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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21-747, N-020
Priority or Standard	S
Submit Date(s)	04/07/2011
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Division / Office	DPARP/ODEII
Reviewer Name(s)	Xu Wang, M.D., Ph.D.
Review Completion Date	08/20/2011
Established Name	Ipratropium bromide and albuterol sulfate inhalation spray
(Proposed) Trade Name	Combivent Respimat Inhalation Spray
Therapeutic Class	β2 agonist, anticholinergic combination
Applicant	Boehringer Ingelheim
Formulation(s)	Oral inhalation spray
Dosing Regimen	One inhalation (20/100 mcg) four times a day. Patients may take additional inhalations as needed. The total number of inhalations should not exceed six in 24 hours.
Indication(s)	For use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator, who continue to have evidence of bronchospasm, and who require a second bronchodilator
Intended Population(s)	Patients with COPD

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical recommendation for this application is an “Approval” action.

This is a complete response submission for Combivent inhalation spray delivered via the Respimat device. The proposed drug product, Combivent Respimat (20 and 100 mcg of ipratropium bromide and albuterol per actuation, respectively) Inhalation Spray, was developed to replace the currently marketed Combivent Inhalation Aerosol CFC-MDI because of the ongoing CFC phase out of CFC-containing medications in response to the U.S. agreement with the global treaty for removal of substances that damage the ozone layer (i.e., the Montreal Protocol).

The efficacy of Combivent Respimat (20/100 mcg) Inhalation Spray has been demonstrated in the original NDA submission dated October 7, 2008. However, the safety data submitted in the original NDA were not sufficient to support approval. While the safety data evaluated from a 12-week pivotal study for Combivent Respimat (20/100 mcg) Inhalation Spray, a 12-week study for Combivent Respimat 40/200 mcg, and a 6-month study for ipratropium Respimat, revealed no specific safety concerns, the program lacked long term (one year) safety data to evaluate the safety and patient acceptability of Combivent Respimat, especially given the unique nature of the Respimat delivery device. As a replacement for Combivent Inhalation Aerosol CFC-MDI that has been broadly used by patients with COPD, Combivent Respimat (20/100 mcg) Inhalation Spray is expected to be used regularly in COPD patient population. Thus long term safety and patient acceptability data are important to support the approval of the proposed drug product. Therefore, a complete response action was given to the NDA 21-747 original submission on 8/07/2009. The Division stated in the CR letter that "To support approval of Combivent Respimat Inhalation Spray for use in patients with COPD, provide data from a long-term study (or studies) with treatment duration of at least one year." Because of the time line of the CFC phase out and the patients’ need for a product to replace the Combivent Inhalation Aerosol CFC-MDI, the Division decided that interim 24-week safety data from the ongoing one year safety and patient acceptability study can be accepted for the assessment of the long term safety and patient acceptability for the basis of approval and that the final report for the one-year data could be submitted post-approval as a labeling supplement.

In the present complete response submission, the Applicant provided interim 24-week safety data from a long term safety and patient acceptability study. A total of 470 patients with COPD were randomized into 3 treatment groups: Combivent Respimat Inhalation Spray (20/100 mcg), Combivent Inhalation Aerosol CFC-MDI, and the free combination of Atrovent HFA (ipratropium bromide) inhalation aerosol and albuterol

HFA inhalation aerosol. The interim 24-week safety data showed that the scores of performance and patient satisfaction in the Combivent Respimat (20/100 mcg) Inhalation Spray group, as measured by the Patient Satisfaction and Preference Questionnaire (PASAPQ) performance domain, were significantly higher than that in the Combivent Inhalation Aerosol CFC-MDI, and the free combination of Atrovent HFA (ipratropium bromide) Inhalation Aerosol and albuterol HFA inhalation aerosol groups. There are no new safety signals revealed in the interim 24-week data of the long term safety and patient acceptability study. The Applicant also submitted preliminary safety data for the remaining 6 months of the study in June 2011. A preliminary review of the data showed that the data were consistent with the interim 24-week data, and there were no unexpected safety signals and issues of patient satisfaction for Combivent Respimat (20/100 mcg) Inhalation Spray.

1.2 Risk Benefit Assessment

Combivent Respimat (20/100 mcg) Inhalation Spray was developed to replace the currently marketed Combivent Inhalation Aerosol CFC-MDI for use in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator. The proposed drug product consists of Combivent inhalation spray delivered via the Respimat device. Each inhalation delivers 20 mcg ipratropium bromide and 100 mcg albuterol (base) per spray from the mouthpiece.

The efficacy of Combivent Respimat (20/100 mcg) Inhalation Spray has been demonstrated in the original NDA submission dated October 7, 2008 [NDA 21-747 N-000, Clinical Review, 07/02/2009, Xu Wang, M.D., Ph.D.]. However, the safety data submitted in the original NDA were not sufficient to support approval. Safety data were evaluated from a 12-week pivotal study for Combivent Respimat (20/100 mcg) Inhalation Spray, a 12-week study for Combivent Respimat 40/200 mcg, and a 6-month study for ipratropium Respimat. There were no safety signals identified from these studies. However, there were no long term (one year) studies for any Respimat inhaler to evaluate its long term safety and patient acceptability.

In the present complete response submission, the Applicant, as agreed upon with the Division, provided interim 24-week safety data from a long term safety and patient acceptability study. In the study, 470 patients with COPD were randomized into 3 treatment groups: Combivent Respimat (20/100 mcg) Inhalation Spray, Combivent Inhalation Aerosol CFC-MDI, and the free combination of Atrovent HFA (ipratropium bromide) inhalation aerosol and albuterol HFA inhalation aerosol. The interim 24-week data showed that the scores of performance and patient satisfaction in the Combivent Respimat (20/100 mcg) Inhalation Spray group, as measured by the Patient Satisfaction and Preference Questionnaire (PASAPQ) performance domain, were significantly higher than that in the Combivent Inhalation Aerosol CFC-MDI, and the free combination of Atrovent HFA (ipratropium bromide) inhalation aerosol and albuterol

HFA inhalation aerosol groups. There are no new safety signals revealed in the interim 24-week safety data of the long term safety and patient acceptability study. The Applicant submitted preliminary data for the remaining 6 months of the study in June 2011. A preliminary review of the data showed that the data were consistent with the interim 24-week safety data, and there were no unexpected safety signals and issues of patient satisfaction for Combivent Respimat (20/100 mcg) Inhalation Spray. Thus, based on the long-term safety not revealing any new safety concerns and the acceptable patient use data submitted in this Complete Response, there is an acceptable risk benefit assessment for the proposed Combivent Respimat product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant has agreed to submit the final report of the long term safety and patient acceptability study as a labeling supplement after the action date of this complete response submission.

2 Introduction and Regulatory Background

2.1 Product Information

This NDA is submitted in support of Combivent inhalation spray delivered via the Respimat device. The proposed trade name is Combivent Respimat (20/100 mcg) Inhalation Spray.

Combivent inhalation spray is a combination of ipratropium bromide and albuterol sulfate. Ipratropium bromide is an anticholinergic bronchodilator chemically related to atropine. Ipratropium bromide is a white to off-white crystalline substance freely soluble in water and methanol, slightly soluble in ethanol, and insoluble in lipophilic solvent such as ether, chloroform, and fluorocarbons. Albuterol sulfate is a relatively selective beta2 adrenergic agonist bronchodilator. Albuterol is the generic name in the United States. In Europe albuterol is called salbutamol and that is the name used in this NDA submission. Albuterol is a white to off-white crystalline substance freely soluble in water and slightly soluble in ethanol, chloroform, and ether.

The drug product Combivent Respimat (20/100 mcg) Inhalation Spray consists of a sterile aqueous inhalation solution of ipratropium bromide and albuterol sulfate in a 4.5 mL cartridge and a Respimat inhaler. Excipients include water for injection,

benzalkonium chloride, edetate disodium and hydrochloric acid. Respimat inhaler is an oral inhalation device that uses mechanical energy to generate a slow moving aerosol cloud of medication. The cartridge with the inhalation solution and the Respimat inhaler are supplied as two entities in one package. Prior to first use, the patient inserts the cartridge into the device and prime the inhaler. Each inhalation delivers 20 mcg ipratropium bromide/100 mcg albuterol (base) per spray from the mouthpiece.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are several drug classes available for relief of bronchospasm in patients with COPD. These include beta-adrenergic agents, anticholinergic agents, combination beta agonists and anticholinergics, methylxanthines, and combination corticosteroid/long-acting beta agonists. Table 1 listed currently available drugs in the United States for treatment of COPD.

Table 1 Currently available drugs for treatment of COPD

Brand name	Generic name	Drug class	Formulation
Ventolin and others	albuterol	Short-acting β-agonist	MDI, Inhalation solution
Serevent Diskus	salmeterol	Long-action β-agonist	DPI
Foradil Aerolizer	formoterol	Long-action β-agonist	DPI
Brovana	R,R formoterol	Long-action β-agonist	Inhalation solution
Atrovent and others	ipratropium	Short-acting anticholinergic	MDI, Inhalation solution
Spiriva HandiHaler	tiotropium	Long-action anticholinergic	DPI
Many brands	theophylline	methylxanthine	Tablet/capsule/injectable
Combivent	Ipratropium/albuterol	Combination product	MDI
Duoneb and others	Ipratropium/albuterol	Combination product	Inhalation solution
Advair Diskus	Fluticasone/salmeterol	Combination product	DPI

DPI: dry powder inhaler; MDI: metered dose inhaler

2.3 Availability of Proposed Active Ingredient in the United States

Ipratropium bromide is currently marketed as Atrovent inhalation aerosol MDI (NDA 20-393, 20-394), Atrovent HFA-MDI (NDA 21-527) and Atrovent inhalation solution (NDA 20-228) as single ingredient drug, and as an active ingredient of combinations of Duoneb inhalation solution (NDA 20-950) and Combivent Inhalation Aerosol CFC-MDI (20-291). Multiple generic drug products are also available for ipratropium bromide as single ingredient drug products and in combination drug products. Albuterol sulfate is currently marketed as Ventolin HFA-MDI (NDA 20-983), Proair HFA-MDI (NDA 21-457), Proventil HFA-MDI (NDA20-503), and as available as an active ingredient of combinations of Duoneb inhalation solution (NDA 20-950) and Combivent inhalation aerosol MDI (20-291). Multiple generic drug products are also available for albuterol sulfate as single ingredient drug products and in combination drug products. No major safety concerns have been identified post approval for ipratropium bromide and albuterol sulfate products.

2.4 Important Safety Issues With Consideration to Related Drugs

Ipratropium bromide is a short-acting, anticholinergic bronchodilator that is approved for use in patients with COPD. Ipratropium bromide has proved to be relatively safe in the COPD patient population. According to the product label for Atrovent HFA, 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.

Albuterol is approved for use in patients with obstructive airway disease including asthma and COPD. Albuterol is a commonly used short-acting beta2 adrenergic bronchodilator that has proved to be safe in patient with obstructive airway disease. According to the product label for Ventolin HFA, the product, like all other sympathomimetic agents, should be used with caution in patients with underlying cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Immediate hypersensitivity reactions may occur after administration of albuterol sulfate inhalation aerosol, as demonstrated by cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Combivent Respimat (20/100 mcg) Inhalation Spray was developed to replace the currently marketed Combivent Inhalation Aerosol CFC-MDI that is currently the only ipratropium/albuterol MDI marketed in the United State, although several ipratropium/albuterol solutions are available for use with a nebulizer. Because of the ongoing CFC phase out of CFC-containing medications in response to the U.S. agreement with the global treaty for removal of substances that damage the ozone layer (i.e. the Montreal Protocol), the proposed Combivent Respimat is important to the patients who are using Combivent CFC-MDI that will eventually become unavailable after the rule is finalized.

Combivent Inhalation Aerosol CFC-MDI (NDA 20-291) was approved October 24, 1996. The approved dosage of Combivent Inhalation Aerosol CFC-MDI is ipratropium bromide 36 mcg/albuterol sulfate 206 mcg (delivered as two inhalations of 18/103 mcg) four times daily for patients with COPD. (b) (4) . In last 7 - 8 years the Applicant has had several interactions over the study design and endpoints of the clinical trials for Combivent Respimat with the Agency. A Special Protocol Assessment of the pivotal clinical trial for Combivent Respimat submitted and reviewed by the Division in 2001

[IND 57,948, Special Protocol Assessment, Medical Officer Review, Raymond F. Anthracite, M.D., November 7, 2001]. The Phase 3 clinical trial (Study 1012.46) necessary to support approval the planned NDA submission were further discussed in a pre-NDA meeting on September 24, 2003 [IND 57,948, Pre-NDA Package Review, Carol Bosken, M.D., September 30, 2003; IND 57,948, Pre-NDA Meeting Minutes, October 24, 2003].

The clinical trial (Study 1012.46) was completed in 2004. Study 1012.46 was a Phase 3, randomized, double-blind, 12-week, parallel group study in 1,148 patients with COPD. In this study, there were five study medications including both Respimat and CFC placebos: (1) Combivent Respimat 40/200 mcg, (2) Combivent CFC 36/206 mcg, (3) ipratropium Respimat 40 mcg, (4) placebo Respimat, and (5) placebo CFC all administered four times daily. The primary efficacy endpoint was FEV_1 AUC_{0-6} at study day 85. All active treatments were superior to placebo. In addition, there was a numerical separation of Ipratropium Respimat from Combivent Respimat from the 4 hour time point which reached statistical significance at the FEV_1 AUC_{6-8} hour interval. The study results demonstrated that the ipratropium Respimat mono-therapy (treatment 3) comparator produced better FEV_1 values than the Combivent Respimat (treatment 1) at the end of an 8-hour dosing interval on study days 29, 57 and 85, thus not showing the combination was superior to the individual active ingredients. PK data showed that, despite similar nominal doses, there were higher drug exposures from the Respimat device than from the CFC-MDI. (b) (4)

The Applicant therefore developed a lower dosage form of Combivent Respimat (20/100 mcg). Since December 2005 the Division and the Applicant have discussed the study protocol several times [IND 57,948, Meeting Minutes, January 9, 2006; IND 57,948, Meeting Minutes, May 11, 2006; and IND 57,948, Biometrics Review, Feng Zhou, June, 12, 2006]. The proposed pivotal study (Study 1012.56) was similar in study design and endpoints to the Study 1012.46 except for the decreased delivering doses of ipratropium and albuterol. The Division agreed that the study would be a randomized, double-blind, double-dummy, parallel-group, active-control, 12-week study in approximately 1,500 patients with COPD. The patients would be randomized 1:1:1 to receive (1) Combivent Respimat 20/100 mcg plus placebo Combivent CFC-MDI, (2) Combivent CFC-MDI 36/206 mcg plus placebo Combivent Respimat, and (3) ipratropium bromide Respimat 20 mcg plus placebo Combivent CFC-MDI, all administered four times daily. The agreed upon co-primary endpoints, with each having to achieve a 5% level of significance, were:

(1) Non-inferiority of Combivent Respimat 20/100 mcg to Combivent CFC-MDI 36/206 mcg in FEV_1 AUC from 0 to 6 hours at Day 85,

(2) Superiority of Combivent Respimat 20/100 mcg to ipratropium bromide Respimat 20 mcg in FEV_1 AUC from 0 to 4 hours at Day 85 (to assess the albuterol contribution to the combination product), and
(3) Non-inferiority of Combivent Respimat 20/100 mcg to ipratropium bromide Respimat 20 mcg in FEV_1 AUC from 4 to 6 hours at Day 85.

The non-inferiority margin was 50 ml for the lower limit of the confidence interval.
In a pre-NDA meeting on January 16, 2008, the Division accepted the Applicant's plan to submit the NDA with only one pivotal clinical study 1012.56 to support the efficacy of Combivent Respimat with reservations: "The Division does have reservations regarding your plan to perform a single "pivotal" clinical trial especially since previous studies have failed to demonstrate that the combination is superior to each of its components. However, if efficacy findings are robust, a single trial may be sufficient to establish efficacy." [IND 57,948, Pre-NDA Meeting Minutes, February 1, 2008]

The Applicant filed the original NDA for the Combivent Respimat (20/100 mcg) Inhalation Spray on October 7, 2008. In the original submission, the efficacy of Combivent Respimat (20/100 mcg) Inhalation Spray was supported by a 12-week pivotal clinical study in patients with COPD. Pulmonary function of patients with COPD, as evaluated as FEV_1 AUC change from test day baseline, was shown to be positively impacted by treatment with Combivent Respimat (20/100 mcg) Inhalation Spray and by Combivent CFC-MDI 36/206 mcg alike. The primary efficacy endpoints demonstrated that Combivent Respimat (20/100 mcg) Inhalation Spray was non-inferior to Combivent CFC-MDI 36/206 mcg, superior to ipratropium bromide 20 mcg during 0 to 4 hours post-dosing, and non-inferior to ipratropium bromide 20 mcg during 4 to 6 hours post-dosing. The superiority of Combivent Respimat (20/100 mcg) Inhalation Spray to ipratropium bromide 20 mcg during 0 to 4 hours post-dosing demonstrated the efficacious contribution of albuterol component in the combination product. However, the safety data submitted in the original NDA, which consisted of data from the 12-week pivotal study for Combivent Respimat (20/100 mcg) Inhalation Spray, a 12-week study for Combivent Respimat 40/200 mcg, and a 6-month study for ipratropium Respimat, were not sufficient to support approval as the program lacked long-term safety and device use data.

A complete response action was given to the NDA 21-747 original submission on 8/07/2009. The Division stated in the CR letter that "To support approval of Combivent Respimat Inhalation Spray for use in patients with COPD, provide data from a long-term study (or studies) with treatment duration of at least one year." Because of the time line of the CFC phase out and the patients' need for a product to replace the Combivent Inhalation Aerosol CFC-MDI, the Division decided that interim 24-week data from the ongoing one year safety and patient acceptability study can be accepted for the assessment of the long term safety and patient acceptability, provided that the final report of the whole year's data would be submitted on a later date as a labeling supplement.

The present complete response submission was filed on April 7, 2011, providing interim 24-week data of a long term safety and patient acceptability study. The preliminary data from the remaining 6 months of the study was received by the Agency in June 2011.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This is a paper submission. The submission is adequately organized and indexed to allow a review. The review of the data did not reveal any specific irregularities that would raise concerns regarding data integrity. No DSI audit will be requested for the present submission of the interim data report of the long term safety study.

In the previous review cycle, DSI audits were conducted at three study sites where enrolled the largest number of patients in the pivotal phase 3 study. Audit of the site did not show any major irregularities. All studies were conducted in accordance with accepted ethical standards.

3.2 Compliance with Good Clinical Practices

The Applicant stated that the clinical trial was conducted in compliance with the principles laid down in the Declaration of Helsinki (1996 Version), in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP), and in accordance with applicable regulatory requirements [m5, Volume 5.1, Section 5]. The Applicant also provided debarment certification [m1, Volume 1.1, Section 3.3].

3.3 Financial Disclosures

The Applicant provided financial disclosures for investigators participating in the study [m1, Volume 1.1, Section 3.4]. The investigators did not have financial interests requiring disclosure.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The product Combivent Respimat consists of a sterile aqueous inhalation solution of ipratropium bromide and albuterol sulfate in a 4.5 mL cartridge and a Respimat inhaler. Respimat inhaler is a novel oral inhalation device that uses mechanical energy to generate a slow moving aerosol cloud of medication. The cartridge with the inhalation solution and the Respimat inhaler are supplied as two entities in one package. Prior to first use, the patient inserts the cartridge into the device and prime the inhaler.

The cartridge that contains the drug solution consists of (b) (4) an aluminum cylinder (b) (4)) and a tamper protection seal. (b) (4)

Being a novel device, the Respimat inhaler was developed with several interim versions. For Combivent Respimat, two versions of the device are of importance: the Respimat version A4 – it has been used in the phase 3 program, delivering 40 mcg of ipratropium bromide and 200 mcg of albuterol per actuation. the Respimat version A5, which is intended for the commercial product; it has been used in primary stability studies and in phase 3 program, delivering 20 mcg ipratropium bromide/100 mcg albuterol (base) per spray from the mouthpiece. (b) (4) . The Respimat A5 inhaler is the final inhaler intended to be marketed, and used in the long term safety and patient acceptability study.

The inhalation solution in an unopened cartridge is sterile. (b) (4) manufacturing has been chosen and has been assured by validation. (b) (4) (b) (4) . In addition to sterility testing of the unopened

cartridge, (b) (4) test is also performed and validated to assure microbial control.

Detailed CMC information can be found in ONDQA Review [NDA 21-747, ONDQA Review, Edwin Jao, Ph.D.].

4.2 Clinical Microbiology

No clinical microbiology data is applicable to this NDA.

4.3 Preclinical Pharmacology/Toxicology

This Application was submitted under Section 505(b)(2) of the Food, Drug & Cosmetic Act, which permits that the submission relies on the Agency's previous pre-clinical and clinical findings to support the approval of the propose drug product.

There were no new animal pharmacology data in this submission. There were no new genetic toxicity data, carcinogenicity data, or reproductive toxicology data in this submission. The relevant toxicology data for albuterol and ipratropium had been reviewed and considered previously in setting acceptable specifications in other products. Overall, the pharmacology and toxicology review team concluded that the application has submitted adequate nonclinical safety data to support registration of Combivent Respimat Inhalation Sprays, the available nonclinical data are considered supportive of the intended use of Combivent Respimat Inhalation Sprays, and the approval of the application is recommended from the nonclinical perspective [NDA 21-747, Pharmacology and Toxicology Review, Luqi Pei, Ph.D.].

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Ipratropium bromide is an anticholinergic (parasympatholytic) agent which, based on animal studies, appears to inhibit vagally-mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released at the neuromuscular junctions in the lung. Albuterol is a short-acting β_2-adrenergic receptor agonist used for the relief of bronchospasm. Activation of β_2-adrenergic receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in the intracellular concentration of cyclic AMP. This increase of cyclic AMP leads to the lowering of intracellular ionic calcium concentrations, resulting in relaxation. Albuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles.

4.4.2 Pharmacodynamics

No new pharmacodynamic data are included in the present submission. Since Combivent Respimat is an inhalation spray intended for local effect in the pulmonary tract, pharmacodynamic relationships for efficacy with regard to blood levels are not informative.

4.4.3 Pharmacokinetics

There are no pharmacokinetic data in the present complete response submission. The pharmacokinetics of Combivent Respimat (20/100 mcg) Inhalation Spray has been reviewed and compared to currently approved Combivent Inhalation Aerosol CFC MDI in the previous review cycle. Detailed information can be found in the Clinical Pharmacology Review [NDA 21-747, Clinical Pharmacology Review, Partha Roy, Ph.D.].

Briefly, in the 162 patients the ipratropium systemic exposure in three treatment groups was comparable, as evaluated by AUC_{0-6} and Cmax. Plasma albuterol PK parameters were obtained in 108 patients. In the 52 patients who received Combivent Respimat (20/100 mcg) Inhalation Spray the albuterol AUC_{0-6} and Cmax were approximately 75% of those in the 56 patients who received Combivent Inhalation Aerosol CFC-MDI 36/206 mcg treatment. Since Combivent Respimat is an inhalation spray intended for local effect in the pulmonary tract, the pharmacokinetic profile is primarily useful for safety determination (Table 2). With the comparable systemic exposure for ipratropium and lower systemic exposure for albuterol comparing to the approved drug product Combivent CFC-MDI, the test drug product Combivent Respimat (20/100 mcg) Inhalation Spray should not pose additional systemic safety problems comparing to the approved and marketed drug product.

Table 2 Plasma PK parameters for ipratropium and albuterol in COPD patients

PK parameter	Combivent Respimat 20/100 mcg (A) N=52	Combivent CFC-MDI 36/206 mcg (B) N=56	Ipratropium Respimat 20 mcg (C) N=54	Ratio of means	
				A/B	A/C
Ipratropium					
AUC_{0-6} (h.pg/mL)					
Mean	127.51	122.59	115.42	1.04	1.10
(90% CI)	(110.24, 147.48)	(106.97, 140.50)	(100.57, 132.47)		
Cmax (pg/mL)					
Mean	33.46	33.80	35.11	0.99	0.95
(90% CI)	(28.94, 38.69)	(29.40, 38.86)	(30.54, 40.37)		
Cmin (pg/mL)					
Mean	15.25	16.08	14.84	0.95	1.03
(90% CI)	(13.76, 16.92)	(14.56, 17.76)	(13.43, 16.39)		
Albuterol					
AUC_{0-6} (h.ng/mL)					
Mean	4.09	5.52	---	0.74	---
(90% CI)	(3.54, 4.72)	(4.82, 6.34)	---		

Cmax (ng/mL)					
Mean	0.91	1,20	---	0.76	---
(90% CI)	(0.79, 1.04)	(1.05, 1.37)	---		
Cmin (ng/mL)					
Mean	0.43	0.60	---	0.71	---
(90% CI)	(0.36, 0.52)	(0.51, 0.72)	---		

(Source: Volume 5.19, Section 5.3.5.1, p147-150)

5 Sources of Clinical Data

The source of clinical data in this review is the interim 24-week safety data report from a one year long term safety and patient acceptance study (1012.62). Based on the agreement between the Agency and the sponsor, the data from the remaining 6 months should be submitted at least 4 weeks before the action date in order for the Division to have an overall assessment of the safety data for the entire 12 months prior to taking action. The Applicant submitted the preliminary data from the remaining 6 months of the study in June, 2011.

5.1 Tables of Studies/Clinical Trials

Table 3 Summary of clinical study reviewed in this application

Study #	Study type	Treatment groups	Number of subjects	Treatment duration	Study design	Diagnosis, age of subjects
1012.62	Long term safety and patient acceptability study	Combivent R* 20/100 mcg, QID Combivent CFC-MDI 36/206 mcg, QID Atrovent HFA 34 + Albuterol HFA 180 mcg, QID	157/157** 156/154 157/154	48 weeks (24 weeks for interim data analysis)	Randomized, open-label, long term safety and patient acceptability study	COPD 62.9 years (mean age)

* Respimat; ** entered/treated

5.2 Review Strategy

This is a review of the interim 24-week safety data from a one year long term safety and patient acceptability study. The preliminary data from the remaining 6 months of the study will also be examined to have an overall assessment of the safety and patient acceptability of the proposed drug product.

