a harmful effect on the ozone layer, all CFC products are being phased out. HFA is a safer propellant for the atmosphere.

The sponsor has normalized the FEV₁ AUC₀₋₆ above test-day baseline by dividing by 6 in the submission and called it FEV₁ AUC₀₋₆ above test-day baseline. This creates a weighted average of FEV₁ above baseline. Dividing an AUC by the number of hours in it allows an AUC_{0-6hours} to be compared to an AUC_{0-4 hours}. This division by 6 should be kept in mind when considering the amount of treatment effect.

Ipratropium Bromide will sometimes be denoted by Ipr Br in the tables in this review.

2.2 DATA SOURCES

Datafiles were provided in the sponsor's December 06, 2002 electronic submission. They were included in \\CDSESUB1\N21527\N_000\2002-12-06\crt\datasets\ise. Each study in that folder had its own folder with AUC and Peak FEV₁ data in a pft.xpt dataset.

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 PLACEBO CONTROLLED STUDIES

3.1.1.1 STUDY 244.2498

This was a randomized, double-blind, double dummy, single dose, multi-center, 5-period crossover study comparing Ipratropium Bromide HFA 21 mcg, Ipratropium Bromide HFA 42 mcg, Ipratropium Bromide CFC 21 mcg, Ipratropium Bromide CFC 42 mcg, and placebo in COPD patients. There were 10 treatment sequences balanced with each treatment occurring twice in a period. Four patients in each sequence group were to be enrolled in the study. This study used the 3rd generation device. There was a three to seven day washout period between treatment visits. {Since Ipratropium bromide is a QID drug there should be no carry-over effects after washout.}

PFTs were done pre-treatment and at 15, 30, 60 and 90 minutes and 2, 3, 4, 5 and 6 hours after treatment.

At each treatment visit, the patient took one puff from four different canisters to blind the study. The 42 mcg doses were given as two puffs of the 21 mcg doses.

There were originally 4 centers that were to be entered into the study with 10 patients per center. If a patient dropped before completing all treatments, a new replacement patient was to be entered. One center did not enroll any patients. The supplies from this center were given to one of the other 3 centers. [This unbalancing among centers is not of major importance since this is a crossover study where all patients receive each treatment.]

AUC_{0-6 hours} of FEV₁ above test-day baseline was analyzed with an analysis of variance including center, subject (center), treatment, and period as factors, and test-day baseline FEV₁ as a covariate.

There were 41 patients who enrolled in this study. One patient received only Ipratropium Bromide 42 mcg CFC. This patient was not included in the crossover analysis. A replacement patient on a different treatment sequence was used causing slight treatment imbalance with respect to treatments within periods.

The period effect was not significant in the primary analysis (p=0.5504).

The table below gives the adjusted treatment means, standard errors, and p-values compared to placebo. All active treatments were significantly different from placebo.

Table 1 Adjusted Means for FEV₁ AUC₀₋₆ above Test-Day Baseline and P-values Compared to Placebo.

	Adjusted Mean		
Treatment	AUC ₀₋₆	Standard Error	P-value Vs Placebo
<u>HFA</u>			
Ipr Br 21mcg	0.179	0.0101	0.0001
Ipr Br 42mcg	0.215	0.0100	0.0001
<u>CFC</u>			
Ipr Br 21mcg	0.198	0.0103	0.0001
Ipr Br 42mcg	0.220	0.0103	0.0001
Placebo	0.055	0.0103	

The table below provides the pairwise comparisons between the adjusted treatment means of FEV₁ AUC₀₋₆ (liters) above test-day baseline for the corresponding dose strengths of Ipratropium Bromide HFA and Ipratropium Bromide CFC.

Table 2 Difference between Adjusted Treatment Means of FEV₁ AUC₀₋₆ above Test-Day Baseline of Ipratropium Bromide HFA and Ipratropium Bromide CFC and 90% confidence Limits.

	Adjusted Mean					
	AUC ₀₋₆ for Ipr Br		Difference	Std. Error	90%	
			Between	Of the	Confidence	
Dose	HFA	CFC	Treatments	Difference	Interval	P-value
21 mcg	0.179	0.198	-0.019	0.014	(-0.042, 0.004)	0.1721
42 mcg	0.215	0.220	-0.005	0.014	(-0.028, 0.018)	0.7162

This table shows that the 42 mcg dose of the HFA formulation provided comparable efficacy to the 42 mcg CFC formulation with respect to FEV₁ AUC₀₋₆ above test-day baseline. The 21 mcg doses were comparable but the 42 mcg dose of the CFC product is the labeled dosage.

