

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-527**

**MEDICAL REVIEW(S)**

## **DIVISION DIRECTOR'S MEMORANDUM**

Date: November 17, 2004

To: NDA 21-527

From: Badrul A. Chowdhury, MD, PhD  
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Atrovent HFA (ipratropium bromide HFA) Inhalation Aerosol

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

This memorandum comments on the review findings of the complete response to our previous approvable action taken on this application on October 9, 2003. The application was not approved in the previous cycle because of outstanding CMC issues. The CMC issues are now resolved and there are no outstanding issues from other disciplines. Therefore, the action on this application will be an APPROVAL.

My previous memorandum that summarizes the whole development program for this application is appended to this summary.

Detailed review of the CMC section can be found in Dr. Peri's review. The CMC concerns that precluded approval in the previous review cycles were insufficient information on the safety, quality, and methods for the analysis of the drug product. In addition several DMFs were also found to be inadequate. The applicant has now provided adequate data to support approval of the product. There are minor issues that do not directly impact the safety of use of the drug and the applicant has agreed to address these post approval. The applicant will conduct toxicology studies to qualify some leachables that are present in the product. Post-approval qualification of the specific leachables is acceptable because of previous marketing history of similar products and data that is in the Division's knowledge. The applicant will also conduct stability studies to provide and evaluate data for foreign particulates as a function of time, and to fully characterize the variability of the aerodynamic particles size of the drug product. These and other post-approval agreements are detailed in Dr. Peri's review.

The product label was extensively reviewed by all disciplines of this Division, and by DDMAC, DMETS, and DSRCS. The Division and the applicant have agreed on a final labeling text. The labeling is similar to the currently marketed CFC containing Atrovent Inhalation Aerosol, which this product will ultimately replace.

**DIVISION DIRECTOR'S MEMORANDUM**

Date: October 9, 2003

To: NDA 21-527

From: Badrul A. Chowdhury, MD, PhD  
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Atrovent (ipratropium bromide) HFA Inhalation Aerosol

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

**Administrative and Introduction**

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) submitted an NDA for Atrovent (ipratropium bromide) HFA Inhalation Aerosol as a 505(b)(1) application that was received by the Agency on December 9, 2002. The current product is being developed by BIPI to ultimately replace the CFC containing Atrovent Inhalation Aerosol that is currently marketed in the United States by BIPI. Atrovent Inhalation Aerosol has a long marketing history in the United States having been approved since 1986. The clinical program is therefore relatively brief; the pivotal studies include two 12-week efficacy and safety studies, and one 1-year safety study. The major complicating issue with this application is on the drug product, specifically the device, with the applicant changing the device in the middle of the clinical development program. The major issues that preclude approving this application in this first review cycle is in chemistry and manufacturing as detailed in the CMC discipline review and commented briefly below.

**Chemistry, Manufacturing, and Controls, and Establishment Evaluation**

All information pertaining to the drug substance is referred to a DMF, which was reviewed and found to be adequate. The drug product is a solution MDI that is manufactured for BIPI by 3M Pharmaceuticals at the Northridge, California, USA, facility. The same facility also manufactures other MDI products containing ipratropium bromide.

The device has gone through 3 iterations, the last one being called the 3<sup>rd</sup> generation device. This issue is further complicated by the fact that the applicant used different in vitro comparison methods in determining the aerodynamic particle size distribution (APSD) for the three generations of products. The 1<sup>st</sup> and 2<sup>nd</sup> generation devices are no longer manufactured, but were used in all of the pivotal clinical studies. The major changes occurred between the 1<sup>st</sup> and 2<sup>nd</sup> generation drug products (changes in the material of construction and internal diameter of the valve stem), and the changes between the 2<sup>nd</sup> and 3<sup>rd</sup> generation were relatively minor. From the 2<sup>nd</sup> generation to the 3<sup>rd</sup> generation device, BIPI attempted to optimize the product by \_\_\_\_\_ and making other changes to minimize the leachables

observed in the drug product. The exact changes and the potential consequences of the changes are detailed in the CMC review of Dr. Peri and also commented in the Medical Officer Review and Medical Team Leader memorandum. The disciplines concluded that the changes made from the 2<sup>nd</sup> to the 3<sup>rd</sup> generation device did result in some change to the particle size distribution of the aerosolized drug; however there were some clinical data to link the 3<sup>rd</sup> generation device with the earlier device, which were used in the pivotal clinical trials. In concur with that conclusion.

There are several outstanding issues that BIPI will need to resolve from the CMC point of view before the drug product can be approved. Although the formulation is stated to be a solution there is a significant change in the profile of the fine particle fraction (increase in larger particles) under accelerated stability conditions. This phenomenon is rather unusual for a solution formulation and BIPI has to demonstrate that the formulation remains a solution on stability and meets the appropriate performance criteria for particle size distribution and medication delivery. The safety of \_\_\_\_\_ (leachable \_\_\_\_\_) to support chronic administration has to be demonstrated. A significant number of specification issues remain deficient including certain acceptance criteria, analytical methods and method validation. There are also a number of deficiencies pertaining to the containing closure system. These are discussed in detail in Dr. Peri's review.

#### **Pharmacology and Toxicology**

The applicant did not conduct any new preclinical data for this application because ipratropium is an approved product, and HFA has already been studied and BIPI has right of reference to the data. Dr. Whitehurst has several comments for the product label, which will be communicated to the applicant.

#### **Clinical and Statistical**

The pivotal clinical studies were two 12-week efficacy and safety studies (244.1405 and 244.1408) and one one-year safety study (244.2453). These studies are reviewed in detail in Dr. Purohit-Sheth's excellent medical review.

The patients enrolled in the three pivotal studies were adults 40 years of age and older with a diagnosis of COPD. The mean percent predicted FEV1 across studies ranged from 38% to 40% and mean percent FEV1/FVC ranged from 46% to 54%. Over 90% of the study subjects were white and 60% to 70% were male. The demographics were generally representative of the COPD patient population in the United States. The two 12-week studies were similar in design and both were placebo and active controlled, however, only one study (244.1405) was placebo controlled. The active comparator was Atrovent Inhalation Aerosol CFC. The two studies demonstrated that Atrovent HFA was superior to placebo (in the placebo controlled study, 244.1405) and comparable to Atrovent CFC (in both 12-week studies) as assessed by the FEV1 AUC 0-6 hours and peak FEV1 response. The studies are adequate to support efficacy of Atrovent HFA. Safety data from the two 12-week studies are also supportive of safety. Further safety data was obtained from the one 1-year study, which also supported safety of Atrovent HFA. The

Clinical Team has concluded that the overall efficacy and safety database of Atrovent HFA is adequate to support approval and I concur with that conclusion.

One complicating issue with the clinical program was the use of the 1<sup>st</sup> and 2<sup>nd</sup> generation devices in the pivotal studies, which have some differences with the 3<sup>rd</sup> generation device. In the 1-year study both the 1<sup>st</sup> and 2<sup>nd</sup> generation devices were used, however, all patients used the 2<sup>nd</sup> generation device after 18 weeks. This provided 34 weeks of efficacy data with the 2<sup>nd</sup> generation device. Since the differences between the 2<sup>nd</sup> and 3<sup>rd</sup> generation products are relatively minor, an indirect link for the efficacy of the 3<sup>rd</sup> generation product can be established. In addition, there was one single-dose efficacy study (244.2498) where the 3<sup>rd</sup> generation device was used. This study demonstrated that Atrovent HFA 42 mcg and Atrovent CFC 42 mcg were superior to placebo and comparable to one another. This study is detailed in Dr. Purohit-Sheth's review. Based on the totality of the data the CMC team and the clinical team have concluded that there is adequate indirect and direct information to support the safety and efficacy of the 3<sup>rd</sup> generation Atrovent HFA Inhalation Aerosol product, and I concur with that conclusion.

#### **Clinical Pharmacology and Biopharmaceutics**

The clinical pharmacology studies are reviewed in detail in Dr. Suarez-Sharp's excellent review. No major issues were identified and the Office of Clinical Pharmacology and Biopharmaceutics team has recommended approval and I concur with that recommendation. A point of note is that the multiple dose PK study (244.2480) in COPD patients using the 3<sup>rd</sup> generation device showed that the systemic exposure to ipratropium was lower in the HFA product compared to the CFC product. Given this observation, there is no reason to expect a different systemic adverse event profile with the 3<sup>rd</sup> generation device compared to the earlier generation devices, which were used in the pivotal clinical studies.

#### **Data Quality, Integrity, and Financial Disclosure**

No DSI audit of clinical study sites was requested or conducted for this application. Ipratropium is not a new molecular entity and a CFC formulation of the drug is already marketed in the United States, and during the review process of this application no irregularities that would raise question on the data integrity were found. No ethical issues are present. All studies were conducted in accordance with accepted ethical standards. No financial disclosure issues are present. The applicant submitted an acceptable financial disclosure statement and statements of good clinical practice.

#### **Pediatric Consideration**

Ipratropium is approved for COPD, which is primarily an adult disease. Therefore, specific pediatric studies would not be required of this product.

**Product Name**

The proprietary name of Atrovent is approved and used by BIPI for the product line containing ipratropium.

**Labeling**

BIPI has submitted a product label that conforms to the general requirements of labeling. The labeling was not extensively reviewed because the application is not heading towards an approval action because of CMC deficiencies.

**Recommendation and Action**

The clinical studies submitted with this application are sufficient to support efficacy and safety of Atrovent HFA Inhalation Aerosol for use in COPD patients. There are outstanding CMC issues that need to be addressed before this application can be approved. Therefore, the action on this application will be APPROVABLE.

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Badrul Chowdhury  
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## Medical Team Leader Review Memorandum

Memorandum to File:

NDA 21-527

**Drug Products:** Atrovent® (ipratropium bromide) HFA Inhalation Aerosol  
**Sponsor:** Boehringer Ingelheim  
**Memo Date:** September 25, 2003  
**Memo From:** Lydia I. Gilbert-McClain, MD, Clinical Team Leader (Actg)

This memorandum is to document the secondary review of Dr. Tejashri Purohit-Sheth's Primary Medical Officer Review of the above-listed NDA for Atrovent® (ipratropium bromide) HFA Inhalation Aerosol and to provide a brief summary of the pertinent interdisciplinary findings. For full details of the clinical development program and the clinical findings please refer to Dr. Purohit-Sheth's excellent review.

Background/Administrative History

Atrovent® (ipratropium bromide) Inhalation Aerosol with chlorofluorocarbons (CFCs) as the propellant is approved for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. Atrovent® has a fairly long marketing history having been approved and marketed in the U.S. since 1986. Because of the mandatory phase out of the ozone-depleting CFC-containing drug products, The sponsor (Boehringer Ingelheim) developed a program to reformulate Atrovent® with Hydrofluoroalkane 134a (HFA). The development program was conducted under IND 45, 938 and the IND was opened on August 1, 1994. Several changes were made to the device during the development program and the timing of these changes was such that the to-be-marketed product was not used to conduct the pivotal phase 3 studies. The changes were limited to the device and there were no changes made to the formulation. The sponsor no longer had any of the earlier devices ( 1<sup>st</sup> and 2<sup>nd</sup> generation devices) by the time the clinical program was completed and therefore, bridging studies with the earlier products and the to-be-marketed 3<sup>rd</sup> generation product could not be conducted.

Pre-NDA meetings were held with the sponsor on January 16th and March 27, 2002. The Division agreed that a dose counter was not necessary to gain approval but the sponsor was informed that they needed to develop one. Additional agreements were reached between the Division and the sponsor in a Telecon on April 2, 2002 regarding patient tolerability of the to-be-marketed product. The sponsor was informed that the pharmacokinetic studies with the 3<sup>rd</sup> generation product that the sponsor had already conducted would be adequate to address the Division's concerns about patient tolerability of the to-be-marketed product. During this NDA review cycle the sponsor met with the Division to discuss their development plan for the dose counter.

The propose indication for Atrovent® HFA is the same as for Atrovent® CFC at the same dose and dosing regimen. The proposed label submitted with the application is similar to the currently approved label for Atrovent® except for the data specific to Atrovent ® HFA.

#### OVERVIEW OF CLINICAL PROGRAM

The main efficacy and safety data are derived from two 12-week pivotal efficacy studies and a one-year safety study. Supporting efficacy data come from a single-dose PK study in COPD patients using the 3<sup>rd</sup> generation (to-be-marketed) product. Although this is a single-dose study, it is important not only for the pK information it provides but from the standpoint of efficacy since this is the only study that provides efficacy data with the 3<sup>rd</sup> generation product in COPD patients. Given that this development program was a switch program, the sponsor really only needed one pivotal 12-week efficacy study to establish efficacy therefore, the sponsor conducted an adequate number of studies to assess efficacy. The ideal situation was for the pivotal studies to have been conducted with the to-be-marketed formulation but this was not the case with this program. Therefore, the clinical implications of the changes that were made to the device during development would need to be taken into account in the assessment of the results of the clinical studies.

The patient population enrolled in the 3 pivotal studies were adults  $\geq 40$  years of age with a history of COPD. The mean age of the patients was  $\sim 65$  years and spirometric data at baseline confirmed that the majority of subjects had moderate to severe COPD. The mean % predicted FEV<sub>1</sub> across studies ranged between 38 – 40% and the mean % FEV<sub>1</sub>/FVC ranged between 46 – 54%. Over 90% of the population was white and 60 - 70% were male. This demographic is consistent with what is know about the predominance of the disease in the Caucasian male population and does not necessarily represent a flaw in the patient selection. Both efficacy studies were conducted with the 1<sup>st</sup> generation product and the one-year safety study was conducted with both the 1<sup>st</sup> and the 2<sup>nd</sup> generation products.

#### Efficacy

The 2 efficacy studies 244.1405 and 244.1408 were of similar design and had active-control (Atrovent® CFC) arms. Study 244.1405 also included a placebo control and was the larger (n = 507) of the two studies. Study 244-1405 was conducted in the U.S. Study 244.1408 randomized a smaller number (n =174) of patients and was conducted in the U.K. A separate one-year safety study (study 244.2453) was conducted in the U.S.A. and a total of 456 patients were randomized.

The 12-week efficacy studies demonstrated that Atrovent ® HFA was superior to placebo and comparable to Atrovent CFC as assessed by the FEV<sub>1AUC 0-6 hours</sub> (L) and peak FEV<sub>1</sub> (L). response The mean FEV<sub>1AUC 0-6 hours</sub> (L) on the final test day for HFA placebo was 0.018 L compared to 0.141 L for Atrovent® HFA ( p = 0.0001). Atrovent ® HFA had comparable FEV<sub>1</sub> results to Atrovent ® CFC in the two studies. In study 244.1405 a higher dose (84 mcg BID) of Atrovent ® HFA was also evaluated and no dose response was seen.

Efficacy data were also collected in the one-year long-term safety study. Atrovent HFA showed comparable efficacy to Atrovent CFC over the one-year period. Of interest is the fact that both the 1<sup>st</sup> and 2<sup>nd</sup> generation products were used in this one-year study. Although the sponsor could not separately analyze the data of the subjects who received each generation of product, the patients in the study were administered the products in such a manner that by Visit 4 all patients had switched over to the 2<sup>nd</sup> generation product. Therefore there are efficacy data from patients who have received up to 34 weeks of treatment with the 2<sup>nd</sup> generation product and these data demonstrate comparable efficacy as assessed by the FEV<sub>1</sub> AUC<sub>0-6</sub> hours (L). The FEV<sub>1</sub>AUC<sub>0-6</sub> hours (L) for these three clinical trials are shown below.

**Comparison of FEV<sub>1</sub> AUC<sub>0-6</sub> between the Three Pivotal Studies (Final Test Day)**

Endpoint	Treatment	Study 244.1405 liters (SEM)	Study 244.1408 liters (SEM)	Study 244.2453 liters (SEM)
FEV <sub>1</sub> AUC <sub>0-6</sub> (liters)	HFA-Placebo*	0.018 (0.021)	-----	-----
	Atrovent HFA 42 mcg QID	0.141 (0.014)	0.10 (0.01)	0.117 (0.010)
	Δ vs. placebo	0.123 L (p=0.0001)		
	Atrovent CFC 42 mcg QID	0.127 (0.014)	0.10 (0.02)	0.117 (0.014)

The data from the single-dose PK study 244.2498 showed that the bronchodilatory effect of Atrovent® HFA as measured by the mean FEV<sub>1</sub> AUC<sub>0-6</sub> hours was statistically significantly better than placebo (0.215 L Atrovent® HFA vs. 0.06 L placebo) and comparable to Atrovent® CFC (0.220 L). The effect size in this trial is numerically greater than what was observed in the pivotal studies primarily because the sponsor only enrolled patients who had a positive (> 15% improvement in FEV1) bronchodilator response to Atrovent®.

Safety

The adverse event profile of Atrovent ® HFA did not reveal any new adverse events of concern neither were there any safety signals that were of concern. Since Atrovent (ipratropium bromide) has been on the market for over 17 years, its safety profile is fairly well characterized. Therefore, in addition to the assessment of the overall safety of the product, the safety studies were designed to collect additional safety information that might be specifically related to the new formulation. The patient number and duration of exposure was adequate to assess safety.

A total of 1162 patients were exposed to Atrovent® HFA during the development program and of these 305 were exposed for one year. The most commonly reported adverse events across treatment groups were upper respiratory tract infection (23%), bronchitis (17%), COPD exacerbation (16%) dyspnea and sinusitis (7%) with a relatively similar frequency among individual treatment groups. These AEs are similar to AEs

reported in other COPD trials. The most commonly reported anticholinergic effects were dry mouth (3%) and constipation (2%). Other events such as urinary retention, worsening of narrow angle glaucoma, or tachycardia were reported infrequently or not at all. Paradoxical bronchospasm (defined as a decrease of greater than 15% in FEV<sub>1</sub> compared to baseline occurring within the first 30 minutes following drug administration) was assessed in the phase 3 trials. Paradoxical bronchospasm was reported more frequently in the placebo groups and more with HFA compared to the active treatment groups. However, there was no trend seen for the development of paradoxical bronchospasm with Atrovent® HFA. Additionally, the reported cases of paradoxical bronchospasm were not associated with symptoms or need for rescue medication. There were 21 deaths in the pivotal trials but none were related to Atrovent but rather reflected underlying disease states of the patient population. Likewise, serious adverse events were not drug-related.

### INTERDISCIPLINARY ISSUES

- Chemistry, Manufacturing and Controls

For a detailed review please refer to Dr. Prasad Pei's excellent CMC review. The main CMC issues with this product relate to the changes in the device made during development. Most of the changes occurred from the 1<sup>st</sup> to the 2<sup>nd</sup> generation product. These changes included (1) The valve stem material was changed from \_\_\_\_\_ (2) The inner diameter of the valve stem was reduced from \_\_\_\_\_ mm (3) The mouth piece actuator seat (where the valve stem sits) was changed to accommodate the smaller valve stem and (4) The stainless steel alloy for the aerosol container was changed \_\_\_\_\_ Throughout all these changes, the formulation remained the same. From the 2<sup>nd</sup> generation to the 3<sup>rd</sup> generation the sponsor attempted to optimize the product by \_\_\_\_\_ to minimize the leachables observed in the drug product.

As a result of these changes, differences in the particle size distribution were seen in the different products. From the Anderson Cascade PSD it was noted that the 3<sup>rd</sup> generation product had a higher percentage of fine particles (\_\_\_\_\_ deposited on the filter and a lower percentage of particles in the respirable fraction (\_\_\_\_\_ compared to the first generation product. However, the 2<sup>nd</sup> and 3<sup>rd</sup> generation products appear to have comparable particle size distribution (PSD) for all stages of the cascade impactor except the filter with the 3<sup>rd</sup> generation product having a higher percentage of particles deposited on the filter. It was also noted that the 3<sup>rd</sup> generation product delivered more active drug than the 1<sup>st</sup> or 2<sup>nd</sup> generation product. These PSD differences do not appear to have impacted the efficacy or safety of the drug product as evaluated in the clinical trials therefore, from a clinical standpoint, no additional clinical studies are warranted

However, there are other CMC issues that must be addressed prior to approval. Based on PSD findings there are serious stability issues that need to be resolved. It was noted that the amount of ipratropium bromide at various stages decreased significantly over time (\_\_\_\_\_. Several issues relating to the container closure system were communicated to the sponsor in an IR letter during the review cycle. Also, corrosion was

observed in two canisters when stored at 25/60 for — Several types and amounts of foreign particulates were found in the formulation which based on the sponsor's calculation could be as high as — per actuation. While it is not entirely unusual to find particulate material in MDIs the amount observed in this drug product appears to be very high. The clinical significance/relevance of this observation is unknown and it would be difficult (if not impossible) to design a clinical trial to evaluate this and the sponsor would be asked to characterize these particulate materials further.

- Clinical Pharmacology and Biopharmaceutics

For details of the clinical pharmacology and Biopharmaceutics, please see Dr. Sandra Suarez-Sharps- excellent review for details. All the PK studies were comparative studies between the HFA and CFC products. The PK studies conducted in healthy volunteers, demonstrated that the exposure to ipratropium bromide was higher in the CFC products compared to the HFA. Single dose and multiple dose (7 days) PK studies in COPD patients were conducted with the 3<sup>rd</sup> generation (to-be-marketed) product and revealed that the exposure to ipratropium bromide was lower in the HFA product compared to the CFC product as shown in the table below.

Parameter	Atrovent HFA 84 mcg	Atrovent CFC 84 mcg
<b>Single Dose</b>		
AUC <sub>0-6 hr</sub> ( pg*hr/mL)	196.8	269.4
C <sub>max</sub> (pg/mL)	58.9	92.7
<b>Multiple Dose</b>		
AUC <sub>0-6 hr</sub> ( pg*hr/mL)	265.1	359.5
C <sub>max</sub> (pg/mL)	82.1	101.8

Given this observation, one can expect better systemic safety with the 3<sup>rd</sup> generation product and since all the clinical studies included comparisons between the HFA and the CFC products a direct PK link between the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> generation Atrovent products is not needed.

- Preclinical pharmacology/toxicology

The sponsor did not submit any new preclinical data with this application and given that ipratropium bromide is an approved drug product and the HFA has already been studied, additional pre-clinical data were not required.

## CONCLUSIONS

Taken together, the efficacy and safety data support approval of Atrovent ® HFA. Although the pivotal studies were not conducted with the 3<sup>rd</sup> generation product, there are efficacy data from the 2<sup>nd</sup> generation product and the 3<sup>rd</sup> generation (albeit a single-dose study) that are supportive. From the PSD perspective, the 2<sup>nd</sup> generation and 3<sup>rd</sup> generation products are reasonably comparable and the changes made from the 2<sup>nd</sup> generation to the 3<sup>rd</sup> generation were mainly change of manufacturer ( the — 3 ; Overall these changes should not impact the efficacy of the drug product. Additionally, no new safety signals

were noted in the clinical trials and the systemic exposure of the 3<sup>rd</sup> generation product is lower compared to Atrovent CFC in COPD patients. Therefore, systemic safety of Atrovent ® HFA compared to CFC is not a concern.

RECOMMENDATIONS

NDA 21-527 is APPROVABLE. Additional clinical studies are not warranted but the CMC issues outlined in the CMC review need to be resolved before the product can be approved.

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Badrul Chowdhury  
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MEDICAL OFFICER  
I concur



## **I. Introduction**

Boehringer Ingelheim initially submitted an NDA for Atrovent HFA Inhalation Aerosol in December 2002. From a clinical standpoint, the data were adequate to support approval; however, due to several CMC issues, the application received an approvable action. On May 14, 2004, Boehringer Ingelheim submitted a complete response. This current submission is the Final Safety Update for this NDA at this time. This brief review summarizes this safety update.

## **II. Safety Update**

Atrovent HFA is approved in 60 countries as of April 1, 2004, with the most sales currently reported in Netherlands, Germany, and Australia. A Phase 4 safety study is scheduled to begin in the UK to support the approval of Atrovent HFA there. There are no other preclinical or clinical studies that are ongoing or planned at this time.

Since the cut-off date for the Four-Month Safety Update, March 1, 2003 through April 1, 2004, Boehringer Ingelheim received 4 spontaneous safety reports, describing events from post-marketing experience outside the U.S. (there were no deaths or SAEs reported). These events are briefly summarized below.

- 49 year old female with asthma complained that drug was ineffective
- 67 year old female with asthma complained of burning sensation on tongue, ear pain and balance disorder, and headache
- 84-year old female with asthma complained of burning sensation on lips and sensation of suffocation; Atrovent was used previously without similar complaints in the past; therapy was discontinued and symptoms resolved without any treatment
- 62 year old female with asthma/COPD complained of severe irritation in eyes, skin of the ace, and oral mucosa; was using "cortisone" spray concomitantly; symptoms did not resolve with discontinuation of treatment

*Reviewer's comments: Since these were spontaneous reports (from outside U.S.), very limited information was provided. There is insufficient information to establish causality. Additionally, symptoms could have been due to concomitant illnesses or medications. Review of these events does not warrant modification of the label that is currently under review.*

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**CLINICAL REVIEW**

NDA #21-527, Ipratropium bromide

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**MEDICAL OFFICER REVIEW**

**Division Of Pulmonary and Allergy Drug Products (HFD-570)**

<b>APPLICATION:</b> NDA #21-527	<b>TRADE NAME:</b> Atrovent® HFA
<b>APPLICANT/SPONSOR:</b>	<b>USAN NAME:</b> Ipratropium bromide
<b>MEDICAL OFFICER:</b> Tejashri Purohit-Sheth, MD, FACAAI	
<b>TEAM LEADER:</b> Lydia Gilbert-McClain, MD, FCCP	<b>CATEGORY:</b> Bronchodilator
<b>DUE DATE:</b> 9/25/03	<b>ROUTE:</b> Oral Inhalation

**RECOMMENDED REGULATORY ACTION**

<b>IND/NEW STUDIES:</b>	<input type="checkbox"/> SAFE TO PROCEED	<input type="checkbox"/> CLINICAL HOLD	
<b>NDA/SUPPLEMENTS:</b>	<input type="checkbox"/> FILEABLE	<input type="checkbox"/> NOT FILEABLE	
	<input type="checkbox"/> APPROVAL	<input checked="" type="checkbox"/> APPROVABLE	<input type="checkbox"/> NOT APPROVABLE
<b>OTHER ACTION:</b>			

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# CLINICAL REVIEW

NDA #21-527, Ipratropium bromide

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**CLINICAL REVIEW OF NDA # 21-527****EXECUTIVE SUMMARY****1. RECOMMENDATIONS****1.1. Recommendation on Approvability**

From a clinical standpoint, the data submitted in this NDA provide acceptable support for Approval. The data demonstrate that ipratropium bromide HFA inhalation aerosol 42 mcg four times a day provides statistically significant bronchodilation compared to placebo and comparable bronchodilation compared to the currently approved product ipratropium bromide inhalation aerosol with CFC propellants (Atrovent®) in patients with chronic obstructive pulmonary disease (COPD). The safety profile of ipratropium bromide HFA inhalation aerosol was acceptable and comparable to Atrovent®.

**1.2. Recommendation on Phase 4 Studies and/or Risk Management Steps**

No specific phase 4 studies or Risk Management steps are warranted for this product.

**2. SUMMARY OF CLINICAL FINDINGS****2.1. Background and Administrative Issues**

Ipratropium bromide is a quaternary ammonium derivative of atropine which functions as a bronchodilator by blocking the bronchoconstriction effects of acetylcholine. It is currently marketed in several formulations, to include a CFC metered-dose inhaler, a solution, and in combination with albuterol sulfate (Combivent® Inhalation Aerosol).

As CFC propellants are being phased out due to deleterious effects on the ozone layer, production of inhalation products that use CFC as propellants is to be ultimately banned in accordance with the agreements of the Montreal Protocol. To comply with this, the sponsor reformulated ipratropium bromide using hydrofluoroalkane (HFA) 134a propellant.

The drug development program for this product was discussed with the FDA in a pre-IND meeting in December 1992. The product was developed under IND 45, 938 which was opened on August 1, 1994. During development, the sponsor changed the delivery device so that three different generations of products were made. The three Phase III pivotal studies were performed using the 1<sup>st</sup> and 2<sup>nd</sup> generation products which are no longer available. The to-be-marketed product is the 3<sup>rd</sup> generation product. The main development changes were to the device with no changes made to the formulation and most of the changes occurred from the 1<sup>st</sup> to the 2<sup>nd</sup> generation device. The sponsor was unable to perform any bridging studies comparing the 1<sup>st</sup> and 2<sup>nd</sup> generation products to the 3<sup>rd</sup> generation product since the 1<sup>st</sup> and 2<sup>nd</sup> generation products were no longer manufactured. In a pre-NDA meeting with the Division on 6/26/02, the Division agreed that a single dose, dose-ranging study using the 3<sup>rd</sup> generation product would be acceptable in addition to a pharmacokinetic study

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evaluating single and multiple dose pharmacokinetic parameters using the 3<sup>rd</sup> generation product.

The sponsor submits this original NDA as a 505(b) 1 application for the prescription use of ipratropium bromide monohydrate (HFA-134a) inhalation aerosol (Atrovent® HFA Inhalation Aerosol). The proposed indication is the — maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The recommended dose is two inhalations four times a day. The labeled dose of each inhalation is 21 mcg of ipratropium bromide from the valve.

### 2.2. Brief Overview of Clinical Program

The sponsor submitted clinical study reports for 11 trials in this application: two 12-week phase III pivotal studies in COPD (244.1405 and 244.1408), one 1-year long-term safety study (244.2453) in COPD, one single dose efficacy and safety study in COPD patients (244.2498), two phase I PK studies in healthy volunteers (244.1401 and 244.1402), one phase II PK study in COPD patients (244.2480), a phase II single dose confirmation study (244.1403), a cumulative dose trial (244.1404), and two phase III 12-week trials in asthma (244.1407 and 244.1409).

As a result of changes in the drug delivery device, these clinical studies were performed with three different generations of Atrovent HFA drug product. With the exception of studies 244.2480 (3<sup>rd</sup> generation product) and 244.2498 (3<sup>rd</sup> generation product), all of the studies were performed using the 1<sup>st</sup> generation drug product. Additionally, in 244.2453, patients used both the 1<sup>st</sup> and 2<sup>nd</sup> generation products.

In these 11 clinical studies, a total of 1758 subjects were randomized, of which 1558 subjects (88.6%) completed the trials. A total of 1162 were randomized to Atrovent HFA (all doses) and 1047 (90.10%) completed the clinical trials. This was comparable to both placebo (91.27%) and Atrovent CFC (90.34%).

Conclusions regarding the efficacy of ipratropium bromide HFA were derived from three pivotal Phase III studies (244.1405, 244.1408 and 244.2453), and one Phase II dose confirmation study (244.2498). Study 244.1405 was a 12-week, randomized, double-blind, placebo and active controlled parallel group study in 507 COPD patients comparing Atrovent HFA 42 mcg to Atrovent HFA 84 mcg, Atrovent CFC 42 mcg and placebo. Study 244.1408 was a 12-week, randomized, double-blind, active controlled trial comparing Atrovent HFA 42 mcg to Atrovent CFC 42 mcg in 174 COPD patients. Study 244.2453 was an open label, randomized, active controlled trial comparing Atrovent HFA 42 mcg to Atrovent CFC 42 mcg as well, in 456 COPD patients. Study 244.2498 was a 5-treatment, multi-center, randomized, double-blind, single-dose, crossover trial in 41 COPD subjects designed to bridge the product (device/drug) used in the clinical Phase III clinical program to the proposed commercial product.

These studies enrolled males and females ages 40 years and older, with a history of COPD, a smoking history of  $\geq 10$  pack-years, an  $FEV_1 \leq 65\%$  and an  $FEV_1/FVC \leq 70\%$ . Patients with any significant disease other than COPD were excluded from study participation. The majority of the study population for the three pivotal studies and Study 244.2498 was

Caucasian (96%) with a mean age of 65.5 years. Males comprised 61% of the study population as compared to females (39.1%). The mean smoking history in pack-years ranged from 45.6 years to 71.9 years. The mean time to diagnosis of COPD across these studies ranged from 7.3 to 7.8 years. The mean FEV<sub>1</sub> ranged between 0.978 to 1.076 liters across studies, the mean FEV<sub>1</sub> percent predicted ranged from 38.9 to 40.4% of predicted, and the FEV<sub>1</sub>/FVC ranged from 46.7 to 48.1% across studies. Patients in these studies were adequately matched with the placebo and active comparators.

### 2.3. Efficacy

Efficacy conclusions were based on review of 3 pivotal Phase III clinical trials and one Phase II, single-dose, linking study. The primary support for efficacy was derived from the results of a 12-week, randomized, double-blind, placebo, and active-controlled study, Study 244.1405. Secondary supporting evidence is provided by a 12-week, randomized, double-blind, active-controlled study, 244.1408; a one-year, open-label, randomized, active-controlled safety study, 244.2453; and a single dose, dose confirmation study, 244.2498.

All of these studies demonstrated the efficacy of Atrovent HFA ipratropium bromide. In a 12-week, placebo and active controlled study (Study 244.1405), the sponsor demonstrated that the 1<sup>st</sup> generation Atrovent HFA 42 mcg product was efficacious compared to placebo ( $p < 0.0001$ ), and comparable to Atrovent CFC 42 mcg based on the primary efficacy endpoint FEV<sub>1</sub> AUC<sub>0-6</sub> and peak FEV<sub>1</sub> response. Study 244.1408, a second 12-week active controlled study, also supported the comparable efficacy of the 1<sup>st</sup> generation Atrovent HFA 42 mcg and CFC 42 mcg products. Study 244.2453 was a one-year, open-label active controlled study which supported both the efficacy of the 1<sup>st</sup> and 2<sup>nd</sup> generation products. In this study, after 18 weeks of treatment, all patients received the 2<sup>nd</sup> generation product; results from the final two visits, Week 26 and Week 52, corresponded to 8 and 34 weeks of treatment with the 2<sup>nd</sup> generation product, respectively. The sponsor assessed efficacy of the 3<sup>rd</sup> generation Atrovent HFA 42 mcg product in Study 244.2498. Although, this was a single-dose study, the data are valuable to support efficacy of the 3<sup>rd</sup> generation product. This study demonstrated that Atrovent HFA 42 mcg and CFC 42 mcg were statistically superior to placebo and comparable to one another for the pre-specified primary efficacy endpoint. Thus, the submitted studies provide short and long-term efficacy data for the 1<sup>st</sup> and 2<sup>nd</sup> generations, and short-term efficacy for the 3<sup>rd</sup> generation.

There is no direct evidence for long-term efficacy with the 3<sup>rd</sup> generation drug product. However, an indirect link for long-term efficacy can be derived from the pivotal studies which used the 1<sup>st</sup> and 2<sup>nd</sup> generation drug products. Efficacy was demonstrated at day one (following single doses) and at the final visit for all three of the pivotal studies, suggesting that there is no tachyphylaxis to the active ingredient. Although the device changed between the generations of products and the respirable fraction of drug was found to be higher in the 3<sup>rd</sup> generation, the formulation remained the same in the three generations of products. It would therefore be expected that the 3<sup>rd</sup> generation product should not demonstrate tachyphylaxis since this was not seen in the other generations indirectly supporting long-term efficacy for the third generation product.

In conclusion, the data submitted in this application to support the efficacy of the to-be-marketed 3<sup>rd</sup> generation Atrovent HFA product are acceptable and demonstrate superior

efficacy of Atrovent HFA as compared to placebo and comparable efficacy to the currently marketed Atrovent CFC MDI.

## 2.4. Safety

The safety data are derived from the two 12-week efficacy studies (244.1405, 244.1408) and an open-label, randomized multicenter one-year safety study. These trials were conducted with the 1<sup>st</sup> generation (Studies 244.1405, 244.1408, 244.2453) and the 2<sup>nd</sup> generation (Study 244.2453) Atrovent HFA 42 mcg products. Two studies (Studies 244.2498 and 244.2480) were conducted with the to-be-marketed 3<sup>rd</sup> generation Atrovent HFA 42mcg product. The former is a single-dose study and the latter is a 7-day pharmacokinetic study.

Adverse events were reported frequently in these studies, with 844 patients (74%) reporting at least one adverse event. Adverse events were reported in 432 patients (79%) in the Atrovent HFA 42 mcg group, in 257 patients (77%) in the Atrovent CFC 42 mcg group, in 63 patients (50%) in the Atrovent HFA 84 mcg group, in 44 patients (71%) in the placebo HFA group and in 48 patients (73%) in the CFC placebo treatment group.

The most commonly occurring AEs in the Atrovent 42 mcg group included upper respiratory tract infection (23%), bronchitis (17%), COPD exacerbation (16%), dyspnea (7%), sinusitis (7%), headache (6%), urinary tract infection (6%), and influenza like symptoms (6%). Occurring less frequently were household accident, pneumonia, rhinitis, coughing, pharyngitis, nausea, dry mouth, dyspepsia, and vomiting. The incidence of adverse events was comparable between Atrovent HFA 42 mcg and Atrovent CFC 42 mcg. When these adverse events were compared to Atrovent HFA 84 mcg, no dose response effect was noted.

Adverse events—as judged by the investigator—to be drug related, were reported in 104 patients (9%). The most common AEs judged to be treatment related in the Atrovent HFA 42 mcg were dry mouth (1.6%—compared to 0.9% in the Atrovent CFC 42 mcg group) and taste perversion (0.9%—compared to 0.3% in the Atrovent CFC 42 mcg group). Headache and coughing occurred in the Atrovent HFA 42 mcg treatment group less frequently (0.7%) as compared to the Atrovent CFC 42 mcg group, 1.5% for headache and 1.2% for coughing, respectively.

To evaluate for anticholinergic side effects, data from all Phase II and Phase III trials were pooled, in which, 200 patients (13%) reported at least one adverse event that may be considered to be an anticholinergic side effect. The most commonly reported of these events in the total study population were nausea (n=38, 2%), dry mouth (n=37, 2%) and constipation (n=30, 2%) and were similar in the Atrovent HFA and CFC treatment groups. Any other anticholinergic adverse events were rare (< 1% of the population). No dose response effect was observed for any anticholinergic adverse event when compared to placebo and Atrovent HFA 84 mcg.

There were a total of 21 deaths reported in the three pivotal studies (none were reported in any of the other 8 studies). Fourteen deaths occurred during the randomized treatment period, while seven occurred post-treatment. Of these 14 deaths, 9 (0.97%) were reported in the Atrovent HFA 42 mcg group, 3 (0.52%) in the Atrovent CFC 42 mcg group, 1 (0.45%) in the Atrovent HFA 84 mcg group, and 1 (0.60%) in the HFA placebo group. Pulmonary carcinoma was reported in five patients as the cause of death, COPD exacerbation was

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reported in four patients, and acute renal failure, pancreatitis, cardiac arrest, bronchitis, adenocarcinoma, gastro-intestinal disorder, abnormal renal function and respiratory insufficiency were each reported once as a cause of death. Given the study population and disease under study, the causes of death are not unexpected and these deaths are not felt by this reviewer to be treatment related.

Serious adverse events were reported by 145 patients (13%). The incidence of SAEs was similar between the Atrovent HFA 42 mcg group (79 patients, 14%) and Atrovent CFC 42 mcg (45 patients, 13%), and comparatively lower in the HFA placebo (7 patients, 11%) and Atrovent HFA 84 mcg (9 patients, 7%). The most frequently reported SAEs were COPD exacerbation (51 patients, 4%) and pneumonia (26 patients, 2%). In the Atrovent HFA 42 mcg, 23 patients (4%) reported COPD exacerbation and 15 patients (3%) reported pneumonia. Again no dose response effects were noted with comparison with Atrovent HFA 84 mcg. Again, given the study population and disease under study, these SAEs are not unexpected, and do not appear to be treatment related.

Consistent trends or changes attributable to Atrovent HFA 42 mcg were not noted in laboratory parameters, vital signs, physical examinations, or EKGs. Nor were there any consistent trends to suggest paradoxical bronchospasm with Atrovent HFA 42 mcg.

Subgroup analysis of AEs did not reveal any consistent or clinically meaningful differences between Atrovent HFA 42 mcg and CFC 42 mcg with respect to age, gender, or race. Analysis of drug-disease severity interaction revealed a rank ordering effect with respect to COPD exacerbations: with the percentage of patients reporting COPD exacerbations increasing with increasing disease severity; this finding was noted in both treatment groups and is not unexpected.

As most of the above safety information is from studies where the 1<sup>st</sup> and 2<sup>nd</sup> generation products of Atrovent HFA 42 mcg were utilized, safety information from the two studies using the 3<sup>rd</sup> generation product is also salient to this application, as they utilize the to-be-marketed product. The most commonly reported AEs in these studies were headache, diarrhea, skin rash, household accident and pancreatitis. No deaths were reported in these studies and two SAEs were reported: pancreatitis and respiratory failure. None of these are felt to be treatment related. No clinically meaningful changes in laboratory parameters, vital signs, or EKGs were noted in these studies.

Additionally, Study 244.2480 reveals that there is less systemic exposure to ipratropium bromide following 84 mcg of HFA-MDI than following 84 mcg of CFC-MDI. This is reassuring since less systemic exposure reduces the safety concern.

In conclusion, the safety assessments performed in the pivotal studies were satisfactory and Atrovent HFA 42 mcg was found to be safe when compared to the currently marketed Atrovent CFC 42 mcg product. However, it should be noted that the 3<sup>rd</sup> generation drug product has not been studied in any long-term trials, although there are two short-term trials (one single-dose and one 7-day PK study). Generally, to be assured of safety, a long-term safety study should be conducted; however, the PK studies reviewed demonstrate that the systemic exposure is lower in the 3<sup>rd</sup> generation HFA 42 mcg product compared to the currently marketed Atrovent CFC 42 mcg treatment group and therefore, it is doubtful that a long-term study with the 3<sup>rd</sup> generation product would reveal any significant safety concerns.

Executive Summary

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### 2.5. Dosing

The proposed dose of ipratropium bromide HFA inhalation aerosol in patients with chronic obstructive pulmonary disease is two puffs (42 mcg, 21 mcg per inhalation) four times a day. The proposed dose and dosing interval have been acceptably supported by the clinical studies submitted in this application. Furthermore, the sponsor has shown comparative safety and efficacy to the 42 mcg dose of the currently marketed Atrovent CFC MDI.

### 2.6. Special Populations

Pharmacokinetic parameters were compared for the geriatric population, >65 years of age with the <65 years of age. The results indicate that the pharmacokinetic behavior is comparable between the geriatric population and younger patients.

Subgroup analysis for both safety and efficacy were performed with respect to gender, age, and race. The applicant analyzed the adverse data for potential gender, age and race interactions; however, no consistent trends were noted with respect to gender or age. Since greater than 95% of the study population was White, subgroup analysis for race was not meaningful. Similarly, consistent trends for gender, age, and race with respect to efficacy were also absent.

The effect of hepatic or renal impairment has not been studied and is not warranted. Blood level and renal excretion studies show that ipratropium is not readily absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract. Atrovent HFA has not been studied in pregnant women; however, based on animal data no teratogenicity was observed with doses approximately 50 to 120 times the maximum recommended human daily inhalation dose. At approximately 2,900 times the maximum recommended human daily inhalation dose, embryotoxicity was observed. Based on the above, Atrovent HFA was classified as pregnancy category B.

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## CLINICAL REVIEW

### 1. INTRODUCTION AND BACKGROUND

#### 1.1. Introduction

This NDA is submitted to support the approval of Atrovent® HFA Inhalation Aerosol as a bronchodilator for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. Atrovent® (ipratropium bromide) is a quaternary ammonium derivative of atropine and functions as a bronchodilator by blocking the bronchoconstrictor effects of acetylcholine on bronchial smooth muscle. It is currently marketed in a metered dose inhaler (using the CFC propellant), solution formulation, and in combination with albuterol sulfate (COMBIVENT® Inhalation Aerosol).

Atrovent HFA Inhalation Aerosol was developed to replace the currently available Atrovent® CFC MDI. As part of the Montreal Protocol, products with CFC as the propellant are being phased out. To comply with the Montreal protocol, the sponsor developed this product as a "switch program" in keeping with the guidance in the FDA's 1994 *Points to Consider* document.

The sponsor submitted three Phase III pivotal studies to support the safety and efficacy of Atrovent HFA. Two twelve-week, randomized, double blind, parallel studies and an open-label, one-year long-term safety study. During development, the sponsor changed the valve in the delivery device twice such that three different generations of Atrovent HFA products have been evaluated. The three pivotal studies were performed using the 1<sup>st</sup> and 2<sup>nd</sup> generation products; however, the to-be-marketed product is the 3<sup>rd</sup> generation product. The sponsor was unable to directly compare the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> generation products since the 1<sup>st</sup> and 2<sup>nd</sup> generation products are no longer manufactured. This dilemma was discussed with the FDA and an agreement was reached that two additional studies using the 3<sup>rd</sup> generation product would be required. The sponsor submits two additional studies with the 3<sup>rd</sup> generation product: one single-dose, dose ranging, efficacy study and one single/multiple dose pharmacokinetic study.

#### 1.2. Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Atrovent® HFA Inhalation Aerosol is a pressurized meter-dose aerosol unit for oral inhalation that contains a solution of ipratropium bromide. Each actuation delivers 21 mcg of ipratropium bromide from the valve and — mcg from the mouth piece.

The proposed indication is as a bronchodilator for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. The proposed dose is two inhalations four times a day, not to exceed 12 inhalations in a 24 hour period. The indication section does not refer to any specific age group; however, COPD is a disease of adults and as such all of the pivotal

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studies were performed in patients  $\geq$  40 years of age. The clinical studies section should include this information.

### 1.3. State of Armamentarium for Indication(s)

Bronchodilators are the only currently approved drugs for COPD in the U.S.A. Currently available bronchodilators include several short acting beta<sub>2</sub>-agonists (e.g. albuterol, bitolterol, metaproterenol, pirbuterol, and terbutaline), long-acting beta<sub>2</sub> agonist (e.g. salmeterol and formoterol), the short-acting anti-cholinergic agent ipratropium and theophylline. These products are available in different formulations, including solutions and metered dose inhalers for oral inhalation, as well as various formulations for oral ingestion. Additionally, the short-acting beta<sub>2</sub>-agonist albuterol is available in combination with ipratropium as Combivent® inhalation aerosol. Currently, corticosteroids and mucokinetic agents are not approved for use in COPD in the U.S.A.

### 1.4. Important Milestones in Product Development

Ipratropium bromide is an approved drug substance under the following NDAs held by Boehringer Ingelheim Pharmaceuticals Inc.:

- NDA 19-085 Atrovent Inhalation Aerosol (CFC)
- NDA 20-393 Atrovent Nasal Spray 0.03%
- NDA 20-394 Atrovent Nasal Spray 0.06%
- NDA 20-228 Atrovent Inhalation Solution
- NDA 20-291 Combivent Inhalation Aerosol (CFC)

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The development plan for Phase II/III protocols were discussed with the FDA in a pre-IND meeting in December 1992. At this meeting, it was agreed that the sponsor would need the following to support the clinical comparability of Atrovent HFA to Atrovent CFC MDI: (1). A single-dose, dose-ranging study, (2). A single 12-week Phase 3 trial (placebo-controlled) in COPD patients, and (3). A 1-year safety study in COPD patients. The initial IND for Atrovent HFA was opened in August 1, 1994 under IND 45,938; however, it was placed on clinical hold for lack of Phase I data in healthy volunteers. It was removed from clinical hold on November 30, 1994. A CMC end of Phase II meeting was held with the FDA in September 1995 to discuss specifications, stability protocols, in vitro studies required to support changes in the valve and canister, extraction studies and HFA-134a impurity specifications.

After the Phase III clinical program was completed, a Type B meeting was held on May 26, 2000 to discuss the need for additional clinical studies, because of changes that had been made to the valve in the to-be-marketed device. At this meeting, it was agreed that the sponsor submit two additional clinical studies with the 3<sup>rd</sup> generation device: a phase I multiple-dose PK study comparing high doses of Atrovent HFA to "CFC (84 mcg) and a phase II single-dose, dose ranging study. Additionally, the FDA requested that the sponsor provide additional information regarding valve delivery and medication delivery for the 3<sup>rd</sup> generation product, particle size distribution, plume geometry and characterization of the \_\_\_\_\_ in the formulation. Clinical and CMC pre-NDA meetings were held on January 16, 2002 and March 27, 2002, respectively. [Vol. 1, P2] At the clinical pre-

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NDA meeting, it was agreed that the human PK and bioavailability program was complete and the FDA made some requests on how the information in the NDA should be organized. At the CMC pre-NDA meeting agreements were made regarding regulatory specifications, acceptance criteria for medication delivery, impurities testing, dose counter, and executive batch records.

The sponsor subsequently submitted this application on December 6, 2002 seeking approval for Atrovent HFA Inhalation Aerosol for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease.

### 1.5. Other Relevant Information

Atrovent HFA has been approved in 9 countries and is currently launched in 2 countries, outside of the United States. [Vol. 1, P.2] The sponsor states that there have been no withdrawals of marketing applications in any foreign country nor have there been any requests by health authorities for withdrawal or modifications of warnings and /or use section of the Summaries of Product Characteristics for any reason. [Vol. 1, P. 92]

### 1.6. Important Issues with Pharmacologically Related Agents

Ipratropium bromide (CFC) is a short-acting, anticholinergic bronchodilator that is manufactured by Boehringer Ingelheim and is approved for use in patients with COPD. It is currently marketed in a metered dose inhaler (using the CFC propellant), solution formulation, and in combination with albuterol sulfate (COMBIVENT® Inhalation Aerosol). Ipratropium bromide is also approved as a nasal spray. Ipratropium bromide has proven to be relatively safe in the COPD patient population. The product label for Atrovent Inhalation Aerosol states that the product should be used with caution in patients with narrow angle glaucoma, prostatic hypertrophy, or bladder neck obstruction. These precautions are based on the potential systemic anticholinergic effects of the drug, and cases of precipitation or worsening of narrow-angle glaucoma and acute eye pain have been reported. Cases of hypotension and allergic-type reactions have also been reported. Tiotropium is a long-acting, anticholinergic bronchodilator also manufactured by Boehringer Ingelheim. However, is awaiting FDA approval.

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## 2. CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

### 2.1. Chemistry, Manufacturing and Controls

Atrovent HFA Inhalation Aerosol has been formulated as a solution, in contrast to the currently available CFC-based formulation, which is a suspension. The solution contains the active ingredient ipratropium bromide monohydrate, citric acid, IFN-134a, dehydrated alcohol, and purified water. Ipratropium bromide 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. [Vol. 1, p. 36 and p. 106]

Atrovent HFA Inhalation Aerosol is a pressurized metered-dose aerosol unit for oral inhalation which yields 200 inhalations. The sponsor states that each actuation delivers 21 mcg of ipratropium bromide from the valve and 2 mcg from the mouth piece. However, the Division's chemistry reviewer, Dr. Prasad Peri, finds that the data support that 17 mcg is delivered from the mouth piece.

The drug substance will be manufactured at Boehringer Ingelheim Pharma KG, Germany; testing will be conducted in 3M pharmaceuticals will conduct testing of excipients, manufacture of bulk drug product, and testing of drug product (release and stability (except for tests for leachables). The sponsor will be responsible for testing canister mouthpiece (except extractable tests for canister), labeling the canister into final packaging into cartons, and as an alternate site for stability testing of drug product except leachables. The sponsor will test drug product for the impurity and the sponsor will perform extractives testing for the sponsor testing for stainless steel canisters, leachables testing of drug product, and will be an alternate site for the stability testing of drug product excel for [Vol. 1, P.6]

Several modifications to the ipratropium bromide HFA-MDI product were made during its development. The sponsor states that these changes in the container closure system were made to: (1). lower the levels of moisture that can leach into the formulation over time, (2). improve the compatibility of the aerosol canister, valve spring and valve stem with the formulation, and (3). improve the overall robustness of the product by enhancing the mechanical strength of the valve seals. [N-000-BM, 3/13/03; p 5]

These changes resulted in three different generations of Atrovent HFA products. The most significant change was between the 1<sup>st</sup> and 2<sup>nd</sup> generation product. The valve was changed to a stainless steel valve to decrease corrosion and maintain strength. The valve spring was changed to diminish corrosion. The valve stem components were changed to increase the compatibility of the container with the formulation. These changes resulted in a shift of the aerodynamic particle size distribution towards smaller particles.

The changes from 2<sup>nd</sup> to 3<sup>rd</sup> generation products were relatively minor. The biggest change occurred in the valve stem as a result of manufacturer change. These changes also resulted in a shift of the aerodynamic particle size

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distribution towards smaller particles — , however, when looking at the particle size distribution from the cascade impactor, the particle size was comparable between the 2<sup>nd</sup> and 3<sup>rd</sup> generation products, especially in the respirable fraction, except that there was a higher percentage of fine particles deposited on the filter in the 3<sup>rd</sup> generation product.

Despite these changes to the device, the formulation remained nearly identical across formulations. The significant changes to Atrovent HFA during product development are summarized in Table 1.

**Table 1. Development Summary of Product Changes**

	First Generation	Second Generation	Third Generation
<b>Pivotal Clinical Studies in COPD</b>	244.1405	244.2453	244.2480
	244.1408		244.2498
	244.2453		
<b>Aerosol Container:</b> Stainless Steel Alloy	canister	canister	canister
<b>Formulation</b>			
-net fill		/	
-net fill			
-ipratropium bromide monohydrate			
<b>Aerosol Valve</b>			
Description			
Nominal Metering Volume			
Valve Spring			
-manufacturer			
Valve Stem			
-manufacturer			
-material			
-inner diameter			
Valve			
Components			
-manufacturer			
-material			
-manufacturer			

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## 2.2. Animal Pharmacology and Toxicology

### 2.2.1. Pharmacology

This application does not contain any new non-clinical pharmacology information. Relevant information has been cross-referenced to the original Atrovent CFC application. [Vol. 1, p. 123]

Conclusions and Recommendations

**2.2.2. Toxicology**

The sponsor conducted comparative nonclinical toxicology and toxicokinetic experiments to demonstrate the comparability of the two product formulations (HFA and CFC) and thereby validate the use of existing ipratropium toxicology data. Additionally, experiments were conducted to assess the toxicological potential of ipratropium degradation products, a new excipient and its degradation products, extractive/leachables and residues associated with the new drug delivery system.

The results of these experiments reveal that the toxicologic and toxicokinetic profiles of Atrovent HFA and Atrovent CFC are the same. The sponsor has thus cross-referenced the original Atrovent CFC application for toxicology. Additionally, ipratropium and excipient degradation products, extractives, leachables, residues and particulates were not found to pose any toxicological risks for humans using this product. [Vol. 1, p 127]

**2.3. Microbiology**

Not applicable

**2.4. Statistics**

The information presented in this Medical Officer Review has been based on review of the efficacy data with Dr. Jim Gebert. See Dr. Jim Gebert's statistical review for further details.

**3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS****3.1. Previously Established Data**

The following information was reported in NDA 19-085 for Atrovent® CFC Inhalation Aerosol. Most of the administered dose is swallowed as shown by fecal excretion studies. Ipratropium bromide is not readily absorbed into the systemic circulation either from pulmonary vasculature or gastrointestinal tract exposure as demonstrated by blood level and renal excretion studies. The elimination half-life is about 2 hours after inhalation or intravenous administration. Ipratropium bromide is minimally bound (0-9% in vitro) to plasma albumin and alpha<sub>1</sub>-acid glycoprotein. It is partially metabolized to inactive ester hydrolysis products and following intravenous administration, approximately 50% of the dose is excreted unchanged in the urine. [Dr. Sandra Suarez's (Pharmacology and Biopharmaceutics Reviewer) NDA review, 21-527]

**3.2. Pharmacokinetic Data from this NDA**

As the container closure system for Atrovent HFA was optimized during development to improve its performance in the commercial phase, three different generations of products were made. However, the sponsor has not provided a PK link between the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> generation Atrovent HFA products. Based on the review of the three pharmacokinetic studies submitted in this NDA, this link is not necessary. The rationale stems from the fact that all of the PK studies and the clinical trials were comparative studies between Atrovent HFA and CFC.

The sponsor performed three pharmacokinetic studies to assess the relative systemic exposure to ipratropium bromide when delivered by HFA versus CFC propellants. Studies 244.1401 and 2444.1402 were Phase I studies conducted in healthy volunteers using the 1<sup>st</sup> generation product. These studies demonstrated that the systemic exposure to ipratropium bromide as measured by C<sub>max</sub> and AUC following Atrovent HFA 1<sup>st</sup> generation was significantly higher (up to 35-40%) compared to the systemic exposure following Atrovent CFC. Study 244.2480 was conducted in COPD patients using the 3<sup>rd</sup> generation (to-be-marketed) product. This study showed that the systemic exposure following administration of Atrovent HFA was up to 40% lower compared to the systemic exposure following administration of Atrovent CFC.

### 3.2.1. Study 244.2480

As this was the only study evaluating pharmacokinetics of the 3<sup>rd</sup> generation product in COPD patients, the important conclusions from this study will be summarized from Dr. Sandra Suarez's NDA Review.

Study 244.2480 was an open-label, two-treatment, randomized, crossover trial to determine the pharmacokinetic systemic exposure comparability of 84 mcg ipratropium bromide HFA-134a inhalation aerosol (HFA-MDI 84 mcg) and 84 mcg Atrovent® CFC Inhalation Aerosol (CFC-MDI 84 mcg) in patients with COPD. The study enrolled 30 patients with 29 patients with a mean age of 63.7 completing the study.

#### Clinical Pharmacology Outcomes

This section contains a brief review of the clinical pharmacology results. The reader is referred to Dr. S. Suarez's Clinical Pharmacology and Biopharmaceutics Review, NDA-21-527 for additional information.

Thirty patients were randomized to the study; however, the PK analysis included 29 subjects for the single-dose assessment and 28 subjects for the steady state assessment. [Vol. 91, p. 131]

For the primary PK specified endpoint, following single doses of study drug administration, the 24-hour urine collection contained an average of 5.1 mcg of unchanged ipratropium bromide following HFA-MDI administration and 6.6 mcg of unchanged ipratropium bromide following CFC-MDI administration. The difference of 1.5 mcg was not statistically significant between the two study treatments (p=0.1488). Although not statistically different, the urinary excretion tended to be lower following HFA-MDI as compared to CFC-MDI for the 24-hour urine collection, 0-1 hour urine collection at steady state, and 0-6 hour collection at steady state. [Vol. 91, p. 135, 136]

For the other secondary parameters, the systemic exposure was lower following HFA-MDI administration compared to CFC-MDI. The mean C<sub>max</sub> and total AUC were 36% and 27% lower, respectively, following single doses of HFA-MDI administration compared to CFC-MDI administration. The mean C<sub>max</sub> and total AUC were 19% and 26% lower, respectively, following multiple doses of HFA-MDI as compared to CFC-MDI. These results are summarized below in the following table.

Although there was a trend to a higher C<sub>max</sub> and AUC<sub>0-6</sub> values for patients older than 65 years, the differences were not deemed clinically significant and it was concluded that there is no age effect on PK following repeat doses of HFA-MDI. [Dr. Suarez's Clinical Pharmacology and Biopharmaceutics Review, NDA 21-527]

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The following table summarizes the mean pharmacokinetic parameters for ipratropium bromide following single and multiple dose of Atrovent HFA and Atrovent CFC.

**Table 2. Study 244.2480, Mean Pharmacokinetic Parameters For Ipratropium Bromide Following Single And Multiple Doses Of Atrovent HFA(3<sup>rd</sup> Generation Product) And Atrovent CFC Given At A Dose Of 84 µG Daily For One Week**

Parameter	HFA-MDI 84 µg	CFC-MDI 84 µg
<b>Single Dose</b>		
AUC <sub>0-6hr</sub> (pg*hr/mL)	196.8	269.4
Cmax (pg/mL)	58.9	92.7
<b>Multiple dose</b>		
AUC <sub>0-6hr</sub> (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

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### 3.2.2. Pharmacokinetic Conclusions

These studies demonstrate a lower systemic exposure to Atrovent HFA in the target population as compared to Atrovent CFC. In lieu of a direct PK link between the different generations of Atrovent HFA, this indirect link comparing the systemic exposure to Atrovent CFC is an acceptable alternative. In the clinical trials, Atrovent HFA and CFC demonstrated comparable safety, and this lower systemic exposure to Atrovent HFA as compared to CFC strengthens these clinical findings. As there are no long-term safety studies with the 3<sup>rd</sup> generation Atrovent HFA product, this finding of lower systemic exposure as compared to Atrovent CFC is reassuring.