5.3 Discussion of Individual Studies/Clinical Trials

The long term safety and patient acceptability study (1012.62) was initiated November 5, 2009, (b) (4)

This 6-month interim report was completed February 3, 2011 by Mo Ghafouri Ph.D., Luyan Dai Ph.D., (b) (4) at Boehringer Ingelheim Pharmaceuticals, Inc. at Ridgefield, CT 06877.

The study was a Phase 3, one-year, randomized, open-label safety and patient acceptability study of Combivent Respimat (20/100 mcg) Inhalation Spray in comparison to Combivent Inhalation Aerosol (36/206 mcg) CFC-MDI and the free combination of Atrovent HFA (ipratropium bromide 34 mcg) Inhalation Aerosol and albuterol HFA inhalation aerosol (180 mcg) in patients with COPD. A total of 688 COPD patients enrolled into the study and 470 patients were randomized into following 3 treatment groups: (1) Combivent Respimat Inhalation Spray (each actuation delivered 20 mcg ipratropium bromide and 100 mcg albuterol base, equivalent to 120 mcg albuterol sulfate, from the mouthpiece) four times daily, each Combivent Respimat contains 120 actuations; (2) Combivent Inhalation Aerosol CFC-MDI (two actuations, each actuation delivered 18 mcg ipratropium bromide and 103 mcg albuterol sulfate, equivalent to 90 mcg albuterol base, from the mouthpiece) four times daily, each Combivent Inhalation Aerosol CFC-MDI contains 200 actuations; and (3) Atrovent HFA (two actuations, each actuation delivered 17 mcg ipratropium bromide from the mouthpiece) plus Ventolin HFA (two actuations, each actuation delivered 103 mcg albuterol sulfate, equivalent to 90 mcg albuterol base, from the mouthpiece) four times daily, both Atrovent HFA and Ventolin HFA contain 200 actuations.

The primary objective of this study is to evaluate long-term safety and patient acceptability of Combivent Respimat (20/100 mcg) Inhalation Spray. The study protocol stated that to identify any adverse event with incidence rate of at least 2%, a sample size of 150 patients per treatment group will give at least 95% chance to observe at least one patient with that adverse event. From the estimation based on a previous 12-week study on Combivent Respimat (20/100 mcg) Inhalation Spray and Combivent Inhalation Aerosol CFC-MDI, the mean Performance domain score of Patient Satisfaction and Preference Questionnaire (PASAPQ) would be 70 and the standard deviation would be 20 for the Combivent Respimat Inhalation Spray group after 48 weeks on treatment. A sample size of 150 patients per treatment group would be able to detect an 8-point difference in the Performance domain score between the two treatment groups with 90% power and using a two-sided 5% significance level, assuming a mean Performance domain score of 70 for the Combivent Respimat Inhalation Spray group and a standard deviation of 20 (two sample t-test).

Patient inclusion criteria included ≥40 years of age, being a current smoker or ex-smoker with a history of ≥pack-years, and diagnosed COPD with a post-bronchodilator

FEV1 ≤80% of predicted normal and FEV_1/FVC ≤70%. Predicted normal values are calculated following European Coal and Steel Community (ECSC) equations:

Males: FEV1 predicted (L) = 4.30 x (height (inch)/39.37) - 0.029 x age (yr) - 2.49
Females: FEV1 predicted (L) = 3.95 x (height (inch)/39.37) - 0.025 x age (yr) - 2.60
Or
Males: FEV1 predicted (L) = 4.30 x (height (meter)) - 0.029 x age (yr) - 2.49
Females: FEV1 predicted (L) = 3.95 x (height (meter)) - 0.025 x age (yr) - 2.60

Exclusion criteria included significant diseases other than COPD (i.e. myocardial infarction, heart failure, life-threatening cardiac arrhythmia, malignancy except for fully cured squamous cell carcinoma or treated basal cell carcinoma, cystic fibrosis, bronchiectasis, asthma, tuberculosis), history of thoracotomy with pulmonary resection, history of significant alcohol or drug abuse, oxygen therapy for >1 hour per day (except for CPAP for sleep apnea, using beta blockers except for the treatment of non-narrow angle glaucoma, using corticosteroids at a dose in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day, pregnant or nursing women, known hypersensitivity to anticholinergic drugs or any component of the test drugs, participating in any pulmonary rehabilitation program or scheduled to participate in any such program during the study period.

The primary analysis of this interim report was the comparison of patient acceptability between the Combivent Respimat (20/100 mcg) Inhalation Spray and the Combivent Inhalation Aerosol (36/206 mcg) CFC-MDI groups in terms of the Performance domain score using Patient Satisfaction and Preference Questionnaire (PASAPQ) at 24 weeks. The questionnaire consists of 15 answers to the question “How satisfied are you:”

1).with the overall feeling of inhaling your medicine?
2). with the feeling that the inhaled dose goes to your lungs?
3). that you can tell the amount of medication left in your inhaler?
4). that the inhaler works reliably?
5). with the ease of inhaling a dose from the inhaler?
6). with the instructions for use?
7). with the size of your inhaler?
8). that the inhaler is durable (hard wearing)?
9). with the ease of cleaning your inhaler?
10). with using the inhaler?
11). with the speed at which medicine comes out of the inhaler?
12). with the ease of holding the inhaler during use?
13). with the overall convenience of carrying the inhaler with you?
14). Overall, how satisfied are you with your inhaler?

15). Please indicate your willingness to continue using the inhaler that you used during the study by providing a value between 0 indicating that you would not be willing to continue using this inhaler and 100 indicating that you would definitely be willing to continue.

The answers are measured using a 7-point scale for questions 1 to 14 (1 means very dissatisfied and 7 means very satisfied) and a 100-point scale for question 15. The first 13 questions generate the Performance domain (7 questions: Q1-5 and Q10-11) and the Total Score domain (all 13 questions). Question 14 asks for overall satisfaction with the device used in the study, and Question 15 asks for willingness to continue with the device used in the study.

Secondary analyses included dropout rate, other PASAPQ scores (such as total score, Scores for individual questions), Clinical COPD questionnaire (CCQ), Physician's Global Evaluation, COPD exacerbation, rescue medication use, FEV_1 and FVC change from test-day baseline. Physician's Global Evaluation is an overall evaluation of the patient condition at a 1 to 8 scale with 1 representing the poorest and 8 the excellent condition. A COPD exacerbation was defined as a complex of lower respiratory events symptoms (increase or new onset) related to the underlying COPD, with the duration of 3 days or more, requiring a change in treatment. The complex of lower respiratory events / symptoms comprised at least 2 of the following: shortness of breath, sputum production (volume), occurrence of purulent sputum, cough, wheezing, and chest tightness. CCQ contains 10 questions about the airway symptoms and overall health of the past week. The answers to the questions are measured using a 0 to 6 scale with 0 as never, 1 as hardly ever, 2 as a few times, 3 as several times, 4 as many times, 5 as great many times, and 6 as almost all the time. The 10 questions are listed below:

On average, during the past week, how often did you feel:

- Short of breath at rest?
- Short of breath doing physical activities?
- Concerned about getting a cold or your breathing getting worse?
- Depressed (down) because of your breathing problem?
- Did you cough?
- Did you produce phlegm?

On average, during the past week, how limited were you in these activities because of your breathing problems?

- Strenuous physical activities (such as climbing stairs, hurrying, doing sports)?
- Moderate physical activities (such as walking, housework, carrying things)?
- Daily activity at home (such as dressing, washing yourself)?
- Social activities (such as talking, being with children, visiting friends/relatives)?

The study flow chart is shown in Table 4 below. The study subjects were to visit clinical centers 7 times during this study. Detailed written instructions and training for the use of the MDI and Respimat inhalers were given to the patient at Visit 1 and Visit 2. Patients were instructed on how to prepare the inhaler for use (including inserting the cartridge into the inhaler and priming the unit) and using the Combivent Respimat

inhaler. The MDIs were dispensed in their commercial packaging; and patients were re-trained as necessary on the correct priming technique in preparation for use, and use and care of each MDI. Patients who were randomized to Atrovent HFA/albuterol HFA were instructed to use albuterol first, then Atrovent. Patients were to assemble (Combivent Respimat only), prime and care for their inhalers at home between visits. Patients were requested to self-administer the inhalations from the Respimat inhaler or MDI 4 times daily at approximately equally spaced intervals: upon arising, mid-day, early evening, and prior to retiring. At all subsequent visits, the investigator or qualified study personnel observed the inhalation procedure and reinforced the correct inhalation technique. Additionally, routine phone calls were made between visits to patients as a safety check, as well as to assess their understanding of proper inhalation and device utilization. The patient recorded the daily doses (number of puffs) of test medication in a patient specific diary card. If a patient missed a dose, that dose was to be taken at the next scheduled time and the missed dose noted in the Daily Diary Card.

At every clinic visit, a new inhaler was put into use by the patient regardless of the amount remaining in the currently used inhaler. The new inhaler was to be used to administer test-drug for pulmonary function testing. Each newly dispensed inhaler was to be assembled (Combivent Respimat only) and prepared for first use by the patient under the observation of qualified study personnel prior to administration of the dose, including priming of the inhaler according to labeled instructions. At each clinic visit, oral inhalation of 2 puffs of the Combivent CFC-MDI, or 2 puffs of Atrovent HFA and 2 puffs of albuterol HFA, or 1 puff of the Combivent Respimat was to be self-administered by the patient in a seated position under the direct supervision of the investigating physician or qualified study personnel. Enough medication was to be dispensed (including reserve inhalers) by the study staff to the patient at each visit to last until the subsequent visit. All used and unused trial medication was to be returned to the clinic at the next visit. Any inhaler that was reported to have malfunctioned by the patient or study staff was to be returned to BI for further investigation.

Table 4 Study 1012.62 flow chart

	Screening / Baseline	**Treatment period**					
Visit	1	2	3	4	5	6	7
Test day	-28 to -21	1	22 ± 5	85 ± 5	169 ± 5	253 ± 5	337 ± 5
Weeks on therapy	-4 to -3	0	3	12	24	36	48
Informed consent	X						
Demographics	X	X					
Medical history	X	X					
MDI training	X						
Respimat inhaler training		X					
Physical exam (with vital signs)	X	X			X		X
12-lead ECG	X						
Dispense drug for baseline	X						

Serum pregnancy test	X	X		X	X	X	X
Collect drug for baseline period		X					
Randomization		X					
PFT[#]	X	X		X	X		X
Inclusion/exclusion criteria	X	X					
Dispense daily patient record	X	X	X	X	X	X	
Collect & review daily pt record		X	X	X	X	X	X
Dispense rescue albuterol MDI	X	X	X	X	X	X	
Review e-diary patient record		X	X	X	X	X	X
Dispense investigational drugs		X	X	X	X	X	
Collect investigational drugs			X	X	X	X	X
Adverse events	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X
PASAPQ[$]		X	X	X	X	X	X
CCQ[%]		X	X	X	X	X	X
Physician's global evaluation		X	X	X	X	X	X
Drug accountability check		X	X	X	X	X	X
Treatment compliance		X	X	X	X	X	X
Follow-up phone calls*							

(Source: m5, Volume 5.1, pages 53-54)
Pulmonary Function Test, performed at 15 minutes before and 1 hour post the treatment
$ Patient satisfaction and Preference Questionnaire
% Clinical COPD Questionnaire
* At weeks 8, 16, 20, 28, 32, 40, and 44

Administration of albuterol as rescue medication was allowed at any time during the study. A different brand of albuterol MDI (other than the study medication) was provided for rescue, and the number of puffs used for rescue was to be recorded by the patient in the Daily Diary Card.

The following medications were allowed for control of acute exacerbations during the treatment period:

- PRN albuterol inhalation aerosol (MDI) (provided by BI and its use to be recorded on the Patient Daily Diary Card);
- Temporary increases in the dose of theophylline preparations of up to 7 days each were allowed during the study. If the increases or additions occurred prior to pulmonary function testing days, the testing was to be postponed for 2 days or to a maximum of 7 days after the last increased or additional dose was given;
- Addition of oral steroids or temporary increases in the dose of steroids up to 7 days was allowed during the study. Pulmonary function testing was not to occur within 7 days of the last administered dose in the case of a steroid increase or addition. Pulmonary function testing was to be postponed up to 14 days to meet this restriction;

- The use of antibiotics was not restricted and was to be used as medically necessary for exacerbations and other infections.

The following medications (other than the study medications) were not allowed during the baseline period or the treatment period:

- Short acting anti-cholinergic drugs including additional Atrovent Inhalation Aerosol and Atrovent Inhalation Solution by oral inhalation and for use in treating the common cold, Atrovent Nasal Spray 0.06%;
- 2. Additional Combivent Inhalation Aerosol or combination ipratropium bromide/ albuterol solution for nebulization;
- Oral beta adrenergics or long acting beta adrenergics such as salmeterol and formoterol;
- Short acting beta agonist other than the provided albuterol MDI;
- Long-acting anticholinergic.

Treatment compliance was checked by the number of puffs taken of study medications into the Daily Diary Card. The investigator/study staff reviewed these records with the patient at each study visit to assess treatment compliance. The investigator / study staff also examined the inhalers use since last visit. The Combivent Respimat dose indicator was monitored for concurrence with the diary. Patients were to have used at least 1 inhaler per month.

6 Review of Efficacy

Efficacy Summary

No efficacy assessment was conducted or required in the present complete response submission. The efficacy of Combivent Respimat (20/100 mcg) Inhalation Spray has been demonstrated in the original NDA submission dated October 7, 2008. In the original submission, the efficacy of Combivent Respimat (20/100 mcg) Inhalation Spray was supported by a 12-week pivotal clinical study in patients with COPD. Pulmonary function of patients with COPD, as evaluated as FEV_1 AUC change from test day baseline, was shown to be positively impacted by treatment with Combivent Respimat 20/100 mcg Inhalation Spray and by Combivent CFC-MDI 36/206 mcg alike. The primary efficacy endpoints demonstrated that Combivent Respimat (20/100 mcg) Inhalation Spray was non-inferior to Combivent CFC-MDI 36/206 mcg, superior to ipratropium bromide 20 mcg during 0 to 4 hours post-dosing, and non-inferior to ipratropium bromide 20 mcg during 4 to 6 hours post-dosing. The superiority of Combivent Respimat 20/100 mcg Inhalation Spray to ipratropium bromide 20 mcg during 0 to 4 hours post-dosing demonstrated the efficacious contribution of albuterol component in the combination product. The study results were robust. Based on the agreement between the Applicant and the Division in pre-NDA meetings, the efficacy

data from one pivotal study are sufficient to form the basis of approval for Combivent Respimat (20/100 mcg) Inhalation Spray for the proposed indication in patients with COPD. For a detailed discussion of efficacy demonstrated for the Combivent Respimat product see the primary clinical review for NDA 21-747 N-000 by Xu Wang, M.D., Ph.D., dated 07/02/2009.

6.1 Indication

The proposed indication is stated as "Combivent Respimat is indicated for patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator."

7 Review of Safety

Safety Summary

In the review cycle of the original NDA, the safety data were evaluated from a 12-week pivotal study for Combivent Respimat (20/100 mcg) Inhalation Spray, a 12-week study for Combivent Respimat 40/200 mcg, and a 6-month study for ipratropium Respimat. There were no safety signals identified from these studies.

In the present complete response submission, the Applicant provided interim 24-week data from a long term safety and patient acceptability study. In the study, 470 patients with COPD were randomized into 3 treatment groups: Combivent Respimat (20/100 mcg) Inhalation Spray, Combivent Inhalation Aerosol CFC-MDI, and the free combination of Atrovent HFA (ipratropium bromide) Inhalation Aerosol and albuterol HFA inhalation aerosol. The interim 24-week data showed that the scores of performance and patient satisfaction in the Combivent Respimat (20/100 mcg) Inhalation Spray group, as measured by the Patient Satisfaction and Preference Questionnaire (PASAPQ) performance domain, were significantly higher than that in the Combivent Inhalation Aerosol CFC-MDI, and the free combination of Atrovent HFA (ipratropium bromide) Inhalation Aerosol and albuterol HFA inhalation aerosol groups. There are no new safety signals revealed in the interim 24-week data of the long term safety and patient acceptability study. The Applicant submitted preliminary data for the remaining 6 months of the study in June 2011. A preliminary review showed that the one year's safety data were consistent with the interim 24-week data, and there were no unexpected safety signals and issues of patient satisfaction for Combivent Respimat (20/100 mcg) Inhalation Spray.

Since there is no Respimat product approved for marketing in the United States, the Applicant provided post-marketing experience reports for two Respimat product approved in Europe (Berodual Respimat and Spiriva Respimat). The post-marketing data cover the period from 2004 to June 2010, and reveal no new safety signals or patient acceptability issues for the 2 Respimat products.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This safety review included safety and patient acceptability data from interim 24-week safety data from a one year long term safety and patient acceptability study and the post-marketing experience reports for two Respimat products approved in Europe (Berodual Respimat and Spiriva Respimat). The preliminary data from the remaining 6 months of the study is also evaluated.

7.1.2 Categorization of Adverse Events

The applicant's categorization of AE data by system, organ, class and preferred term according to the MedDRA dictionary version 13.1 were appropriately coded. The AE categorization and preferred terms in the study was appropriate to classify the AEs in the patients with COPD. Because of the extensive safety database with the marketed Combivent CFC product, specific safety assessments such as ECGs and laboratory tests were not required. Spirometry was, however, monitored throughout the study.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable. The Applicant submitted interim 24-week data from a long term safety and patient acceptability study only.

7.2 Adequacy of Safety Assessments

The interim 24-week safety data of the one year long term safety and patient acceptability study are reviewed. Also the preliminary review is performed for the preliminary data of the remaining 6 months study period. The clinical experience is adequate to evaluate the long term safety and patient acceptability of the proposed drug product [Guidance fro Industry Points to Consider: Clinical Development Program for MDI and DPI Drug Products. September 19, 1994].

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 465 patients were randomized and received at least one dose of study medication. There were 157 received Combivent Respimat (20/100 mcg), 154 received Combivent CFC-MDI 36/206 mcg and 154 received Atrovent 34 mcg + Ventolin 180 mcg. The mean and median exposures for the interim safety analysis for all treatment groups were 245.9 and 261 days, respectively. The total patient exposure days for Combivent Respimat 20/100 mcg, Combivent CFC-MDI 36/206 mcg, and the free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA (180 mcg) were 39,727, 38,941, and 35,666, respectively. Mean exposures in Combivent Respimat (20/100 mcg) Inhalation Spray and in Combivent Inhalation Aerosol (36/206 mcg) were similar (253 and 252.9 days, respectively). There was a less exposure to the free combination of Atrovent HFA (ipratropium bromide 34 mcg) Inhalation Aerosol and albuterol HFA inhalation aerosol (180 mcg) treatment (231.6 days). Table 5 below lists the total and group exposure to the trial medications.

Table 5 Exposure to trial medications, study 1012.62

Exposure	Total	Combivent Respimat 20/100	Combivent CFC-MDI 36/206	Atrovent 34 + Ventolin 180
Total treated patients	465	157	154	154
Treatment duration: days (%)				
1-14 days	9 (1.9)	4 (0.8)	2 (0.4)	2 (0.4)
15-42 days	12 (2.6)	7 (1.4)	7 (1.4)	12 (2.5)
43-70 days	11 (2.4)	24 (4.9)	21 (4.3)	29 (6.0)
71-168 days	33 (7.1)	16 (3.3)	17 (3.5)	17 (3.5)
169-252 days	149 (32.0)	435 (89.5)	444 (90.4)	423 (87.6)
253-322 days	171 (36.8)			
>322 days	80 (17.2)			
Exposure (days) Sum	114334	39727	38941	35666
Mean	245.9	253	252.9	231.6
Median	261	274	264	252

(Source: m5, Volume 5.1, p87)

Demographics and basic characteristics of patients in the study

Patients' baseline demographic information is summarized in Table 6. Overall, 58.7% and 41.3% of the treated patients are males and females, respectively. In terms of race or ethnic groups, 93.5% of the patients are white. The African American and Asian/Native American are 6.2% and 0.2% of the study patients, respectively. The average age among of the patient population is 62.9 years old. Over 50% of the patients are in the range from 40 to 64 years old. The average smoking history is 54.3 pack-years, and the mean COPD duration is 7.6 years. The three treatment groups are comparable with respect to the baseline demographic characteristics.

Table 6 Summary of patient demographics, study 1012.62

Demographics	Total N (%)	Combivent Respimat 20/100 N (%)	Combivent MDI 36/206 N (%)	Atrovent 34 plus Ventolin 180 N (%)
Total treated	465	157	154	154
Sex Male	273 (58.7)	92 (58.6)	84 (54.5)	97 (63.0)
Female	192 (41.3)	65 (41.4)	70 (45.5)	57 (37.0)
Race White	435 (93.5)	148 (94.3)	143 (92.9)	144 (93.5)
Black	29 (6.2)	9 (5.7)	11 (7.1)	9 (5.8)
Asian/Native American	1 (0.2)	0	0	1 (0.6)
Age Mean (years)	62.9	63.0	62.6	63.0
40 - 64 years	263 (56.6)	90 (57.3)	91 (59.1)	82 (53.2)
65 – 74 years	156 (33.5)	51 (32.5)	47 (30.5)	58 (37.7)
≥75 years	46 (9.9)	16 (10.2)	16 (10.4)	14 (9.1)
Height Mean (cm)	170.8	170.6	170.6	171.1
Smoking history				
Ex-smoker	223 (48.0)	83 (52.9)	61 (39.6)	79 (51.3)
Current smoker	242 (52.0)	74 (47.1)	93 (60.4)	75 (48.7)
Smoking history(pack-years)				
Mean	54.3	53.6	53.6	55.6
SD	26.6	24.5	29.7	25.4
COPD duration (yrs) Mean	7.6	8.1	7.3	7.5
SD	6.2	6.7	6.1	5.8

(Source: m5, Volume 5.1, page 68)

The study population is relatively balanced across treatment groups at baseline in the PFT evaluation. Patients' baseline (pre-bronchodilator screening) FEV_1 values are summarized in Table 7. The overall mean baseline FEV_1 was 1.337 liters. The overall mean baseline FVC was 2.648 liters, and FEV_1/FVC ratio was approximately 50.3%, respectively.

Table 7 Baseline (pre-bronchodilator screening) spirometry data, study 1012.62

Spirometry		Total	Combivent Respimat 20/100	Combivent MDI 36/206	Atrovent 34 plus Ventolin 180
Total treated		465	157	154	154
FEV_1 (liters)	**N**	462	157	151	154
	Mean	1.337	1.321	1.377	1.315
	SD	0.542	0.489	0.573	0.563
	Median	1.240	1.220	1.270	1.250
% predicted FEV_1*	**Mean**	47.0	46.7	48.2	46.1
	SD	15.4	13.7	15.5	17.0
	Median	47.4	47.8	47.6	46.3
FVC (liters)	**Mean**	2.648	2.578	2.713	2.655
	SD	0.852	0.754	0.926	0.871
	Median	2.585	2.500	2.670	2.605
FEV_1/FVC (%)	**Mean**	50.3	51.3	50.5	49.0
	SD	11.3	11.3	10.6	11.9
	Median	50.5	51.2	50.2	50.0

* Predicted FEV_1 value was calculated by the European Coal and Steel Community (ECSC) formula.
(Source: m5, Volume 5.1, page 70)

The overall mean post-bronchodilator FEV_1, FVC and FEV_1/FVC ratio were 1.487 and 2.909 liters, and 51.0, respectively (Table 8). These measurements are similar across treatment groups. The mean FEV_1 reversibility to albuterol at screening was 13.3%, with a slightly lower percent change of FEV_1 in the free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA inhalation aerosol (180 mcg) group (10.8%), compared to that of the Combivent Respimat Inhalation Spray (20/100 mcg) group (14.3%) and the Combivent Inhalation Aerosol (36/206 mcg) group (14.8%), respectively.

Table 8 Post-bronchodilator spirometry data at screening*, study 1012.62

Spirometry		Total	Combivent Respimat 20/100	Combivent MDI 36/206	Atrovent 34 plus Ventolin 180
Total treated		465	157	154	154
FEV_1 (liters)	**N**	465	157	154	154
	Mean	1.487	1.493	1.537	1.431
	SD	0.565	0.530	0.589	0.565
	Median	1.410	1.410	1.460	1.410
% predicted FEV_1	**Mean**	52.3	52.7	54.9	50.3
	SD	15.8	14.5	15.6	17.1
	Median	53.3	54.0	55.6	49.6
FVC (liters)	**Mean**	2.909	2.883	2.964	2.880
	SD	0.899	0.838	0.937	0.923
	Median	2.790	2.740	2.930	2.737
FEV_1/FVC (%)	**Mean**	51.0	51.9	51.7	49.5
	SD	11.2	10.7	10.6	12.1
	Median	50.7	50.2	51.8	59.6
FEV_1 change (liters)	**Mean**	0.153	0.172	0.170	0.116
	SD	0.170	0.183	0.185	0.131
FEV_1 change (%)	**Mean**	13.3	14.3	14.8	10.8
	SD	13.7	13.7	15.2	11.8

* Measured 30 minutes after inhaling 400 mcg of albuterol.
(Source: m5, Volume 5.1, pages 71, 128)

Study patient disposition

Study patient disposition is summarized in Table 9 below. A total of 470 patients were randomized into the treatment groups in study 1012.62. Five of the randomized patients were not treated. Reasons they were not treated included patient decision not to participate (3 patients), COPD exacerbation (1 patient) and inability to stop prohibited medication (1 patient). Of the 465 treated patients, 82 patients (17.6%) discontinued treatment before database lock for this 24-week interim data analysis. Of those who discontinued treatment, 20 patients (4.3%) refused continuation of medication, 38 (8.2%) discontinued due to an adverse event including worsening of study disease, 9 (1.6%) discontinued due to non-compliance, and 6 (1.3%) lost follow up. The free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA

inhalation aerosol (180 mcg) group had the highest rate of early discontinuation (24.7%), and the rate of early discontinuation due to refuse to the trial medication (7.8%). The Combivent Respimat Inhalation Spray (20/100 mcg) group and the Combivent Inhalation Aerosol (36/206 mcg) group had similar rate of early discontinuation and early discontinuation due to refuse to the trial medication, suggesting that the study patients were equally accepting the Combivent Respimat Inhalation Spray (20/100 mcg) and the Combivent Inhalation Aerosol (36/206 mcg), but less accepting the free combination treatment of two inhalers.