The period effect was not significant in the analysis of peak FEV₁ above test-day baseline (p=0.5874).

The table below gives the adjusted treatment means for peak FEV₁ above test-day baseline, standard errors, and p-values compared to placebo. All active treatments were significantly different from placebo.

Table 3 Adjusted Means for Peak FEV₁ above Test-Day Baseline and P-values Compared to Placebo.

Treatment	Adjusted Mean	Standard Error	P-value Vs Placebo
	Peak FEV ₁		
<u>HFA</u>			
Ipr Br 21mcg	0.294	0.0122	0.0001
Ipr Br 42mcg	0.323	0.0121	0.0001
<u>CFC</u>			
Ipr Br 21mcg	0.312	0.0125	0.0001
Ipr Br 42mcg	0.333	0.0124	0.0001
Placebo	0.149	0.0124	

The table below provides the pairwise comparisons between the adjusted treatment means of Peak FEV₁ (liters) above test-day baseline for the corresponding dose strengths of Ipratropium Bromide HFA and Ipratropium Bromide CFC.

Table 4 Difference between Adjusted Treatment Means of Peak FEV₁ above Test-Day Baseline of Ipratropium Bromide HFA and Ipratropium Bromide CFC and 90% Confidence Limits.

Dose	Adjusted Mean		Difference	Std. Error	90% Confidence Interval	P-value
	HFA	CFC				
21 mcg	0.294	0.312	-0.018	0.0165	(-0.0452,0.0096)	0.2827
42 mcg	0.323	0.333	-0.009	0.0166	(-0.0367,0.0182)	0.5772

This study shows that a single dose of Ipratropium Bromide HFA 42 mcg was significantly different from placebo and comparable to a single dose of Ipratropium

Bromide CFC 42 mcg for Peak FEV₁ above test-day baseline and AUC₀₋₆ above test-day baseline.

3.1.1.2. STUDY 244.1405

This was a randomized, double-blind, double dummy, multi-dose, multi-center, parallel group study comparing Ipratropium Bromide HFA 21 mcg, Ipratropium Bromide HFA 42 mcg, Ipratropium Bromide CFC 21 mcg, and placebo each given 2 doses QID over 12 weeks of treatment in COPD patients. This study used the 1st generation device.

Randomization was done in blocks of eight, one patient was randomized to placebo HFA, two patients to 42 mcg HFA, two patients to 84 mcg HFA, one patient to placebo CFC, and two patients to 42mcg CFC. Although the sponsor expected the 42 mcg doses would be comparable, they included the larger 84 mcg dose for investigative purposes.

There were 31 centers entering patients into the study. The sponsor's analyses created 7 pooled centers (15, 6), (16,30), (20,21), (29,10), (31,7), (32,17), (33,1). The sponsor's statistical documentation stated that these centers were pooled so that each of the pooled centers had at least one block. {This is not a randomization block like the true randomization blocks in the other centers.} There were 24 centers in the sponsor's analyses. {The treatment effects are unestimable without pooling. Considering the large difference between active treatments and placebo, these comparisons would be significant however pooling was done. If treatment by center interaction is removed from the model active treatments are significantly different from placebo without pooling.}

Each test dose consisted of two inhalations QID. A blinding device was said to be used to blind all study medications.

Ipratropium Bromide CFC was allowed during the two-week baseline period but not as concomitant medication during the 12-week treatment period.

Serial PFTs over 8 hours were conducted at baseline, and at 15, 30, 60, 90 minutes, and 2, 3, 4, 5, 6, 7, and 8 hours on Days 1, 29, 57, and 85.

Although the protocol specified FEV₁ AUC from 0 to 4 hours above test-day baseline and peak change from test-day baseline in FEV₁ would be the primary endpoints, AUC from 0 to 6 hours above test-day baseline was substituted for the AUC from 0 to 4 hours above test-day baseline. Using AUC from 0 to 6 hours was done for consistency of analyses. Since the drug will have a QID dosing recommendation, this substitution is reasonable.