## 4. DESCRIPTION OF CLINICAL DATA AND SOURCES

### 4.1. Sources of Clinical Data

The clinical data submitted in support of this NDA are derived from the studies performed as part of the Applicant's development program from Section 8, volumes 45-94 of this NDA. The application does not rely on any reports in the medical literature or other sources of data.

### 4.2. Overview of Clinical Trials

This submission contains 11 controlled studies, 2 are Phase I, 4 are Phase II, and 5 are Phase III. Of the Phase III studies, 3 are conducted in COPD patients, and 2 are conducted in asthmatics. Note that Boehringer Ingelheim is not seeking an indication for asthma.

The 11 studies are outlined in the following two tables, Summary of Pivotal Studies, and Summary of Supporting Studies.

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**Table 3. Summary of Pivotal Studies**

Study	Design	Treatment	Patients	Evaluations
244.1405 (US)	Phase III, 12-week, multicenter, randomized, parallel group, double-blind, placebo and active controlled trial in COPD patients age $\geq$ 40 years  1 <sup>st</sup> generation product used.	Atrovent HFA 21 mcg: 2 puffs QID Atrovent HFA 42 mcg: 2 puffs QID Atrovent CFC 21 mcg: 2 puffs QID 2 Placebos	507  (602 screened)	<u>Primary Efficacy</u> • FEV <sub>1</sub> AUC <sub>0-6</sub> • Peak FEV <sub>1</sub> Response  Safety Assessments
244.1408 (UK)	Phase III, 12-week, multicenter (16), randomized, double-blind, parallel, active controlled trial in COPD patients age $\geq$ 40 years  1 <sup>st</sup> generation product used	Atrovent HFA 21 mcg: 2 puffs QID Atrovent CFC 21 mcg: 2 puffs QID	174 (number screened not mentioned)	<u>Primary Efficacy</u> • Pre-dose weekly mean of am and pm PEFrs  • PEFR analysis during run-in period and the randomized period  • Safety Assessments
244.2453 (US)	Phase III, 1-year safety, multi-center (19), randomized, open-label, parallel group, active controlled study in COPD patients age $\geq$ 40 years  1 <sup>st</sup> and 2 <sup>nd</sup> generation products used	Atrovent HFA 21 mcg: 2 puffs QID Atrovent CFC 21 mcg: 2 puffs QID	456  (516 screened)	<u>Primary Endpoint</u> Safety  <u>Secondary Efficacy Endpoints</u> • FEV <sub>1</sub> AUC <sub>0-6</sub> • FEV <sub>1</sub> Peak change from test day baseline

**Table 4. Summary of Supporting Studies**

	Design	Dosage	Patients	Evaluations
244.1401 (Germany)	Phase I, double-blind, placebo controlled, 3-period crossover, safety and tolerability, PK trial in healthy volunteers ( 6 males and 6 females) age > 21 years; treatment duration of 7 days  1 <sup>st</sup> generation product used	Atrovent HFA 40 mcg: 4 puffs QID Atrovent CFC 20 mcg: 4 puffs QID Placebo HFA	12	• Airway Resistance  • PK  • Safety
244.1402 (Germany)	Phase I, double-blind, 4-way crossover, placebo and active controlled, single dose, pharmacokinetic and safety study in healthy volunteers >21 years of age; treatment duration is 1 day.  1 <sup>st</sup> generation product used	Atrovent HFA 20 mcg: 2 puffs Atrovent HFA 40 mcg: 2 puffs HFA placebo Atrovent CFC 20 mcg:	12	• PK  • Safety

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	Design	Dosage	Patients	Evaluations
		2puffs		
244.1403 (US)	Phase II, randomized, cross-over, double-blind, active and placebo-controlled, balanced incomplete block design dose confirmation study in COPD patients age $\geq$ 40 years; single test doses were administered on each of 4 test days.  Each patient received 4 of the 7 treatments, and 40 patients were to receive test doses of each treatment 1 <sup>st</sup> generation product used	Atrovent HFA 10.5 mcg: 2 puffs Atrovent HFA 21 mcg: 2 puffs Atrovent HFA 42 mcg: 2 puffs Atrovent CFC 10.5 mcg: 2 puffs Atrovent CFC 21 mcg: 2 puffs Placebo HFA Placebo CFC	70	<u>Primary Efficacy</u>  • FEV <sub>1</sub> AUC <sub>0-4</sub> change from baseline  Safety
244.1404 (France)	Phase II, randomized, double-blind, active controlled, 1 period cross-over, cumulative dose-response study in COPD patients age $\geq$ 40 years; treatment duration of 1 day 1 <sup>st</sup> generation product used	Atrovent HFA 20 mcg: *T0: 1 puff T50: 1 puff T100: 2 puffs T150: 4 puffs T200: 8 puffs  Atrovent CFC 20 mcg: same as for Atrovent HFA  *T= at Time in mins.	31	<u>Primary Efficacy</u>  • Change from baseline in FEV <sub>1</sub> to 45 mins after last dose  Safety
244.2498 (US)	Phase II, multicenter, double-blind, single-dose, crossover, active and placebo controlled comparability study in COPD patients $\geq$ 40 years 3 <sup>rd</sup> generation product used	Five, single dose treatments of: Atrovent HFA 21 mcg Atrovent HFA 42 mcg Atrovent CFC 21 mcg Atrovent CFC 42 mcg Placebo for HFA and CFC	41	<u>Primary Efficacy Endpoint</u>  • Average FEV <sub>1</sub> response calculated as AUC <sub>0-6</sub> compared to baseline  Safety
244.2480 (US)	Phase II, randomized, open-label, 2-treatment, cross-over pharmacokinetic trial in COPD patients age $\geq$ 40 years; duration of 1 week for each treatment 3 <sup>rd</sup> generation product used	Atrovent HFA 21 mcg: 4 puffs QID days 2-7 (after single dose on day 1) Atrovent HFA 21 mcg: 4 puffs QID days 2-7 (after single dose on day 1)	30	• PK • Safety
244.1407 (UK)	Phase III, 12-week, multi-center, randomized, parallel group, active controlled trial in asthmatics aged 18-65 years. 1st generation product used	Atrovent HFA 21 mcg: 2 puffs QID Atrovent CFC 21 mcg: 2 puffs QID	234	<u>Primary Endpoint</u>  • Safety  <u>Secondary Endpoint</u>  • Change from baseline in FEV <sub>1</sub> AUC <sub>0-6</sub>

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	Design	Dosage	Patients	Evaluations

### 4.3. Postmarketing Experience

As Atrovent HFA has not been approved in the U.S., there is no U.S. post-marketing information available. However, Atrovent HFA has been approved in 9 countries and is currently launched in 2 countries, outside of US (Germany and Netherlands). [Vol. 1, P.2] Countries where Atrovent HFA is currently approved are: Belgium/Luxembourg, Denmark, Finland, Germany, Greece, Netherlands, Spain, Switzerland, and Japan.

The sponsors state that there have been no withdrawals of marketing applications in any foreign country nor have there been any requests by health authorities for withdrawal or modifications of warnings and /or use section of the Summaries of Product Characteristics for any reason. [Vol. 1, P. 92]

### 4.4. Literature Review

The sponsor has submitted references for seven publications based on six clinical studies that were conducted in the clinical development program. This reviewer has briefly reviewed these and has not identified any safety or efficacy concerns. The conclusions for these were that Atrovent HFA 42 mcg is comparable in efficacy and safety to Atrovent CFC 42 mcg. [Vol. 45, p. 150-153]

This reviewer also performed a Medline search using *Atrovent HFA* and the following three publications resulted and were briefly reviewed. The *Taylor et al* has been submitted by the sponsor. These publications also conclude that the HFA product is comparable to the CFC product in terms of safety and efficacy; however, both Huchon et al and Maesen et al, <sup>1</sup>state

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1. Taylor et al. Ipratropium Bromide HFA Study Group. Ipratropium bromide hydrofluoroalkane inhalation aerosol is safe and effective in patients with COPD. *Chest*. 2001 Oct; 120(4):1253-61.

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that more patients complained of taste perversion with the HFA product as compared to the CFC product. This is most likely secondary to the HFA component.

### 5. CLINICAL REVIEW METHODS

#### 5.1. Conduct of the Review

This NDA contains data from 11 clinical trials to support the safety and efficacy of Atrovent HFA for the indication of bronchospasm associated with chronic obstructive disease, including chronic bronchitis and emphysema. The appendix to this NDA review contains the reviews for 8 of the 11 studies. Studies 244.1403 and 244.1404 were omitted as they were single-dose, Phase II studies that would not offer any additional useful information in support of the application. Study — was omitted —

Conclusions regarding the efficacy of ipratropium bromide HFA were derived from three pivotal Phase III studies, one Phase II dose confirmation study, and CMC data comparing the different generations of drug products developed for ipratropium bromide HFA. Efficacy review focused on the indirect and direct links to establish efficacy of the third generation product.

Conclusions regarding safety were based on the eight reviewed clinical studies, focusing on the three Phase III pivotal studies and the two studies using the 3<sup>rd</sup> generation Atrovent HFA 42 mcg product (244.2498 and 244.2480). In some cases the pooled results from all Phase II and Phase III studies were reviewed in the ISS. Each pivotal study was reviewed individually and discussed with the Medical Team Leader. During the review, input was obtained from the primary reviewer of each of the disciplines involved in the review – namely CMC (Dr. Prasad,) Biopharm (Dr. Suarez-Sharp) and Biostatistics (Dr. Jim Gebert).

#### 5.2. Materials Consulted and Documentation

This Medical Officer Review is based on the materials submitted in the original NDA submission, various General correspondence submitted by the Applicant as a response to the Division's request for specific information, and review of relevant information from CMC, Biopharmaceutics and Statistics.

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2. Huchon et al. Comparison of the safety of drug delivery via HFA- and CFC-metered dose inhalers in CAO. *Eur Respir J.* 2000 Apr; 15(4):663-9.
  3. Maesen et al. Therapeutic equivalence of a novel HFA 134a-containing metered-dose inhaler and the conventional CFC inhaler (Berodual) for the delivery of a fixed combination of fenoterol/ipratropium bromide. A randomized double-blind placebo-controlled crossover study in patients with asthma. *Respiration.* 1997; 64(4):273-80.

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**5.3. Data Quality and Integrity**

At the filing and planning meeting for this NDA it was agreed that a DSI audit was not needed. The active ingredient ipratropium bromide has been previously approved and the HFA product is for the same indication as the approved CFC product. None of the investigators involved in the study were subject of a "for cause" inspection. Boehringer Ingelheim is a privately owned company and is not publicly traded, and as such there were no financial disclosures that would necessitate an audit.

**5.4. Ethical Standards**

Boehringer Ingelheim certified that it did not and would not use the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b)] of the Federal Food, Drug and cosmetic Act in connection with Atrovent® HFA Inhalation Aerosol. [Vol. 1, p. 274]

Furthermore, all U.S. studies in this NDA were conducted in compliance with the rule and regulations specified in Title 21 CFR part 50 for Informed Consent regulations and Part 56 for Institutional Review Boards Regulations. In addition, trials were conducted in accordance with the Declaration of Helsinki. Prior to participation in each study, each patient/subject provided written informed consent. [Vol. 45, p. 21]

**5.5. Financial Disclosure**

Boehringer Ingelheim Pharmaceuticals, Inc. is a subsidiary of Boehringer Ingelheim GmbH. This is a privately held company that is not publicly traded on any stock exchange, has no equity available to investigators and state that they do not provide compensation to investigators based on the outcome of studies. No investigators can own a proprietary interest in a product or trademark, licensing agreement or patent owned by the company. Of the 11 studies, only two were conducted as of February 2, 1999 that would be covered by the Financial Disclosure Rule (21 CFR 54). Of all of the disclosure forms returned, there were no investigators that had any financial disclosures; however, there were 3 sub-investigators who did not return the appropriate disclosure forms. Boehringer Ingelheim certifies, based on invoice payment records, that none of these investigators received any grants that exceeded \$25,000. Prior to February 2, 1999, there were 3 COPD efficacy studies and 2 dose-confirmation studies that would also be covered by 21 CFR 54; however, Boehringer Ingelheim certifies that no investigators had any disclosable financial arrangements with them.

**6. INTEGRATED REVIEW OF EFFICACY****6.1. Brief Statement of Conclusions**

Efficacy conclusions were based on review of 3 pivotal Phase III clinical trials and one Phase II, single dose, linking study. The primary support for efficacy was derived from the results of a 12-week, randomized, double-blind, placebo, and active-controlled study, Study 244.1405. Secondary supporting evidence is provided by a 12-week, randomized, double-blind, active-controlled study, 244.1408; a one-year, open-label, randomized, active-controlled safety study, 244.2453; and a single dose, dose confirmation study, 244.2498.

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All of these studies demonstrated efficacy of Atrovent HFA ipratropium bromide; however, the three pivotal studies were conducted with the first generation Atrovent HFA ipratropium product, whereas, the to-be-marketed product is the third generation product. The single-dose, dose confirmation study, 244.2498, is the only study that provides direct efficacy data with the third generation product. Indirect linking for the efficacy of the 3<sup>rd</sup> generation product is demonstrated in two ways: an in vitro link between the 2<sup>nd</sup> and 3<sup>rd</sup> generation products, and a single dose study comparing the efficacy of the 3<sup>rd</sup> generation product to the currently available Atrovent CFC ipratropium bromide drug product.

Indirect linking of the efficacy from the first generation product to the second generation product is derived from the one year safety study, 244.2453. In this study, subjects received both the first generation and the second generation products. Although the first generation product is quite different from the third generation product, the second generation product is fairly similar to the third generation product. In vitro comparisons between the three generations reveal that the amount of active drug delivered per actuation in milligrams is higher for the third generation product as compared to the first and second generation products; however, the quantity of drug in the  $\mu\text{g}$  range is lower for the third compared to the first, and fairly similar between the second and third generation products. Since subjects received the 2<sup>nd</sup> generation product for 30 weeks in the one year safety study—the results of which demonstrated efficacy of the 2<sup>nd</sup> generation product—and since the 3<sup>rd</sup> generation and 2<sup>nd</sup> generation products are fairly comparable, it is reasonable to conclude that the efficacy for the 3<sup>rd</sup> generation product is supported.

Direct evidence for efficacy of the 3<sup>rd</sup> generation product was demonstrated by study 244.2498; however, this was a single dose study. The 3<sup>rd</sup> generation product demonstrated comparable efficacy to the currently marketed Atrovent CFC product following single doses of drug. However, there is no direct evidence for long-term efficacy with the 3<sup>rd</sup> generation drug product. Again, an indirect link for long-term efficacy can be derived from the pivotal studies which used the 1<sup>st</sup> and 2<sup>nd</sup> generation drug products. Efficacy was demonstrated at day one (following single doses) and at the final visit for all three of the pivotal studies, suggesting that there is no tachyphylaxis to the active ingredient. Although changes in the device affected drug delivery to some extent, the formulation is the same in the three generations of products. It would therefore be expected that the 3<sup>rd</sup> generation product would not demonstrate any tachyphylaxis either, indirectly supporting long-term efficacy for the third generation product.

### 6.2. General Approach to the Efficacy Review

Conclusions regarding the efficacy of ipratropium bromide HFA were derived from three pivotal Phase III studies, one Phase II dose confirmation study, and CMC data comparing the different generations of drug products developed for ipratropium bromide HFA. These studies included two pivotal Phase III studies, Studies 244.1405 and 244.1408, and one single dose, dose confirmation study, Study 244.2498. These studies are outlined below.

**Table 5. Summary of Studies Reviewed Supporting Efficacy**

Study	Design	Treatment	Patients	Evaluations
244.1405	Phase III, 12-week, multicenter, randomized, parallel group, double-	Atrovent HFA 21 mcg: 2 puffs QID	507 (602)	Primary Efficacy • FEV <sub>1</sub> AUC <sub>0-6</sub>

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Study	Design	Treatment	Patients	Evaluations
(US)	blind, placebo and active controlled trial in COPD patients age $\geq$ 40 years	Atrovent HFA 42 mcg: 2 puffs QID Atrovent CFC 21 mcg: 2 puffs QID 2 Placebos	screened)	<ul style="list-style-type: none"> <li>• Peak FEV<sub>1</sub> Response</li> </ul> Safety Assessments
244.1408 (UK)	Phase III, 12-week, multicenter (16), randomized, double-blind, parallel, active controlled trial in COPD patients age $\geq$ 40 years	Atrovent HFA 21 mcg: 2 puffs QID Atrovent CFC 21 mcg: 2 puffs QID	174 (number screened not mentioned)	<u>Primary Efficacy</u> <ul style="list-style-type: none"> <li>• Pre-dose weekly mean of am and pm PEFRs</li> <li>• PEFr analysis during run-in period and the randomized period</li> </ul> <ul style="list-style-type: none"> <li>• Safety Assessments</li> </ul>
244.2453 (US)	Phase III, 1-year safety, multi-center (19), randomized, open-label, parallel group, active controlled study in COPD patients age $\geq$ 40 years	Atrovent HFA 21 mcg: 2 puffs QID Atrovent CFC 21 mcg: 2 puffs QID	456 (516 screened)	<u>Primary Endpoint</u> Safety <u>Secondary Efficacy Endpoints</u> <ul style="list-style-type: none"> <li>• FEV<sub>1</sub> AUC<sub>0-6</sub></li> <li>• FEV<sub>1</sub> Peak change from test day baseline</li> </ul>
244.2498 (US)	Phase II, multicenter, double-blind, single-dose, crossover, active and placebo controlled comparability study in COPD patients > 40 years	Five, single dose treatments of: Atrovent HFA 21 mcg Atrovent HFA 42 mcg Atrovent CFC 21 mcg Atrovent CFC 42 mcg Placebo for HFA and CFC	41	<u>Primary Efficacy Endpoint</u> <ul style="list-style-type: none"> <li>• Average FEV<sub>1</sub> response calculated as AUC<sub>0-6</sub> compared to baseline</li> </ul> <u>Safety</u>

During the development of Atrovent HFA, the sponsor changed the delivery device two times. The two 12-week pivotal studies (Studies 244.1405 and 244.1408) were done with the first generation product and the one-year safety (Study 244.2453) study was done using both the first and second generation products. There is only one study (Study 244.2498) utilizing the 3<sup>rd</sup> generation product to provide efficacy for the to-be-marketed product. Efficacy review will focus on the indirect and direct links to establish efficacy for the third generation product.

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### 6.3. Description of Trials

#### 6.3.1. Overview

Three phase III pivotal studies and one single-dose study were submitted to support efficacy. Study 244.1405 was a 12-week randomized, double-blind, placebo and active controlled parallel group trial; Study 244.1408 was a 12-week randomized, double-blind, active controlled, parallel group trial; Study 244.2453 was a 1-year open-label, randomized, active controlled, parallel group safety study; and Study 244.2498 was a randomized, double-blind, placebo, and active controlled, single dose study using the 3<sup>rd</sup> generation Atrovent HFA product. The protocols are briefly summarized below and the results will be discussed in the next section, Section 6.4.

#### 6.3.2. Study #244.1405, Multiple Dose Comparison of Ipratropium Bromide HFA-134a and Ipratropium Bromide CFC in a 12-week, Double-Blind, Parallel Group Study in Adults with Chronic Obstructive Pulmonary Disease (COPD)

This was a 12-week, randomized, double-blind, parallel-group, placebo and active-controlled, multi-center study evaluating the efficacy and safety of ipratropium bromide HFA-134a vs. ipratropium bromide CFC and placebo in 507 adults with chronic obstructive pulmonary disease (COPD), conducted in the United States. This study consisted of 8 total visits, to include a screening visit, followed by a two-week baseline period. During this baseline period, all screened subjects received open label Atrovent® Inhalation Aerosol (CFC-MDI, two puffs, 21 mcg, four times a day). After this baseline period, 507 eligible patients were randomized to receive either ipratropium bromide HFA 42 mcg (two puffs, 21 mcg, each), ipratropium bromide HFA (84 mcg (two puffs, 42 mcg each), placebo HFA, ipratropium bromide CFC 42 mcg (two puffs, 21 mcg each) or placebo CFC QID for twelve weeks. [Vol. 61, p. 27] Patients were eligible if they had a history of COPD (defined as an  $FEV_1 \leq 65\%$  of predicted and a  $FEV_1/FVC \leq 70\%$ ), a smoking history of  $\geq 10$  pack-years, and age  $\geq 40$  years. Subjects were randomized in a 2:1 ratio between active treatment and placebo in blocks of eight. Subjects returned on Days 15, 29, 43, 57, 71, and 85 for follow up (every two weeks). Eight-hour pulmonary function testing was conducted on days 1, 29, 57, and 85 at the following intervals: pre-treatment, 15, 30, 60, and 90 minutes, and 2, 3, 4, 5, 6, 7, and 8 hours post-dose. At the final visit, day 85, laboratory tests, and EKGs, in addition to PFTs were repeated.

The primary efficacy endpoints were  $FEV_1$  AUC<sub>0-6</sub> and Peak  $FEV_1$  response. Secondary efficacy endpoints were  $FEV_1$  AUC<sub>0-4</sub>,  $FEV_1$  AUC<sub>4-6</sub>,  $FEV_1$  AUC<sub>6-8</sub>, onset of 15% increase from baseline in  $FEV_1$ , duration of 15% increase from baseline in  $FEV_1$ , time to peak  $FEV_1$  change from baseline,  $FEV_1$  changes from test-day baseline at each timepoint,  $FEV_1$  total area under the curve, FVC AUC<sub>0-4, 0-6, 4-6, 6-8</sub>, and peak response and changes from baseline at each timepoint, Physician's global evaluation, COPD symptom scores (wheezing, shortness of breath, coughing and tightness of chest), and rescue albuterol use. The sponsor did not specify a specific timepoint as the primary endpoint; however, the sponsor assessed these endpoints on Days 1, 29, 57, and 85.

**6.3.3. Study #244.1408. A Multiple Dose Comparison of Ipratropium Bromide HFA-MDI and Atrovent® MDI in a 12-week, Double-Blind, Parallel Group Study in Patients with Chronic Obstructive Pulmonary Disease (COPD)**

This was a 12-week, randomized, double-blind, parallel-group, active-controlled, multicenter comparison study evaluating the efficacy and safety of ipratropium bromide HFA-134a vs. ipratropium bromide CFC in 174 adults with chronic obstructive pulmonary disease (COPD), conducted in the United Kingdom. Following an initial screening visit (Visit 1), patients entered a two-week run-in phase where patients took two puffs four times a day of ATROVENT®-MDI (CFC). At the end of this period, patients who continued to meet inclusion criteria (age 40 years and older, history of COPD—defined as an  $FEV_1 \leq 65\%$  of predicted and a  $FEV_1/FVC \leq 70\%$ , and a smoking history of 10 pack-years or greater) and were stable on allowed concomitant therapy were randomized to either ipratropium bromide HFA-21 mcg (HFA-MDI) or ipratropium bromide CFC-21 mcg (CFC-MDI)—two puffs four times daily for 12 weeks. Patients had five more follow up visits (Visits 2, 3, 4, 5, and 6) after the start of the study. On Visits 2, 4, and 6, PFTs and vitals were measured, in addition to review of AEs, concomitant medications and diary data. On visits 3 and 5, PFTs were not performed; however, review of adverse events, concomitant medications, and diary card data were done. Pulmonary Function Testing was measured pre-dose and at 5, 15, 30, 60, 90, and 120 minutes after inhalation of two puffs of study medication and at hourly intervals thereafter for a total of six hours. [Vol. 71, p. 53]

The primary efficacy endpoints were pre-dose weekly mean of morning and evening PEFRs and PEFR analyzed during the run-in period and the randomized period (switch-effect). Secondary efficacy endpoints were  $FEV_1$  AUC<sub>0-6</sub>: area under the curve for 0-6 hours for  $FEV_1$ , peak bronchodilatory response:  $FEV_1$  max, onset and duration of therapeutic response, time to  $FEV_1$  max, FVC AUC<sub>0-6</sub> and FVC max, changes from baseline at all timepoints for  $FEV_1$  and FVC.

**6.3.4. Study #244.2453. One-Year Safety-In-Use Study of Ipratropium Bromide HFA-134a in Adults with Chronic Obstructive Pulmonary Disease (COPD)**

This was a 52-week, randomized, open-label, active controlled, multi-center long term safety study in 456 patients 40 years and older with COPD, conducted in the United States, evaluating the long-term safety of ipratropium bromide monohydrate HFA-134a as compared to Atrovent® CFC-MDI. The study consisted of a screening visit (Visit 0) at which time a physical examination, laboratory tests, and a 12-lead EKG were conducted. This was followed by a two-week baseline period during which patients were asked to take two puffs of Atrovent® Inhalation Aerosol (CFC-MDI) four times a day. Eligible patients—aged 40 years and older, a diagnosis of COPD (defined as an  $FEV_1 \leq 65\%$  of predicted and a  $FEV_1/FVC \leq 70\%$ ), and a smoking history of 10 pack-years or greater—were randomized (Day1) in a 2:1 manner to receive 2 puffs four times a day for 52- weeks of either Atrovent HFA or Atrovent CFC. After randomization, subjects had an additional 6 follow up visits. Pulmonary Function Testing was performed at the screening visit, Visits 1, 3, 5, and 7, corresponding to Days 1, Weeks 12, 26 and 52 of treatment. Pulmonary Function Testing was measured pre-dose and at 5, 15, 30, 60, 90, and 120 minutes after inhalation of two puffs of study medication and at hourly intervals thereafter for a total of six hours. Patients

were required to record their peak flow measurements each morning prior to morning medication, recording the best of three blows.

Since this was an open-label one-year safety study, safety was the primary endpoint in the study. However, efficacy was evaluated using the following variables (for spirometry). Assessments were done at Visits 1, 3, 5 and 7):

- FEV<sub>1</sub> AUC 0-6 hours (FEV<sub>1</sub> AUC<sub>0-6</sub>)
- FEV<sub>1</sub> AUC 0-4 hours (FEV<sub>1</sub> AUC<sub>0-4</sub>)
- FEV<sub>1</sub> peak change from test day baseline
- FEV<sub>1</sub> onset of therapeutic response
  - Therapeutic response was defined as those FEV<sub>1</sub> measurements exceeding 15% of test day baseline. Onset and duration of a 15% increase from baseline are clinically important descriptors of therapeutic response.
- FEV<sub>1</sub> duration of therapeutic response
- FEV<sub>1</sub> time to peak (change from test day baseline) response
- FEV<sub>1</sub> response at each timepoint (changes from test day baseline)
- FEV<sub>1</sub> Total area under the curve 0-6 hours (TAUC<sub>0-6</sub>)
- FVC AUC from 0-4 hours (FVC AUC<sub>0-4</sub>)
- FVC AUC<sub>0-6</sub>
- FVC peak change from test day baseline and change from test day baseline at each timepoint
- Physician's global evaluation
- COPD symptom score
- PEFrs

**6.3.5. Study 244.2498. A Single-Dose, Double-Blind, Crossover Trial to Determine the Comparability of Ipratropium Bromide HFA-134a Inhalation Aerosol to the Market Standard, ATROVENT® CFC Inhalation Aerosol, in Patients with Chronic Obstructive Pulmonary Disease (COPD)**

This was a 5-treatment, multi-center, randomized, double-blind, single-dose, crossover trial of 41 male and female patients 40 years and older with chronic obstructive pulmonary disease, designed to bridge the product (device/drug) used in the clinical Phase III clinical program to the proposed commercial product. [Vol. 90, p. 4, 17, 19] The study consisted of six total visits including the screening visit. Following an initial screening visit, 41 eligible patients were randomized into the study. Patients received one of the five treatments on each test day in a randomized, crossover design. At each treatment visit, patients took one puff from four different canisters to blind the study (although only the specified treatment dose was given). The sponsor specified 10 treatment sequences balanced with each treatment occurring twice a period; four patients in each sequence group were to be enrolled in the study.

Pulmonary function testing was conducted at each visit; however, a six-hour PFT was conducted following study drug administration at Visits 2-6. At Visits 3-6, patients were required to have a pre-treatment FEV<sub>1</sub> within + 15% of their pre-treatment FEV<sub>1</sub> from Visit

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2; patients were rescheduled if they did not meet this criterion. There was a washout period of 3-7 days between each visit.

### 6.4. Results

#### 6.4.1. Patient Disposition

Patient disposition for the three pivotal studies is outlined below in Table 2. For Study 244.2498 conducted in a crossover fashion, 41 patients were randomized to the study, and only one patient discontinued from the study secondary to a death in the family. For the three pivotal studies, 80 % of subjects or greater completed the studies with discontinuation secondary to adverse events ranging from 5-13% and lack of efficacy ranging from 0-2%. For the parallel group studies, the results were comparable between placebo and Atrovent HFA-MDI for Study 244.1405 and between Atrovent HFA-MDI 42 mcg and Atrovent CFC-MDI 42 mcg for Study 244.1408. These results are presented below.

**Table 6. Summary of Patient Disposition by Treatment Groups for the Three Phase III Studies Study 244.1405, Study 244.1408, and Study 244.2453**

	Placebo HFA n (%)	Atrovent HFA-MDI 42 mcg n (%)	Atrovent HFA- MDI 84 mcg n (%)	Placebo CFC n (%)	Atrovent CFC-MDI 42 mcg n (%)
<b>Study 244.1405</b>					
Total Treated	62	125	127	66	127
Total Completed	55 (89)	117 (94)	109 (86)	51 (77)	112 (88)
Discontinuations Secondary to:					
Adverse Events	4 (7)	6 (5)	7 (6)	8 (12)	14 (11)
Lack of Efficacy	0	0	2 (2)	0	0
Other	3 (5)	2 (7)	9 (7)	7 (11)	1 (1)
<b>Study 244.1408</b>					
Total Treated	-----	118	-----	-----	56
Total Completed	-----	94 (80)	-----	-----	46 (82)
Discontinuations Secondary to:					
Adverse Events	-----	15 (13)	-----	-----	6 (11)
Lack of Efficacy	-----	0	-----	-----	0
Other	-----	9 (8)	-----	-----	4 (7)
<b>Study 244.2453</b>					
Total Treated	-----	305	-----	-----	151
Total Completed	-----	263 (86)	-----	-----	124 (82)
Discontinuations					
Adverse Events	-----	22 (7)	-----	-----	11 (7)
Lack of Efficacy	-----	3 (1)	-----	-----	3 (2)

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	Placebo HFA n (%)	Atrovent HFA-MDI 42 mcg n (%)	Atrovent HFA- MDI 84 mcg n (%)	Placebo CFC n (%)	Atrovent CFC-MDI 42 mcg n (%)
Other	-----	17 (6)	-----	-----	13 (9)

Source: Vol. 46, p. 30

### 6.4.2. Demographics and Baseline Characteristics

Patient demographics and baseline characteristics are summarized in Tables 3 and 4 below. For all studies reviewed in the ISE, 95% or greater of the study population was White, 0.6-4.6% of the population was Black across the studies, and 0-0.4% was Asian. The mean age of the study population in the four studies ranged from 65.2 to 67.1 years. In all three pivotal studies as well as Study 244.2498, the majority of patients were male (ranging from 55.9 to 70.7% across the studies). The mean smoking history in pack-years ranged from 45.6 years to 71.9 years. The mean time to diagnosis of COPD across all studies ranged from 7.3 to 7.8 years. In the parallel group studies, these results were fairly similar between treatment groups.

**Table 7. Demographics for Studies 244.1405, 244.1408, 244.2453 and 244.2498**

	Study 244.1405	Study 244.1408	Study 244.2453	Study 244.2498
<b>Total Treated</b>	<b>507</b>	<b>174</b>	<b>456</b>	<b>41</b>
Sex				
n (%)				
Male	313 (61.7)	123 (70.7)	255 (55.9)	29 (70.7)
Female	194 (38.3)	51 (29.3)	201 (44.1)	12 (29.3)
Race				
n (%)				
White	489 (96.4)	173 (99.4)	35 (95.4)	40 (97.6)
Black	16 (3.2)	1 (0.6)	21 (4.6)	1 (2.4)
Asian	2 (0.4)	0	0	0
Age				
Mean (years)	65.5	66	65.2	67.1
SD	8.3	7.4	9.0	7.0
Range	41-87	40-83	40-87	48-79
Height				
Mean (in)	67.4	65.8	67.1	67.7
SD	3.8	3.5	3.8	3.8
Range	55-79	56-74	51-78	59-75
Weight				
Mean (lb)	165.9	151.8	161.9	173.6
SD	37.7	34.5	39.5	37.0
Range	73-334	66-271	75-315	116-260
Smoking History (pack-years)				
Mean	60.5	45.6	60.8	71.9
SD	28.5	20.7	31.5	32.6
Range	10-88	4.4-113	10-210	20-160
Time since Dx of COPD (years)				
Mean	7.4	7.3	7.3	7.8
SD	7.1	8.5	6.4	5.7
Range	0-63	0-49	0-39	1-31

Source: Vol. 46, p. 80-81; Vol. 90, p.38

The overall baseline spirometry results for the study population are summarized by study in Table 4. The mean FEV<sub>1</sub> ranged between 0.978 to 1.076 liters across studies, the FEV<sub>1</sub>

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percent predicted ranged from 38.9 to 40.4% of predicted, and the FEV<sub>1</sub>/FVC ranged from 46.7 to 48.1% across studies. These results are presented in the table below.

**Table 8. Summary of Baseline Spirometry by Study**

	Study 244.1405	Study 244.1408	Study 244.2453	Study 244.2498
<b>Total Treated</b>	<b>507</b>	<b>174</b>	<b>456</b>	<b>41</b>
FEV <sub>1</sub> (L)				
Mean	1.063	0.978	1.022	1.076
SD	0.440	0.396	0.414	0.3803
Range	0.20-2.46	0.31-2.24	0.13-2.25	0.490-2.06
Percent Predicted FEV <sub>1</sub> (%)				
Mean	40.023	38.856	39.547	40.4
SD	13.985	13.894	14.953	12.4
Range	10.25-77.36	11.67-73.11	4.34-132.06	21-70
Percent FEV <sub>1</sub> /FVC (%)				
Mean	48.06	54.06	46.69	48.1
SD	11.34	13.86	11.78	8.9
Range	21.9-70.4	26.9-100.0	8.4-77.0	29-68

Source: Vol. 46, p. 82; Vol. 90, p.39

### 6.4.3. Overall Efficacy Results of the Pivotal Studies and Study 244.2498

The four studies supporting efficacy for Atrovent-HFA demonstrated superior efficacy of Atrovent HFA to placebo in the placebo controlled trials (Study 244.1405 and Study 244.2498) and comparable efficacy to Atrovent-CFC in the active controlled studies (all four studies reviewed in this ISE). Although the primary efficacy endpoints varied somewhat between trials, two of the most consistently used efficacy endpoints, FEV<sub>1</sub> AUC<sub>0-6</sub> and Peak FEV<sub>1</sub> response, are reviewed to compare efficacy between the four studies. Although the utility of cross-study comparisons is limited, presenting data in this manner will allow for a general comparability between studies, and in this case, comparability between the different generations of Atrovent-HFA products used in product development.

The following table summarizes these results. Note that the results represent values obtained on the final test day. For the most part, results on other test days were similar. Although another dose (21 mcg) of Atrovent (HFA and CFC) was studied in these trials, it is not depicted in this table since the main dose of interest was the 42 mcg dose for both active comparators. See the Appendix for further details for results with the other studied doses as well as for other timepoints.

**Table 9. Comparison of FEV<sub>1</sub> AUC<sub>0-6</sub> and Peak FEV<sub>1</sub> Response between the Three Pivotal Studies and Study 244.2498 for the Final Test Day†**

Endpoint	Treatment	Study 244.1405 liters (SEM)	Study 244.1408 liters (SEM)	Study 244.2453 liters (SEM)	Study 244.2498 liters (SEM)
FEV <sub>1</sub> AUC <sub>0-6</sub> (liters)	HFA- Placebo*	0.018 (0.021)	-----	-----	0.06 (0.01)
	Atrovent HFA 42 mcg	0.141 (0.014)	0.10 (0.01)	0.117 (0.010)	0.215 (0.010)
	CFC Placebo	0.014 (0.020)	-----	-----	-----

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Endpoint	Treatment	Study 244.1405 liters (SEM)	Study 244.1408 liters (SEM)	Study 244.2453 liters (SEM)	Study 244.2498 liters (SEM)
	Atrovent CFC 42 mcg	0.127 (0.014)	0.10 (0.02)	0.117 (0.014)	0.220 (0.010)
	HFA- Placebo*	0.139 (0.024)	-----	-----	0.15 (0.01)
Peak FEV <sub>1</sub> Response§ (liters)	Atrovent HFA 42 mcg	0.295 * (0.016)	0.23 (0.02)	0.253 (0.010)	0.32 (0.01)
	CFC Placebo	0.140 (0.023)	-----	-----	-----
	Atrovent CFC 42 mcg	0.262 * (0.016)	0.23 (0.02)	0.256 (0.015)	0.33 (0.01)

† For Study 244.1405, final test day results correspond to day 85; for Study 244.1408, final test day results correspond to Day 85; for Study 244.2453, final test day results correspond to Day 365; for Study 244.2498, final test day results correspond to Day 1, since this was a single dose study

\*For Study 244.2498, a differentiation is not made between the placebos, and the value listed here represents all placebo patients

§Peak FEV<sub>1</sub> response was defined as the maximum observed change from the test day baseline FEV<sub>1</sub>.

Source: Vol. 46, p. 94-98, 183

As can be seen by the above table, the FEV<sub>1</sub> AUC<sub>0-6</sub> and Peak FEV<sub>1</sub> responses for the final test day for the three pivotal studies show fairly similar results. However, it is apparent that for Study 244.2498, the FEV<sub>1</sub> AUC<sub>0-6</sub> and Peak FEV<sub>1</sub> responses are higher compared to the other three studies. The mean FEV<sub>1</sub> AUC<sub>0-6</sub> for Atrovent-HFA 42 mcg ranged from 0.10-0.215 liters, for Atrovent-CFC 42 mcg ranged from 0.10-0.220 liters, and for HFA placebo ranged from 0.06 to 0.018 liters. The peak FEV<sub>1</sub> response ranged from 0.23 to 0.32 liters for Atrovent-HFA 42 mcg, 0.23 to 0.33 liters for Atrovent-CFC 42 mcg, and 0.139 to 0.15 for placebo. For FEV<sub>1</sub> AUC<sub>0-6</sub>, the results of 0.215 to 0.220 liters for Study 244.2498 are greater as compared to 0.117 to 0.141 liters for the active treatments for the other three studies. These results may suggest that the third generation product may be more efficacious compared to the first and second generation studies, since the results of Study 244.2498 demonstrate efficacy with the third generation product. However, a difference in study design between the three pivotal studies and Study 244.2498 must be taken into account. Whereas in the three pivotal studies, the patients who were enrolled into the study had to have a diagnosis of COPD and did not have to demonstrate a 15% reversibility with Atrovent-CFC 42 mcg; for study 244.2498, eligible patients had to have COPD and were also required to demonstrate 15% reversibility with Atrovent-CFC 42 mcg. This indicates that the study population for Study 244.2498 was enriched with a more reversible population. This may explain the differences in efficacy parameters observed between Study 244.2498 and the other three pivotal studies.

*Reviewer's comments: As none of the pivotal studies were done with the third generation, to-be-marketed product, it was anticipated that Study 244.2498, the only study with efficacy data, albeit single dose efficacy, would provide reassurance of efficacy for the third generation product. However, the sponsor enriched the study population for this single dose study, such that the results may not be as useful for cross-study comparisons. Additionally, as this study used the to-be-marketed product in an enriched population, the efficacy results may not be generalizable to the whole population; however, these limitations aside, the*

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*results undoubtedly do demonstrate efficacy with the third generation product, and it is reassuring to note that the results with the third generation product demonstrate greater  $AUC_{0-6}$  and Peak  $FEV_1$  responses as compared to the first and second generation products. Although there is no way to be absolutely certain of the results had Study 244.2498 not used an enriched population, the efficacy of the 3<sup>rd</sup> generation product is suggested by the larger numerical results for the  $AUC_{0-6}$  and Peak  $FEV_1$  responses. It may be reasonable to suggest that since the in vitro data suggest that the 2<sup>nd</sup> and 3<sup>rd</sup> generation products are fairly comparable based on the available data submitted by the sponsor, that if this study was conducted in a non-enriched population, the results would have been comparable to the three pivotal studies. This is further supported by the numerical values for these parameters for Atrovent-CFC 42 mcg. Since Atrovent CFC 42 mcg was the active comparator for all 4 studies, and  $FEV_1$   $AUC_{0-6}$  and peak  $FEV_1$  response are known for this product, the difference between the pivotal studies and Study 244.2498 can indirectly provide a measurement of the effect of enriching the population for Study 244.2498. It would be expected that the numerical values would be similar for Atrovent CFC 42 mcg across all studies; however, the numerical results for  $FEV_1$   $AUC_{0-6}$  and peak response are greater in Study 244.2498 compared to the three pivotal studies. Since the results in Study 244.2498 are comparable between Atrovent HFA 42 mcg and Atrovent CFC 42 mcg, it suggests that Atrovent HFA 42 mcg would have had more comparable values to the pivotal studies in terms of  $FEV_1$   $AUC_{0-6}$  and peak  $FEV_1$  response were the study population not enriched..*

For the two parameters,  $FEV_1$   $AUC_{0-6}$  and peak  $FEV_1$  response, the difference between placebo and Atrovent-HFA 42 mcg was statistically significant with a p-value of 0.001 for the placebo controlled trials (Study 244.1405 and 244.2498); for the active controlled trials (Study 244.1408 and Study 244.2453), the p-values were greater than 0.1 for the comparison between Atrovent-HFA 42 mcg and Atrovent-CFC 42 mcg. Thus, these studies do demonstrate that Atrovent-HFA 42 mcg is statistically superior to placebo and comparable to the currently available Atrovent CFC 42 mcg product. Furthermore, efficacy for the 3<sup>rd</sup> generation Atrovent HFA-MDI product was demonstrated.

#### 6.4.4. Primary Efficacy Endpoints

##### 6.4.4.1. Study 244.1405

The primary efficacy variables were the  $FEV_1$  derived  $AUC_{0-6}$  above baseline and peak change from test-day baseline. The sponsor did not specify one timepoint for the primary efficacy variables. It is apparent that the sponsor used four separate timepoints as the efficacy endpoints: Day 1, Day 29, Day 57, and Day 85. [Vol. 61, p. 34]

For all timepoints, the ANOVA test did not demonstrate any treatment by center effects or baseline effects for both co-primary endpoints. However, treatment effects were noted at the 0.0001 significance level.

For all timepoints, ipratropium bromide HFA-42 mcg and ipratropium bromide CFC-42 mcg were significantly more effective than placebo in terms of  $FEV_1$   $AUC_{0-6}$  and peak response. The pairwise comparisons to placebo of the same formulation showed statistically significant differences for each of the active treatment groups ( $p=0.0001$ ). The active treatments were not significantly different from one another with an exception on Day 1. On Day 1, there was a statistically significant difference ( $p=0.02$ ) in  $FEV_1$   $AUC_{0-6}$  and Peak

change from baseline between ipratropium bromide HFA-42 mcg and HFA 84 mcg. [Vol. 63, p. 193] On subsequent test days, this difference was not present.

#### 6.4.4.2. Study 244.1408

The primary efficacy endpoints for this study were change from baseline in the pre-dose mean of morning and evening PEFRs with respect to the last week of recorded diary card data and PEFR comparison analysis during the run-in period and randomization period.

The mean change from baseline with respect to pre-dose morning and evening PEFRs for the HFA-MDI group were higher (6.4 L/min and 7.2 L/min for AM and PM PEFRs, respectively) compared to the CFC-MDI (3.5 L/min and 4.6 L/min for the AM and PM PEFRs, respectively). The mean difference between the two groups was 2.9 L/min for morning PEFR and 2.6 L/min for the evening PEFR. The difference between the two treatment groups was not statistically significant based on the 90% confidence interval. The p-value for this difference was 0.6 (at a preset alpha of 0.1). On this primary efficacy endpoint, the treatment groups were comparable, and as defined by the sponsor, therapeutically comparable. [Vol. 71, p. 58-59; vol. 72, p. 76, 92]

To evaluate the "switch-effect" from ipratropium bromide CFC during the run-in phase to the ipratropium bromide HFA during the randomization phase, weekly pre-dose mean morning and evening PEFRs for the two groups during the first week following randomization to treatment were compared using analysis of covariance. [Vol. 71, p. 335]. The weekly pre-dose mean morning and evening PEFRs for the two groups during the first week following randomization to treatment were compared using analysis of covariance. The 90% confidence interval for this difference in the morning PEFRs was -6.7 to 5.5 and the corresponding p-value was 0.8653. The 90% confidence interval for this difference in the evening PEFRs was -11.4 to -0.64 L/min with a corresponding p-value of .0659. The CFC-MDI group had a mean evening PEFR of 207.7 L/min and the HFA-MDI group had 201 L/min. However, the final week of treatment showed a greater mean for the HFA-MDI group (216.4 L/min) as compared to the CFC-MDI group (210.0 L/min) (p = 0.0659). These results suggest that there was no significant difference between treatment groups after switching from Atrovent® CFC-MDI to Atrovent HFA MDI.

#### 6.4.4.3. Study 244.2453.

For this study, the primary endpoint was safety; however, for efficacy evaluation, this reviewer focused on FEV<sub>1</sub> AUC<sub>0-6</sub> and FEV<sub>1</sub> peak response, as these were the primary efficacy endpoints in the 12-week, randomized, double-blind placebo and active controlled trial, Study 244.1405.

The FEV<sub>1</sub> derived AUC<sub>0-6</sub> above baseline was analyzed for Visits 1, 3, 5, and 7, corresponding to day 1, Week 12, Week 26, and Week 52 of treatment. Generally, the LS Means were comparable between treatment groups (Atrovent-HFA 42 mcg and Atrovent-CFC 42 mcg) for all time points except Visit 3. For Visits 1, 5, and 7, there was no significant difference between the LS Means between the treatment groups, and the 90% confidence intervals intersected 0, with corresponding p-values >0.05 for these timepoints. For Visit 3, the difference in LS Means between the treatment groups was 0.0372 with 90% CI of -0.0653 to -0.0092 with a corresponding p-value of 0.0292. [Vol. 77, p. 74; Vol. 80, p. 313-316; Vol. 81, p. 14-17, 55-88, and 96-99]

*Reviewer's comments: The reader is reminded that two different HFA drug products were used for this study, 1<sup>st</sup> and 2<sup>nd</sup> generation Atrovent HFA products (the differences are reviewed in the Chemistry sections above). The Division asked the sponsor to do a subset analysis to compare the differences between the efficacies of the two generations of HFA products used. The sponsor stated that this could not be done since the number of patients was different between the two generation products and patients were not randomized to different generation products. [N-000-BM, 3/13/03; p. 4] However, after Visit 4, all patients had switched over to the 2<sup>nd</sup> generation HFA product. Therefore, efficacy results for Visits 5 (Week 26 of study) and 7 (Week 52 of study) represent 8 and 34 weeks of treatment, respectively, with the 2<sup>nd</sup> generation product.*

With respect to the second efficacy endpoint, the LS Mean FEV<sub>1</sub> peak changes from baseline were comparable between both treatment groups, and there were no statistically significant differences between the treatments at any timepoint. The difference between treatments ranged from 3 ml to 25 ml. The corresponding p-values for the differences at each time point were greater than 0.18. Based on the prespecified definition, the study demonstrated therapeutic equivalence on this endpoint.

#### 6.4.4.4. Study 244.2498

For the primary efficacy analysis, the primary efficacy variable was FEV<sub>1</sub> AUC<sub>0-6</sub>. The pre-dose unadjusted mean baseline measurements for FEV<sub>1</sub> were comparable, ranging from 1.075 liters to 1.090 liters for all treatments.

All active doses of ipratropium bromide were effective in terms of the primary efficacy variable. The mean difference in the adjusted mean FEV<sub>1</sub> AUC<sub>0-6</sub> between active treatments (Atrovent HFA 42 mcg and Atrovent CFC 42 mcg) and placebo ranged from 124 to 165 ml. Both HFA-MDI (21 mcg and 42 mcg) and CFC-MDI (21 mcg and 42 mcg) were statistically superior to placebo (p=0.0001). No statistically significant differences were noted between the two active treatments for either dose. The difference in the adjusted mean FEV<sub>1</sub> AUC<sub>0-6</sub> between HFA-MDI 42 mcg and CFC-MDI 42 mcg was 5 ml (p=0.762).

#### 6.4.5. Secondary Efficacy Endpoints

In all four studies, spirometric secondary endpoints (see study descriptions above) supported the primary efficacy endpoints. In terms of time to onset, time to peak response, and duration of action, the sponsor provided median responses for all four studies. Means were not provided for this data and the data are quite variable among individual patients in all studies. Keeping these limitations in mind, the median time to therapeutic response, the time to peak response, and duration of response for all test days for Atrovent HFA 42 mcg and Atrovent CFC 42 mcg are provided below in the table below. For Atrovent HFA 42 mcg and CFC 42 mcg, the median time to onset of a therapeutic response across all studies ranged between 12.3 and 37.6 mins and 13 and 63.8 mins, respectively. The median time to peak response ranged from 60 to 90 minutes for Atrovent HFA 42 mcg and between 60 to 120 minutes for Atrovent CFC 42 mcg. The median durations of therapeutic responses were quite variable across studies for Atrovent HFA 42 mcg (1 to 4.8 hours) and Atrovent CFC 42 mcg (0.8 to 5.4 hours).

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**Table 10. Comparison of Median Time to Therapeutic Response\*, Median Time to Peak Response, and Median Duration of Therapeutic Response for Atrovent HFA 42 mcg and Atrovent CFC 42 mcg for Studies 244.1405, 244.1408, 244.2453 and 244.2498.**

	Study 244.1405		Study 244.1408		Study 244.2453		Study 244.2498	
	HFA 42 mcg	CFC 42 mcg						
<b>Median Time to Therapeutic Response (mins)†</b>	14-17.5	15-18	12.3-37.6	19.8-63.8	14-21	15-27	14.5	13.0
<b>Median Time to Peak Response (mins) †</b>	90	90	60	60	60-90	90	90	120
<b>Median Duration of Therapeutic Response (hours) †</b>	2.0-2.8	2.3-3.1	1.0-3.0	0.8-2.5	2.3-3.1	1.8-3.8	4.8	5.4

\* Therapeutic Response was defined as an FEV<sub>1</sub> of at least 1.15 times the pre-dose value.

† Note that these ranges are median ranges for all test days in a given study. The medians for all visits for FEV<sub>1</sub> median times and onsets of therapeutic response and time to peak responses varied widely among individual patients based on line listings. For Study 244.2498, the median results (and not ranges) are provided as this is a single dose study.

Source: Vol. 46, p. 27, 107; Vol. 71, p. 71,140; Vol. 77, p. 76

*Reviewer's comments: These secondary efficacy results are presented as the sponsor describes them (albeit differently) in the label. The sponsor states that " —*

*Since the sponsor provides the median and not mean results for these parameters, the significance of these results is unclear. Even if one were to consider median responses for these parameters acceptable, it is clear the label does not accurately reflect the submitted data. Not only do these parameters vary widely across studies for the median results, but vary quite significantly among individual patients as well in all studies. It is difficult to reach firm conclusions regarding the onset and duration of therapeutic response and time to peak response from the data submitted.*

### 6.4.6. Subgroup Analysis of Response

The sponsor used the data from the 12-week placebo and active-controlled trial Study 244.1405 to perform subgroup analyses. The subgroup analyses were done for the primary efficacy variable FEV<sub>1</sub> AUC<sub>0-6</sub> and FEV<sub>1</sub> peak response at all timepoints (Test Days 1, 29, 57 and 85). The sponsor performed the following subgroup analyses:

- Age category (< 65 years, ≥ 65 years)
- Gender (male, female)
- Smoking history (ex-smokers, current smokers)
- Duration of COPD (< 5 years, ≥ 5 years and < 10 years, ≥ 10 years)
- Disease Severity

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#### 6.4.6.1. Effect of Age

The FEV<sub>1</sub> AUC<sub>0-6</sub> responses for the age subgroups, < 65 years and ≥ 65 years demonstrated statistically significance differences compared to placebo (p-values ranged 0.003 to 0.0001) for both age subgroups analyzed. For subgroup analyses, ANOVA was used, and this did not demonstrate a significant treatment by age interactions for FEV<sub>1</sub> AUC<sub>0-6</sub>.

For the Peak FEV<sub>1</sub> responses, all active treatment groups were statistically superior compared to placebo for both age subgroups analyzed (p-values ranged from 0.0001 to 0.0187). The ANOVA testing for treatment by age subgroup interaction for Peak FEV<sub>1</sub> responses resulted in statistically significant interactions for test days 57 (p-value of 0.03) and 85 (p-value of 0.02). These interactions, however, did not appear to be related to either placebo or Atrovent HFA 42 mcg. It appears that these differences may be attributed to Atrovent HFA 84 mcg. [Vol. 46, p. 198, 269] No meaningful differences were noted between the two age groups for Atrovent HFA 42 mcg in terms of Peak FEV<sub>1</sub> response.

For both parameters, Atrovent HFA 42 mcg and CFC 42 mcg were comparable for both subgroups on all test days.

#### 6.4.6.2. Effect of Gender

There were more males than females in all treatment arms. For both FEV<sub>1</sub> AUC<sub>0-6</sub> and Peak FEV<sub>1</sub> response, both Atrovent HFA 42 mcg and CFC 42 mcg demonstrated statistically superior results compared to placebo at all timepoints tested (p-values ranged from 0.0001 to 0.0006). For both parameters, Atrovent HFA 42 mcg and CFC 42 mcg were comparable for both subgroups on all test days. In terms of ANOVA testing for treatment by gender subgroup interaction, statistically significant interactions for FEV<sub>1</sub> AUC<sub>0-6</sub> (p-value of 0.04) and Peak FEV<sub>1</sub> response (p-value of 0.0073) were noted on Day 29 only. These effects were attributed to an effect noted for Atrovent HFA 84 mcg, which demonstrated greater mean FEV<sub>1</sub> AUC<sub>0-6</sub> and Peak FEV<sub>1</sub> response in males as compared to females. No gender effect was noted for either Atrovent HFA 42 mcg or CFC 42 mcg.

#### 6.4.6.3. Effect of Smoking Status

There were a greater number of ex-smokers in all treatment groups as compared to current smokers. For both FEV<sub>1</sub> AUC<sub>0-6</sub> and Peak FEV<sub>1</sub> response, both Atrovent HFA and CFC 42 mcg demonstrated statistically significant differences compared to placebo (p-values for both parameters ranging from 0.0006 to 0.0085), and were comparable to each other for both subgroups at all time points. No statistically significant treatment by smoking status interactions were noted for either parameter tested.

#### 6.4.6.4. Effect of COPD Duration

The sponsor studied three subgroups for these analyses: < 5 years, ≥ 5 years and < 10 years, and ≥ 10 years duration. There were more patients in the < 5 years category (229) compared to the other two categories (142 and 134 for ≥ 5 years and < 10 years and ≥ 10 years, respectively). ANOVA testing did not demonstrate any significant treatment by COPD duration interaction for either FEV<sub>1</sub> AUC<sub>0-6</sub> or Peak FEV<sub>1</sub> response.

#### 6.4.6.5. Effect of Disease Severity

The sponsor categorized three subgroups—FEV<sub>1</sub> <35% predicted (n=226), FEV<sub>1</sub> 35% and < 50% (n=160), and ≥ 50% (n= 119)—for subgroups analysis. The greatest number of patients were in the FEV<sub>1</sub> <35% predicted subgroup. Both Atrovent HFA and CFC 42 mcg were statistically superior to placebo at all timepoints for FEV<sub>1</sub> AUC<sub>0-6</sub> and Peak FEV<sub>1</sub> response (p-values ranged from 0.0258 to 0.0007). No statistically significant treatment by disease severity interactions were observed for either FEV<sub>1</sub> AUC<sub>0-6</sub> or Peak FEV<sub>1</sub> response.

#### 6.4.6.6. Subgroup Analyses Conclusions

The subgroups analyses performed did not reveal any significant effects of age, gender, smoking history, COPD duration or disease severity on the efficacy of Atrovent HFA 42 mcg or Atrovent CFC 42 mcg.

### 6.5. Efficacy Discussion and Conclusions

To support the efficacy of Atrovent HFA 42 mcg for the maintenance treatment of bronchospasm associated with COPD, the sponsor submitted 3 phase III pivotal studies and one single dose ranging study with the to-be-marketed product. Per the FDA *Points to Consider 1994* document for a “switch program”, a sponsor is required to submit one dose ranging study, one 12-week placebo and active controlled trial and one one-year long term safety trial. The sponsor has met these requirements in terms of the three phase III trials submitted for review in this application.

However, difficulties arise in the interpretation of efficacy for these three phase III pivotal studies since the sponsor changed the Atrovent HFA 42 mcg drug product during its development. The changes involved the drug delivery device and did not significantly affect the formulation. In the two Phase III pivotal studies (Studies 244.1405 and 244.1408) meeting the FDA requirements for a *switch program*, the sponsor used the 1<sup>st</sup> generation Atrovent HFA product. The one-year safety study (Study 244.2453) used both the 1<sup>st</sup> and 2<sup>nd</sup> generation product. The to-be-marketed product is the 3<sup>rd</sup> generation product, which is more comparable to the 2<sup>nd</sup> generation product. To provide support for the efficacy and safety of the 3<sup>rd</sup> generation product, the sponsor submitted the results of a single-dose, dose-ranging study with the 3<sup>rd</sup> generation product, Study 244.2498. It is clear that the sponsor has not met the requirements for a *switch program* using the 3<sup>rd</sup> generation, to-be-marketed product.

Since the sponsor is unable to provide direct comparisons between the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> generation products in a linking study (the 1<sup>st</sup> and 2<sup>nd</sup> generation products are no longer available), direct and indirect links have been made to support the efficacy of the 3<sup>rd</sup> generation product utilizing results of the 3 phase III pivotal studies and Study 244.2498 and in vitro comparisons between the different generation of products.

In the 12-week, placebo and active controlled study (Study 244.1405), the sponsor demonstrated that the 1<sup>st</sup> generation Atrovent HFA 42 mcg product was efficacious compared to placebo, and comparable to Atrovent CFC 42 mcg. Study 244.1408, a second 12-week active controlled study, supports the comparable efficacy of the 1<sup>st</sup> generation Atrovent HFA 42 mcg and CFC 42 mcg products. Study 244.2453, the one-year, open-label active controlled study, supports the efficacy of both the 1<sup>st</sup> and 2<sup>nd</sup> generation products. In

this study, after 18 weeks of treatment, all patients received the 2<sup>nd</sup> generation product. Results from the final two visits, Week 26 and Week 52, correspond to 8 and 34 weeks of treatment with the 2<sup>nd</sup> generation product, respectively. The sponsor provided efficacy data for the 3<sup>rd</sup> generation product in Study 244.2498. Although, this was single dose study, the data are valuable to support efficacy for the 3<sup>rd</sup> generation product. One may argue that the study population was enriched to only include patients that demonstrated 15% reversibility with Atrovent CFC 42 mcg. However, this does not diminish the fact that Atrovent HFA 42 mcg and CFC 42 mcg were statistically superior to placebo and comparable to one another for the pre-specified primary efficacy endpoint. Additionally, the results for FEV<sub>1</sub> AUC<sub>0-6</sub> were greater for both products as compared to the three pivotal studies where the population was not enriched. Thus, the submitted studies provide short and long-term efficacy data for both the 1<sup>st</sup> and 2<sup>nd</sup> generation products and single-dose efficacy for the 3<sup>rd</sup> generation product.