Table 9 Disposition of randomized patients and reasons for discontinuation, study 1012.62

Patients	Total	Combivent Respimat 20/100	Combivent CFC-MDI 36/206	Atrovent 34 plus Ventolin 180
Randomized	470	157	156	157
Not treated	5	0	2	3
Treated	465	157	154	154
Completed (%)	383 (82.4)	137 (87.3)	130 (84.4)	116 (75.3)
Prematurely discontinued trial medication (%)	82 (17.6)	20 (12.7)	24 (15.6)	38 (24.7)
AEs due to study disease worsening (%)	17 (3.7)	4 (2.5)	5 (3.2)	8 (5.2)
AEs due to other conditions (%)	21 (4.5)	6 (3.8)	6 (3.8)	9 (5.8)
Non-compliance (%)	9 (1.6)	1 (0.6)	5 (3.2)	3 (1.9)
Lost to follow-up (%)	6 (1.3)	3 (1.9)	2 (1.3)	1 (0.6)
Refused to continue (%)	20 (4.3)	4 (2.5)	4 (2.6)	12 (7.8)
Other (%)	9 (1.9)	2 (1.3)	2 (1.3)	5 (3.2)

(Source: m5, Volume 5.1, pages 64, 115)

Protocol deviations

Important protocol violations (PV) are defined as deviations from the protocol-defined inclusion criteria that could potentially alter the analyses, or that would put the patient at risk. Deviations from the pre-specified spirometry criteria are deemed important protocol violations. In total, 18 patients (3.8%) had important protocol violations, approximately equally distributed across treatment groups, 5 patients (3.2%) in the Combivent Respimat Inhalation Spray (20/100 mcg) group, 8 patients (5.1%) in the Combivent Inhalation Aerosol (36/206 mcg) group, and 5 patients (3.2%) in the free combination of Atrovent 34 and Ventolin 180 group. Among those patients with protocol violations, 7 patients (1.5%) were taking long term prohibited medication that may had an impact on their safety or efficacy, 5 patients (1.1%) had FEV_1 >80% of predicted normal value or FEV_1/FVC > 70% at the first visit, 2 patients had a wrong randomization number, 2 patients with errors on treatment or inhaler, one patient was participating in another study, and one patient was sick. Since the overall number of PV is small, the potential impact on the trial result is considered minor.

Compliance

In the Patient Diary, patients recorded the self-administered number of actuations of investigational product. The investigator/study staff reviewed these records with the patient at each study visit to assess treatment compliance. Patient compliance was evaluated using the mean number of actuations of study medication per day during the two weeks prior to each clinic visit. The mean compliance was calculated as the total number of actuations recorded as having been taken by the patient during the 2 weeks prior to each clinic visit divided by the number of days with non-missing data for each patient (Table 10). At day 169 (week 24), there were 87.9%, 87%, and 78.6% of patients recorded compliance data in the Combivent Respimat Inhalation Spray (20/100 mcg) group, the Combivent Inhalation Aerosol (36/206 mcg) group, and the free combination of Atrovent 34 and Ventolin 180 group, respectively. The majority of the patients were 80% to 120% compliant with the trial medication.

Table 10 Trial medication compliance recorded during the 24 weeks, study 1012.62

Treatment group	**Combivent Respimat 20/100**		**Combivent CFC-MDI 36/206**		**Atrovent 34 plus Ventolin 180**	
	N	**%**	**N**	**%**	**N**	**%**
Treated patients	157		154		154	
Patients recorded compliance						
Baseline (Day 1)	157	100	154	100	154	100
Day 22	154	98.1	150	97.4	146	94.8
Day 85	144	91.7	143	92.9	131	85.1
Day 169 (week 24)	138	87.9	134	87.0	121	78.6
% compliance[1] at week 24						
50% - <80%	1	0.6	2	1.3	2	1.3
80% - ≤120%	137	87.3	131	85.1	119	77.3
>120%	0	0	1	0.6	0	0

1 Percentage compliance was calculated as the number of puffs the patient actually took divided by the number the patient should have taken during the treatment period.
(Source: m5, Volume 5.1, page 153)

7.2.2 Explorations for Dose Response

This is a long term safety and patient acceptability study. There was no dose response study in the submission.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was submitted as part of this application.

7.2.4 Routine Clinical Testing

Because of the extensive safety database with the marketed Combivent CFC product, specific safety assessments such as ECGs and laboratory tests were not required. Spirometry was, however, monitored throughout the study.

7.2.5 Metabolic, Clearance, and Interaction Workup

A workup for metabolic, clearance, and interactions was not conducted as part of this application since the same chemical entities (ipratropium bromide and albuterol sulfate) are already marketed as a combination drug product (Combivent Inhalation Aerosol MDI) or individual drug product (Atrovent MDI for ipratropium bromide and Ventolin MDI for albuterol sulfate).

7.3 Major Safety Results

7.3.1 Deaths

Three patients had adverse events with a fatal outcome during the treatment phase of the study. One additional fatal AE was reported during the vital status follow-up in patients who were discontinued prematurely (Pt. 40602). Three patients (Pt. 40652, 40753, and 40602) were in the Atrovent 34 mcg + Ventolin 180 mcg treatment group and one (Pt. 41359) in the CVT R 20/100 group. Short case presentations are provided for each patient below.

Patient 40602
This was a 61-year-old white female patient with COPD who was randomized into the trial (Atrovent 34 mcg + Ventolin 180 mcg). The patient presented to the doctor with complaints of abdominal pain, diarrhea, and steatorrhea after 110 days on the treatment. An ultrasound was done that revealed gallstones and a CT scan revealed a mass on the pancreas. The patient was admitted to the hospital with cholecystitis for a laparoscopic cholecystectomy and possible pancreas and liver biopsies. The mass on the pancreas was biopsied and revealed to be inoperable metastatic pancreatic adenocarcinoma. The patient withdrew from the study and died 4 months later as a result of the metastatic pancreatic adenocarcinoma. The investigator considered the events to be not related to administration of study drug.

Patient 40652
This was a 65-year-old male patient with COPD who was randomized into the trial (Atrovent 34 mcg + Ventolin 180 mcg). The patient was found at home by his son slumped over on around 137 day of the treatment with unknown etiology. 911 was called and the patient was transported to the hospital by an ambulance. While at the hospital, the patient experienced several other events including respiratory failure,

hypotension, cardiomyopathy, multiple cerebral vascular accidents, elevated cardiac enzymes, right lower lung infiltrate, lung mass right lobe, hyperkalemia, and cardiac arrhythmia-lethal. The specific order of these events was not known. The cardiac arrhythmia was considered cause of death. The investigator considered that the events were not related to study medication.

Patient 40753
A 70-year-old white male patient with COPD was randomized to the Atrovent 34 mcg + Ventolin 180 mcg treatment group. The patient experienced dizziness, worsening of headache, left hand weakness, nausea and vomiting on about 157 day on the treatment. The patient experienced malaise and reported to the hospital. He was eventually diagnosed with non-small cell lung cancer stage IV with metastasis to brain and liver, and died. The investigator considers the events to be not related to the administration of study medication.

Patient 41359
A 49-year-old female patient with COPD was randomized to the Combivent Respimat 20/100 mcg treatment. The patient experienced respiratory failure and was found dead at home on the 62 day with the treatment. The cause of death was listed on the death certificate as respiratory failure. No autopsy was performed. The investigator considers the event to be not related to the administration of study drug.

Two additional fatal cases were reported to the sponsor since the database lock during writing of this interim report. Patient 42502 died on from sepsis and Patient 42503 died of unknown causes (investigation ongoing). Both patients had been randomized to Combivent CFC-MD! 36/206 and both events were considered not related to the treatment.

Reviewer's comment:
It appears that all the 6 deaths in the studies were not test drug products related. All the deaths were attributed to concomitant serious diseases, conditions, or accidents.

7.3.2 Nonfatal Serious Adverse Events

Nonfatal Serious Adverse Events (SAEs) occurred in a total of 54 patients (11.6%) across all treatment groups (Table 11). The highest frequency of SAEs was in the free combination A 34 plus V 180 group (14.3%), followed by Combivent CFC-MDI 36/206 mcg group (11.0%), and the Combivent Respimat 20/100 mcg group (9.6%). The frequency of SAE across treatment groups was similar for three treatment groups.

The most frequently occurred SAE was respiratory, thoracic and mediastinal disorders, involving in total of 22 patients (4.7%). The majority of SAEs in this category was COPD exacerbation (17 patients), which was not a safety signal in a long tern COPD study.

Table 11 Serious adverse event frequency (%) in primary system organ class, study 1012.62

SAEs	Total (%)	Combivent Respimat 20/100 N (%)	Combivent CFC-MDI 36/206 N (%)	A 34 + V180 N (%)
Total treated patients	465 (100)	157 (100)	154 (100)	154 (100)
Patients with any SAE*	54 (11.6)	15 (9.6)	17 (11.0)	22 (14.3)
Renal and urinary disorders	5 (1.1)	1 (0.6)	2 (1.3)	2 (1.3)
Cardiac disorders	8 (1.7)	4 (2.5)	2 (1.3)	2 (1.3)
Gastrointestinal disorders	4 (0.8)	1 (0.6)	1 (0.6)	2 (1.3)
General disorders	2 (0.4)	0	1 (0.6)	1 (0.6)
Infections & infestations	13 (2.8)	6 (3.8)	3 (1.9)	4 (2.6)
Pneumonia	6 (1.3)	4 (2.5)	1 (0.6)	1 (0.6)
Injury	1 (0.2)	0	1 (0.6)	0
Musculoskeletal & connective tissue disorders	2 (0.4)	0	1 (0.6)	1 (0.6)
Neoplasms	9 (1.9)	1 (0.6)	2 (1.3)	6 (3.9)
Nervous system disorders	3 (0.6)	0	2 (1.3)	1 (0.6)
Respiratory, thoracic & mediastinal disorders	22 (4.7)	9 (5.7)	6 (3.9)	7 (4.5)
COPD exacerbation	17 (3.7)	7 (4.5)	4 (2.6)	6 (3.9)
Blood system disorders	1 (0.2)	0	1 (0.6)	0
Congenital/genetic disorders	1 (0.2)	0	1 (0.6)	0
Endocrine disorders	1 (0.2)	0	1 (0.6)	0
Metabolism disorders	1 (0.2)	0	0	1 (0.6)
Skin & subcutaneous tissue disorders	1 (0.2)	0	0	1 (0.6)
Vascular disorders	2 (0.4)	0	1 (0.6)	1 (0.6)
Investigations	2 (0.4)	0	0	2 (1.3)

*The total patients with SAEs may not be the same as the sum of SAE frequencies, because more than one SAE may be reported for one patient.
(Source: m5, Volume 5.1, pages 246 - 249)

Reviewer's comment:
The serious adverse events were occurred at similar frequencies across treatment groups. The most frequently occurred SAE was COPD exacerbation in all treatment groups. It is common in patients with COPD to have fluctuations in symptom severity as a natural course of the disease. It appears no safety signals revealed in evaluating SAEs in this clinical study.

7.3.3 Dropouts and/or Discontinuations

A total of 36 patients (7.7%) had adverse events leading to treatment discontinuation (Table 12). By treatment groups, the free combination Atrovent 34 mcg plus Ventolin 180 mcg group had the highest rate of patient withdrawal due to adverse events (11.0%), followed by Combivent CFC-MDI 36/206 mcg group (6.5%), and the Combivent Respimat 20/100 mcg group (5.7%). The common adverse events leading to withdrawal across treatment groups and clinical studies were respiratory system disorders. COPD exacerbation in turn was the single most common reason of

withdrawal from the clinical studies. The adverse events that lead to withdrawal from the study were not a new safety signal for the test drugs in patients with COPD.

Table 12 Adverse events leading to treatment discontinuation, study 1012.62

SAEs	Total (%)	Combivent Respimat 20/100 N (%)	Combivent CFC-MDI 36/206 N (%)	A 34 + V180 N (%)
Total treated patients	465 (100)	157 (100)	154 (100)	154 (100)
Patient with SAEs leading to treatment discontinuation	36 (7.7)	9 (5.7)	10 (6.5)	17 (11.0)
Cardiac disorders	1 (0.2)	0	0	1 (0.6)
Gastrointestinal disorders	1 (0.2)	1 (0.6)	0	0
General disorders	2 (0.4)	0	1 (0.6)	1 (0.6)
Infections & infestations	5 (1.1)	2 (1.3)	2 (1.3)	1 (0.6)
Pneumonia	2 (0.4)	1 (0.6)	1 (0.6)	0
Neoplasms	7 (1.5)	1 (0.6)	2 (1.3)	4 (2.6)
Nervous system disorders	1 (0.2)	0	0	1 (0.6)
Respiratory, thoracic & mediastinal disorders	24 (5.2)	7 (4.5)	6 (3.9)	11 (7.1)
COPD exacerbation	13 (2.8)	4 (2.5)	3 (1.9)	6 (3.9)
Metabolism disorders	1 (0.2)	0	0	1 (0.6)

(Source: m5, Volume 5.1, pages 242 - 243)

7.3.4 Significant Adverse Events

The significant adverse events were those adverse events that lead to early withdrawal from the study described in above section 7.3.4. Those were not a new safety concern for the test drugs in patients with COPD.

7.3.5 Submission Specific Primary Safety Concerns

In addition to assessing long-term safety, a primary objective of this long term study was to assess patient acceptability of the Respimat device as measured by the Performance domain of the PASAPQ, which collected patients' level of satisfaction. The results of the patient acceptability endpoints will be discussed in this section with the safety evaluation following.

The answers to questions Ql of the PASAPQ (the overall feeling of inhaling the medication), Q2 (the feeling that the inhaled dose goes to the lungs), Q3 (tellng the amount of medication left in your inhaler), Q4 (the reliability of the inhaler), Q5 (the ease of inhaling a dose from the inhaler), Ql0 (using the inhaler) and Ql1 (the speed at which medication comes out of the inhaler) as recorded on the PASAPQ. All these individual answers were rated from 1 (very dissatisfied) to 7 (very satisfied). The PASAPQ Performance score was computed as the mean score expressed on a scale from 0 (very dissatisfied) to 100 (very satisfied).

The primary outcome, PASAPQ performance domain score, was significantly higher with Combivent Respimat (20/100 mcg) Inhalation Spray compared to Combivent Inhalation Aerosol (36/206 mcg) and the free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA inhalation aerosol (180 mcg) for all evaluated time points through week 24 [Table 13, Figure 1].

At baseline, patients showed a similar level of satisfaction when using Combivent Inhalation Aerosol (36/206 mcg) among three treatment groups given that the observed mean score of PASAPQ Performance domain was 74.7, 76.6 and 74.1 in the Combivent Respimat (20/100 mcg) Inhalation Spray, Combivent Inhalation Aerosol (36/206 mcg) and A 34+V 180 treatments, respectively. After randomization, a statistically significantly higher PASAPQ Performance score was observed at Day 22 ($p=0.0006$), Day 85 ($p<0.0001$) and Day 169 ($p<0.0001$) when comparing the Combivent Respimat (20/100 mcg) Inhalation Spray to Combivent Inhalation Aerosol (36/206 mcg) groups. Combivent Respimat (20/100 mcg) Inhalation Spray was also statistically superior to the free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA inhalation aerosol (180 mcg) at each of the time points for the PASAPQ Performance domain score at Day 22, Day 85 and Day 169 (Week 24). At Week 24 (Day 169) the difference in the adjusted mean for Combivent Respimat Inhalation Spray (20/100 mcg) vs. Combivent Inhalation Aerosol (36/206 mcg) was 8.4, and the difference between Combivent Respimat (20/100 mcg) Inhalation Spray and the free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA inhalation aerosol (180 mcg) was 7.0. These differences are statistically significant. Combivent Inhalation Aerosol (36/206 mcg) showed similar mean scores as the free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA inhalation aerosol (180 mcg) at every visit during the 24 weeks.

Table 13 Comparison of PASAPQ performance domain scores* over time, study 1012.62

					Treatment difference		
Test Day	Treatment	N	Mean (SD)	Adjusted mean (SE)	Adjusted mean (SE)	95% CI	p-value
Baseline	CVT R 20/100	157	74.7(14.40)				
	CVT CFC36/206	154	76.6(16.66)				
	A 34 + V 180	154	74.1(15.35)				
Day 22	CVT R 20/100	157	84.2 (13.09)	84.6 (1.07)			
	CVT CFC36/206	152	79.8 (14.38)	79.3 (1.09)	5.3(1.52)	(2.29, 8.28)	0.0006
	A 34 + V 180	153	76.5 (16.62)	77.2 (1.08)	7.4 (1.52)	(4.41, 10.39)	<0.0001
Day 85	CVT R 20/100	149	85.9 (14.20)	85.8 (1.14)			
	CVT CFC36/206	148	78.6 (14.18)	77.9 (1.15)	7.9(1.63)	(4.73, 11.12)	<0.0001
	A 34 + V 180	146	75.8 (16.95)	76.2 (1.16)	9.6(1.63)	(6.45, 12.84)	<0.0001
Day 169	CVT R 20/100	142	85.9(16.16)	85.8 (1.22)			
	CVT CFC36/206	142	78.7(15.79)	77.4 (1.23)	8.4 (1.73)	(4.97, 11.78)	<0.0001
	A 34 + V 180	130	79.3(15.74)	78.8 (1.27)	7.0 (1.76)	(3.52, 10.43)	<0.0001

* Adjusted mean was based on Mixed-effect Model Repeated Measure (MMRM) adjustment, including fixed categorical effects of treatment, test day, treatment by test day interaction, as well as the continuous covariates of baseline and baseline by test day interaction.
(Source: m5, Volume 5.1, p 75)

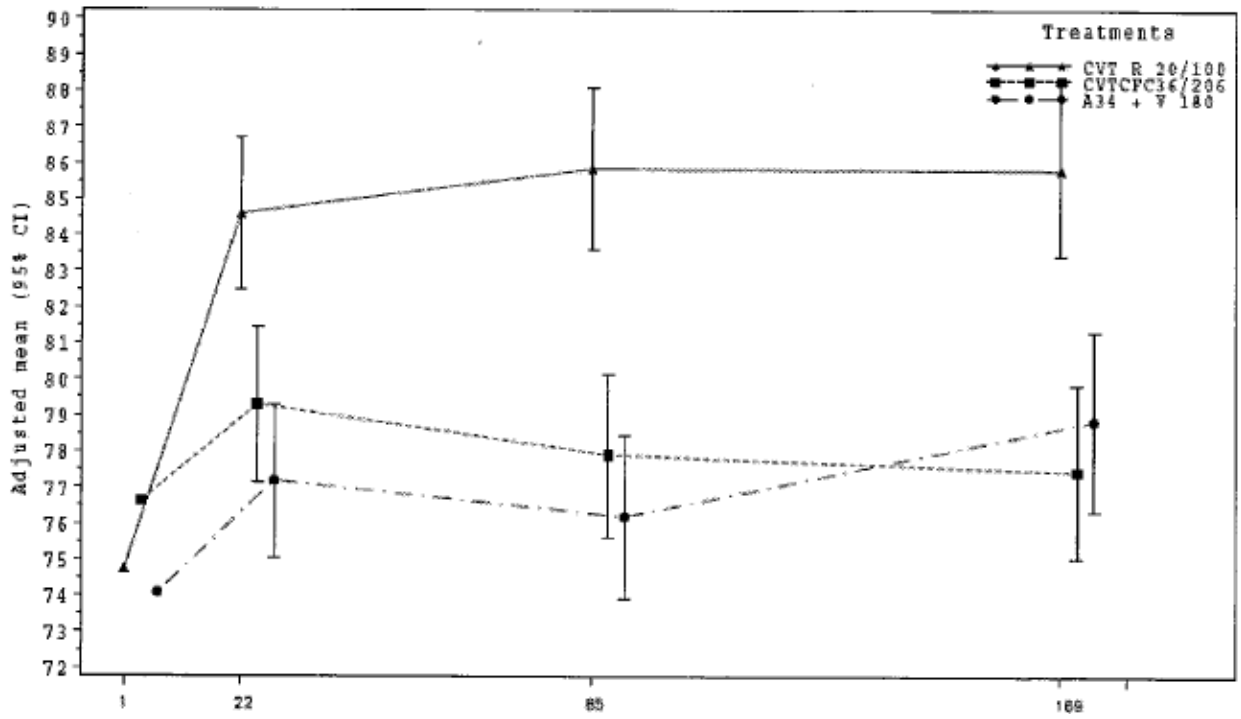

Figure 1 PASAPQ performance domain scores of 3 treatment groups, study 1012.62 (Source: m5, Volume 5.1, p 76)

Subgroup analyses

Subgroup analyses were performed for different gender groups, patients over 65 years of age versus those under 65 years of age, race (white vs. non-white), smoking status (current smokers vs. ex-smokers), and concomitant corticosteroid use (used inhaled and/or oral corticosteroid at randomization vs. not used). In the interim data analyses at week 24 (day 169), PASAPQ Performance domain scores did not show significant difference between subgroups within gender, age, smoking status, and concomitant corticosteroid use (Table 14). Comparisons among three treatment groups ahowed that Combivent Respimat (20/100 mcg) Inhalation Spray was superior to both Combivent Inhalation Aerosol (36/206 mcg) and the free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA inhalation aerosol (180 mcg) in all subgroups in terms of patients' satisfaction level, measured by PASAPQ Performance domain score.

Table 14 Sub-group analyses of PASAPQ performance domain score, study 1012.62

	Combivent R 20/100 mcg (A)		Combivent MDI 36/206 mcg (B)		A 34 mg Plus V 180 mcg (C)		Treatment difference in adjusted mean (p value)	
Subgroups	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**A-B**	**A-C**
Gender								
Male	84.27	1.68	77.22	1.75	78.52	1.67	7.05 (0.0040)	5.74 (0.0162)
Female	88.02	1.72	77.99	1.85	79.31	1.89	10.03 (<0.0001	8.71 (0.0008)
Age								
<65	87.62	1.62	77.84	1.69	79.85	1.58	9.78 (<0.0001)	7.97 (0.0007)
65+	83.40	1.88	78.85	1.98	77.38	1.95	8.75 (0.0142)	6.02 (0.0275)
Race								
Non-white	89.48	3.85	78.10	3.59	82.91	3.67	13.38 (0.0185)	6.57 (0.2232)
White	85.80	1.28	77.50	1.30	78.57	1.34	8.10 (<0.0001)	7.02 (0.0002)
Smoking								
Ex-	83.94	1.78	75.20	2.06	77.41	1.86	8.74 (0.0017)	6.53 (0.0123)
Current	87.27	1.71	78.96	1.52	80.39	1.75	8.31 (0.0003)	6.97 (0.0048)
Use steroid								
Yes	85.54	1.77	76.19	2.01	77.89	2.02	9.35 (0.0007)	7.64 (0.0055)
No	85.45	1.67	78.09	1.54	79.64	1.63	7.37 (0.0013)	5.81 (0.0133)

(Source: m5, Volume 5.1, pages 84 – 85)

Secondary patient acceptability outcomes

Many secondary acceptability endpoints were assessed including Patient Dropout Rate, willingness to continue to use the Respimat inhaler, Overall Satisfaction Score from PASAPQ, Symptom Score from Clinical COPD Questionnaire (CCQ), Physician's Global Evaluation (PGE), FEV_1 and FVC change from test day baseline. In general these endpoints supported the primary acceptability objective that patients believed the device performed as well if not better than Combivent CFC MDI and the combination of the individual treatments. Below, the results for several of the more relevant secondary endpoints are described.

Patient Dropout Rate

The dropout rates are summarized in Table 15 below. At week 24, a total of 18 and 17 patients prematurely discontinued the treatment in the Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg groups, respectively, compared to 31 patients in the free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA inhalation aerosol (180 mcg) group. Within patients who prematurely discontinued the treatment, 11 patients in the free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA inhalation aerosol (180 mcg) group refused to continue the medication, and only 4 and 3 patients refused to continue their medication in the Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg groups, respectively. The free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA inhalation aerosol (180 mcg) group had higher overall early dropout rate and more patients refused to continue the medication than

other two treatment groups, suggesting that patients would more likely to accept the Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 than the combination treatment. The early dropout rates were similar in the Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg groups.

The higher rate of early dropout over time in the free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA inhalation aerosol (180 mcg) group is also shown in Figure 2 below. The Kaplan-Meier curve for time to early dropout in the free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA inhalation aerosol (180 mcg) group is higher than the other 2 treatment groups from the beginning to week 24 of the study. For the Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg groups, the probabilities of early dropout over time are similar.