The primary endpoints were analyzed at each test day with an analysis of covariance with factors: center, treatment, and treatment-by-center interaction and test-day baseline as covariate. Inclusion of test-day baseline as covariate and treatment-by-center interaction was decided prior to unblinding. The protocol mentioned that these would be investigated and included, if significant. The treatment-by-center interaction was never significant in

the primary analyses. Baseline was significant for the analysis of peak FEV₁ above test-day baseline, but not for FEV₁ AUC₀₋₆ above test-day baseline.

The sponsor's statistical documentation mentioned that the sponsor tested for treatment-by-baseline interaction and sometimes found it to be significant for some of the primary efficacy variables on some of the test-days. The sponsor stated that the slopes were fairly close. [This reviewer found that including treatment-by-baseline had only a small effect on the estimates of least squares means. Active treatments were still significantly different from their corresponding placebo.]

The sponsor made no adjustments of p-values for multiple comparisons. The sponsor also did not specify which day was considered to be primary.

A total of 507 patients were randomized into the study. Two patients were withdrawn during the Day 1 serial PFT testing when it was discovered that they should have been excluded (one on chronic oxygen therapy and the other on chronic antihistamine therapy). Thus there were 505 patients (62 placebo HFA, 124 Ipratropium Bromide HFA 42 mcg, 126 Ipratropium Bromide 84 mcg, 66 placebo CFC, and 127 Ipratropium Bromide CFC 42 mcg) at 31 centers.

For patients withdrawing from the study after Day 1, data from the last visit was carried forward to estimate data on later test-days. To estimate random, middle, missing spirometry measurements, linear interpolation between adjacent measurements were used. For values at the end of the test-day missing for reasons unrelated to the patient's response to treatment, the last observed value was used as an estimate. For values at the end of the test-day missing due to shortness of breath or other COPD symptoms, the minimum spirometry value observed on that test-day (even possibly the pre-dose value) was used as the estimate. [Although not pre-specified, these rules appear reasonable. It is unlikely that the p-values comparing active treatments with placebo would be greatly affected by any reasonable method of handling missing data.]

Linear interpolation was used to estimate values if the measurement occurred outside of the assessment window: (5 minutes for the 15 and 30 minute assessment and 10 minutes for the latter assessments).

The treatment groups were comparable at baseline in demographic variables and baseline pulmonary function.

Tables A and B at the end of this review give the adjusted treatment means for FEV₁ AUC₀₋₆ above test-day baseline and FEV₁ Peak above test-day baseline. All active treatments were significantly different from the placebo of their formulation for both FEV₁ AUC₀₋₆ above test-day baseline and FEV₁ Peak above test-day baseline on all test days. The only significant difference among active treatments was between the 84 mcg HFA dose and the 42 mcg CFC dose at Day 1 for both Peak FEV₁ above test-day baseline and FEV₁ AUC₀₋₆ above test-day baseline.

The table below provides the 90% confidence intervals between the 42mcg dose of Ipratropium Bromide CFC and the two HFA doses. The 42 mcg doses were fairly comparable as was the HFA 84 mcg dose with the 42 mcg CFC dose at all evaluations except on Day 1. These results support the recommendation of the 42 mcg dose of the HFA formulation.

Table 5 Summary of the Tests for Therapeutic Equivalence between Ipratropium Bromide CFC 42 mcg and Ipratropium Bromide HFA 42 and 84 mcg- Endpoint Analysis of the Intent-to-Treat Dataset

Comparison of Ipratropium bromide CFC, 42 mcg to:						
	Ipratropium bromide HFA, 42 mcg			Ipratropium bromide HFA, 84 mcg		
	Difference (HFA42mcg -CFC)	Std Error	90% Confidence Interval	Difference (HFA84mcg - CFC)	Std Error	90% Confidence Interval
FEV₁ AUC₀₋₆						
Day 1	0.024	0.020	(-0.009,0.056)	0.045	0.020	(0.013, 0.077)
Day 29	-0.012	0.020	(-0.045,0.022)	-0.006	0.020	(-0.039,0.028)
Day 57	-0.015	0.020	(-0.047,0.018)	-0.007	0.020	(-0.039,0.025)
Day 85	0.014	0.020	(-0.019,0.047)	0.002	0.020	(-0.031,0.034)
FEV₁ PEAK						
Day 1	0.040	0.023	(0.003,0.078)	0.052	0.023	(0.015, 0.090)
Day 29	0.000	0.024	(-0.038,0.039)	-0.004	0.023	(-0.043,0.035)
Day 57	-0.001	0.022	(-0.037,0.034)	0.005	0.021	(-0.031,0.040)
Day 85	0.033	0.023	(-0.005,0.072)	0.004	0.023	(-0.034,0.042)