However, the issue still remains that the sponsor has not provided long-term efficacy data for the 3<sup>rd</sup> generation product. Indirect links may help support long term efficacy for the 3<sup>rd</sup> generation product. Since the available CMC in vitro data submitted thus far, suggests that the 2<sup>nd</sup> and 3<sup>rd</sup> generation products may be fairly comparable (for the most part), the results of the one-year long term study may support long-term efficacy for the 3<sup>rd</sup> generation product. Additionally, Atrovent CFC 42 mcg has been used as the active comparator in all active controlled trials. Since these trials provide comparable results for 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> generation Atrovent HFA 42 mcg to Atrovent CFC 42 mcg, an indirect link in support of efficacy of the to-be-marketed drug product can be established. In all of these trials, regardless of the generation of Atrovent HFA product used, comparable efficacy to Atrovent CFC 42 mcg was demonstrated. Furthermore, in the three phase III trials using the 1<sup>st</sup> and/or 2<sup>nd</sup> generation products, no tachyphylaxis was demonstrated. Although the Atrovent HFA device has changed during development, the formulation remained essentially the same between the three generations. Therefore, it is expected that tachyphylaxis would not be demonstrated with the 3<sup>rd</sup> generation product since it contains the same formulation as the 1<sup>st</sup> and 2<sup>nd</sup> generation products.

In conclusion, although the sponsor did not provide direct long-term efficacy data with the to-be-marketed product in a 12-week, placebo and active controlled trial, indirect links support the efficacy of the 3<sup>rd</sup> generation product.

## 7. INTEGRATED REVIEW OF SAFETY

This section reviews the safety data from the clinical studies submitted in this application.

### 7.1. Summary and Conclusions

The sponsor submitted 11 studies, of which three were Phase III pivotal studies in COPD patients. Two were 12-week, randomized, double-blind, active controlled (Study 244.1405 had an additional placebo control arm), parallel group multicenter trials. The third was an open-label, randomized multicenter one-year safety study. In all studies, Atrovent HFA 42 mcg was compared to Atrovent CFC 42 mcg. Additionally, in Study 244.1405, a placebo arm and an Atrovent HFA 42 mcg treatment arm were also evaluated. It should be noted that these trials were conducted with the 1<sup>st</sup> generation (Studies 244.1405, 244.1408,

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244.2453) and the 2<sup>nd</sup> generation (Study 244.2453) Atrovent HFA 42 mcg products. Two studies (Studies 244.2498 and 244.2480) were conducted with the to-be-marketed 3<sup>rd</sup> generation Atrovent HFA 42mcg product. The former is a single-dose study and the latter is a 7-day pharmacokinetic study.

In the pivotal studies, the majority of patients were White (96%) as compared to Black (3%) and Asian (<1%). The mean age of the study population was 65.5 years and was comparable across all treatments. A greater percentage of the study population was male (61%) as compared to female (39%). The population had moderate to severe COPD with a mean FEV<sub>1</sub> of 1.03 liters corresponding to a mean FEV<sub>1</sub> % predicted of 39.4% and a mean FEV<sub>1</sub>/FVC of 48.43%. In the two 12-week trials, 89% of the patients were exposed to Atrovent HFA 42 mcg for greater than 10 weeks and in the one-year safety study, 88% of patients were exposed to 42 mcg for greater than 39 weeks (274 days).

Adverse events were fairly common in these studies, with 844 patients (74%) experiencing at least one adverse event. Adverse events were noted in 432 patients (79%) in the Atrovent HFA 42 mcg group, in 257 patients (77%) in the Atrovent CFC 42 mcg group, in 63 patients (50%) in the Atrovent HFA 84 mcg group, in 44 patients (71%) in the placebo HFA group and in 48 patients (73%) in the CFC placebo treatment group.

The most commonly occurring AEs in the Atrovent 42 mcg group included upper respiratory tract infection (23%), bronchitis (17%), COPD exacerbation (16%), dyspnea (7%), sinusitis (7%), headache (6%), urinary tract infection (6%), and influenza like symptoms (6%). Occurring less frequently were household accident, pneumonia, rhinitis, coughing, pharyngitis, nausea, dry mouth, dyspepsia, and vomiting. The incidence of adverse events was comparable between Atrovent HFA 42 mcg and Atrovent CFC 42 mcg. When these adverse events were compared to Atrovent HFA 84 mcg, no dose response effect was noted.

Adverse events—as judged by the investigator—to be drug related, were reported in 104 patients (9%). The most common AEs judged to be treatment related in the Atrovent HFA 42 mcg were dry mouth (1.6%—compared to 0.9% in the Atrovent CFC 42 mcg group) and taste perversion (0.9%—compared to 0.3% in the Atrovent CFC 42 mcg group). Headache and coughing occurred in the Atrovent HFA 42 mcg treatment group less frequently (0.7%) as compared to the Atrovent CFC 42 mcg group, 1.5% for headache and 1.2% for coughing, respectively.

To evaluate for anticholinergic side effects, data from all Phase II and Phase III trials was pooled, in which, 200 patients (13%) reported at least one adverse event that may be considered to be an anticholinergic side effect. The most commonly reported events in the total study population were nausea (n=38, 2%), dry mouth (n=37, 2%) and constipation (n=30, 2%). Any other anticholinergic adverse events were rare (< 1% of the population). The incidence of these adverse events was similar between Atrovent HFA 42 mcg and Atrovent CFC 42 mcg: dry mouth and nausea (3% and 2% in Atrovent HFA 42 mcg and CFC 42 mcg, respectively) and constipation (2%) in each. No dose response effect was observed for any anticholinergic adverse events when compared to placebo and Atrovent HFA 84 mcg.

There were a total of 21 deaths reported in the three pivotal studies (none were reported in any of the other 8 studies). Fourteen deaths occurred during the randomized treatment

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period, while seven occurred post-treatment. Of these 14 deaths, 9 (0.97%) were reported in the Atrovent HFA 42 mcg group, 3 (0.52%) in the Atrovent CFC 42 mcg group, 1 (0.45%) in the Atrovent HFA 84 mcg group, and 1 (0.60%) in the HFA placebo group. Pulmonary carcinoma was reported in five patients as the cause of death, COPD exacerbation was reported in four patients, and acute renal failure, pancreatitis, cardiac arrest, bronchitis, adenocarcinoma, gastro-intestinal disorder, abnormal renal function and respiratory insufficiency were each reported once as a cause of death. Given the study population and disease under study, the causes of death are not unexpected and these deaths are not felt by this reviewer to be treatment related.

Serious adverse events were reported by 145 patients (13%). The incidence of SAEs was similar between the Atrovent HFA 42 mcg group (79 patients, 14%) and Atrovent CFC 42 mcg (45 patients, 13%), and comparatively lower in the HFA placebo (7 patients, 11%) and Atrovent HFA 84 mcg (9 patients, 7%). The most frequently reported SAEs were COPD exacerbation (51 patients, 4%) and pneumonia (26 patients, 2%). In the Atrovent HFA 42 mcg, 23 patients (4%) reported COPD exacerbation and 15 patients (3%) reported pneumonia. Again no dose response effects were noted with comparison with Atrovent HFA 84 mcg. Again, given the study population and disease under study, these SAEs are not unexpected, and do not appear to be treatment related.

Consistent trends or changes attributable to Atrovent HFA 42 mcg were not noted in laboratory parameters, vital signs, physical examinations, or EKGs. Nor were there any consistent trends to suggest paradoxical bronchospasm with Atrovent HFA 42 mcg.

Subgroup analysis of AEs did not reveal any consistent or clinically meaningful differences between Atrovent HFA 42 mcg and CFC 42 mcg with respect to age, gender, or race. Analysis of drug-disease severity interaction revealed a rank ordering effect with respect to COPD exacerbations: with the percentage of patients reporting COPD exacerbations increasing with increasing disease severity; this finding was noted in both treatment groups and is not unexpected.

As most of the above safety information is from studies where the 1<sup>st</sup> and 2<sup>nd</sup> generation products of Atrovent HFA 42 mcg were utilized, safety information from the two studies using the 3<sup>rd</sup> generation product is also salient to this application, as they utilize the to-be-marketed product. The most commonly reported AEs in these studies were headache, diarrhea, skin rash, household accident and pancreatitis. No deaths were reported in these studies and two SAEs were reported: pancreatitis and respiratory failure. None of these are felt to be treatment related. No clinically meaningful changes in laboratory parameters, vital signs, or EKGs were noted in these studies.

Additionally, Study 244.2480 reveals that there is less systemic exposure to ipratropium bromide following 84 mcg of HFA-MDI than following 84 mcg of CFC-MDI. This is reassuring since less systemic exposure reduces the safety concern.

In conclusion, the safety assessments performed in the pivotal studies were satisfactory and Atrovent HFA 42 mcg was found to be safe when compared to the currently marketed Atrovent CFC 42 mcg product. However, it should be noted that the 3<sup>rd</sup> generation drug product has not been studied in any long-term trials, although there are two short-term trials (one single-dose and one 7-day PK study). Generally, to be assured of safety, a long-term safety study should be conducted; however, the PK studies reviewed demonstrate that the

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systemic exposure is lower in the 3<sup>rd</sup> generation HFA 42 mcg product compared to the currently marketed Atrovent CFC 42 mcg treatment group and therefore, it is doubtful that a long-term study with the 3<sup>rd</sup> generation product would reveal any significant safety concerns.

**7.2. Methods and Content (Materials Utilized in Review)**

The sponsor submitted clinical study reports for 11 trials in this application: two 12-week phase III pivotal studies in COPD (244.1405 and 244.1408), one 1-year long-term safety study (244.2453) in COPD, one single dose efficacy and safety study in COPD patients (244.2498), two phase I PK studies in healthy volunteers (244.1401 and 244.1402), one phase II PK study in COPD patients (244.2480), a phase II single dose confirmation study (244.1403), a cumulative dose trial (244.1404), and two phase III 12-week trials in asthma (244.1407 and 244.1409). In these trials, safety was assessed by adverse event monitoring, physical examinations, vital signs, laboratory testing and electrocardiograms. All adverse events were classified as serious or non-serious according to standard CFR defined nomenclature. The terms used to report adverse events were classified using the Boehringer Ingelheim-World health Organization-Adverse Reaction Terminology (BI-WHO-ART). The following table summarizes the 11 studies.

**Table 11. Summary of Clinical Studies by Type of Study and Region**

Type of Study	Total Number of Studies (subjects)	Number of U.S. Studies (subjects)	European Studies (subjects)
Phase I single dose	1 (12)	0	1 (12)
Phase I multiple dose	1 (12)	0	1 (12)
Phase II single dose	3 (142)	2 (111)	1 (31)
Phase II multiple dose	1 (30)	1 (30)	
Phase III 12-week multiple dose	4 (1106)	1 (507)	3 (599)
Phase III one-year multiple dose	1 (456)	1 (456)	0
<b>Total</b>	<b>11 (1758)</b>	<b>5 (1104)</b>	<b>6 (654)</b>

Source: Vol. 47, p. 18

The main focus for safety evaluation will be on the three phase III pivotal studies. Safety findings from the two studies in which the 3<sup>rd</sup> generation product was used (244.2480 and 244.2498) will also be briefly summarized. Additionally, any significant findings from any of the other studies reviewed in the Appendix will also be presented.

**7.3. Disposition and Demographics/Baseline Characteristics**

**7.3.1. Patient Disposition**

A total of 1758 subjects were randomized to 11 clinical trials, in which 1558 subjects (88.6%) completed the trials. A total of 1162 were randomized to Atrovent HFA (all doses) and 1047 (90.10%) completed the clinical trials. This was comparable to the percentage of completers in both the placebo (91.27%) and Atrovent CFC (90.34%) groups. From these

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trials, a total of 116 subjects (6.60%) discontinued from the trials secondary to an adverse event, and 39 subjects (2.22%) discontinued secondary to worsening of COPD. In the Atrovent HFA treatment groups, 66 subjects (5.68%) discontinued secondary to an adverse event compared to 12 subjects (4.76%) in the placebo groups, and 38 subjects (5.83%) in the Atrovent CFC treatment groups. The frequency of discontinuations secondary to COPD was fairly similar between Atrovent HFA (1.38%) and placebo treatment groups (1.98%). A comparatively greater percentage of patients discontinued from the clinical trials secondary to COPD in the Atrovent CFC treatment groups (2.76%). These results are displayed in the following table.

**Table 12. Summary of Patient Participation of All Subjects Exposed to Atrovent HFA in Clinical Trials Compared to Atrovent CFC and Placebo**

	Total All Treatment n (%)	Atrovent HFA all doses n (%)	Placebo n (%)	Atrovent CFC all doses n (%)
Total Randomized	1758	1162	252	652
Total Completed	1558 (88.62)	1047 (90.10)	230 (91.27)	589 (90.34)
<b>Discontinuation Secondary to:</b>				
Adverse Event	116 (6.60)	66 (5.68)	12 (4.76)	38 (5.83)
Worsening of COPD	39 (2.22)	16 (1.38)	5 (1.98)	18 (2.76)
Worsening of Other Pre-Existing Disease	5 (0.28)	2 (0.17)	1 (0.40)	2 (0.31)
Other Adverse Event	72 (4.10)	48 (4.13)	6 (2.38)	18 (2.76)
Lack of Efficacy	8 (0.46)	5 (0.43)	0	3 (0.46)
Non-compliant	7 (0.40)	4 (0.34)	1 (0.40)	2 (0.31)
Lost to Follow-up	15 (0.85)	7 (0.60)	1 (0.40)	7 (1.07)
Consent Withdrawn	26 (1.48)	14 (1.20)	4 (1.59)	8 (1.23)
Other	28 (1.59)	19 (1.64)	4 (1.59)	5 (0.77)

Source: Vol. 47, p. 22

### 7.3.2. Demographics and Baseline Characteristics

As the main focus for the safety evaluation is on the Phase III studies (244.1405, 244.1408, and 244.2453), the demographics and baseline characteristics are presented for these studies. In the Phase III pivotal studies, the overall mean age for patients was 65.5 years and was comparable across all treatments. Ninety-six percent of patients were White, three percent were Black, and less than one percent of patients were Asian. The majority of patients in the trials were male (61% male vs. 39% females). The patient population had moderate to severe COPD with a mean FEV<sub>1</sub> of 1.03 liters, a mean FEV<sub>1</sub> % predicted of 39.4% and a mean FEV<sub>1</sub>/FVC of 48.43%. This was comparable across treatment groups. Overall, baseline demographics and spirometry were similar across treatment groups. These results are summarized below.

**Table 13. Demographics and Baseline Characteristics of All Patients Randomized to the Three Phase III Trials by Treatment**

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	Total	HFA		CFC	
	All Patients*	42 mcg n (%)	placebo n (%)	42 mcg n (%)	placebo n (%)
<b>Total Patients</b>	<b>1137</b>	<b>548</b>	<b>62</b>	<b>334</b>	<b>66</b>
SEX					
Male	691 (61)	333 (61)	36 (58)	200 (60)	39 (59)
Female	446 (39)	215 (39)	26 (42)	134 (40)	27 (41)
RACE					
White	1097 (96)	526 (96)	57 (92)	325 (97)	64 (97)
Black	38 (3)	22 (4)	4 (6)	8 (2)	2 (3)
Asian	2 (< 1)	0	1 (2)	1 (<1)	0
Mean Age (years)	65.5	65.3	66.5	65.9	62.8
Mean Height (in.)	67.0	66.9	67.2	66.8	67.6
Mean Weight (lbs.)	162.2	159.9	174.2	160.6	168.4
Smoking Hx (pack-years)	58.3	57.7	61.0	58.3	57.1
Duration of COPD (years)	9.3	9.5	8.9	8.8	10.5
Mean Baseline FEV <sub>1</sub> (L)	1.03	1.02	1.06	1.03	1.06
Mean FEV <sub>1</sub> %Predicted	39.44	39.26	40.46	39.81	38.24
FEV <sub>1</sub> /FVC (%)	48.43	48.14	49.88	49.46	46.98

\*This column includes patients who received the Atrovent HFA 84 mcg doses as well; this was not included in this table as this dose was not submitted for approval.

Source: Vol. 47, p. 26

### 7.4. Description of Patient Exposure

A total of 1758 patients/subjects were randomized in eleven controlled clinical studies, of which, 24 were healthy volunteers, 1309 were COPD patients, 234 were adult asthmatics and 191 pediatric asthmatics. All studies were double blind with the exception of the two open-label studies: 244.2453 (one-year safety study) and 244.2480 (Phase II PK study). A total of 962 patients were exposed to at least one dose of Atrovent HFA 42 mcg; in most instances, patients were dosed 42 mcg four times a day, except in single-dose studies, the cumulative dose study and the pediatric asthma study. Of these 962 patients, a total of 658 COPD patients were exposed to at least one dose of Atrovent HFA 42 mcg. Additionally, 249 and 111 patients, were exposed to the 84 and 21 mcg doses of Atrovent HFA, respectively. The following table summarizes the clinical studies and number of subjects exposed to Atrovent HFA and the placebo and active controls.

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**Table 14. Number of Subjects Exposed to Atrovent HFA and Placebo HFA in Clinical Studies\* Categorized by Treatment and Study Type**

Study Duration	Atrovent HFA (mcg/dose)†						
	0 mg Placebo	21 mcg	42 mcg	84 mcg	168 mcg	336 mcg	
	n	n	n	n	n	n	
<b>Clinical Pharmacology Studies</b>							
<b>Human Pharmacology</b>							
244.1401	1 week	12	-----	-----	12	-----	-----
244.1402	single dose	12	-----	12	12	-----	-----
244.2480	1 week	-----	-----	-----	30	-----	-----
<b>Dose Ranging</b>							
244.1403	single dose	37	40	39	37	-----	-----
244.1404	cumulative dose	-----	31	31	31	31	31
244.2498	single dose	40	40	40	-----	-----	-----
<b>Phase III Controlled Studies</b>							
<b>Phase COPD III Trials</b>							
244.1405	12 weeks	62	-----	125	127	-----	-----
244.1408	12 weeks	-----	-----	118	-----	-----	-----
244.2453	12 weeks	-----	-----	305	-----	-----	-----
<b>Phase III Asthma Trials</b>							
244.1407	12 weeks	-----	-----	159	-----	-----	-----
244.1409	12 weeks	-----	-----	133§	-----	-----	-----
<b>TOTAL</b>		163	111	962	249	31	31

\* All clinical trials were conducted in COPD patients except for Studies 244.1401, 244.1402, 244.1407 and 244.1409. The first two were conducted in healthy volunteers and the latter two were conducted in asthma patients.

† In most studies, these doses were administered q.i.d except in single dose and the cumulative dose studies (or as otherwise indicated)

§ t.i.d dosing

Source: Vol. 47, p. 19-20

In terms of extent of patient exposure related to time, the mean exposures to Atrovent HFA 42 mcg for Studies 244.1405, 244.1408, and 244.2453 were 84, 76.5, and 332 days, respectively. This was comparable to Atrovent CFC 42 mcg in all studies and to placebo in Study 244.1405 (the only placebo Phase III pivotal study). In the two twelve-week trials, 89% of patients were exposed to Atrovent HFA 42 mcg for greater than 10 weeks. In the one-year safety study, 88% of patients were exposed to 42 mcg for greater than 39 weeks (274 days). These results are presented in the following table.

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**Table 15. Extent of Exposure from the Three Pivotal Phase III Studies: 244.1405, 244.1408, and 244.2453.**

Exposure	Study 244.1405			Study 244.1408		Exposure	Study 244.2453	
	HFA Placebo n=62 n (%)	HFA 42mcg n=125 n (%)	CFC 42mcg n=127 n (%)	HFA 42mcg n=118 n (%)	CFC 42mcg n=56 n (%)		HFA 42mcg n=305 n (%)	CFC 42mcg n=151 n (%)
1-14 days	2 (3.2)	2 (1.6%)	3 (2.3)	4 (4)	1 (2)	1-42 days	6 (1.9)	7 (4.6)
15-28 days	2 (3.2)	0	4 (3.1)	3 (3)	5 (9)	43-84 days	14 (4.5)	4 (2.6)
29-42 days	1 (1.6)	2 (1.6)	0	5 (4)	0	85-126 days	5 (1.6)	4 (2.6)
43-56 days	2 (3.2)	2 (1.6)	6 (4.7)	4 (4)	2 (4)	127-182 days	8 (2.6)	5 (3.3)
57-70 days	0	1 (0.8)	0	2 (2)	0	183-273 days	3 (0.9)	2 (1.3)
71-84 days	7 (11.2)	24 (19.1)	20 (15.7)	41 (35)	15 (27)	274-358 days	30 (9.8)	21 (13.9)
85-98 days	45 (72.5)	87 (69.6)	9 (72.4)	58 (49)	31 (55)	359-372 days	223 (73)	99 (65.5)
99-112 days	3 (4.8)	4 (3.2)	1 (0.7)	1 (1)	2 (4)	373-387 days	16 (5.2)	5 (3.3)
> 112 days	0	2 (1.6)	0	-----	-----	> 387 days	0	4 (2.6)
Mean Exposure in days	81	84	80	76.5	77.4	Mean Exposure (days)	332	325

Source: Vol. 61, p. 83; Vol. 71, p. 86; Vol. 77, p. 84

### 7.5. Safety Findings from Phase III Pivotal Clinical Studies

The safety results of the two 12-week pivotal and one 1-year safety study are reviewed in depth in this section in an integrated fashion. The adverse events, anticholinergic AEs, deaths, serious adverse events, laboratory, vital signs, physical examinations, and EKGs of significance for these studies follow.

#### 7.5.1. Adverse Events

Adverse events (AEs) were fairly common in these studies, where 844 patients (74%) experienced adverse events. Adverse events were noted in 432 patients (79%) in the Atrovent HFA 42 mcg group, in 257 patients (77%) in the Atrovent CFC 42 mcg group, in 63 patients (50%) in the Atrovent HFA 84 mcg group, in 44 patients (71%) in the placebo HFA group and in 48 patients (73%) in the CFC placebo treatment group. A greater percentage of patients in the Atrovent HFA 42 mcg group experienced AEs as compared to the Atrovent HFA 84 mcg group, suggesting an absence of dose response effect. The incidence of AEs was comparable between Atrovent HFA 42 mcg and Atrovent CFC 42 mcg.

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Adverse events occurring at a frequency of  $\geq 3\%$  in any active treatment group are displayed in the following table. The most commonly occurring AEs in the Atrovent 42 mcg group included upper respiratory tract infection (23%), bronchitis (17%), COPD exacerbation (16%), dyspnea (7%), sinusitis (7%), headache (6%), urinary tract infection (6%), and influenza-like symptoms (6%). Occurring less frequently were household accident, pneumonia, rhinitis, coughing, pharyngitis, nausea, dry mouth, dyspepsia, and vomiting. The incidence of adverse events was comparable between Atrovent HFA 42 mcg and Atrovent CFC 42 mcg.

Although the Atrovent HFA 84 mcg is not going to be marketed, the results have been presented to look for a dose response effect when compared to Atrovent HFA 42 mcg and HFA placebo. A dose response effect is suggested when comparing placebo with Atrovent HFA 42 mcg and Atrovent 84 mcg for pain (nonspecific), nausea and vomiting; however, the frequency of these adverse events was quite low (5% or less). These results are summarized in the following table.

**Table 16. Adverse Events (AE) Occurring in  $\geq 3\%$  of Patients Receiving Atrovent HFA or CFC**

	Placebo HFA n (%)	Atrovent HFA 42 mcg n (%)	Atrovent HFA 84 mcg n (%)	Placebo CFC n (%)	Atrovent CFC 42 mcg n (%)	Total of All Treatments n (%)
<b>Total Treated</b>	<b>n=62</b>	<b>n=548</b>	<b>n=127</b>	<b>n=66</b>	<b>n=334</b>	<b>n=1137</b>
Total with any AE	44 (71)	432 (79)	63 (50)	48 (73)	257 (77)	844 (74)
<b>BODY AS A WHOLE-GENERAL DISORDERS</b>						
Accident household	3 (5)	25 (5)	2 (2)	0	14 (4)	44 (4)
Back Pain	1 (2)	24 (4)	2 (2)	1 (2)	10 (3)	38 (3)
Headache	4 (6)	35 (6)	6 (5)	6 (9)	24 (7)	75 (7)
Influenza like symptoms	3 (5)	34 (6)	2 (2)	0	11 (3)	50 (4)
Pain	1 (2)	14 (3)	5 (4)	0	5 (1)	25 (2)
<b>CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS</b>						
Dizziness	2 (3)	16 (3)	3 (2)	1 (2)	8 (2)	30 (3)
<b>GASTROINTESTINAL DISORDERS</b>						
Diarrhea	0	21 (4)	2 (2)	0	8 (2)	31 (3)
Dyspepsia	0	17 (3)	1 (<1)	1 (2)	11 (3)	30 (3)
Dry Mouth	2 (3)	16 (3)	3 (2)	0	7 (2)	28 (2)
Nausea	1 (2)	21 (4)	6 (5)	2 (3)	8 (2)	38 (3)
Vomiting	0	9 (2)	4 (3)	0	4 (1)	17 (1)
<b>RESPIRATORY SYSTEM DISORDERS</b>						
Bronchitis	3 (5)	94 (17)	4 (3)	5 (8)	50 (15)	156 (14)
COPD exacerbation	8 (13)	90 (16)	14 (11)	9 (14)	60 (18)	181 (16)
Coughing	4 (6)	23 (4)	5 (4)	4 (6)	15 (4)	51 (4)
Dyspnea	1 (2)	39 (7)	2 (2)	4 (6)	21 (6)	67 (6)
Pharyngitis	2 (3)	22 (4)	2 (2)	1 (2)	9 (3)	36 (3)

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	Placebo HFA n (%)	Atrovent HFA 42 mcg n (%)	Atrovent HFA 84 mcg n (%)	Placebo CFC n (%)	Atrovent CFC 42 mcg n (%)	Total of All Treatments n (%)
<b>Total Treated</b>	<b>n=62</b>	<b>n=548</b>	<b>n=127</b>	<b>n=66</b>	<b>n=334</b>	<b>n=1137</b>
Pneumonia	1 (2)	26 (5)	2 (2)	0	13 (4)	42 (4)
Rhinitis	3 (5)	28 (5)	1 (<1)	2 (3)	7 (2)	41 (4)
Sinusitis	3 (5)	36 (7)	4 (3)	1 (2)	29 (9)	73 (6)
URI	9 (15)	126 (23)	15 (12)	12 (18)	71 (21)	233 (20)
<b>URINARY SYSTEM DISORDERS</b>						
Urinary Tract Infection	0	35 (6)	1 (<1)	1 (2)	18 (5)	55 (5)

Source: Vol. 48, p. 2

### 7.5.1.1. Drug Related Adverse Events

Of the 844 patients (74%) reporting AEs in the three pivotal studies, 104 patients (9%) reported at least one adverse event that was judged by the investigator to be treatment related. A total of 51 patients (9.3%) in the Atrovent HFA 42 mcg group and 29 patients (8.7%) in the Atrovent CFC 42 mcg reported at least one AE that was considered to be treatment related. In the overall study population, headache (14%), dry mouth (14%), and taste perversion (12%) were the most commonly reported AEs considered to be treatment related. The most common AEs judged to be treatment related in the Atrovent HFA 42 mcg were dry mouth (1.6%—compared to 0.9% in the Atrovent CFC 42 mcg group) and taste perversion (0.9%—compared to 0.3% in the Atrovent CFC 42 mcg group). Headache and coughing occurred in the Atrovent HFA 42 mcg treatment group less frequently (0.7%) as compared to the Atrovent CFC 42 mcg group, 1.5% for headache and 1.2% for coughing, respectively. Headache and coughing were each reported in 2.3% of placebo treatment groups, dry mouth was reported in 2 patients in the placebo treatment groups (1.6%), and taste perversion was reported in none of the placebo treatment groups. [Vol. 47, p. 34-37]

*Reviewer's comments: Dry mouth, taste perversion, and coughing could certainly be considered treatment related and this reviewer is in agreement with this assessment.*

### 7.5.1.2. Adverse Events of Special Concern

As this is an anticholinergic drug, special attention was given to potential pharmacologic systemic adverse events. For this section, the sponsor collated information from all Phase II and Phase III studies (including the asthma trials). This is acceptable as this pooled approach would better characterize any such adverse events.

In these Phase II and Phase III studies, 200 patients (13%) reported at least one adverse event that may be considered to be an anticholinergic side effect. The most commonly reported events in the total population were urinary tract infection (n=55, 4%), pharyngitis (n=52, 3%), dry mouth (n=37, 2%), and constipation (n=30, 2%). All other events were reported in less than 1% of the population. The incidence of these adverse events was similar between Atrovent HFA 42 mcg and Atrovent CFC 42 mcg: urinary tract infection (4% in each), pharyngitis (4% and 3% in Atrovent HFA 42 mcg and CFC 42 mcg, respectively), dry mouth and nausea each (3% and 2% in Atrovent HFA 42 mcg and CFC 42

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mcg, respectively), and constipation (2%) in each. The incidence of tachycardia, glaucoma, urinary retention, micturition disorder, abnormal vision and xerophthalmia was low ( $\leq 1\%$ ). When compared to Atrovent HFA 84 mcg, there was no dose response effect noted for these anticholinergic side effects. These results are summarized in the following table.

*Reviewer's comments: The sponsor lists urinary tract infection and pharyngitis as anticholinergic adverse events, and excludes nausea as an anticholinergic adverse event. It is conceivable that urinary tract infection may be secondary to urinary stasis (an anticholinergic adverse event); however, the rationale for pharyngitis being an anticholinergic adverse event is unclear. For completeness sake, this reviewer has listed these adverse events as anticholinergic as summarized by the sponsor. Additionally, nausea has been added. As this is an anticholinergic drug, the occurrence of these adverse events is expected. The overall incidence is low and comparable to the currently marketed Atrovent CFC 42 mcg product.*

**Table 17. Anticholinergic Adverse Events Reported in Phase II and Phase III Trials\***

	HFA	Atrovent HFA			CFC	Atrovent CFC	All Patients
	n (%)	n (%)			n (%)	n (%)	n (%)
	Placebo n=142	21 mcg n=80	42 mcg n=787	84 mcg n=197	Placebo n=106	42 mcg n=490	n=1543
<b>Total with any AE</b>	7 (5)	1 (1)	118 (15)	10 (5)	6 (6)	57 (12)	200 (13)
<b>GASTROINTESTINAL DISORDERS</b>							
Constipation	1 (<1)	0	16 (2)	2 (1)	1 (<1)	10 (2)	30 (2)
Dry Mouth	0	0	21 (3)	3 (2)	0	10 (2)	37 (2)
Dysphagia	2 (1)	0	0	1 (<1)	0	0	1 (<1)
Nausea	1 (<1)	0	21 (3)	6 (3)	2 (2)	8 (2)	38 (2)
<b>HEART RATE AND RHYTHM DISORDERS</b>							
Tachycardia	0	1 (1)	7 (<1)	0	0	6 (1)	14 (<1)
Supraventricular Tachycardia	0	0	1 (<1)	0	0	0	1 (<1)
<b>RESPIRATORY SYSTEM DISORDERS</b>							
Pharyngitis	2 (1)	0	33 (4)	2 (1)	1 (<1)	14 (3)	52 (3)
<b>URINARY SYSTEM DISORDERS</b>							
Micturition Disorder	1 (<1)	0	0	1 (<1)	0	0	2 (<1)
Micturition Frequency	1 (<1)	0	5 (<1)	0	1 (<1)	2 (<1)	9 (<1)
Urinary Retention	1 (<1)	0	3 (<1)	0	1 (<1)	0	5 (<1)
Urinary Tract Infection	0	0	35 (4)	1 (<1)	1 (<1)	18 (4)	55 (4)
<b>VISION DISORDERS</b>							
Glaucoma	0	0	5 (<1)	1 (<1)	0	0	6 (<1)
Vision Abnormal	0	0	8 (1)	0	1 (<1)	3 (<1)	12 (<1)
Xerophthalmia	0	0	1 (<1)	0	0	0	1 (<1)

Source: Vol. 47, p. 58

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### 7.5.2. Deaths

Of the 11 trials submitted in this application, 21 deaths were reported. These occurred in the three phase III pivotal studies. No deaths were reported in any of the other studies. Fourteen deaths occurred during the randomized treatment period, while seven occurred post-treatment. Of these 14 deaths, 9 (0.97%) were reported in the Atrovent HFA 42 mcg group, 3 (0.52%) in the Atrovent CFC 42 mcg group, 1 (0.45%) in the Atrovent HFA 84 mcg group, and 1 (0.60%) in the HFA placebo group. Pulmonary carcinoma was reported in five patients as the cause of death, COPD exacerbation was reported in four patients, and acute renal failure, pancreatitis, cardiac arrest, bronchitis, adenocarcinoma, gastro-intestinal disorder, abnormal renal function and respiratory insufficiency were each reported once as a cause of death. Some patients had more than one reason listed as cause of death. This is summarized in the following table.

**Table 18. Adverse Events\* Resulting in Death in Phase III Pivotal Studies**

	Patient Number	HFA Placebo n	Atrovent HFA 42 mcg n	Atrovent HFA 84 mcg n	Atrovent CFC 42 mcg n
<b>GASTROINTESTINAL DISORDERS</b>					
Gastrointestinal Disorder NOS	2563				1
Pancreatitis	2176		1		
<b>CARDIOVASCULAR DISORDERS</b>					
Cardiac Arrest	3198		1		
<b>NEOPLASM</b>					
Adenocarcinoma NOS	3225		1		
Pulmonary Carcinoma	2015 2090 2184 2605 2836	1	2	1	1
<b>RESPIRATORY SYSTEM DISORDERS</b>					
Bronchitis	122		1		
COPD Exacerbation	122 1899 1963 2956		3		1
<b>RENAL DISORDERS</b>					
Acute Renal Failure	3031		1		
Renal Function Abnormal	3225		1		

\*Some patients had more than one adverse event listed as cause of death

Source: Vol. 47, p. 40-43

The nine deaths that occurred in the Atrovent HFA 42 mcg treatment group during the randomization period are summarized below.

Study 244.1405

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- Patient 1899 was a 59 yr old white female who was treated for a COPD exacerbation 13 days into treatment with Lorabid, Floxin, Depomedrol, Prednisone, and Doxycycline. The patient had persistent symptoms and was referred to a pulmonary rehabilitation center, and discontinued from the trial about 2 weeks later. She continued to have persistent COPD symptoms, and a month later she had a productive cough with yellow sputum, tightness in the back with sweats and fatigue for which she was treated with Doxycycline and Biaxin. The exacerbation did not resolve and 35 days later the patient was rushed to the ER for severe COPD; she died that day of a COPD exacerbation and heart failure.
- Patient 1963 was a 79-year old white male who was found collapsed on the floor with agonal breathing (a respiratory rate of 4/min) and a pulse of 80 bpm, 35 days after randomization into treatment. Shortly after intubation, the patient developed asystole, was successfully resuscitated and transferred to the ICU on mechanical ventilation with a diagnosis of post-cardiopulmonary arrest, acute respiratory failure and exacerbation of severe COPD. He was diagnosed with severe anoxic, ischemic injury and three days later he died of respiratory arrest. The cause of death was reported as respiratory failure and severe COPD.
- Patient 2090 was an 81 year old white female who was hospitalized for chest pain 12 days into treatment with study drug and treated with Ventolin successfully. However, a chest x-ray revealed a mass, and subsequent evaluation led to the diagnosis of small cell carcinoma of the lung with metastasis. The patient was discontinued from the trial after 44 days of treatment, and died one month after discontinuation from the trial, with the cause of death listed as small cell carcinoma with metastasis.
- Patient 2176 was a 55 year old white male who was admitted to the hospital with pancreatitis and upper GI bleeding secondary to erosive duodenitis 40 days into treatment with study drug. The patient subsequently developed complications leading to septic shock, cardiopulmonary arrest, acute renal failure, pneumonia, encephalopathy and thrombocytopenia. The patient was discontinued from the trial and subsequently died, with the cause of death listed as complications secondary to pancreatitis. [Vol. 67, p.200-203]

### Study 244.1408

- Patient #122 was a 68 year old male who seventy days after being randomized, was hospitalized for severe COPD exacerbation caused by an episode of acute bronchitis; the patient's respiratory status continued to deteriorate, despite apparent appropriate therapy, and the patient subsequently died five days later; the cause of death was COPD exacerbation caused by acute bronchitis.

### Study 244.2453

- Patient No. 2605 was a 61 year old white male who died of right lung cancer 351 days after initiation of therapy.
- Patient No. 3031 was a 66 year old white male was initially hospitalized for COPD exacerbation 275 days into treatment, with worsening respiratory failure that led to intubation/ICU admission; he then developed renal failure and subsequently died of renal failure.

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- Patient No. 3198 was a 69 year old white male who was diagnosed with a CVA 12 days into treatment, recovered from a carotid endarterectomy, continued in the trial and 182 days into treatment, was brought into the ER following an unwitnessed cardiac arrest and died within 24 hours of cardiac arrest.
- Patient No. 3225 was a 65 year old white male who died of metastatic adenocarcinoma and worsening renal function 158 days after initiation of treatment.

*Reviewer's comments: Overall, the incidence of death was low, and although it was slightly higher in the Atrovent HFA 42 mcg (0.97%) as compared to the Atrovent CFC 42 mcg (0.52), the causes of death in these studies are not unexpected given the study population. Furthermore, no dose response effect was noted when compared to placebo (0.60%) and Atrovent HFA 84 mcg (0.45%).*

### 7.5.3. Serious Adverse Events

In the three pivotal studies, of the 1137 randomized patients, 145 (13%) reported at least one serious adverse event (SAE). The incidence of SAEs was similar between the Atrovent HFA 42 mcg group (79 patients, 14%) and Atrovent CFC 42 mcg (45 patients, 13%), and comparatively lower in the HFA placebo (7 patients, 11%) and Atrovent HFA 84 mcg (9 patients, 7%). The most frequently reported SAEs were COPD exacerbation (51 patients, 4%) and pneumonia (26 patients, 2%). In the Atrovent HFA 42 mcg, 23 patients (4%) reported COPD exacerbation and 15 patients (3%) reported pneumonia. The incidence of COPD exacerbation and pneumonia in the Atrovent CFC 42 mcg group was 6% (19 patients) and 2% (8 patients), respectively. All other SAEs occurred at an incidence of <1% and for these studies, the narratives have been reviewed and no SAEs of concern were identified. Given the study population, these SAEs are not unexpected and again no dose response was noted when Atrovent HFA 42 mcg was compared to placebo and Atrovent 84 mcg. Serious adverse events occurring in >1 patient in the Atrovent HFA 42 mcg are summarized below.

**Table 19. Serious Adverse Events Occurring in >1 Patient in the Atrovent HFA 42 mcg Group in the Three Phase III Pivotal Studies**

	Placebo HFA n (%)	Atrovent HFA 42 mcg n (%)	Atrovent HFA 84 mcg n (%)	Placebo CFC n (%)	Atrovent CFC 42 mcg n (%)	Total of All Treatments n (%)
<b>Total Treated</b>	<b>n=62</b>	<b>n=548</b>	<b>n=127</b>	<b>n=66</b>	<b>n=334</b>	<b>n=1137</b>
Total with any AE	7 (11)	79 (14)	9 (7)	5 (8)	45 (13)	145 (13)
<b>CARDIOVASCULAR DISORDERS</b>						
Angina Pectoris	0	2 (<1)	0	0	3 (<1)	5 (<1)
Atherosclerosis	0	2 (<1)	0	0	0	2 (<1)
Cerebrovascular Dz.	0	2 (<1)	0	0	2	4 (<1)
Cor Pulmonale	0	2 (<1)	1 (<1)	0	0	3 (<1)
Transient Ischemic Attack	0	3 (<1)	1 (<1)	0	0	4 (<1)
<b>GASTROINTESTINAL DISORDERS</b>						

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	Placebo HFA n (%)	Atrovent HFA 42 mcg n (%)	Atrovent HFA 84 mcg n (%)	Placebo CFC n (%)	Atrovent CFC 42 mcg n (%)	Total of All Treatments n (%)
<b>Total Treated</b>	<b>n=62</b>	<b>n=548</b>	<b>n=127</b>	<b>n=66</b>	<b>n=334</b>	<b>n=1137</b>
Abdominal Pain	0	2 (<1)	0	1 (2)	1 (<1)	4 (<1)
Cholecystitis	0	2 (<1)	0	0	0	2 (<1)
Cholelithiasis	1 (2)	2 (<1)	0	0	0	3 (<1)
Gastritis	0	2 (<1)	0	0	0	2 (<1)
<b>INFECTIOUS DISORDERS</b>						
Bacterial Infection	1 (2)	2 (<1)	0	0	0	3 (<1)
Sepsis	0	2 (<1)	0	0	0	(1)
<b>MUSCULOSKELETAL DISORDERS</b>						
Pathologic Fracture	0	2 (<1)	0	0	0	2 (<1)
<b>NEOPLASMS</b>						
Basal Cell Carcinoma	0	4 (<1)	0	0	1 (<1)	5 (<1)
Pulmonary Carcinoma	1 (2)	3 (<1)	1	0	2 (<1)	7 (<1)
<b>RESPIRATORY SYSTEM DISORDERS</b>						
Bronchitis	0	2 (<1)	0	0	1 (<1)	3 (<1)
COPD exacerbation	2 (3)	23 (4)	5 (4)	2 (3)	19 (6)	51 (4)
Pleural Effusion	0	2 (<1)	0	0	0	2 (<1)
Pneumonia	1 (2)	15 (3)	2 (2)	0	8 (2)	26 (2)
<b>URINARY SYSTEM DISORDERS</b>						
Urinary Retention	0	2 (<1)	0	0	0	2 (<1)
<b>VISION DISORDERS</b>						
Cataract	0	2 (<1)	0	0	0	2 (<1)

Source: Vol. 47, p. 45-50

### 7.5.4. Adverse Events Leading to Study Withdrawal

In the three pivotal studies, 88 patients out of 1137 (8%) discontinued prematurely due to adverse events. The most common reason for discontinuation was COPD exacerbation (26 patients, 2%). The greatest percentage of patients discontinued secondary to COPD exacerbation in the CFC placebo treatment group (4 patients, 6%), followed by placebo HFA (2 patients, 3%), Atrovent HFA 84 mcg (4 patients, 3%) and Atrovent CFC 42 mcg (10 patients, 3%). The Atrovent HFA 42 mcg group had the lowest incidence (6 patients, 1%) of study withdrawal secondary to COPD exacerbation. Bronchitis, dyspnea, nausea, and pneumonia were other reasons for premature withdrawal from the study which occurred in greater than one patient in the Atrovent HFA 42 mcg treatment group. Adverse events leading to premature discontinuation occurring in greater than one patient in the Atrovent HFA 42 mcg treatment group are summarized in the following table.

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**Table 20. Adverse Events Leading to Study Withdrawal Occurring in >1 Patient in the Atrovent HFA 42 mcg Treatment Group in the Three Phase III Pivotal Studies**

	Placebo HFA n (%)	Atrovent HFA 42 mcg n (%)	Atrovent HFA 84 mcg n (%)	Placebo CFC n (%)	Atrovent CFC 42 mcg n (%)	Total of All Treatments n (%)
<b>Total Treated</b>	<b>n=62</b>	<b>n=548</b>	<b>n=127</b>	<b>n=66</b>	<b>n=334</b>	<b>n=1137</b>
Total with any AE	4 (6)	40 (7)	8 (6)	9 (14)	27 (8)	88 (8)
Bronchitis	0	3 (<1)	0	0	2 (<1)	5 (<1)
COPD Exacerbation	2 (3)	6 (1)	4 (3)	4 (6)	10 (3)	26 (2)
Dyspnea	0	2 (<1)	0	3 (5)	1 (<1)	6 (<1)
Nausea	0	2 (<1)	1 (<1)	0	1 (<1)	4 (<1)
Pneumonia	0	2 (<1)	1 (<1)	0	4 (1)	7 (<1)

Source: Vol. 47, p. 189-192

### 7.5.5. Paradoxical Bronchospasm in Phase III COPD Trials

The sponsor defined paradoxical bronchospasm as a decrease of greater than 15% in FEV<sub>1</sub> values— as compared to baseline—within the first 30 minutes following drug administration.

In Study 244.1405, 47 patients (9%) had FEV<sub>1</sub> results suggesting paradoxical bronchospasm; however, the majority were in the placebo HFA (10 patients, 16.1%) and placebo CFC (fifteen patients, 22.7) groups. In comparison, five patients (4%) in the Atrovent HFA 42 mcg, seven patients (5.5%) in the Atrovent HFA 84 mcg, and ten patients (7.9%) in the CFC 42 mcg treatment groups had paradoxical bronchospasm. In none of these cases was there any associated shortness of breath or need for rescue medication.

In Study 244.1408, paradoxical bronchospasm was reported in 12 patients (7%). The incidence of paradoxical bronchospasm was higher in the CFC 42 mcg treatment group (nine patients, 16%) as compared to the HFA 42 mcg group (three patients, 3%).

In Study 244.2453, 32 patients (7%) reported paradoxical bronchospasm. In contrast to the other trials, the incidence was slightly higher in the Atrovent HFA 42 mcg treatment group (23 patients, 7.5%) as compared to the Atrovent CFC 42 mcg treatment group (9 patients, 5.9%). No associated shortness of breath was noted, nor was rescue medication required when this decrease in FEV<sub>1</sub> was noted.

Overall, combining the results of all three studies, it does not appear that there is a tendency for the development of paradoxical bronchospasm with Atrovent HFA 42 mcg.

### 7.5.6. Vital Signs and Physical Examination

#### 7.5.6.1. Vital Signs

On each pulmonary function test day, pulse rate and blood pressure were measured prior to inhalation of study drug and at pre-specified intervals (see study protocols for pivotal studies) post-inhalation. For acute changes in vital signs, the pre-inhalation values on any given test day were compared at vitals obtained at peak drug effect. For chronic changes,

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the pre-inhalation values on the first test day were compared to pre-inhalation values on the last test day.

In general, in Atrovent HFA 42 mcg, Atrovent CFC 42 mcg, and placebo, there was a tendency toward a lower heart rate, systolic and diastolic blood pressures. However, there were no clinically meaningful differences noted between treatment groups. In terms of chronic changes in vital signs, there were no differences between the three treatment groups.

#### **7.5.6.2. Physical Examination**

When physical examinations were compared at baseline with the examinations at study discontinuation, no clinically meaningful differences between the treatment groups were noted (Atrovent HFA 42 mcg, Atrovent CFC 42 mcg, and placebo). Any significant changes in physical examination were reported as adverse events.

#### **7.5.7. Laboratory Observations and EKG Evaluations**

Laboratory testing was performed at baseline and at the final visit in most Phase II and all Phase III pivotal studies. Hematology, blood chemistries, and urinalysis were performed on all subjects. When active treatments were compared to each other or to placebo, no consistent differences were noted between treatment groups. No consistent trends were identified.

EKG evaluations were done at baseline and at the end of the trial in the two twelve-week phase III trials and at baseline Week 12, 26, and 52 in the one-year safety study. As with the laboratory evaluations, no consistent trends between active treatments and placebo were noted. No clinically meaningful differences in EKGs were noted.

#### **7.5.8. Subgroup Analysis**

The sponsor performed the following analyses: oral and inhaled corticosteroids, theophylline, drug-age interaction, drug-smoking status interaction, drug-disease severity interaction, drug-gender interaction, and drug race interaction.

##### **7.5.8.1. Drug-Oral and Inhaled Corticosteroid Interaction**

In terms of adverse events in inhaled corticosteroid non-users and users, there were no meaningful differences between Atrovent HFA 42 mcg and CFC 42 mcg in non-users and users.

For oral corticosteroid interactions, the percentage of non-users who reported adverse events was lower (74% in both Atrovent HFA 42 mcg and Atrovent CFC 42 mcg) as compared to oral corticosteroid users (96% for Atrovent HFA 42 mcg and 90% for Atrovent CFC 42 mcg). This may be because the oral corticosteroid users were sicker and may have used the oral corticosteroids during a COPD exacerbation.

##### **7.5.8.2. Drug-Theophylline Interaction**

The percentage of theophylline non-users who reported adverse events (78% for both Atrovent HFA 42 mcg and Atrovent CFC 42 mcg) was similar to the percentage of

theophylline users who reported adverse events (81% and 73% in the Atrovent 42 mcg and Atrovent CFC 42 mcg treatment groups, respectively).

In terms of individual AEs, bronchitis and upper respiratory tract infections were reported at a higher rate (19% and 25% for bronchitis and URI, respectively) in theophylline users taking Atrovent HFA 42 mcg as compared to theophylline users taking Atrovent CFC 42 mcg (10% and 16% for bronchitis and URI, respectively). The sponsor reasons that this imbalance may be secondary to the small number of theophylline users who were involved in this comparison (22%). This reviewer is uncertain of the clinical significance of this finding.

#### **7.5.8.3. Drug-Age Interaction**

To determine the effect of age on adverse events during treatment with Atrovent HFA 42 mcg and Atrovent CFC 42 mcg, the sponsor performed a subgroup analysis on patients less than 65 years of age and greater than or equal to 65 years of age.

The frequency of AEs was similar in the less than 65 years of age category (79% and 73% for Atrovent HFA 42 mcg and Atrovent CFC 42 mcg, respectively) to the 65 years of age and older category (79% and 80% for Atrovent HFA 42 mcg and CFC 42 mcg, respectively). However, edema, dizziness, constipation, dyspepsia, dry mouth, tachycardia, arthritis aggravated, dyspnea and cataract tended to occur more frequently in the 65 years of age and older group. Headache, household accidents, nausea, vomiting, pharyngitis, and sinusitis occurred more frequently in the less than 65 years of age group. These differences between the age groups were comparable between Atrovent HFA 42 mcg and Atrovent CFC 42 mcg. No consistent age related AEs were noted for any one treatment group.

#### **7.5.8.4. Drug-Smoking Status Interaction**

The sponsor analyzed the effect of smoking status on AEs by dividing patients into ex-smokers and current smokers. The frequency of AEs was similar between ex-smokers (79% and 77% for Atrovent HFA 42 mcg and Atrovent CFC 42 mcg) and current smokers (78% for both treatment groups). The "current smoker" group was associated with a slightly higher incidence of headache, influenza-like symptoms, bronchitis and cataract formation in both treatment groups, whereas COPD exacerbations were reported at a higher rate in ex-smokers.

#### **7.5.8.5. Drug-Disease Severity Interaction**

Subgroup analyses were performed on the following categories: severe COPD ( $FEV_1 < 35\%$  predicted), moderate COPD ( $FEV_1$  between 35-50% inclusive) and mild COPD ( $FEV_1 > 50\%$  predicted). In these categories, the incidence of AEs was 77%, 82%, and 79% in the Atrovent HFA 42 mcg group and 75%, 80%, and 77% in the Atrovent CFC 42 mcg group, respectively. A rank ordering effect was noted with COPD exacerbations, with the percentage of patients reporting COPD exacerbations increasing with increasing disease severity; this finding was noted in both treatment groups and is not unexpected. No other consistent differences were noted.

#### 7.5.8.6. Drug-Gender Interaction

To determine the effect of gender on AEs, the percentage of patients with adverse events was compared for males and females. Females reported AEs at a slightly higher frequency (83% and 81% in the Atrovent HFA 42 mcg and CFC 42 mcg, respectively) than males (76% and 75%, respectively). The incidence of the following was higher in females as compared to males in the Atrovent HFA 42 mcg treatment group: back pain (7% vs. 3%); headache (9% vs. 5%); diarrhea (6% vs. 2%); dyspepsia (6% vs. 1%); pneumonia (6% vs. 4%); sinusitis (11% vs. 4%); upper respiratory infection (31% vs. 18%); urinary tract infection (11% vs. 3%); and conjunctivitis (4% vs. 0%). The same differences were noted in the Atrovent CFC 42 mcg as well, with the exception of URIs and pneumonia. Upper respiratory infections (23% vs. 19%) and pneumonia (6% vs. 1%) occurred more frequently in males in the Atrovent CFC 42 mcg treatment group.

*Reviewer's comments: These gender effects were compared with the HFA 84 mcg treatment group, and no consistent trends/gender effects were noted.*

#### 7.5.8.7. Drug-Race Interaction

The sponsor compared the incidence of AEs between Whites and Blacks. As the majority of the study population was White, no clinically meaningful comparisons can be made.

### 7.6. Miscellaneous Studies

As has been discussed earlier, the to-be-marketed product, is a third generation Atrovent HFA 42 mcg product, and the pivotal studies were done with the first generation Atrovent HFA 42 mcg product. There are two studies where the third generation product was used: Study 244.2498 (a single-dose efficacy trial) and 244.2480 (a 7-day PK trial). The safety findings from these studies follow.

#### 7.6.1. Study 244.2498

This was a 5-treatment, multi-center, randomized, double-blind, single-dose, crossover trial in 41 male and female patients 40 years and older with chronic obstructive pulmonary disease, designed to bridge the product (device/drug) used in the clinical Phase III clinical program to the proposed commercial product. Patients received single doses of HFA-MDI 21 mcg, HFA-MDI 42 mcg, CFC-MDI 21 mcg, CFC-MDI 42 mcg, and placebo administered in a cross-over fashion.

Twelve patients reported 24 AEs by midnight on the day of study drug administration. The most commonly reported AE was rhinitis; it was reported in 4 patients (9.8%): 1 during the screening period and in 3 during the washout period. Headache, diarrhea and skin rash, were each reported in 2 patients (4.9%). All other noted AEs were reported in one patient. No AEs were reported during the treatment period for Atrovent HFA 42 mcg, CFC 42 mcg, or placebo. Only three patients reported AEs during any treatment period, one during the HFA-MDI 21 mcg and two during the CFC-MDI 21 mcg treatment period. The rest were reported during the screening period (5 patients, 12.2%), washout period (7 patients, 17.1%) or post-treatment (1 patient, 2.4%).

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No deaths occurred during this study and only one SAE was reported. A 68 year old white female reported increased congestion and shortness of breath one day prior to Visit 6 (final visit). The patient received the final treatment (HFA-42 mcg) on Visit 6, and the following day was hospitalized for respiratory failure (for which the patient was intubated) and viral infection; the respiratory failure lasted for 5 days and the viral infection lasted for 17 days. The patient was reported to have recovered with a sufficient follow-up visit.

No clinically meaningful changes were noted in laboratory observations or vital signs.

### 7.6.2. Study 244.2480

This was a two-center, two-treatment, open-label, randomized, cross-over study designed to compare the pharmacokinetic parameters of 84 mcg of HFA-MDI and 84 mcg of CFC-MDI in COPD patients. The pharmacokinetic analysis reveals that there is less systemic exposure to ipratropium bromide following 84 mcg of HFA-MDI than following 84 mcg of CFC-MDI. This is reassuring from a safety standpoint.

Five patients experienced 6 adverse events: 2 patients (6.7%) and 3 patients (10.3%) in the HFA-MDI and CFC-MDI treatment periods, respectively. All reported adverse events occurred in one subject each. The two AEs in the HFA-MDI group were a house hold accident (black eye) and pancreatitis. One subject had phlebitis reported in the post-treatment period. There were no reported COPD exacerbations during this study.

No deaths were reported, and one SAE was reported in this study. The SAE was reported in a 59 year old white male who had elevated LFTs at the screening visit, which was an entry criteria protocol violation. One day after the patient completed the HFA-MDI randomized period, he developed abdominal pain and was hospitalized with a subsequent diagnosis of pancreatitis; the patient also developed phlebitis at the site of his PICC line a week later. The patient was discharged from the hospital after resolution of his symptoms; additional history revealed that he was an alcoholic. This reviewer does not feel that this SAE was related to study drug administration.

No clinically meaningful changes in laboratory parameters, vital signs, or EKGs were noted in this study.

No safety concerns have arisen from this study. Overall, in this study the 3<sup>rd</sup> generation HFA-MDI product had comparable safety to the currently marketed CFC-MDI Atrovent product.

### 7.7. Literature Review of Safety

The sponsor has submitted several references in the ISS. These have been briefly reviewed and no safety concerns have arisen. The conclusions are similar for all of these: Atrovent HFA 42 mcg and Atrovent CFC 42 mcg are comparable in terms of both efficacy and safety.

### 7.8. Postmarketing Surveillance

As Atrovent HFA is not approved in the U.S., there is no U.S. post-marketing information; however, the sponsor states that there have not been any spontaneous reported AEs from marketing experience anywhere in the world where Atrovent HFA is approved as of 3/1/2003. [N-000-SU, 4/3/03, p. 1]

Conclusions and Recommendations

### 7.9. Safety Update

The sponsor submitted a 4-month safety update [N-000-SU, 4/3/03] to satisfy the safety update regulations in the CFR. However, no additional Atrovent HFA safety data were generated and there are no ongoing or completed Atrovent HFA trials that would contribute to any new safety information that was not submitted in the original NDA application.

### 7.10. Drug Withdrawal, Abuse, and Overdose Experience

The sponsor states that abuse potential by inhalation is unlikely since Atrovent is not readily absorbed into the systemic circulation either from the lung or the gastrointestinal tract, as confirmed by blood level and renal excretion studies. Furthermore, autoradiographic studies in rats have shown that Atrovent does not penetrate the blood-brain barrier. The sponsor does not expect Atrovent HFA to be subject to abuse. In the clinical development program for Atrovent HFA, the sponsor states that no overdose or abuse of the study drug was reported. [Vol. 45, p. 148-149]

### 7.11. Adequacy of Safety Testing

The safety assessments performed in the pivotal studies were satisfactory. However, the reader is reminded that the drug product used in the pivotal studies is not the to-be-marketed product. The 3<sup>rd</sup> generation drug product has not been studied in any long-term trials, although there are two short-term trials (one single-dose and one 7-day PK study).

Generally, to be assured of safety, a long-term safety study should be conducted; however, the PK studies reviewed demonstrate that the systemic exposure is lower in the 3<sup>rd</sup> generation HFA 42 mcg product as compared to the currently marketed Atrovent CFC 42 mcg treatment group. Given that the systemic exposure is lower, and that no safety concerns have arisen from the two short-term studies with the 3<sup>rd</sup> generation product, it is doubtful that a long-term study with the 3<sup>rd</sup> generation product would reveal any significant safety concerns.

### 7.12. Labeling Safety Issues and Postmarketing Commitments

There are no labeling safety issues and no Postmarketing commitments are needed.

## 8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The proposed dose of Atrovent HFA is 42 mcg, administered as two inhalations four times a day. This is acceptable based on reviewed two clinical studies: Study 244.1405 and Study 244.2498. Study 244.1405 was a 12-week, randomized, double-blind, placebo, active controlled study with two doses of Atrovent HFA studied: 42 mcg and 84 mcg. In this study, the 84 mcg dose was not noted to have any superior efficacy as compared to the 42 mcg dose. In the single-dose study, 244.2498, Atrovent HFA 21 mcg and 42 mcg were compared. The 42 mcg dose did have better efficacy as compared to the 21 mcg dose—mean FEV<sub>1</sub> AUC<sub>0-6</sub> of 0.215 liters with the 42 mcg dose as compared to 0.179 liters with the 21 mcg dose. Based on these studies, the 42 mcg dose is supported.

The interval may be supported by Study 244.2498, which is the only study that has any efficacy data using the 3<sup>rd</sup> generation, to-be-marketed product. In this study, the median duration of action for Atrovent HFA 42 mcg was 4.8 hours and Atrovent CFC 42 mcg was 5.4 hours. This may support the QID dosing. However, the sponsor has summarized the data in terms of medians and not means, and the utility of medians to classify such data may be limited.