Table 15 Comparison of early dropout in treatment groups, study 1012.62

Test Day	Combivent R 20/100 mcg (A)		Combivent MDI 36/206 mcg (B)		A 34 mg Plus V 180 mcg (C)		Treatment difference in percentage (p value*)	
	No	%	No	%	No	%	A-B	A-C
Early dropout	18	11.5	17	11.0	31	20.1	0.43 (1.000)	-8.66 (0.043)
Early dropout due to AE of COPD exacer.	4	2.5	4	2.6	6	3.9	-0.05 (1.000)	-1.35 (0.539)
Early dropout due to other AEs	5	3.2	3	1.9	8	5.2	1.24 (0.723)	-2.01 (0.410)
Early dropout due to lost to f/u	2	1.3	2	1.3	0	0	-0.02 (1.000)	1.27 (0.498)
Early dropout due to refused cont. medication	4	2.5	3	1.9	11	7.1	0.60 (1.000)	-4.60 (0.067)

*The p values are from Fisher's exact test without adjustment for multiple comparisons.
(Source: m5, Volume 5.1, page 199)

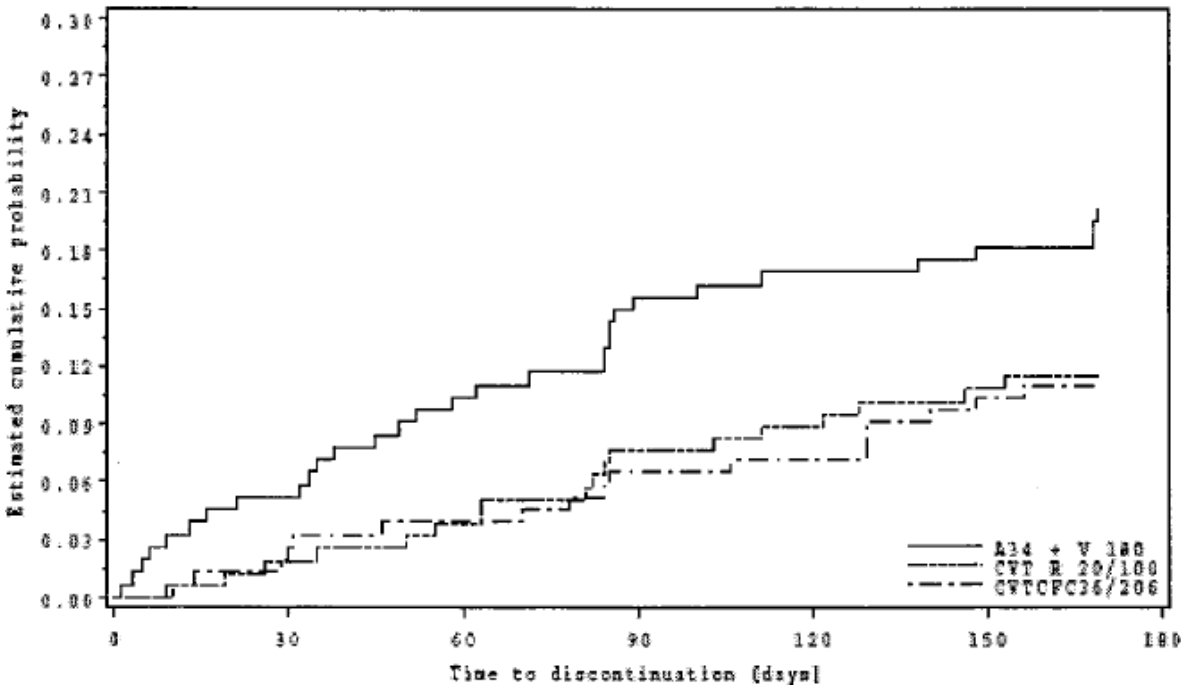

Figure 2 Kaplan-Meier curves of time to discontinuation (Source: m5, Volume 5.1, page 81)

Willingness to continue using the inhaler

The willingness to continue using the inhalers is evaluated by PASAPQ Q15 (willingness to continue using the inhaler, between 0 indicating that you would not be willing to continue using this inhaler and 100 indicating that you would definitely be willing to continue). Table 16 below shows that the baseline scores were similar across treatment groups. By week 24, patients were similarly wiling to continue on the treatment when receiving the Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206, but less likely willing to continue treatment with the individual products.

Table 16 Scores for willingness to continue using the inhaler (from PASAPQ Q15), study 1012.62

					Treatment difference		
Test Day	Treatment	N	Mean (SD)	Adjusted mean (SE)	Adjusted mean (SE)	95% CI	p-value
Baseline	CVT R 20/100	157	90.7(18.80)				
	CVTCFC36/206	154	90.9(17.68)				
	A 34 + V 180	154	86.6(21.76)				
Day 22	CVT R 20/100	157	93.9(15.48)	93.6(1.38)			
	CVTCFC36/206	152	92.7(17.14)	92.4(1.41)	1.3(1.97)	(-2.62, 5.13)	0.5261
	A 34 + V 180	153	88.4(21.17)	89.2(1.41)	4.4(1.98)	(0.52, 8.28)	0.0264
Day 85	CVT R 20/100	149	93.2 (18.57)	92.2(1.87)			
	CVTCFC36/206	148	90.1(20.82)	89.4(1.88)	2.7(2.65)	(-2.46, 7.96)	0.3006
	A 34 + V 180	146	83.8(28.65)	83.8(1.90)	8.3(2.67)	(3.11, 13.59)	0.0019
Day 169	CVT R 20/100	142	94.3(14.15)	92.8(1.66)			
	CVTCFC36/206	142	92.4(17.09)	90.7(1.67)	2.1(2.35)	(-2.52, 6.74)	0.3704
	A 34 + V 180	130	88.0(24.96)	84.9(1.72)	7.9(2.39)	(3.20, 12.60)	0.0011

Adjusted mean was based on Mixed-effect Model Repeated Measure (MMRM) adjustment, including fixed categorical effects of treatment, test day, treatment by test day interaction, as well as the continuous covariates of baseline and baseline by test day interaction. (Source: m5, Volume 5.1, page 82)

Overall Satisfaction Score from PASAPQ

The overall satisfaction score from PASAPQ was the response to PASAPQ Q14 (Overall, how satisfied are you with your inhaler). The answer was rated from 1 (very dissatisfied) to 7 (very satisfied). The data summarized in the Table 17 below showed that in this 24-week interim report there were no significant differences in the overall satisfaction scores among Combivent Respimat (20/100 mcg) Inhalation Spray, Combivent Inhalation Aerosol (36/206 mcg), and the free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA inhalation aerosol (180 mcg), as measured by PASAPQ.

Table 17 Comparison of overall satisfaction score from PASAAPQ, study 1012.62

Test Day	Treatment	N	Mean (SD)	Adjusted mean (SE)	Treatment difference		
					Adjusted mean (SE)	95% CI	p-value
Baseline	CVT R 20./100	157	5.8(1.21)				
	CVT CFC36/206	154	5.9(1.24)				
	A 34 + V 180	154	5.8(1.10)				
Day 22	CVT R 20./100	157	6.2(0.98)	6.2(0.08)			
	CVT CFC36/206	152	6.1(1.01)	6.1(0.08)	0.2(0.12)	(-0.05, 0.42)	0.1167
	A 34 + V 180	153	5.8(1.33)	5.9(0.08)	0.4(0.12)	(0.13, 0.59)	0.0026
Day 85	CVT R 20./100	149	6.2(1.18)	6.2(0.09)			
	CVT CFC36/206	148	6.1(0.98)	6.0(0.09)	0.1(0.13)	(-0.11, 0.39)	0.2633
	A 34 + V 180	146	5.7(1.25)	5.8(0.09)	0.4(0.13)	(0.16, 0.66)	0.0013
Day 169	CVT R 20./100	142	6.3(1.07)	6.3(0.09)			
	CVT CFC36/206	142	6.0(1.04)	6.0(0.09)	0.3(0.12)	(0.08, 0.55)	0.0102
	A 34 + V 180	130	5.9(1.14)	5.8(0.09)	0.4(0.12)	(0.19, 0.68)	0.0005

* Adjusted mean was based on Mixed-effect Model Repeated Measure (MMRM) adjustment, including fixed categorical effects of treatment, test day, treatment by test day interaction, as well as the continuous covariates of baseline and baseline by test day interaction.
(Source: m5, Volume 5.1, p 77)

FEV_1 and FVC change from test day baseline

Pulmonary function test was performed in this long term safety and patient acceptability study as an objective measure that shows the proposed drug product is efficacious in the long term study, and therefore, provided support to the patient acceptability. The FEV_1 and FVC change from test day baseline are summarized in Tables 18 and 19 below. Data showed that all three treatments increased FEV_1 and FVC in the study population, and there was no significant difference between the Combivent Respimat (20/100 mcg) Inhalation Spray, Combivent CFC-MDI, and the free combination of Atrovent HFA (ipratropium bromide 34 mcg) and albuterol HFA inhalation aerosol (180 mcg).

Table 18 Comparison of FEV_1 change from test day baseline, study 1012.62

Test Day	**Combivent R 20/100 mcg (A)**		**Combivent MDI 36/206 mcg (B)**		**A 34 mg Plus V 180 mcg (C)**		**Treatment difference in adjusted mean (p value)**	
Adjusted* FEV_1 change (L)	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**A-B**	**A-C**
Day 1	0.22	0.015	0.21	0.015	0.21	0.015	0 (0.8282)	0.01 (0.6587)
Day 85	0.23	0.017	0.19	0.017	0.19	0.017	0.04 (0.1313)	0.04 (0.1360)
Day 169	0.21	0.016	0.21	0.017	0.21	0.017	0 (0.9826)	0 (0.9382)

* Adjusted mean was based on Mixed-effect Model Repeated Measure (MMRM) adjustment, including fixed categorical effects of treatment, test day, treatment by test day interaction, as well as the continuous covariates of baseline and baseline by test day interaction.
(Source: m5, Volume 5.1, p 178)

Table 19 Comparison of FVC change from test day baseline, study 1012.62

Test Day	Combivent R 20/100 mcg (A)		Combivent MDI 36/206 mcg (B)		A 34 mg Plus V 180 mcg (C)		Treatment difference in adjusted mean (p value)	
Adjusted* FVC change (L)	Mean	SE	Mean	SE	Mean	SE	A-B	A-C
Day 1	0.37	0.026	0.34	0.026	0.36	0.026	0.03 (0.4145)	0.02 (0.6584)
Day 85	0.38	0.027	0.31	0.027	0.35	0.027	0.07 (0.0631)	0.03 (0.4378)
Day 169	0.32	0.030	0.34	0.031	0.35	0.044	-0.02 (0.5955)	-0.03 (0.5684)

* Adjusted mean was based on Mixed-effect Model Repeated Measure (MMRM) adjustment, including fixed categorical effects of treatment, test day, treatment by test day interaction, as well as the continuous covariates of baseline and baseline by test day interaction.
(Source: m5, Volume 5.1, p 183)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 20 below summarized the total and the frequency of patients with adverse events with an incidence of 3% or greater by treatment groups. The common adverse events were respiratory system disorders, accounting for about a half of adverse event cases in the study. The single most common adverse event was COPD exacerbation. Overall, 15.9% of patients had an exacerbation of COPD, followed by 7.1 % of patients with upper respiratory tract infections, and 5.2% of patients reporting bronchitis. Although the Combivent Respimat 20/100 mcg group tends to have a lightly lower number of patients with adverse events, there were no significant differences among 3 treatment groups.

Table 20 Adverse events* and percentage (≥3%) in preferred terms by treatment groups, study 1012.62

System organ class/Preferred term	CVT R 20/100	CVTCFC36/206	A 34 + V 180	Total
Number of patients	157 (100.0)	154 (100.0)	154 (100.0)	465 (100.0)
Total with adverse events	96 (61.1)	99 (64.3)	101 (65.6)	296 (63.7)
Gastrointestinal disorders	10 (6.4)	14 (9.1)	18 (11.7)	42 (9.0)
Vomiting	0 (0.0)	3 (1.9)	5 (3.2)	8 (1.7)
General disorders and administration site conditions	11 (7.0)	8 (5.2)	8 (5.2)	27 (5.8)
Chest pain	5 (3.2)	1 (0.6)	1 (0.6)	7 (1.5)
Infections and infestations	45 (28.7)	48 (31.2)	45 (29.2)	138 (29.7)
Bronchitis	7 (4.5)	8 (5.2)	9 (5.8)	24 (5.2)
Nasopharyngitis	5 (3.2)	6 (3.9)	8 (5.2)	19 (4.1)
Sinusitis	2 (1.3)	8 (5.2)	8 (5.2)	18 (3.9)
Upper respiratory tract infection	11 (7.0)	12 (7.8)	10 (6.5)	33 (7.1)
Urinary tract infection	3 (1.9)	3 (1.8)	7 (4.5)	13 (2.8)
Respiratory, thoracic and mediastinal disorders	46 (29.3)	51 (33.1)	47 (30.5)	144 (31.0)
Chronic obstructive pulmonary disease	22 (14.0)	26 (16.9)	26 (16.9)	74 (15.9)
Cough	10 (6.4)	4 (2.6)	5 (3.2)	19 (4.1)
Dyspnoea	3 (1.9)	8 (5.2)	9 (5.8)	20 (4.3)
Vascular disorders	7 (4.5)	6 (3.9)	8 (5.2)	21 (4.5)
Hypertension	5 (3.2)	3 (1.9)	3 (1.9)	11 (2.4)

*The total patients with AEs may not be the same as the sum of AE frequencies, because more than one AE may be reported for one patient. (Source: m5, Volume 5.1, page 91)

Inhalation complaints and malfunctioning inhalers

All device malfunctions and complaints were recorded and reviewed. At the time of data lock for the 24-week interim report, a total of 4 device complaints were recorded. There were 3 complaints for the Combivent Respimat (incorrect dose counting, device base detached, no medication released). However, only one complaint fro the Combivent Respimat (device base detached) was confirmed. There was also one complaint for the Ventolin MDI (device sticking).

7.4.2 Laboratory Findings

Due to the extensive experience with the marketed Combivent CFC-MDI product, laboratory tests were conducted only at baseline in this study.

7.4.3 Vital Signs

Vital signs consisted of blood pressure and pulse rate. Blood pressure and pulse rate were measured and recorded at each clinical visit in the study. The results of vital sign evaluation did not indicate any clinically relevant differences in mean changes and marked changes among the treatment groups.

7.4.4 Electrocardiograms (ECGs)

Due to the extensive experience with the marketed Combivent CFC-MDI product, ECGs were assessed only at baseline in this study.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted in this application

7.4.6 Immunogenicity

Since albuterol and ipratropium are small molecules, immunogenicity is not a concern; thus, immunogenicity was not evaluated as part of this application.

7.5 Other Safety Explorations

7.5.5 Drug-Drug Interactions

There are no drug interaction studies have been conducted with Combivent Respimat and other medications commonly used in the treatment of COPD. COPD patients in clinical studies for Combivent Respimat were permitted for stabilized therapy with low dose of oral corticosteroids, orally inhaled corticosteroids, theophylline preparations, mucolytic agents, leukotriene receptor antagonists, and as needed albuterol inhalation. No interactions were observed between these drugs and Combivent Respimat. The Applicant stated that “Combivent Respimat has been used concomitantly with other drugs, including those commonly used in the treatment of COPD (e.g., sympathomimetic bronchodilators, methylxanthines, and steroids) without adverse drug reactions.”

Reviewer’s comment:
The statement in Section DRUG INTERACTION in the proposed labeling for Combivent Respimat (20/100 mcg) Inhalation Spray is the same as that in the approved labeling for Combivent Inhalation Aerosol MDI.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies in animals did not suggest carcinogenic potential for ipratropium and albuterol. No safety signals from clinical trials suggest carcinogenic potential for the proposed drug product.

7.6.2 Human Reproduction and Pregnancy Data

No clinical data are available for pregnancies exposed to tiotropium or for nursing females. Because COPD is a disease that generally occurs only in older patients with a significant smoking history, clinical trials only enrolled patients greater than 40 years of age.

7.6.3 Pediatrics and Assessment of Effects on Growth

COPD is a disease of adult population. The studies in children would be impossible or highly impractical. An assessment of effect on growth does not apply to this application. The Applicant requested a PREA waiver for the proposed drug product. This reviewer recommends the PREA waiver be granted to Combivent Respimat (20/100 mcg) Inhalation Spray.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of drug overdose were reported in the study. Ipratropium bromide and albuterol sulfate are not controlled substances and have no known abuse potential. No withdrawal effects were reported in the study.

7.7 Additional Submissions / Safety Issues

The Applicant submitted preliminary data for the remaining 6 months of the study in June 2011. A preliminary review of the data showed that the data were consistent with the interim 24-week data. Figure 3 below shows the primary endpoint, PASAPQ performance domain score, obtained from the preliminary data of the one year period. As discussed in Section 7.1, the Performance domain of the PASAPQ collected patients' level of satisfaction for the administered drug product. The PASAPQ Performance score was computed as the mean score expressed on a scale from 0 (very dissatisfied) to 100 (very satisfied). At baseline, patients showed a similar level of satisfaction among three treatment groups, the Combivent Respimat Inhalation Spray (20/100 mcg), Combivent Inhalation Aerosol (36/206 mcg) and the combination A 34+V 180 treatment. After randomization, a statistically significantly higher PASAPQ

Performance score was observed at Day 22, Day 85 and Day 169 (the day of the data lock for the interim 24-week report), and the trend continues at Day 253 and 337 (the end of the long term study). A preliminary review showed that the safety data for the remaining 6 months of the study were consistent with the interim 24-week data, and there were no unexpected safety signals and issues of patient satisfaction for Combivent Respimat (20/100 mcg) Inhalation Spray.

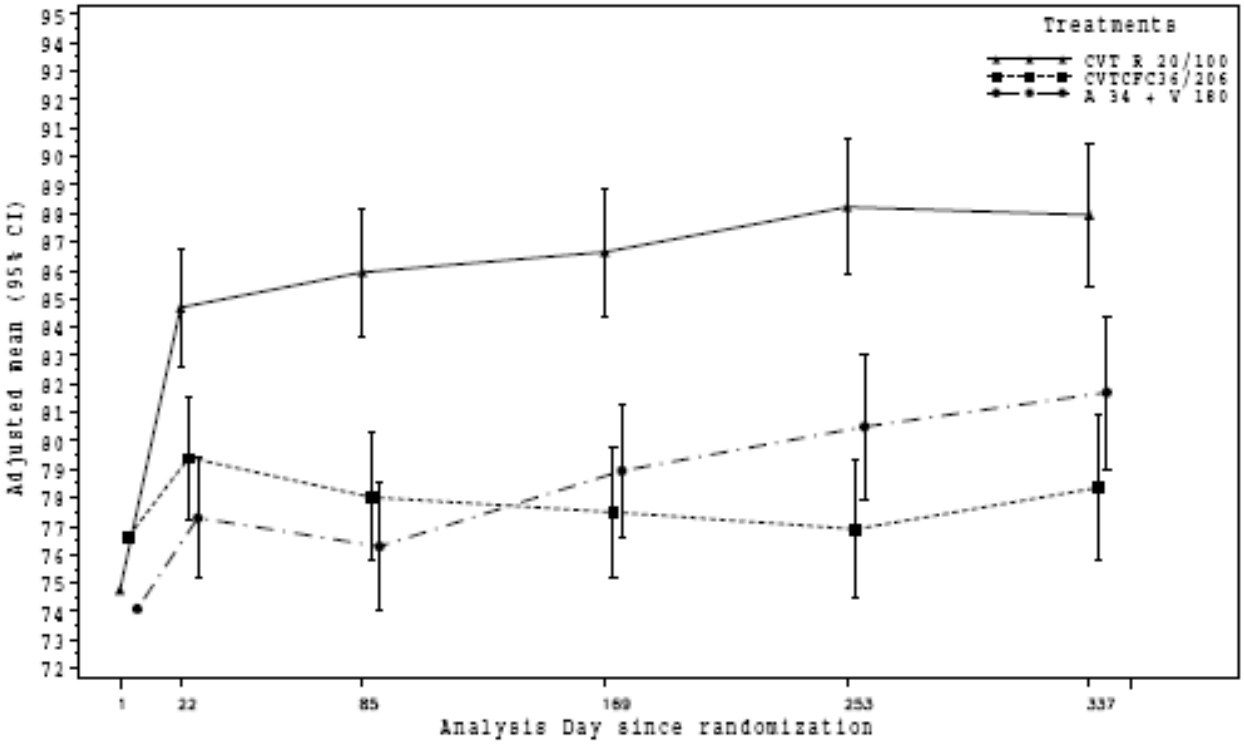

Figure 3 One year PASAPQ performance domain scores, preliminary data

8 Postmarket Experience

Currently the Combivent Respimat is not approved in the United Stated. Also there are no other products approved for marketing in the United States that utilize the Respimat device. However, there are 2 Respimat products, Berodual Respimat and Spiriva Respimat, approved in Europe. In EU market, Berodual Respimat contains 20 mcg iprotropium and 50 mcg fenoterol per puff, is indicated for the prevention and treatment of bronchospasm in asthma and COPD; Spiriva Respimat contains 2.5 mcg tiotropium per puff, and is indicated for the maintenance treatment of COPD. The post-marketing experience of these 2 Respimat products provides certain information in terms of the patient use experience for the Respimat device. Because the device is being used with

different drug products, the safety experience is not transferable to the Combivent Respimat product.

The Applicant provided post-marketing experience reports for the Berodual Respimat from its ex-factory sales in year 2004 until June 2010, and for the Spiriva Respimat from its ex-factory sales in 2007 until June 2010. The database searched was the Applicant's Global Pharmacovigilance Database (GPD). The results are summarized in Table 21 below. The total sales of Berodual Respimat and Spiriva Respimat were over (b) (4) and (b) (4) cartridges, with the estimated patient exposures of 171,263 and 335,943 patient-years, respectively. The GPD search showed that there were 202 adverse events for Berodual Respimat and 892 adverse events for Spiriva Respimat. Because there are no Respimat products approved and marketed in the United States, a special attention is paid to the product complaints reported for the 2 Respimat products in Europe. In the GPD search, 18 and 9 product complaints were reported as adverse events for Berodual Respimat and Spiriva Respimat, respectively. The most common product complaints were less or decreased drug effect. According to the Applicant, one case of "manufacturing defect" for Berodual Respimat was confirmed. For Spiriva Respimat, 2 cases of product were confirmed (one as "defective spray", and one as "metallic particle in valve"). Considering the number of cartridges soled and the large number of patient-years of exposure to the Respimat products, the 3 confirmed product complaints are not a safety concern for the Respimat device.

Table 21 Post-marketing experience for Respimat products in Europe

Product	Number of cartridges	Patient-years of exposure	Total AEs reported	Product complaint reported as AE
Berodual Respimat	(b) (4)	171,263	202	18
Spiriva Respimat	(b) (4)	335,943	892	9
Total	(b) (4)	507,206	1,094	27

Source: m5, Volume 5.36, pages 6-7, 41-44)

Reviewer's comment:
The post marketing adverse events and Respimat complaints in the EU for the approved 2 Respimat products did not reveal evidence of any specific device use issues related to the Respimat in COPD patients.

9 Appendices

9.1 Literature Review/References

There is no literature review included in this NDA submission. The Applicant has not published the data from clinical trials of the Combivent Respimat development program.

9.2 Labeling Recommendations

Detailed labeling review has been performed in the previous review cycle. In the present complete response submission, the Applicant submitted revised product labeling, which will be reviewed against the Agency's comment to the Applicant in the previous review cycle and to include the interim 24-week data from the long term safety and patient acceptability study.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was not held for this NDA. The two active ingredients in this drug product (ipratropium bromide and albuterol sulfate) are well studied molecules, and the combination of the two active ingredients has been accepted in the United States and abroad.

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/s/

XU WANG
08/20/2011

ANTHONY G DURMOWICZ
08/20/2011

MEDICAL OFFICER REVIEW
Division Of Pulmonary, Allergy, and Rheumatology Products (HFD-570)

APPLICATION:	NDA 21-747	**TRADE NAME:**	COMBIVENT RESPIMAT
APPLICANT/SPONSOR:	Boehringer Ingelheim	**USAN NAME:**	iprotropium bromide and albuterol sulfate inhalation spray
MEDICAL OFFICER:	Xu Wang, M.D., Ph.D.		
TEAM LEADER:	Anthony G. Durmowicz, M.D.	**CATEGORY:**	Beta 2 agonist, anticholinergic combination
DATE:	05/06/11	**ROUTE:**	Oral inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
04/07/11	04/08/11	NDA 21-747, N-020	CR resubmission

RELATED APPLICATIONS

Document Date	Application Type	Comments
10/07/08	NDA 21-747	NDA submission
02/01/08	IND 57,948	Pre-NDA meeting minutes
10/24/03	IND 57,948	Pre-NDA meeting minutes

REVIEW SUMMARY: This is a CR resubmission for Combivent Respimat (ipratropium bromide 20 mcg/albuterol sulfate 100mcg) Inhalation Spray. This product was developed as a propellant-free replacement for Combivent Inhalation Aerosol CFC-MDI. This NDA has significant public health implications because of the ongoing CFC phase out of CFC-containing medications in response to the US agreement with the global treaty for removal of substances that damage the ozone layer. Combivent CFC-MDI is currently the only ipratropium/albuterol MDI marketed in the US. Thus the proposed Combivent Respimat is important to patients who are using Combivent CFC-MDI that will eventually become unavailable.

The original NDA was submitted on 10/7/2008 with one pivotal study, which demonstrated the efficacy of the test drug product: at day 85, Combivent Respimat 20/100 was non-inferior to Combivent CFC 36/206 in FEV_1 AUC_{0-6} and to Ipratropium Respimat 20 in FEV_1 AUC_{4-6} (95% CI within the non-inferiority margin of 50 mL). Combivent Respimat 20/100 was also superior to Ipratropium Respimat 20 in FEV_1 AUC_{0-4} (95% CI above the margin of 50 mL). However, the lack of long-term (one year) safety data with Combivent Respimat was an approvability concern. A complete response action was given to the NDA 21-747 on 8/07/2009. The Division stated in the CR letter that "To support approval of Combivent Respimat Inhalation Spray for use in patients with COPD, provide data from a long-term study (or studies) with treatment duration of at least one year." In a subsequent T-con, the Division agreed that "The 6-month interim data from the safety and patient acceptance study is acceptable for submission for review in the complete response." The Division also stated that "The data from the remaining 6 months should be submitted at least 4 weeks before the action date in order for the Division to have an overall assessment of the safety data for the entire 12 months prior to taking action."