3.1.2. ACTIVE CONTROLLED STUDIES

3.1.2.1. STUDY 244.2453

This was a randomized, open-label, multi-dose, multi-center, parallel group study comparing Ipratropium Bromide HFA 21 mcg and Ipratropium Bromide CFC 21 mcg, each given 2 doses QID over 12 weeks of treatment in COPD patients. Patients could take up to two extra doses of their medication daily. This study used the 1st generation device.

There were 30 active centers enrolling patients into this study. Although the study was open label, randomization occurred in an unblinded fashion using a third party administrator. Once the treatment was assigned, neither the patient nor the investigator was blind to treatment.

Serial PFTs were done over 6 hours on Days 1, Weeks 12, 26, and 52. The same rules that were used in Study 244.1408 for the primary efficacy variables were used to handle missing values in this study.

During the baseline period the patients received open-label Atrovent Inhalation Aerosol (two puffs, QID).

Twice as many patients were randomized to Ipratropium Bromide HFA compared to Ipratropium Bromide CFC. Three hundred and five patients were randomized to Ipratropium Bromide HFA of whom 263 completed the trial. One hundred and fifty one patients were randomized to Ipratropium Bromide CFC, of whom 124 completed the trial.

Tables 6 and 7 below provide the adjusted treatment means and p-values comparing treatments for FEV₁ AUC₀₋₆ above test-day baseline and Peak FEV₁ above test-day baseline. At Week 12, the CFC dose gave higher values for both FEV₁ AUC₀₋₆ and Peak FEV₁. The whole serial FEV₁ curve for the CFC formulation was above the curve for the HFA formulation at this visit.

Table 6 Adjusted Mean FEV₁ AUC₀₋₆ above Test-day Baseline in Liters (Standard Error of Mean) and P-value Comparing Treatments.

	Ipratropium Bromide HFA 42 mcg (N=281)		Ipratropium Bromide CFC 42 mcg (N=138)		p-Value
	Mean	Std. Err.	Mean	Std. Err.	
Day 1	0.148	0.010	0.143	0.014	0.7868
Week 12	0.137	0.010	0.174	0.014	0.0292
Week 26	0.134	0.010	0.141	0.014	0.6624
Week 52	0.117	0.010	0.117	0.014	0.9892

Means are adjusted for center and treatment-by-center interaction. Test-day baseline was used as a covariate. Standard errors are identical after rounding

Table 7 Adjusted Mean Peak FEV₁ Change from Baseline in Liters (Standard Error of Mean) and P-values comparing treatments.

	Ipratropium Bromide HFA 42 mcg (N=281)		Ipratropium Bromide CFC 42 mcg (N=138)		p-Value
	Mean	Std. Err.	Mean	Std. Err.	
Day 1	0.287	0.011	0.276	0.016	0.5684
Week 12	0.275	0.011	0.301	0.016	0.1832
Week 26	0.276	0.012	0.282	0.017	0.7681
Week 52	0.253	0.010	0.256	0.015	0.8332

Means are adjusted for center and treatment-by-center interaction. Test-day baseline was used as a covariate.

Table 8 below provides the 90% confidence limits on the comparison of the two formulations. The two formulations were fairly comparable except for the Week 12 visit results for AUC₀₋₆ above test-day baseline.