## 9. USE IN SPECIAL POPULATIONS

### 9.1. Evaluation of Applicant's Gender, Age, Race, or Ethnicity Efficacy and Safety Analyses and Adequacy of Investigation

#### 9.1.1. Efficacy

##### 9.1.1.1. Effect of Gender

There were more males than females in all treatment arms. For both FEV<sub>1</sub> AUC<sub>0-6</sub> and Peak FEV<sub>1</sub> response, both Atrovent HFA 42 mcg and CFC 42 mcg demonstrated statistically superior results compared to placebo at all timepoints tested (p-values ranged from 0.0001 to 0.0006). For both parameters, Atrovent HFA 42 mcg and CFC 42 mcg were comparable for both subgroups on all test days. In terms of ANOVA testing for treatment by gender subgroup interaction, statistically significant interactions for FEV<sub>1</sub> AUC<sub>0-6</sub> (p-value of 0.04) and Peak FEV<sub>1</sub> response (p-value of 0.0073) were noted on Day 29 only. These effects were attributed to an effect noted for Atrovent HFA 84 mcg, which demonstrated greater mean FEV<sub>1</sub> AUC<sub>0-6</sub> and Peak FEV<sub>1</sub> response in males as compared to females. No gender effect was noted for either Atrovent HFA 42 mcg or CFC 42 mcg.

##### 9.1.1.2. Effect of Age

The FEV<sub>1</sub> AUC<sub>0-6</sub> responses for the age subgroups, < 65 years and ≥ 65 years demonstrated statistically significance differences compared to placebo (p-values ranged 0.003 to 0.0001) for both age subgroups analyzed. For subgroup analyses, ANOVA was used, and this did not demonstrate any significant treatment by age interactions for FEV<sub>1</sub> AUC<sub>0-6</sub>.

For the Peak FEV<sub>1</sub> responses, all active treatment groups were statistically superior compared to placebo for both age subgroups analyzed (p-values ranged from 0.0001 to 0.0187). The ANOVA testing for treatment by age subgroup interaction for Peak FEV<sub>1</sub> responses resulted in statistically significant interactions for test days 57 (p-value of 0.03) and 85 (p-value of 0.02). These interactions, however, did not appear to be related to either placebo or Atrovent HFA 42 mcg. It appears that these differences may be attributed to Atrovent HFA 84 mcg. [Vol. 46, p. 198, 269] No meaningful differences were noted between the two age groups for Atrovent HFA 42 mcg in terms of Peak FEV<sub>1</sub> response.

For both parameters, Atrovent HFA 42 mcg and CFC 42 mcg were comparable for both subgroups on all test days.

**9.1.1.3. Effect of Race**

As the majority of the study population was White (96%), a subgroup efficacy analysis was not performed.

**9.1.2. Safety****9.1.2.1. Effect of Gender**

To determine the effect of gender on AEs, the percentage of patients with adverse events was compared for males and females. Females reported AEs at a slightly higher frequency (83% and 81% in the Atrovent HFA 42 mcg and CFC 42 mcg, respectively) than males (76% and 75%, respectively). The incidence of the following was higher in females as compared to males in the Atrovent HFA 42 mcg treatment group: back pain (7% vs. 3%); headache (9% vs. 5%); diarrhea (6% vs. 2%); dyspepsia (6% vs. 1%); pneumonia (6% vs. 4%); sinusitis (11% vs. 4%); upper respiratory infection (31% vs. 18%); urinary tract infection (11% vs. 3%); and conjunctivitis (4% vs. 0%). The same differences were noted in the Atrovent CFC 42 mcg as well, with the exception of URIs and pneumonia. Upper respiratory infections (23% vs. 19%) and pneumonia (6% vs. 1%) occurred more frequently in males in the Atrovent CFC 42 mcg treatment group.

*Reviewer's comments: These gender effects were compared with the HFA 84 mcg treatment group, and no consistent trends/gender effects were noted.*

**9.1.2.2. Effect of Age**

To determine the effect of age on adverse events during treatment with Atrovent HFA 42 mcg and Atrovent CFC 42 mcg, the sponsor performed a subgroup analysis on patients less than 65 years of age and greater than or equal to 65 years of age.

The frequency of AEs was similar in the less than 65 years of age category (79% and 73% for Atrovent HFA 42 mcg and Atrovent CFC 42 mcg, respectively) to the 65 years of age and older category (79% and 80% for Atrovent HFA 42 mcg and CFC 42 mcg, respectively). However, edema, dizziness, constipation, dyspepsia, dry mouth, tachycardia, arthritis aggravated, dyspnea and cataract tended to occur more frequently in the 65 years of age and older group. Headache, household accidents, nausea, vomiting, pharyngitis, and sinusitis occurred more frequently in the less than 65 years of age group. These differences between the age groups were comparable between Atrovent HFA 42 mcg and Atrovent CFC 42 mcg. No consistent age related AEs were noted for any one treatment group.

**9.1.2.3. Effect of Race**

As the majority of the study population was White, no clinically meaningful comparisons can be made with regard to race.

**9.2. Pediatric**

This drug is indicated for COPD. Since COPD is a disease of older adults, pediatric studies for the indication of COPD were not performed.

### 9.3. Geriatric

Pharmacokinetic parameters were compared for the geriatric population, >65 years of age with the <65 years of age. The results indicate that the pharmacokinetic behavior is comparable between the geriatric population and younger patients.

### 9.4. Comments on Data Available or Needed in Other Populations (Such as Renal or Hepatic Compromised Patients, Use in Pregnancy)

As this drug has been poorly studied in non-Caucasian patients, information on other races should be gathered. Although the sponsor has not studied renal or hepatic compromised patients, further studies in this population is not warranted as ipratropium bromide is poorly absorbed into the circulation following oral inhalation.

The sponsor has not studied this drug in pregnant women; however, based on animal study findings, this drug has been designated by the sponsor as Pregnancy Category B.

## 10. CONCLUSIONS AND RECOMMENDATIONS

### 10.1. Conclusions Regarding Safety and Efficacy

From a clinical standpoint, the data submitted in this NDA provide acceptable support for Approval. The data demonstrate that ipratropium bromide HFA inhalation aerosol 42 mcg four times a day provides statistically significant bronchodilation compared to placebo and comparable bronchodilation compared to the currently approved product ipratropium bromide inhalation aerosol with CFC propellants (Atrovent®) in patients with chronic obstructive pulmonary disease (COPD). The safety profile of ipratropium bromide HFA inhalation aerosol was acceptable and comparable to Atrovent®.

### 10.2. Recommendations on Approvability

From a clinical standpoint, this application is approval.

### 10.3. Labeling

The label has been preliminarily reviewed. These comments are preliminary labeling comments only and the final labeling comments will be provided once all of the CMC issues have been adequately addressed and this application is nearing approval.

#### 10.3.1. Labeling Comments to Sponsor

##### Comment 1

In the *Clinical Studies* section, paragraph 6, delete “ —

##### Comment 2

Under the *Precautions* section, subsection *Pediatrics*, delete —

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### Comment 3

In the *Adverse Events* section, recreate Table 3.1:1 to pool the results from all of the three pivotal trials (244.1405, 244.1408, and 244.2453) as done in Source Volume 48, p. 2. It is acceptable to pool the two placebo group results in the modified table.

### Comment 4

In the *Adverse Events* section, delete the final paragraph beginning with

**APPEARS THIS WAY  
ON ORIGINAL**

## APPENDIX

### 11. DETAILED STUDY REVIEWS

This NDA presents evidence from 11 clinical trials to support the safety and efficacy of Atrovent HFA for the indication of bronchospasm associated with chronic obstructive disease, including chronic bronchitis and emphysema. This appendix reviews 8 of the 11 studies. Studies 244.1403 and 244.1404 were omitted as they were single dose, Phase II studies that would not offer any additional useful information in the review of this NDA. Study — was omitted —

#### 11.1. Study #244.1405, Multiple Dose Comparison of Ipratropium Bromide HFA-134a and Ipratropium Bromide CFC in a 12-week, Double-Blind, Parallel Group Study in Adults with Chronic Obstructive Pulmonary Disease (COPD)

##### 11.1.1. Protocol

###### 11.1.1.1. Investigators and Centers

Protocol #: 244.1405

Title: Study #244.1405, Multiple Dose Comparison of Ipratropium Bromide HFA-134a and Ipratropium Bromide CFC in a 12-week, Double-Blind, Parallel Group Study in Adults with Chronic Obstructive Pulmonary Disease (COPD)

Study Dates: Initiated March 21, 1995. Completed March 13, 1996

Sites: 31 sites in the United States [Vol. 61, p. 31]

Investigators: 31 Principal Investigators

IRB: All 31 principal investigators have received appropriate IRB approval. The approval letters were reviewed for all. [Vol. 62, p. 12-114]

Ethical Considerations: The investigators agreed to conduct this study according to the Principles of Good Clinical Practices (GCP).

Source: Volume 61, pages 2, 20-23, 31; Volume 62, section 15.3.1

###### 11.1.1.2. Objective

The objective of this study was to compare the bronchodilator efficacy of two doses of ipratropium bromide HFA-134a, ipratropium bromide inhalation aerosol (containing CFC) and placebo formulations of each in patients with chronic obstructive pulmonary disease. An additional objective is to compare the safety profiles of ipratropium bromide HFA-134a and ipratropium bromide CFC.

### 11.1.1.3. Overall Design

This was a 12-week, randomized, double-blind, parallel-group, placebo and active-controlled, multi-center study evaluating the efficacy and safety of ipratropium bromide HFA-134a vs. ipratropium bromide CFC and placebo in 507 adults with chronic obstructive pulmonary disease (COPD), conducted in the United States from March 21, 1995 to March 13, 1996.

### 11.1.1.4. Study Population

Approximately 400 patients were planned for enrollment, 20 from each of 20 centers. [Vol. 61, P. 29] To achieve this goal, 23 sites were initiated; however, in order to meet enrollment goals and timelines, ten new sites were added. Two sites did not enroll any patients, leaving 31 active sites. [Vol. 61, p. 31] A total of 602 patients were screened and a total of 507 patients aged 40 and older with relatively stable, moderate to severe chronic obstructive pulmonary disease, were randomized to the study.

#### 11.1.1.4.1. Inclusion Criteria [Vol. 61, p.29, 210]

For inclusion in the study, all patients must:

- Have a diagnosis of chronic obstructive pulmonary disease according to the following criteria:
  - Patients must have relatively stable, moderate to severe airway obstruction with an  $FEV_1 \leq 65\%$  of predicted normal and  $FEV_1/FVC \leq 70\%$
- Be male or female age 40 years and older
- Have a smoking history of more than 10 pack-years—a pack-years is defined as the equivalent of smoking one pack of cigarettes per day for a year.
- Be able to satisfactorily administer the medication, perform pulmonary function tests and maintain record during the study period as required in the protocol.

#### 11.1.1.4.2. Exclusion Criteria [Vol. 61, p.29, 210]

The following are exclusion criteria:

- Patients with significant disease other than chronic obstructive pulmonary disease will be excluded. A significant disease is defined as a disease which in the opinion of the investigator may either put the patient at risk because of participation in the study or a disease which may influence the results of the study or the patient's ability to participate in the study.
- Patients with clinically significant abnormal baseline hematology, blood chemistry or urinalysis if the abnormality defines a disease listed as an exclusion criterion.
- All patients with SGOT > 80 IU/L, SGPT > 80 IU/L, bilirubin > 2 mg/dl, or creatinine > 2 mg/dl will be excluded regardless of the clinical condition. Repeat laboratory evaluation will not be conducted in these patients.
- Patients with a recent (i.e., one year or less) history of myocardial infarction

- Patients with a recent history (i.e., three years or less) of cardiac failure, patients with cardiac arrhythmias requiring drug therapy, patients receiving any beta-blockers and patients on chronic oxygen therapy.
- Patients with known active tuberculosis.
- Patients with a history of life-threatening pulmonary obstruction, or a history of cystic fibrosis or bronchiectasis.
- Patients who have undergone thoracotomy.
- Patients with any viral infection or febrile illness including upper respiratory infection during the six-week period preceding the Screening Visit.
- Patients with know hypersensitivity to anticholinergic drugs.
- Patients with know symptomatic prostatic hypertrophy or bladder-neck obstruction.
- Patients with know narrow-angle glaucoma.
- Patients who are on cromolyn sodium or nedocromil sodium.
- Patients who are on antihistamines.
- Pregnant or nursing women and women of childbearing potential not using a medically approved means of contraception (i.e., oral contraceptives, intrauterine devices, diaphragm or Norplant®).
- Patient who have taken an investigational drug within one month prior to the screening visit.
- Patients with history of asthma, allergic rhinitis or atopy or who have a blood eosinophil count above 600/mm<sup>3</sup>. A repeat eosinophil count will not be conducted in these patients.
- Patients with alcoholism or drug abuse.

*11.1.1.4.3. Prohibited Medications [Vol. 61, p. 214]*

The following are medications that were not allowed throughout the study period (from initial screening visit through the 12-week treatment period):

- any other investigational drug products (one month prior to screening visit)
- all beta-blockers
- cromolyn sodium/nedocromil sodium
- oral beta agonists or long-acting beta agonists such as salmeterol and formoterol
- antihistamines
- chronic oxygen therapy

*Reviewer's comments: the sponsor does not specify the duration of exclusion from therapy prior to study, with the exception of investigational drugs.*

*11.1.1.4.4. Allowed Therapy* [Vol. 61, p. 214]

- Medications allowed during the baseline period, but not allowed during the 12-week treatment period:
  - Atrovent®
- Medications allowed if stabilized for at least six weeks prior to, and throughout the study period:
  - Oral corticosteroids (only if the patient is stabilized on minimal doses of steroids, equivalent to < 10 mg of prednisone daily or 20 mg every other day)
  - Inhaled corticosteroids
  - Theophylline preparations
  - Mucolytic agents not containing bronchodilators
- Bronchodilators allowed to control acute exacerbations as medically necessary during the 12-week treatment period
  - Inhaled albuterol
  - Theophylline preparation (Two 5-day increases or additions were allowed during the 12-week treatment period. If the increases or additions occur prior to PFTs on Days 1, 29, 57, and 85, the testing will be postponed for two, but not more than seven days after the last increased or additional dose is given.)
  - Two 7-day temporary increases in the dose or addition of, oral steroids are allowed during the 12-week treatment period. If a burst occurs prior to pulmonary function testing Days 1, 29, 57, and 85, the testing will be postponed for two, but not more than seven days after the last increased or additional dose is given.

**11.1.1.5. Study Procedure**

This randomized, double-blind, active and placebo controlled study consisted of 8 total visits, to include a screening visit, followed by a two-week baseline period. During this baseline period, all screened subjects received open label Atrovent® Inhalation Aerosol (CFC-MDI, two puffs, 21 mcg, four times a day). After this baseline period, patients who still met the inclusion criteria and were stable on allowed therapy, were randomized to receive either ipratropium bromide HFA 42 mcg (two puffs, 21 mcg, each), ipratropium bromide HFA (84 mcg (two puffs, 42 mcg each), placebo HFA, ipratropium bromide CFC 42 mcg (two puffs, 21 mcg each) or placebo CFC QID for twelve weeks. [Vol. 61, p. 27] A blinding device was used to blind all study medications—further information on the blinding device was not apparent in the application. Subjects were randomized in a 2:1 ratio between active treatment and placebo in blocks of eight. Subjects returned on Days 15, 29, 43, 57, 71, and 85 for follow up (every two weeks). Eight-hour pulmonary function testing was conducted on days 1, 29, 57, and 85 at the following intervals: pre-treatment, 15, 30, 60, and 90 minutes, and 2, 3, 4, 5, 6, 7, and 8 hours post-dose. To ensure adherence to the washout requirements, theophylline levels were measured prior to pulmonary function testing in those subjects taking theophylline. At the final visit, day 85, laboratory tests, and EKGs, in

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addition to PFTs were repeated. The following table summarizes the flow chart for the study.

**Table 21. Study 244.1405: Procedure Flow Chart**

Trial Period	Screen	Treatment Period (12 weeks)						
Visit	Screening visit	1	2	3	4	5	6	7
Day	-14	1	15	29	4	57	71	85
Medical History	✓							
Physical Examination	✓							✓
Laboratory Tests (hematology, chemistry and U/A)	✓							✓
12-Lead EKG	✓							✓
Pulmonary Function Test	✓	✓		✓		✓		✓
Vital Signs	✓	✓		✓		✓		✓
Theophylline level	✓	✓		✓		✓		✓
Symptom Scores, Global Evaluation, Summary of Medication used		✓	✓	✓	✓	✓	✓	✓
Medication Administered		✓		✓		✓		✓
Medication Dispensed		✓	✓	✓	✓	✓	✓	✓
Dispense Medication Record	✓	✓	✓	✓	✓	✓	✓	
Atrovent/Albuterol dispensed	✓							
Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant Medications	✓	✓	✓	✓	✓	✓	✓	✓

Source: Vol. 61, p. 39

### 11.1.1.5.1. Treatments [Vol. 61, p. 32]

The following table presents the five randomized treatments in this study.

**Table 22. Study 244.1405, Treatments**

Treatment	Lot Number	Dosing
Ipratropium bromide monohydrate HFA-134a 21mcg/inh	PD 1456	2 puffs QID
Ipratropium bromide monohydrate HFA-134a 42mcg/inh	PD 1458	2 puffs QID
Placebo HFA-134a inhalation aerosol	PD 1457	2 puffs QID
Ipratropium bromide CFC 21 mcg/inh	PD 1488	2 puffs QID
Placebo CFC inhalation aerosol	PD 1381	2 puffs QID

Source: Vol. 61, p. 32

*Reviewer's comments: Since initiation of the development plan for Atrovent HFA, the sponsor has had to change the final product secondary to chemistry, manufacturing, and control issues. In this process, the sponsor has produced three Atrovent HFA products: 1<sup>st</sup> generation, 2<sup>nd</sup> generation, and 3<sup>rd</sup> generation. The sponsor proposes to market the 3<sup>rd</sup> generation product; however, this study has been conducted with the 1<sup>st</sup> generation Atrovent HFA product. Review of subsequent studies will determine if there is an adequate link between the first generation and third generation products.*

### 11.1.1.6. Efficacy Parameters [Vol. 61, p. 34-35]

Primary

- FEV<sub>1</sub> AUC<sub>0-6</sub>
- Peak FEV<sub>1</sub> response

*Reviewer's comments: there is a discrepancy in the primary efficacy endpoint between the study description and the original protocol. Originally, FEV<sub>1</sub> AUC<sub>0-4</sub> was listed as the primary efficacy endpoint. However, the sponsor changed it to FEV<sub>1</sub> AUC<sub>0-6</sub> "because the FDA medical reviewer expressed an interest in the endpoint FEV<sub>1</sub> AUC<sub>0-6</sub>" and the sponsor has seen consistent results with AUC<sub>0-4</sub> and AUC<sub>0-6</sub>. [Vol. 61, p. 47, p.223] This change has been discussed with Dr. Jim Gebert, the statistician assigned to this NDA; he does not feel that this will affect the analysis to any significant degree.*

Secondary

- FEV<sub>1</sub> AUC<sub>0-4</sub>, FEV<sub>1</sub> AUC<sub>4-6</sub>, FEV<sub>1</sub> AUC<sub>6-8</sub>
- Onset of 15% increase from baseline in FEV<sub>1</sub>
- Duration of 15% increase from baseline in FEV<sub>1</sub>
- Time to peak FEV<sub>1</sub> change from baseline
- FEV<sub>1</sub> changes from test-day baseline at each timepoint
- FEV<sub>1</sub> total area under the curve
- FVC AUC<sub>0-4, 0-6, 4-6, 6-8</sub>, and peak response and changes from baseline at each timepoint
- Physician's global evaluation
- COPD symptom scores (wheezing, shortness of breath, coughing and tightness of chest)
- Amount of albuterol used to control acute exacerbations during the 12-week treatment period

**11.1.1.7. Safety Evaluations**

- Adverse Events
- Laboratory testing
  - Hematology: CBC, absolute eosinophil count
  - Chemistry: alkaline phosphatase, LDH, SGOT, SGPT, glucose, calcium, inorganic phosphorus, uric acid, BUN, creatinine, total protein, albumin, and total protein
  - Urinalysis
- EKG
- Vital signs
- PFTs

**11.1.1.8. Statistical Plan**

To establish the efficacy of ipratropium bromide HFA, each dose was compared to a placebo and to ipratropium bromide CFC. The null hypothesis tested was that the mean response to

each of the doses of ipratropium bromide HFA was equal to the mean response to placebo HFA for the two primary endpoints: FEV<sub>1</sub> AUC<sub>0-6</sub> and peak FEV<sub>1</sub> response. Additionally, the sponsor compared the efficacy of ipratropium bromide HFA 42 mcg and ipratropium bromide CFC 42 mcg using a 90% confidence interval for the mean differences between the treatments in terms of FEV<sub>1</sub> AUC<sub>0-6</sub> and peak response.

#### 11.1.1.8.1. Sample Size Considerations

The primary comparison of interest was between ipratropium HFA and placebo. The sponsor based the sample size calculation on data from previous trials with similar compounds in patients with COPD, using the endpoint FEV<sub>1</sub> AUC<sub>0-4</sub>. A sample size of 400 was selected to allow 100 patients in each of the ipratropium bromide HFA (42 mcg and 84 mcg) group, 100 patients in the ipratropium bromide CFC group, and 100 patients in the placebo (50 in the 42 mcg HFA placebo and 50 in the 84 mcg HFA placebo) groups. This would ensure a 90% power to detect a 90 ml difference between ipratropium bromide HFA 42 mcg and placebo HFA or between ipratropium bromide HFA 84 mcg and placebo HFA in adjusted mean FEV<sub>1</sub> AUC<sub>0-4</sub> at a 5% significance level assuming a standard deviation of 160 ml. [Vol. 61, p. 45]

*Reviewer's comments: This reviewer discussed with Dr. Jim Gebert, biostatistician the fact that 507 patients were randomized, when only 400 were planned. Taking into account attrition during the study, the higher number randomized would ensure that there would be an adequate number of subjects in each treatment group that would complete the study.*

#### 11.1.1.8.2. Handling of Missing Data

Missing data was handled differently for a few parameters. For patients withdrawn from the study, the last observation was carried forward to estimate the missing data. To estimate random, middle or missing spirometry measurements for patients not withdrawn, linear interpolation between the two adjacent measurements was used. If the data for the last measurement was missing, then the last observation was carried forward. Similarly, linear interpolation was used if the PFT was not performed within the following time windows:  $\pm 5$  minutes for the 15 and 30 observations and  $\pm 10$  minutes for the later observations. For physician's global evaluation, COPD symptom scores and albuterol dosing scores, the last observation was carried forward. [Vol. 61, p. 46]

#### 11.1.1.8.3. Primary Efficacy Analyses

The primary efficacy endpoints were analyzed using ANOVA, with the statistical model including center, treatment, treatment by center, and baseline values as covariates. The pairwise treatment comparisons of each dosage strength of ipratropium bromide HFA to placebo HFA were planned to establish efficacy. [Vol. 61, p. 47] There were two primary efficacy endpoints in the comparisons: FEV<sub>1</sub> AUC<sub>0-6</sub> and the peak change from baseline in FEV<sub>1</sub>. The intent-to-treat population was the primary analysis population, defined as all patients randomized to the study.

*Reviewer's comments: It is unclear from the application what timepoints were compared. It is apparent that the sponsor has compared the primary efficacy endpoints on each of the*

*pulmonary function testing days: day 1, 29, 57, and 85. The sponsor states that no statistical adjustments were made for multiple comparisons.*

#### 11.1.1.8.4. Secondary Efficacy Analyses

Most of the secondary analyses were done using ANOVA as described in the primary efficacy analyses section. The secondary efficacy parameters are depicted below:

- FEV<sub>1</sub> AUC<sub>0-4</sub>, FEV<sub>1</sub> AUC<sub>4-6</sub>, FEV<sub>1</sub> AUC<sub>6-8</sub>
- Onset of 15% increase from baseline in FEV<sub>1</sub>
- Duration of 15% increase from baseline in FEV<sub>1</sub>
- Time to peak FEV<sub>1</sub> change from baseline
- FEV<sub>1</sub> changes from test-day baseline at each timepoint
- FEV<sub>1</sub> total area under the curve (FEV<sub>1</sub> TAUC)
- FVC AUC<sub>0-4, 0-6, 4-6, 6-8</sub>, and peak response and changes from baseline at each timepoint
- Physician's global evaluation was evaluated using the following scale:
  - 1-2 = poor
  - 3-4 = fair
  - 5-6 = good
  - 7-8 = excellent
- COPD symptom scores (wheezing, shortness of breath, coughing and tightness of chest)
- Amount of albuterol used to control acute exacerbations during the 12-week treatment period

For FEV<sub>1</sub> TAUC, physician's global evaluation, COPD symptom scores and albuterol dosing scores, responses obtained on Day 1, prior to the first test dose, were used as baseline covariates. All statistical tests performed on secondary endpoints were meant to be exploratory.

### 11.1.2. Results

#### 11.1.2.1. Patient Disposition

Of the 602 patients screened for this study, 507 (84%) were randomized to the study. Of the 507 patients randomized to the study, 444 (88%) completed the study. All subjects randomized to the study were included in the safety analysis. [Vol. 61, p. 51]; however, two patients were excluded from the efficacy analysis secondary to being on prohibited medications (protocol violation) on Day 1. [Vol. 61, p. 45] The ipratropium bromide HFA-42 mcg, HFA-84 mcg, and ipratropium bromide CFC-42 mcg groups consisted of 125, 127, and 127 patients, respectively. The placebo groups were similar to each other as well, 62 for the HFA placebo group, and 66 for the CFC placebo group.

Sixty-three patients discontinued from the study. The number of discontinuations was similar between most of the groups. The highest (22.7 %) and lowest (6.4%) discontinuation rates occurred in the CFC placebo group and the HFA-42-mcg group, respectively. The greatest percentage of discontinuation secondary to adverse events occurred in the CFC-placebo (12.1%) and the ipratropium bromide CFC-42 mcg (11.8%) groups. Discontinuations secondary to lack of efficacy were low; a total of two patients withdrew from the study (ipratropium bromide HFA-84 mcg) group for this reason.

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Discontinuations secondary to worsening COPD were lower in all of the ipratropium bromide HFA groups as compared to the CFC groups. Noncompliance was an uncommon reason for discontinuation from the study.

**Table 23. Study 244.1405, Patient Disposition**

Treatment	Number of Patients (%)					
	HFA Placebo	HFA-42 mcg	HFA-84 mcg	CFC Placebo	CFC-42 mcg	Total
Number of patients randomized and treated	62	125	127	66	127	507
Number of patients completing study	55 (88.7)	117 (93.6)	109 (85.8)	51 (77.3)	112 (88.2)	444 (87.6)
Number of patients discontinued	7 (11.3)	8 (6.4)	18 (14.2)	15 (22.7)	15 (11.8)	63 (12.4)
<b>Reasons for Discontinuation from the Study</b>						
Adverse Event	4 (6.5)	6 (4.8)	7 (5.5)	8 (12.1)	14 (11)	39 (7.7)
Worsening of COPD	1 (1.6)	3 (2.4)	2 (1.6)	4 (6.1)	6 (4.7)	16 (3.2)
Worsening of other Disease	0	1 (0.8)	0	1 (1.5)	1 (0.8)	3 (0.6)
Other AE	3 (4.8)	2 (1.6)	5 (3.9)	3 (4.5)	7 (5.5)	20 (3.9)
Lack of Efficacy	0	0	2 (1.6)	0	0	2 (0.4)
Other	2 (3.2)	1 (0.8)	3 (2.4)	4 (6.1)	1 (0.8)	11 (2.2)
Non-compliant	0	0	1 (0.8)	1 (1.5)	0	2 (0.4)
Lost to F/U	1 (1.6)	1 (0.8)	0	0	1 (0.8)	3 (0.6)
Consent withdrawn	1 (1.6)	0	2 (1.6)	3 (4.5)	0	6 (1.2)
Unspecified	1 (1.6)	1 (1.6)	6 (4.7)	3 (4.5)	0	11 (2.2)

Source: Vol. 61, p. 50

### Protocol Violations

The sponsor summarizes the protocol violations into two types: type 1 violations, potentially affecting safety/efficacy and type 2 violations, minor deviations not affecting safety/efficacy. None of the protocol violations affected safety analysis. Two randomized subjects were excluded from the intent to treat efficacy analysis secondary to violations of protocol exclusion criteria. Both subjects were discontinued from the study when it was learned that they were on excluded medications at Visit 1 during PFT testing. [Vol. 1, p. 52]

A total of 123 protocol violations occurred in the study. There were 29, 30, and 34 protocol violations in the ipratropium bromide CFC 42 mcg, HFA 42 mcg, and HFA 84 mcg groups, respectively. The number of protocol violations was lower in the two placebo groups: 12 in the CFC placebo and 18 in the HFA placebo. [N-000-BM, 5-7-03; SDL p. 2001-2025] A total of 67 protocol violations occurred in the study secondary to violations of inclusion/exclusion criteria. Thirty-one patients had history of asthma or allergy, seven patients had a history of thoracotomy, three had a history of congestive heart failure, two had a history of a life-threatening pulmonary embolism, four patients had a history of cancer, one had a cardiac arrhythmia, and one had symptomatic benign prostatic hypertrophy. Eight patients were using prohibited medications: Seven (1.4%) were taking beta-blockers (six were taking eye drops and one was taking Levobunolol) and one (0.2%) was taking Tilade. [Vol. 61, p. 161] Six patients were randomized with an FEV<sub>1</sub> greater than 65 % of predicted normal. Three patients had elevated theophylline levels, and four patients did not follow the 12-hour washout of short acting bronchodilators prior to PFT. [Vol. 61, p.51-52]

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*Reviewer's comments: The sponsor does not provide a breakdown of protocol violations per group. This information was obtained from the line listings Appendix 15.12, listing 7. This reviewer does not feel that the six patients who were randomized with greater than 65 % FEV<sub>1</sub> of predicted normal, should significantly impact efficacy analysis.*

### 11.1.2.2. Demographics and Other Baseline Characteristics

#### 11.1.2.2.1. Demographics

Treatment groups were similar at baseline with respect to mean age, gender, race, height, weight, duration of COPD, and time since COPD diagnosis. The overall mean age for the study population was 65.5± 8.3 years. The range was 41-87 years, which was similar between treatment groups. Greater than 50% of subjects in all treatment arms were older than 65 years of age. The majority of subjects were male (313 males compared to 194 females). The male to female ratio was similar between all treatment groups. The study population was predominantly White: 489 (96 percent). In comparison, 16 (3 percent), 2 (0.4 percent) were yellow. The mean duration of COPD was 9.4 years with a mean time since COPD diagnosis of 7.4 years. The mean smoking history was 61 pack- years, and similar between all groups. The following table summarizes the baseline demographics.

**Table 24. Study 244.1405, Baseline Demographics and Other Characteristics**

Characteristic	Number of Patients (%)					
	HFA Placebo	HFA-42 mcg	HFA-84 mcg	CFC Placebo	CFC-42 mcg	Total
Total treated	62	125	127	66	127	507
Sex						
Male	36 (58)	81 (65)	83 (65)	39 (59)	74 (58)	313 (62)
Female	26 (42)	44 (35)	44 (35)	27 (41)	53 (42)	194 (38)
Race						
White	57 (92)	121 (97)	125 (98)	64 (97)	122 (96)	489 (96)
Black	4 (6)	4 (3)	2 (2)	2 (3)	4 (3)	16 (3)
Yellow	1 (1.6)	0	0	0	1 (0.8)	2 (0.4)
Calculated Age, Mean year	66.5	66.1	65.7	62.8	65.6	65.5
40-45 years	1 (1.6)	0	1 (0.8)	2 (3.0)	2 (1.6)	6 (1.2)
46-50 years	2 (3.2)	1 (0.8)	3 (2.4)	4 (6.1)	1 (0.8)	11 (2.2)
51-55 years	3 (4.8)	11 (8.8)	11 (8.7)	10 (15.2)	13 (10.2)	48 (9.5)
56-60 years	5 (8.1)	21 (16.8)	16 (12.6)	9 (13.6)	16 (12.6)	67 (13.2)
61-65 years	17 (27.4)	27 (21.6)	30 (23.6)	12 (18.2)	29 (22.8)	115 (22.7)
>65 years	34 (54.8)	65 (52.0)	66 (52.0)	29 (43.9)	66 (52.0)	260 (51.3)
Smoking history, Mean	61.0	62.7	60.6	57.1	59.8	60.5
Standard Deviation	30.6	24.8	32.6	24.9	28.5	28.5
Range	15-160	10-138	10-188	15-135	17.5-174	10-188
Mean years of COPD	8.9	10.1	9.1	10.5	8.8	9.4
Standard Deviation	9.4	9.1	6.8	8.8	6.7	8.0
Range	1.0-49	0.2-58	1.0-33	1.0-43	0.8-40	0.2-58
Time since COPD Dx* (yrs)	6.9	7.4	7.2	8.0	7.7	7.4
Standard Deviation	6.9	6.9	6.1	8.3	7.8	7.1
Range	0-41.2	0-40.6	0-33.5	0.1-62.8	0.1-62.8	0-62.8

\* diagnosis

Source: Vol. 61, p. 53

*11.1.2.2.2. Baseline Spirometry*

All groups were similar in terms of spirometry. Mean baseline FEV<sub>1</sub> was 1.06 L for all treatment groups. The FEV<sub>1</sub> was slightly higher for the ipratropium bromide HFA-42 mcg group, and slightly lower for the ipratropium bromide CFC-42 mcg group. The average FEV<sub>1</sub>% predicted for all treatment groups was 40.0% with a range of 10.3-77.2. The mean for this parameter was similar across all treatments. Similarly, the FEV<sub>1</sub>/FVC was similar across all groups, with a mean for all treatment groups of 48.1%.

**Table 25. Study 244.1405, Baseline Spirometry**

Characteristic	HFA Placebo n = 62	HFA-42 mcg n= 125	HFA-84 mcg n=127	CFC Placebo n=66	CFC-42 mcg n=127	All Treatments n=507
Mean Baseline FEV <sub>1</sub> (L)	1.06	1.12	1.06	1.06	1.02	1.06
FEV <sub>1</sub> % predicted of normal	40.5	42.3	39.3	38.2	39.2	40.0
Standard deviation	14.7	14.6	13.3	13.9	13.7	14.0
Range	13.3-65.3	11.0-77.2	10.3-65.1	16.4-64.8	13.7-66.8	10.3-77.2
Mean Baseline FVC (L)	2.1	2.3	2.3	2.3	2.1	2.2
FEV <sub>1</sub> /FVC	49.9	48.4	47.0	47.0	48.4	48.1

Source: Vol. 61, p. 54

Of the 507 randomized patients, 473 (93 %) were taking concomitant pulmonary medication therapy 6 weeks prior to and/or during the study. Inhaled steroids were the most frequently used concomitant therapy (194 patients, 38.3 %), followed by oral theophylline (142 patients, 28 %), and oral steroids (78 patients, 15.4 %). Inhaled beta-agonists, Atrovent, and oxygen were used by 29 patients (5.7 %), 16 patients (3.2%) and 16 patients (3.2%), respectively. [Vol. 61, p. 55]

Rescue medication was allowed on the pulmonary function test days; however, if rescue medication was needed, PFT was terminated before the medication was given to the patients. Of the randomized patients, 87 patients (17 %) were taking rescue medications, and the most frequently used drugs were: inhaled albuterol (82 patients, 16%), inhaled study drug (14 patients, 2.8%), and oral theophylline (8 patients, 1.6%). [Vol. 61, p. 56]

*11.1.2.2.3. Concomitant Diagnoses and Therapies*

The sponsor does not provide a summary of concomitant diagnoses or therapies. Line listings for concomitant diagnoses are not provided; however, in the line listings for concomitant therapies, indications for these therapies are provided. The line listings are organized by therapies and centers, and it is very difficult to sort these by treatment group, since a comparison is not provided in these 131 pages; however, perusal through these listings, given the limitations, appears to show similarity between treatment groups (this cannot be conclusively stated given the limitations described above). [Vol. 63, p. 11-142]

**11.1.2.3. Compliance**

Compliance was assessed by the investigator from the daily worksheet given to the patients where they were required to indicate each dose of study drug or rescue medication

(albuterol) used. The investigator was to record the patients' usual daily dosing regimen and the number of puffs of albuterol that was taken during the two-week period preceding the visit in the CRF. [Vol. 61, p. 34]

*Reviewer's comments: The sponsor has failed to include any information on compliance. This information has been requested from the sponsor.*

**11.1.2.4. Efficacy Endpoint Outcomes**

Efficacy analyses were performed on all randomized patients, with the exception of two patients that were withdrawn following Visit 1 medication administration for entry criteria violations—one each from the ipratropium bromide HFA 42 mcg and 84 mcg groups. All other patients withdrawn from the study who had efficacy data were included in the efficacy analysis using endpoint analysis (last observation carried forward) to estimate missing data. These patients constituted the Intent-to-Treat population, N=505. [Vol. 61, p. 31, 57]

Endpoint analyses were performed to account for withdrawals after Day 1 and in one case for a protocol violation. The need for endpoint analysis was greatest in the CFC placebo group (22.7 %), lowest in the HFA-42 mcg group (5.6 %), and similar between the other three treatment groups (11.3-16 %). The following table summarizes these results.

**Table 26. Study 244.1405, Number and Percentage of Patients Requiring Endpoint Analysis**

	HFA Placebo n = 62	HFA-42 mcg n = 124	HFA-84 mcg n = 126	CFC Placebo n = 66	CFC-42 mcg n = 127
Day 29	5 (8.1)	3 (2.4)	10 (7.9)	5 (7.6)	8 (6.3)
Day 57	7 (11.3)	6 (4.8)	17 (13.5)	11 (16.7)	12 (9.4)
Day 85	7 (11.3)	7 (5.6)	17 (13.5)	15 (22.7)	15 (11.8)

Source: Vol. 61, p. 59

*Reviewer's comments: Approximately 15 % of the data had to be estimated by the last observation carried forward (with the exception of CFC placebo where it was higher). This reviewer doubts that this would significantly impact the final results. This issue was discussed with DPADP Biometrics Reviewer, Dr. Jim Gebert, and he felt that this is not unexpected in a 12-week COPD trial. This would not affect the analysis too much especially if the percentages of patients requiring endpoint analysis were similar. In this case, the fact that the group with the highest number of patients whose data needed estimation was the CFC placebo, would if anything, underestimate the efficacy of the active treatments compared to placebo.*

**11.1.2.4.1. Primary Efficacy Analysis**

The primary efficacy variables were the FEV<sub>1</sub> derived AUC<sub>0-6</sub> above baseline and peak change from test-day baseline. The sponsor did not specify one timepoint for the primary efficacy variables. It is apparent that the sponsor used four separate timepoints as the efficacy endpoints: Day 1, Day 29, Day 57, and Day 85. [Vol. 61, p. 34]

For all timepoints, the ANOVA test did not demonstrate any treatment by center effects or baseline effects for both co-primary endpoints. However, treatment effects were noted at the 0.0001 significance level.

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For all timepoints, ipratropium bromide HFA-42 mcg and 84 mcg, and ipratropium bromide CFC-42 mcg were significantly more effective than placebo in terms of FEV<sub>1</sub> AUC<sub>0-6</sub> and peak response. The pairwise comparisons to placebo of the same formulation showed statistically significant differences for each of the active treatment groups (p=0.0001). The following three tables summarize the primary efficacy analyses.

**Table 27. Study 244.1405, Adjusted Mean FEV<sub>1</sub> AUC<sub>0-6</sub> in Liters (SEM) Endpoint Analysis of the ITT Data Set**

	HFA Placebo n = 62	HFA-42 mcg n = 124	HFA-84 mcg n = 126	CFC Placebo n = 66	CFC-42 mcg n = 127
Day 1	0.003 (0.021)	0.148 * (0.014)	0.168 * (0.014)	0.013 (0.019)	0.124 * (0.014)
Day 29	-0.009 (0.021)	0.135 * (0.014)	0.141 * (0.014)	-0.008 (0.020)	0.147 * (0.014)
Day 57	-0.005 (0.021)	0.117 * (0.014)	0.124 * (0.014)	0.011 (0.019)	0.131 * (0.014)
Day 85	0.018 (0.021)	0.141 * (0.014)	0.129 * (0.014)	0.014 (0.020)	0.127 * (0.014)

\* p = 0.0001 for the comparison to placebo of the same formulation for pairwise comparisons

Source: Vol. 61, p. 65

**Table 28. Study 244.1405, Adjusted Mean Peak Change from Baseline in Liters (SEM) Endpoint Analysis of the ITT Data Set**

	HFA Placebo n = 62	HFA-42 mcg n = 124	HFA-84 mcg n = 126	CFC Placebo n = 66	CFC-42 mcg n = 127
Day 1	0.143 (0.024)	0.295 * (0.016)	0.307 * (0.016)	0.138 (0.022)	0.255 * (0.016)
Day 29	0.111 (0.025)	0.286 * (0.017)	0.282 * (0.017)	0.116 (0.023)	0.286 * (0.017)
Day 57	0.113 (0.023)	0.266 * (0.015)	0.272 * (0.015)	0.121 (0.021)	0.267 * (0.015)
Day 85	0.139 (0.024)	0.295 * (0.016)	0.266 * (0.016)	0.140 (0.023)	0.262 * (0.016)

\* p=0.0001 for the comparison to placebo of the same formulation

Source: Vol. 61, p. 65

**Table 29. Study 244.1405, P-Values fro Pairwise Comparisons of the LS Means for FEV<sub>1</sub> AUC<sub>0-6</sub> and Peak FEV<sub>1</sub> Change from Baseline for Day 85 for ITT Data Set**

Pairwise Comparison	Mean FEV <sub>1</sub> AUC	Mean Peak FEV <sub>1</sub> Change
	P-values	P-values
HFA-MDI 42 mcg vs. HFA-Placebo	0.0001	0.0001
CFC-MDI 42 mcg vs. CFC-Placebo	0.0001	0.0001
HFA-MDI 42 mcg vs. CFC-MDI 42 mcg	0.4960	0.1495
HFA-MDI 42 mcg vs. HFA-MDI 84 mcg	0.5468	0.2034

Vol. 64, p.17, p. 29

The results for Day 85 have been shown. The Day 1, 29, and 57 results were similar to Day 85 for all endpoints and comparisons (with one exception, summarized below) and have not been displayed; the p-value was 0.0001 for all pairwise comparisons between each active treatment and placebo for these days. [Vol. 63, p. 193, 205, 237, 249, 281, and 292] The active treatments were not significantly different from one another with an exception on Day 1. On Day 1, there was a statistically significant difference ( $p=0.02$ ) in  $FEV_1$  AUC<sub>0-6</sub> and Peak change from baseline between ipratropium bromide HFA-42 mcg and HFA 84 mcg. [Vol. 63, p. 193] On subsequent test days, this difference was not present.

*Reviewer's comments: The fact that the sponsor specified two co-primary endpoints without using the Bonfieri adjustment was discussed with DPADP Biometrics Reviewer, Dr. Jim Gebert. He stated that based on the Höchberg Principle, if both primary endpoints have a significance level at or below the specified alpha (0.05 for this study), then the results are considered significant. For this study,  $p < 0.05$  for both primary endpoints and for all pairwise comparisons between active treatment and placebo. The Höchberg Principle also applies to the multiple comparisons done within each primary endpoint. Although the sponsor has not adjusted for multiple comparisons (i.e. ipratropium HFA-42 mcg vs. placebo, HFA-84 mcg vs. placebo, CFC-42 mcg vs. placebo, etc.), each of the pairwise comparisons between active and placebo treatments has a p-value of 0.0001. This is quite significant such that the results would be similar even if adjustment was done for multiplicity.*

#### 11.1.2.4.2. Secondary Efficacy Analyses

##### Derived endpoints based on $FEV_1$ and FVC

The sponsor states that these secondary endpoints were intended to further characterize the  $FEV_1$  and FVC time profiles. A therapeutic response to test dose was defined as those  $FEV_1$  measurements exceeding 15% of test-day baseline.

- $FEV_1$  AUC from 0-4 hours, 4-6 hours, and 6-8 hours

For  $FEV_1$  AUC<sub>0-4</sub> and  $FEV_1$  AUC<sub>4-6</sub>, pairwise comparisons between the active treatments and respective placebos demonstrated greater numerical improvements at all timepoints for the active treatments

*Reviewer's comments: It is interesting to note that the  $FEV_1$  AUC<sub>6-8</sub> was not meaningfully different from the placebo groups for pairwise comparisons between and active groups at the two latter time points. As the duration of action for short-acting anticholinergics is typically 3-4 hours, this is not unexpected.*

- Onset of 15% increase from baseline in  $FEV_1$

The median onsets of therapeutic response ranged from 14-17.5 minutes and 12.5-22 minutes for ipratropium bromide HFA-42 mcg and HFA-84 mcg, respectively, on all test days. The median onset for ipratropium bromide CFC-42 mcg ranged from 15-19 minutes. For the placebo groups, the majority of patients did not achieve 15% increases from test day baseline on any of the test days. [Vol. 61, p. 61]

- Duration of 15% increase from baseline FEV<sub>1</sub>

Median durations of action for the ipratropium bromide HFA-42 mcg, HFA-84 mcg, and CFC 42-mcg were 2-2.8 hours, 1.6-4.6, and 2.3-3.1 hours, respectively. All of the active treatment groups demonstrated greater durations of actions than the placebo groups. There was no meaningful difference for pairwise comparisons between the active treatment groups.

The sponsor points out that in previous studies with ipratropium bromide—(formulation not specified)—the median duration of action was about 3-4 hours. The results of this study demonstrate an unexpected lower duration of action. The sponsor proposes that this difference may be explained by the definition used for median duration of therapeutic response (12 % vs. 15 %).

The median durations of action are higher when the therapeutic response is defined as 12% increases from test-day baselines. These values were 2.4-3.6 hours, 2.7-4.6 hours, and 3.3-4.1 hours for ipratropium bromide HFA-42 mcg, HFA-84 mcg, and CFC-42 mcg, respectively.

- Time to peak FEV<sub>1</sub> change from baseline

The median time to peak response for each of the active treatment groups on Days 1, 29, and 57 was 90 minutes. On day 85, the median time to peak was 90 minutes for ipratropium bromide HFA-42 mcg, 60 minutes for ipratropium bromide HFA-84-mcg, and 60 minutes for CFC-42 mcg. In comparison, the median time to peak for each of the placebo groups was 120 minutes.

*Reviewer's comments: The sponsor provided several pieces of data to assess the onset of and duration of a therapeutic response. However, everything is presented as Median values and not means and the utility of looking at this information with respect to medians may be limited.*

- FEV<sub>1</sub> total area under the curve (TAUC)

At all time points, the active treatments demonstrated numerically greater improvements than their respective placebo formulation. In addition, ipratropium bromide HFA-84 mcg had a numerically greater increase in TAUC than ipratropium bromide CFC-42 mcg on all test days.

- FVC AUC from 0-4, 0-6, 4-6, and 6-8 hours, peak response and changes from baseline at each timepoint

On all test days, the two dosage strengths of ipratropium bromide HFA (42-mcg and 84-mcg) were better than placebo for FVC<sub>0-6</sub> and peak response. Ipratropium bromide CFC-42 mcg was better than placebo for FVC<sub>0-6</sub> at all time points. For peak response, the CFC-42 mcg treatment group was better compared to placebo on Days 29, 57, and 85. [Vol. 61, p. 62]

#### Other Secondary Endpoints

- Physician's Global Assessment

This secondary endpoint was assessed at each of the follow up visits (Day 1, Day 15, Day 29, Day 43, Day 57, Day 71 and Day 85) using an 8 point scale: 1-2=poor, 3-4=fair, 5-6 good, and 7-8=excellent. The sponsor reports that all adjusted mean scores were between 4.8 and 5.4, corresponding to "fair" to "good." The sponsor states that HFA-42 mcg and 84 mcg had consistently more favorable scores as compared to the other groups. [Vol. 61, p.155] On four out of the six follow up visits, the two active HFA formulations demonstrated more favorable results as compared to the placebo.

*Reviewer's comments: The specifics regarding how this assessment was conducted are not described in either the procedure section or the results section of this study—it is not clear when this evaluation was conducted (i.e. pre and/or post-PFT?) and what criteria were used by the investigator for this global assessment (symptoms, exercise tolerance, severity of exacerbations, etc.)—therefore, specific conclusions can't be drawn for this endpoint.*

- COPD symptom scores

Each of the symptoms of wheezing, shortness of breath, coughing and chest tightness was evaluated by a 4-point scale: 0=not present, 1=mild, 2=moderate and 3=severe on all of the follow up visits. Adjusted mean wheezing scores were less than one (not present to mild symptoms) for all treatment groups on Day 1 and at all follow up visits with a range of 0.56 to 0.98. For shortness of breath, adjusted means ranged between 1.08-1.60 (mild leading towards moderate) for all groups at all follow up visits. For coughing, the range for the adjusted mean was 0.72 to 1.18 (mild symptoms) for all groups at all time points. For chest tightness, the adjusted means were lower and ranged between 0.39 to 0.72 for all groups for entire study period. There were no consistent differences between active treatment and placebo for any symptom score. There was no separation between the curves of the adjusted mean for any symptom score. [Vol. 61, p.62, 156-159]

- Amount of albuterol used to control acute exacerbations during the 12-week treatment period

Albuterol dosing scores were assessed using the following scale: 0=none, 1= <2, 2=2, 3=3, 4=4, 5=5, and 6= >5 times per day. Adjusted mean albuterol dosing scores were between 1.87-2.87, corresponding to an average use of albuterol about two to three times per day. The placebo groups reported slightly higher use of albuterol as compared to the active treatment groups. The active treatment groups were comparable with each other in terms of albuterol use. [Vol. 61, p. 63, 79, 160] The placebo HFA and CFC groups used albuterol 2.4 and 2.8 times a day overall. In comparison, the ipratropium bromide HFA-42 mcg, HFA-84 mcg, and CFC-42 mcg used albuterol 2.2 times a day. [Vol. 61, p. 82]

*Reviewer's comments: The sponsor assessed albuterol dosing scores on how many times per day albuterol was used; however, the sponsor does not state how many puffs were used at any given time during the day. Based on review of sample diary provided in this submission— the instructions to the patients states that rescue albuterol use should be checked as one dose equals 2 puffs—this reviewer is assuming that two puffs were given at each time when albuterol was used. [Vol. 61, p. 285]*

**11.1.2.5. Safety Outcomes**

All 507 randomized patients were included in the safety analysis. In addition, the sponsor included nine non-randomized patients who experienced adverse events during the two-week baseline period. [Vol. 61, p. 82]

*11.1.2.5.1. Extent of Exposure*

A total of 507 patients were randomized to five treatments in this study. A total of 62, 125, and 127 patients were treated with placebo HFA, ipratropium bromide HFA-42 mcg, and HFA-84 mcg, respectively. Similarly, 66 patients received placebo CFC and 127 patients received ipratropium bromide CFC-42 mcg.

The majority of patients received 85-89 days of treatment. The mean duration of exposure was 81, 84, and 78 days for the placebo HFA, ipratropium bromide HFA-42 mcg, and HFA-84 mcg, respectively. The mean duration of exposure for the placebo CFC and ipratropium CFC-42 mcg was 77 and 80 days, respectively. In the placebo HFA, ipratropium HFA-42 mcg, and HFA-84 mcg, 88.7%, 94.4%, and 86.6% of patients received 71 or more days of treatment, respectively. In the placebo CFC and ipratropium CFC-42 mcg, 83.3% and 89.8% received greater or equal to 71 days of treatment, respectively. The extent of exposure information is presented in the following table.

**Table 30. Study 244.1405, Extent of Exposure**

	HFA Placebo n = 62	HFA-42 mcg n= 125	HFA-84 mcg n=127	CFC Placebo n=66	CFC-42 mcg n=127
1-14 days	2 (3.2%)	2 (1.6%)	8 (6.2%)	1 (1.5%)	3 (2.3%)
15-28 days	2 (3.2%)	0	2 (1.5%)	3 (4.5%)	4 (3.1%)
29-42 days	1 (1.6%)	2 (1.6%)	1 (0.8%)	4 (6.0%)	0
43-56 days	2 (3.2%)	2 (1.6%)	4 (3.1%)	1 (1.5%)	6 (4.7%)
57-70 days	0	1 (0.8%)	2 (1.5%)	2 (3.0%)	0
71-84 days	7 (11.2%)	24 (19.1%)	23 (18.1%)	10 (15.1%)	20 (15.7%)
85-98 days	45 (72.5%)	87 (69.6%)	82 (64.5%)	45 (68.1%)	92 (72.4%)
99-112 days	3 (4.8%)	4 (3.2%)	5 (3.9%)	0	1 (0.7%)
> 112 days	0	2 (1.6%)	0	0	0
Mean Exposure in days	81	84	78	77	80

Source: Vol. 61, p. 83

*11.1.2.5.2. Adverse Events*

The percentage of patients reporting AEs was similar in both placebo groups and slightly higher as compared to the active treatment groups. The frequency of AE reporting in the two ipratropium bromide HFA-42 mcg and CFC 42-mcg was comparable. In comparison, a smaller percentage of patients reported AEs in the ipratropium bromide HFA-84 mcg. Overall, 44 patients (71.0%) in the placebo HFA group, 81 patients (64.8%) in the ipratropium bromide HFA-42 mcg group, 63 patients (49.6%) in the HFA-84 mcg group, 48 patients (72.7%) in the placebo CFC group, and 85 patients (66.9%) in the ipratropium bromide CFC-42 mcg group reported adverse events during the study period.

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A total of 234 patients (46.2%) reported AEs of mild intensity, 149 (29.4%) reported AEs of moderate intensity, and 51 patients (10.1%) reported severe AEs. [Vol. 61, p. 85]

### 11.1.2.5.2.1. More Common Adverse Events

The most commonly reported adverse events were rhinitis, chronic obstructive airway disease, headache, and bronchitis. Rhinitis (including rhinorrhea, cold, and upper respiratory tract infection) was reported by 11 (17.7%), 19 (15.2%), 17 (13.4%), 13 (19.7%), and 17 (13.4%) patients in the placebo HFA, ipratropium bromide HFA-42 mcg, HFA-84 mcg, CFC placebo, and ipratropium bromide CFC-42 mcg groups, respectively. Eight patients (12.9%), 12 patients (9.6%), 14 patients (11.0%), 9 patients (13.6%), and 18 patients (14.2%) reported COPD (including COPD exacerbation) in the placebo HFA, ipratropium bromide HFA-42 mcg, HFA-84 mcg, CFC placebo, ipratropium bromide CFC-42 mcg groups, respectively. Headache occurred in 4 patients (6.5%) receiving placebo HFA, 8 patients (6.4%) receiving ipratropium bromide HFA-42 mcg, 6 patients (4.7%) receiving HFA-84 mcg, 6 patients (9.1%) receiving CFC placebo, and 14 patients (11.0%) receiving ipratropium bromide CFC-42 mcg, respectively. [Vol. 61, p. 84]

Overall, the distribution of adverse events across all of the treatment groups was similar, with the exception of headache, nausea, vomiting, diarrhea, gastro-intestinal disorder, dyspnea, and rash. Headache was reported more frequently in the CFC treatment groups (9.1-11%) as compared to the HFA groups (4.7%-6.5%). The two active HFA treatment groups had a higher incidence of nausea as compared to the other treatment groups (5 patients (4.0%) in the HFA-42 mcg group, 6 patients (4.7%) in the HFA-84 mcg group, as compared to 1 patient (1.6%) in the placebo HFA group, 2 patients (3.0%) in the placebo CFC, and 1 patient (0.8%) in the CFC-42 mcg group). Vomiting was reported only in the HFA-84 mcg group (4 patients, 3.1%) and CFC-42 mcg group (1 patient, 0.8%). Gastrointestinal disorder and diarrhea was only reported in the active treatment groups (0.8%-2.4% of patients). Dyspnea was reported more commonly in the CFC treatment groups (4.5-6.3% of patients) as compared to the HFA groups (2.6%-3.2%). Rash was only observed in 3 patients (2.4%) in the HFA-42 mcg group and 1 patient (0.8%) in the HFA-84 mcg group. [Vol. 61, p.85]

**Table 31. Study 244.1405, Adverse Events Occurring in >3% of Patients in the HFA Active Treatment Groups**

	HFA Placebo n = 62 n (%)	HFA-42 mcg n = 124 n (%)	HFA-84 mcg n = 126 n (%)	CFC Placebo n = 66 n (%)	CFC-42 mcg n = 127 n (%)
<b>Total AEs Reported</b>	<b>44 (71)</b>	<b>81 (64.8)</b>	<b>63 (49.6)</b>	<b>48 (72.7)</b>	<b>85 (66.9)</b>
<b>General Disorders</b>					
Headache	4 (6.5)	8 (6.4)	6 (4.7)	6 (9.1)	14 (11)
Pain	4 (6.5)	5 (4.0)	8 (6.3)	0	2 (1.6)
Chest Pain	0	4 (3.2)	2 (1.6)	1 (1.5)	2 (1.6)
Flu like symptoms	3 (4.8)	4 (3.2)	2 (1.6)	0	3 (2.4)
<b>Nervous System Disorders</b>					
Insomnia	1 (1.6)	4 (3.2)	1 (0.8)	1 (1.5)	1 (0.8)

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	HFA Placebo n = 62 n (%)	HFA-42 mcg n = 124 n (%)	HFA-84 mcg n = 126 n (%)	CFC Placebo n = 66 n (%)	CFC-42 mcg n = 127 n (%)
Dizziness	2 (3.2)	6 (4.8)	3 (2.4)	1 (1.5)	5 (3.9)
<b>Gastrointestinal System Disorders</b>					
Dry Mouth	2 (3.2)	6 (4.8)	3 (2.4)	0	3 (2.4)
Nausea	1 (1.6)	5 (4.0)	6 (4.7)	2 (3.0)	1 (0.8)
Vomiting	0	0	4 (3.1)	0	1 (0.8)
<b>Respiratory System Disorders</b>					
COPD	8 (12.9)	12 (9.6)	14 (11.0)	9 (13.6)	18 (14.2)
Rhinitis	11 (17.7)	19 (15.2)	17 (13.4)	13 (19.7)	17 (13.4)
Coughing	4 (6.5)	5 (4.0)	5 (3.9)	4 (6.1)	5 (3.9)
Bronchitis	3 (4.8)	4 (3.2)	4 (3.1)	5 (7.6)	11 (8.7)
Dyspnea	1 (1.6)	4 (3.2)	2 (1.6)	3 (4.5)	8 (6.3)
Pharyngitis	4 (6.5)	2 (1.6)	4 (3.1)	1 (1.5)	8 (6.3)
Sinusitis	3 (4.8)	2 (1.6)	4 (3.1)	2 (3.0)	8 (6.3)

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*Reviewer's comments: No clinically meaningful differences in adverse events between treatment groups were observed.*

### 11.1.2.5.2.2. Treatment Related Adverse Events

There were 56 patients who had AEs that were judged by the investigator to be possibly related to administration of study drug. Nine of these were patients who received open label Atrovent® Inhalation Aerosol during the two-week baseline. The most common AEs after randomization judged by the investigator to be possibly related to study drug were headache, coughing, and pharyngitis. [Vol. 61, p. 85]

*Reviewer's comments: It is unlikely that headache and pharyngitis are treatment related; however, it is possible that cough could be a treatment related adverse event. However, the highest incidence of cough was noted in both placebo groups, therefore, it is unlikely that it is caused by the active treatments but causality due to the propellant cannot be excluded.*

### 11.1.2.5.2.3. Serious Adverse Events, Deaths, and Pregnancies

#### Serious Adverse Events

Serious adverse events were reported in 41 patients during the active study period. Four patients (0.8%) experienced serious adverse events (SAEs) during the pre-treatment period and nine patients during the post-treatment period. Seven patients (11.3%) in the placebo HFA group, nine patients (7.2%) in the ipratropium bromide HFA-42 mcg group, nine patients (7.1%) in the 84-mcg group, five patients (7.6%) in the placebo group, and 11 patients (8.7%) in the CFC-42 mcg group reported serious adverse events. None of the reported SAEs were judged to be related to study drug administration. [Vol. 61, p. 99]

The most commonly reported SAEs were COPD exacerbation and pneumonia. This was reported in two patients (3.2%) receiving placebo HFA, five patients (4.0%) receiving HFA-42 mcg, five patients (3.9%) receiving HFA-84 mcg, two patients (3.0%) receiving placebo CFC, five patients (3.9%) receiving CFC-42 mcg, and three patients (0.6%) post-treatment.