The present CR resubmission includes the 6-month interim data report from a one year safety and patient acceptance study 1012.62. Study 1012.62 is a Phase 3, one-year, randomized, open-label safety and patient acceptability study of Combivent Respimat Inhalation Spray (20/100 mcg) in comparison to Combivent Inhalation Aerosol (36/206 mcg) and the free combination of Atrovent HFA (ipratropium bromide 34 mcg) Inhalation Aerosol and albuterol HFA inhalation aerosol (180 mcg) in adult patients with COPD. The primary endpoint is the difference in performance domain score using Patient Satisfaction and Preference Questionnaire (PASAPQ) at 24 weeks. This CR resubmission includes interim data from a long term safety and patient acceptance study to address the deficiency identified in the CR letter. The filing is appropriately indexed to allow review.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

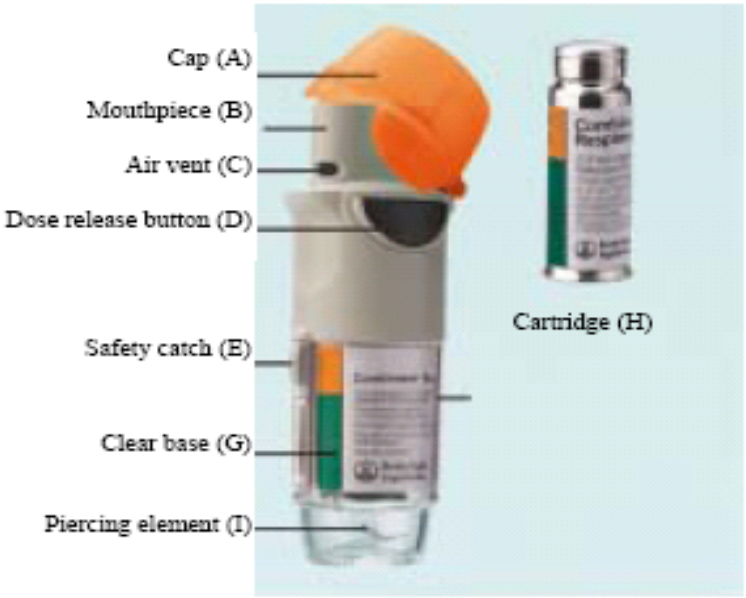
IND/NEW STUDIES:	___	**SAFE TO PROCEED**	___	**CLINICAL HOLD**
NDA/SUPPLEMENTS:	X	**FILEABLE**	X	**NOT FILEABLE**

1. GENERAL INFORMATION AND BACKGROUND

This is a complete response submission for Combivent Respimat (ipratropium bromide 20 mcg/albuterol sulfate 100mcg) Inhalation Spray. The original submission is a 505(b)(2) application because the pharmacology/toxicology data on albuterol was not conducted by or on behalf of the sponsor and the sponsor is relying on the Agency's previous pharmacology toxicology findings in support of the application. This product was developed as a propellant-free replacement for Combivent Inhalation Aerosol CFC-MDI (NDA 20-291, approved October 24, 1996). The proposed labeling indication is the same as that for Combivent Inhalation Aerosol CFC-MDI: for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator, who continue to have evidence of bronchospasm, and who require a second bronchodilator. The proposed dosage is one inhalation (20/100 mcg) four times a day. Patients may take additional inhalations as needed. The total number of inhalations should not exceed six in 24 hours. The sponsor has provided a hybrid electronic and paper submission of an eNDA and CTD format.

The product Combivent Respimat consists of a sterile aqueous inhalation solution of ipratropium bromide and albuterol sulfate in a 4.5 mL cartridge and a Respimat inhaler. Respimat inhaler is an oral inhalation device that uses mechanical energy to generate a slow moving aerosol cloud of medication. The cartridge with the inhalation solution and the Respimat inhaler are supplied as two entities in one package. Prior to first use, the patient inserts the cartridge into the device and prime the inhaler. Each inhalation delivers 20 mcg ipratropium bromide/ 100 mcg albuterol (base) per spray from the mouthpiece. The Combivent Respimat inhaler and the cartridge are shown in Figure 1.

Figure 1: The RESPIMAT inhaler



This NDA has significant public health implications because of the ongoing CFC phase out of CFC-containing medications in response to the U.S. agreement with the global treaty for removal of substances that damage the ozone layer (i.e. the Montreal Protocol). The FDA proposed rule to ban Combivent CFC (and 6 other CFC-containing products) from the market otherwise know as the "Seven Moiety Rule" was published last year and the final rule is targeted to be published in June 2009. The final rule will establish the last date for the removal of the 7 CFC- containing MDI moieties in the US market. Combivent CFC-MDI is currently the only ipratropium/albuterol MDI marketed in the US, although several ipratropium/albuterol solutions are available for use with a nebulizer. Thus the proposed Combivent Respimat is important to the patients who are using Combivent CFC-MDI that will eventually become unavailable after the rule is finalized.

Combivent Inhalation Aerosol CFC-MDI (NDA 20-291) was approved October 24, 1996. The approved dosage of Combivent Inhalation Aerosol CFC-MDI is ipratropium bromide 36 mcg/albuterol sulfate 206 mcg (delivered as two inhalations of 18/103 mcg) four times daily for patients with COPD. (b) (4) In last 7 - 8 years the Applicant has had several interactions over the study design and endpoints of the clinical trials for Combivent Respimat with the Agency. A Special Protocol Assessment of the pivotal clinical trial for Combivent Respimat submitted and reviewed by the Division in 2001 [IND 57,948, Special Protocol Assessment, Medical Officer Review, Raymond F. Anthracite, M. D., November 7, 2001]. The pivotal clinical trial (Study 1012.46) and the planned NDA submission were further discussed in a pre-NDA meeting on September 24, 2003 [IND 57,948, Pre-NDA Package Review, Carol Bosken, M. D., September 30, 2003; IND 57,948, Pre-NDA Meeting Minutes, October 24, 2003].

The study 1012.46 was completed in 2004. Study 1012.46 was a Phase 3, randomized, double-blind, 12-week, parallel group study in about 1100 patients with COPD. In this study, there were five study medications including both Respimat and CFC placebos: (1) Combivent Respimat 40/200 mcg, (2) Combivent CFC 36/206 mcg, (3) ipratropium Respimat 40 mcg, (4) placebo Respimat, and (5) placebo CFC all administered four times daily. The primary efficacy endpoint was FEV_1 AUC_{0-6} at study day 85. All active treatments were superior to placebo. In addition, there was a numerical separation of Ipratropium Respimat from Combivent Respimat from the 4 hour time point which reached statistical significance at the FEV_1 AUC_{6-8} hour interval. The study results demonstrated that the ipratropium Respimat monotherapy (treatment 3) comparator produced better FEV_1 values than the Combivent Respimat (treatment 1) at the end of an 8-hour dosing interval on study days 29, 57 and 85, thus not showing the combination was superior to the individual active ingredients. PK data showed that, despite similar nominal doses, there were higher drug exposures from the Respimat device than from the CFC MDI. (b) (4)

The Applicant therefore developed a lower dosage form of Combivent Respimat (20/100 mcg). Since December 2005 the Division and the Applicant have discussed the study protocol several times [IND 57,948, Meeting Minutes, January 9, 2006; IND 57,948, Meeting Minutes, May 11, 2006; and IND 57,948, Biometrics Review, Feng Zhou, June, 12, 2006]. The study 1012.56 was similar in study design and endpoints to the Study 1012.46 except for the decreased delivering doses of ipratropiun and albuterol. The Division agreed that the study would be a randomized, double-blind, double-dummy, parallel-group, active-control, 12-week study in approximately 1500 patients with COPD. The patients would be randomized 1:1:1 to receive (1) Combivent Respimat 20/100 mcg plus placebo Combivent CFC-MDI, (2) Combivent CFC-MDI 36/206 mcg plus placebo Combivent Respimat, and (3) iprotropium bromide Respimat 20 mcg plus placebo Combivent CFC-MDI, all administered four times daily. The agreed upon co-primary endpoints, with each having to achieve a 5% level of significance, were:

(1) Non-inferiority of Combivent Respimat 20/100 mcg to Combivent CFC-MDI 36/206 mcg in FEV_1 AUC from 0 to 6 hours at Day 85,
(2) Superiority of Combivent Respimat 20/100 mcg to iprotropium bromide Respimat 20 mcg in FEV_1 AUC from 0 to 4 hours at Day 85 (to assess the albuterol contribution to the combination product), and
(3) Non-inferiority of Combivent Respimat 20/100 mcg to iprotropium bromide Respimat 20 mcg in FEV_1 AUC from 4 to 6 hours at Day 85.

The non-inferiority margin would be 50 ml for the lower limit of the confidence interval. In a pre-NDA meeting on January 16, 2008, the Division accepted the Applicant's plan to submit the NDA with only one pivotal clinical study 1012.56 to support the efficacy of Combivent Respimat with reservations: "The Division does have reservations regarding your plan to perform a single "pivotal" clinical trial especially since previous studies have failed to demonstrate that the combination is superior to each of its components. However, if efficacy findings are robust, a single trial may be sufficient to establish efficacy." [IND 57,948, Pre-NDA Meeting Minutes, February 1, 2008]

The original NDA was submitted on October 7, 2008. The pivotal study 1012.56 is entitled "A comparison of ipratropium bromide/albuterol delivered by the Respimat inhaler to Combivent Inhalation Aerosol and ipratropium bromide delivered by the Respimat in a 12-week, double-blind, safety and efficacy study in adults with chronic obstructive pulmonary disease." The specific objectives of this study were to (1) demonstrate non-inferiority (between 0-6 hours) of Combivent Respimat 20/100 mcg and Combivent CFC-MDI 36/206 mcg on Day 85, (2) demonstrate the superiority (between 0-4 hours) of Combivent Respimat 20/100 mcg over ipratropium Respimat 20 mcg on Day 85, and (3) demonstrate the non-inferiority (between 4-6 hours) of Combivent Respimat 20/100 mcg over ipratropium Respimat 20 mcg on Day 85. In addition, the steady state pharmacokinetics (PK) of the study medication was evaluated in a subgroup of patients over one dosing interval after 4 weeks of therapy.

In study 1012.56, patients first entered a 2-week baseline run-in period in which they were given Atrovent HFA-MDI (18 mcg ipratropium bromide per actuation) and

albuterol HFA-MDI as needed. All patients had to have a diagnosis of COPD and must have had the following spirometric criteria at Visit 1 (screening) and Visit 2 (start of treatment): a clinical diagnosis of COPD, ≥10 pack-year smoking history, a relatively stable, moderate to severe airway obstruction with pre-bronchodilator FEV ≤65% of predicted normal and FEV_1 ≤70% of FVC. Patients who successfully completed this phase were randomized into the double-blind study treatment groups.

There were three primary efficacy endpoints listed below. The efficacy outcomes are summarized following each efficacy endpoint.

(1) Comparison of AUC between test-day baseline FEV_1 and the FEV_1 change from test day baseline curve from 0 to 6 hours (FEV_1 AUC_{0-6}) divided by six at Day 85 (the end of the treatment period), for comparison of Combivent Respimat 20/100 mcg to Combivent CFC-MDI 36/206 mcg

			Difference	
Treatment	No. of patients	Mean (SE) in L	Mean (SE) in L	95% CI in L
COMBIVENT RESPIMAT 20/100 mcg	474	0.145 (0.007)	-0.003 (0.010)	-0.022, 0.015
COMBIVENT CFC-MDI 36/206 mcg	482	0.149 (0.007)		

(2) Comparison of AUC between test-day baseline FEV_1 and the FEV_1 change from test-day baseline curve from 0 to 4 hours (FEV_1 AUC_{0-4}) divided by four at Day 85 (the end of the treatment period), for comparison of Combivent Respimat 20/100 mcg to ipratropium Respimat 20 mcg

			Treatment difference	
Treatment	No. of patients	Mean (SE) in L	Mean (SE) in L	P-value
COMBIVENT RESPIMAT 20/100 mcg	474	0.189 (0.007)	0.047 (0.010)	<.0001
Ipratropium RESPIMAT 20 mcg	468	0.142 (0.007)		

(3) Comparison of AUC between test-day baseline FEV_1 and the FEV_1 change from test-day baseline curve from 4 to 6 hours (FEV_1 AUC_{4-6}) divided by two at Day 85 (the end of the treatment period), for comparison of Combivent Respimat 20/100 mcg to ipratropium Respimat 20 mcg

			Treatment difference	
Treatment	N	Mean (SE) (L)	Mean (SE) (L)	95% CI (L)
COMBIVENT RESPIMAT 20/100 mcg	447	0.056 (0.008)		
			-0.017 (0.011)	-0.039, 0.005
Ipratropium RESPIMAT 20 mcg	427	0.073 (0.008)		

The following Figure graphically demonstrated that at day 85, Combivent Respimat 20/100 was non-inferior to Combivent CFC 36/206 in FEV_1 AUC_{0-6} and to Ipratropium Respimat 20 in FEV_1 AUC_{4-6} (95% CI within the non-inferiority margin of 50 mL). Combivent Respimat 20/100 was also superior to Ipratropium Respimat 20 in FEV_1 AUC_{0-4} (95% CI above the margin of 50 mL).

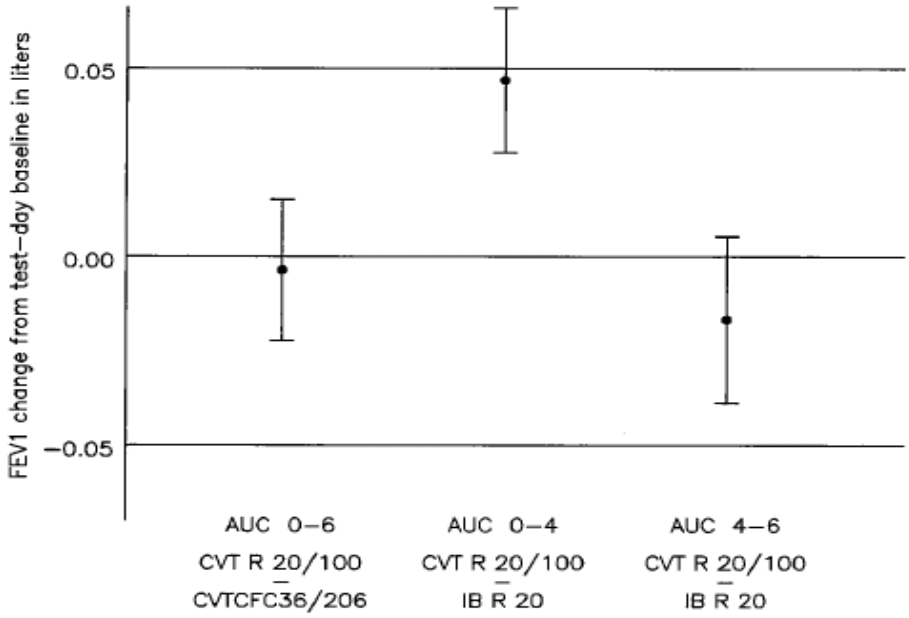


Figure 4:1.5: 1 Day 85 mean treatment differences and 95% confidence intervals, results for the three primary endpoints (Trial 1012.56)

Secondary efficacy endpoints of the study 1012.56 included (1) FEV_1 AUC on Days 1, 29, and 57 (AUC_{0-6}, AUC_{0-4}, and AUC_{4-6}), (2) peak FEV_1 in the 2-hour interval after treatment on Days 1, 29, 57 and 85, (3) peak FEV_1 response (change from test-day baseline) on Days 1, 29, 57 and 85, (4) onset of therapeutic FEV1 response on Days 1, 29, 57 and 85, (5) duration of therapeutic FEV_1 response on Days 1, 29, 57 and 85, (6) time to peak FEV_1 response on Days 1, 29, 57 and 85, (7) forced vital capacity (FVC)

AUC_{0-6} and peak on Days 1, 29, 57 and 85, (8) trough peak expiratory flow rate (PEFR) measured by the patient at home once a day (weekly mean) during the treatment period, (9) individual FEV_1 and FVC measurements at each measurement time, (10) amount of beta-agonist therapy used (i.e., weekly mean number of salbutamol doses during day and, separately, at night) as rescue medication during the treatment period, (11) concomitant medication usage, including corticosteroids during the treatment period, (12) daily symptom scores (weekly mean) over the treatment period, (13) number (%) of patients with at least one COPD exacerbation, as well as number and length of COPD exacerbations during the treatment period, and (14) physician's global evaluation on Days 1, 29, 57 and 85.

Safety endpoints were (1) all adverse events during the treatment period, (2) pulse rate (PR) and blood pressure (BP) in conjunction with spirometry, (3) physical examination, and (4) electrocardiogram (ECG) at screening and end of treatment.

The sponsor submitted a 6-month study (244.2484) for ipratropium bromide Respimat to support the long term safety of the Respimat device. Study 244.2484 was a randomized, double-blind within device, placebo and active controlled, parallel group study. The test agent was ipratropium bromide Respimat at 20 and 40 mcg doses. The active comparator was 36 mcg ipratropium bromide CFC MDI. The drugs were given four times daily for 24 weeks. Subjects had to be >40 years old, had a clinical diagnosis of COPD, a ≥10 pack-year smoking history, and a FEV_1 ≤65%. Of the 646 patients enrolled, 546 completed the study. The patients had a mean age of 65.8 and a mean FEV_1 of 1.01 L. The primary outcome was FEV_1 AUC_{0-6} change from baseline on Day 85. The safety profiles of the two doses of ipratropium Respimat were similar to that of the ipratropium bromide CFC MDI. All treatments were well tolerated. No clinically relevant differences in vital signs or laboratory tests between treatments were observed.

In a mid-cycle review teleconference on March 11, 2009, the Division communicated to the sponsor that the lack of long-term (one year) safety data with Combivent Respimat was an approvability concern because there has been no Respimat device in the US market. Data from long term safety and patient acceptance studies would be needed to support the proposed drug device combination. Subsequently, the Sponsor submitted a one-year safety and patient acceptability study protocol under IND 57,948 on May 18, 2009. The original NDA was given a Complete Response on August 7, 2009. In the CR letter, the Division stated that “The submitted data do not provide substantial evidence of safety to support long-term use of Combivent Respimat Inhalation Spray in patients with chronic obstructive pulmonary disease (COPD)." "To support approval of Combivent Respimat Inhalation Spray for use in patients with COPD, provide data from a long-term study (or studies) with treatment duration of at least one year." [NDA 21747, CR letter, 8/7/2009]

The sponsor had a teleconference with the Division on January 25, 2010 to discuss the planned resubmission in response to the deficiency with regard to the long term safety concern. The Division agreed that "The 6-month interim data from the safety and patient acceptance study is acceptable for submission for review in the complete response.

Whether the submitted data are acceptable for approval is a review issue." The Division also stated that "The data from the remaining 6 months should be submitted at least 4 weeks before the action date in order for the Division to have an overall assessment of the safety data for the entire 12 months prior to taking action." [NDA 21-747, Type C Meeting Minutes, 2/22/2010] Subsequently, the sponsor submitted the interim data of 24 weeks from the long term (one year) safety and patient acceptance study 1012.62 on April 7, 2011.

Reviewer's comment:
The present submission of the interim data of 24 weeks from the long term (one year) safety and patient acceptance study is acceptable based on the agreements reached between the sponsor and the Division.

2. FOREIGN MARKETING AND REGULATORY HISTORY

Combivent Respimat is not approved in any country. Combivent inhalation aerosol CFC (MDI) has been approved and marketed in the United States October 24, 1996. The Applicant has been marketing Combivent inhalation solution Unit Dose Vial (UDV) in European Union (approved in the United Kingdom on March 22, 1994). In the United States, there are several ipratropium/albuterol inhalation solution products in the market, including DuoNeb by Dey Laboratories (NDA 20-950, approved on March 21, 2001) and several generic forms of ipratropium/albuterol inhalation solution for nebulization.

3. ITEMS REQUIRED FOR FILING AND REVIEWER COMMENTS (21 CFR 314.50)

The following items were included in this submission:

- Form FDA 356h [Volume 1, Section 1.1.2]
- Debarment certification [Volume 1, Section 1.3.3]
- Financial disclosure statement: From FDA 3454 [Volume 1, Section 1.3.4]
- Proposed labeling and annotated labeling [Volume 1, Section 1.14]
- Case report forms for clinical studies are provided as electronic files available at the CDER Electronic Document Room (crf\crftoc.pdf). Individual patient data lists are provided as electronic files available at the CDER Electronic Document Room (crf\datasets\).
- List of referenced products [Volume 1, Section 1.4.4]
- Environmental assessment has been addressed in the original NDA submission [Volume 1.1, Section 1.12.14]
    - The Applicant has requested a categorical exclusion from this requirement because approval of this NDA would not increase the amount of the active moieties because they are in current use at the same total daily levels for iprotropium bromide and albuterol sulfate. This NDA has been developed as a non-CFC containing product to replace the currently approved product COMBIVENT inhalation Aerosol (NDA 20-291) that contains a CFC-based propellant. The Applicant therefore claims that this NDA represents an additional environmental benefit. [Volume 1.1, Section 1.12.14]

- Request for waiver of pediatric studies has been addressed in the original NDA submission [Volume 1.1, Section 1.9.1]
  - The Applicant states that this NDA has been developed as a non-CFC containing product to replace the currently approved product COMBIVENT inhalation Aerosol (NDA 20-291) for the indication of using in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a secondary bronchodilator. COPD is a progressive chronic respiratory disorder that most often develops in smokers and former smokers in their middle age. COPD is not a disease affecting pediatric patients. The Applicant hereby requests a full waiver of the requirements of 21 CFR 314.55(c)(2) Pediatric Use Information.

4. CLINICAL EFFICACY AND SAFETY STUDIES

This submission includes the 6-month interim data report from a one year safety and patient acceptance study (1012.62). Based on the agreement between the Agency and the sponsor, the data from the remaining 6 months should be submitted at least 4 weeks before the action date in order for the Division to have an overall assessment of the safety data for the entire 12 months prior to taking action.

Study 1012.62 is a Phase 3, one-year, randomized, open-label safety and patient acceptability study of Combivent Respimat Inhalation Spray (20/100 mcg) in comparison to Combivent Inhalation Aerosol (36/206 mcg) and the free combination of Atrovent HFA (ipratropium bromide 34 mcg) Inhalation Aerosol and albuterol HFA inhalation aerosol (180 mcg) in adult patients with COPD. The primary endpoint is the difference in performance domain score using Patient Satisfaction and Preference Questionnaire (PASAPQ) at 24 weeks.

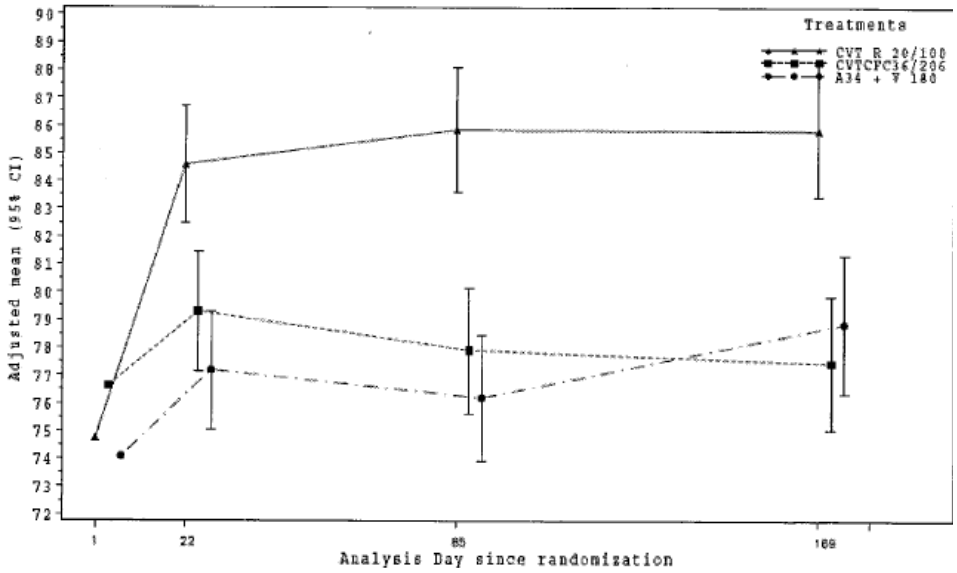


Figure 2. PASAPQ Scores in 3 treatment groups

The primary endpoint, PASAPQ performance domain score, was significantly higher with Combivent Respimat Inhalation Spray (20/100 mcg) compared to Combivent Inhalation Aerosol (36/206 mcg) and the free combination of Atrovent HFA (ipratropium bromide 34 mcg) Inhalation Aerosol and albuterol HFA inhalation aerosol (180 mcg) for all evaluated time points through Week 24 [Figure 2]. At Week 24 (Day 169) the difference in the adjusted mean for Combivent Respimat Inhalation Spray (20/100 mcg) vs. Combivent Inhalation Aerosol (36/206 mcg) was 8.4, and the difference between Combivent Respimat Inhalation Spray (20/100 mcg) and the free combination of Atrovent HFA (ipratropium bromide 34 mcg) Inhalation Aerosol and albuterol HFA inhalation aerosol (180 mcg) was 7.0. These differences are statistically significant.

Secondary endpoints included patient dropout rate, Overall Satisfaction Score from PASAPQ, symptom score from Clinical COPD Questionnaire (CCQ), Physician's Global Evaluation (PGE), FEV_1 and FVC change from baseline, rescue medication use, and COPD exacerbations. The number and pattern of patients who dropped out of the trail was similar for the Combivent Respimat Inhalation Spray (20/100 mcg) and Combivent Inhalation Aerosol (36/206 mcg) treatment groups, but was almost twice as high in the free combination group [Figure 3]. The percentage of patients who refused to continue was also highest in the free combination group (7.8%) versus the Combivent Respimat Inhalation Spray (20/100 mcg) group (2.5%).

No significant differences were observed among treatment groups for the secondary endpoints CCQ symptom domain, Physician's Global Evaluation, FEV_1 and FVC change from test-day baseline, and COPD exacerbations.