Table 8 Summary of the Tests for Therapeutic Equivalence between Ipratropium Bromide HFA 42 mcg and Ipratropium Bromide 42 mcg CFC

	Comparison Of Ipratropium bromide HFA 42 mcg to Ipratropium bromide 42 mcg CFC		
	Difference In Adjusted Means (HFA-CFC)	Standard Error	90% confidence Interval
FEV₁ AUC₀₋₆			
Day 1	0.005	0.017 ^a	(-0.023, 0.032)
Week 12	-0.037	0.017 ^a	(-0.065, -0.009)
Week 26	-0.008	0.017 ^a	(-0.036, 0.021)
Week 52	0.000	0.017 ^a	(-0.028, 0.027)
FEV₁ Peak			
Day 1	0.011	0.020	(-0.021, 0.044)
Week 12	-0.025	0.019	(-0.056, 0.006)
Week 26	-0.006	0.021	(-0.041, 0.028)
Week 52	-0.004	0.018	(-0.033, 0.026)

^a Standard Errors are identical after rounding

3.1.2.2. STUDY 224.1408

This was a randomized, double-blind, multi-dose, multi-center, parallel study comparing Ipratropium Bromide HFA 21 mcg and Ipratropium Bromide CFC 21 mcg, each given 2 doses QID over 12 weeks of treatment in COPD patients. Patients could take up to two extra doses of their medication daily. This study used the 1st generation device.

There were 16 active centers enrolling patients into this study.

Serial PFTs were done over 6 hours on Days 1, Weeks 6, and 12. The same rules that were used in Study 244.1408 for the primary efficacy variables were used to handle missing values in this study.

During the baseline period the patients received open-label Atrovent Inhalation Aerosol (two puffs, QID).

The primary efficacy assessments in this study were morning and evening PEFr. This was done to address questions like whether the patients showed an effect from switching from the CFC formulation (used during run-in) to the HFA formulation (used during the treatment period). The PEFr means a week before randomization were compared to the PEFr means a week after randomization. This review will focus more on the FEV₁ Peak and AUC₀₋₆ for consistency with the other studies but the PEFr results will be briefly mentioned.

Twice as many patients were randomized to Ipratropium Bromide HFA compared to Ipratropium Bromide CFC. One hundred and eighteen patients were randomized to Ipratropium Bromide HFA of whom 94 (80%) completed the trial. Fifty-six patients were randomized to Ipratropium Bromide CFC, of whom 46 (82%) completed the trial.

Tables 9 and 10 below provide the adjusted treatment means and p-values comparing treatments for FEV₁ AUC₀₋₆ above test-day baseline and Peak FEV₁ above test-day baseline.

Table 9 Adjusted Means for FEV₁ AUC₀₋₆ above test-day baseline.

	CFC-MDI	HFA-MDI
Day 1		
Adjusted mean	1.035 L	1.041L
Std error	0.018L	0.013L
N	56	118
Day 42		
Adjusted mean	1.013 L	1.059L
Std error	0.018L	0.013L
N	48	104
Day 84		
Adjusted mean	1.041 L	1.050L
Std error	0.020 L	0.015L
N	47	96

Table 10 Adjusted Means for Peak FEV₁ above test-day baseline.

	CFC-MDI	HFA-MDI
Day 1		
Adjusted mean	1.165 L	1.168L
Std error	0.022L	0.016L
N	56	118
Day 42		
Adjusted mean	1.158 L	1.181L
Std error	0.021L	0.015L
N	48	104
Day 84		
Adjusted mean	1.173 L	1.182L
Std error	0.023 L	0.017L
N	47	96

Table 11 below provides the 90% confidence limits on the comparison of the two formulations. The two formulations were fairly comparable except for the Day 42 visit results for AUC₀₋₆ above test-day baseline.

Table 11 Evaluation of the Difference between treatment groups with respect to Peak FEV₁ above test-day baseline and FEV₁ AUC₀₋₆ above test-day baseline.

Treatment Contrast	Difference in Adjusted Means (SE)	90% Confidence Interval for Diff.
FEV ₁ Peak		
Day 0	0.0034 L (0.0252 L)	(-0.0383, 0.0451)
Day 42	0.0227 L (0.0245 L)	(-0.0179, 0.0634)
Day 84	0.0085 L (0.0268 L)	(-0.0359, 0.0529)
FEV ₁ AUC ₀₋₆		
Day 0	0.0066 L (0.0204 L)	(-0.0272, 0.0403)
Day 42	0.0452 L (0.0211 L)	(0.0101, 0.0802)
Day 84	0.0096 L (0.0236 L)	(-0.0295, 0.0487)

The mean Morning and Evening PEFR a week after randomization were comparable to the mean a week before randomization for the CFC group and the HFA group with the largest difference between the Evening PEFR for the CFC group who were taking CFC throughout. No difference between groups were seen in mean Morning PEFR (p=0.8653). The evening PEFR difference was not significant at the 0.05 significance level (p=0.0659).