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Pneumonia was reported in two patients outside the study period (one pre and one post-treatment), two patients (1.6%) in the placebo HFA group, two patients (1.6%) in the ipratropium bromide HFA-84 mcg group, two patients (1.6%) in the CFC-42 mcg group, and one (0.2%) in the post-treatment period. Other SAEs were not consistently observed in the treatment groups and occurred in less than 1% of patients treated with the active HFA formulations. [Vol. 61, p. 102-106] The following table summarizes these results.

**Table 32. Study 244.1405, Number of Patients (%) with SAEs Focusing on Respiratory SAEs**

	HFA Placebo n=62	HFA-MDI 42 mcg n=125	HFA-MDI 84 mcg n=127	CFC Placebo n=66	CFC-MDI 42 mcg n=127
Total with SAE	7 (11.3)	9 (7.2)	9 (7.1)	5 (7.6)	11 (8.7)
Respiratory SAEs					
COPD	2 (3.2)	5 (4.0)	5 (3.9)	2 (3.0)	5 (3.9)
Pneumonia	1 (1.6)	0	2 (1.6)	0	2 (1.6)
Pulmonary HTN	0	0	1 (0.8)	0	0
Sinusitis	1 (1.6)	0	0	0	0
Source: Vol. 61, p. 102					

Interestingly, more patients in the active treatment groups compared to placebo experienced COPD, however, the percentage was similar for the HFA and the CFC treatment groups.

### Serious AEs in the HFA-42 mcg treatment group

A total of nine patients (7.2%) had SAEs in the HFA-MDI 42 mcg group: five patients had COPD exacerbations, one patient had small cell carcinoma, one patient had nephrolithiasis, one patient had pancreatitis and one patient had abdominal pain/diarrhea.

**Patient 1761** was a 65-year old white female who was admitted to the hospital for a COPD exacerbation 76 days into study drug treatment. She was treated with IV Solumedrol, IV Zinaceft, and Theodur and event resolved. Patient 1899 was a 59 yr old white female who was treated for a COPD exacerbation 13 days into treatment with Lorabid, Floxin, Depomedrol, Prednisone, and Doxycycline. The patient had persistent symptoms and was referred to a pulmonary rehabilitation center, and discontinued from the trial about 2 weeks later. She continued to have persistent COPD symptoms, and a month later she had a productive cough with yellow sputum, tightness in the back with sweats and fatigue for which she was treated with Doxycycline and Biaxin. The exacerbation did not resolve and 35 days later the patient was rushed to the ER for severe COPD; she died that day of a COPD exacerbation and heart failure.

**Patient 1963** was a 79-year old white male who was found collapsed on the floor with agonal breathing (a respiratory rate of 4/min) and a pulse of 80 bpm, 35 days after randomization into treatment. Shortly after intubation, the patient developed asystole, was successfully resuscitated and transferred to the ICU on mechanical ventilation with a diagnosis of post-cardiopulmonary arrest, acute respiratory failure and exacerbation of severe COPD. He was diagnosed with severe anoxic, ischemic injury and three days later he

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died of respiratory arrest. The cause of death was reported as respiratory failure and severe COPD.

**Patient 2090** was an 81 year old white female who was hospitalized for chest pain 12 days into treatment with study drug and treated with Ventolin successfully. However, a chest x-ray revealed a mass, and subsequent evaluation led to the diagnosis of small cell carcinoma of the lung with metastasis. The patient was discontinued from the trial after 44 days of treatment, and died one month after discontinuation from the trial, with the cause of death listed as small cell carcinoma with metastasis.

**Patient 2154** was a 69 year old white male who experienced a COPD exacerbation 11 days into treatment. The patient was treated with standard therapy and symptoms resolved within four days; study medication was stopped during hospitalization, but was restarted after resolution of exacerbation.

**Patient 2251** was a 53 year old white female who was hospitalized 56 days into treatment for a COPD exacerbation that lasted 10 days; she was treated with standard therapy (study drug was stopped during hospitalization, but was restarted after recovery).

**Patient 1647** was a 69 year old white male admitted for evaluation of abdominal pain and diarrhea 74 days into treatment; the patient was treated with Lomotil and was discharged after negative laboratory and radiological work up; symptoms resolved in five days.

**Patient 1921** was a 61 year old white male who underwent lithotripsy for nephrolithiasis 66 days into treatment with study drug; he subsequently was admitted for renal colic and vomiting. His hospital course was complicated by a Mallory Weiss tear and hematemesis; the patient recovered after one day.

**Patient 2176** was a 55 year old white male who was admitted to the hospital with pancreatitis and upper GI bleeding secondary to erosive duodenitis 40 days into treatment with study drug. The patient subsequently developed complications leading to septic shock, cardiopulmonary arrest, acute renal failure, pneumonia, encephalopathy and thrombocytopenia. The patient was discontinued from the trial and subsequently died, with the cause of death listed as complications secondary to pancreatitis. [Vol. 67, p.200-203]

### Serious AEs in the HFA-84 mcg treatment group

Nine patients (7.6%) reported SAEs in the HFA-84 mcg treatment group: five patients had COPD exacerbations, one had an esophageal obstruction/perforation, one had a transient ischemic attack, one had a pneumonia/gastroenteritis, and one had coronary artery disease/CABG. These events are briefly summarized.

**Patient 1509** was an 81 year old white female who was hospitalized for a COPD exacerbation 81 days into treatment, treated with standard therapy, and the event resolved after four days; she was discontinued from the trial.

**Patient 1797** was a 72-year old white who was hospitalized for a COPD exacerbation 39 days into treatment with study drug; upon admission patient was found to have an electrolyte imbalance an intermittent Mobitz II block (which resolved after first respiratory nebulization). The patient was discharged from the hospital after treatment with standard therapy and remained in the trial.

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**Patient 1981** was a 60-year old white male who was discontinued from the study after hospitalization for exacerbation of COPD, cor pulmonale, and pulmonary hypertension. The patient improved on standard therapy and was discharged one week later. Patient 2015 was a 68 year old white male who was hospitalized for a COPD exacerbation and pneumonia 16 days into treatment; subsequent evaluations led to the diagnosis of bronchogenic carcinoma with local and distant metastases. The patient died 11 days later secondary to respiratory failure.

**Patient 2191** was a 73 year old white male who was admitted for a COPD exacerbation 81 days into treatment, treated with standard therapy, recovered and discharged nine days later; he continued in the trial.

**Patient 2132** was a 62 year old white male was admitted for a right middle lobe pneumonia with associated nausea/vomiting/diarrhea; he was treated with standard therapy and recovered in six days; he continued in the trial after resolution of symptoms.

**Patient 2255** was a 64 year old white male who was hospitalized with an esophageal obstruction five days into treatment; his medical course was complicated by an esophageal perforation and severe mediastinitis; the patient slowly recovered and was discharged 66 days later.

**Patient 2285** was a 66 year old white male who was hospitalized for coronary artery disease 51 days into treatment; he underwent triple coronary bypass surgery, and was treated with adequate therapy, and was discharged in stable condition after 10 days; he continued in the study. [Vol. 67, p.203-206]

### Serious AEs in the CFC –42 mcg treatment group

Eleven patients (8.7%) in the CFC-MDI treatment group experienced SAEs, of which five had COPD exacerbations, two had pneumonia, one had thoracic muscle strain, two had GI chest pain, one had laryngeal cancer, and one had multiple myeloma. Brief descriptions of these events follow.

**Patient 1569** (69 year old white female) had a COPD exacerbation 85 days into treatment, was treated with standard therapy, recovered and continued with clinical trial.

**Patient 1575** was a 64 year old white male admitted for a COPD exacerbation 27 days into treatment, treated with standard therapy and recovered within 24 hours; he was discontinued from the trial.

**Patient 1642** was a 61 year old white male who experienced a COPD exacerbation 12 days into treatment, recovered six days after standard therapy and was discontinued from the trial upon hospitalization.

**Patient 1904** was a 63 year old white male hospitalized with a COPD exacerbation and pneumonia 54 days into treatment, who recovered after standard therapy 30 days later; he was discontinued from the study.

**Patient 2218** was a 55 year old white who was also admitted for a COPD exacerbation and pneumonia (51 days into treatment); he was treated with standard therapy and recovered eight days later; he was discontinued from the trial.

**Patient 2282** was a 67 year old white female who was admitted 12 days into treatment for a COPD exacerbation and was treated successfully with standard therapy; she was discontinued from the study as well.

**Patient 1638** was a 65 year old black male who was admitted to rule out a myocardial infarction 46 days into treatment; his subsequent work up was negative and he was diagnosed with a thoracic muscle strain; he continued in the study.

**Patient 1646** was discontinued on the first test day following diagnosis of laryngeal carcinoma.

**Patients 1662** (64 year old white female) and **1863** (58 year old white female) were admitted for chest pain and subsequently diagnosed with chest pain secondary to gastrointestinal etiology, and treated with standard therapy. Both continued in the trial.

**Patient 1983** was a 68 year old white male who was discontinued from the trial 23 days after starting treatment when he was diagnosed with multiple myeloma. [Vol. 67, p. 209-211]

#### Serious AES in the Placebo group

Seven patients (11.3%) and five patients (7.6%) in the HFA placebo and CFC placebo groups, respectively, experienced SAEs. In the HFA placebo group, two patients experienced COPD and the remaining five experienced other SAES.

**Patients 1840** (74 year old white male, discontinued from the study) and **2123** (64 year old white female, continued in the study) experienced COPD exacerbations, 6 days into treatment and 79 days into treatment, respectively. They were treated with standard therapy and recovered.

**Patient 2184** (57 year old white male) was admitted for worsening shortness of breath 33 days into treatment and was subsequently diagnosed with non-small cell lung cancer. The patient was discontinued from the trial and died eight months later.

**Patient 2298** was a 42-year old white female who was diagnosed with a sinus infection 28 days into treatment, which failed to recover, resulting in a sinus surgery; patient was discontinued from the trial.

**Patient 1886** was a 69 year old white male was diagnosed with atrial fibrillation 85 days after treatment after prescription with standard therapy; he was hospitalized 28 days post-completion of the trial for this condition; the outcome is unknown to the sponsor. **Patient 1553** (68 year old white female) was diagnosed with cholelithiasis 33 days into treatment and underwent a cholecystectomy and was discontinued from the study. Of the five patients in the CFC placebo who had SAEs, two had COPD exacerbations:

**Patient 1640** (66 year old white male had symptoms 68 days into treatment and **Patient 1895** (62 year old white male admitted 78 days into treatment).

**Patient 1726** was a 70 year old white female with peripheral vascular surgery who underwent elective bypass surgery. **Patient 66** year old white male was hospitalized with an acute myocardial infarction six days into treatment and subsequently underwent angioplasty.

**Patient 2022** was a 61 year old white male who was hospitalized for cardiac monitoring following a near syncopal episode 18 days after initiation of therapy. [Vol. 67, p.198-200, 207-208]

*Reviewer's comments: Overall, there were no clinically meaningful differences in the incidence or types of SAEs between the different treatment groups. The fact that COPD exacerbations occurred at a greater incidence than any of the other SAEs is not unexpected given the nature of this trial and study population.*

Deaths

Nine deaths were reported during the study period. Six deaths occurred secondary to events that began prior to the completion of the 85-day study period and three deaths occurred secondary to events that began after the completion of the 85-day study period. [Vol. 61, p. 98] The six deaths that occurred due to events prior to completion of the study period occurred only in the HFA treatment groups: one in the HFA placebo group, four in the HFA-42 mcg group, and one in the HFA-84 mcg group. The patient who received placebo HFA had pulmonary carcinoma listed as cause of death. Of the four patients who received HFA-42 mcg, two patients died secondary to COPD exacerbation, one died secondary to pulmonary carcinoma, and one died secondary to pancreatitis. The deaths have been summarized in detail in the previous section (Serious Adverse Events).

The three deaths that occurred after completion of the 85-day study period were attributed to COPD exacerbation (one patient who received HFA-42 mcg), pulmonary carcinoma (one patient who received HFA-84 mcg) and COPD exacerbation and abdominal malignancy/hepatic metastases (one patient who received CFC-42 mcg). The patient, who died of COPD exacerbation, was diagnosed with an acute myocardial infarction three days after study completion. This patient also had a colonic perforation 16 days after completing the study (diagnosed with diverticulosis during the study). [Vol. 61, p. 98]

The sponsor has not provided any pregnancy information in this study and given the mean age of the subjects enrolled it is anticipated that there were no pregnancies during this study.

11.1.2.5.2.4. Withdrawals Secondary to Adverse Events

Forty-two patients withdrew from the study secondary to adverse events. The greatest number of discontinuations secondary to AEs occurred in the placebo CFC group (9, 13.6%) and in the CFC-42 mcg group (12, 9.4%). In the other groups, 4.0-6.5% of patients discontinued secondary to AEs. COPD was the most common AE that led to study withdrawal. Two patients (3.2%) in the placebo HFA group, two patients (1.6%) in the HFA-42 mcg group, four patients (3.1%) in the HFA-84 mcg, four patients (6.1%) in the placebo CFC group, and seven patients (5.5%) in the CFC-42 mcg group discontinued due to COPD. Dyspnea was a cause for study withdrawal only in the placebo CFC group (3 patients, 4.5%). Pulmonary carcinoma was a cause for study discontinuation in three patients (one in each in the HFA treatment groups) Pneumonia was a cause for discontinuation in two patients in the CFC-42 mcg group. Other AEs leading to study withdrawal occurred in only one patient for any given AE. [Vol. 61, p. 99-109]

These results with a focus on pulmonary system disorders are summarized in the table below.

**Table 33. Study 244.1405, Number of Patients with Withdrawals Secondary to Adverse Events with Focus on Pulmonary Disorders**

	HFA	HFA-MDI	HFA-MDI	CFC	CFC-MDI

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	Placebo n=62	42 mcg n=125	84 mcg n=127	Placebo n=66	42 mcg n=127
<b>Total Withdrawals Secondary to AE</b>	4 (6.5)	5 (4.0)	8 (6.3)	9 (13.6)	12 (9.4)
<b>Pulmonary System Disorders</b>					
COPD	2 (3.2)	2 (1.6)	4 (3.1)	4 (6.1)	7 (5.5)
Pulmonary Carcinoma	1 (1.6)	1 (0.8)	1 (0.8)	0	0
Cough	0	0	0	1 (1.5)	0
Dyspnea	0	0	0	3 (4.5)	0
Pulmonary Hypertension	0	0	1 (0.8)	0	0
Pneumonia	0	0	1 (0.8)	0	2 (1.6)

Source: Vol. 61, p. 106-109

### 11.1.2.5.2.5. Laboratory Adverse Events [Vol. 61, p. 111-141]

Mean changes from baseline in laboratory values for those patients who had both baseline and final laboratory evaluations were generally similar between all treatment groups. Overall, the mean percentage of eosinophils increased (greater in the two placebo groups as compared to the active treatment groups), and lymphocytes decreased (fairly similar between all treatment groups).

Clinically significant laboratory AEs were reported for two patients in the CFC-42 mcg group, two patients in the HFA-42 mcg group, and two patients in the placebo CFC group. Hematuria (which was normal after repeat U/A six days later) and elevated SGPT and SGOT (normalized with repeat testing two weeks after final visit) were reported in the CFC-42 mcg group. Hematuria and anemia was reported in the HFA-42 mcg group. The patient with hematuria still had hematuria on repeat testing two months later; however, this was not felt to be treatment related as judged by the investigator. The patient with anemia was diagnosed with metastatic breast cancer three months later. The two patients in the placebo CFC had anemia (s/p vascular surgery) and new onset diabetes. These were not felt to be treatment related.

*Reviewer's comments: No clinically meaningful or consistent trends in laboratory changes were observed between treatment groups.*

### 11.1.2.5.2.6. Vital Signs and Other

No significant changes were observed in mean systolic and diastolic blood pressure or heart rate. [Vol. 61, p. 190-195]

Clinically significant EKG changes as judged by the investigator were reported in five patients. However, the investigator did not feel any of these changes were related to investigational drug. Arrhythmia was noted in one patient receiving placebo HFA. Two patients receiving HFA-84 mcg had EKG changes. One patient had intermittent Mobitz II heart block noted while hospitalized for a COPD exacerbation; the heart block resolved after four days. The other patient was noted to have atrial fibrillation during hospitalization for

pneumonia; this resolved three hours after treatment with dioxin. Sinus arrhythmia and PVCs were reported in one patient who received placebo CFC group. One patient had bigeminy one-week post-treatment—the patient received HFA-84 mcg during the study—it occurred after CABG, and resolved the same day. [Vol. 61, p. 144] These findings do not appear to be treatment related.

Paradoxical bronchospasm was suggested in forty-seven patients who had a decrease of greater than 15% in their FEV<sub>1</sub> values as compared to baseline within the first 30 minutes following study drug administration on at least one test day. The majority of these patients were in the two placebo treatment groups. These findings were noted in 10 patients (16.1%) in the placebo HFA group, five patients (4%) in the HFA-42 mcg group, seven patients (5.5%) in the HFA-84 mcg group, ten patients (7.9%) in the CFC-42 mcg group, and fifteen patients (22.7%) in the placebo CFC group, with most patients in the active treatment groups having a recovery time of 60 minutes. [Vol. 61, p. 196-201] These decreases were not associated with any symptoms and did not require rescue medication. [Vol. 61, p. 145]

### 11.1.3. Discussion and Conclusions

This study demonstrated that ipratropium bromide HFA 42-mcg and HFA 84-mcg were both statistically superior to placebo on the pre-specified primary efficacy endpoints: FEV<sub>1</sub> AUC<sub>0-6</sub> and peak change from baseline ( $p=0.0001$ ). The mean peak change from baseline in FEV<sub>1</sub> in the HFA-42 mcg and the HFA-84 mcg was 0.266-0.295 L and 0.266-0.307 L, respectively. Although the sponsor did not adjust for multiple comparisons, both endpoints were statistically significant for the comparisons between the active treatments and their respective placebos taking into account the Höchberg principle. There were no statistically significant differences between ipratropium bromide HFA-42 mcg and CFC-42 mcg at any timepoint for either primary efficacy endpoint. Additionally, ipratropium bromide HFA-84 mcg was not superior to ipratropium bromide HFA-42 mcg at any timepoint for any of the primary efficacy endpoints. This indicates that the higher dose of ipratropium bromide HFA (84 mcg) does not have any efficacy advantage over the lower dose (42 mcg). Other secondary spirometric efficacy measures such as FEV<sub>1</sub>AUC<sub>0-4</sub>, FEV<sub>1</sub>AUC<sub>0-6</sub>, TAUC, FVC<sub>0-6</sub> and FVC peak responses, supported the primary efficacy findings. Other secondary efficacy measures such as the Physician global assessment, COPD symptoms, and albuterol use were less interpretable but overall did appear to support the primary efficacy findings although there was no demonstrable difference in COPD symptom scores between treatment groups.

Onset and duration of a therapeutic response defined as a 15% increase in FEV<sub>1</sub> from baseline were presented as median values and showed that the ipratropium bromide both HFA and CFC had a median onset ranging from 12.5 to 22 minutes with a peak response of 60 – 90 minutes and a median duration ranging 2.0 – 3.1 hours. These data were not presented as mean data and overall conclusions are limited with only median data available. However, even the limited the data do support the current label warning that ipratropium not be used for the treatment of acute bronchospasm.

Generally, ipratropium bromide HFA formulations were observed to be safe. The overall incidence of adverse events was comparable across all treatment groups, although the incidence was a little lower (52%) in the ipratropium bromide 84-mcg group. Discontinuations due to adverse events were lower in the HFA groups (4-6.5%) as compared

to the CFC groups (9.4-13.6%). Serious adverse events were slightly higher in the placebo HFA group (11.3%) compared to the other treatment groups (7.1-8.7%). Adverse events such as urinary retention, mydriasis, or exacerbation of narrow angle glaucoma that can be directly associated with the use of an anticholinergic agent were not reported in this study. Nine deaths were observed during the study period. None of the serious adverse events or deaths appeared to be related to administration of study drug. No clinically significant laboratory, vital sign, physical examination, or EKG changes appeared to be related to treatment drug. Forty-seven patients had a decrease of greater than 15% in their FEV<sub>1</sub> values as compared to baseline within the first 30 minutes following study drug administration on at least one test day suggestive of paradoxical bronchospasm. However, the majority of these patients (16.1-22.7%) were in the two placebo treatment groups and the event resolved with 30 minutes of onset without the need for medical intervention.

In conclusion, this study supports the efficacy and safety of ipratropium bromide HFA 42 mcg and HFA 84 mcg. It suggests that both HFA-MDI 42 mcg and CFC-MDI 42 mcg have comparable efficacy and in terms of respiratory, the HFA-MDI 42 mcg may be safer. However, ipratropium bromide HFA 84 mcg did not demonstrate any significant advantages over the HFA 42 mcg dose. This study supports the proposed marketing ipratropium bromide dose of 42 mcg.

**11.2. Study #244.1408. A Multiple Dose Comparison of Ipratropium Bromide HFA-MDI and Atrovent® MDI in a 12-week, Double-Blind, Parallel Group Study in Patients with Chronic Obstructive Pulmonary Disease (COPD)**

**11.2.1. Protocol**

**11.2.1.1. Investigators and Centers**

Protocol #: 244.1408

Title: A Multiple Dose Comparison of Ipratropium Bromide HFA-MDI and Atrovent® MDI in a 12-week, Double-Blind, Parallel Group Study in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Study Dates: Initiated November 1994. Completed February 1996.

Sites: 31 sites in the United Kingdom [Vol. 71, p. 16]

Investigators: 16 Principal Investigators

IRB: All principal investigators have received approval by their respective Research Ethics Committees. [Vol. 71, p. 21]

Ethical Considerations: This study was conducted according to the Declaration of Helsinki as revised by the 41<sup>st</sup> World Medical Assembly, Hon Kong, September 1989. [Vol. 71, p.21]

Source: Volume 71, pages 2, 16, 21; Volume 62, section 15.3.1

### 11.2.1.2. Objective

The primary objective of this study was to compare the safety and efficacy of ipratropium bromide HFA-MDI with the established ATROVENT® MDI (CFC) in a 12-week, double-blind, parallel group study in patients with chronic obstructive pulmonary disease (COPD).

### 11.2.1.3. Overall Design

This was a 12-week, randomized, double-blind, parallel-group, active-controlled, multicenter comparison study evaluating the efficacy and safety of ipratropium bromide HFA-134a vs. ipratropium bromide CFC in 174 adults with chronic obstructive pulmonary disease (COPD), conducted in the United Kingdom from November 1994 to February 1996.

### 11.2.1.4. Study Population

A total of 150 patients aged 40 years and older with chronic obstructive pulmonary disease were required to complete the study. It was anticipated that 300 patients were to be recruited to meet this goal. To achieve this target number, patients were recruited from 16 centers in the United Kingdom, with the expectation that each center would contribute 12 evaluable patients.

#### 11.2.1.4.1. Inclusion Criteria [Vol. 71, p. 22-23]

Patients were included in the study if they:

- had a documented diagnosis of COPD as defined by the American Thoracic Society
- had a baseline FEV<sub>1</sub> <65% of predicted, and an FEV<sub>1</sub> /FVC <70%, having abstained from bronchodilators for the specified study period (see below)
- were a current smoker or ex-smoker with a smoking history of more than 10 pack years
- had stable dosage of all pulmonary medication in the 6 weeks prior to Visit 1
- were able to be trained in the use of the MDI and peak flow meter
- were able to be trained to perform technically satisfactory pulmonary function tests

#### 11.2.1.4.2. Exclusion Criteria [Vol. 71, p.23-24]

Patients were excluded from the study if they:

- used more than 8 puffs of rescue  $\beta_2$  agonist therapy on any one day of the run-in period
- had a history of asthma, allergic rhinitis or atopy
- had a blood eosinophil count at screening above 600/mm<sup>3</sup>
- had any significant disease other than COPD (a significant disease was defined as a disease which in the opinion of the investigator may either put the patient at risk because of participation in the study, or a disease which may influence the results of the study or the patient's ability to participate in the study).

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- had SGOT levels twice the upper limit of the normal range, bilirubin levels 1.5 times the upper limit of the normal range, and creatinine levels 1.25 times the upper limit of the normal range
- had active tuberculosis
- had a history of cancer within the last five years
- had a history of pulmonary resection greater than one lobe
- had an URI within 6 weeks prior to Visit 1
- had a history of life threatening pulmonary obstruction, pulmonary complications of AIDS, cystic fibrosis, or bronchiectasis
- had an intolerance to aerosolized ipratropium bromide containing products, known hypersensitivity to any of the MDI ingredients
- were currently using beta-blocker medication
- were currently using oral corticosteroids at a dose of >10mg.day prednisolone in the 6 weeks prior to Visit 1
- had glaucoma and/or prostatic hypertrophy
- were pregnant or nursing women and women of childbearing potential not using a medically approved means of contraception
- had previous participation in the randomization of this study
- had concomitant or recent (within the last 2 months) use of investigational (non-marketed) drug

### *11.2.1.4.3. Allowed Therapy*

The following therapies were permitted:

- salbutamol or terbutaline MDI as rescue medicine only
- oral steroids equivalent to 10 mg prednisolone/day provided that the patients had been on regular low dose therapy for at least 6 weeks prior to the screening visit and maintained this stable dose level throughout the study
- one 14-day increase in oral steroids for an acute oral COPD exacerbation
- one 14-day course of antibiotics
- inhaled steroids at a constant dose
- theophylline preparations (patients were required to withhold theophylline on the day of pulmonary function testing)
- other prescription and OTC medications for the treatment of conditions other than COPD were permitted with the exception of those listed in the next section

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### 11.2.1.4.4. Prohibited Therapy

The following table summarizes the excluded therapies.

**Table 34. Study 244.1408, Prohibited Therapy and Time Required for Abstinence**

		For Screening	For Test Days*
Inhaled		Minimum Number of Time From Last Dose	
β <sub>2</sub> -agonists	short acting	8 hours	8 hours
	Long acting	48 hours	Not allowed
Anticholinergics	short acting	8 hours	Not allowed
	Long acting	12 hours	Not allowed
Randomized treatment		N/A	8 hours
Oral			
β <sub>2</sub> -agonists	short-acting	18 hours	Not allowed
	Long-acting	36 hours	Not allowed
Theophylline	short acting	24 hours	24 hours
	Slow release	48 hours	48 hours
Beta-blockers		6 weeks	N/A
Investigational Drugs		6 weeks	N/A

\*On pulmonary function testing days, these were the requirements

Source: Vol. 71, p. 31

### 11.2.1.4.5. Withdrawal Criteria [Vol. 71, p. 24- 25]

#### Study Termination

The protocol allowed for premature termination for any of the following reasons:

- If any interim toxicological or pharmacological findings necessitated the withdrawal of the trial medication
- If serious adverse events occurred more frequently than expected
- At the request of the appropriate regulatory authorities
- At the Company's discretion

#### Withdrawal Criteria for Individual Patients [Vol. 71, p. 25]

The following represent withdrawal criteria for individual patients:

- If patients developed any intercurrent illness or experienced any adverse event which, in the investigator's opinion may have affected the patient's response to the study drug
- If a change in dosage of maintenance pulmonary medication was required
- If more than 14 day course of antibiotics and/or more than one increased dosage (i.e. dosages greater than the equivalent of 10 mg prednisolone/day) or a course of oral steroids lasting longer than 14 days was required for the treatment of an acute exacerbation of COPD
- If unacceptable adverse events developed (which may or may not be related to study medication)
- Failure to comply with the study protocol

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- If a patient wished to withdraw from the study

Any patient withdrawn from the study was given a full physical examination including an EKG, hematology and biochemistry screen and urinalysis. The data from these patients were included in the Intention-to-Treat analysis.

### 11.2.1.5. Study Procedure [Vol. 71, p. 37-41]

A multicenter, randomized double blind, parallel group study employing an unbalanced treatment randomization (two-thirds HFA and one-third CFC) was conducted to compare the safety and efficacy of ipratropium bromide HFA (21 mcg/puff) to ipratropium bromide CFC (21 mcg/puff).

Following an initial screening visit (Visit 1), patients entered a two-week run-in phase where patients took two puffs four times a day of ATROVENT®-MDI (CFC). At the end of this period, patients who continued to meet inclusion criteria and were stable on allowed concomitant therapy, were randomized to either ipratropium bromide HFA-21 mcg (HFA-MDI) or ipratropium bromide CFC-21 mcg (CFC-MDI)—two puffs four times daily for 12 weeks. Patients had five more follow up visits (Visits 2, 3, 4, 5, and 6) after the start of the study. On Visits 2, 4, and 6, PFTs and vitals were measured, in addition to review of AEs, concomitant medications and diary data. On visits 3 and 5, PFTs were not performed; however, review of adverse events, concomitant medications, and diary card data was done. The procedure flow chart is depicted below.

**Table 35. Study 244.1408, Procedure Flow Chart**

	Screening Visit	Randomized Treatment Phase				
	Study Day -14	0	21	42	63	84
Visit	1	2	3	4	5	6
Informed Consent	v					
Medical History	v					
Physical Examination	v					v
EKG*	v					v
Laboratory Investigations*	v					v
PFT*	v	v		v		v
Vital Signs*	v	v		v		v
Issue Diary Cards	v	v	v	v	v	
Issue Atrovent CFC MDI	v					
Issue Study Inhalers		v		v		
Review Diary Cards		v	v	v	v	v
Review Adverse Events		v	v	v	v	v
Review Concomitant Medication	v	v	v	v	v	v
Issue Peak Flow Meter	v					
Training on MDI/Peak Flow Meter	v					

\*Further particulars are described below under *Efficacy Parameters* and *Safety Assessments* sections  
Vol. 71, p. 38

**11.2.1.5.1. Treatments**

Patients were randomized to receive one of the following medications administered as two puffs four times a day:

- ATROVENT® MDI (CFC) containing 21 mcg/puff (ipratropium bromide CFC)  
Batch number PD 1385 (expiration date: November 1995)  
Batch number PD 1488 (expiration date: August 1996)
- Ipratropium bromide HFA-MDI containing 21 mcg/puff (ipratropium bromide HFA)  
Batch number PD 1456 (expiration date: June 1996)

The sponsor used the 1<sup>st</sup> generation ipratropium bromide HFA-MDI product for this study. Blinding was established in this study by using a blinding device, an adapted plastic cover that masked the physical differences in the appearance of the canisters. [Vol. 71, p. 29]

**11.2.1.6. Efficacy Parameters**

Pulmonary Function Testing (FEV<sub>1</sub> and FVC) was conducted at the screening visit to assess eligibility, and at Study Visits 2, 4, and 6 (Days 0, 42, and 84). Pulmonary Function Testing was measured pre-dose and at 5, 15, 30, 60, 90, and 120 minutes after inhalation of two puffs of study medication and at hourly intervals thereafter for a total of six hours. [Vol. 71, p. 53]

For domiciliary recording of PEF<sub>R</sub>, patients were instructed to use the  peak flow meter twice daily before the morning and evening dose of study MDI and rescue inhaler. At each time point, the best of three readings was recorded in the patients' diary.

**11.2.1.6.1. Primary Efficacy Variables** [Vol. 71, p.32]

- Pre-dose weekly mean of morning and evening PEF<sub>R</sub>s
- PEF<sub>R</sub> analyzed during the run-in period and the randomized period (switch-effect)

**11.2.1.6.2. Secondary Efficacy Variables** [Vol. 71, p. 33]

- FEV<sub>1</sub> AUC<sub>0-6</sub>: area under the curve for 0-6 hours for FEV<sub>1</sub>
- Peak bronchodilatory response: FEV<sub>1</sub> max
- Onset and duration of therapeutic response
- Time to FEV<sub>1</sub> max
- FVC AUC<sub>0-6</sub> and FVC max
- Changes from baseline at all timepoints for FEV<sub>1</sub> and FVC

**11.2.1.7. Safety Evaluations** [Vol. 71, p. 34-37]

The following safety evaluations were conducted during the study:

1. Adverse events (AEs)

- ◆ During the study, particular attention was paid to AEs such as cough, wheezing, and paradoxical bronchospasm following inhalation of randomized treatment.
  - ◆ Paradoxical bronchospasm was defined as a  $\geq 15\%$  fall in FEV<sub>1</sub> below baseline and/or the need for rescue medication and/or spontaneous reporting by the patient of any event indicative of bronchospasm within 30 minutes following inhalation of study medication. A fall of  $\geq 15\%$  in FEV<sub>1</sub> without associated symptoms, complaints or need for rescue medication was not recorded as an AE, but it was evaluated statistically. [Vol. 71, p. 36]
  - ◆ Adverse events were analyzed during the run-in and randomized treatment period to evaluate for a switch-effect (from ipratropium bromide CFC to ipratropium bromide HFA).
2. Pulse rate and blood pressure pre-dose and at 60 minutes post dose
    - ◆ Vital signs were taken at the screening visit (Visit 1), prior to dosing and at 60 minutes after administration of study drug on the test days (Visit 2, 4, and 6)
  3. Changes in physical examination (end of treatment compared to baseline)
  4. Changes in resting EKG (end of treatment compared to baseline)
    - ◆ Performed at both baseline (Visit 1) and the final visit (Visit 6, or on withdrawal from the study) for each patient
  5. Changes in hematology, blood chemistry and urinalysis (end of treatment compared to baseline)
    - ◆ Hematology: CBC and an absolute count
    - ◆ Blood Chemistry: alkaline phosphatase, LDH, SGOT, SGPT, glucose, calcium inorganic phosphorus, uric acid, urea nitrogen, creatinine, total protein, albumin, and total bilirubin.
    - ◆ Urinalysis: hemoglobin, glucose and ketone measurements
  6. Use of rescue medication

**11.2.1.8. Statistical Plan**

This study was designed as a multicenter, multidose, randomized, double-blind, parallel group study to compare the safety and efficacy of ipratropium bromide HFA to ipratropium bromide CFC in patients with COPD using a 2:1 randomization scheme. The study was conducted to test the hypothesis that the new ipratropium bromide HFA formulation was comparable to the standard ipratropium bromide CFC.

The Null hypothesis was: the new HFA formulation is inferior to the standard CFC available formulation. The alternate hypothesis was: the new HFA formulation is comparable or superior to the standard CFC formulation. All statistical tests were performed using a one sided-test at the 5% significance level. [Vol. 71, p. 44] However, the sponsor states that due to the large number of primary and secondary endpoints in this study, all statistical tests were to be interpreted in a descriptive way only. [Vol. 71, p. 44]

*Reviewer's comments: This is one of the three pivotal Phase III studies to establish efficacy and safety of ipratropium bromide HFA. Typically, the two twelve-week efficacy studies should be placebo controlled; however, as the other pivotal study #244.1405, used both placebo and the same active control, and this is a switch program, comparison of the HFA product to the approved CFC product would be an acceptable study design.*

#### 11.2.1.8.1. Sample Size

The sponsor based the sample size calculation on data from previous trials with similar compounds in patients with COPD. A sample size of 150 was selected with 100 in the ipratropium bromide HFA-42 mcg group and 50 patients in the CFC-42 mcg group. This size was estimated to evaluate the stated hypothesis for FEV<sub>1</sub> AUC<sub>0-6</sub> and FEV<sub>1</sub> max at week 12. The two treatments would be considered to have comparable efficacy if the one-sided confidence intervals for the mean difference between the two treatment groups (for FEV<sub>1</sub> AUC<sub>0-6</sub> and FEV<sub>1</sub> max) was fully contained in the equivalence region, defined as greater than 120 ml. [Vol. 71, p. 143] This sample size allowed for a power of 95% to detect adverse events having an incidence rate of 3%. [Vol. 71, p. 45]

#### 11.2.1.8.2. Handling of Missing Data

For AUC calculations, middle random missing FEV<sub>1</sub> values were estimated using linear interpolation of the two adjacent measurements. For missing FEV<sub>1</sub> values at the end of the time profiles, the minimum observed FEV<sub>1</sub> value on that test day for any given patient was used as an estimate.

The calculation for weekly PEFRs and puffs of rescue medication included all patients with at least four available readings; when a patient had less than four available readings in a week, the mean for that week was estimated using the last observation carried forward method.

For those patients who discontinued the study during the 12-week period, no individual patient value was carried forward with the exception of the already mentioned AUC/PEFR calculations on a given test day. [Vol. 71, p. 46]

*Reviewer's comments: For patients that discontinued from the study, it is unclear how a final value was estimated if the last observation was not carried forward.*

#### 11.2.1.8.3. Primary Efficacy Endpoints

The sponsor evaluated two primary efficacy endpoints: the change from baseline in the pre-dose mean of morning and evening PEFRs with respect to the last week of recorded diary card data and PEFR comparison analysis during the run-in period and randomization period. For the first primary efficacy endpoint, the mean for the last week of the run-in period was subtracted from the mean for the last week of diary card data. An analysis of variance was used to test the Null hypothesis that the new HFA formulation is inferior to the standard CFC formulation. A 90% confidence interval for the mean difference between the two treatment groups was used to determine if the two formulations were of comparable efficacy—the sponsor refers to this as therapeutic equivalence in the submission. The primary timepoint of interest was week 14 unless the patient withdrew from the study earlier, in which case the last recorded week was used. [Vol. 71, p. 335]

To evaluate the “switch-effect” from ipratropium bromide CFC during the run-in phase to the ipratropium bromide HFA during the randomization phase, weekly pre-dose mean morning and evening PEFs for the two groups during the first week following randomization to treatment were compared using analysis of covariance. [Vol. 71, p. 335]

#### 11.2.1.8.4. Secondary Efficacy Endpoints

- FEV<sub>1</sub> AUC<sub>0-6</sub>: area under the curve for 0-6 hours for FEV<sub>1</sub>
- Peak bronchodilatory response: FEV<sub>1</sub> max
- Onset and duration of therapeutic response
  - ◆ A therapeutic response was defined as those FEV<sub>1</sub> measurements exceeding 1.15 times pre-dose values. Onset of therapeutic response was calculated by interpolation of a line formed between the last FEV<sub>1</sub> value recorded before a therapeutic response and the first measured value falling above the therapeutic response. Duration of therapeutic response was defined as that interval between the onset and termination of the response. . [Vol. 71, p. 338]
- Time to FEV<sub>1</sub> max
- FVC AUC<sub>0-6</sub> and FVC max
- Changes from baseline at all timepoints for FEV<sub>1</sub> and FVC

The endpoints FEV<sub>1</sub> AUC<sub>0-6</sub>, FEV<sub>1</sub> max and AUC<sub>0-6</sub> for both FVC and FVCmax were evaluated using the absolute values. The AUC was calculated using the trapezoidal rule and the pre-planned timepoints. At Visits 2, 4, and 6, the above endpoints were evaluated using an analysis of covariance. Therapeutic equivalence was tested using the one-sided confidence intervals for the adjusted mean differences (for both FEV<sub>1</sub> and FEV<sub>1</sub> max) at Visit 6; equivalence was declared if these values were completely contained in the equivalence region described as greater than 120 ml. [Vol. 71, p. 48]

## 11.2.2. Results

### 11.2.2.1. Patient Disposition

Of the 174 patients randomized for entry into the study, 144 (83%) completed the study. Fifty-six (32%) were assigned to the ipratropium CFC (CFC-MDI) group and 118 (68%) to the ipratropium bromide HFA (HFA-MDI) group. In the CFC-MDI and HFA-MDI group, 46 patients (82%) and 94 patients (80%) completed the study.

A total of 34 patients (18%) discontinued from the study. The percentages of discontinuations from each group were fairly similar (18% for the CFC-MDI as compared to 20% for the HFA-MDI). A slightly higher percentage of patients discontinued from the study secondary to adverse events in the HFA-MDI group (13%) as compared to the CFC-MDI group (11%). Overall, the number of patients discontinuing from the study secondary to worsening of COPD was 5%; and a greater percentage of these subjects were in the CFC-MDI group (7%) compared to the HFA-MDI group (4%). Only two patients (4%) in the CFC-MDI group and 1 patient (1%) in the HFA-MDI group were discontinued secondary to non-compliance. Two subjects in the HFA-MDI group but none in the CFC group were

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discontinued secondary to withdrawal of consent. Two subjects in the HFA-MDI group were lost to follow-up. The following table summarizes these patient disposition results.

**Table 36. Study 244.1408 Patient Disposition**

	Number of Patients (%)		
	CFC-MDI	HFA-MDI	Total
Total Randomized and Treated	56 (100)	118 (100)	174 (100)
Total Completed	46 (82)	94 (80)	140 (80)
Total Discontinuations	10 (18)	24 (20)	34 (20)
Total with Protocol Violations	31 (55)	66 (56)	97 (56)
<b>Reasons for Discontinuation</b>			
Adverse Events	6 (11)	15 (13)	21 (12)
Worsening of COPD	4 (7)	5 (4)	9 (5)
Worsening of other pre-existing disease	1 (2)	0	1 (1)
Other	1 (2)	10 (8)	11 (6)
Non-compliance with protocol	2 (4)	1 (1)	3 (2)
Lost to follow-up	0	2 (2)	2 (1)
Consent Withdrawn	0	2 (2)	2 (1)
Other	2 (4)	4 (3)	6 (3)

Source: Vol. 71, p. 50

### Protocol Violations [N-000-B2, 7/8/03; p. 20-24]

A total of 97 patients (55.7%) had major protocol violations in the study, 31 patients (55%) in the CFC-MDI group and 66 patients (56%) in the HFA-MDI treatment group. [Vol. 72, p. 9-12] A major protocol violation was defined as one which may affect the patient's response to treatment or resulted in an incomplete evaluation of either safety or efficacy data. Examples of major protocol violations were: spirometry outside time window, inhalation of study drug > 10 minutes after baseline spirometry, predicted FEV<sub>1</sub> > 65% of normal, FEV<sub>1</sub>/FVC > 70%, missing lab data, incomplete diary, visit outside time window, spirometry, and failed exclusion/inclusion criteria. These protocol violations occurred in both treatment groups.

Thirteen patients (11%) in the HFA-MDI group and seven (12.5%) in the CFC-MDI group had data that was not evaluable for safety secondary to a major protocol violation. These patients were not analyzed in the per protocol population; however, they were included in the Intent-to-Treat analysis population.

*Reviewer's comments: The sponsor does not summarize the protocol violations at all. Appendix 15.9.2, listing 1.1.1 and 1.1.2 is referenced. However, it is difficult to further elaborate on the protocol violations from this format of presentation. Perusal of the line listings demonstrates that similar percentages of patients in each treatment group had major protocol violations of a similar type..*

### **11.2.2.2. Demographics and Other Baseline Characteristics**

#### *11.2.2.2.1. Demographics* [Vol. 71, p. 52]

Treatment groups were similar at baseline with respect to mean age, gender, race, height and duration of COPD. The mean age for the study population was 66 ± 7.4 years. The range was 40-83 years, which was slightly wider for the HFA-MDI group. The majority of subjects were male, 123 (71%) as compared to female, 51 (29%). This ratio was similar

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between both treatment groups. All but one of the study patients were Caucasian; with one black patient in the HFA-MDI group. The mean height for the study population was 166.9 cms  $\pm$  8.8. The mean duration of COPD was 7.1 years  $\pm$  8.4. The range was 0-49 years.

*Reviewer's comments: The sponsor references Appendix 15.12, Listing 2 as source data for baseline demographic data, this reviewer is unable to locate this in the study volumes. Of particular interest to this reviewer, is the age distribution of the study population. This information will be requested from the sponsor.*

There were small differences between treatment groups at baseline in terms of weight, smoking history, and alcohol consumption. The mean weight in the study population overall in kilograms was 68.9 (152 lbs.)  $\pm$  15.7, with a range 30-123 (66 lbs-270 lbs.). The mean weight was 73.1 kg (161 lbs.) in the CFC-MDI group and 66.9 kg (147 lbs.) in the HFA-MDI group. Overall, 72% of the study population were ex-smokers compared to 28% who were current smokers. There were a greater proportion of current smokers in the HFA-MDI group (31%) as compared to the CFC-MDI group (23%). A greater percentage of patients in the HFA-MDI (27%) were non-drinkers as compared to the CFC-MDI group (14%). One patient in the CFC-group was stated to have excessive alcohol consumption, but none in the HFA-MDI group. These results are summarized below.

**Table 37. Study 244.1408, Demographic and Baseline Characteristics**

Characteristic		CFC-MDI n=56 (%)	HFA-MDI n=118 (%)	Total n=174 (%)
Sex	n (%)			
	Male	39 (70)	84 (71)	123 (71)
	Female	17 (30)	34 (29)	51 (29)
Race	n (%)			
	White	56 (100)	117 (99)	173 (99)
	Black	0	1 (1)	1 (1)
Age	Mean (years)	68.1	65.1	66
	Range	54-80	40-83	40-83
Height	Mean (cms)	166.3	167.2	166.9
	Range	150-188	142-188	142-188
Weight	Mean (kg)	73.1	66.9	68.9
	Range	38-123	30-120	30-123
	Missing Data	0	1	1
Smoking History (pack-years) n (%)				
	Smoking History	43 (77)	82 (69)	125 (72)
	Current Smoker	13 (23)	36 (31)	49 (28)
Alcohol History n (%)				
	Non-Drinker	8 (14)	32 (27)	40 (23)
	Average Consumption	47 (84)	86 (73)	133 (76)
	Excessive Consumption	1 (2)	0	1 (1)
Duration of COPD (years)				
	Mean	7.1	7.2	7.1
	Range	0-37	0-49	0-49

Source Vol. 71, p. 52

*Reviewer's comments: The sponsor lists the weight range of patients as 30-123 kg, which corresponds to 66-270 lbs. The study protocol calls for adults ages 40 and older. It would*

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be interesting to know how many patients had such low weights, and the reasons for this. Typically, younger children weigh 66 lbs.; it would be very unusual for adults to weigh so little without a severe concurrent illness. Although many smokers are very thin, 66 lbs. seems very low. The sponsor was asked to clarify this and to provide more information on the smoking history (i.e. the mean packs per year smoked and the range). Addendum: The sponsor provided some of this information in a correspondence dated 7/8/03. Nine patients in the study weighed less than 45 kg (100 lbs). All of these patients were 83 lbs or more ages 57-75 years; however, one patient (57 years old) was 66 lbs; her height was 148 cm (57"). The sponsor did not provide an explanation for the patient's low weight. However, the low weight may be due to her short stature. [N-000-B2, 7/8/03; p. 4]

### 11.2.2.2. Baseline Spirometry

The mean baseline for the study population was 0.98 liters  $\pm$  0.40 and the mean percent of predicted normal FEV<sub>1</sub> was 37.4%  $\pm$  13.5. The FEV<sub>1</sub> measurements ranged between 11.21-73.21% of predicted. The two treatment groups were comparable with respect to their baseline spirometry.

**Table 38. Study 244.1408, Baseline Spirometry in All Randomized Patients**

Characteristic		CFC-MDI	HFA-MDI	Total
		n=56	n=118	n=174
Baseline FEV <sub>1</sub> (L)	Mean	0.97	0.98	0.98
	Std Dev	0.40	0.39	0.40
	Range	0.44-2.19	0.31-2.24	0.31-2.24
Baseline FVC (L)	Mean	1.78	1.92	1.87
	Std Dev	0.69	0.72	0.71
	Range	0.46-3.40	0.45-3.95	0.45-3.95
%Predicted Normal FEV <sub>1</sub> (L)	Mean	38.15	36.98	37.6
	Std Dev	13.89	13.37	13.51
	Range	17.20-66.43	11.21-73.21	11.21-73.21

Source Vol. 71, p. 53

### 11.2.2.3. Baseline PEFr

The PEFr during the screening period were similar for both treatment groups. The mean morning PEFrs were slightly higher for the CFC-MDI group (192.9 and 192.1 for weeks 1 and 2, respectively) than for the HFA-MDI group (181 and 185 for weeks 1 and 2, respectively) but this difference is insignificant given the variability of PEFr measurements. These results are summarized below.

**Table 39. Study 244.1408, Weekly Mean PEFrs during Screening Period (L/min)**

	CFC-MDI			HFA-MDI		
	Mean	SEM	n	Mean	SEM	n
<b>Morning PEFr</b>						
Diary Week 1	192.9	9.4	54	181.0	6.1	112
Diary Week 2	192.1	9.8	55	185.0	6.3	117
<b>Evening PEFr</b>						
Diary Week 1	203.7	9.1	54	197.0	6.6	114
Diary Week 2	201.0	9.4	55	201.9	6.6	117

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*Reviewer's comments: It should be noted that patients are receiving Atrovent® CFC-MDI during this screening period so these are not true baseline values, but reflect the data on the active comparator drug in this study.*

### 11.2.2.2.4. Concomitant Diagnoses

A total of 51 patients (91.1%) in the CFC-MDI group and 106 patients (89.8%) had concomitant diagnoses. The most common diagnoses were hypertension NOS (18.6% HFA vs. 12.5% CFC), adverse effect of drug substance (HFA 12.7% vs. 7.1% CFC), angina pectoris (11.9% HFA vs. 14.3% CFC) and emphysema (HFA 9.3% vs. CFC 5.4%). Overall, the frequency of concomitant diagnoses was similar. The following table summarizes the most common diagnoses in both treatment groups.

**Table 40. Study 244.1408, Number of Patients (%) with Concomitant Diagnoses Occurring at a Frequency of 5% or Greater in Either Treatment Group**

	CFC-MDI n=56 n (%)	HFA-MDI n=118 n (%)
<b>Total Number with Concomitant Disease</b>	51 (91.1)	106 (89.8)
Abnormal EKG	2 (3.6)	7 (5.9)
Adverse Effect of Med/Biologic NOS	4 (7.1)	15 (12.7)
Angina Pectoris NOS	8 (14.3)	14 (11.9)
Cataract NOS	3 (5.4)	1 (0.8)
Chronic Ischemic Heart Disease NOS	4 (7.1)	4 (3.4)
Congenital Hiatal Hernia	3 (5.4)	5 (4.2)
Contracted Palmar Fascia	3 (5.4)	1 (0.8)
Diabetes Mellitus	3 (5.4)	1 (0.8)
Duodenal Ulcer NOS	3 (5.4)	3 (2.5)
Edema	3 (5.4)	4 (3.4)
Emphysema NEC	3 (5.4)	11 (9.3)
Esophageal Disorder NEC	3 (5.4)	1 (0.8)
Fluid Overload	3 (5.4)	2 (1.7)
Headache	0	6 (5.1)
Hypertension NOS	7 (12.5)	22 (18.6)
Old MI	4 (7.1)	3 (2.5)
Pneumonia, Organism NOS	3 (5.4)	3 (2.5)
Stomach Function Disease NEC	2 (3.6)	6 (5.1)
Varicose Vein of Legs	3 (5.4)	3 (2.5)

N-000-B2, 7/8/03; p. 316-320

### 11.2.2.2.5. Concomitant Medications

A total of 51 patients (91.1%) in the CFC-MDI treatment group and 110 (99.3%) of patients in the HFA-MDI treatment group took concomitant medications. The most common respiratory class of medications taken were steroids: beclomethasone dipropionate (CFC 55.4% vs. HFA 52.5%), budesonide (CFC 12.5% vs. HFA 15.3%), prednisolone (CFC 12.5% vs. HFA 6.8%), and fluticasone propionate (CFC 10.7% vs. HFA 5.1%). Salbutamol was used by 4 patients (7.1%) in the CFC-MDI treatment group compared to 11 patients (9.3%) in the HFA-MDI treatment group. Oxygen was used by three patients in each group (CFC, 5.4%; HFA, 2.5%). The most common non-respiratory concomitant medications were ASA (CFC 16.1% vs. HFA 14.4%), amoxicillin (CFC 21.4% vs. HFA 6.8%),

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Paracetamol (CFC 7.1% vs. HFA 11.9%), and Nifedipine (CFC 10.7% vs. 6.8%). These results are summarized below.

**Table 41. Study 244.1408, Number (%) of Patients Using Concomitant Medications at a Frequency of 6% or Greater in Either Treatment Group during the Randomized Treatment Period**

	CFC-MDI n=56 n (%)	HFA-MDI n=118 n (%)
<b>Total Number with Concomitant Medications</b>	51 (91.1)	110 (93.2)
<b>Respiratory Medications</b>		
Aminophylline	2 (3.6)	11 (9.3)
Beclomethasone dipropionate	31 (55.4)	62 (52.5)
Budesonide	7 (12.5)	18 (15.3)
Fluticasone propionate	6 (10.7)	6 (5.1)
Oxygen*	3 (5.4)	3 (2.5)
Prednisolone	7 (12.5)	8 (6.8)
Salbutamol	4 (7.1)	11 (9.3)
Theophylline	4 (7.1)	10 (8.5)
<b>Other Medications</b>		
Acetylsalicylic Acid	9 (16.1)	17 (14.4)
Amoxicillin	12 (21.4)	8 (6.8)
Frumil (combination of amiloride and furosemide)	4 (7.1)	9 (7.6)
Furosemide	4 (7.1)	8 (6.8)
Glyceryl trinitrate	3 (5.4)	11 (9.3)
Nifedipine	6 (10.7)	8 (6.8)
Paracetamol	4 (7.1)	14 (11.9)
Ranitidine	4 (7.1)	5 (4.2)

N-000-B2, 7/8/03; p. 306-314

*Reviewer's comments: Overall, both treatment groups were fairly comparable with respect to concomitant medications. Of particular interest is the fact that over 70% of the subjects were on inhaled corticosteroids.*

### 11.2.2.3. Compliance

The sponsor did not perform any specific compliance checks to ensure that the patients were taking the randomized treatment as instructed. Patients recorded the number of puffs of rescue medication used in the diary cards; however, the number of puffs of trial medication was not recorded. Clinical trial supplies were returned to the sponsor; however, no compliance evaluation was performed. [Vol. 71, p. 32]

*Reviewer's comments: As the sponsor has not assessed compliance, the study results will need to be interpreted cautiously.*

### 11.2.2.4. Efficacy Endpoint Outcomes

#### 11.2.2.4.1. Data Sets Analyzed

For the primary efficacy endpoint of weekly mean PEFs, patients were required to have at least 4 available PEF readings in a week in order for that week to be included in the analysis. The sponsor used an intent-to-treat (ITT) analysis for this endpoint and the last

week of the diary card data was used regardless of the time point during the study at which the patient's last week occurred.

For spirometry, the sponsor analyzed both the ITT and the per-protocol data sets. The ITT data set was defined as the data set that included all patients with spirometric data on a given test day. The per-protocol data set excluded all patients with serious protocol violations and no pulmonary function data on a given test day (0, 42, 84). The sponsor analyzed an additional data set to exclude data from center 52 secondary to "technical problems" which were not defined in the submission. [Vol. 71, p. 55]

#### 11.2.2.4.2. Primary Efficacy Analyses

##### **Change From Baseline in the Pre-Dose Mean of Morning and Evening PEFRs With Respect To the Last Week of Recorded Diary Card Data**

The mean change from baseline in the pre-dose morning and evening PEFRs with respect to the last week of recorded diary card data was compared using analysis of variance. In order to obtain the change from baseline, the mean for the last week of the run-in period was subtracted from the mean for the last week of diary card data. An analysis of variance was used to test the Null hypothesis that the new HFA formulation is inferior to the standard CFC formulation. A 90% confidence interval for the mean difference between the two treatment groups was used to determine if the two formulations had comparable efficacy. The primary timepoint of interest was diary card week 14 unless the patient withdrew from the study earlier, in which case the last recorded week was used. [Vol. 71, p. 335]

The mean PEFRs tended to increase from baseline to the last week in both treatment groups; however, this increase was greater in the HFA-MDI group. In the HFA-MDI group, the p-value for the change from baseline to the last week was 0.067 for a preset alpha of 0.1. For the CFC-MDI group, the corresponding value was 0.49. [Vol. 71, p. 58-59; vol. 72, p. 76]

The mean change from baseline with respect to pre-dose morning and evening PEFRs for the HFA-MDI group were higher (6.4 and 7.2 for AM and PM PEFRs, respectively) compared to the CFC-MDI (3.5 and 4.6 for the AM and PM PEFRs, respectively). The mean difference between the two groups was 2.9 for morning PEFr and 2.6 for the evening PEFr. The difference between the two treatment groups was not statistically significant based on the 90% confidence interval. The p-value for this difference was 0.6 (at a preset alpha of 0.1). On this primary efficacy endpoint, the treatment groups were comparable, and as defined by the sponsor, therapeutically equivalent. [Vol. 71, p. 58-59; vol. 72, p. 76, 92]

The means for the change from baseline to the last week of morning and evening PEFRs and the 90% confidence interval for the difference between the HFA-MDI and CFC-MDI are shown in the table below.

*Reviewer's comments: The last week of pre-dose morning and evening PEFRs is the last week of treatment, Week 12. Although the sponsor has not specifically stated this, it is interpreted from the procedure that Week 14 of diary card data corresponds to Week 12 of treatment, with the diary card data including two weeks of the baseline period*

**Table 42. Study 244.1408, Mean Change from Baseline to Treatment Week 12 in Pre-dose Morning and Evening PEFRs (L/min) for Atrovent HFA Compared to CFC**

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	CFC-MDI n = 54	HFA-MDI n = 114	Mean Treatment Difference Between HFA and CFC	90% Confidence Interval for the Difference
<b>Morning PEFR</b>				
Mean	3.5	6.4	2.9	-7.3 to 13.1
SEM	5.1	3.5	6.1	
<b>Evening PEFR</b>				
Mean	4.6	7.2	2.6	-7.8 to 12.9
SEM	5.2	3.6	6.3	

Vol. 71, p. 58,

*Reviewer's comments: As the baseline values represent measurements done during the screening period while patients were taking Atrovent® CFC-MDI, these results suggest that there may be a trend towards greater improvement from baseline in the HFA-MDI group as compared to the CFC-MDI group (one would not expect any difference in the CFC-MDI group since the patients were receiving the same drug throughout both the baseline screening period and the active treatment phase). Although the p-value is less than the pre-specified alpha for HFA-MDI group with respect to morning PEFR change from baseline, the results are not statistically significant, as adjustment for multiplicity has not been done. For two comparisons, using the Bonferroni adjustment, the p-value would have to be 0.05 (0.1/2); as such, this result falls above this alpha. Peak Flows are highly variable and a few liters/min difference between groups is inconsequential.*

### PEFRs Comparison Analysis during the Run-In Period and Randomization Period

The second primary efficacy endpoint was PEFR comparison analysis during the run-in period and randomization period. To evaluate the "switch-effect" from ipratropium bromide CFC during the run-in phase to the ipratropium bromide HFA during the randomization phase, weekly pre-dose mean morning and evening PEFRs for the two groups during the first week following randomization to treatment were compared using analysis of covariance. [Vol. 71, p. 335]

The mean morning and evening PEFRs (L/min) during the 2-week run-in period were similar for the CFC-MDI and HFA-MDI groups. The mean morning PEFR (L/min) at randomization (192.1 L/min) was similar to the PEFR one week following randomization (193 L/min) for the CFC-MDI group. Similarly, for the HFA-MDI group, it was 185 L/min at randomization and 184 L/min one week later. The evening PEFRs showed similar trends. [Vol. 71, p. 57]

**Table 43. Study 244.1408, Switch-Effect (The Week Immediately Prior And The Week Immediately After Randomization In Morning And Evening PEFRs (L/Min))**

	CFC-MDI			HFA-MDI		
	Mean	SEM	n	Mean	SEM	n
<b>Morning PEFR</b>						
Week just prior to randomization	192.1	9.8	55	185.0	6.3	117
Week just after randomization	193.0	10.0	54	184.0	6.5	113
Week 14 (last week of treatment)	198.1	12.9	44	197.2	8.5	89
<b>Evening PEFR</b>						
Week just prior to randomization	201.0	9.4	55	201.9	6.6	117
Week just after randomization	207.7	9.8	54	201.3	6.3	113
Week 14 (last week of treatment)	210.0	12.8	44	216.4	9.1	89

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The weekly pre-dose mean morning and evening PEFRs for the two groups during the first week following randomization to treatment were compared using analysis of covariance. The 90% confidence interval for this difference in the morning PEFRs was -6.7 to 5.5 and the corresponding p-value was 0.8653. The 90% confidence interval for this difference in the evening PEFRs was -11.4 to -0.64 with a corresponding p-value of .0659. The CFC-MDI group had a mean evening PEFr of 207.7 and the HFA-MDI group had 201. However, the final week of treatment showed a greater mean for the HFA-MDI group (216.4) as compared to the CFC-MDI group (210.0) (p = 0.0659). These results suggest that there was no significant difference between treatment groups after switching from Atrovent® CFC-MDI to Atrovent HFA MDI.