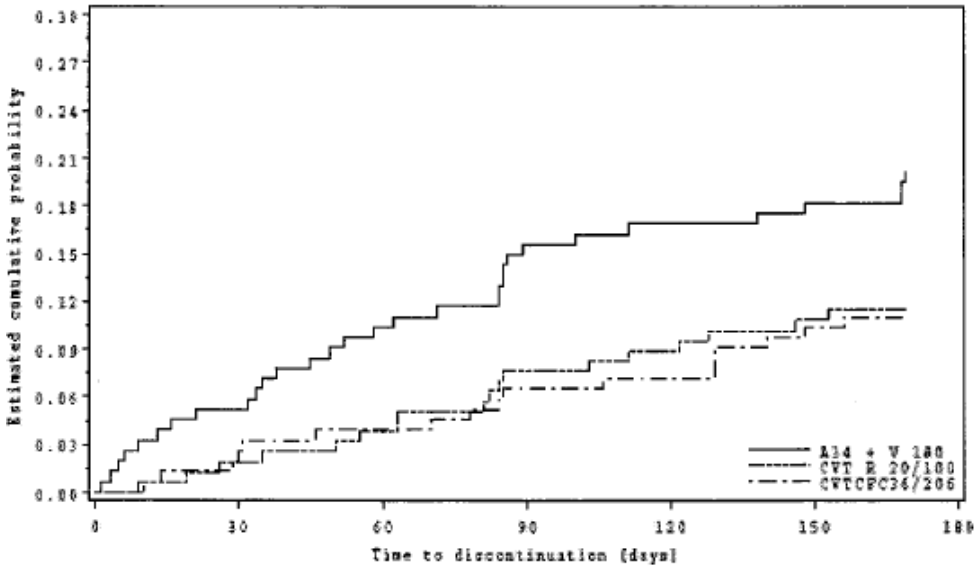


Figure 3. Patient drop out in 3 treatment groups, Kaplan-Meier curve

During the 24 Week interim analysis period, the overall adverse event frequencies were comparable in the Combivent Respimat Inhalation Spray (20/100 mcg) (61.1%), Combivent Inhalation Aerosol (36/206 mcg) (64.3%) and the free combination of Atrovent HFA (ipratropium bromide 34 mcg) Inhalation Aerosol and albuterol HFA inhalation aerosol (180 mcg) (65.6%) treatment groups. The most frequently occurring adverse events in this study population were respiratory system events and infections. Overall, 15.9% of patients had an exacerbation of COPD, followed by 7.1 % of patients with upper respiratory tract infections, and 5.2% of patients reporting bronchitis. COPD exacerbations were numerically less frequent in the Combivent Respimat Inhalation Spray (20/100 mcg) group (14.0%) compared to the other two treatment groups (16.9% each). Serious adverse events were experienced by 54 patients (11.6%). Across treatment groups, the free combination group had the highest frequency of SAEs (14.3%) compared to the Combivent Respimat Inhalation Spray (20/100 mcg (9.6%) and Combivent Inhalation Aerosol (36/206 mcg) (11.0%) groups. Four deaths were reported before the interim database lock and two additional death cases were reported after database lock for this interim report (1 patient received Combivent Respimat Inhalation Spray (20/100 mcg), 2 patients received Combivent Inhalation Aerosol (36/206 mcg) and 3 patients received the free combination). The sponsor stated that none of the fatal events was considered related to study treatments.

5. BRIEF REVIEW OF PROPOSED LABELING

Proposed labeling and annotated labeling has been included in this submission. The product labeling has been reviewed in the previous review cycle. The revision was sent to the sponsor in the CR letter on August 7, 2009. Review of the labeling in the present submission will focus on the addition of the long term safety data

6. DSI REVIEW/AUDIT

In the previous review cycle, DSI audits were conducted at three study sites where enrolled the largest number of patients in the pivotal phase 3 study. Audit of the site did not show any major irregularities. All studies were conducted in accordance with accepted ethical standards.

No DSI audit will be requested for the present submission of the interim data report of the long term safety study. Preliminary review of the data did not reveal any specific irregularities that would raise concerns regarding data integrity.

7. SUMMARY AND RECOMMENDATION

This is a complete response submission for Combivent Respimat (ipratropium bromide 20 mcg/albuterol sulfate 100mcg) Inhalation Spray. This product was developed as a propellant-free replacement for Combivent Inhalation Aerosol CFC-MDI (NDA 20-291,

approved 10/24/1996). This NDA has significant public health implications because of the ongoing CFC phase out of CFC-containing medications in response to the US agreement with the global treaty for removal of substances that damage the ozone layer (i.e. the Montreal Protocol). Combivent CFC-MDI is currently the only ipratropium/albuterol MDI marketed in the US. Thus the proposed Combivent Respimat is important to patients who are using Combivent CFC-MDI that will eventually become unavailable.

The original NDA was submitted on October 7, 2008 with one pivotal study (1012.56) entitled "A comparison of ipratropium bromide/albuterol delivered by the Respimat inhaler to Combivent Inhalation Aerosol and ipratropium bromide delivered by the Respimat in a 12-week, double-blind, safety and efficacy study in adults with chronic obstructive pulmonary disease." The study demonstrated the efficacy of the test drug product: at day 85, Combivent Respimat 20/100 was non-inferior to Combivent CFC 36/206 in FEV_1 AUC_{0-6} and to Ipratropium Respimat 20 in FEV_1 AUC_{4-6} (95% CI within the non-inferiority margin of 50 mL). Combivent Respimat 20/100 was also superior to Ipratropium Respimat 20 in FEV_1 AUC_{0-4} (95% CI above the margin of 50 mL). However, the lack of long-term (one year) safety data with Combivent Respimat was an approvability concern because there has been no Respimat device in the US market. A complete response action was given to the NDA 21-747 on 8/07/2009. The Division stated in the CR letter that "The submitted data do not provide substantial evidence of safety to support long-term use of Combivent Respimat Inhalation Spray in patients with chronic obstructive pulmonary disease (COPD)." "To support approval of Combivent Respimat Inhalation Spray for use in patients with COPD, provide data from a long-term study (or studies) with treatment duration of at least one year." In a subsequent teleconference, the Division agreed that "The 6-month interim data from the safety and patient acceptance study is acceptable for submission for review in the complete response." The Division also stated that "The data from the remaining 6 months should be submitted at least 4 weeks before the action date in order for the Division to have an overall assessment of the safety data for the entire 12 months prior to taking action."

The present CR resubmission includes the 6-month interim data report from a one year safety and patient acceptance study 1012.62. Study 1012.62 is a Phase 3, one-year, randomized, open-label safety and patient acceptability study of Combivent Respimat Inhalation Spray (20/100 mcg) in comparison to Combivent Inhalation Aerosol (36/206 mcg) and the free combination of Atrovent HFA (ipratropium bromide 34 mcg) Inhalation Aerosol and albuterol HFA inhalation aerosol (180 mcg) in adult patients with COPD. The primary endpoint is the difference in performance domain score using Patient Satisfaction and Preference Questionnaire (PASAPQ) at 24 weeks.

This CR resubmission includes interim data from a long term safety and patient acceptance study to address the deficiency identified in the CR letter. The filing is appropriately indexed to allow review.

8. TIME LINE FOR REVIEW

Write-up will be concomitant with the review process. The draft review will be completed at least 2 months prior to the due date. Mid cycle review meeting is scheduled on 06/06/2011. The PDUFA goal day is 10/07/2011.

9. COMMENTS FOR THE SPONSOR

None

Reviewed by:

_____
Xu Wang, M.D., Ph.D.
Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products

_____
Anthony G. Durmowicz, M.D.
Medical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

cc: Original NDA 21-747
HFD-570/Division File
HFD-570/Durmowicz/Medical Team Leader
HFD-570/Wang/Medical Reviewer
HFD-870/Roy/Clinical Pharmacology Reviewer
HFD-580/Schroeder/CMC Reviewer
HFD-570/Pei/Pharmacology/Toxicology Team Leader
HFD-715/Davi/Biometrics Reviewer
HFD-570/Nabavian/CSO

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/s/

XU WANG
05/11/2011

ANTHONY G DURMOWICZ
05/11/2011

SUMMARY REVIEW OF REGULATORY ACTION

Date:	August 7, 2009
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	21-747
Applicant Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission:	October 8, 2008
PDUFA Goal Date:	August 8, 2009
Proprietary Name:	Combivent Respimat Inhalation Spray
Established Name:	Ipratropium bromide and albuterol sulfate
Dosage form:	Inhalation Spray
Strength:	Ipratropium bromide (monohydrate) 20 mcg and albuterol 100 mcg (equivalent to albuterol sulfate 120 mcg)
Proposed Indications:	Chronic Obstructive Pulmonary Disease
Action:	Complete response

1. Introduction

Boehringer Ingelheim Pharmaceuticals, Inc., (BIPI) submitted this 505(b)(2) new drug application for use of Combivent Respimat Inhalation Spray (ipratropium bromide 20 mcg and albuterol 100 mcg) [referred to as Combivent Respimat 20/100 subsequently in this document] for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator. The proposed dose is one inhalation four times a day. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include beta-adrenergic agents, anticholinergic agents, combination products containing beta-adrenergic agents and anticholinergic agents, combination of long-acting beta-adrenergic agents and corticosteroids, and methylxanthines. Combivent is a combination of the beta-adrenergic albuterol, and the anticholinergic ipratropium bromide. There are two fixed dose combination products containing albuterol and ipratropium bromide currently marketed in the United States. These are Combivent Inhalation Aerosol, a CFC-propelled metered-dose inhaler, marketed by BIPI, and DuoNeb Inhalation Solution, for use in nebulizers, marketed by Dey. Combivent Inhalation Aerosol is proposed to be removed from the market in the United States because of the Montreal Protocol agreements that restrict the use of ozone depleting

substances such as CFCs.[1] BIPI proposes to market Combivent Respimat 20/100 as a replacement product for Combivent Inhalation Aerosol.

(b) (4) In 2003, BIPI completed a phase 3 clinical study to support marketing of a Combivent Respimat Inhalation Spray product containing 200 mcg of albuterol compared to 100 mcg of albuterol in the current product. That Combivent Respimat Inhalation Spray (ipratropium bromide 20 mg and albuterol 200 mg) [referred to as Combivent Respimat 20/200 subsequently in this document] failed to show superiority of the combination product over the single ingredients in the phase 3 study. Rather the ipratropium single ingredient product produced a numerically superior FEV1 response over the combination product towards the end of the dosing interval. Pharmacokinetic data showed higher drug exposure from the Respimat product compared to the CFC-propelled product. (b) (4) Subsequently, BIPI developed a lower albuterol strength product, Combivent Respimat 20/100, which is the subject of this application.

There are no products using the Respimat device marketed in the United States. (b) (4) More recently BIPI developed a Respimat product containing tiotropium (Spiriva Respimat) and has conducted multiple studies, including long-term studies, with that product.

3. Chemistry, Manufacturing, and Controls

The drug substances albuterol and ipratropium bromide are well known compounds that are approved as active components in other inhalation dosage forms as single ingredient products and as combination products. The product Combivent Respimat Inhalation Spray is composed of a Combivent Respimat cartridge and a Combivent Respimat inhaler. The Combivent Respimat cartridge is a 4.5 mL plastic container crimped into an aluminum cylinder that contains sterile aqueous solution of albuterol sulfate and ipratropium bromide in excipients benzalkonium chloride (b) (4) edetate disodium (b) (4)), water for injection, and hydrochloric acid ((b) (4) . Combivent Respimat Inhalation Spray will be supplied in a carton containing one Combivent Respimat cartridge and one Combivent Respimat inhaler. Prior to first use, the patient or care provider will place the Combivent Respimat cartridge into the Combivent Respimat inhaler and prime the unit. To actuate the product, the patient will turn the bottom of the inhaler 180°, which will cause a small volume of the

[1] Use of ozone-depleting substances; Removal of essential-use designations. Proposed Rule published in Federal Register Vol 72, No. 111, Page 32030; June 11, 2007

formulation to be metered into a chamber and compress a spring. The patient will then press a trigger, which will release the spring to provide mechanical energy that will propel the formulation through a nozzle (b) (4) and create an aerosol cloud that will emit gently from the mouthpiece of the product. The assembled Combivent Respimat Inhalation Spray will deliver 120 metered actuations. After the 120 metered actuations are delivered, a locking mechanism will be engaged and no more actuations can be dispensed. The Combivent Inhalation Spray should be discarded after the locking mechanism is engaged or 3 months after first use, whichever comes first.

BIPI submitted adequate stability data to support an expiry of (b) (4) for the drug product (whereas (b) (4) expiry was proposed) that consists of the Respimat device and the unassembled cartridge containing the formulation (stored separately), and 3 months after the cartridge is assembled with the Respimat Inhaler.

The steps needed to use the product and the internal mechanisms of the product are rather complex. (b) (4) a consultation with CDRH was obtained because of the complexity of the product. The CDRH review did not raise any concern with the manufacturing and quality of the product, but raised concerns on performance testing with regards to human factors. BIPI has performed adequate specific patient handling studies with Respimat. In two phase 3 studies conducted for Combivent Respimat Inhalation Sprays and in two phase 3 studies conducted for Spiriva Respimat, patient handling of the device was assessed and representative devices used in clinical studies were tested for in vitro performance characteristics. These assessments did not suggest any significant problems with patient handling, performance, and robustness of the Respimat device. The only issue that was identified was that some older patients or patients with hand joint problems may need assistance with initial assembly of the cartridge and the Respimat Inhaler.

The device had undergone some changes during clinical studies. The phase 3 clinical studies were conducted with the A4 version of the Respimat, and the to-be-marketed product is the A5 version. (b) (4) . BIPI has submitted adequate in vitro data to link the two versions of the device.

The drug substance and drug product including the Respimat device are manufactured at a Boehringer Ingelheim facility in Ingelheim am Rhein, Germany. All manufacturing and testing facilities associated with this drug product have acceptable establishment evaluation status. All DMFs associated with this application were also found to be acceptable.

4. Nonclinical Pharmacology and Toxicology

No new significant pharmacology and toxicology studies were submitted with this application. BIPI submitted inhalation toxicity studies using an aqueous albuterol solution containing the excipient benzalkonium chloride for 2 weeks in rats and 3 months in dogs, and a 13-week inhalation toxicity study of EDTA and benzalkonium chloride in rats. These studies did not reveal any new safety findings of concern.

5. Clinical Pharmacology and Biopharmaceutics

The general clinical pharmacology and biopharmaceutic considerations for albuterol and ipratropium have been previously characterized as single ingredient products and also as combination products. BIPI obtained blood samples from the pivotal phase 3 study to assess comparative bioavailability between Combivent Respimat 20/100 and CFC-propelled Combivent Inhalation Aerosol at steady state. For ipratropium, the two combination products were comparable for all PK parameters. For albuterol, the systemic exposure with Combivent Respimat 20/100 was about 25% less than CFC-propelled Combivent Inhalation Aerosol. These findings suggest that Combivent Respimat 20/100 should not possess any additional systemic drug burden for both drug components compared to the marketed Combivent Inhalation Aerosol product.

6. Clinical Microbiology

The inhalation solution is manufactured using (b) (4) .

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1.

Table 1. Combivent Respimat Inhalation Spray clinical studies

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N[§] (ITT)	Study Year#	Countries
1012.56	Efficacy and safety	12 weeks	≥ 40	CR 20/100 mcg CA 36/206 mg IR 20 mcg	474 482 468	2008	USA, Europe, Latin America, Asia
1012.46	Efficacy and safety	12 weeks	≥ 40	CR 20/200 mcg CA 36/206 mg IR 20 mcg Pbo	343 180 250 335	2004	USA
244.2447	Dose ranging, Crossover	Single dose	≥ 40	IR 10 mcg IR 20 mcg IR 40 mcg IR 80 mcg IR 160 mcg	116	1996	USA

243.7	Dose ranging, Crossover	Single dose	≥ 40	AR 25 mcg AR 50 mcg AR 100 mcg AR 200 mcg Pbo	62	1997	USA
244.2484	Safety	6 months	≥ 40	IR 20 mcg IR 40 mcg Atr 36 mcg Pbo R Pbo Atr	180 177 172 58 59	1999	Canada

* CR = Combivent Respimat Inhalation Spray; CA = Combivent Inhalation Aerosol, CFC-propelled; IR = Ipratropium Respimat Inhalation Spray; AR = Albuterol Respimat Inhalation Spray; Atr = Atrovent Inhalation Aerosol; Pbo = Placebo; Pbo R = Placebo Respimat; Pbo Atr = Placebo Atrovent
§ For study 1012.56 the N for "PFT Full Analysis Set", which excludes subjects from a center that had data not verifiable at the source. The ITT same sizes were 493, 498, and 489, for the three groups, respectively.
# Year study subject enrollment ended

Of the listed studies listed above, study 1012.56 is relevant to this application from an efficacy and safety standpoint. Study 1012.46 was conducted with a higher dose of Combivent Respimat and is relevant from a safety standpoint. The other three studies are of remote relevance and are not discussed further in this review. Of the other studies, two were single dose studies with single ingredient products to guide selection of the doses (studies 244.2447, and 243.7), and the other one was a safety study conducted with single ingredient ipratropium bromide (244.2484).

The design and conduct of study 1012.56 is briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

b. Design and conduct of study 1012.56

Study 1012.56 was randomized, double-blind, double-dummy, parallel-group in design, conducted in patients with COPD. The study had a 2-week run-in period, followed by a 12-week double-blind treatment period. The objective of the study was to demonstrate the contribution of albuterol and ipratropium in the combination product. The study did not employ a typical factorial design, but rather used CFC-propelled Combivent Inhalation Aerosol as an active comparator and used a non-inferiority approach. This approach was acceptable because of prior data that exists with the single ingredient products and combination products containing these active ingredients. The Division and BIPI agreed upon design and conduct of the study and non-inferiority margin.

The primary efficacy endpoints were based on timed serial spirometry for FEV1 after 12-week treatment (day 85). The mean change from baseline in FEV1 calculated as area under the curve (AUC) of the FEV1 change from the test day baseline on day 85 divided by the time period of the AUC was used as the primary efficacy endpoint for treatment comparisons. There were 3 pre-specified primary efficacy endpoint comparisons on day 85 as follows. (1) Mean FEV1 using AUC over 0 to 6 hours to determine non-inferiority of Combivent Respimat 20/100 to Combivent Inhalation Aerosol. The non-inferiority margin was 0.05 L for the 95% confidence interval, i.e., the lower bound of the 2-sided 95% confidence interval for the mean FEV1 difference, Combivent Respimet 20/100

minus Combivent Inhalation Aerosol, is above -0.05 L. The intent of this comparison was to assess comparability of the two products. (2) Mean FEV1 using AUC over 0 to 4 hours to determine superiority of Combivent Respimat 20/100 to ipratropium Respimat 20 mg. The intent of this comparison was to show contribution of the albuterol component. (3) Mean FEV1 using AUC 4 to 6 hours to determine non-inferiority of Combivent Respimat 20/100 to ipratropium Respimat 20 mcg. The non-inferiority margin was 0.05 L for the 95% confidence interval. The intent of this comparison was to show contribution of the ipratropium component.

Safety assessments in the study included recording of adverse events, vital signs, physical examinations, clinical laboratory measures, and ECG.

c. Efficacy findings and conclusions

The clinical program supports efficacy of Combivent Respimat Inhalation Spray as a bronchodilator in patients with COPD.

In the pivotal efficacy study the 3 pre-specified primary efficacy endpoints were met (Table 2). Combivent Respimat 20/100 was non-inferior to Combivent Inhalation Aerosol at 0 to 6 hours, superior to ipratropium Respimat at 0 to 4 hours showing the contribution of albuterol and non-inferior to ipratropium Respimat at 4 to 6 hours showing the contribution of ipratropium. The effect was consistent at other treatment days during the study (Figure 1). The secondary efficacy variables were also supportive (data not shown in this review).

A single study using the non-inferiority approach in this specific program is adequate to conclude efficacy of Combivent Respimat 20/100 as a bronchodilator and to establish contribution of albuterol and ipratropium in the combination product. The reasons are established efficacy of both albuterol and ipratropium as bronchodilators in COPD patients, and the established efficacy of Combivent Inhalation Aerosol, a combination product with the same active ingredients which was also used as an active comparator in this study. Furthermore, this study was built on top of study 1012.46 that used Combivent Respimat 20/200, which showed efficacy, however, with issues including adequate albuterol efficacy. In study 1012.46, the single ingredient ipratropium produced a numerically higher in FEV1 response than Combivent Respoimat 20/200 towards the end of the dosing interval. For Combivent Respimat 20/100, the combination product was non-inferior to ipratropium on pre-specified margin for the whole dosing interval (0 to 6 hours) and for the last two hours of the dosing interval (4 to 6 hours). The non-inferiority margin was set by taking into consideration the results of 1012.46.

Table 2. Summary of primary efficacy endpoints, mean FEV1 AUC in Liters (L) on test day 85

		n	Mean in L	Treatment difference in L	
				Mean	95% CI
FEV1 AUC 0-6 hr	Combivent Respimat 20/100	474	0.145	-0.003	-0.022, 0.015
	Combivent Inhalation Aerosol	482	0.149		
FEV1 AUC 0-4 hr	Combivent Respimat 20/100	474	0.189	0.047	0.028, 0.066
	Ipratropium Respimat 20	468	0.142		
FEV1 AUC 4-6 hr	Combivent Respimat 20/100	447	0.056	-0.017	-0.039, 0.005

		n	Mean in L	Treatment difference in L	
				Mean	95% CI
	Ipratropium Respimat 20	427	0.073		

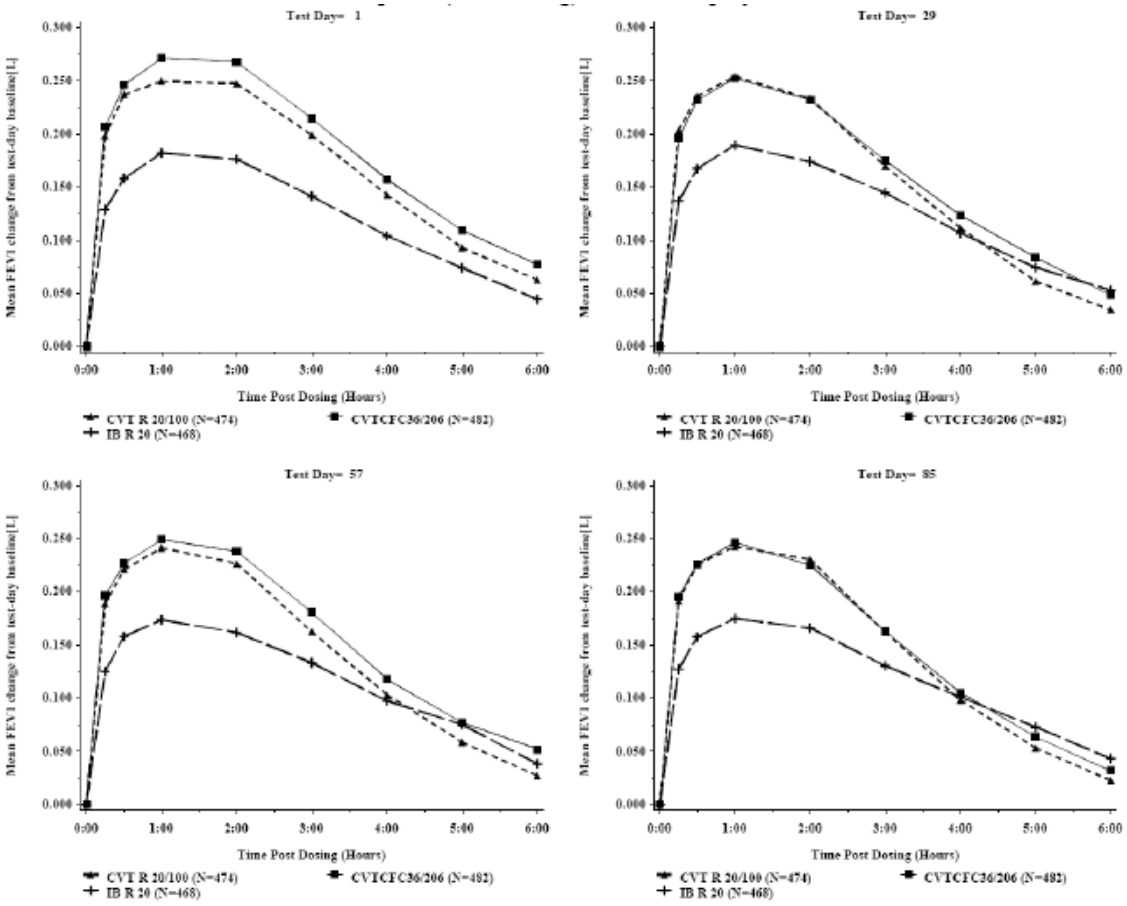

Figure 1. FEV1 time profile change on days 1, 29, 57, and 85

8. Safety

a. Safety database

The safety assessment of Combivent Respimat for COPD patients is based on studies shown in Table 1. The safety database is not adequate for approval of this product.

b. Safety findings and conclusion

There were a total of 11 deaths in the two clinical studies. The number of deaths was generally similar across treatment groups and from causes expected in this study population. The percentages of patients with serious adverse events were higher in the Combivent Inhalation Aerosol treated patients (6.7%) compared to the Combivent Respimat Inhalation Spray treated patients (2.9%). The pattern of serious adverse events and other adverse events did not raise any new safety concerns.

The main safety concern is lack of long-term safety data with Combivent Respimat Inhalation Spray. Although Combivent Inhalation Aerosol was approved with no long term study (no 6-month of 12-month study), the device for Combivent Inhalation Aerosol is the typical press and breathe metered dose inhaler that has been in the market for a long time and is a familiar device for patients. This is not the case with Combivent Respimat. There are no products using the Respimat device marketed in the United States. (b) (4) BIPI later developed a Respimat product containing tiotropium (Spiriva Respimat) and has conducted multiple studies, including long-term studies, with that product, but Spiriva Respimat is not a marketed product in the United States.