3.1 EVALUATION OF SAFETY

Since this is a switch program, the safety information about Ipratropium follows mainly from the approved CFC formulation. The safety data collected was consistent with the CFC formulation safety information.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Since this is a switch program, if no major differences between the CFC and HFA products are detected then the special population information about Ipratropium follows mainly from the approved CFC formulation. The data collected were consistent with the CFC formulation subpopulation information.

5. OVERALL CONCLUSIONS

If the chemistry issues can be resolved, Ipratropium Bromide HFA is approvable. Ipratropium Bromide was significantly different from placebo in FEV₁ AUC₀₋₆ above test-day baseline and Peak FEV₁ above test-day baseline in Studies 244.2498 and 244.1405. There might be slight differences between the CFC and HFA formulations in efficacy but only sporadic significant differences were seen in the four studies comparing the HFA and CFC formulations with inconsistent numeric superiority seen in FEV₁ AUC₀₋₆ above test-day baseline or Peak FEV₁ above test-day baseline.

6. PRIMARY, CONCURRING REVIEWERS AND DISTRIBUTION LIST

This review contains 14 pages of text and one additional page of tables.

cc:

Archival NDA 21527

HFD-570

HFD-570 /Ms Jafari

HFD-570/Dr. Purohit-Sheth

HFD-710/Dr. Anello

HFD-715/Dr. Wilson

HFD-715/Dr. Gebert

**APPEARS THIS WAY
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Table A Adjusted Mean FEV₁ AUC₀₋₆ in Liters (Standard Errors of the Mean)
Endpoint Analysis of the Intent-To-Treat Data set

		HFA-134a			CFC		
		Placebo (N=62)	Ipr Br 42 mcg (N=124)	Ipr Br 84 mcg (N=126)	Placebo (N=66)	Ipr Br 42 mcg (N=127)	
Day 1		0.003 (0.021)	0.148 ^b (0.014)	0.169 ^{b,c} (0.014)	0.013 (0.019)	0.124 ^b (0.014)	
Day 29		-0.009 (0.021)	0.135 ^b (0.014)	0.141 ^b (0.014)	-0.008 (0.020)	0.147 ^b (0.014)	
Day 57		-0.005 (0.021)	0.117 ^b (0.014)	0.124 ^b (0.014)	0.011 (0.019)	0.131 ^b (0.014)	
Day 85		0.018 (0.021)	0.141 ^b (0.014)	0.129 ^b (0.014)	0.014 (0.020)	0.127 ^b (0.014)	

^a Means are adjusted for center and treatment-by-center interaction, Test-day baseline is used as covariate

^b p<0.05 for the comparison to placebo of the same formulation

^c p<0.05 for the comparison to CFC Ipratropium Bromide 42 mcg

Table B Adjusted Mean FEV₁ Peak Change from Baseline in Liters (Standard Errors of the Mean)
Endpoint Analysis of the Intent-To-Treat Data set

		HFA-134a			CFC		
		Placebo (N=62)	Ipr Br 42 mcg (N=124)	Ipr Br 84 mcg (N=126)	Placebo (N=66)	Ipr Br 42 mcg (N=127)	
Day 1		0.143 (0.024)	0.295 ^b (0.016)	0.307 ^{b,c} (0.016)	0.138 (0.022)	0.255 ^b (0.016)	
Day 29		0.111 (0.025)	0.286 ^b (0.017)	0.282 ^b (0.017)	0.116 (0.023)	0.286 ^b (0.017)	
Day 57		0.113 (0.023)	0.266 ^b (0.015)	0.272 ^b (0.015)	0.121 (0.021)	0.267 ^b (0.015)	
Day 85		0.139 (0.024)	0.295 ^b (0.016)	0.266 ^b (0.016)	0.140 (0.023)	0.262 ^b (0.016)	

^a Means are adjusted for center and treatment-by-center interaction, Test-day baseline is used as covariate

^b p<0.05 for the comparison to placebo of the same formulation

^c p<0.05 for the comparison to CFC Ipratropium Bromide 42mcg

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/s/

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9/17/03 08:59:19 AM
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9/22/03 11:09:06 AM
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