#### 11.2.2.4.3. Secondary Efficacy Analyses

The endpoints FEV<sub>1</sub> AUC<sub>0-6</sub>, FEV<sub>1</sub> max and AUC<sub>0-6</sub> for both FVC and FVCmax were evaluated using the absolute values. The AUC was calculated using the trapezoidal rule and the pre-planned timepoints. At Visits 2, 4, and 6, the above endpoints were evaluated using an analysis of covariance. Therapeutic equivalence was tested using the one-sided confidence intervals for the adjusted mean differences (for both FEV<sub>1</sub> and FEV<sub>1</sub> max) at Visit 6; equivalence was declared if these values were completely contained in the equivalence region described as greater than 120 ml. [Vol. 71, p. 48] The data described is for the ITT population.

##### FEV<sub>1</sub> AUC<sub>0-6</sub>: area under the curve for 0-6 hours for FEV<sub>1</sub>

The adjusted mean (adjusted for test day baseline FEV<sub>1</sub> and center) for the CFC-MDI group at Visit 6 was 1.041L (SEM 0.020 L) and for the HFA-MDI group was 1.050 L (0.015 L). The 90% confidence interval for the difference between the two groups at Visit 6 (0.0096) was -0.0295 to 0.0487 (p = 0.6853). [Vol. 71, p. 66; Vol. 72, p. 109] Since the adjusted mean difference was not greater than 120 ml and was completely contained in the equivalence region, the sponsor concluded that both treatments had comparable efficacy. Both treatments showed similar efficacy when Center # 52 (n = 19) was excluded from the analysis and when the ITT and the per-protocol populations were analyzed as well. [Vol. 71, p. 70]

*Reviewer's comments: Although the FEV<sub>1</sub> AUC<sub>0-6</sub> was defined as secondary endpoint, it is a more reliable endpoint than PEFr and the finding of comparable efficacy in both treatment groups is supportive of the efficacy of the HFA formulation..*

##### Peak bronchodilatory response: FEV<sub>1</sub> max

The adjusted mean for FEV<sub>1</sub> max at Visit 6 was comparable for both treatments. For CFC-MDI 1.173 L (SEM 0.023 L) and for HFA-MDI 1.182 L (SEM 0.017). The difference between the two groups was 0.0085. The 90% confidence interval for this difference was -0.0359, 0.0529 (p = 0.7522). [Vol. 71, p. 66-67; Vol. 71, p. 102]

##### Onset and Duration of Therapeutic Response and Time to Peak Response

A therapeutic response was defined a 15% improvement above test day pre-dose baseline. [Vol. 71, p. 71, 140] Onset of therapeutic response was calculated by interpolation of a line formed between the last FEV<sub>1</sub> value recorded before a therapeutic response and the first

measured value falling above the therapeutic response. Duration of therapeutic response was defined as that interval between the onset and termination of the response. [Vol. 71, p. 338]

For those patients who did not achieve a therapeutic response, the sponsor arbitrarily assigned an extreme value of 999 for the median onset of therapeutic response and a 0 for the duration of therapeutic response, so as not to exclude these patients. [Vol. 71, p. 71] The percentage of patients achieving a therapeutic response for FEV<sub>1</sub> was higher in the HFA-MDI group (49-62%) compared to the CFC-MDI (43-54%). The following table summarizes these results.

**Table 44. Study 244.1408, Patients Achieving a Therapeutic Response within 30 Minutes Post-Dose**

	FEV <sub>1</sub>		FVC	
	CFC-MDI	HFA-MDI	CFC-MDI	HFA-MDI
Visit 2 (Day 0) n (%)	30/56 (54)	73/118 (62)	31/56 (55)	68/118 (58)
Visit 4 (Day 42, Week 6) n (%)	21/48 (44)	63/104 (61)	22/48 (46)	61/104 (59)
Visit 6 (Day 84, Week 12) n (%)	20/47 (43)	47/96 (49)	18/47 (38)	54/96 (56)

Source: Vol. 71, p. 72

For the times to onset and durations of therapeutic response, and the times to peak response, medians have been presented since the data was skewed. The duration and onset of therapeutic response vary between treatment groups, within treatment groups, between and within visits, and between and in the same patients on a given test day for both FEV<sub>1</sub> and FVC. The ranges for FEV<sub>1</sub> median time to onset, duration of therapeutic response and time to peak response for all visits were 2-360 minutes, 1-359 minutes, and 5-360 minutes. [Vol. 72, p. 342-356] The medians for all visits for FEV<sub>1</sub> and FVC for median times and onset of therapeutic response and time to peak response varied widely among individual patients and no firm conclusions can be made regarding these data.

FVC AUC<sub>0-6</sub> and FVC max

The adjusted means for the FVC AUC<sub>0-6</sub> at Visit 6 were 1.866 L ± 0.046 for CFC-MDI and 1.947 L ± 0.034 for the HFA-MDI group. The mean difference was 0.0813. For the FVC max, the adjusted means at Visit 6 were 2.109 L ± 0.054 for CFC-MDI and 2.218 L ± 0.040 for the HFA-MDI group and the mean difference was 0.1083. [Vol. 72, p. 116, 123] These data suggest that both treatments for these secondary endpoints are comparable.

**11.2.2.5. Safety Outcomes**

All 174 randomized patients were included in the safety evaluation of adverse events. However, not all of these patients were eligible for the laboratory parameters and physical examination parameters secondary to either missing data or protocol violations.

*11.2.2.5.1. Extent of Exposure*

The dosing regimen for all patients was two puffs of the MDI four times a day for 12 weeks (84 days). The mean duration of treatment exposure was comparable for both treatment groups. The means for the CFC-MDI and HFA-MDI groups were 77.4 days and 76.5 days, respectively. Eighty percent of patients in the CFC-MDI group and 77 percent of patients

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in the HFA-MDI group had greater than or equal to 11 weeks of study drug exposure. The duration of total exposure is similar between treatment groups. [Vol. 71, p. 75]

**Table 45. Extent of Exposure in Weeks**

	CFC-MDI n = 56	HFA-MDI n = 118
Duration of Exposure (Weeks)	n (%)	n (%)
Up to 1	1 (2)	2 (2)
1-2	0	2 (2)
2-3	2 (4)	2 (2)
3-4	3 (5)	1 (1)
4-5	0	2 (2)
5-6	0	3 (3)
6-7	1 (2)	2 (2)
7-8	1 (2)	2 (2)
8-9	0	0
9-10	0	2 (2)
10-11	3 (5)	9 (8)
11-12	12 (21)	32 (27)
12-13	24 (43)	46 (39)
13-14	7 (13)	12 (10)
14-15	2 (4)	1 (1)
Mean (days)	77.4	76.5
Standard Deviation	22.9	20.7

Source: Vol. 71, p. 76

### 11.2.2.5.2. Adverse Events

Of the 174 randomized patients, 113 (64.9%) reported a total of 242 AEs (all causalities). In the CFC-MDI, 40 (71.4%) subjects reported 78 AEs and in the HFA-MDI treatment group 73 (61.9%) subjects reported 164 AEs. There were 3 (5%) subjects in the CFC-MDI group, and 12 (10%) subjects in the HFA-MDI group who had serious AEs. Four (7.1%) and 14 (11.9%) subjects discontinued from the study secondary to AEs in the CFC-MDI and HFA-MDI treatment groups, respectively. [Vol. 71, p. 81, 84; Vol. 73, p. 11, 13]

**Table 46. Study 244.1408, Adverse Events, All Causalities**

	CFC-MDI n (%)	HFA-MDI n (%)
Randomized	56	118
Number of AEs	78	164
Subjects with AEs	40 (71.4)	73 (61.9)
Subjects with Serious AEs	3 (5)	12 (10)
Subjects with Severe AEs	7 (12.5)	18 (15.3)
Subjects discontinued due to AEs	4 (7.1)	14 (11.9)

Vol. 71, p. 81,84; Vol. 73, p. 11, 13

The most frequently reported AEs occurred in the respiratory system. Bronchitis was the most frequently reported AE, occurring in 10 (17.9%) subjects and 20 (16.9%) of patients in the CFC-MDI and HFA-MDI treatment groups, respectively followed by dyspnea (~13% in both groups). COPD exacerbations were reported more frequently in the CFC-MDI group (12.5%) than the HFA-MDI group (6.8%). Rhinitis, cough, headache, abdominal

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pain/dyspepsia, and urinary tract infection were reported more frequently in the CFC-MDI group. Upper respiratory tract infection, influenza-like symptoms, nausea, vomiting, dry mouth, epistaxis, and, pharyngitis were reported more frequently in the HFA-MDI group, all less than an incidence of 5%. Overall, the reported AEs were generally comparable between treatment groups. Adverse events occurring in any treatment group at an incidence of 3% or greater are presented in the table below.

**Table 47. Adverse Events Occurring in Any Treatment Group at an Incidence of 2%, Regardless of Causality\***

Adverse Event	CFC-MDI n = 56 n (%)	HFA-MDI n = 118 n (%)
<b>BODY AS A WHOLE</b>		
Headache	2 (3.6)	1 (0.8)
Influenza-Like symptoms	1 (1.8)	5 (4.2)
Leg Pain	2 (3.6)	1 (0.8)
<b>GASTROINTESTINAL DISORDERS</b>		
Abdominal Pain	3 (5.4)	3 (2.5)
Dyspepsia	3 (5.4)	1 (0.8)
Nausea	1 (1.8)	5 (4.2)
Stomatitis	2 (3.6)	0
Vomiting	0	6 (5.1)
<b>RESPIRATORY DISORDERS</b>		
Bronchitis	10 (17.9)	20 (16.9)
COPD Exacerbation	7 (12.5)	8 (6.8)
Cough	2 (3.6)	2 (1.7)
Dyspnea	7 (12.5)	15 (12.7)
Pharyngitis	0	4 (3.4)
Rhinitis	4 (7.1)	5 (4.2)
Upper Respiratory Tract Infection	1 (1.8)	5 (4.2)
<b>URINARY SYSTEM DISORDERS</b>		
Urinary Tract Infection	3 (5.4)	3 (2.5)
<b>VISION DISORDERS</b>		
Abnormal Vision	2 (3.6)	0

\* AEs during the run-in period are excluded

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An adverse event evaluated via spirometry, not listed in the table above, was paradoxical bronchospasm. Paradoxical bronchospasm was defined as a fall in FEV<sub>1</sub> of greater than or equal to 15% below baseline within 30 minutes following inhalation of study drug. This was noted at a greater frequency in the CFC-MDI group than in the HFA-MDI group. Nine patients (16%) in the CFC-MDI group had paradoxical bronchospasm, as compared to three patients (3%) in the HFA-MDI group. [Vol. 71, p. 82] The sponsor does not provide further information regarding recovery time for patients with paradoxical bronchospasm.

Treatment Related Adverse Events [Vol. 71, p. 79, 80]

The incidence of treatment related adverse events as judged by the investigator was similar between the two treatment groups. Overall, 8 patients (14.2%) in the CFC-MDI group and 20 patients (16.9%) in the HFA-MDI group had at least one AE that was considered to be treatment related by the investigator. No single AE judged to be treatment related was reported at an incidence of greater than 6%.

In the CFC-MDI treatment group, two reports of cough, and one report each of nausea, exacerbation of COPD, EKG abnormality, blurred vision, and elevated GGT were considered to be treatment related.

In the HFA-MDI treatment group, three reports each of pharyngitis and dry mouth, two reports of epistaxis, and one report each of cough, rhinitis, dyspepsia, nausea, headache, palpitations, urinary retention, frequency of micturition, cor pulmonale, myalgia, tremor, and taste perversion were judged to be treatment related. Dry mouth, nausea, urinary retention, and frequency of micturition can be expected with anticholinergics.

Respiratory Adverse Events Analyzed for Switch-Effect [Vol. 71, p.78]

The sponsor has analyzed the number and percentage of patients with at least one respiratory AE in the run-in period and compared this to the two weeks following randomization, to analyze the "switch-effect." Overall, 4% of subjects reported any respiratory AEs in the run-in period and 10% in the two weeks following randomization. During the run-in period, when all subjects received Atrovent® CFC-MDI, 7 subjects (6%) in the HFA-MDI randomized group had respiratory AEs. Following randomization, subjects receiving CFC-MDI reported a greater percentage of AEs (13%) as compared to the subjects receiving HFA-MDI (9%). The subjects randomized to the HFA-MDI group were the subjects who received different treatments during the run-in and two weeks after randomization period; in this group, there was a slightly higher percentage of subjects reporting respiratory AEs following the switch to HFA-MDI therapy. However, it should be noted that in the CFC-MDI randomized group, where no change in therapy occurred, an even higher change was noted between the run-in period and the two weeks following randomization. Essentially, no switch-effect was noted in terms of respiratory AEs.

*11.2.2.5.3. Deaths, Serious Adverse Events, and Pregnancies*Deaths

There was one death reported during the study period while the patient was receiving active treatment. This occurred in Patient #122, a 68 year old male who was randomized to HFA-MDI. Seventy days after being randomized to this treatment the patient was hospitalized for severe COPD exacerbation caused by an episode of acute bronchitis; the patients respiratory status continued to deteriorate, despite apparent appropriate therapy, and the patient subsequently died five days later; the cause of death was COPD exacerbation caused by acute bronchitis. [Vol. 71, p. 83; Vol. 73, p. 58]

Another death occurred; in a patient who had been discontinued from the study. Patient #87 withdrew from the study secondary to a COPD exacerbation, and recovered. However, 27 days after study discontinuation, this patient died as a result of a second COPD exacerbation

with a possible pulmonary embolism. The deaths are unlikely to be related to the study drug.

#### Serious Adverse Events

Serious adverse events were reported by 15 patients (9%), and occurred at a greater frequency in the HFA-MDI treatment group. Of the 15 patients with reported serious adverse events, 3 were in the CFC-MDI treatment group (5%) and 12 in the HFA-MDI group (10%). There were nine (5%) withdrawals from the study secondary to serious adverse events, one in the CFC-MDI treatment group and eight in the HFA-MDI treatment group.

In the CFC-MDI group, patients #117, 187 and 87 had serious adverse events for which hospitalization was required. Patient #117 was a 60 year old male with COPD who was admitted for epigastric pain, duodenitis, and melena on day 44 of treatment; he was withdrawn from the study. Patient # 187 was a 68 year old male who had bronchitis leading to a COPD exacerbation and was admitted to the hospital; he received standard therapy and recovered, however, he was withdrawn from the study. Patient #87 was a 75 year old male was admitted with a COPD exacerbation; this patient recovered; however, 27 days post study discontinuation, he had bronchitis and another COPD exacerbation, and subsequently died as a result. None of these events were judged by the investigator to be treatment related. All patients received greater than 76 days of treatment. [Vol. 71, p. 110]

In the HFA-MDI group, 12 patients had serious adverse events. Patient #122 died as a result of bronchitis/COPD exacerbation, as described above. Patient #82 was a 50 year old male (at 38 days of treatment) was hospitalized for a COPD exacerbation, and recovered. Both patients were withdrawn from the study and did recover. After three days on treatment, patient #11 (63 year old male), was hospitalized with cor pulmonale, and was withdrawn from the study. Patient #85 was a 71 year old female was hospitalized for pneumonia and weight decrease after 84 days of treatment, and study drug was discontinued. Patient #193 (48 year old male) was hospitalized after 36 days of study drug treatment for abdominal pain, vomiting, and duodenitis; this patient recovered and was not withdrawn from the study. Patients #152 (78 year old male), had a fracture on day 6 of treatment, patient # 159 (79 year old male) was hospitalized for anemia on day 22 of treatment and patient # 61 (72 year old male) was hospitalized for micturition frequency on day 16 of treatment; the latter two were discontinued from the study. Two patients, #116 (62 year old male) and 106 (65 year old female) were withdrawn from the study after 40 days and 67 days of treatment, respectively, for cerebrovascular disorder. Patient #3 (71 year old female) was diagnosed with a disabling cataract; she remained on study drug (days of treatment is listed as unknown by the sponsor). The only two adverse events judged to be related to study drug by the investigator were cor pulmonale and micturition frequency; however, this reviewer feels that it is unlikely that these events are treatment related. Urinary retention would most likely be the expected effect given the pharmacological properties of the drug and cor pulmonale would be expected to be the result of a long standing lung disease [Vol. 71, p. 110-111; Vol. 73, p.187-194]

*Reviewer's comments: Given the disease under investigation, and the age of the population studied, the serious adverse events listed are not unexpected; and in this reviewer's assessment, these adverse events are not treatment related.*

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*The sponsor does not provide any information on pregnancies and this reviewer assumes that, given the study population, there were no pregnancies during the study. However, the sponsor would be asked to submit this information. Information on withdrawals secondary to AEs were not summarized in a separate section. The SAEs section summarizes which patients withdrew due to serious AEs however.*

### Laboratory Adverse Events

Laboratory tests were done at the Screening Visit and after 12 weeks of treatment, or earlier if the patient withdrew from the study prematurely. Changes in laboratory values were considered clinically relevant if patients had normal values at screening, and subsequently at the final visit had values outside the normal range. [Vol. 71, p. 86]

Overall, the changes in the laboratory parameters were comparable between the treatment groups with a few exceptions. Of the 56 patients randomized to the CFC-MDI group, 50-53 had final results and of the 118 randomized to the HFA-MDI group, 105-109 had final results. A greater percentage of patients in the CFC-MDI group had abnormal final values for sodium, glucose, GGT, hemoglobin, platelets, and eosinophils, and lymphocytes. In the HFA-MDI group, the LDH was lower in a greater percentage of patients. The changes in laboratory parameters between screening and the final visits demonstrating directional change are summarized in the table below.

**Table 48. Study 244.1408, Number and Percentage of Evaluable Patients with Directional Changes in Laboratory Parameters between Screening and Final Visit**

Parameter	Number of Patients		Normal Baseline-Low at Final Visit		Normal Baseline-High at Final Visit	
	CFC-MDI	HFA-MDI	CFC-MDI n (%)	HFA-MDI n (%)	CFC-MDI n (%)	HFA-MDI n (%)
Sodium	53	109	4 (8)	4 (4)	0	0
Glucose	53	109	0	0	5 (9)	5 (5)
GGT	53	109	0	0	8 (15)	3 (3)
LDH	50	107	0	4 (4)	1 (2)	1 (1)
Hemoglobin	53	107	4 (8)	1 (1)	1 (2)	1 (1)
Hematocrit	53	107	4 (8)	2 (2)	1 (2)	4 (4)
Platelets	53	107	0	0	3 (6)	1 (1)
Lymphocytes	52	107	4 (8)	5 (5)	2 (4)	1 (1)
Eosinophils	52	105	0	0	2 (4)	1 (1)

Source: Vol. 71, p. 89

The percentage of patients with changes in laboratory parameters was generally low (less than or equal to 8 percent). It is apparent that the HFA-MDI had fewer changes as compared to the CFC-MDI group.

The sponsor considered three patients to have clinically important changes; all of these were for the laboratory parameter GGT. Patient 2 was randomized to the HFA-MDI group, and his abnormal values were attributed to possible effects of alcohol consumption. He had an increase in the GGT from 48 to 157, without any significant increase in AST or ALT. [Vol. 71, p. 88] Patients 96 and 108 had elevated GGT in the CFC-MDI group; the former's GGT increased from 44 IU/L to 254 IU/L and the latter's increased from 51 to 68 IU/L. The significance of these results was unclear to the investigator.

*Reviewer's comments: No clinically meaningful changes attributable to HFA-MDI were noted.*

#### Vitals, and Other Safety Variables

Vital signs (blood pressure and pulse) were measured at baseline and 60 minutes post-inhalation of study drug on each test day. There were no clinically significant changes from baseline in blood pressure or pulse between treatment groups. [Vol. 71, p. 92-93]

Only two patients in the study –one in each treatment group–had any significant changes in their EKGs at the final visit as compared to baseline. Patient #40 was randomized to the CFC-MDI group and was found to have widespread T-wave flattening without any other significant findings. No cause for this has been provided. Patient #79 was randomized to the HFA-MDI treatment group and was found to have multiple ventricular ectopies; this finding was not considered to be treatment related by the investigator. [Vol. 71, p. 93-94] This reviewer does not feel that these changes are clinically meaningful.

#### Use of Rescue Medication

After the screening visit, patients were issued either a salbutamol or terbutaline MDI as rescue medication. And they were asked to record the number of puffs used daily in their diary card. The changes from baseline in the mean for the total number of puffs of rescue medication used per day during the last week of recorded diary card data were compared using analysis of variance.

The mean number of puffs of rescue medication use increased slightly in the CFC-MDI from baseline to the final week and decreased in the HFA-MDI group. The mean number of puffs for the last week of the screening period (baseline) was 4.15 puffs for the CFC-MDI treatment group and 4.54 puffs for the HFA-MDI treatment group. The weekly mean day and night number of rescue medication for the CFC-MDI group at baseline were 3.67 puffs and 0.48 puffs, respectively. For the HFA-MDI group, the corresponding values for day and night rescue medication use at baseline were 4.01 and 0.54 puffs, respectively. For the final week, the mean total, day, and night rescue medication use was 4.10, 3.57, and 0.57 puffs, respectively for the CFC-MDI group. For the HFA-MDI group, the final week means for total, day, and night rescue medication use were 4.38, 3.79, and 0.65 puffs, respectively.

There was no meaningful difference between treatment groups in the change from baseline to the final week for the total number of puffs of rescue medication used per day by analysis of variance. The mean difference between treatment groups was  $-0.58$ . This suggests that both drugs were comparable in terms of rescue medication use.

#### **11.2.3. Discussion and Conclusions**

In this study both treatment groups had similar baseline characteristics. A significant percentage of patients ( $> 50\%$ ) had major protocol violations that might impact the efficacy results. Efficacy was comparable between the CFC MDI to the MDI as evaluated by PEF<sub>R</sub>, FEV<sub>1</sub>AUC<sub>0-6</sub>, and FEV<sub>1</sub> max.

Up to 62% of subjects in the HFA group achieved a therapeutic response (15% improvement in FEV<sub>1</sub>) compared to 54% in the CFC group. The time to peak response was very variable among individual patients in both treatment groups. There were no unique safety concerns

identified from the safety analysis. The HFA group had a higher percentage of serious AEs (10%) compared to the CFC (5%) group however, none of these AEs were drug-related and appear to be related to underlying disease. A randomization imbalance in terms of patient characteristics might be responsible for this difference observed in the clinical trial. The AE profile was similar overall except that paradoxical bronchospasm was reported with a higher frequency in the CFC MDI group.

In spite of the limitations, the study is supportive of the comparable efficacy and safety of ipratropium bromide HFA-134a and ipratropium bromide CFC-MDI.

### **11.3. Study #244.2453. One-Year Safety-In-Use Study of Ipratropium Bromide HFA-134a in Adults with Chronic Obstructive Pulmonary Disease (COPD)**

#### **11.3.1. Protocol**

##### **11.3.1.1. Investigators and Centers**

Protocol #: 244.2453

Title: One-Year Safety-In-Use Study of Ipratropium Bromide HFA-134a in Adults with Chronic Obstructive Pulmonary Disease (COPD)

Study Dates: Initiated 01 April 1996. Completed 26 September 1997.

Sites: 32 sites in the United States [Vol. 79, p. 38-40]

Investigators: 32 Principal Investigators

IRB: All principal investigators have received approval by their respective Investigational Review Boards. [Vol. 78, p. 165-243; Vol. 79, p.9-25] Most of the investigators received approval from:  
Western Institutional Review Board  
3535 Seventh Avenue, S.W., Olympia, WA 98502  
The few others received IRB approval from their respective clinical centers.

Ethical Considerations: This study was conducted according with the Declaration of Helsinki as revised by the 41<sup>st</sup> World Medical Assembly, Hong Kong, September 1989, Good Clinical Practices and 21 CFR, parts 50, 56, and 312. [Vol. 79, p. 172]

Source: Volume 77, pages 2; Vol. 78, p. 165-243; Vol. 79, p. 9-25,38-40

##### **11.3.1.2. Objective**

The objective of this study was to evaluate the long-term safety of ipratropium bromide monohydrate HFA-134a in patients with chronic obstructive pulmonary disease (COPD). [Vol. 77, p. 25]

### 11.3.1.3. Overall Design

This was a 52-week, randomized, open-label, active controlled, multi-center long term safety study in 456 patients 40 years and older with COPD, conducted in the United States between April 1, 1996 to September 26, 1997, evaluating the long-term safety of ipratropium bromide monohydrate HFA-134a as compared to Atrovent® CFC-MDI.

### 11.3.1.4. Study Population

A total of at least 375 patients of either sex, 40 years or older with COPD were required to complete the trial. To fulfill this requirement, each of 19 centers was expected to enroll at least 20 patients. Originally 25 sites were initiated; however, to meet enrollment goals, a total of 32 sites were initiated resulting in the enrollment of 456 patients. [Vol. 77, p. 28, 30]

#### 11.3.1.4.1. Inclusion Criteria [Vol. 77, p. 28]

Patients were included in the study if they:

- Had a diagnosis of COPD according to the following criteria:
  - Patients must have relatively stable, moderate to severe airway obstruction with an  $FEV_1 \leq 65\%$  of predicted normal and  $FEV_1 / FVC \leq 70\%$
- Were male or female patients 40 years of age or older.
- Had a smoking history of more than 10 pack-years.
- Were able to satisfactorily administer the medication, perform pulmonary function test and maintain record during the study period as required in the protocol.

#### 11.3.1.4.2. Exclusion Criteria [Vol. 77, p. 29]

Patients were excluded from study enrollment if they:

- Had any significant disease other than COPD—a significant disease was defined as a disease which in the opinion of the investigator may either put the patient at risk because of participation in the study or a disease which may influence the result of the study or the patient's ability to participate in the study.
- Had clinically significant abnormal baseline hematology, blood chemistry or urinalysis, if the abnormality defined a disease listed as an exclusion criterion.
- Had SGOT > 80 IU/L, SGPT > 80 IU/L, bilirubin > 2 mg/dl, or creatinine > 2 mg/dl
- Had a history of asthma, allergic rhinitis or atopy or who have a blood eosinophil count above  $600/mm^3$ .
- Had a recent (i.e., one year or less) history of myocardial infarction.
- Had a recent history (i.e., three years or less) of cardiac failure, had cardiac arrhythmia requiring drug therapy, were taking systemic beta-blockers, or were on chronic daytime oxygen therapy.

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- Had known active tuberculosis.
- Had a history of cancer within the last five years, with the exception of basal cell carcinoma.
- Had a history of life-threatening pulmonary obstruction, or a history of cystic fibrosis or bronchiectasis.
- Had a pulmonary resection.
- Had undergone a thoracotomy.
- Had a viral infection or febrile illness including upper respiratory infections during the six-week period preceding the Screening /visit.
- Had a known hypersensitivity to anticholinergic drugs.
- Had a known symptomatic prostatic hypertrophy or bladder-neck obstruction.
- Had known narrow-angle glaucoma.
- Were receiving cromolyn sodium or nedocromil sodium.
- Were receiving antihistamines.
- Were pregnant or nursing women and women of childbearing potential not using a medically approved means of contraception (i.e., oral contraceptive, intrauterine devices, diaphragm, or Norplant®).
- Had taken an investigational drug within one month or 6 half-lives (whichever is longer) of the drug prior to the screening visit or patients currently enrolled in another research study.
- Had alcoholism or drug abuse.

### *11.3.1.4.3. Withdrawal Criteria* [Vol. 77, p. 30]

Patients were allowed to withdraw from the study at any time for any reason, either upon their own request or at the direction of the investigator or the sponsor. The reasons for withdrawal were documented on the CRF. All data for the withdrawn patients were included in the safety analyses. Adverse events present at the time of patient withdrawal were followed-up until resolution or until further follow-up was determined to be adequate by the investigator and the clinical monitor.

### *11.3.1.4.4. Prohibited Concomitant Medications* [Vol. 77, p. 33]

The following medications were not allowed throughout the study period, from initial screening visit through the 52-week treatment period:

- all other investigational drugs
- all systemic beta-blockers
- cromolyn sodium

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- nedocromil sodium
- Atrovent® inhalation aerosol (in addition to randomized treatment), Atrovent® Inhalation Solution, or Combivent®

The sponsor does not provide information on the duration of time that this therapy must be withheld prior to initiation of study.

### 11.3.1.4.5. Allowed Therapy [Vol. 77, p. 34]

The following medications were allowed during the study period if the patients were stabilized for at least six weeks prior to and throughout the study period:

- oral corticosteroids only if the patient was stabilized on doses equivalent to 10 mg or less of Prednisone daily or 20 mg or less every other day
- orally inhaled corticosteroids
- theophylline preparations (excluding 24-hour preparations)
- mucolytic agents not containing bronchodilators

Patients were also allowed to take beta agonists as needed throughout the study period, in addition to their usual COPD medications above with the exception of Atrovent® inhalation aerosol (in addition to randomized treatment), Atrovent® Inhalation Solution, or Combivent®.

### 11.3.1.5. Study Procedure

The study was designed as a multicenter, randomized, open-label, parallel group study. The study consisted of a screening visit (Visit 0) at which time a physical examination, laboratory tests, and a 12-lead EKG were conducted. This was followed by a two-week baseline period during which patients were asked to take two puffs of Atrovent® Inhalation Aerosol (CFC-MDI) four times a day. The baseline could be extended up to six weeks to allow for stabilization of medication requirements. Stable patients were randomized to study medication (Visit 1) for a 52-week treatment period following the baseline period. At subsequent follow up visits patients had assessments done as outlined in the Table 29 below. [Vol. 77, p. 34, 39-43]

**Table 49. Study 244.2453, Procedure Flow Chart**

	Screening	Treatment Period						
Visit	0	1	2	3	4	5	6	7
Day/Week	Day – 14	Day 1	Week 6	Week 12	Week 18	Week 26	Week 39	Week 52
Informed Consent	Pre-screening							
Medical History	v							
Physical Examination	v			v		v		v
Vital Signs	v	v		v		v		v
Laboratory Tests	v			v		v		v
12-Lead EKG	v			v		v		v
Pulmonary Function Tests	v	v		v		v		v
Atrovent® Inhalation Aerosol dispensed (open-label)	v							

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	Screening		Treatment Period					
Visit	0	1	2	3	4	5	6	7
Day/Week	Day - 14	Day 1	Week 6	Week 12	Week 18	Week 26	Week 39	Week 52
Symptom Score Evaluation		√	√	√	√	√	√	√
Global Evaluation		√	√	√	√	√	√	√
Summary of Medication Used		√	√	√	√	√	√	√
Medication Dispensed (study drug)		√	√	√	√	√	√	√
Daily patient Record Dispensed	√	√	√	√	√	√	√	
PEFR Record Dispensed	√	√	√	√	√	√	√	
Adverse Events Review	√	√	√	√	√	√	√	√
Concomitant Medication Review	√	√	√	√	√	√	√	√

Source: Vol. 77, p. 39

### 11.3.1.6. Study Treatments

Patients were randomized in a 2:1 manner to Atrovent HFA or Atrovent CFC to receive two inhalations four times a day for 52-weeks. The lot numbers for the HFA product were as follows:

- Ipratropium bromide HFA-MDI 21 mcg/puff (HFA-MDI) inhaler PD-1456, expiration date 12/96
  - PD-1693, expiration date 9/96
  - PD-1763, expiration date 11/97
  - PD-1764, expiration date 11/97
- Lot numbers and expiration dates for the CFC product were not provided.

The sponsor had to re-supply the HFA-MDI twice during the course of the study period, once prior to the expiration date of Lot No. PD-1456 and again secondary to stability concerns for Lot No. PD-1693. [Vol. 77, p. 22]

The sponsor used both the first generation and second generation products for this study. Of the 305 patients randomized to the HFA-MDI treatment group, 186 patients receive the first generation products and 119 received the second generation product at the start of the trial. Of the 186 patients who started with the first generation product, by visit 2 (6 weeks after start of trial), 93 (counting discontinuations) were still receiving the first generation product and 79 were receiving the second-generation product. By visit 3 (test day 85), 12 were still receiving the first generation product, and 160 were receiving the second-generation product. All patients received the second generation HFA-MDI product after Visit 4 (Week 18). [N-000-BM, p. 4]

#### 11.3.1.6.1. Randomization Scheme

An unbalanced randomization scheme was used for this study. For the randomization, a block size of six was used. In each block of six, four patients were randomized to HFA-MDI and two to CFC-MDI.

### 11.3.1.7. Efficacy Parameters

Efficacy parameters were FEV<sub>1</sub> variables, COPD symptom scores, PEFs, and the physician global evaluations. The primary objective of the study was to assess safety with efficacy as secondary. Baseline spirometry was performed at the screening visit and additionally on each of the four test days throughout the 52-week treatment period. On the test days (Visits 1, 3, 5, and 7), pulmonary function testing was performed pre-treatment, 15, 30, 60, 90 minutes and 2, 3, 4, 5, and 6 hours after drug administration. Patients were required to have a 24-hour washout of theophylline preparations, 48-hour washout of long-acting oral or inhaled beta adrenergic bronchodilators and 12-hour washout of short-acting bronchodilators, Atrovent® CFC-MDI and any study drug prior to PFT on all test days.

For PEF, patients were required to record their peak flow measurements each morning prior to morning medication, recording the best of three blows. Patients were asked to do peak flow testing immediately upon rising after clearing of mucous. [Vol. 77, p. 41]

#### Efficacy Variables

- FEV<sub>1</sub> AUC 0-6 hours (FEV<sub>1</sub> AUC<sub>0-6</sub>)
- FEV<sub>1</sub> AUC 0-4 hours (FEV<sub>1</sub> AUC<sub>0-4</sub>)
- FEV<sub>1</sub> peak change from test day baseline
- FEV<sub>1</sub> onset of therapeutic response
  - Therapeutic response was defined as those FEV<sub>1</sub> measurements exceeding 15% of test day baseline. Onset and duration of a 15% increase from baseline are clinically important descriptors of therapeutic response.
- FEV<sub>1</sub> duration of therapeutic response
- FEV<sub>1</sub> time to peak (change from test day baseline) response
- FEV<sub>1</sub> response at each timepoint (changes from test day baseline)
- FEV<sub>1</sub> Total area under the curve 0-6 hours (TAUC<sub>0-6</sub>)
- FVC AUC from 0-4 hours (FVC AUC<sub>0-4</sub>)
- FVC AUC<sub>0-6</sub>
- FVC peak change from test day baseline and change from test day baseline at each timepoint
- Physician's global evaluation
  - This evaluation represented the investigator's assessment of the overall condition of the patient's disease since the last visit. This evaluation was based on the need for concomitant therapy, number and severity of exacerbations, severity of cough, ability to exercise, amount of wheezing, since last visit. This was rated on a scale from 1 to 8, with 1 being poor and 8 being excellent. [Vol. 78, p. 31]

- COPD symptom score
  - COPD symptom scores comprised wheezing, shortness of breath, coughing, and chest tightness, each rated on a scale from 0-3 (0 = not present, 1 = mild, 2 = moderate, and 3 = severe). [Vol. 78, p. 30]

- PEFrs

Any statistical tests performed on these endpoints were meant to be interpreted in an exploratory fashion. Statistical tests were performed to establish comparable efficacy between the two treatment groups. This was evaluated based on FEV<sub>1</sub> AUC<sub>0-6</sub> and FEV<sub>1</sub> peak change from baseline. Comparable efficacy was established if the confidence intervals computed for the mean differences between treatment were completely contained in the equivalence region, predefined as  $\pm 90$  ml. [Vol. 77, p. 35]

### 11.3.1.8. Safety Evaluations

The following safety evaluations were conducted:

- Adverse events (AEs)
  - Adverse events were recorded at each visit and every three weeks in between visits by telephone. The date of onset, time of onset, minutes since last dose, end date, end time, intensity of event, therapy required, action taken with the study drug due to the event, outcome of the event, and the investigator's assessment of whether the event was possibly caused by study drug were all recorded. [Vol. 77, p. 36]
  - An adverse event was defined as an unwanted reaction, side effect or other event that occurred during the course of the clinical trial, whether or not the event was considered drug related. Adverse events were rated as mild (awareness of a sign or symptom which is easily tolerated), moderate (discomfort enough to cause interference with usual activity), severe (incapacitating with inability to do work or usual activity). [Vol. 78, p. 26]. The definition of serious adverse events was consistent with the regulatory definition. [Vol. 78, p. 26]
- Pulse rate and blood pressure pre-dose and at 60 minutes post dose
  - Vital signs were taken at the screening visit (Visit 0), and at Visits 1, 3, 5, and 7. Vitals were taken at baseline on these four test days, and at 15, 30, 60, and 90 minutes and 2, 3, 4, 5, 6 hours after study drug administration. They were measured immediately before pulmonary function testing with the patient seated after five minutes of rest. [Vol. 77, p. 38]
- Changes in physical examination (end of treatment compared to baseline)
- Changes in resting EKG (end of treatment compared to baseline)
  - Performed at both baseline (Visit 0) and at Visits 3, 5, and 7 (final visit)
- Changes in hematology, blood chemistry and urinalysis (end of treatment compared to baseline [Vol. 77, p. 38])
  - Hematology: CBC and an absolute eosinophil count

- Blood Chemistry: alkaline phosphatase, LDH, SGOT, SGPT, glucose, calcium inorganic phosphorus, uric acid, urea nitrogen, creatinine, total protein, albumin, and total bilirubin.
  - Urinalysis: microscopic examination, glucose, pH, and specific gravity
  - Laboratory tests were performed at screening (Visit 0), and at Visits 3, 5, and 7 (final visit) after 8 hours of fasting.
- Use of rescue medication

#### 11.3.1.9. Statistical Plan

This study was designed as a multicenter, multidose, randomized, open-label, active-controlled, parallel group study aimed at evaluating the long-term safety of ipratropium bromide HFA, primarily by comparisons of the adverse event profiles of HFA-MDI and CFC-MDI. A secondary endpoint was to evaluate the long-term bronchodilator efficacy of ipratropium bromide HFA.

For the safety analyses, the null hypothesis tested was that there were no differences between treatment groups with respect to the relative frequencies of COPD exacerbations and cough. For efficacy, the null hypothesis tested was that the mean responses following HFA-MDI were equal to the mean responses observed following CFC-MDI. These efficacy hypotheses were tested using FEV<sub>1</sub> AUC<sub>0-6</sub> and FEV<sub>1</sub> peak response, where the 90% confidence intervals of the mean differences between treatments in terms of FEV<sub>1</sub> AUC<sub>0-6</sub> and FEV<sub>1</sub> peak response were determined. [Vol. 77, p. 46] Comparable efficacy between the two treatments was established if the confidence intervals computed for the mean differences between treatment were completely contained in the equivalence region, predefined as  $\pm 90$  ml. [Vol. 77, p. 35]

Two-tailed tests were performed and there were no interim analyses.

##### 11.3.1.9.1. Sample Size [Vol. 77, p. 66]

The sponsor based the sample size on the FDA document "Points to Consider: Clinical Development Programs for MDI and DPI Drug Products" (1994), which requires that at least 200 hundred patients should be studied for one year with the study drug being evaluated for approval. The protocol therefore specified that 250 patients be assigned to the HFA-MDI group in order to have 200 complete the study, anticipating a 20% drop out rate.

To allow for adequate comparisons between the HFA-MDI and CFC-MDI, the sponsor specified that 125 patients be assigned to the CFC-MDI group anticipating that 100 patients in this group complete the trial with a 20% drop out rate.

##### 11.3.1.9.2. Handling of Missing Data [Vol. 77, p. 47]

Missing efficacy data was handled using endpoint analyses—last observation carried forward (LOCF)—and linear interpolation of adjacent values. To be included in the analysis, a patient had to have a minimum of one baseline measurement and one post-dose FEV<sub>1</sub> measurement on Visit 1 and a baseline and one post-dose measurement on one of the subsequent test days (Visits 3, 5, or 7). If a patient met these minimum requirements, the missing data were handled by endpoint analysis defined as the last observation carried forward.

Endpoint analysis was also used to estimate data for patients with serious protocol violations on visits 3, 5, and 7. Additionally, missing data for the endpoints of physician's global assessment and COPD symptom scores were estimated by last observation carried forward. For PEFr readings, data was summarized as bi-weekly means, if patients had at least seven daily values for a two-week interval. If fewer than seven daily values were available, missing data was also estimated by the last observation carried forward.

Another method for handling missing data was linear interpolation. Linear interpolation between the two adjacent measurements was used to estimate middle missing spirometry measurements. If the end data was missing, then the last available value was used to estimate the end measurements. Also, if spirometry was not performed within the specified time windows ( $\pm 5$  minutes for the 15 and 30 minutes and  $\pm 10$  minutes for the other observations), then linear interpolation was used to estimate the measurements using the two adjacent values.

#### 11.3.1.9.3. Efficacy Endpoints

The change from baseline at all time points for FEV<sub>1</sub> AUC<sub>0-6</sub> hours and the FEV<sub>1</sub> peak response were the main endpoints for analysis of efficacy. The null hypothesis was that the mean responses following ipratropium bromide HFA were equal to the mean responses observed following ipratropium bromide CFC. This was tested using the 90% confidence intervals of the mean difference between treatments for FEV<sub>1</sub> AUC<sub>0-6</sub> hours and the FEV<sub>1</sub> peak response at all of the timepoints (test days 1, 3, 5, and 7). [Vol. 77, p. 46] Other efficacy endpoints evaluated were:

- FEV<sub>1</sub> AUC 0-4 hours (FEV<sub>1</sub> AUC<sub>0-4</sub>)
- FEV<sub>1</sub> onset of therapeutic response
- FEV<sub>1</sub> duration of therapeutic response
- FEV<sub>1</sub> time to peak (change from test day baseline) response
- FEV<sub>1</sub> response at each timepoint (changes from test day baseline)
- FEV<sub>1</sub> Total area under the curve 0-6 hours (TAUC<sub>0-6</sub>)
- FVC AUC from 0-4 hours (FVC AUC<sub>0-4</sub>)
- FVC AUC<sub>0-6</sub>
- FVC peak change from test day baseline and change from test day baseline at each timepoint
- Physician's global evaluation
- COPD symptom score
- PEFrs

### 11.3.2. Results

#### 11.3.2.1. Patient disposition

A total of 584 patients signed the consent and 516 were screened. Of these, 456 patients were randomized to the study, and 387 (84.9%) completed the trial. Of the 305 assigned to the HFA-MDI group and the 151 assigned to the CFC-MDI group, a total of 263 (86%) and

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124 (82%) completed the trial in the HFA-MDI and CFC-MDI groups, respectively. [Vol. 77, p. 46, 51]

A total of 69 patients (15.1%) discontinued from the study. A greater percentage discontinued from the CFC-MDI group (17.9%) as compared to the HFA-MDI group (13.8%). Discontinuations secondary to adverse events were comparable between treatment groups (~7% for each group). Overall, the number of patients discontinuing from the study secondary to worsening of COPD was low (5 patients, 1.1%); however, a greater percentage of subjects were withdrawn secondary to this reason in the CFC-MDI group (2%) as compared to the HFA-MDI group (0.7%). A fairly low number of patients discontinued from the study secondary to lack of efficacy (3 in each treatment group). No patients discontinued from the secondary to non-compliance. A total of 5 patients in the study were lost to follow-up, 15 withdrew consent (8 in the HFA-MDI group and 7 in the CFC-MDI group). These results are presented in the following table.

**Table 50. Study 244.2453, Patient Disposition**

	Number of Patients (%)		
	HFA-MDI	CFC-MDI	Total
Total Randomized and Treated	305	151	456
Total Completed	263 (86.2)	124 (82.1)	387 (84.9)
Total Discontinuations	42 (13.8)	27 (17.9)	69 (15.1)
<b>Reasons for Discontinuation</b>			
Adverse Events	22 (7.2)	11 (7.3)	33 (7.2)
Worsening of COPD	2 (0.7)	3 (2.0)	5 (1.1)
Worsening of other pre-existing disease	1 (0.3)	0	1 (0.2)
Other	19 (6.2)	8 (5.3)	27 (5.9)
Lost to follow-up	2 (0.7)	3 (2.0)	5 (1.1)
Consent Withdrawn	8 (2.6)	7 (4.6)	15 (3.3)
Other	7 (2.3)	3 (2.0)	10 (2.2)

Source: Vol. 77, p. 52

### Protocol Violations

Protocol violations were divided into two categories: type 1 violations (potentially affecting safety/efficacy analyses) and type 2 (minor violations not affecting safety/efficacy analyses). All randomized patients were included in the safety analyses; however, for the efficacy analyses, a total of 37 patients were excluded secondary to protocol violations.

A total of 136 (85 [33.8%] HFA group, and 51 [33.8% CFC group] patients had protocol violations considered "important" by the sponsor. [Vol. 87, p. 9-37] These violations were not defined as type one or two in the line listings; however, in the text, the sponsor summarized type 1 protocol violations. [Vol. 77, p. 53]

There were 75 patients with type I protocol violations but these were not broken down by treatment group. A total of 58 patients had entry criteria violations, 7 patients were using beta-blockers, 6 were randomized with an FEV<sub>1</sub> greater than 65% of predicted normal, and four patients did not observe the appropriate washout periods for pulmonary function testing.

Of the 58 patients with entry criteria violations, a little less than half (24) had a history of asthma or allergy. Nine patients had undergone a thoracotomy procedure and 12 patients

had cardiac arrhythmias requiring therapy. Five patients had a history of cancer within the last five years, and two patients had symptomatic benign prostatic hypertrophy. Two patients were taking oral prednisone at a dose greater than 20 mg every other day. Three patients had history of a viral or febrile illness in the six weeks prior to screening and one patient was enrolled in another research study. [Vol. 77, p. 53]

*Reviewer's comments: Perusal of line listings suggests that both treatment groups had similar types of protocol violations.*

**11.3.2.2. Demographics and Other Baseline Characteristics**

Demographics

Treatment groups were similar at baseline with respect to age, gender, race, height, weight, smoking history, mean duration of COPD and time since diagnosis of COPD. The mean age for the study population was 65.2 ± 9.0 with a range of 40-87. There were 164 patients (53.7%) in the HFA-MDI treatment group, and 75 patients (49.7) in the CFC-MDI group who were older than 65 years of age. [Vol. 79, p. 215-233, counted this reviewer from the line listings] More than half of the patients in this study were male (55.9%) as compared to female (44.1%). The majority of subjects were Caucasian (95.4%) and 21 (4.6%) were black. There was no representation of other races in the study. Both groups were comparable in height and weight. The mean height for the study was 67.1 (range of 51-71 inches) inches and the mean weight was 161.9 lbs. (range of 75-315 lbs.). The mean smoking history in pack-years was 60.8 (range of 10-210). In the HFA-MDI treatment group, 182 patients (59.7%) were ex-smokers, and in the CFC-MDI group, 90 (59.6%) were ex-smokers. [Vol. 79, p. 215-233, counted by this reviewer from the line listings] A slightly greater percentage of patients in the HFA-MDI group were non-drinkers (53.8%) as compared to the CFC-MDI group (46.4%). Duration of COPD was similar between treatment groups. The mean duration for the study population was 9.1 years with a range of 0-38 years. The mean time since diagnosis of COPD was 7.3 years (range of 0-38.7 years) in the study population, 7.5 years in the HFA-MDI treatment group, and 6.8 years in the CFC-MDI treatment group. These results are summarized in Table 28 below.

**Table 51. Study 244.2453, Demographics and Baseline Characteristics**

Characteristic		HFA-MDI n=305	CFC-MDI n=151	Total n=456
Sex	n (%)			
	Male	168 (55.1)	87 (57.6)	255 (55.9)
	Female	137 (44.9)	64 (42.2)	210 (44.1)
Race*	n (%)			
	Caucasian	288 (94.4)	147 (97.4)	435 (95.4)
	Black	17 (5.6)	4 (2.6)	21 (4.6)
Age	Mean (years)	65.1	65.4	65.2
	Range	40-87	42-87	40-87
Height	Mean (in)	67.1	67.0	67.1
	Range	51.0-76.0	53.0-78.0	51.0-78.0
Weight	Mean (lbs.)	162.8	160.2	161.9
	Range	75-315	80-261	75-315

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	HFA-MDI	CFC-MDI	Total
Characteristic	n=305	n=151	n=456
Smoking History (pack-years) n (%)			
Mean	60.7	61.1	60.8
Range	10.0-210.0	12.0-189.0	10.0-210.0
Alcohol History n (%)			
Non-Drinker	164 (53.8)	70 (46.4)	234 (51.3)
Average Consumption	141 (46.2)	81 (53.6)	222 (48.7)
Duration of COPD (years)			
Mean	9.3	8.8	9.1
Range	0-38	1-26	0-38
Time Since COPD Diagnosis (years)			
Mean	7.5	6.8	7.3
Range	0-38.7	0-26.6	0-38.7

*Reviewer's comments: For study entry, the patients had to have a diagnosis of COPD; however, the length of time for this diagnosis is not summarized. Per line listings, in the HFA-MDI treatment group, 136 out of 305 (44.6%) patients had a time to diagnosis of COPD of less than 5 years. Of these, 45 (14.8%) were diagnosed under a year prior to study entry, and 13 (4.3%) were listed as having the time 0.0. In the CFC-MDI group, 64 patients (42.3%), 17 patients (11.3%), and 4 patients (2.6%) had a time to COPD diagnosis of less than five years, less than 1 year, and 0.0, respectively. All of the patients in both groups with a time of 0.0 listed as the time to diagnosis of COPD, had at least a 30 pack-year history of smoking, with the majority having a greater than 50 pack year history of smoking. This reviewer concludes that patients with time to diagnosis of COPD of 0 years did in fact have of COPD based their long-standing smoking history. [Vol. 79, p. 215-233]*

### Baseline Spirometry

The mean FEV<sub>1</sub> for the study population was 1.02 ± 0.41 liters, and for the HFA-MDI and CFC-MDI groups was 1.00 ± 0.40 and 1.02 ± 0.44, respectively. The mean FEV<sub>1</sub> % of predicted normal was 38.89 (range of 11.59 to 132.1) in the HFA-MDI group and 40.94 (4.33 to 78.7) in the CFC-MDI group. The mean FEV<sub>1</sub>/FVC was 46.1 in the HFA-MDI group and 47.8 in the CFC-MDI group.

**Table 52. Study 244.1408, Baseline Spirometry for all Randomized Patients**

	HFA-MDI	CFC-MDI	Total
Characteristic	n=305	n=151	n=456
Baseline FEV <sub>1</sub> (L)	Mean	1.00	1.06
	Std Dev	0.40	0.44
	Range	0.27-2.21	0.13-2.25
Baseline FVC (L)	Mean	2.20	2.20
	Std Dev	0.70	0.80
	Range	0.57-5.18	0.73-4.44
Predicted Normal FEV <sub>1</sub> (L)	Mean	2.60	2.60
	Std Dev	0.60	0.60
	Range	1.07-4.25	0.99-4.12
%Predicted Normal FEV <sub>1</sub> (L)	Mean	38.89	40.94
	Std Dev	14.89	15.10

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Characteristic		HFA-MDI	CFC-MDI	Total
		n=305	n=151	n=456
Range		11.59-132.1	4.33-78.70	4.33-132.1
FEV <sub>1</sub> /FVC (%)	Mean	46.1	47.8	46.7
	Std Dev	11.3	12.6	11.8
	Range	18.1-77.0	8.4-70.1	8.4-77.0

Source Vol. 77, p. 56

*Reviewer's comments: Although the range for FEV<sub>1</sub> % of predicted was 11.59-132% for the HFA-MDI treatment group, only one patient had a value of 132%. This patient was considered an entry criteria violation. Additionally, there were only a total of 23 patients (7.5%) in the HFA-MDI group who had FEV<sub>1</sub> % predicted between 60-69%; the rest were all under 60% predicted. In the CFC-MDI group, there was only one patient with an FEV<sub>1</sub> % predicted of 78%; the rest were less than or equal to 70%, with only 15 patients (9.9%) having FEV<sub>1</sub> % predicted in the 60-70% range. The baseline spirometry supports that the study population had COPD.*

### Concomitant Pulmonary Medications

A total of 243 patients (79.6%) in the HFA-MDI treatment group and 113 patients (74.8%) in the CFC-MDI group took concomitant pulmonary medications 6 weeks prior to randomization. The most frequently used class of pulmonary medication during this period inhaled beta-agonists used by 73.1% and 73.5% of patients in the HFA-MDI and CFC-MDI groups, respectively. This was followed by inhaled anticholinergics (47.3%) and inhaled steroids (37.7%). Oral steroids were used by 7.2% of patients in the HFA-MDI group and by 5.9% of patients in the CFC-MDI group. Twenty percentage of the study population took oral theophylline 6 weeks prior to randomization. Twenty-one patients (6.8%) in the HFA-MDI group and 8 patients (5.2%) in the CFC-MDI treatment group used oxygen prior to randomization into the study. Both treatment groups were comparable for the most part for baseline pulmonary medication concomitant therapies prior to randomization. Table 30 summarizes these data. [Vol. 77, p. 61-62]

**Table 53. Concomitant Pulmonary Medications by Therapeutic Class Taken During the Six Weeks Prior to Randomization at a Frequency of Greater than 1% per Class**

	HFA-MDI	CFC-MDI	Total
	n=305 n (%)	n=151 n (%)	n=456 n (%)
Total taking concomitant pulmonary meds.	243 (79.6)	113 (74.8)	356 (78.0)
Inhaled Anticholinergics (Atrovent)	146 (47.8)	70 (46.3)	216 (47.3)
Inhaled Beta-Agonists	223 (73.1)	111 (73.5)	334 (73.2)
Short-Acting	189 (61.9)	96 (63.5)	285 (63.5)
Long-Acting	34 (11.1)	15 (9.9)	49 (10.7)
Oral Beta-Agonists	13 (4.2)	7 (4.6)	20 (4.3)
Oxygen	21 (6.8)	8 (5.2)	29 (6.3)
Inhaled Steroids (Oral)	113 (37)	59 (39)	172 (37.7)
Nasal Steroids	10 (3.2)	6 (3.9)	16 (3.5)
Oral Steroids	22 (7.2)	9 (5.9)	31 (6.7)
Oral Theophylline	61 (20)	30 (19.8)	91 (19.9)

Source Vol. 77, p. 61-62

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*Reviewer's comments: It is interesting to note that six percent of the study population required oxygen therapy prior to initiation of therapy; however, "chronic daytime oxygen therapy" was defined as an exclusion criterion [Vol. 77, p. 29]. Since this number is relatively low, it is doubtful that this would affect any results. However, it is unclear to this reviewer if this oxygen therapy was chronic daytime therapy or something that was given temporarily during a hospitalization for COPD.*

Table 33 represents concomitant pulmonary medications taken during the 6-week period prior to initiation of treatment, and table 31 represents concomitant medications by therapeutic class taken during the treatment period at a frequency of greater than 1% in any class. A slightly higher percentage of patients (81.3%) were taking concomitant pulmonary medications during the treatment period as compared to prior to initiation of therapy (78%). Additionally, a higher percentage of patients (82%) took inhaled beta-agonists during the treatment period as compared to prior to initiation of therapy (73%). There were a greater percentage of patients in the CFC-MDI group who took inhaled beta-agonists as compared to the HFA-MDI group. A considerably higher percentage of subjects were using concomitant oxygen therapy (18%) during the active treatment period as compared to the 6 weeks prior to initiation of therapy (6%). Oral steroid use was also reported to occur at a greater frequency during the treatment phase as compared to the period prior to initiation of therapy. Seven percent of the study population received intravenous steroids during the treatment phase of the study; none was reported during the 6 weeks prior. For the most part, the two treatment groups were fairly similar for concomitant pulmonary medication during the treatment phase of the study. [Vol. 77, p. 63-65]

**Table 54. Concomitant Pulmonary Medications by Therapeutic Class Taken During the Treatment Period at a Frequency of Greater than 1% in any Class**

	HFA-MDI	CFC-MDI	Total
Total Randomized and Treated	n=305 n (%)	n=151 n (%)	n=456 n (%)
Total Taking Concomitant Pulmonary Medications	251 (82.2)	120 (79.4)	371 (81.3)
Inhaled Anticholinergics (Atrovent)	13 (4.2)	4 (2.6)	17 (3.7)
Nasal Anticholinergics (Atrovent Nasal Spray)	8 (2.6)	4 (2.6)	12 (2.6)
Inhaled Beta-Agonists	243 (79.7)	129 (85.4)	372 (81.6)
Short-Acting	204 (66.8)	108 (71.5)	312 (68.4)
Long-Acting	39 (12.7)	21 (13.9)	60 (13.1)
Oral Beta-Agonists	19 (6.2)	8 (5.2)	27 (5.9)
Ephedrine	0	2 (1.3)	2 (0.4)
Oxygen	56 (18.3)	25 (16.5)	81 (17.7)
Inhaled Steroids (Oral)	126 (41.3)	62 (41.0)	188 (41.2)
Injected Steroids	20 (6.5)	3 (1.9)	23 (5.0)
Intravenous Steroids	21 (6.8)	13 (8.6)	34 (7.4)
Nasal Steroids	34 (11.1)	20 (13.2)	54 (11.8)
Oral Steroids	89 (29.1)	38 (25.1)	127 (27.8)
Oral Theophylline	65 (21.3)	33 (21.8)	98 (21.4)
Zafirlukast	6 (1.9)	1 (0.6)	7 (1.5)

Source Vol. 77, p. 63-65

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*Reviewer's comments: An increase in the frequency of concomitant pulmonary medications was noted in general during the treatment period as compared to the 6 weeks prior to initiation of treatment. However, this is expected as the treatment phase of 52-weeks was compared to a period of 6 weeks prior to initiation of therapy. Patients with COPD followed for a one-year period tend to have worsening of disease and this is reflected in the additional need of concomitant pulmonary medications during the one-year treatment phase of the study.*

*The sponsor has referenced Appendix 15.12.3 as data listings for concomitant Diagnoses and Disease; however, this section does not appear to present in this reviewer's copy. This reviewer has scanned the concomitant medication line listings and their respective indications, and there does not appear to be any clinically meaningful differences between the two treatment groups in terms of concomitant diagnoses.*

### 11.3.2.3. Compliance

The investigator assessed compliance by reviewing the Daily patient Record with the patient at follow up visits. The investigator recorded the patient's usual daily dosing regimen of investigational drug during the period preceding the visit. The patient was also contacted by telephone every three weeks throughout the 52-week treatment period to review the study drug dosing. [Vol. 77, p. 34]

Throughout the 52-week treatment period, compliance was adequate for both treatment groups. Compliance (patients who took the study drug four times a day as specified) was higher in the HFA-MDI treatment group (>88 %) compared to the CFC-MDI treatment group (> 81%). Less than one percent of patients in either group took the study drug less than or equal to three times a day. The remaining subjects took study drug either five or six times a day. The following table summarizes the compliance results categorized according to reporting periods.