The lack of long-term safety with Combivent Respimat Inhalation Spray as an approvability concern was discussed with BIPI during review of this application. BIPI has proposed to conduct a 12-month safety and efficacy study designed primarily to assess safety and device handling issues with Combivent Respimat 20/100 in COPD patients. The study will compare Combivent Respimat 20/100 to Combivent Inhalation Aerosol and also to two single ingredient albuterol and ipratropium products given together. The study will provide long-term safety data with Combivent Respimat 20/100 in COPD patients, and will also provide data to support Combivent Respimat 20/100 as a replacement product for Combivent Inhalation Aerosol. The study protocol was reviewed during this application review period and comments were transmitted to BIPI. This action letter will note this deficiency of lack of long-term safety data.

c. REMS/RiskMAP

Not relevant because Combivent Respimat 20/100 will not be approved in this review cycle. Other products containing albuterol or ipratropium or combination of both do not have REMS and RiskMAP, and, barring any new safety findings, Combivent Respimat 20/100 will not require REMS or RiskMAP when approved.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Albuterol and ipratropium are well studies molecules, and there are other fixed dose combination product containing these two active ingredients approved and marketed in the US with similar indication. The efficacy and safety findings seen in the clinical program were fairly obvious. There were no issues that warrant discussion at an advisory committee meeting.

10. Pediatric

COPD is an adult disease, therefore, specific pediatric studies would not be required that relate to this action specific to COPD. This application was discussed with PeRC and it was decided that a full waiver should be granted because studies would be impossible or highly impracticable because the disease does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited four sites recommended by the review team. These sites enrolled the largest number of patients in the pivotal phase 3 study. Audit of the site did not show any major irregularities. During review of this application the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. A total of 7 investigators had significant financial interest in BIPI. The number of subjects that these investigators enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that these financial interests could have influenced or biased the results of these studies.

c. Other

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

There are no issues with the proprietary name as the root name Combivent is already in the market for a similar product, which will be removed from the market in favor of this product. The further qualifiers for the device name Respimat, and dosage form of Inhalation Spray are also acceptable.

b. Physician Labeling

BIPI submitted a label in the Physician's Labeling Rule format that generally contains information consistent with other similar products. The label was reviewed by various disciplines of this Division and by DDMAC. Various changes to different sections of the label were recommended to reflect the data accurately and better communicate the findings to health care providers. Further labeling review will be done in the subsequent review cycle. The action letter will contain a revised label and some additional labeling comments.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines. The action letter will contain some comments on the carton and container.

d. Patient Labeling and Medication Guide

The Patient Counseling Information was not reviewed in this review cycle because the physician labeling is not finalized. The product does not need a Medication Guide.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The application will not be approved in this review cycle. The submitted program does not have any long-term data that can assure safety and acceptable patient handling of the product long-term.

The comment below is for the action letter.

The submitted data do not provide substantial evidence of safety to support long-term use of Combivent Respimat Inhalation Spray in patients with chronic obstructive pulmonary disease (COPD). While efficacy of Combivent Respimat Inhalation Spray has been demonstrated, there is no data beyond 12 weeks to support long-term use of the product in patients with COPD.

To support approval of Combivent Respimat Inhalation Spray for use in patients with COPD, provide data from a long-term study (or studies) with treatment duration of at least one year. In the study compare the safety and efficacy of Combivent Respimat Inhalation Spray to the currently marketed Combivent Inhalation Aerosol, and to currently marketed albuterol and ipratropium single ingredient inhalation aerosols administered together. In the study also assess patient handling, and acceptance of Combivent Respimat Inhalation Spray.

b. Risk Benefit Assessment

The submitted data are not adequate to conduct a full risk benefit assessment of Combivent Respimat Inhalation Aerosol. Although Combivent Respimat Inhalation Spray demonstrated efficacy and safety in the single pivotal 12-week study, no long-term study was conducted to support safety, acceptable device handling, and patient acceptance of Combivent Respimat Inhalation Spray as a replacement product for Combivent Inhalation Aerosol. BIPI will need to conduct a one-year study to support long-term use of Combivent Respimat Inhalation Spray in COPD patients. Data from such a study is required to conduct risk-benefit assessment.

c. Post-marketing Risk Management Activities

Not relevant because the application will not be approved.

d. Post-marketing Study Commitments

Not relevant because the application will not be approved.

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/s/

BADRUL A CHOWDHURY
08/07/2009

Cross Discipline Team Leader Review

Date	August 4th, 2009
From	Lydia Gilbert-McClain, M.D., FCCP
Subject	Cross Discipline Team Leader Review
NDA/BLA # Supplement#	21-747
Applicant	Boehringer Ingelheim
Date of Submission	October 7, 2008
PDUFA Goal Date	August 8, 2009
Proprietary Name / Established (USAN) names	Combivent Respimat Inhalation Spray/ Ipratropium bromide and albuterol sulfate
Dosage forms / Strength	
Proposed Indication(s)	1. For use in patients with chronic obstructive pulmonary disease (COPD) on a regulator aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator
Recommended	Complete response

1. Introduction

Boehringer Ingelheim Pharmaceuticals Inc. submitted a 505(b)(2) new drug application (NDA), dated October 7, 2008 (FDA receipt date October 8, 2008) for Combivent Respimat Inhalation Spray for use in patients with chronic obstructive disease (COPD) on a regular aerosol bronchodilator who require treatment with an additional inhaler. This is a combination product of an anticholinergic (ipratropium bromide) and a beta-adrenergic agonist (albuterol). The PDUFA date for this application is August 8, 2009. The review summarizes the salient aspects of the review and my recommendations on approvability. For details please refer to the primary discipline reviews. There are no disagreements among the disciplines and I concur with the efficacy and safety findings and conclusions reached in the clinical and statistical reviews.

2. Background

Combivent Respimat Inhalation Spray has a very long development history. BI began the Combivent Respimat program in 1999 but the initial discussion about the Combivent Respimat program took place in 1994. (b) (4) . The impetus to do this is due to the phase-out from the market of CFC- containing medications. CFCs (chlorofluorocarbons) are ozone-depleting substances which are harmful to the environment. On January 1, 1989, the Unites States became a Party to the Montreal Protocol on Substances that Deplete the Ozone Layer. In terms of

medications the goal is to ultimately remove all CFC-containing products from the market. CFC-containing medications received an essential use designation under 21 CFR 2.125 (e) which allowed them to be marketed for a period of time during which alternative formulations that do not contain CFCs would be developed.

The Respimat inhaler is a mechanically engineered design that produces an aerosol mist from a solution without the use of propellants, and therefore, this product would be an acceptable replacement for its CFC counterpart Combivent inhalation aerosol. (b) (4) By this time, other non-CFC containing aerosols were approved for albuterol [Proventil HFA (1996) and Ventolin HFA (2001)], and Atrovent HFA was approved 3 years later in November 2004.

(b) (4)

There have been numerous interactions between BI and the Agency on the development program for Combivent Respimat. BI submitted a protocol for Special Protocol Assessment (SPA) for a phase 3 pivotal study for a Combivent Respimat product containing 40 mcg ipratropium bromide and 200 mcg albuterol (Combivent Respimat 40/200) on November 7, 2001. Six months later, (May 2002), an End of phase 2 meeting was held and the agreements established at the earlier interactions with the Agency were reaffirmed. Namely, that BI could submit one pivotal efficacy and safety study with Combivent Respimat and that 6-month safety (b) (4) would be sufficient to support the long term safety of the Respimat device. A pre-NDA meeting was held in October 2003. The results of the first pivotal study did not support the efficacy of Combivent Respimat 40/200 because the study did not demonstrate the contribution of the individual active ingredients as required by the regulation set forth in 21 CFR 300.50. Following multiple interactions with the Division (Type C meeting January 2006, End-of phase 2 meeting May 2006) which focused on the efficacy aspect of the application, BI revised the phase 3 program and designed a second efficacy study to address the combination rule using a lower nominal dose (20/100) of Combivent Respimat. The Division and BI agreed with the final design of the study, including efficacy endpoints, and statistical analysis. Subsequently, another PreNDA meeting was held on February 8, 2008 and the Division agreed with the proposed contents of the planned NDA.

3. CMC/Device

- General product quality considerations

This new drug product is an inhalation spray delivered via the Respimat device. The drug substance is comprised of albuterol and ipratropium bromide. Once the device is actuated, it delivers 20 mcg of ipratropium bromide and 100 mcg of albuterol (equivalent to 120 mcg of albuterol sulfate) from the mouthpiece. The volume of each actuation is 11.4 microliters (mcl). The formulation is a sterile solution comprised of albuterol sulfate and ipratropium bromide as active ingredients, benzalkonium hydrochloride (b) (4) and EDTA (sodium edetate) (b) (4), water for injection, and (b) (4) hydrochloric acid. The drug product is labeled for 120 actuations for commercial products and 60 actuations for physician samples. A dose is (b) (4) actuations and the Respimat device contains an actuation counter.

The Respimat device has not been previously marketed in the U.S. The device is a hand-held, multi-dose, oral inhalation device that uses mechanical energy to generate a slow moving cloud of medication from a metered volume of drug solution. The Combivent sterile aqueous solution is contained in a 4.5 mL (b) (4) plastic container crimped inside an aluminum cartridge. Before use, the cartridge is fitted through the base of the inhaler. Twisting the base of the inhaler compresses a spring that draws a metered volume (b) (4) of solution from the cartridge into the dosing chamber of the inhaler. When the inhaler is actuated, a spring is released (b) (4) to form the slow-moving aerosol cloud.

- Facilities review/inspection

All the facilities inspections have been completed but the final reports are pending from one (b) (4).

- Other notable issues (resolved or outstanding)

There are no notable outstanding CMC issues other than the final reports of the inspections from the site (b) (4)

4. Nonclinical Pharmacology/Toxicology

There are no outstanding pharmacology/toxicology issues. The toxicology data for albuterol and ipratropium bromide alone and in combination have been previously characterized in the preclinical review for the Combivent inhalation aerosol product. There was no new preclinical information about the active ingredients albuterol and ipratropium bromide. The application included inhalation toxicity studies (2 weeks in rats and 3 months in dogs) of (b) (4) an aqueous albuterol solution containing benzalkonium chloride (excipient), and a 13-week inhalation toxicity study of EDTA and benzalkonium chloride in rats. These studies did not reveal any safety concerns.

5. Clinical Pharmacology/Biopharmaceutics

The Combivent Respimat is a combination of the anticholinergic ipratropium bromide and the beta$_2$-adrenergic agonist albuterol sulphate. The clinical pharmacology characteristics of Combivent are derived from the previous information for the individual ingredients. Given that this is an orally inhaled product, the majority of the delivered dose is deposited in the gastrointestinal (GI) tract.

Ipratropium bromide is a quaternary amine and hence it is not readily absorbed into the systemic circulation either from the surface of the lung or from the GI tract. Following inhalation or intravenous administration, the elimination half-life of ipratropium is about 2 hours, and 3.9 hours for albuterol following intravenous administration. The pharmacokinetic profile of Combivent 20/100 was evaluated in a subset of patients in the pivotal study 1012.56. The plasma concentration for ipratropium was low (peak 33pg/ml) and the majority of study participants had levels below the level of quantification (<10 pg/ml) by 4 to 6 hours post dose. The steady-state systemic exposure of albuterol from Combivent Respimat was less than the albuterol exposure from Combivent CFC MDI.

There was no pharmacokinetic drug-drug interaction between albuterol and ipratropium. There were no specific pharmacokinetic studies conducted to evaluate potential drug-drug interactions with other drugs. There does not appear to be any significant pharmacokinetic differences for albuterol or ipratropium due to age or gender.

6. Clinical Microbiology

The product is a sterile solution and the sterilization method (b) (4) There are no outstanding microbiology issues that would prevent approval of the product.

7. Clinical/Statistical- Efficacy

A total of 11 clinical studies were submitted in the NDA application. Of these studies, the clinical studies that formed the basis for the NDA review were: (i) two 12-week efficacy and safety studies, of which one is the pivotal efficacy study and the other, the supporting efficacy and safety study (with a higher nominal dose of Combivent Respimat); (ii) two dose ranging studies in COPD patients (one each with albuterol and ipratropium); and (iii) one 6-month safety study with ipratropium delivered via the Respimat inhaler. (b) (4) . The table below outlines the studies that formed the basis for the NDA review.

Table 1 (Selected) Clinical Studies in the Combivent Respimat NDA

Trial No	Objectives	Design	Test Products	No of patients	Study initiated (year)	Study sites
***1012.56**	**Efficacy and safety**	**Randomized, double-blind, double-dummy, active control parallel group**	**Combivent Respimat 20/100 mcg, Combivent CFC MDI 36/206 mcg, Ipratropium Respimat 20 mcg**	**1460**	**2006**	**179 total sites 87 U.S. sites**
1012.46	Efficacy and safety		Combivent Respimat 40/200, Combivent CFC MDI 36/206, Ipratropium Respimat 40 mcg	1118	2002	150 U.S. sites
244.2447	Dose ranging	Randomized DB PC 4-period incomplete cross-over	Ipratropium Respimat 10,20, 40,80,160 mcg Ipratropium CFC MDI 18 and 36 mcg	116	1995	5 U.S. sites
243.7	Dose ranging	Randomized DB PC cross-over study	Salbutamol Respimat 25, 50, 100, 200 Salbutamol CFC-MDI 100, 200 mcg, Placebo	62**	1996	4 U.S. study sites
244.2484	Efficacy and Safety	Randomized DB, parallel-group, placebo-controlled study	Ipratropium Respimat 20 mcg, 40 mcg Ipratropium CFC MD 36 mcg Ipratropium Respimat placebo Ipratropium CFC MDI placebo	646	1998	36 sites in Canada

*The pivotal efficacy study
**There is an error in the Primary Medical officer review page 161 where Table 63 cites the n as 56 the correct number is 62

A brief overview of the clinical efficacy study program for Combivent Respimat including the dose-ranging studies with the monotherapy products for dose selection for the Combivent Respimat product is described below.

Dose-ranging studies

Study 243.7 and 244.2447 were salbutamol (albuterol) and ipratropium bromide placebo-controlled single dose dose-ranging studies conducted in patients with COPD. The salbutamol dose-ranging study evaluated single doses 25, 50, 100, and 200 mcg delivered in the Respimat device. Salbutamol CFC-MDI 100 mcg and 200 mcg were included as active comparators. The ipratropium bromide dose ranging study evaluated doses of 10, 20, 40, 80 and 160 mcg delivered in the Respimat device and ipratropium CFC-MDI 18 and 36 mcg were included as active comparators. All doses of salbutamol and ipratropium were more efficacious than placebo. Numerically the salbutamol 100 and 200 doses delivered via the Respimat performed similarly to the salbutamol CFC-MDI 100 mcg. Likewise, the ipratropium 20 mcg and 40 mcg delivered via the Respimat performed similarly to the ipratropium CFC-MDI 36 mcg.

Efficacy Studies

There is one pivotal efficacy study (1012.56) and one supporting efficacy study (1012.46).

Study 1012.56

This study was conducted to evaluate the bronchodilator efficacy (and safety) of Combivent Respimat 20/100 in patients with COPD. As a combination product containing ipratropium bromide and albuterol, the typical study design to satisfy the combination rule (21 CFR 300.50) would have been a full factorial design where Combivent Respimat was compared to each of its individual active ingredients and demonstrate contribution by showing statistical superiority of the combination to each of the individual components for the claimed benefit. The design of this study was different in that (a) albuterol single ingredient was not included in the study and (b) a non-inferiority design was used. With this approach, the study was designed to fulfill three efficacy objectives all of which had to be met in order to support efficacy. These efficacy objectives were selected to take into account the known duration of action of the individual ingredients albuterol (up to 4 hours), and ipratropium (up to 6 hours), and the established bronchodilator efficacy of Combivent CFC-MDI. Conceptually, albuterol (in the combination) would be expected to work up to 4 hours therefore, a comparison of Combivent Respimat to ipratropium Respimat over the last 2 hours of the dosing interval (4 -6 hours) should demonstrate non-inferiority. Using a similar rationale, the comparison of Combivent Respimat to ipratropium Respimat over the first 4 hours (0 – 4 hours) should demonstrate superiority of Combivent Respimat to ipratropium Respimat alone and therefore, confirm the efficacy contribution of the albuterol component to the bronchodilator efficacy of Combivent. With this rationale, the study had three co-primary efficacy variables and comparisons as follows:

The three primary efficacy variables were defined as:

1) The mean FEV_1 over 0-6 hours post dose, defined as the AUC of the change from test-day baseline in FEV_1 over 0- 6 hours post-dose divided by 6 hours (FEV_1AUC_{0-6}hr)

2) The mean FEV_1 over 0-4 hours post-dose defined as the AUC of the change for test-day baseline in FEV_1 over 0 -4 hours post-dose divided by 4 hours (FEV_1AUC_{0-4hr} and

3) The mean FEV_1 over 4-6 hours post-dose defined as the AUC of the change from test-day baseline in FEV_1 over 4-6 hours post-dose divided by 2 hours (FEV_1AUC_{4-6hr})

Test-day baseline was the FEV_1 recorded prior to inhaling the dose of randomized medication on the test day.

The three primary efficacy comparisons were:

1) Non-inferiority of Combivent Respimat to Combivent CFC-MDI in FEV_1AUC_{0-6} hr on Test Day 85

2) Superiority of Combivent Respimat to ipratropium Respimat monotherapy in FEV_1AUC_{0-4} hr on Test Day 85 (this comparison would demonstrate the contribution of albuterol in the combination product)

3) Non-inferiority of Combivent Respimat to ipratropium Respimat monotherapy in FEV_1AUC_{4-6} hr on Test Day 85 (this comparison would demonstrate the contribution of ipratropium bromide in the combination product)

Boehringer Ingelheim proposed a non-inferiority margin of 50 ml and the Division concurred with the non-inferiority threshold. Secondary efficacy endpoints included FEV_1AUC on Days 1, 29,and 57, and several FEV_1 measures to assess time to onset of bronchodilation and duration of response (peak FEV_1, onset and duration of therapeutic FEV1 response), PEFR, as needed beta-agonists used, symptom scores, and physician's global evaluation on test Days 1, 29, 57, and 85.

Patients enrolled in the study had to have a diagnosis of COPD and had to meet spirometry criteria consistent with moderate to severe airway obstruction (i.e. $FEV_1 \leq 65\%$ predicted and $FEV_1/FVC \leq 70\%$ predicted) at screening, a smoking history of more than 10 pack years (i.e. smoking the equivalent of one 20-pack cigarettes/day/ year). The exclusion criteria were appropriate and included exclusion of patients with symptomatic prostatic hypertrophy or bladder neck obstruction, and patients with known narrow angle glaucoma.

Following the initial screening visit for patient eligibility assessment, patients received Atrovent (ipratropium) MDI (HFA or CFC depending on what was available in the study country) 2 puffs four times a day for two weeks. Following the run-in period, patients were randomized to one of the following three study treatment administered 4 times daily:

- Combivent Respimat (20/100 mcg) 1 puff + Placebo Combivent CFC-MDI 2 puffs
- Ipratropium bromide Respimat 20 mcg 1 puff + Placebo Combivent CFC-MDI 2 puffs
- Combivent CFC-MDI (18/103 mcg) 2 puffs + Placebo Combivent Respimat 1 puff

Patients were given the Respimat inhaler and the cartridge separately, and they had to assemble the product themselves. As a precaution against patients not having medication in the event of an inhaler malfunction, each study medication kit comprised of 2 Respimat inhalers, 2 cartridges, and two MDIs. The patients received instructions so that one set of inhalers were the primary inhalers and the other set of inhalers, the spare inhalers. Patients were instructed to use a spare inhaler only in the event that the primary inhaler malfunctions. The patients had to return any malfunctioning inhaler which would be returned to Boehringer Ingelheim for testing. Patients were seen every 28 days and were required to bring all inhalers at each study visit. At each visit, a new set of inhalers were given.

Patients who were on stable doses of inhaled steroids, theophylline preparations, mucolytic agents (not containing bronchodilators), and leukotriene receptor antagonists (prescribed for conditions other than asthma or excluded allergic conditions) for at least 6 weeks prior to screening were allowed to remain on those medications. As needed albuterol (salbutamol) was permitted as well as temporary use of oral steroids per investigator judgment to treat COPD exacerbations, and temporary increases in theophylline, and antibiotics as deemed appropriated for COPD exacerbations.

Patients recorded their study medication and any as needed albuterol/salbutamol use in an e-dairy. This e-diary also incorporated an electronic peak flow meter that is able to capture peak flow measurements. These data were later downloaded on a computer. In this way, the investigators reviewed the peak flow data and medication compliance with the patient at each study visit (every 28 days). At each visit baseline FEV_1 was measured (FEV_1 prior to inhaling study medication) and spirometry was obtained out to 6 hours following inhaling study medication. In addition to medication compliance, adverse events and concomitant therapy were evaluated at each visit. Patients were instructed to return with all inhalers (Respimat devices, cartridges, and MDIs) at each study visit.

To evaluate the device acceptability, to patients, a device questionnaire was administered to patients at 37 U.S. sites. The questionnaire consisted of 10 questions that asked about patient satisfaction with using the device, following the instructions to use the device, durability of the device, and the feeling of whether they were getting the medication into their lungs. In addition to the patient satisfaction survey, 100 normally functioning devices were collected from patients when the dose indicator reached the 30 dose mark (7 day supply left) from the 120 doses available for each inhaler for end-of-use testing. End-of use testing included plume shape, dose accuracy, and particle size distribution.

Results

A total of 1480 patients 40 to 88 years (mean 64) of age were randomized in the study and of these patients, data from 1460 patients were available for the efficacy analyses. Data from 20 patients from a French site could not be verified (by the sponsor) and so data from these patients were not included in the analysis. The patient disposition is outlined in the table below. The characteristics of the patients enrolled in the study were fairly similar. The patients had a diagnosis of COPD on average about 8.4 years and a mean FEV_1 % predicted at screening of 41.4% and FEV_1/FVC of 44.8. All patients were either current or former smokers, and the mean number of pack-years was 53.2. The mean age of patients in the study was 64 years, the majority (65%) was male and 89% were Caucasian. These demographic characteristics were matched across the treatment groups.

Compliance was assessed using the data downloaded from the e-diary and was evaluated at each study visit using the mean weekly number of actuations of study medication/day during the randomization period. The overall percentage compliance was calculated as the % of actual number of actuations of study medication divided by the total number of study actuations of study medication that the patient should have taken.

From the e-diary results the majority of patients were compliant with recording the study medication information in the diary and only a very small percentage of patients (0.08%) of the 1460 patients (fairly evenly distributed across the treatment groups) were not compliant in recording in the e-diary. Compliance was assessed for each inhaler (Respimat and MDI) and approximately 66% of patients had an overall percentage compliance of 80 - < 120%. A total of 39 (2.67%) patients recorded compliance of >120% with the Respimat devices compared to 0 patients reporting a 120% compliance with the MDI inhalers, but the mean number of puffs per day was 3.5 for the Respimat inhalers and 6.4 for the MDI (the total daily dose of the Respimat was 4 puffs and 8 puffs for the MDI.

Table 2. Patient Disposition Study 1012.56

Patient Disposition N (%)	**Combivent Respimat 20/100 N (%)**	**Combivent CFC-MDI 36/206 N (%)**	**Ipratropium Respimat 20 N (%)**	**Total N (%)**
Randomized	493	498	489	1480
Excluded from data set	7	7	6	20
*Modified ITT	486	491	483	1460
Completed	438 (90.1)	436 (88.8)	422 (87.4)	1296 (88.7)
Early discontinuation	48 (9.9)	55 (11.2)	20 (4.1)	164 (11.2)
Discontinuations due to:				
adverse events	19 (3.9)	34 (7.8)	35 (8.2)	88 (6)
Non-compliance	7 (1.4)	4 (0.8)	9 (1.9)	20 (1.4)
Lost to follow up	2 (0.4)	1 (0.2)	4 (0.8)	7 (0.5)
Withdrew consent	12 (2.5)	11 (2.2)	10 (2.1)	33 (2.3)
Other	8 (1.6)	5 (1.0)	3 (0.6)	16 (1.1)

* Since data could not be verified for 20 patients from one site, all the study results (efficacy and safety) are based on the patient population n of 1460. Protocol violations were few and do not impact the interpretation of the study results. In terms of efficacy, the three co-primary efficacy endpoints were met for all three primary efficacy comparisons as shown in the Table 3 below.

Table 3. Primary Efficacy Endpoints and Comparisons Study 1012.56

	Combivent Respimat (n = 474)	**Combivent CFC (n = 482)**	**Ipratropium Respimat (n = 468)**	**Combivent Respimat vs. Combivent CFC** **(FEV_1 AUC $_{0\text{-}6hr}$)**	**Combivent Respimat vs. Ipratropium Respimat** **($FEV_1AUC_{0\text{-}4hr}$)**	**Combivent Respimat vs. Ipratropium Respimat** **($FEV_1AUC_{4\text{-}6hr}$)**
Test day baseline Mean (SE) L	1.112 (0.010)	1.106 (0.010)	1.114 (0.010)			
Primary Endpoints						
$FEV_1AUC_{0\text{-}6\ hr}$ Mean (SE)	0.145 (0.007)	0.149 (0.007)	--	-0.003 (0.010) 95% CI (-0.022, 0.015)		
$FEV_1AUC_{0\text{-}4\ hr}$ Mean (SE)	0.189 (0.007)	---	0.142 (0.007)	--	0.047 (0.010) 95% CI (0.028, 0.066) P <0.001	
$FEV_1AUC_{4\text{-}6\ hr}$ Mean (SE)	0.056 (0.008)	---	0.073 (0.008)	---	---	-0.017 (0.011) 95%CI (-0.039, 0.005)

The results demonstrate that Combivent Respimat 20/100 mcg is non-inferior to Combivent inhalation aerosol 36/206 in terms of mean $FEV_1AUC_{0\text{-}6hr}$ and non-inferior to Ipratropium Respimat in terms of $FEV_1AUC_{4\text{-}6}$ hrs. In both instances, the lower bound of the 95% CI for the point estimate for the difference from Combivent Respimat was more than -50 ml (see Table 3). The demonstration of non-inferiority between Combivent Respimat and Ipratropium Respimat in the $FEV_1AUC_{4\text{-}6\ hr}$ demonstrates the contribution of ipratropium in the combination product, and the demonstration of superiority of Combivent Respimat compared to Ipratropium Respimat for the $FEV_1AUC_{0\text{-}4}$ hours

satisfies the demonstration of the efficacy contribution of albuterol in the combination product. The efficacy results were similar across age, and gender. The majority of patients were Caucasians so an effect on race could not be ascertained.