**Table 55. Study 244.2453, Compliance During the Treatment Period**

Reporting period (days)	Treatment	Number of patients	Daily Dose of Study Medication			
			≤3 Times n (%)	4 Times n (%)	5 Times n (%)	6 Times n (%)
1-43	HFA-MDI	281	1 (0.4)	252 (89.7)	18 (6.4)	10 (3.6)
	CFC-MDI	138	2 (1.4)	118 (85.5)	12 (8.7)	6 (4.3)
43-85	HFA-MDI	281	1 (0.4)	252 (89.7)	18 (6.4)	10 (3.6)
	CFC-MDI	138	1 (0.7)	119 (86.2)	12 (8.7)	6 (4.3)
85-127	HFA-MDI	279	0	257 (92.1)	15 (5.4)	7 (2.5)
	CFC-MDI	134	0	118 (88.1)	10 (7.5)	6 (4.5)
127-183	HFA-MDI	272	0	240 (88.2)	19 (7.0)	13 (4.8)
	CFC-MDI	130	1 (0.8)	111 (85.4)	9 (6.9)	9 (6.9)
183-274	HFA-MDI	270	1 (0.4)	241 (89.3)	17 (6.3)	11 (4.1)
	CFC-MDI	129	0	108 (83.7)	10 (7.8)	11 (8.5)
274-365	HFA-MDI	265	0	234 (88.3)	20 (7.5)	11 (4.2)
	CFC-MDI	127	1 (0.8)	103 (81.1)	10 (7.9)	13 (10.2)

Source: N-000-BM (5/30/03), p. 8

**11.3.2.4. Efficacy Endpoint Outcomes**

*11.3.2.4.1. Data Sets Analyzed*

Although a total of 456 patients were randomized to the study, the sponsor only analyzed the data sets for 419 of the 456 randomized patients. A total of 37 patients (one with FEV<sub>1</sub> 132% predicted at baseline) were excluded from the efficacy analysis. Of these 37 patients, 24 (7.9%) and 13 (8.6%) were from the HFA-MDI and CFC-MDI treatment groups, respectively.

*11.3.2.4.2. Efficacy Analyses*

*This reviewer will focus on FEV<sub>1</sub> AUC<sub>0-6</sub> and FEV<sub>1</sub> peak response, as these were the primary efficacy endpoints in the 12-week, randomized, double-blind placebo and active controlled trial, Study 244.1405.*

**FEV<sub>1</sub> AUC<sub>0-6</sub> above Baseline**

The FEV<sub>1</sub> derived AUC<sub>0-6</sub> above baseline was analyzed for Visits 1, 3, 5, and 7, corresponding to day 1, Week 12, Week 26, and Week 52 of treatment. Generally, the LSMeans were comparable between treatment groups for all time points except Visit 3. For Visits 1, 5, and 7, there was no significant difference between the LSMeans between the treatment groups, and the 90% confidence intervals intersected 0, with corresponding p-values >0.05 for these timepoints. For Visit 3, the difference in LSMeans between the treatment groups was 0.0372 with 90% CI of -0.0653 to -0.0092 with a corresponding p-value of 0.0292. [Vol. 77, p. 74; Vol. 80, p. 313-316; Vol. 81, p. 14-17, 55-88, and 96-99]

*Reviewer's comments: The sponsor does not feel that this is clinically significant, and this reviewer agrees with this assessment.*

The following table summarizes these results.

**Table 56. Study 244.2453, Adjusted\* LSMean for FEV<sub>1</sub> AUC<sub>0-6</sub> in Liters (SEM)**

Visit**	HFA-MDI	CFC-MDI	Difference between Treatments	90% CI for Difference	P-Value
1	0.149 (0.010)	0.145 (0.014)	0.0046	-0.0233 to 0.0324	0.7868
3	0.137 (0.010)	0.174 (0.014)	0.0372	-0.0653 to -0.0092	0.0292
5	0.134 (0.010)	0.141 (0.014)	0.0076	-0.0365 to 0.0212	0.6624
7	0.117 (0.009)	0.117 (0.014)	0.0002	-0.0276 to 0.0272	0.9892

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

\*\* Visit 1 responses are to a single test dose of medication. Visits 3, 5, and 7 correspond to 12, 26, and 52 weeks of treatment, respectively.

Source: Vol. 77, p. 74; Vol. 80, p. 313-316; Vol. 81, p. 14-17, 55-88, and 96-99

*Reviewer's comments: The reader is reminded that two different HFA drug products were used for this study, 1<sup>st</sup> and 2<sup>nd</sup> generation Atrovent HFA products (the differences are*

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reviewed in the Chemistry sections above). The Division asked the sponsor to do a subset analysis to compare the differences between efficacy for the two generations of HFA products used. The sponsor stated that this could not be done since the number of patients was different between the two generation products and patients were not randomized to different generation products. [N-000-BM, 3/13/03; p.4] However, after Visit 4, all patients had switched over to the 2<sup>nd</sup> generation HFA product. Therefore, efficacy results for Visits 5 and 7 represent 26 and 52 weeks of treatment, respectively, with the 2<sup>nd</sup> generation product.

This becomes very important as the sponsor did not conduct a clinical study to link the first and third generation products. The changes between the second and third generation product appear to be minor (a change in the  $\curvearrowright$  in the aerosol valve) and it is unclear what impact (if any) it would have on the performance of the product compared to the second generation product. However, depending on the CMC assessment of the change, these data may be useful as they would represent data from the product that is most closely linked (2<sup>nd</sup> generation) to the to-be-marketed product (3<sup>rd</sup> generation).

### Peak Change in FEV<sub>1</sub> from Test-Day Baseline

The LS Mean FEV<sub>1</sub> peak changes from baseline were comparable between both treatment groups, and there were no statistically significant differences between the treatments at any timepoint. The difference between treatments ranged from 3 ml to 25 ml. The corresponding p-values for the differences at each time point were greater than 0.18. Based on the prespecified definition, the sponsor demonstrates therapeutic equivalence on this endpoint. The following table summarizes these results. [Vol. 77, p. 74; Vol. 80, p. 325-328; Vol. 81, p. 26-29, 68-71, and 108-111]

**Table 57. Study 244.2453, Adjusted\* LS Mean FEV<sub>1</sub> Peak Change from Baseline in Liters (SEM)**

Visit**	HFA-MDI	CFC-MDI	Difference between Treatments	90% CI for Difference	P-Value
1	0.287 (0.011)	0.276 (0.016)	0.0046	-0.0214 to 0.0441	0.5684
3	0.275 (0.011)	0.301 (0.016)	0.0252	-0.0565 to 0.0060	0.1832
5	0.276 (0.012)	0.282 (0.017)	0.0062	-0.0407 to 0.0284	0.7681
7	0.253 (0.010)	0.256 (0.015)	0.0038	-0.0334 to 0.0258	0.8332

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

\*\* Visit 1 responses are to a single test dose of medication. Visits 3, 5, and 7 correspond to 12, 26, and 52 weeks of treatment, respectively.

Source: Vol. 77, p. 74; Vol. 80, p. 325-328; Vol. 81, p. 26-29, 68-71, and 108-111

*Reviewer's comments: As the sponsor was unable to provide a subset analysis comparing the efficacy of the two generation of products used in this study, the efficacy between the two treatments at Visit 5 and 7 was compared. Dr. Gebert recommended that efficacy be compared for both FEV<sub>1</sub> AUC<sub>0-6</sub> and Peak FEV<sub>1</sub> response for only those patients who did not have a last observation carried forward (carrying forward results would confound the results with subjects who may have used the 1<sup>st</sup> generation product and had some of these*

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values carried forward to represent Visit 5 and 7 values). For FEV<sub>1</sub> AUC<sub>0-6</sub>, and Peak FEV<sub>1</sub>, the number of patients evaluable, were 338 and 313, respectively. Analyses of these patients demonstrated that at both visits for both timepoints, the two treatment groups had comparable efficacy, with  $p > 0.5$  for comparison between the difference in these primary variables.

### 11.3.2.4.3. Additional Efficacy Analyses

#### Mean FEV<sub>1</sub> Test Day Baselines

The adjusted mean FEV<sub>1</sub> test day baselines were generally comparable between groups, with the exception of Visit 1. The CFC-MDI treatment group test day baselines tended to be higher compared to the HFA-MDI treatment group baselines with the biggest difference noted at Visit 1.

**Table 58. Study 244.2453, Adjusted\* Mean FEV<sub>1</sub> Test Day Baselines in Liters (SEM)**

	HFA-MDI n = 281	CFC-MDI n = 138
Visit1**	0.958 (0.024)	1.055 (0.035)
Visit 3	0.969 (0.026)	1.014 (0.038)
Visit 5	0.948 (0.026)	1.035 (0.038)
Visit 7	0.959 (0.027)	1.009 (0.039)

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

\*\* Visit 1 responses are to a single test dose of medication. Visits 3, 5, and 7 correspond to 12, 26, and 52 weeks of treatment, respectively.

Source: Vol. 77, p. 74; Vol. 80, p. 325-328; Vol. 81, p. 26-29, 68-71, and 108-111

#### Median Onset of Therapeutic Response, Median Time to Peak FEV<sub>1</sub> Response, and Median Duration of Therapeutic Response

Therapeutic response was defined as 15% increase from test day baseline in FEV<sub>1</sub>. The median onset of therapeutic response ranged from 14-21 minutes in the HFA-MDI treatment group and 15-27 minutes in the CFC-MDI treatment group. The median time to peak FEV<sub>1</sub> response was 90 minutes at all time points for CFC-MDI group and for Visits 1, 3, and 7 for the HFA-MDI group. In the HFA-MDI group, at Visit 5, the median time to peak response in FEV<sub>1</sub> was 60 minutes. The median duration of therapeutic response ranged from 2.32 to 3.07 hours and 1.79 to 3.78 hours in the HFA-MDI and CFC-MDI treatment arms, respectively. In the HFA-MDI and CFC-MDI groups, there were 19-24 % and 16-28% of patients who did not achieve a therapeutic response, respectively. This was similar between both groups.

**Table 59. Study 244.2453, Median Onset of Therapeutic Response and Median Time to Peak FEV<sub>1</sub> Response, and Median Duration of Therapeutic Response**

	HFA-MDI n = 281	CFC-MDI n = 138
<b>Median Onset (minutes)</b>		

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Visit 1*	14.0	19.0
Visit 3	14.0	15.0
Visit 5	15.0	25.0
Visit 7	21.0	27.0
<b>Median Time to Peak (minutes)</b>		
Visit 1	90	90
Visit 3	90	90
Visit 5	60	90
Visit 7	90	90
<b>Median Duration of Therapeutic Response (hours)</b>		
Visit 1	3.07	2.35
Visit 3	2.67	3.78
Visit 5	2.48	1.79
Visit 7	2.32	2.02

\*Visit 1 responses are to a single test dose of medication. Visits 3, 5, and 7 correspond to 12, 26, and 52 weeks of treatment, respectively.

Source: Vol. 77, p. 76

### Adjusted Mean FVC AUC<sub>0-6</sub> and Peak Change from Baseline

The baseline FVC measurements for all test days were similar between the two treatment groups. The mean FVC AUC<sub>0-6</sub> ranged from 0.273 to 0.318 liters in the HFA-MDI treatment group and 0.290 to 0.365 in the CFC-MDI treatment group. The peak changes in FVC ranged from 0.616 to 0.668 liters and 0.591 to 0.688 liters in the HFA-MDI and CFC-MDI treatment groups, respectively. [Vol. 77, p. 78]

### Adjusted Mean PEFV Values

The adjusted (for center and treatment-by-center interaction) LS means between the treatment groups were fairly similar; however, the values tended to be slightly higher in the CFC-MDI treatment group. At visit 1, 3, 5, and 7, the mean PEFVs for the HFA-MDI treatment group were 216, 227.1, 228.9, and 230.3, respectively. For the CFC-MDI treatment group, the corresponding mean PEFVs were 225.3, 230.5, 232.5, and 230.1. [Vol. 77, p. 175-176]

### Physician's Global Assessment

Global assessment scores were comparable between both treatment groups. The adjusted mean physician global assessment scores ranged between 4.9 and 5.4, corresponding to the high end of "fair" and low end of "good." For Visits 1 and 7, the scores were slightly lower for the HFA-MDI treatment groups. At all other visits (2-6), the scores were quite similar. [Vol. 77, p. 170]

### COPD Symptom Scores

COPD symptom scores were comparable between both treatment groups. COPD symptom scores of wheezing, coughing and chest tightness were all less than 1.0, indicating that these symptoms were mild. Shortness of breath scores were between 1.2-1.4, indicating mild to moderate severity. [Vol. 77, p. 171-174]

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### 11.3.2.5. Safety Outcomes

All 456 randomized patients were included in the safety analysis. A total of 305 patients were randomized to the HFA-MDI treatment group and 151 patients were randomized to the CFC-treatment group.

#### 11.3.2.5.1. Extent of Exposure

The HFA-MDI treatment group had a higher mean duration of exposure (332 days) compared to the CFC-MDI group (325 days). The percentage of patients receiving 359-372 days of treatment was 73% in HFA-MDI group and 66% in the CFC-MDI group, 78% and 72% of patients in the HFA-MDI and CFC-MDI treatment groups respectively, received greater than 358 days of treatment.

**Table 60. Study 244.2453, Extent of Exposure**

	Number of Patients (%)	
	HFA-MDI	CFC-MDI
Total Randomized and Treated	305	151
1-42 days	6 (1.9)	7 (4.6)
43-84 days	14 (4.5)	4 (2.6)
85-126 days	5 (1.6)	4 (2.6)
127-182 days	8 (2.6)	5 (3.3)
183-273 days	3 (0.9)	2 (1.3)
274-358 days	30 (9.8)	21 (13.9)
359-372 days	223 (73.1)	99 (65.5)
373-387 days	16 (5.2)	5 (3.3)
> 387 days	0	4 (2.6)
Mean Exposure (days)	332	325

Source: Vol. 77, p. 84

#### 11.3.2.5.2. Adverse Events

Of the 456 randomized patients, 278 (91.1%) patients in the HFA-MDI treatment group and 132 (87.4%) patients in the CFC-MDI treatment group reported adverse events (AEs). Of these patients, 86 experienced adverse events prior to randomization and 25 patients experienced adverse events after discontinuation of trial drug. Serious adverse events (SAEs) were reported by 89 patients during the active treatment phase: 58 patients (19%) in the HFA-MDI treatment group and 31 patients (20.5%) in the CFC-MDI group. Adverse events led to the withdrawal of 32 patients after randomization. [Vol. 77, p. 85, 106, 107]

The most frequently reported adverse events occurred in the respiratory tract. The most commonly reported AEs in the HFA group were Rhinitis [including rhinorrhea, congestion, sneezing, cold, and URI (121, 39%), COPD exacerbation (70, 23%), and bronchitis (69, 22.6%). These events were reported with similar frequency in the CFC group. Sinusitis was reported by 34 patients (11.1%) and 21 patients (13.9%) in the HFA-MDI and CFC-MDI treatment groups, respectively. The incidence of coughing was comparable in both treatment groups. Other respiratory AEs were fairly similar between treatment groups as well; however, epistaxis was reported more frequently in the patients receiving HFA-MDI.

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Overall, the incidence of AEs was similar for both treatment groups, with a few exceptions. In the HFA group 6.6% of patients reported back pain compared to the CFC group (2.6%). Influenza-like symptoms were experienced by 25 patients (8.2%) in the HFA group compared to 7 patients (4.6%) in the CFC group. Dizziness was reported more commonly in the HFA-MDI group (3%) compared to the CFC-MDI group (1.3%). Pharyngitis occurred in 17 patients (5.6%) in the HFA-MDI treatment group compared to four patients (2.6%) in the CFC-MDI treatment group. Conjunctivitis (n = 6) and glaucoma (n=4) were reported only in the HFA group, but more patients in the CFC group (4%) experienced gastritis compared to the HFA group (1%) [Vol. 77, p. 86]

**Table 61. Study 244.2453, Adverse Events Reported at a Frequency Greater Than or Equal to 3% in Either Treatment Group**

	HFA-MDI n = 305 n (%)	CFC-MDI n = 151 n (%)	Total n = 456 n (%)
<b>Adverse Event</b>			
<b>Total Adverse Events</b>	<b>278 (91.1)</b>	<b>132 (87.4)</b>	<b>410 (89.9)</b>
<b>BODY AS A WHOLE</b>			
Back Pain	20 (6.6)	4 (2.6)	24 (5.3)
Headache	20 (6.6)	8 (5.3)	28 (6.1)
Influenza-Like symptoms	25 (8.2)	7 (4.6)	32 (7.0)
Edema, Peripheral	10 (3.3)	5 (3.3)	15 (3.3)
Pain	35 (11.5)	16 (10.6)	51 (11.2)
<b>CARDIOVASCULAR DISORDERS</b>			
Abnormal EKG	9 (3.0)	3 (2.0)	12 (2.6)
Hypertension	9 (3.0)	6 (4.0)	15 (3.3)
Tachycardia	7 (2.3)	5 (3.3)	12 (2.6)
<b>CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS</b>			
Dizziness	9 (3.0)	2 (1.3)	11 (2.4)
Insomnia	10 (3.3)	6 (4.0)	16 (3.5)
<b>ENDOCRINE/METABOLIC</b>			
Hypercholesterolemia	1 (3.3)	5 (3.3)	6 (1.3)
<b>GASTROINTESTINAL DISORDERS</b>			
Abdominal Pain	6 (2.0)	5 (3.3)	11 (2.4)
Constipation	12 (3.9)	5 (3.3)	17 (3.7)
Diarrhea	15 (4.9)	5 (3.3)	20 (4.4)
Dyspepsia	14 (4.6)	5 (3.3)	19 (4.2)
Gastritis	3 (1.0)	6 (4.0)	9 (2.0)
Gastrointestinal Disorder NOS	7 (2.3)	5 (3.3)	12 (2.6)
Nausea	11 (3.6)	6 (4.0)	17 (3.7)
<b>GENITOURINARY SYSTEM DISORDERS</b>			
Urinary Tract Infection	30 (9.8)	12 (7.9)	42 (9.2)
<b>INFECTIOUS DISEASES</b>			
Infection	9 (3.0)	4 (2.6)	13 (2.9)
Monilliasis	5 (1.6)	5 (3.3)	10 (2.2)
<b>MUSCULOSKELETAL DISORDERS</b>			
Arthritis Aggravated	10 (3.3)	4 (2.6)	14 (3.1)

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	HFA-MDI n = 305 n (%)	CFC-MDI n = 151 n (%)	Total n = 456 n (%)
<b>Adverse Event</b>			
<b>PSYCHIATRIC DISORDERS</b>			
Anxiety	12 (3.9)	2 (1.3)	14 (3.1)
Depression	6 (2.0)	5 (3.3)	11 (2.4)
<b>RESPIRATORY DISORDERS</b>			
Bronchitis	69 (22.6)	29 (19.2)	98 (21.5)
COPD Exacerbation	70 (23.0)	35 (23.2)	105 (23.0)
Cough	16 (5.2)	8 (5.3)	24 (5.3)
Dyspnea	20 (6.6)	6 (4.0)	26 (5.7)
Pharyngitis	17 (5.6)	4 (2.6)	21 (4.6)
Pneumonia	25 (8.2)	10 (6.6)	35 (7.7)
Rhinitis	121 (39.7)	54 (35.8)	175 (38.4)
Sinusitis	34 (11.1)	21 (13.9)	55 (12.1)
<b>VISION DISORDERS</b>			
Cataract	10 (3.3)	7 (4.6)	17 (3.7)

\* AEs during the run-in period are excluded

Source: Vol. 77, p. 88-105

A total of 313 patients (68.6%) experienced AEs of mild intensity, 289 (65.4%) experienced AEs of moderate intensity, and 111 (24.3%) experienced AEs of severe intensity during the active treatment period.

### Treatment Related AEs

Thirty-five patients had AEs that were judged by the investigator to be treatment related. Of these events, this reviewer concluded that dry mouth (1.3%), taste perversion (1.3% HFA, 0.7% CFC) and dysphonia, cough and throat tightness which were reported by 2 patients in the HFA group might be treatment-related. The other adverse events (headache, dizziness, and micturition frequency) are probably not drug-related.

### *11.3.2.5.3. Deaths, Serious Adverse Events, and Withdrawals Secondary to AEs*

#### Deaths

There were ten deaths reported during the course of the study. Seven deaths occurred due to events that began prior to completion of the one-year treatment period and three deaths were due to events that began after the patients discontinued study treatment. Of the seven deaths that occurred prior to completion of the one-year treatment period, four occurred in the HFA-MDI treatment group, and three occurred in the CFC-MDI treatment group. The most common cause of death was malignancies and none of the deaths were treatment related. In the HFA-MDI group, Patient No. 2605 (61 year old white male) died of right lung cancer, Patient No. 3031 (66 year old white male was initially hospitalized for COPD exacerbation 275 days into treatment, with worsening respiratory failure that led to intubation/ICU admission who developed renal failure) died of renal failure, Patient No. 3198 (69 year old white male who was diagnosed with a CVA 12 days into treatment, recovered from a carotid endarterectomy, continued in the trial and 182 days into treatment) was brought into the ER following an unwitnessed cardiac arrest and died within 24 hours of cardiac arrest and

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Patient No. 3225 ( 65 year old white male) died of metastatic adenocarcinoma and worsening renal function. In the CFC-MDI treatment group, the cause of death was reported as intra-abdominal catastrophe in Patient No. 2563 (69 year old white male who developed severe abdominal distension leading to breathlessness and subsequently collapsed), squamous cell carcinoma right lung in Patient No. 2836 (78 year old white male who was diagnosed with cancer 86 days into treatment and died four months after study discontinuation), and COPD exacerbation and respiratory failure in Patient No. 2956 (78 year old white male who was admitted to the ICU for a severe COPD exacerbation leading to respiratory failure 213 days after starting the study). Of the three patients randomized to HFA-MDI who died of events that began after discontinuation from the trial, Patient 2718 died of metastatic lung cancer one day after discontinuation from the study, Patient 2858 died of sepsis and hepatocellular carcinoma less than 6 weeks after discontinuation of the study, and Patient 2985 died of malignant mesothelioma four weeks of discontinuation from the study for left pleural effusion. [Vol. 77, p. 106; Vol. 87, p. 68-93]

### Serious Adverse Events (SAEs)

Serious adverse events were reported in 89 patients during the active treatment period. The incidence of serious adverse events was similar between the two groups. Fifty-eight patients (19.0%) in the HFA-MDI and 31 patients (20.5%) in the CFC-MDI treatment groups reported serious adverse events. Six patients experience serious adverse events during the two-week run-in-period and eight patients experienced SAEs post-treatment.

Other than respiratory SAEs, no other consistent SAEs in a specific system organ class were noted. The most commonly reported SAEs were COPD exacerbation and pneumonia. COPD was reported in 15 patients (4.9%) and 13 patients (8.6%) in the HFA-MDI and CFC-MDI treatment groups, respectively. Pneumonia was reported in 14 patients (4.6%) treated with HFA-MDI and in 6 patients (4.0%) treated with CFC-MDI, respectively. Serious adverse events occurring at a frequency of 1.0 % or greater in any group are depicted in the following table.

**Table 62. Study 244.2453, Number of Patients (Percentage) with Serious Adverse Events Occurring at a Frequency of One Percent or Greater**

	HFA -MDI n = 305 n (%)	CFC -MDI n = 151 n (%)
<b>Total number of patients with SAEs</b>	<b>58 (19)</b>	<b>31 (20.5)</b>
<b>Adverse Event</b>		
COPD	15 (4.9)	13 (8.6)
Pneumonia	14 (4.6)	6 (4.0)
Angina Pectoris	2 (0.7)	3 (2.0)
Cerebrovascular Disease	3 (1.0)	2 (1.3)
Pulmonary Carcinoma	2 (0.7)	2 (1.3)
Gastrointestinal Disease NOS	0	2 (1.3)
Basal Cell Carcinoma	4 (1.3)	1 (0.7)

Source: Vol. 77, p. 108-112

*Reviewer's comments: This reviewer has read all of the case summaries for the SAEs and does not feel that there are any clinically meaningful differences between the two treatment*

groups. Given the nature of the trial and the age of the study population, these SAEs are not unexpected and do not appear to be treatment related.

Withdrawals Secondary to Adverse Events

After randomization, 21 patients (6.9%) in the HFA group and 11 (7.3%) in the CFC group withdrew from the study secondary to adverse events. The most common adverse events leading to discontinuations were respiratory events which were reported in six patients (2.0%) in the HFA group and five patients (3.3%) in the CFC group. In the HFA group, bronchitis, COPD, dyspnea, pulmonary hypertension, pleural effusion and pneumonia were reported each in one patient. COPD and pneumonia were reported in two patients, and dyspnea and respiratory insufficiency was reported in one patient in the CFC group. Urinary tract disorders, (renal failure, abnormal renal function, urethral disorder and UTI) were each reported in one patient in the HFA group and none in the CFC group [Vol. 77, p. 113-115] The following table summarizes the respiratory adverse events leading to study withdrawal; the other adverse events are not listed as no more than one patient had any other listed adverse event.

**Table 63. Study 242.2453, Number (%) of Patients who Withdrew Secondary to Adverse Events with a Focus on Respiratory Adverse Events**

	HFA-MDI (n=305) n (%)	CFC-MDI (n=151) n (%)
<b>Total Withdrawals Due to Adverse Events</b>	<b>21 (6.9)</b>	<b>11 (7.3)</b>
<b>Respiratory Adverse Events</b>	<b>6 (2)</b>	<b>5 (3.3)</b>
Bronchitis	1 (0.3)	0
COPD	1 (0.3)	2 (1.3)
Dyspnea	1 (0.3)	1 (0.7)
Pulmonary HTN	1 (0.3)	0
Pleural Effusion	1 (0.3)	0
Pneumonia	1 (0.3)	2 (1.3)
Respiratory Insufficiency	0	1 (0.7)

Source Vol. 77, p. 115

*11.3.2.5.4. Laboratory Adverse Events*

Overall, the mean change from baseline to final visit in terms of laboratory parameters was similar between both treatment groups, with a few exceptions and overall, there were no clinically significant differences between treatment groups for percentage of patients with laboratory abnormalities. Generally, the changes in laboratory values were not clinically important (i.e. not outside the normal range and/or not requiring clinical intervention). However, there was one patient in the CFC-MDI group who developed hepatitis prior to Visit 7 and had elevated LFTs and 10 subjects (3.2%) in the HFA-MDI group, developed Diabetes/hyperglycemia compared to one subject (0.7%) in the CFC-MDI group. There were other minor differences between treatment groups which are summarized in the table

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below. It is unlikely that these differences represent treatment effects, but more reflective of the patient population under study.

**Table 64. Study 244.2453, Number of Patients (%) with Laboratory Abnormalities Reported as Adverse Events Occurring at a Frequency of 1% or Greater in Either Group**

Adverse Event	HFA -MDI n = 305 n (%)	CFC -MDI n = 151 n (%)
Diabetes mellitus	5 (1.6)	1 (0.7)
Hypercholesterolemia	1 (0.3)	5 (3.3)
Hyperglycemia	5 (1.6)	0
Hypokalemia	4 (1.3)	1 (0.7)
Anemia	5 (1.6)	1 (0.7)
Hematuria	3 (1.0)	1 (0.7)

Source: Vol. 77, p. 156-157

### *11.3.2.5.5. Vital Signs, Physical Examination and Other Safety Parameters*

Percentage of patients with clinically significant changes in vital signs was similar between both treatment groups. There were no clinically significant differences between the two treatment groups. [Vol. 77, p. 158, 264]

Clinically significant EKG changes from baseline—as judged by the investigator—were reported in 23 patients (7.5%) receiving HFA-MDI and in 9 patients (5.9%) receiving CFC-MDI. The changes reported as adverse events were generally related to ECG changes that might be expected of this patient population such as changes consistent with chest pain/ischemia, left axis deviation, right bundle branch block, septal infarct, cor pulmonale, sinus bradycardia, increased PR interval and cardiomegaly; left anterior fascicular hemiblock; non-specific T-wave abnormalities; arrhythmia, PVCs and sinus tachycardia. Two episodes of tachycardia on EKG, one in each treatment group, were judged by the investigator to be clinically related. [Vol. 77, p. 158]

Paradoxical bronchospasm, defined as a decrease in FEV<sub>1</sub> of greater than 15% within half hour of study drug administration on any given test day, was noted in 32 patients (23 patients (7.5%) in the HFA group and 9 patients (5.9%) in the CFC- group. Most patients tended to improve within 60-90 minutes and those that did not, seemed to have a higher baseline on that given test day compared to any of the other test days. [Vol. 77, p. 265-268] This finding was not associated with any shortness of breath or other symptoms and did not require the use of rescue medication. [Vol. 77, p. 158]

The use of rescue medication during the 6-hour PFT testing was not significantly different between the treatment groups. Rescue medicine use was reported in 4% of patients in the HFA-MDI group and in 3% of patients in the CFC-MDI group. [Vol. 77, p. 158]

### **11.3.3. Conclusion**

Study 244.2453 was a 52-week, randomized, open-label, active controlled, multi-center, long-term safety study in 456 patients 40 years and older with COPD, conducted in the United States. The duration of total exposure was slightly greater for the HFA-MDI group as

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compared to the CFC-MDI group however the majority of patients in both groups received 359-372 days of treatment.

Treatment groups were similar at baseline with respect to age, gender, race, height, weight, smoking history, mean duration of COPD and time since diagnosis of COPD. The mean age for the study population was 65.2 years. Ninety-five percent of the study population was White. A slightly greater percentage of patients in the HFA-MDI group (82%) compared to the CFC-MDI group (79%) took concomitant pulmonary therapy 6 weeks prior to randomization and throughout the study and baseline FEV<sub>1</sub> was slightly higher for the CFC group as compared to the HFA group. This suggests that the patients in the HFA-MDI group may have been sicker than the patients in the CFC-MDI group.

A greater percentage of patients discontinued from the CFC-MDI group (17.9%) as compared to the HFA-MDI group (13.8%). Discontinuations secondary to adverse events were comparable between treatment groups (~7% for each group). As the primary endpoint for this study was safety, all efficacy endpoints were considered secondary. However, the two main efficacy endpoints, FEV<sub>1</sub> AUC<sub>0-6</sub> and peak change in FEV<sub>1</sub> from baseline, were used to establish therapeutic equivalence between the two drugs. The data is supportive of the comparable efficacy of both drugs. The efficacy data generated at Weeks 26 and 52 of the study were from patients using the second generation drug product. These data may provide an indirect link to the first generation product provided that the changes made to the aerosol valve from the 2<sup>nd</sup> generation product do not impact the product's performance.

Both treatment groups were fairly similar in terms of safety, with some minor differences whose clinical significance is unclear. The majority of patients reported at least one adverse event. Of the 456 randomized patients, 278 (91.1%) patients in the HFA-MDI treatment group and 132 (87.4%) patients in the CFC-MDI treatment group reported adverse events (AEs) which are not unusual for a one-year study and for the patient population under study. Rhinitis, COPD exacerbation, and bronchitis were the most commonly reported AEs in both treatment groups, however, the percentage of serious events of COPD exacerbations was higher in the CFC group (8.6%) compared to the HFA-MDI group (4.9%). Back pain, influenza-like symptoms, pharyngitis, and some vision disorders occurred at a greater frequency in the HFA-MDI group compared to the CFC-MDI treatment group. The main cause of death was malignancy and there were no treatment-related deaths. No clinically meaningful differences between treatments were observed in laboratory parameters, vital signs, or EKG findings.

The results of this study suggest that Atrovent HFA-MDI (first and second generation products) has comparable efficacy. Safety results also suggest that the drugs are comparable, with no safety signals of concern observed with the HFA formulation.

**11.4. Study 244.2498. A Single-Dose, Double-Blind, Crossover Trial to Determine the Comparability of Ipratropium Bromide HFA-134a Inhalation Aerosol to the Market Standard, ATROVENT® CFC Inhalation Aerosol, in Patients with Chronic Obstructive Pulmonary Disease (COPD)****11.4.1. Protocol****11.4.1.1. Investigators and Centers**

Protocol #: 244.2498

Title: A Single-Dose, Double-Blind, Crossover Trial to Determine the Comparability of Ipratropium Bromide HFA-134a Inhalation Aerosol to the Market Standard, ATROVENT® CFC Inhalation Aerosol, in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Study Dates: Initiated 20 October 2000. Completed 28 February 2001.

Sites: 4 sites in the United States\* [Vol. 90, p. 4]

Investigators: 4 Principal Investigators

IRB: All principal investigators have received approval by their respective Investigational Review Boards. [Vol. 90, p. 5] Most of the investigators received approval from:  
Western Institutional Review Board  
3535 Seventh Avenue, S.W., Olympia, WA 98502  
The few others received IRB approval from their respective clinical centers.

Ethical Considerations: This study was conducted according to the Declaration of Helsinki as revised by the 41<sup>st</sup> World Medical Assembly, Hong Kong, September 1989, Good Clinical Practices.

\* Although 4 sites were planned, only three sites were able to enroll patients; the fourth site did not enroll any patients for this study. [Vol. 90, p. 16]

Source: Volume 90, p. 15

**11.4.1.2. Objective**

The objective of this study was to compare the bronchodilator efficacy of 21 mcg and 42 mcg of ipratropium bromide HFA-134a inhalation aerosol with 21 mcg and 42 mcg ATROVENT® CFC Inhalation Aerosol in patients with chronic obstructive pulmonary disease (COPD).

**11.4.1.3. Overall Design**

This was a 5-treatment, multi-center, randomized, double-blind, single-dose, crossover trial designed to bridge the product (device/drug) used in the clinical Phase III clinical program to the proposed commercial product. The study was conducted in the United States between 20 October 2000 and 28 February 2001 and enrolled 41 male and female patients 40 years and older with chronic obstructive pulmonary disease. [Vol. 90, p. 4, 17, 19]

#### 11.4.1.4. Study Population

The study enrolled 41 male and female patients with COPD 40 years of age and older. Forty-one patients were randomized to treatment and 40 patients were exposed to all five treatments.

##### 11.4.1.4.1. Inclusion Criteria [Vol. 90, p. 19-20]

Patients were included in the study if they:

- were males or females 40 years or older
- had a documented diagnosis of stable, moderate to severe COPD as defined by the American Thoracic Society
  - had a baseline FEV<sub>1</sub> ≤65% of predicted, and a FEV<sub>1</sub> ≤70% of FVC having abstained from bronchodilators for the specified study period (see below)
- had a smoking history of more than 10 pack years
- had an ability to demonstrate an improvement in FEV<sub>1</sub> ≥ 15% within one hour after inhalation of 2 puffs of Atrovent® Inhalation Aerosol (21 mcg per puff)
- had an ability to satisfactorily administer the medication, perform pulmonary function test and maintain records during the study period as required in the protocol
- had a signed Informed Consent Form prior to participation in the trial (i.e., prior to pre-study washout of their usual pulmonary medications and prior to fasting for laboratory tests)

*Reviewer's comments: The sponsor apparently only selected patients for enrollment who have demonstrated an improvement to Atrovent. This can certainly skew the results to favor Atrovent.*

##### 11.4.1.4.2. Exclusion Criteria [Vol. 90, p. 20-21]

Patients were excluded from the study if they:

- Had a history of asthma, allergic rhinitis or atopy, or a blood eosinophil count at screening above 600/mm<sup>3</sup>
- Had any significant disease other than COPD, which put the patient at risk because of participation in the study
- Had clinically relevant baseline hematology, blood chemistry or urinalysis if the abnormality defined a disease listed as an exclusion criterion. Patients with SGOT > 80 IU/L, SGPT > 80 IU/L, bilirubin > 2.0 mg/dL, or creatinine > 2.0 mg/dL were to be excluded regardless of the clinical condition.
- Had a recent myocardial infarction (one year or less), or cardiac failure (three years or less); patients with cardiac arrhythmia requiring therapy, patients receiving any systemic beta-blockers and patients on chronic daytime oxygen therapy were excluded as well.
- Had known active tuberculosis, pulmonary resection or thoracotomy

- Had cancer within the last five years, excluding treated basal cell carcinoma
- Had a history of life-threatening pulmonary obstruction, or a history of cystic fibrosis or bronchiectasis
- Had an upper respiratory infection or COPD exacerbation in the six weeks prior to the screening visit
- Had a known hypersensitivity to anticholinergic drugs
- Had a known symptomatic prostatic hypertrophy or bladder-neck obstruction
- Had known narrow-angle glaucoma
- Were using cromolyn sodium, nedocromil sodium or antihistamines
- were pregnant or nursing women and women of childbearing potential not using a medically approved means of contraception
- had used an investigational drug within one month or 6 half-lives (whichever was longer) of the drug prior to the screening visit or were enrolled currently in another research study
- had a history of alcoholism or drug abuse

*11.4.1.4.3. Allowed Therapy [Vol. 90, p. 23]*

The following therapies were permitted if stabilized for at least six weeks prior to and throughout the study period:

- oral corticosteroids if stabilized on minimal doses (10 mg or less daily or 20- mg or less every other day)
- orally inhaled corticosteroids
- theophylline preparations
- mucolytic agents not containing bronchodilators
- beta-agonists (Ventolin® Inhalation Aerosol) and anticholinergic bronchodilators (Atrovent® and Combivent®)—a washout period of 12 hours was required for these drugs

*11.4.1.4.4. Prohibited Therapy [Vol. 90, p. 23]*

The following medications were not allowed one month prior to the screening visit and throughout the study period:

- All other investigational drugs
- Cromolyn sodium and nedocromil sodium
- Antihistamines
- Systemic beta-blockers

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### 11.4.1.5. Study Procedure

Study 244.2498 was a five-treatment, randomized, double-blind, double-dummy, single-dose, cross-over study to determine the efficacy comparability of 21 and 42 mcg of ipratropium bromide HFA-134a inhalation aerosol (HFA-MDI) and marketed 21 mcg and 42 mcg of Atrovent® CFC Inhalation Aerosol (CFC-MDI) in patients with COPD.

The study consisted of six total visits including the screening visit. Following an initial screening visit, eligible patients were randomized into the study. Patients received one of the five treatments on each test day in a randomized, crossover design. At each treatment visit, patients took one puff from four different canisters to blind the study (although only the specified treatment dose was given). The sponsor specified 10 treatment sequences balanced with each treatment occurring twice a period; four patients in each sequence group were to be enrolled in the study.

Pulmonary function testing was conducted at each visit; however, a six-hour PFT was conducted following study drug administration at Visits 2-6. At Visits 3-6, patients were required to have a pre-treatment FEV<sub>1</sub> within  $\pm 15\%$  of their pre-treatment FEV<sub>1</sub> from Visit 2; patients were rescheduled if they did not meet this criterion. There was a washout period of 3-7 days between each visit. The procedure flow chart is depicted below outlining all of the procedures (to include history, physical examination, laboratory analyses, etc.) and their corresponding time points.

**Table 65. Study 244.2498, Procedure Flow Chart**

	Screening Visit	Randomized Treatment Phase				
Study Day	-7	1	8	15	22	29
Visit	1	2	3	4	5	6
Informed Consent	✓					
Medical History	✓					
Physical Examination	✓					✓
Review of Inclusion/Exclusion Criteria		✓				
EKG*	✓					✓
Laboratory Investigations*	✓					✓
PFT*	✓	✓	✓	✓	✓	✓
Vital Signs*	✓	✓	✓	✓	✓	✓
Administration of Study Drugs		✓	✓	✓	✓	✓
Review Adverse Events	✓	✓	✓	✓	✓	✓
Review Concomitant Medication	✓	✓	✓	✓	✓	✓
Training on MDI	✓					

\*Further particulars are described below under *Efficacy Parameters* and *Safety Assessments* sections  
Vol. 90, p. 24

#### 11.4.1.5.1. Treatments

Patients were randomized to receive one of the following single dose treatments:

- Ipratropium bromide HFA-134a inhalation aerosol 21 mcg (1 puff, 21 mcg)
- Ipratropium bromide HFA-134a inhalation aerosol 42 mcg (2 puffs, 21 mcg each)

- ATROVENT® CFC inhalation aerosol 21 mcg (1 puff, 21 mcg)
- ATROVENT® CFC inhalation aerosol 42 mcg (2 puff, 21 mcg each)
- Placebo HFA/CFC

The sponsor used the 3rd generation ipratropium bromide HFA-MDI product for this study. [Vol.1, p. 108]

#### 11.4.1.6. Efficacy Parameters

Efficacy was evaluated from results of Pulmonary Function Testing (PFT) conducted at Study Visits 1- 6. PFTs were done at the screening visit (Visit1) at baseline and repeated at 15, 30, and 60 minutes following 2 inhalations of Atrovent® Inhalation Aerosol. If patients achieved an FEV<sub>1</sub> increase of at least 15% over baseline, subsequent measurements were not done and the patient was eligible for study entry based of PFT criteria. Once randomized for study entry, PFTs were measured pre-dose and at 15, 30, 60, 90, and 2,3,4,5, and 6 hours after drug administration. [Vol. 90, p. 25]

#### Primary Efficacy Variables [Vol. 90, p. 29]

- FEV<sub>1</sub> AUC<sub>0-6</sub>: area under the curve for 0-6 hours for FEV<sub>1</sub>

#### Secondary Efficacy Variables [Vol. 90, p. 5]

- Peak bronchodilatory response: FEV<sub>1</sub> max
- FVC AUC<sub>0-6</sub>
- FVC max

#### 11.4.1.7. Safety Evaluations [Vol. 90, p. 26-27]

- Adverse events (AEs)
  - ◆ At each visit, patients were asked how they had been feeling since the last visit. The onset, duration, intensity, severity, medication taken, action taken and causality of the adverse event were recorded on the Case Report Form. Serious adverse events were defined as customary per FDA regulations.
  - ◆ The sponsor states that particular attention was paid to AEs such as cough, wheezing, and paradoxical bronchospasm following inhalation of randomized treatment. [Vol. 90, p. 26]
  - ◆ Paradoxical bronchospasm was defined as a  $\geq 15\%$  fall in FEV<sub>1</sub> below baseline and/or the need for rescue medication and/or spontaneous reporting by the patient of any event indicative of bronchospasm within 30 minutes following inhalation. A fall of  $\geq 15\%$  in FEV<sub>1</sub> without associated symptoms, complaints or need for rescue medication was labeled as a symptomatic paradoxical bronchoconstriction.
- Pulse rate and blood pressure pre-dose and at 60 minutes post dose

- ◆ Vital signs were taken and recorded for the same time points for PFT evaluation at all study visits; vitals were measured approximately five minutes prior to PFT evaluation.
- Changes in physical examination: A complete physical examination was performed at screening and at the final visit on all patients. Any new or abnormal findings detected at the final visit were recorded as adverse events.
- Changes in resting EKG (end of treatment compared to baseline)
  - ◆ Performed at both baseline (Visit 1) and the final visit (Visit 6, or on withdrawal from the study) for each patient
- Changes in hematology, blood chemistry and urinalysis (end of treatment compared to baseline)
  - ◆ Hematology: CBC (with diff.) and an absolute eosinophil count
  - ◆ Blood Chemistry: alkaline phosphatase, LDH, SGOT, SGPT, GGT, glucose, potassium, calcium inorganic phosphorus, uric acid, urea nitrogen, creatinine, total protein, albumin, and total bilirubin, chloride, bicarbonate, theophylline (if patients were taking theophylline).
  - ◆ Urinalysis: glucose, protein, hemoglobin, pH, and specific gravity

#### 11.4.1.8. Statistical Plan

##### 11.4.1.8.1. Sample Size

The sponsor based the sample size calculation on data from previous trials with similar compounds in patients with COPD. [Vol. 90, p. 34] Forty patients in each treatment group were required to detect a 0.05L difference between the mean FEV<sub>1</sub> AUC<sub>0-6</sub> following HFA-MDI and CFC-MDI at a 5% alpha with 80% power assuming a standard deviation of 0.11L. This was evaluated using a paired t-test. [Vol. 90, p. 34]

##### 11.4.1.8.2. Handing of Missing Data

The sponsor estimated missing values using other values recorded from the patient on that test-day. Random, middle, missing spirometry measurements were estimated using linear interpolation of the two adjacent measurements. For missing FEV<sub>1</sub> values at the end of the time profiles, the minimum observed FEV<sub>1</sub> value on that test day for any given patient was used as an estimate. [Vol. 90, p. 33]

##### 11.4.1.8.3. Primary Efficacy Analysis

The primary efficacy endpoint was the FEV<sub>1</sub> AUC<sub>0-6</sub>. Area was calculated using the changes from test-day baseline (pre-treatment on each of the visits) and the trapezoidal rule. The statistical model was an ANCOVA with fixed effects for treatment, center, patient within center and visit. Baseline FEV<sub>1</sub> values on each test day were used as covariates. The sponsor did not expect any carryover since test days were separated by three to seven days. [Vol. 90, p. 30]

The primary hypothesis tested whether there was a difference between the HFA-MDI and CFC-MDI. The null hypothesis was that the mean FEV<sub>1</sub> AUC<sub>0-6</sub> following 42 mcg of HFA-MDI was not different from the mean FEV<sub>1</sub> AUC<sub>0-6</sub> following 42 mcg of CFC-MDI. The alternate hypothesis was that the mean FEV<sub>1</sub> AUC<sub>0-6</sub> was different. This was tested on the Intent to Treat (ITT). The ITT was defined as all randomized patients with baselines and at least three hours of data post-treatment to characterize response to treatment on at least two test days. [Vol. 90, p. 30]

In order to validate the study, the sponsor also compared the mean FEV<sub>1</sub> AUC<sub>0-6</sub> for HFA-MDI to placebo. Therefore, the null hypothesis for this was that the mean FEV<sub>1</sub> AUC<sub>0-6</sub> was not different from the mean FEV<sub>1</sub> AUC<sub>0-6</sub> with placebo. [Vol. 90, p. 30]

#### 11.4.1.8.4. Secondary Efficacy Analyses

The following were the secondary efficacy variables used in this study.

- Peak bronchodilatory response: FEV<sub>1</sub> max

Peak FEV<sub>1</sub> response was defined as the maximum change from test-day pre-dose value recorded after inhalation of the test dose.

- Onset and duration of therapeutic response

A therapeutic response was defined as those FEV<sub>1</sub> measurements exceeding 1.15 times pre-dose values at any time during the first two hours of observation. Onset of therapeutic response was calculated by interpolation of a line formed between the time of the first therapeutic response and the time of the observation just prior to the first therapeutic response (even if that was the pre-dose observation). Termination of response was defined as the first fall below 1.15 times pre-dose FEV<sub>1</sub> on two consecutive measurements following a therapeutic response. Duration of therapeutic response was defined as that interval between the onset and termination of the response. [Vol. 90, p. 32]

- FVC AUC<sub>0-6</sub> and FVC max

Peak FEV<sub>1</sub> response, FVC AUC<sub>0-6</sub>, peak FVC response and the individual FEV<sub>1</sub> and FVC timepoints were using similar ANCOVA analysis as described above for the primary efficacy endpoint. [Vol. 90, p. 31]

## 11.4.2. Results

### 11.4.2.1. Patient Disposition

A total of 70 patients were screened for this study. Forty-one patients were randomized to the trial and 40 (97.6%) completed the trial. There was only one discontinuation from the study. This patient withdrew consent secondary to a death in the family.

#### Protocol Violations

Protocol violations were divided into type 1 violations (potentially affecting safety and/or efficacy) and type 2 violations (minor deviations of affecting safety or efficacy analyses). None of the protocol violations affected safety. One patient was excluded from efficacy analyses since this patient only completed one PFT test day (to be included in the ITT as

defined, a patient had to have PFT data on a least two test days). The sponsor states that this patient was replaced. The remaining 40 patients PFTs for each of the five 6-hour PFT test days; a total of 40 patients were included in the efficacy analysis.

The sponsor lists only two Type 2 protocol violations. Both of these patients had entrance criteria violations. Patient 102 had a baseline FEV<sub>1</sub> at Visit 1 which was 70% predicted and patient 148 had a pre-treatment baseline of 69.68%; for inclusion in trial, the FEV<sub>1</sub> had to be at or below 65%. [Vol. 90, p. 36]

*Reviewer's comments: The sponsor does not further elaborate on the results of these protocol violations. This reviewer is assuming from information reported in the first paragraph under protocol violations, that the one patient who was not included in the efficacy analysis was the one who failed entry criteria at the screening visit, Visit 1 and that the patient who had a protocol violation at Visit 2 was included since he had PFT measurements on at least two days. Since the number is so low, it is doubtful that efficacy results would be affected. This reviewer has reviewed the line listings for protocol violations [Vol. 90, p. 285-293] and most of the protocol violations occurred secondary to timing outside of specified range for study drug administration or PFT testing. It is doubtful that this would significantly affect the efficacy analysis.*

**11.4.2.2. Demographics and Other Baseline Characteristics**

Demographics [Vol. 90, p. 38]

Since this trial was of a cross-over design, all patients received each of the five treatments. The demographics for the study population are therefore presented in terms of total. The mean age of the study population was 67.1 with a range of 48-79. The majority of patients were 61 years or older (85%). The majority of patients were male (70.7%) compared to female (29.3%). All patients, with one exception were White; this patient was Black. The mean height was 67.7 inches with a range of 59-75 inches; the mean weight was 173.63 lbs with a range of 116-260 lbs. The study population had a mean smoking history of 71.9 pack-years with a range of 20-160 pack-years. The mean time to diagnosis of COPD was 7.8 years with a range of 1-31 years and a standard deviation of 5.7 years. The baseline demographics and baseline characteristics are depicted below.

**Table 66. Study 244.2498, Demographic and Baseline Characteristics**

Characteristic		Total n=41
Sex	n (%)	
	Male	29 (70.7)
	Female	12 (29.3)
Race	n (%)	
	White	40 (97.6)
	Black	1 (2.4)
Age	Mean (years)	67.1
	SD	7.0
	Range	48-79
Age Distribution		
	41-50	1 (2.4)
	51-60	5 (12.2)

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Characteristic	Total n=41
61-70	21 (51.2)
71-80	14 (34.1)
Height Mean (in)	67.7
SD	3.8
Range	59-75
Weight Mean (lb)	173.63
SD	36.98
Range	116-260
Smoking History (pack-years)	
Mean	71.9
SD	32.6
Range	20-160
Alcohol History n (%)	
Non-Drinker	20 (48.8)
Average Consumption	21 (51.2)
Time since Dx of COPD (years)	
Mean	7.8
SD	5.7
Range	1-31

Source: Vol. 90, p. 38

### Baseline Spirometry

The baseline spirometry supports the inclusion of moderate to severe COPD patients generally. The mean FEV<sub>1</sub> was 1.076 liters with FEV<sub>1</sub> % predicted of 40.4 (range of 21-70, with a standard deviation of 12.4). The mean FEV<sub>1</sub>/FVC was 48.1 % with a range of 29-68 % and standard deviation of 8.9. All patients were selected for trial inclusion to include only patients that responded to Atrovent with a 15% improvement in FEV<sub>1</sub>; this criterion has been met per baseline spirometry results. The mean percent improvement in FEV<sub>1</sub> was 23.7 % with a range of 15-48% and a standard deviation of 8.9%.

**Table 67. Study 244.2498, Baseline Spirometry**

Parameter	Total n=41
FEV <sub>1</sub> (L)	
Mean	1.076
SD	0.3803
Range	0.490-2.06
Percent FEV <sub>1</sub> /FVC (%)	
Mean	48.1
SD	8.9
Range	29-68
Percent Predicted FEV <sub>1</sub> (%)	
Mean	40.4
SD	12.4
Range	21-70

Parameter	Total n=41
Baseline FVC (L)	
Mean	2.251
SD	0.7192
Range	1.60-3.74
Final FEV <sub>1</sub> (L) Post-Atrovent	
Mean	1.315
SD	0.421
Range	0.570-2.37
% Improvement in FEV <sub>1</sub> Post-Atrovent	
Mean	23.7
SD	8.9
Range	15-48

Source: Vol. 90, p. 39

**Concomitant Medical Diagnoses and Medications**

This reviewer has reviewed the line listings for concomitant medical diagnoses and does not feel that these would interfere with analyses of results. [Vol. 90, p. 297-310]

In terms of concomitant medications, 21 patients (51%) were using concomitant salmeterol therapy, 20 patients (49%) were using concomitant inhaled steroids, and 2 patients (4.9%) were using prn oxygen therapy, 1 (2.4%) was taking chronic oral prednisone, and 1 patient (2.4%) received a prednisone taper. [Vol. 90, p. 311-321]

*Reviewer's comments: As this was a crossover study, it is doubtful that any of these concomitant therapies would impact analysis of study results.*

**11.4.2.3. Compliance**

As this was a single-dose study and all study doses were administered at the study site, compliance was not an issue in terms assessing home use of study drug. All investigators and staff confirmed that each patient received the treatment at the study center on each treatment day. Further details on this have not been provided in this submission. This reviewer assumes that the above implies that all patients were compliant.

**11.4.2.4. Efficacy Endpoint Outcomes**

***11.4.2.4.1. Primary Efficacy Analysis***

For the primary efficacy analysis, the primary efficacy variable was FEV<sub>1</sub> AUC<sub>0-6</sub>. The pre-dose unadjusted mean baseline measurements for FEV<sub>1</sub> were comparable, ranging from 1.075 liters to 1.090 liters for all treatments.

All active doses of ipratropium bromide were effective in terms of the primary efficacy variable. The mean difference in the adjusted mean FEV<sub>1</sub> AUC<sub>0-6</sub> between active treatments and placebo ranged from 124 to 165 ml. Both HFA-MDI (21 mcg and 42 mcg) and CFC-MDI (21 mcg and 42 mcg) were statistically superior to placebo (p=0.0001). No statistically significant differences were noted between the two active treatments for either dose. The difference in the adjusted mean FEV<sub>1</sub> AUC<sub>0-6</sub> between HFA-MDI 42 mcg and CFC-MDI

42 mcg was 5 ml ( $p=0.762$ ) and the corresponding difference between the two active treatments with the 21 mcg dose was 19 ml ( $p=0.172$ ). These results are presented in the following two tables.

**Table 68. Study 244.2498, FEV<sub>1</sub> Adjusted Mean AUC<sub>0-6</sub> (in liters) for each Treatment Group with Pairwise Comparisons to Placebo and Active Treatment**

Treatment	Adjusted Mean AUC <sub>0-6</sub> (liters)	Pairwise Comparison to Placebo*		Pairwise Comparison to Active Treatment of Similar Dose	
		Difference Between Treatments (SEM)	p-value	Difference Between Treatments (SEM)	p-value
HFA-MDI 21 mcg	0.179	0.124 (0.014)	0.0001	-0.019 (0.014)	0.1721
HFA-MDI 42 mcg	0.215	0.160 (0.014)	0.0001	-0.005 (0.014)	0.7162
CFC-MDI 21 mcg	0.198	0.143 (0.014)	0.0001	-0.019 (0.014)	0.1721
CFC-MDI 42 mcg	0.220	0.165 (0.014)	0.0001	-0.005 (0.014)	0.7162

\*The Adjusted Mean AUC<sub>0-6</sub> for placebo was 0.055 liters

Source: Vol. 90, p. 42, 43

*Reviewer's comments: Primary efficacy analysis reveals comparable efficacy between the two treatment groups for single doses.*

#### 11.4.2.4.2. Secondary Efficacy Analyses

The secondary efficacy variables were: FEV<sub>1</sub> adjusted mean peak response, FVC AUC<sub>0-6</sub>, median duration of action, median time to peak response, median onset of action and number of patients who achieved a 15% increase in FEV<sub>1</sub> from baseline (pre-treatment).

The results demonstrate that all doses of active treatment resulted in better improvement in the adjusted mean peak FEV<sub>1</sub> response as compared to placebo. Additionally, no clinically meaningful difference was noted between the two active treatments for either the 21 mcg or 42 mcg dose. Baseline means for FVC were comparable, ranged between 2.230 to 2.280 liters. FVC AUC<sub>0-6</sub> was also comparable between the two active treatments, 42 mcg dose. [Vol. 90, p. 47]

A therapeutic response was defined as a 15% increase from baseline (pre-treatment) in FEV<sub>1</sub>. The median time of onset of a therapeutic response was similar between the two active treatments at the 42 mcg dose: 14.5 minutes for the HFA-MDI (42 mcg dose) and 13.0 minutes for the CFC-MDI (42 mcg dose). Median time to peak response was higher for the two CFC-MDI doses as compared to the HFA-MDI doses, 1.5 hours and 2.0 hours for the HFA-MDI (42 mcg) and CFC-MDI (42 mcg) doses, respectively. The median duration of therapeutic response was also somewhat greater for the CFC-MDI treatment group (5.4 hours) as compared to the HFA-MDI treatment group (4.8 hours). The percentage of patients who achieved a therapeutic response was greater in the HFA-MDI group (90%) as compared to the CFC-MDI treatment group (82.5%) for the 42 mcg dose. There were also nine patients (22.5%) who achieved a therapeutic response in the placebo treatment group; however, the median time to peak was 3 hours. These results are presented in the table below.

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**Table 69. Study 244.2498, Median Times to Onset and Duration of 15% Increase from Baseline in FEV<sub>1</sub> (Therapeutic Response), and Time to Peak Response (n=40)**

	HFA-MDI		CFC-MDI		Placebo
	21 mcg	42 mcg	21 mcg	42 mcg	-----
Median Onset of Action (mins)	23.5	14.5	15.0	13.0	-----
Median Time to Peak (hours)	1.5	1.5	1.75	2.0	3.0
Median Duration (hours)	2.7	4.8	3.05	5.4	0
Number of Patients (%) who Achieved a Therapeutic Response	33 (82.5)	36 (90)	34 (85)	33 (82.5)	9 (22.5)

Source: Vol. 90, p. 47

*Reviewer's comments: although this is a single dose study, the HFA-MDI and CFC-MDI are better than placebo and comparable on all endpoints. The significance of 9 patients in the placebo group achieving a therapeutic response is unclear. It could represent a "placebo effect" or the natural course of variability in the FEV<sub>1</sub> on a given day.*

### 11.4.2.5. Safety Outcomes

All 41 patients were included in the safety analysis. [Vol. 90, p. 50] The following table summarizes the general safety outcomes for this study.

**Table 70. Study 244.1408, Adverse Events, All Causalities**

	Total n (%)
Randomized	41
Number of AEs	24
Subjects with AEs	12 (29.3)
Subjects with Serious AEs	1(2.4)
Deaths	0
Subjects discontinued due to AEs	0

#### 11.4.2.5.1. Exposure

Since this was a single dose study, and all treatments were administered at the study center, no diary data were collected. The sponsor states that all investigators and staff confirmed that each patient received the treatment at the study center on each treatment day.

#### 11.4.2.5.2. Adverse Events

Overall, 12 patients (29.3%) experienced 24 adverse events throughout the whole study period. Any adverse event that occurred by midnight of the day of study drug administration was attributed to the treatment. After this time, the period was defined as the washout period. Three patients experienced adverse events occurring by midnight of the day of study drug administration: one patient in the HFA-MDI 21 mcg treatment group and two patients in the CFC-MDI 21 mcg treatment period. No patients had any adverse events by midnight on the day of study drug administration in the HFA-MDI 42 mcg, CFC-MDI 42 mcg, or placebo treatment period. [Vol. 90, p. 50, 51]

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The most commonly reported AE was rhinitis; it was reported in 4 patients (9.8%): 1 during the screening period and in 3 during the washout period. Headache, diarrhea and skin rash, were each reported in 2 patients (4.9%). All other noted AEs were reported in one patient. No AEs were reported during the treatment period for HFA-MDI 42 mcg, CFC-MDI 42 mcg, or placebo. Only three patients reported AEs during any treatment period, one during the HFA-MDI 21 mcg and two during the CFC-MDI 21 mcg treatment period. These results are summarized in Table 48 below. Since there were no AEs reported for the 42 mcg doses of HFA-MDI and CFC-MDI and the placebo period, these columns have been omitted from the table.

**Table 71. Number of Subjects (%) with AEs and the Study/Treatment Period at Onset**

Adverse Events	Study/Treatment Period at Onset of AEs					
	Screening n=41 n (%)	HFA-MDI 21 mcg n=40 n (%)	CFC-MDI 21 mcg n=40 n (%)	Washout Period n=41 n (%)	Post- Treatment n=41 n (%)	Total n=41 n (%)
<b>Total with Any AE</b>	<b>5 (12.2)</b>	<b>1 (2.5)</b>	<b>2 (5.0)</b>	<b>7 (17.1)</b>	<b>1 (2.4)</b>	<b>12 (29.3)</b>
<b>General Disorders</b>						
Accident Household	1 (2.4)	0	0	0	0	1 (2.4)
Back Pain	0	1 (2.5)	0	0	0	1 (2.4)
Fever	0	0	0	1 (2.4)	0	1 (2.4)
Headache	0	0	1 (2.5)	1 (2.4)	0	2 (4.9)
<b>Cardiovascular Disorders</b>						
Hypertension Aggravated	1 (2.4)	0	0	0	0	1 (2.4)
<b>Gastro-intestinal Disorders</b>						
Abdominal Pain	0	0	0	1 (2.4)	0	1 (2.4)
Diarrhea	0	0	0	2 (4.9)	0	2 (4.9)
<b>Infectious Disease</b>						
Viral Infection	0	0	0	0	1 (2.4)	1 (2.4)
<b>Respiratory Disorders</b>						
COPD	0	0	0	1 (2.4)	0	1 (2.4)
Pharyngitis	1 (2.4)	0	0	0	0	1 (2.4)
Respiratory Insufficiency	0	0	0	0	1 (2.4)	1 (2.4)
Rhinitis	1 (2.4)	0	0	3 (7.3)	0	4 (9.8)
Sinusitis	0	0	0	1 (2.4)	0	1 (2.4)
URI	0	0	1 (2.5)	0	0	1 (2.5)
<b>Skin Disorders</b>						
Bullous Eruption	0	0	0	1 (2.4)	0	1 (2.4)
Rash	1 (2.4)	0	0	1 (2.4)	0	2 (4.9)

Source Vol. 90, p. 51

*Reviewer's comments: In the original protocol, for any AE to be attributed to a particular treatment, it must have occurred by 24 hours following study drug administration. However, the sponsor had amended the protocol to change this to any AE occurring by midnight on the day of study drug administration. If the originally defined criteria are used, the patient with respiratory insufficiency would have been attributed to the HFA-MDI 42 mcg treatment group and not the post-treatment period. As this is a single dose study, and*

*COPD exacerbations are common in this patient population, an adverse such as this is not unexpected. This patient is summarized below in the Serious Adverse Events section.*

#### *11.4.2.5.3. Deaths and Serious Adverse Events*

No deaths were reported during this study.

Only one patient reported any serious adverse events. Patient 150 was a 68 year old Caucasian female who reported 3 serious adverse events during this study. This patient reported increased congestion and shortness of breath one day prior to Visit 6 (final visit). The patient received the final treatment (HFA-42 mcg) on Visit 6, and the following day was hospitalized for respiratory failure (for which the patient was intubated) and viral infection; the respiratory failure lasted for 5 days and the viral infection lasted for 17 days. The patient was reported to have recovered with a sufficient follow-up visit. [Vol. 90, p. 52, 65]

*Reviewer's comments: The sponsor does not provide any further information in the Narrative section of SAEs.*

#### *11.4.2.5.4. Laboratory Adverse Events*

In this study, laboratory evaluations were conducted during the screening period and at the end of the study. Laboratory evaluations were not done prior to or after each treatment dosing day, so no particular treatment period can be identified with a particular laboratory change.

There were very few patients with any clinically significant changes in laboratory parameters. Three patients were noted to have increases in alkaline phosphatase (maximum value of 157.7 U/L with a maximal change from baseline of 53.1 U/L). One patient (patient 150) was one of the patients who had an increase in alkaline phosphatase; this patient also had increases in AST, ALT and GGT with the maximum values listed as 74.5 U/L, 90.4 U/L, and 233.1 U/L, respectively. One patient each had increases in potassium and platelets. [Vol. 90, p.53; Vol. 91, p. 80-82]

*Reviewer's comments: The sponsor does not further elaborate on any of these laboratory abnormalities in terms of causation. This reviewer does not feel that these changes are particularly meaningful. In the Integrated Review of Safety, this reviewer will analyze the safety data for any safety concerns.*

#### *11.4.2.5.5. Vitals and Other Safety Variables*

##### Vitals

Vital signs (blood pressure and pulse) were measured at baseline and 15, 30, 60, and 90 minutes and 2 and 3 hours post-inhalation of study drug on each test day. [Vol.90, p. 58]

A greater number and percentage of patients had clinically significant (defined in Table 49) increases in systolic BP during the two HFA-MDI treatment periods. Otherwise, the incidence of clinically significant changes in other vital signs was fairly similar between the different treatment periods. No consistent abnormalities were noted. The results are summarized below.

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**Table 72. Study 244.2498, Number (%) of Patients with Clinically Significant Changes from Baseline**

Change*	HFA-MDI 21	HFA-MDI 42	CFC-MDI 21	CFC-MDI 42	Placebo
	mcg n=40 n (%)	mcg n=40 n (%)	mcg n=40 n (%)	mcg n=41 n (%)	n=40 n (%)
Systolic BP Increased	10 (25.0)	10 (25.0)	6 (15.0)	2 (4.9)	4 (10.0)
Systolic BP Decreased	1 (2.5)	3 (7.5)	2 (5.0)	4 (9.8)	1 (2.5)
Diastolic BP Increased	2 (5.0)	3 (7.5)	1 (2.5)	5 (12.2)	1 (2.5)
Diastolic BP Decreased	4 (10.0)	3 (7.5)	5 (12.5)	5 (12.2)	5 (12.5)
Pulse Increased	2 (5.0)	1 (2.5)	3 (7.5)	2 (4.9)	3 (7.5)
Pulse Decreased	2 (5.0)	5 (12.5)	3 (7.5)	1 (2.4)	1 (2.5)

\*Clinically significant changes from test day baseline in systolic BP, Diastolic BP, and pulse rate are defined as follows:

- Systolic BP: an increase of 25 mm Hg over baseline or below 100 mmHg and a decrease > 10 mmHg below baseline
- Diastolic BP: above 90 mmHg and an increase of >10 mmHg over baseline or below 60 mmHg and a decrease of > 10 mmHg below baseline
- Pulse: greater than 100 bpm and an increase greater than 10% above baseline or below 60 bpm and a decrease of > 10 bpm below baseline

Source: Vol. 90, p. 57,59

*Reviewer's comments: As this is a single dose study involving a relatively small number of patients, and inconsistent results, no conclusions can be reached regarding meaningful changes in vitals. This reviewer will focus on this area in the Integrated Summary of Safety.*

### Use of Rescue Medication

Only one patient required use of rescue medication during any study drug administration day. This patient required treatment with rescue medication (Atrovent Inhalation Aerosol) 15 minutes and 3 hours after 21 mcg of CFC-MDI was administered. No decline in FEV<sub>1</sub> was reported in this patient prior to the use of the rescue medication. [Vol. 90, p. 58]

### Other

No clinically significant changes were reported for either physical examination or EKG.

### **11.4.3. Discussion and Conclusions**

This was a 5-treatment, multi-center, randomized, double-blind, single-dose, crossover trial in 41 male and female patients 40 years and older with chronic obstructive pulmonary disease, designed to bridge the product (device/drug) used in the clinical Phase III clinical program to the proposed commercial product. Patients received single doses of HFA-MDI 21 mcg, HFA-MDI 42 mcg, CFC-MDI 21 mcg, CFC-MDI 42 mcg, and placebo administered in a cross-over fashion. The HFA-MDI drug product used in this study was the third generation product, the to-be-marketed product.

All doses of active treatment were significantly better than placebo for the primary efficacy endpoint of FEV<sub>1</sub> AUC<sub>0-6</sub>. For peak FEV<sub>1</sub>, the active treatments were also favored as compared to placebo. No clinically meaningful changes were noted between the active treatment groups for FEV<sub>1</sub> AUC<sub>0-6</sub> or peak FEV<sub>1</sub> change from baseline.

Twelve patients reported 24 adverse events, with the most common one being rhinitis. There were no deaths reported during this study, and only one patient was reported with an SAE (hospitalization for respiratory failure/viral infection). Generally, this study did not reveal any meaningful differences in safety endpoints between the different treatments.

Although this is a single dose study, this study provides useful information regarding efficacy since the third generation HFA-MDI drug product was used. As with the pivotal studies using the 1<sup>st</sup> and 2<sup>nd</sup> generation products, this study supports the efficacy of the to-be-marketed HFA-MDI drug product, at least in a single dose. No tachyphylaxis has been noted in any of the pivotal studies with the 1<sup>st</sup> generation drug product. Since the formulation is nearly identical between the 1<sup>st</sup> and 3<sup>rd</sup> generation products, it is anticipated that longer studies would also confirm that tachyphylaxis is not an issue with the 3<sup>rd</sup> generation drug product. This would indirectly support long term efficacy of the 3<sup>rd</sup> generation drug HFA-MDI product.

### **11.5. Study 244.2480. An Open-Label, Crossover, Pharmacokinetic Trial to Determine the Comparability of 84 mcg Ipratropium Bromide HFA-134a Inhalation Aerosol to 84 mcg ATROVENT® CFC Inhalation Aerosol, in Patients with Chronic Obstructive Pulmonary Disease (COPD)**

#### **11.5.1. Protocol**

This study was conducted at two centers in the U.S. between 10/27/00 to 4/9/01.

The objective of this study was to compare the pharmacokinetic systemic exposure of 84 mcg ipratropium bromide HFA-134a inhalation aerosol and 84 mcg Atrovent® CFC Inhalation Aerosol following a single dose, at steady state and after 1 week of 84 mcg qid dosing in patients with COPD. [Vol. 91, p. 114]

Study 244.2480 was an open-label, two-treatment, randomized, crossover trial to determine the pharmacokinetic systemic exposure comparability of 84 mcg ipratropium bromide HFA-134a inhalation aerosol (HFA-MDI 84 mcg) and 84 mcg Atrovent® CFC Inhalation Aerosol (CFC-MDI 84 mcg) in patients with COPD. The study was to enroll 28 males and females 40 years and older with a diagnosis of stable, moderate to severe COPD (same definition as the previous studies) with a greater than 10 pack-year history of smoking.

Following an initial screening period, patients received 84 mcg qid of the two treatments for a one-week period in a randomized, crossover fashion. The study consisted of 5 visits: Visit 1 was the screening visit—when all patients underwent a complete history, physical examination, screening pulmonary function testing, screening laboratories and 12-lead EKGs, Visit 2 was the start of the first randomized one-week period, Visit 3 was the end of the first treatment period, Visit 4 was the start of the second randomized treatment period, and Visit 5 was the end of second treatment period as well as the study. There was a washout period of 3-7 days between the two randomized treatment periods (between Visits 3 and 4).

At Visits 2, 3, 4, and 5, blood samples were collected at time 0, 5, 15, 30, 60 minutes and 2, 4, and 6 hours after each dose, for a total of 320 mL of blood collected at each of these visits. At Visits 2 and 4 (1<sup>st</sup> day of each treatment), 24-hour urine was collected. At Visits 3 and 5 (Day 8 of each treatment), three separate aliquots of urine were collected : a Void 15

minutes prior to drug administration, 0-1 hour after drug administration, and 1-6 hours after drug administration.

The two formulations used in this study are as follows:

- Ipratropium bromide Inhalation aerosol 0.021 mcg TTV, 10 mL  
Lot number: PD-2050; Expiration date: 3/02
- Ipratropium bromide monohydrate (HFA-134a) inhalation aerosol 0.021 mcg TTV, 10 mL

Lot number: PD-2041; Expiration date: 07/01

The HFA-MDI drug product used in this study was the 3<sup>rd</sup> generation product, the to-be-marketed formulation/device.

The primary pharmacokinetic endpoint in this study was the amount of the inhaled dose of unchanged ipratropium excreted in the urine over a 24-hour period following a single dose of study drug. Additionally, the amount of inhaled dose of unchanged ipratropium excreted in the urine within the first hour after inhalation (representing the inhaled fraction) and the amount excreted in a 6-hour urine sample was assessed for each formulation. Other pharmacokinetic endpoints were area under the curve for plasma concentration following a single dose and at steady state ( $AUC_{0-6}$ ), peak plasma ipratropium concentration for each formulation ( $C_{max}$ ), time to  $C_{max}$  ( $T_{max}$ ), and trough plasma ipratropium concentration at steady state for each formulation ( $C_{min}$ ). [Vol. 91, p.114]

Safety was assessed by adverse event review, vital signs, laboratory tests (complete blood count and serum chemistries to include liver function tests, total protein, bilirubin, and albumin), physical examination and EKGs at baseline and at the final visit.

No efficacy assessments were made during this study.

### 11.5.2. Results

#### Disposition/Demographics/Baseline Characteristics

A total of 36 patients were screened, 30 patients were randomized, and 29 patients completed the study. One patient prematurely discontinued from the study secondary to an adverse event of pancreatitis. There were eleven patients with protocol violations that could potentially affect pharmacokinetic and safety endpoints. One patient had an entry criteria violation (ALT was elevated at entry), five patients were on study medication for 4 days (patients were included in PK analysis) and one patient received 3 days of study drug during the second randomized period. The latter patient was dropped from the steady state PK analysis, and was replaced. Three patients failed to complete one blood draw each.

The mean age of the patient population was 63.7 years with a range of 48-79 years. Twenty-one patients (70%) were 61 years old or older. Twenty-one patients (70%) were male and 9 patients (30%) were female. Twenty-five patients (83.3%) were White and five patients (16.7%) were Black. The mean smoking history was 76.8 pack-years with a range of 20-160 pack-years. The mean duration of COPD was 10.2 years with a range from 1-36 years. The mean baseline FEV<sub>1</sub> was 1.13 liters with a mean percent-predicted of 39.8% (range of 17% to 65%).

#### Clinical Pharmacology Outcomes

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This section contains a brief review of the clinical pharmacology results. The reader is referred to Dr. S. Suarez's Clinical Pharmacology and Biopharmaceutics Review, NDA-21-527 for additional information.

Thirty patients were randomized to the study; however, the PK analysis included 29 subjects for the single-dose assessment and 28 subjects for the steady state assessment. [Vol. 91, p. 131]

For the primary PK specified endpoint, following single doses of study drug administration, the 24-hour urine collection contained an average of 5.1 mcg of unchanged ipratropium bromide following HFA-MDI administration and 6.6 mcg of unchanged ipratropium bromide following CFC-MDI administration. The difference of 1.5 mcg was not statistically significant between the two study treatments ( $p=0.1488$ ). Although not statistically different, the urinary excretion tended to be lower following HFA-MDI as compared to CFC-MDI for the 24-hour urine collection, 0-1 hour urine collection at steady state, and 0-6 hour collection at steady state. [Vol. 91, p. 135, 136]

For the other secondary parameters, the systemic exposure was lower following HFA-MDI administration as compared to CFC-MDI. The mean  $C_{max}$  and total AUC were 36% and 27% lower, respectively, following single doses of HFA-MDI administration as compared to CFC-MDI administration. The mean  $C_{max}$  and total AUC were 19% and 26% lower, respectively, following multiple doses of HFA-MDI as compared to CFC-MDI. These results are summarized below in Table 50

Although there was a trend to a higher  $C_{max}$  and  $AUC_{0-6}$  values for patients older than 65 years, the differences were not deemed clinically significant and it was concluded that there is no age effect on PK following repeat doses of HFA-MDI. [Dr. Suarez's Clinical Pharmacology and Biopharmaceutics Review, NDA 21-527]

**Table 73. Study 244.2480, Mean Pharmacokinetic Parameters For Ipratropium Bromide Following Single And Multiple Doses Of Atrovent HFA(3<sup>rd</sup> Generation Product) And Atrovent CFC Given At A Dose Of 84  $\mu$ G Daily For One Week**

Parameter	HFA-MDI 84 $\mu$ g	CFC-MDI 84 $\mu$ g
<b>Single Dose</b>		
AUC <sub>0-6hr</sub> (pg*hr/mL)	196.8	269.4
C <sub>max</sub> (pg/mL)	58.9	92.7
<b>Multiple dose</b>		
AUC <sub>0-6hr</sub> (pg*hr/mL)	265.1	359.5
C <sub>max</sub> (pg/mL)	82.1	101.8
T <sub>max</sub> (hrs)	0.27	0.45
C <sub>min</sub> (pg/mL)	28.2	39.9
C <sub>ss</sub> (pg/mL)	44.2	59.9

Dr. Suarez's Review of NDA 21-527

### Safety Outcomes

All of the thirty randomized patients were included in the safety evaluation; however, one patient discontinued from the study after being treated with Atrovent-HFA and did not receive the CFC-MDI, there are only 29 patients included in the CFC-MDI data set.

Five patients experienced 6 adverse events: 2 patients (6.7%) and 3 patients (10.3%) in the HFA-MDI and CFC-MDI treatment periods, respectively. All reported adverse events occurred in one subject each. The two AEs in the HFA-MDI group were a house hold accident (black eye) and Pancreatitis. One subject had phlebitis reported in the post-treatment period. There were no reported COPD exacerbations during this study. The results are presented below.

**Table 74. Study 244.2480, Number (%) of Patients with AEs during Study Period**

Adverse Event	HFA-84 mcg n=30	CFC-84 mcg n=29	Total n=30
Total with AEs	2 (6.7)	3 (10.3)	5 (16.7)
Household Accident	1 (3.3)	0	1 (3.3)
Influenza-like Illness	0	1 (3.4)	1 (3.3)
Dry Mouth	0	1 (3.4)	1 (3.3)
Pancreatitis	1 (3.3)	0	1 (3.3)
Upper Respiratory Illness	0	1 (3.4)	1 (3.3)

Source: Vol. 91, p. 141

There were no deaths in this study. One patient had a serious adverse event. Patient 311 is a 59 year old white male who had elevated LFTs at the screening visit, which was an entry criteria protocol violation. One day after the patient completed the HFA-MDI randomized period, he developed abdominal pain and was hospitalized with a subsequent diagnosis of Pancreatitis; the patient also developed phlebitis at the site of his PICC line a week later. The patient was discharged from the hospital after resolution of his symptoms; additional history revealed that he was an alcoholic. This reviewer does not feel that this SAE was related to study drug administration.

Overall, there were no clinically meaningful changes in laboratory parameters from the baseline visit to the final visit; with the exception of Patient 311 described above (he had laboratory changes consistent with Pancreatitis). There were no consistent trends in vital signs or clinically meaningful changes in EKGs. [Vol. 91, p. 145]

*Reviewer's comments: No specific safety concerns have arisen from this study.*

**11.5.3. Discussion and Conclusions**

This was a two-center, two-treatment, open-label, randomized, cross-over study designed to compare the pharmacokinetic parameters of 84 mcg of HFA-MDI and 84 mcg of CFC-MDI in COPD patients. The pharmacokinetic analysis reveals that there is less systemic exposure to ipratropium bromide following 84 mcg of HFA-MDI than following 84 mcg of CFC-MDI. This is reassuring since less systemic exposure corresponds to greater systemic safety. No safety concerns have arisen from this study. Overall, this study supports that the 3<sup>rd</sup> generation HFA-MDI product may be safer than the currently marketed CFC-MDI Atrovent product due to lower systemic exposure.

**11.6. Study 244.1401 (U95-0343). Tolerability and Preliminary Pharmacokinetics of Ipratropium Bromide HFA-MDI (4 x 80 mcg) in Comparison to Ipratropium Bromide CFC-MDI (4 X 40 mcg) and placebo HFA-MDI after Multiple Inhalational Administration over 7 Days by Healthy Volunteers**

This was a randomized, double-blind, placebo controlled, three-period cross-over PK study in 12 healthy males and females conducted in Germany to obtain safety, tolerability, and pharmacological activity information after the multiple administration of ipratropium bromide HFA (HFA-MDI), ipratropium bromide CFC (CFC-MDI) and placebo. Subjects were administered HFA-MDI 80 mcg qid, CFC-MDI 40 mcg qid and placebo qid for one week periods, followed by a 7-day washout period, in a cross-over design. The first generation HFA-MDI product was used in this study.

Pharmacodynamic, pharmacokinetic, and safety assessments were made. Airway Resistance (Raw) was measured to assess the pharmacologic effect of the study drug. Blood and urine were collected to assess standard pharmacokinetic parameters. Safety was assessed by adverse event review, vital signs, salivary secretion, pupillometry, hematology, serum chemistries and urinalysis.

A total of 12 subjects were screened for this study, 12 were randomized and 12 completed the study (6 males and 6 females). There were no major protocol violations in this study. The mean age of the study population was 34.5 years (range of 24-46). All subjects were White and healthy as judged by the medical examiners.

The results reveal that the airway resistance diminished to a greater degree in the two active treatment groups as compared to placebo. The median change in Raw from baseline in the two active treatment periods ranged from -19.1 to -31.8 cm H<sub>2</sub>O\*s/l for the HFA-MDI period and -10.9 to 31.9 cm H<sub>2</sub>O\*s/l for the CFC-MDI. The median change from baseline in the placebo group ranged from -5.6 to 3.1 cm H<sub>2</sub>O\*s/l. [Vol. 49, p. 27]

Pharmacokinetic evaluation demonstrated that the systemic exposure was greater in the subjects during the HFA-MDI treatment phase as compared to the CFC-MDI treatment phase. The C<sub>max</sub> was 96.3 pg/mL and 60.3 pg/mL for the HFA-MDI and CFC-MDI treatment periods, respectively. The total AUC was also greater with the HFA-MDI product (64.9 ng·h /mL) than with the CFC-MDI product (35.1 ng·h /mL). No drug accumulation was noted with either of the active treatments. [Dr. Suarez's Clinical Pharmacology and Biopharmaceutics Review, NDA 21-527]

The most common adverse event was bitter taste after inhalation, reported in 12 subjects after receiving HFA-MDI, 10 subjects after receiving CFC-MDI and 2 subjects after receiving placebo. Additionally, an orange taste was reported in four subjects after HFA-MDI, in one subject after CFC-MDI, and in six subjects after placebo. Neither of these effects was severe enough to cause study withdrawal. Tussive irritation was reported in one subject after HFA-MDI administration, in four subjects after CFC-MDI administration and in two subjects after placebo. Cough was reported in only one subject and it occurred during the HFA-MDI treatment period. None of these adverse events were classified as severe. There were no deaths, serious adverse events, or withdrawals secondary to adverse events in this study. There were no clinically meaningful differences in vital signs, laboratory evaluations, EKGs, pupillometry or salivary secretion.

In conclusion, this study demonstrates that the systemic exposure is greater after administration of the 1<sup>st</sup> generation HFA-MDI product in healthy volunteers as compared to the CFC formulation. A bitter/orange taste was the most common adverse event noted in this trial. Based on pupillometry and salivary secretion results, it is suggested that no systemic anticholinergic side effects were noted with either of the active treatments.

**11.7. Study 244.1402 (U96-0020). 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**

This was a double-blind, randomized, placebo-controlled, PK, 4-period crossover study aimed to obtain pharmacokinetic, safety and tolerability information following single inhalational doses of Ipratropium bromide HFA-134a in 12 healthy volunteers aged 21 years or older conducted in Germany.

Subjects received single inhalational doses of ipratropium bromide HFA-MDI 40 mcg, HFA-MDI 80 mcg, CFC-MDI 40 mcg, and HFA-placebo in a crossover fashion with a minimum of a two-day washout period. The 1<sup>st</sup> generation HFA-MDI product was used for this study. Pharmacokinetic assessments were made to include blood and urine testing. Safety assessments included adverse events, vital signs, EKG, and routine laboratory evaluations.

The study enrolled 6 white, healthy males and females with a mean age of 33.0 (range of 27-41 years). No subjects discontinued from the study and there were no major protocol violations in this study.

No valuable pharmacokinetic data from blood sampling was gained from this study since the plasma concentrations of ipratropium bromide were very low in a substantial number of samples. [Vol. 58, p. 41] However, renal excretion was evaluated. The 24 hour cumulative renal excretion of ipratropium bromide for the two HFA-MDI doses was significantly higher than that observed for CFC-MDI; the 40 mcg and 80 mcg HFA-MDI doses resulted in a 1.2 and 1.3 fold greater renal excretion as compared to the CFC-MDI. However, no significant differences in the dose normalized renal excretion for the two HFA doses was noted, suggesting that there is no dose-dependent change in bioavailability of ipratropium bromide HFA. Analysis of HFA-134a parameters suggested that this propellant does not accumulate in the body. [Dr. Suarez's Clinical Pharmacology and Biopharmaceutics Review, NDA 21-527]

As with Study 244.1401, the most common adverse event was bitter taste, which was observed in 5, 4, and 5 subjects during the HFA-MDI 40 mcg, HFA-MDI 80 mcg, and the CFC-MDI 40 mcg treatments. This was noted in none during placebo. Headache was reported in 2 subjects each during each of the HFA-MDI active treatments and placebo and in one subject during the CFC-MDI treatment. Dry mouth was reported in one subject during the CFC-MDI treatment. There were no deaths, serious adverse events, or study withdrawal secondary to adverse events. No clinically meaningful changes in vital signs, physical examination, EKG, or laboratory analyses were noted in this study.

In conclusion, although substantial information from plasma concentrations of study drug was lacking, renal excretion results support the previous study in that the systemic exposure with the HFA-MDI 1<sup>st</sup> generation product is greater than the CFC-MDI product in healthy

volunteers. Bitter taste was noted again as a common side effect. Interestingly, this was not noted as a common AE in Study 244.2480, with the 3<sup>rd</sup> generation HFA-MDI product.

**11.8. Study 244.1407. A Multiple Dose Comparison of Ipratropium Bromide HFA-MDI and Atrovent® MDI in a 12 week, Double-Blind, Parallel Group Study in Patients with Bronchial Asthma**

*Reviewer's comments: This is a Phase III trial in asthmatics, utilizing the first generation ipratropium bromide HFA-MDI product. The sponsor is not seeking an indication for asthma; as such, the review of this study will be brief, with the main focus on safety.*

**11.8.1. Protocol**

The objective of this study was to compare the long-term safety profile and efficacy of ipratropium bromide HFA-MDI with that of the established Atrovent® MDI (CFC) in patients with mild to moderate bronchial asthma over a 12-week period. This was a Phase III, multicenter, randomized, double-blind, active-controlled, parallel group comparison study conducted in 234 patients with mild to moderate asthma in the United Kingdom.

The study population was comprised of 234 males and females, 18-65 years of age, with asthma (baseline FEV<sub>1</sub> ≥ 40% and ≤ 80% predicted) with a smoking history of < 10 pack years on stable pulmonary medication without any other significant concomitant disease. [Vol. 67, p. 226, 236]

Following an initial screening visit (Visit 1), patients entered a two-week open-label run-in period when they received two puffs of Atrovent® CFC-MDI (21 mcg/puff) four times a day. The screening visit was followed by five further visits during the 12-week randomized treatment period. At visit 2, patients were randomized to receive 12 weeks of either ipratropium bromide HFA-MDI or ipratropium bromide CFC-MDI, both administered as two puffs by inhalation four times a day (21 mcg/puff for each inhaled study drug). Salbutamol or terbutaline MDI were allowed as rescue medication. Inhaled corticosteroids, theophylline, sodium cromoglycate, and nedocromil sodium were permitted as chronic asthma controller therapies. Inhaled long-acting beta agonists and oral beta agonists were not permitted in this study.

At Visits 1 and 6, patients underwent a physical examination, EKG, and standard laboratory evaluations. At Visits 2, 4, and 6, 6-hour pulmonary function testing (PFT) and vital signs were done. At all visits, adverse events and concomitant therapy were recorded on the CRFs for all patients. Additionally, all patients were required to record their daily morning and evening peak expiratory flow rates (PEFR) and the use of rescue medication during the previous 12 hours in their diary card.

Although the primary endpoint for this study was safety evaluation, efficacy was also assessed. The efficacy parameters were listed as: switch effect comparisons of morning and evening PEFR (between the two-week run-in period and switch to randomized period), change in baseline PEFR compared with treatment period, FEV<sub>1</sub> AUC<sub>0-6</sub>, FEV<sub>1</sub> max, onset and duration of therapeutic response, time to FEV<sub>1</sub> max, FVC AUC<sub>0-6</sub>, and FVC max. PFT measurements were assessed on days 0, 42, and 84 (Visits 2, 4, and 6) at baseline for that study day, and at 5, 15, 30, 60, 90, and 120 minutes and at hourly intervals thereafter for six hours following the inhalation of two puffs of study drug.

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Safety was assessed via adverse event review, vital signs, physical examination, EKG, laboratory assessments, use of rescue medication, and pre-dose weekly mean morning and evening PEFs. Vital signs were recorded at Visits 1, 2, 4, and 6 at baseline and 60 minutes following study drug administration on PFT testing days (Visits 2, 4, and 6). Laboratory evaluations (complete blood count, serum chemistries, and urinalysis), EKGs and physical examinations were conducted at both the screening and final visit as well.

### 11.8.2. Results

#### 11.8.2.1. Disposition

Of the 299 patients screened, 234 were randomized for study entry, and 211 (90% of randomized) completed the study. In the HFA-MDI and CFC-MDI treatment groups, 143 out of 159 randomized patients (90%), and 68 out of 75 randomized patients (91%), respectively, completed the study. A total of 16 patients (7%) discontinued from the study secondary to AEs; a slightly greater percentage of patients discontinued from the study secondary to AEs in the CFC-MDI treatment group (8%) as compared to the HFA-MDI treatment group (6%). Four patients (5%) and three patients (2%) discontinued secondary to worsening asthma in the CFC-MDI and HFA-MDI treatment groups, respectively. The following table summarizes the patient disposition.

**Table 75. Study 244.1407, Patient Disposition**

	CFC-MDI n (%)	HFA-MDI n (%)	Total n (%)
Total Randomized and Treated	75 (100)	159 (100)	234 (100)
Total Completing Study	68 (91)	143 (90)	211 (90)
Total Withdrawals	7 (9)	16 (10)	23 (10)
<b>Reasons for Withdrawal</b>			
Adverse Event	6 (8)	10 (6)	16 (7)
Worsening of Asthma	4 (5)	3 (2)	7 (3)
Other AE	2 (3)	7 (4)	9 (4)
Non-compliance	0	2 (1)	2 (1)
Lost to Follow-Up	1 (1)	2 (1)	3 (1)
Consent Withdrawn	0	1 (<1)	1 (<1)
Other	0	1 (<1)	1 (<1)

Source: Vol. 67, p. 264

#### 11.8.2.2. Protocol Violations

Protocol violations were characterized into two categories, major and minor. Any protocol violation which may have affected the safety or efficacy data for the patient was termed a major protocol violation. There were 128 patients (55%) who had 183 major protocol violations in the study. The HFA-MDI treatment group had a greater percentage of patients with protocol violations—91 patients (57%) had 128 major protocol violations—as compared to the CFC-MDI treatment group—37 patients (49%) had 55 major protocol violations.

*Reviewer's comments: As the main interest in this study is the safety evaluation, and the sponsor is not seeking an asthma indication, the fact that the HFA-MDI group had greater*

*numbers of protocol violations is not too concerning, since all randomized patients were included in the adverse event evaluation.*

**11.8.2.3. Demographics and Other Baseline Characteristics**

*11.8.2.3.1. Demographics*

Treatment groups were similar at baseline with respect to age, race, height, weight, and asthma duration. There were a greater percentage of females in the HFA-MDI treatment group (60%) as compared to the CFC-MDI treatment group (48%). The mean age of the study population was 44.4 years (range of 18-68). The sponsor does not provide further breakdown of age distribution. The majority of the population was White (96%) and a few were Black (4%). The race distribution was similar between both treatment groups. The Demographics are summarized below in Table 53.

**Table 76. Study 244.1407, Demographics and Baseline Characteristics**

Characteristic		CFC-MDI (n=75) n (%)	HFA-MDI (n=159) n (%)	Total (n=234) n (%)
<b>Sex</b>	Male	39 (52)	64 (40)	103 (44)
	Female	36 (48)	95 (60)	131 (56)
<b>Race</b>	White	73 (97)	152 (96)	225 (96)
	Black	2 (3)	7 (4)	9 (4)
<b>Age (years)</b>	Mean	44.8	44.3	44.4
	Range	22-66	18-68	18-68
<b>Height (cms)</b>	Mean	168.6	166.3	167
	Range	147-193	146-193	146-193
<b>Weight (kg)</b>	Mean	77.8	74.4	75.4
	Range	49-126	47-119	47-126
<b>Asthma History (years)</b>				
	Mean Duration	20.5	19.3	19.7
	Range	0.1-58.6	0.2-61.5	0.1-61.5

Source: Vol. 67, p. 267

*11.8.2.3.2. Baseline Characteristics*

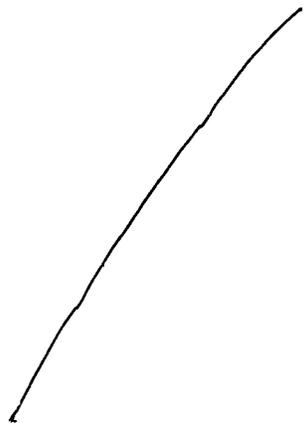
Baseline characteristics were similar between both treatment groups. The mean FEV<sub>1</sub> was 1.97 liters (mean % predicted of 61%) for the CFC-MDI group and 1.91 liters (mean % predicted of 62%) for the HFA-MDI group. Concomitant medication use was also comparable between treatment groups at baseline. The sponsor fails to provide any specific information regarding concomitant medical diagnosis in the narrative portion of this section.

**11.8.2.4. Efficacy Outcomes**

*Reviewer's comments: As the focus for the review of this study is safety, efficacy results are only briefly summarized below.*

Primary Endpoints





**11.8.2.5. Safety Outcomes**

*11.8.2.5.1. Extent of Exposure*

The mean exposure was similar between the two treatment groups, although the CFC-MDI group had a slightly higher exposure (82.9 days) as compared to the HFA-MDI group (80.9 days). Ninety percent of the patients in the CFC-MDI group and 87 percent of the patients in the HFA-MDI group received greater than 11 weeks of treatment in this 12-week study period. The extent of exposure appears adequate. The exposure results are summarized below.

**Table 77. Study 244.1407, Extent of Exposure**

Exposure in Weeks	CFC-MDI (n=75)	HFA-MDI (n=159)
	n (%)	n (%)
up to 1 week	1 (1)	1 (1)
1 to 2	0	2 (1)
2 to 3	1 (1)	3 (2)
3 to 4	1 (1)	1 (1)
4 to 5	0	1 (1)
5 to 6	1 (1)	2 (1)
6 to 7	0	3 (2)
8 to 9	0	1 (1)
9 to 10	0	0
10 to 11	3 (4)	6 (4)
11 to 12	18 (24)	32 (20)
12 to 13	35 (47)	79 (50)
13 to 14	12 (16)	22 (14)
14 to 15	3 (4)	3 (2)
15 to 16	0	2 (1)
Mean Exposure in Days (sd)	82.9 (15.6)	80.9 (18)

Source: Vol. 67, p. 291

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### 11.8.2.5.2. Adverse Events

Of the 234 randomized patients, 158 patients (67.5%) experienced adverse events in this study. In the CFC-MDI group and HFA-MDI group, 52 patients (69.3%) and 106 patients (66.7%), respectively reported adverse events in the study. As expected in an asthma population, the most common adverse events occurred in the respiratory system, with 129 patients (55%) experiencing respiratory system adverse events. The percentage of patients experiencing respiratory adverse events was the same in both treatment groups (55%). The most commonly reported respiratory adverse events were dyspnea, asthma exacerbation, rhinitis, bronchitis, and cough. Dyspnea was reported in 15 patients (20%) and 23 patients (14%) in the CFC-MDI and HFA-MDI treatment groups, respectively. Asthma exacerbation was reported in 11 patients (15%) in the CFC-MDI group and in 21 patients (13%) in the HFA-MDI treatment group. Rhinitis was reported in 13 patients (17%) and in 19 patients (12%) in the CFC-MDI and HFA-MDI treatment groups, respectively. Eight patients (11%) and 22 patients (14%) in the CFC-MDI and HFA-MDI treatment groups, respectively, reported bronchitis. Coughing was reported in similar percentages of patients for both groups (9% in the CFC-MDI and 10% in the HFA-MDI treatment group). The sponsor was particularly interested in the incidence of cough. Most of the reported cough was secondary to URIs or allergic episodes. [Vol. 67, p. 299] The most commonly, non-respiratory reported adverse events were headache and influenza-like symptoms. The results are summarized in the table below.

**Table 78. Study 244.1407, Number (%) of Patients with Adverse Events Occurring at a Greater Incidence than 3% in any Treatment Group**

		CFC-MDI (n=75)	HFA-MDI (n=159)
		n (%)	n (%)
<b>Total with any AE</b>		<b>52 (69.3)</b>	<b>106 (66.7)</b>
<b>General Disorders</b>	Headache	10 (13.3)	25 (15.7)
	Influenza-like symptoms	2 (2.7)	13 (8.2)
<b>Nervous System Disorders</b>	Dysphonia	4 (5.3)	0
<b>Gastrointestinal Disorders</b>	Diarrhea	3 (4.0)	2 (1.3)
	Dry Mouth	3 (4.0)	5 (3.1)
<b>Musculoskeletal Disorders</b>	Myalgia	4 (5.3)	0
<b>Respiratory System Disorders</b>	Asthma	11 (14.7)	21 (13.2)
	Bronchitis	8 (10.7)	22 (13.8)
	Coughing	7 (9.3)	16 (10.1)
	Dyspnea	15 (20)	23 (14.5)
	Pharyngitis	5 (6.7)	11 (6.9)
	Rhinitis	13 (17.3)	19 (11.9)
	URI	4 (5.3)	17 (10.7)

Source: Vol. 69, p.346-351

Bronchospasm was not listed in the table above; however, the incidence was low— 2 patients (3%) in the CFC-MDI group and 2 patients (1%) in the HFA-MDI treatment group had bronchospasm. [Vol. 67, p. 298] However, the incidence of paradoxical bronchospasm, defined as a > 15% fall in FEV<sub>1</sub> below baseline (for any given test day) and/or the need of rescue medication and/or spontaneous reporting by the patient of any event indicative of bronchospasm within 30 minutes following study drug inhalation, was higher. This

occurred in a total of 18 patients (8%), five patients (7%) in the CFC-MDI treatment group, and 13 patients (8%) in the HFA-MDI treatment group. The incidence of this was comparable between both treatment groups. [Vol. 67, p. 296,297]

*Reviewer's comments: Overall, the adverse events occurred at similar frequencies in both groups, and no consistent AEs were observed attributable to HFA-MDI treatment.*

#### Deaths and Serious Adverse Events

There were no deaths reported during this study.

Nine patients had serious adverse events during this study, 4 patients (5.3%) in the CFC-MDI treatment group and 5 patients (3.1%) in the HFA-MDI treatment group. The SAEs in the HFA-MDI group consisted of acute bronchospasm (36 yr old female on day 43), benign intracranial hypertension (61 yr old female on day 1), and asthma exacerbation/infection (64 yr old female on day 56). Two SAEs occurred after study completion: gall bladder calculi (65 yr old female, post-study completion) and abdominal colic (58 yr old female, post-study completion). The SAEs in the CFC-MDI treatment group consisted of acute bronchospasm (30 yr old male on day 43), constipation (73 yr old female on day 56), Hepatitis A (25 yr old male on day 20), and acute asthma (22 yr old female on day 8).

*Reviewer's comments: Aside from bronchospasm and acute asthma, the other SAEs do not appear to be treatment or asthma related. Additionally, in the patient population under study, acute bronchospasm and acute asthma exacerbations are expected. It is doubtful that these were caused by the study drug in this reviewer's opinion.*

#### Withdrawals Due to Adverse Events

There were a total of 16 (7%) withdrawals secondary to AEs, 6 (8%) in the CFC-MDI treatment group 10 (6%) in the HFA-MDI treatment group. The AEs leading to withdrawal in the CFC-MDI treatment group were: asthma exacerbation (2 patients), constipation (1 patient), hepatitis A (1 patient), chest infection (1 patient) and URI (1 patient). The AEs leading to withdrawal in the HFA-MDI group were: acute bronchospasm/acute asthma exacerbation (3 patients), benign intracranial hypertension (1 patient), rash (2 patients), nausea/indigestion/headache (1 patient), mouth ulcers (1 patient), influenza/chest infection (1 patient), and sore dry throat (1 patient).

#### Laboratory Abnormalities, Vitals, EKG, and Rescue Medication Use

No clinically meaningful changes were noted in laboratory evaluations at the final visit as compared to the screening visit. Also, no consistent changes in vitals or EKG were noted between the baseline visit and the final visit. The pattern of rescue medication use was similar between both treatment groups, with a difference of less than 0.3 puffs throughout the study period.

### **11.8.3. Discussion and Conclusions**

This was a 12-week, double-blind, randomized, parallel group trial in 234 males and females ages 18-68 with asthma aimed to compare the safety and efficacy of ipratropium bromide HFA 2 puffs qid (21 mcg/puff) to ipratropium bromide CFC 2 puffs qid (21 mcg/puff).

The two treatment groups were similar at baseline in terms of demographics and baseline spirometry. In terms of efficacy analyses. —————

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Safety analyses revealed that the adverse events were also comparable between the two treatment groups. The most common adverse events were respiratory in nature, which is not unexpected in this patient population. The incidence of paradoxical bronchospasm was comparable between treatment groups. No deaths were reported in the study and the incidence of SAEs was slightly lower in the HFA-MDI treatment group as compared to the CFC-MDI treatment group. No clinically meaningful changes were noted in laboratory evaluations, vital signs, or EKGs. Rescue medication usage was also similar between treatment groups.

In conclusion, this study does not support an efficacy claim in COPD as the patient population under study was asthmatic; however, analysis of safety supports the comparable safety of ipratropium bromide HFA-MDI and ipratropium bromide CFC-MDI in patients 18 to 68 years of age.

**APPEARS THIS WAY  
ON ORIGINAL**

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### DETAILED LABELING CHANGES OR REVISED DRUG LABEL

The label has been preliminarily reviewed. These comments are preliminary labeling comments only and the final labeling comments will be provided once all of the CMC issues have been adequately addressed and this application is nearing approval.

#### Labeling Comments to Sponsor

##### Comment 1

In the *Clinical Studies* section, paragraph 6, delete

##### Comment 2

Under the *Precautions* section, subsection *Pediatrics*, delete

##### Comment 3

In the *Adverse Events* section, recreate Table 3.1:1 to pool the results from all of the three pivotal trials (244.1405, 244.1408, and 244.2453) as done in Source Volume 48, p. 2. It is acceptable to pool the two placebo group results in the modified table.

##### Comment 4

In the *Adverse Events* section, delete the

APPEARS THIS WAY  
ON ORIGINAL

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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.**  
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/s/  
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Tejashri Purohit-Sheth  
9/25/03 01:09:42 PM  
MEDICAL OFFICER

Lydia McClain  
9/25/03 01:24:55 PM  
MEDICAL OFFICER  
I concur. See Team Leader Memo

**MEDICAL OFFICER REVIEW**

**Division Of Pulmonary and Allergy Drug Products (HFD-570)**

<b>APPLICATION:</b> NDA 21-527	<b>TRADE NAME:</b> Atrovent HFA
<b>APPLICANT/SPONSOR:</b> Boehringer Ingelheim	<b>USAN NAME:</b> Ipratropium Bromide Inhalation Aerosol 21 mcg
<b>MEDICAL OFFICER:</b> Tejashri Purohit-Sheth, MD	<b>CATEGORY:</b> Bronchodilator/Anticholinergic
<b>TEAM LEADER:</b> Lydia Gilbert-McClain, MD	<b>ROUTE:</b> Oral Inhalation
<b>DUE DATE:</b> 3 February 2003	

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
9 December 2002	10 December 2002	N-000	Original NDA with 3 pivotal Phase III trials in patients with COPD

**RELATED APPLICATIONS**

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>
	IND 45,938	Original IND for Atrovent HFA

**REVIEW SUMMARY:**

This is an original NDA submitted by Boehringer Ingelheim for the prescription use of Atrovent HFA Inhalation Aerosol, 21 mcg. The proposed indication is for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Boehringer Ingelheim is not seeking an indication for adult or pediatric asthma.

Eleven controlled clinical trials are submitted in support of the safety and efficacy of Atrovent HFA. Four of these trials were placebo controlled and the other 7 were active controlled, to include 2 trials using Atrovent HFA in asthmatics outside the US. This submission is adequate for in-depth review and is fileable.

**OUTSTANDING ISSUES:**

**RECOMMENDED REGULATORY ACTION**

<b>IND/NEW STUDIES:</b>	<input type="checkbox"/> SAFE TO PROCEED	<input type="checkbox"/> CLINICAL HOLD	
<b>NDA/SUPPLEMENTS:</b>	<input checked="" type="checkbox"/> FILEABLE	<input type="checkbox"/> NOT FILEABLE	
	<input type="checkbox"/> APPROVAL	<input type="checkbox"/> APPROVABLE	<input type="checkbox"/> NOT APPROVABLE
<b>OTHER ACTION:</b>			

## I. General Information

Ipratropium bromide is a quaternary ammonium derivative of atropine and has been shown to have bronchodilatory effects when used as an inhalation aerosol. It is currently marketed in several formulations, to include a CFC metered-dose inhaler, a solution formulation, and in combination with albuterol sulfate (Combivent® Inhalation Aerosol).

As CFC propellants are to be phased out as per the Montreal Agreement, the sponsor has submitted this original NDA as a 505(b)1 application for the prescription use of Atrovent HFA. The proposed indication for Atrovent HFA is the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

## II. Regulatory and Foreign Marketing History

### A. Regulatory History

Ipratropium bromide is an approved drug substance under the following NDAs held by Boehringer Ingelheim Pharmaceuticals Inc.:

- NDA 19-085 Atrovent Inhalation Aerosol (CFC)
- NDA 20-393 Atrovent Nasal Spray 0.03%
- NDA 20-394 Atrovent Nasal Spray 0.06%
- NDA 20-228 Atrovent Inhalation Solution
- NDA 20-291 Combivent Inhalation Aerosol (CFC)

[Vol. 1, P. 95]

The development plan for Phase II/III protocols were discussed with the FDA in a pre-IND meeting in December 1992. The initial IND for Atrovent HFA was opened in August 1, 1994 under IND 45,938. An end of Phase II meeting was held with the FDA in 1995, and a Type B meeting was held in May 2000. Clinical and CMC pre-NDA meetings were held in January and March 2002, respectively. [Vol. 1, P2]

### B. Foreign Marketing History

Atrovent HFA has been approved in 9 countries and is currently launched in 2 countries, outside of US. [Vol. 1, P.2] The sponsors state that there have been no withdrawals of marketing applications in any foreign country nor have there been any requests by health authorities for withdrawal or modifications of warnings and /or use section of the Summaries of Product Characteristics for any reason. [Vol. 1, P. 92] The following table summarizes the foreign marketing status of Atrovent HFA.

#### Foreign Marketing Status

Country	Submission	Approval	Launch
Europe			

Country	Submission	Approval	Launch
Belgium/Luxembourg	03 April 2001	14 October 2002	
Denmark	19 March 2001	22 May 2002	
Finland	02 April 2001	08 October 2001	
—	—		
Germany	29 May 2000	29 May 2000	Launch March 2002
Greece	14 March 2001	21 September 2001	
—	—		
—	—		
Netherlands	31 January 2001	14 November 2001	Launch April 2002
—	—		
—	—		
Spain	07 May 2001	24 September 2001	
—	—		
Switzerland	26 March 2001	14 March 2002	
—	—		
<b>Non- European</b>			
—	—		
—	—		
Japan (Teijin)	28 March 2001	15 March 2002	
—	—		
—	—		

Source: Vol. 1, P.93

### III. Items Required for Filing and Reviewer Comments

#### A. Reviewer Comments

This is primarily a non-electronic submission, consisting of 145 original volumes, labeled 1.01-1.45. The electronic section contains mainly the case report tabulations and case report forms.

Boehringer Ingelheim Pharmaceuticals, Inc., is a subsidiary of Boehringer Ingelheim GmbH. This is a privately held company that is not publicly traded on any stock exchange, has no equity available to investigators and does not provide compensation to investigators based on the outcome of studies. No investigators can own a proprietary interest in a product or trademark, licensing agreement or patent owned by the company. Of the 11 studies, only two were conducted as of February 2, 1999 that would be covered by the Financial Disclosure Rule (21 CFR 54). Of all of the disclosure forms returned, there were no investigators that had any financial disclosures; however, there were 3 sub-investigators who did not return the appropriate disclosure forms. Boehringer Ingelheim certifies, based on invoice payment records, that none of these investigators received any grants that exceeded \$25,000. Prior to February 2, 1999, there were 3 COPD efficacy studies and 2 dose-confirmation studies that

would also be covered by 21 CFR 54; however, Boehringer Ingelheim certifies that no investigators had any disclosable financial arrangements with them.

### B. Necessary Elements (21 CFR 314.50)

The sponsor has provided all of the necessary requirements for filing as outlined in the table below.

**Table 1. Necessary Elements**

Item	Type	Status	Location (paper/electronic)
	Application Form (FDA 356h)	Present	Vol. 1, P 4-5
	Formatting for Electronic Filing	N/A	
	Format	N/A	
	Table of Contents / Indexes	N/A	
	Labeling	N/A	
1	Index / Table of Contents	Present	Vol. 1, P 33
2	Samples( if applicable) and Labeling		
	Proposed Package Insert	Present	Vol. 1, P 36
	Proposed Label Text	Present	Vol. 1, P.66-85
	Proposed Medication Guide (if applicable)	N/A	
3	Summary	Present	Vol. 1, P.50-269
	Labeling	Present	Vol. 1, P. 66-85
	Statement of Pharmacologic Class, Scientific Rationale, Intended Use, and Potential Clinical Benefits	Present	Vol. 1. P.86
	Marketing History	Present	Vol. 1, P.92-93
	Chemistry, Manufacturing, & Controls (CMC)	Present	Vol. 1, P.94-122
	Nonclinical Pharmacology and Toxicology	Present	Vol. 1, P.123-135
	Human Pharmacokinetics and Bioavailability	Present	Vol. 1, P.135-137
	Clinical	Present	Vol. 1, P. 139-214
	Benefits vs. Risks	Present	Vol. 1, P.214
4	CMC	Present	Vol. 2-20
	Environmental Impact statement	Categorical Exclusion under 21 CFR 25.31 (b)	Vol. 1, P.19-21
5	Nonclinical Pharmacology and Toxicology	Present	Vol. 21-35
6	Human Pharmacokinetics and Bioavailability	Present	Vol.36-44
8	Clinical	Present	Vol. 45-94
	Controlled studies	Present	Vol. 45-94
	Integrated Summary of Effectiveness	Present	Vol. 46

Item	Type	Status	Location (paper/electronic)
	(subsets for age, gender, and race)		
	Integrated Summary of Safety	Present	Vol. 47
	Potential for Abuse	Present	Vol. 1, P. 214
	Benefits vs. Risks	Present	Vol. 1, P. 215
	Statements of Good Clinical Practice:	Present	Vol. 45, P.22
	Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures	Present	Vol. 45, P.21
	Auditing information	Present	Vol. 45, P.24
9	Safety Updates	N/A	
10	Statistics	Present	Vol. 95-144
11	Case Report Tabulations	Present	<i>Item 11; cr/crttoc.pdf</i>
12	Case Report Forms (for patients who died or did not complete studies)	Present	<i>Item 12; cr/crttoc.pdg</i>
13	Patent Information	Present	Vol. 1, P. 270-271
14	Patent Certification	Present	Vol. 1, P. 272-273
16	Investigator Debarment Certification	Present	Vol. 1, P. 274
17	Field copy certification (if applicable)	Present	Vol.1, P.275
18	User Fee Cover Sheet	Present	Vol.1, P.276-277
19	Financial Disclosure	Present	Vol.1, P.278-280
20	Other		
	Claimed Marketing Exclusivity	N/A	
	Pediatric Use	N/A	

### C. Decision

This application is fileable.

### IV. Clinical Studies

This submission contains 11 controlled studies, 2 are Phase I, 4 are Phase II, and 5 are Phase III. Of the Phase III studies, 3 are conducted in COPD patients, and 2 are conducted in asthmatics. Note that Boehringer Ingelheim is not seeking an indication for asthma.

The 11 studies are outlined in the following two tables, Summary of Pivotal Studies, and Summary of Supporting Studies.

**Table 2. Summary of Pivotal Studies**

Study	Design	Treatment	Patients	Evaluations
244.1405 (US)	Phase III, 12-week, multicenter, randomized, parallel group, double-blind, placebo and active controlled trial in COPD patients age $\geq$ 40 years	Atrovent HFA 21 mcg: 2 puffs QID Atrovent HFA 42 mcg: 2 puffs QID Atrovent CFC 21	507 (602 screened)	<u>Primary Efficacy</u> • FEV <sub>1</sub> AUC <sub>0-6</sub> • Peak FEV <sub>1</sub> Response

Study	Design	Treatment	Patients	Evaluations
		mcg: 2 puffs QID 2 Placebos		Safety Assessments
244.1408 (UK)	Phase III, 12-week, multicenter (16), randomized, double-blind, parallel, active controlled trial in COPD patients age $\geq$ 40 years	Atrovent HFA 21 mcg: 2 puffs QID Atrovent CFC 21 mcg: 2 puffs QID	174 (number screened not mentioned)	<u>Primary Efficacy</u> <ul style="list-style-type: none"> <li>• Pre-dose weekly mean of am and pm PEFrs</li> <li>• PEFR analysis during run-in period and the randomized period</li> <li>• Safety Assessments</li> </ul>
244.2453 (US)	Phase III, 1-year safety, multi-center (19), randomized, open-label, parallel group, active controlled study in COPD patients age $\geq$ 40 years	Atrovent HFA 21 mcg: 2 puffs QID Atrovent CFC 21 mcg: 2 puffs QID	456 (516 screened)	<u>Primary Endpoint</u> Safety <u>Secondary Efficacy Endpoints</u> <ul style="list-style-type: none"> <li>• FEV<sub>1</sub> AUC<sub>0-6</sub></li> <li>• FEV<sub>1</sub> Peak change from test day baseline</li> </ul>

**Table 3. Summary of Supporting Studies**

	Design	Dosage	Patients	Evaluations
244.1401 (Germany)	Phase I, double-blind, placebo controlled, 3-period crossover, safety and tolerability, PK trial in healthy volunteers ( 6 males and 6 females) age > 21 years; treatment duration of 7 days	Atrovent HFA 40 mcg: 4 puffs.QID Atrovent CFC 20 mcg: 4 puffs QID Placebo HFA	12	<ul style="list-style-type: none"> <li>• Airway Resistance</li> <li>• PK</li> <li>• Safety</li> </ul>
244.1402 (Germany)	Phase I, double-blind, 4-way crossover, placebo and active controlled, single dose, pharmacokinetic and safety study in healthy volunteers >21 years of age; treatment duration is 1 day.	Atrovent HFA 20 mcg: 2 puffs Atrovent HFA 40 mcg: 2 puffs HFA placebo Atrovent CFC 20 mcg: 2puffs	12	<ul style="list-style-type: none"> <li>• PK</li> <li>• Safety</li> </ul>
244.1403 (US)	Phase II, randomized, cross-over, double-blind, active and placebo-controlled, balanced incomplete block design dose confirmation study in COPD patients age $\geq$ 40 years; single test doses were administered on each	Atrovent HFA 10.5 mcg: 2 puffs Atrovent HFA 21 mcg: 2 puffs Atrovent HFA 42 mcg:	70	<u>Primary Efficacy</u> <ul style="list-style-type: none"> <li>• FEV<sub>1</sub> AUC<sub>0-4</sub> change from baseline</li> </ul> Safety

	Design	Dosage	Patients	Evaluations
	<p>of 4 test days.</p> <p>Each patient received 4 of the 7 treatments, and 40 patients were to receive test doses of each treatment.</p>	<p>2 puffs</p> <p>Atrovent CFC 10.5 mcg: 2 puffs</p> <p>Atrovent CFC 21 mcg: 2 puffs</p> <p>Placebo HFA</p> <p>Placebo CFC</p>		
244.1404 (France)	Phase II, randomized, double-blind, active controlled, 1 period cross-over, cumulative dose-response study in COPD patients age $\geq$ 40 years; treatment duration of 1 day	<p>Atrovent HFA 20 mcg: *T0: 1 puff T50: 1 puff T100: 2 puffs T150: 4 puffs T200: 8 puffs</p> <p>Atrovent CFC 20 mcg: same as for Atrovent HFA</p> <p>*T= at Time in mins.</p>	31	<p><u>Primary Efficacy</u></p> <ul style="list-style-type: none"> <li>Change from baseline in FEV<sub>1</sub> to 45 mins after last dose</li> </ul> <p>Safety</p>
244.2498 (US)	Phase II, multicenter, double-blind, single-dose, crossover, active and placebo controlled comparability study in COPD patients $\geq$ 40 years	<p>Five, single dose treatments of:</p> <p>Atrovent HFA 21 mcg</p> <p>Atrovent HFA 42 mcg</p> <p>Atrovent CFC 21 mcg</p> <p>Atrovent CFC 42 mcg</p> <p>Placebo for HFA and CFC</p>	41	<p><u>Primary Efficacy Endpoint</u></p> <ul style="list-style-type: none"> <li>Average FEV<sub>1</sub> response calculated as AUC<sub>0-6</sub> compared to baseline</li> </ul> <p>Safety</p>
244.2480 (US)	Phase II, randomized, open-label, 2-treatment, cross-over pharmacokinetic trial in COPD patients age $\geq$ 40 years; duration of 1 week for each treatment	<p>Atrovent HFA 21 mcg: 4 puffs QID days 2-7 (after single dose on day 1)</p> <p>Atrovent HFA 21 mcg: 4 puffs QID days 2-7 (after single dose on day 1)</p>	30	<ul style="list-style-type: none"> <li>PK</li> <li>Safety</li> </ul>
244.1407 (UK)	Phase III, 12-week, multi-center, randomized, parallel group, active controlled trial in asthmatics aged 18-65 years.	<p>Atrovent HFA 21 mcg: 2 puffs QID</p> <p>Atrovent CFC 21 mcg: 2 puffs QID</p>	234	<p><u>Primary Endpoint</u></p> <ul style="list-style-type: none"> <li>Safety</li> </ul> <p><u>Secondary Endpoint</u></p> <ul style="list-style-type: none"> <li>Change from baseline in FEV<sub>1</sub> AUC<sub>0-6</sub></li> <li>FEV<sub>1</sub> max</li> </ul>

	Design	Dosage	Patients	Evaluations

**V. DSI Review / Audit**

After cursory review of this application, a DSI audit is not needed. No discrepancies have been identified at this time. Boehringer Ingelheim is a privately owned company and is not publicly traded, and as such there are no financial disclosures that would necessitate an audit. However, if any irregularity is suspected during the review of this NDA, a DSI audit may be requested.

**VI. Timeline for Review**

**Table 4. Timeline for Review**

Milestone	Target Date for Completion
Stamp Date	December 9, 2003
Study 244.1405	March 20, 2003
Study 244.1408	April 20, 2003
Study 244.2453	May 15, 2003
Study 244.2498	June 1, 2003
Supporting Studies	June 15, 2003
ISS, ISE	July 11, 2003
Label Review	July 18, 2003
Draft Review	August 1, 2003
Wrap-up Meeting	August 15, 2003
Division Goal Date	September 1, 2003
PDUFA Date	October 9, 2003

**VII. Comments to Applicant**

None

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ON ORIGINAL**

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ON ORIGINAL**

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/s/

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Tejashri Purohit-Sheth  
2/3/03 11:54:04 AM  
MEDICAL OFFICER

Lydia McClain  
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