When these comparisons were evaluated on test Days 1, 29, and 57, similar results were noted. Other secondary endpoints such as symptoms and rescue medication use did not show any appreciable difference among treatment groups. Also, the PEFR values across the treatment groups did not show any appreciable difference among treatment groups. Onset and duration of therapeutic effect (bronchodilation) was assessed at various time points at each test day. The definition of bronchodilation used for these assessments (i.e. FEV_1 increase of 15% or greater) is acceptable. Using this definition, the median time to onset of a therapeutic effect was 13 mins on test day 1 and 12 mins on test Day 85. (b) (4)

Assessment of the ease of handling of the device and patient satisfaction was done with a questionnaire at the Week 12 visit. From the responses, it appears that the majority of the patients in this study did not have difficulty using the device and were satisfied that they were getting the medication into their lungs. However, in the Clinical Overview summary (page 57), Boehringer Ingelheim describes summary results for marketing research studies (U04-1260). In that summary, they mention that handling tests were conducted on 514 patients in 5 marketing studies and in the study with the highest sample size (n = 187), patients with hand or joint problems had some difficulties with cartridge insertion and the priming process, and that overall, insertion of the cartridge was identified as the most challenging part of the handling process in patients who had not previously used the Respimat inhaler. For patients with joint problems, opening the lower case was more challenging for them. It would be important to see the full reports of these handling studies in order to guide appropriate instructions for use by patients who may have joint problems.

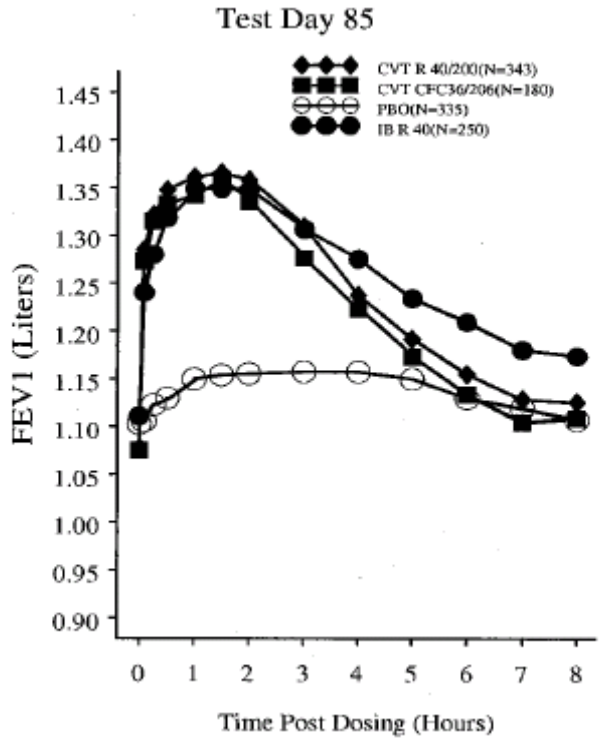
BI also assessed 100 normally functioning Combivent Respimat inhalers while there about 30 doses left and did end-of canister life testing, and noted that the CMC characteristics (spray plume, shape, volume, fine particle fraction of the release spray) was unchanged from the results at batch release.

Study 1012.46

The supporting efficacy study 1012.46 was the first efficacy study conducted for the Combivent Respimat product. A higher strength product (40/200) was used in this study. A total of 1118 COPD patients with similar entry characteristics as that of the study 1012.56 were enrolled. The study design was a randomized double-blinded (within inhaler) placebo and active treatment controlled 5-treatment, parallel group design with treatment duration of 12 weeks. At randomization patients were assigned to the following treatment arms administered 4 times a day: (i) Combivent Respimat 40/200 (n = 345); (ii) Ipratropium bromide Respimat 40 mcg (n = 252); (iii) Combivent CFC MID 36/206 (n = 180); (iv) placebo Respimat (n = 165) and (v) placebo CFC-MDI (n= 176).

The primary objectives of this study were to compare Combivent Respimat 40/200 to Combivent CFC-MDI 36/206, to show superiority of Combivent Respimat 40/200 to Ipratropium Respimat 40 mcg, and to characterize the steady-state pharmacokinetics of the individual components of Combivent Respimat 40/200 after 4 weeks of therapy.

The primary endpoint for the study was the $FEV_1AUC_{0\text{-}6\ hr}$ on Test Day 85. Compared to placebo, all active treatments, Combivent Respimat 40/200, Combivent CFC-MDI 36/206, and Ipratropium Bromide Respimat had a statistically significant FEV_1 response as measured by $FEV_1AUC_{0\text{-}6}$ hours on Day 85 ($p < 0.001$). Combivent Respimat 40/200 was not superior to Ipratropium Respimat 40 mcg for the primary efficacy endpoint of $FEV_1AUC_{0\text{-}6\ hr}$ on Day 85. Combivent Respimat 40/200 and Combivent CFC-MDI 36/206 were evaluated for comparability based on clinical judgment and not formal statistical testing. The $FEV_1AUC_{0\text{-}6\ hr}$ on Test Day 85 was 1.28L (SE = 0.013) for Combivent Respimat 40/200 and 1.26 L (SE = 0.017) for Combivent CFC MDI 36/206, showing a numerical difference in favor of Combivent Respimat 40/200. Although the primary efficacy endpoint was at 6 hours post dose, FEV_1 measurements were assessed out to 8 hours. It was observed that Ipratropium Respimat 40 mcg appeared to perform even better than Combivent Respimat 40/200 over the 4 – 8 hr time period (see figure below copied from the Primary Medical Officer Review Dr. Xu Wang page 146). From these results, the contribution of the individual components to the efficacy of the combination product has not been satisfied. BI explained that the findings as likely due to the dose selection for the Combivent Respimat being too high, and therefore, the second study (1012.56) was conducted with a lower dosage strength (20/100) of Combivent Respimat.



8. Safety

The safety database for Combivent Respimat includes data from the pivotal efficacy and safety 12-week treatment trial with Combivent Respimat 20/100, and data from a higher strength Combivent Respimat 40/200 12-week treatment trial. There are no long term safety data with Combivent Respimat. There is safety data from a 6-month Ipratropium Respimat safety study.

The safety from the pivotal 12-week treatment Combivent 20/100 study did not reveal any new safety signal. Adverse events were compared to the Combivent CFC comparator, and to Ipratropium

Respimat. The safety profile with the higher strength product (Combivent Respimat 40/200) did not reveal any new safety signals.

In the 6-month Ipratropium bromide Respimat study, there was a higher incidence of pharyngitis reported in the Ipratropium and placebo Respimat groups combined (12.3%) compared to the Combivent CFC-MDI and placebo groups (7.4%). The incidences of the other common (≥ 3%) adverse events were similar across the treatment groups.

The overall safety database is not sufficient to support approval of Combivent Respimat as long term safety data with the Combivent Respimat product are lacking. This is important from the standpoint of Combivent Respimat being a new drug product and from the standpoint that this product will be the replacement product for the Combivent CFC MDI currently on the market. The Combivent CFC MDI will ultimately no longer be available, in compliance with the removal of CFC-containing products on the market. The Respimat device is new and there are no Respimat products on the market at this time so that there is no long term experience with the Respimat inhaler. Controlled long-term safety data to compare the Respimat product to the current CFC MDI product are critical to provide information about any potential safety and or device handling issues long term. Since Combivent is going to be used chronically in the COPD population, data from a 12 week study alone is not sufficient to assess long-term safety.

Although Combivent CFC MDI was approved with no long term (12 month safety data), the device for the Combivent CFC is the typical press and breathe MDI inhaler that has been on the market for a long time and is a very familiar device in patients' hands. The lack of long term safety data with Combivent Respimat is an approvability issue. This issue was discussed with the sponsor in a T-con during the review cycle and the sponsor has subsequently proposed to conduct a 12-month safety and efficacy study primarily designed to look at safety and the device handling issues. The protocol was submitted to the IND (IND 57,948) during the review cycle and it was reviewed and comments were provided to the sponsor. The action letter will note the lack of long term safety data as a deficiency that needs to be resolved before the Combivent Respimat can be approved for marketing in the U.S.

9. Advisory Committee Meeting

An AC meeting was not convened for this application. The product is a fixed dose combination of 2 well knows moieties – albuterol and ipratropium and the proposed indication is consistent with the indication for the currently approved CFC version of the product. Because this product is meant to be a CFC-replacement product, the AC meetings that have been held previously to discuss these issues are relevant to this product. On July 14th, 2005, the PADAC met to discuss remaining uses of CFCs in MDIs (with the exception of epinephrine) The Proposed draft Rule for removal of Essential-Use Designations for the remaining 7 Ozone-depleting Substances (metaporterenol, pirbuterol, flunisolide, triamcinolone, cromolyn, nedocromil, and *albuterol/ipratropium (Combivent)* was discussed. Subsequently, the proposed rule (the so called "seven moiety" rule) was published in the federal register June 11, 2007[1] and an FDA Public meeting was convened on August 2nd, 2007. At that meeting, Boehringer Ingelheim indicated that the submission of Combivent Respimat NDA was

[1] Federal Register/vol 72, No 111/Monday June 11, 2007/Docket No. 2006N-0454, RIN 0910-AF93

targeted for the fourth quarter 2008. Thus their NDA submission data was consistent with their projected timeline. The Proposed Rule for the 7 moieties is in the process of being finalized.

10. Pediatrics

The indication for this product is chronic obstructive pulmonary disease (COPD) a disease that is characterized by airflow obstruction in adults due to primarily cigarette and tobacco smoking and to a lesser extent to persistent exposure to air pollutants. This type of obstructive disease does not exist in children and a full waiver should be granted for pediatric assessment. The PERC agreed with the decision to grant a full waiver based on the rationale that the studies would be impractical or impossible to conduct because the disease does not exist in children.

11. Other Relevant Regulatory Issues

An inspection by the Division of Scientific Investigations was conducted and there were no irregularities that would preclude the use of the data for decision making purposes. There are no financial disclosure issues. Since the facilities inspection report is still pending for one of microbial site in Germany, the Office of Compliance has not yet made a recommendation on the application.

12. Labeling

- Proprietary name

The proprietary name was reviewed by our OSE/DMEPA colleagues and the name was found to be acceptable

- Physician labeling

The physician labeling was reviewed by all the disciplines and by the Division of Drug Marketing Advertising and Communication (DDMAC) and labeling comments with a marked up proposed label were sent to the sponsor. The action letter will contain the revised proposed physician label (submitted July 20th, 2009) with additional comments for the sponsor. The label was extensively revised to be consistent with the new Physician Labeling Rule and for consistency with other labels in PLR format. The main outstanding labeling issue is (b) (4) . The (b) (4) of the physician labeling was not resolved at the labeling T-con with the sponsor and this will be conveyed in the labeling comments to the sponsor in the action letter. The primary medical officer's review contains the complete label that was sent to the sponsor in the first labeling fax on June 18th, 2009. On July 20th, BI submitted revised labeling that incorporated the majority of the Division's revisions. There were however, a few areas where BI proposed different labeling. These areas include (b) (4) Of these areas, the main areas of disagreement were (b) (4) Their rationale is not acceptable

[redacted] The following comments along with the revised marked up label should be included in the action letter.

Package Insert Labeling Comments for the Action Letter (Marked up revisions to the clean label submitted on July 20th, 2009 should be incorporated with the action letter)

1) In Section 2 (Dosage and Administration section), it states that if the drug product is [redacted] Revise [redacted] in Sections 2 (Dosage and Administration), Section 11 (Description) , and Section 17 (Patient Counseling Information) of the Package Insert.

2) In Section 5 (Warnings and Precautions) revise the heading in subsection 5.6 to read "Hypersensitivity Reactions Including Anaphylaxis," and delete the word [redacted] from the first line of first sentence. [redacted]

3) In Section 6 (Adverse Reactions) Subsection 6.1, revise the table to include the adverse reactions that occurred at a frequency of ≥ 2% in the COMBIVENT RESPIMAT treatment group. These events cannot be excluded from the Adverse Reactions table, because it is plausible that these events may be drug-related. Revise Table 1 to include these events. Also revise the rest of subsection 6.1 to incorporate the revisions noted in the marked up label.

4) In Section 8 (Use in Specific Populations) Subsection 8.1 (Pregnancy), add " and rabbits" to the sentence "However, albuterol sulfate has been shown to be teratogenic in mice *and rabbits*. In addition, add *"and rabbits"* to the first sentence under "Albuterol" in Section 13 (Nonclinical Toxicology) Subsection 13.2 (Animal Toxicology and Pharmacology).

5) In Section 8 (Use in Specific Populations), Subsection 8.5 (Geriatric Use) delete the words [redacted] from the last sentence as this minimizes the risk.

6) In Section 10 (Overdosage) change [redacted].

7) In section 11 (Description) Retain the statement *"The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the*

actuation of the device and inspiration, through the delivery system." The statement is consistent with language in other orally inhaled product labels.

8) In Section 12 (Pharmacology) Subsection 12.3 (Pharmacokinetics), revise the statement to read (b) (4) [redacted]

9) In Section 14 (Clinical Trials), delete the sentence (b) (4) [redacted]

10) Update the HIGHLIGHTS to incorporate the changes made to the Full Prescribing Information.

- Carton and immediate container labels (if problems are noted)

The Carton and immediate container labels were reviewed by the CMC team and labeling comments will be sent to the sponsor in the action letter. These labeling comments can be found on pages 155 - 156 of Dr. Alan Schroeder's review.

- Patient labeling/Medication guide (if considered or required)

This product does not need a Medication guide. Patient instructions for use labeling were submitted with the application but these were not reviewed in this cycle. Given that the application will not be approved in this cycle, and the physician labeling was very extensive, patient labeling was deferred for the next review cycle. Furthermore, data from the one-year safety study will be important to guide the information needed in the patient instructions for use.

13. Recommendations/Risk Benefit Assessment

- Recommended regulatory action

I recommend that the application be given a complete response.

- Risk Benefit Assessment

A full risk benefit assessment cannot be completed at this time. In the 12-week studies there were no new safety signals. However, in the 6-month study with ipratropium bromide Respimat, a disproportionate number of cases of pharyngitis was seen in the Respimat groups (active and placebo) compared to patients in the CFC MDI groups (active and placebo. It will be important to review the one year safety data carefully, to assess whether the new device portends a different safety profile from that of the MDI device. The beneficial effects of the active ingredients as bronchodilators are well established for the COPD population.

- Recommendation for Postmarketing Risk Management Activities

There are no recommendations for postmarketing studies at this time. It is unlikely that a REMS will be necessary for this product.

- Recommendation for other Postmarketing Study Commitments

A full wavier for pediatric studies under PREA is appropriate for this product because the indication is for a disease that does not exist in children.

- Recommended Comments to Applicant

You have not provided adequate data to support approval of Combivent Respimat 20/100 for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator. While efficacy of Combivent 20/100 has been demonstrated, you have not provided safety data beyond 12 weeks to support the long-term use of Combivent Respimat in patients with COPD.

To support approval of Combivent Respimat 20/100 for use in patients with COPD, provide:

- Data from a long term safety study (ies) with a treatment duration of at least 1 year to compare the safety (and efficacy) of Combivent Respimat 20/100, to the currently marketed Combivent CFC MDI, and currently marketed albuterol and ipratropium bromide MDIs administered together.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21747	ORIG 1		COMBIVENT RESPIMAT

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

/s/

LYDIA I GILBERT MCCLAIN
08/04/2009

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-747
Submission Code	N-000
Letter Date	10/07/08
Stamp Date	10/08/08
PDUFA Goal Date	08/08/09
Reviewer Name	Xu Wang, M.D., Ph.D.
Review Completion Date	07/02/09
Established Name	Ipratropium bromide and albuterol sulfate inhalation spray
(Proposed) Trade Name	Combivent Respimat
Therapeutic Class	β_2 agonist, anticholinergic combination
Applicant	Boehringer Ingelheim
Priority Designation	S
Formulation	Oral inhalation spray
Dosing Regimen	One inhalation (20/100 mcg) four times a day. Patients may take additional inhalations as needed. The total number of inhalations should not exceed six in 24 hours.
Indication	For use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator, who continue to have evidence of bronchospasm, and who require a second bronchodilator
Intended Population	Patients with COPD

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The clinical recommendation for this application is a "complete response" action.

The efficacy of Combivent Respimat (20/100 mcg) Inhalation Spray is demonstrated by a 12-week pivotal clinical study and supported by another 12-week study using a higher dose of Combivent Respimat in patients with chronic obstructive pulmonary disease (COPD). The safety data submitted in the Combivent Respimat (20/100 mcg) Inhalation Spray clinical program are not sufficient to support approval. To support this application, long term assessment is required to evaluate the safety and patient acceptability of the proposed drug product.

1.2 Recommendation on Postmarketing Actions

This section does not apply as the recommended regulatory action is complete response.

1.2.1 Risk Management Activity

This section does not apply as the recommended regulatory action is complete response.

1.2.2 Required Phase 4 Commitments

This section does not apply as the recommended regulatory action is complete response.

1.2.3 Other Phase 4 Requests

This section does not apply as the recommended regulatory action is complete response.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Combivent Respimat (20/100 mcg) Inhalation Spray was developed to replace the currently marketed Combivent Inhalation Aerosol CFC MDI for use in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator. The proposed drug product consists of Combivent inhalation spray delivered via the Respimat device. Each inhalation delivers 20 mcg ipratropium bromide/100 mcg albuterol (base) per spray from the mouthpiece.

The clinical program of Combivent Respimat (20/100 mcg) Inhalation Spray includes one 12-week pivotal study for efficacy and safety of the proposed drug product in patients with COPD, a 12-week efficacy and safety study for a higher dose of Combivent Respimat (40/200 mcg), and a 6-month safety study for ipratropium Respimat. The Applicant also included the reports of multiple studies with the single ingredient components delivered by the Respimat device,

including two dose ranging studies for ipratropium Respimat and albuterol Respimat in the NDA submission to support the dose selection for Combivent Respimat (20/100 mcg) Inhalation Spray. (b) (4)

The efficacy of the proposed drug product Combivent Respimat (20/100 mcg) Inhalation Spray was evaluated in one pivotal study. The pivotal study was a three-treatment, 12-wcek, randomized, multi-national, parallel-group, double-blind, double-dummy, active controlled study. There were 1,480 male or female COPD patients aged 40 or older randomized into treatment groups in this study. Twenty randomized patients in a French study center were excluded because the accuracy of their recorded data could not be verified [Volume 5.19, Section 5.3.5.1, page 92]. Thus, a total of 1,460 patients received the following three treatments:

(1) Combivent Respimat (ipratropium bromide 20 mcg/albuterol 100 mcg) Inhalation Spray, one inhalation 4 times daily plus placebo Combivent CFC-MDI (N=486)
(2) Ipratropium bromide Respimat (ipratropium bromide 20 mcg), one inhalation 4 times daily plus placebo Combivent CFC-MDI (N=483)
(3) Combivent CFC-MDI (ipratropium bromide 36 mcg/albuterol 206 mcg), two inhalations of 18 mcg/103 mcg 4 times daily plus placebo Combivent Respimat (N=491)

The primary efficacy measurement for the 12-week study was FEV_1 response after 12-week treatment (on test day 85). The area under the curve (AUC) of the FEV_1 change from the test day baseline was used as the primary efficacy measurement. Test day baseline was the FEV_1 recorded prior to inhaling the dose of randomized treatment on test day. There were three co-primary efficacy variables in this study:

(1) Mean FEV_1 over 0 to 6 hours post-dose, defined as the AUC of the change from test day baseline in FEV_1 over 0 to 6 hours post-dose divided by 6 hours (FEV_1 AUC_{0-6}). The primary comparison was to determine the non-inferiority of Combivent Respimat 20/100 mcg compared to Combivent Inhalation Aerosol 36/206 mcg over the period of 0 to 6 hours post-treatment on test day 85. The non-inferiority criterion has been set as the difference of the two treatments in mean FEV_1 AUC_{0-6} change is not statistically significant and the 95% confidence interval (CI) of the difference is less than 50 mL.

As noted, Combivent Respimat has been developed to replace currently marketed Combivent Inhalation Aerosol, a CFC-containing product. The first co-primary efficacy variable is to determine if Combivent Respimat is efficaciously comparable to Combivent Inhalation Aerosol in the treatment of COPD patients.

(2) Mean FEV1 over 0 to 4 hours post-dose, defined as the AUC of the change from test day baseline in FEV_1 over 0 to 4 hours post-dose divided by 4 hours (FEV_1 AUC_{0-4}). The primary comparison was to determine the superiority of Combivent Respimat 20/100 mcg compared to ipratropium Respimat 20 mcg over the period of 0 to 4 hours post-treatment on test day 85. The superiority criterion has been set as the difference of the two treatments in mean FEV_1 AUC_{0-4} change is statistically significant and the 95% confidence interval of the difference is more than 50 mL.

The second co-primary efficacy variable is to show the efficacy of the albuterol component of this combination drug product. Albuterol is a short acting β agonist, with

its bronchodilation effect persisting for about 3 to 4 hours. Within the first 4 hours post-dosing, Combivent Respimat 20/100 mcg should be superior to ipratropium Respimat 20 mcg alone in the treatment of COPD patients.

(3) Mean FEV_1 over 4 to 6 hours post-dose, defined as the AUC of the change from test day baseline in FEV_1 over 4 to 6 hours post-dose divided by 2 hours (FEV_1 AUC_{4-6}). The primary comparison was to determine the non-inferiority of Combivent Respimat 20/100 mcg compared to ipratropium Respimat 20 mcg over the period of 4 to 6 hours post-treatment on test day 85. The non-inferiority criterion has been set as the difference of the two treatments in mean FEV_1 AUC_{4-6} change is not statistically significant and the 95% confidence interval of the difference is less than 50 mL.

The third co-primary efficacy variable is to show the efficacy of the ipratropium component of this combination drug product. When the effect of albuterol fades after 4 hours of administering the combination product, the brochodilation effect of Combivent Respimat 20/100 mcg should be comparable to that of ipratropium Respimat 20 mcg in the treatment of COPD patients.

The safety evaluation included adverse events, vital signs, physical examination, clinical laboratory tests, and ECG from the pivotal study and supportive studies. Noticeably, there were no long term (one year) safety studies in this NDA submission to assess the long term safety and patient acceptability of the proposed drug product.

1.3.2 Efficacy

From an efficacy perspective, the results of the pivotal study are sufficient to support approval of Combivent Respimat (20/100 mcg) Inhalation Spray for the indication of the treatment in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator, who continue to have evidence of bronchospasm, and who require a second bronchodilator.

There were 1,424 study subjects that provided PFT data in the efficacy analyses. On test day 85, the Combivent Respimat (20/100 mcg) Inhalation Spray group had a mean FEV_1 AUC_{0-6} change from test day baseline of 145 mL compared to 149 mL for the Combivent CFC-MDI 36/206 mcg group. The difference was -4 mL with the 95% CI of -22 mL to 15 mL. The criterion of non-inferiority was met and the Combivent Respimat (20/100 mcg) Inhalation Spray was considered non-inferior to Combivent CFC-MDI 36/206 mcg, because the lower bound of the 95% CI of the difference was more than -50 mL.

The Combivent Respimat (20/100 mcg) Inhalation Spray group had a 189 mL mean change in FEV_1 AUC_{0-4}, and the ipratropium Respimat 20 mcg group had a 142 mL mean change in FEV_1 AUC_{0-4} from test day baseline on test day 85. The difference of the mean change in FEV_1 AUC_{0-4} from test day baseline was 47 mL, with a p-value of <0.0001 and 95% CI from 28 to 66 mL. The result showed that Combivent Respimat (20/100 mcg) Inhalation Spray was superior to ipratropium Respimat 20 mcg in the mean changes in FEV_1 AUC_{0-4} from test day baseline. This demonstrated the efficacy contribution of albuterol in this combination product.

Albuterol is a short acting β agonist, with its bronchodilation effect persisting for about 3 to 4 hours. The FEV_1 AUC_{4-6} was design to measure the efficacy of ipratropium component of the

combination product. The Combivent Respimat (20/100 mcg) Inhalation Spray group had a mean FEV_1 AUC_{4-6} change of 56 mL from test day baseline compared to 73 mL for the ipratropium Respimat 20 mcg group on test day 85. The difference in the mean change in FEV_1 AUC_{4-6} between two groups was 17 liters. This difference was slightly in favor of the ipratropium Respimat (20 mcg) Inhalation Spray group, but it was not statistically significant (95% CI: -39 to 5 mL). Also the 95% confidence interval of the difference is less than 50 mL. The result demonstrated that the Combivent Respimat (20/100 mcg) Inhalation Spray was non-inferior to ipratropium Respimat 20 mcg in the mean change in FEV_1 AUC_{4-6} from test day baseline.

Subgroup analyses were performed for different gender groups and patients over 65 years of age versus those under 65 years of age. In this 12-week study no differences in FEV_1 AUC change from test day baseline were identified within males versus females or in patients over 65 years of age versus those under 65 years of age. There were too few African-American subjects to adequately assess differences in effects in that population.

1.3.3 Safety

Safety was evaluated from the pivotal study, a 12-week study for Combivent Respimat 40/200 mcg, and a 6-month study for ipratropium Respimat. There are no long term (one year) studies for any Respimat inhaler to evaluate its safety and patient acceptability. As a replacement of Combivent MDI that has been broadly used by patients with COPD, Combivent Respimat (20/100 mcg) Inhalation Spray is expected to be used regularly in the COPD patient population. Long term assessment is needed to evaluate the long term safety and patient acceptability of the proposed drug product. The Applicant has proposed a one year study to evaluate the safety and patient acceptability of the proposed drug product in patients with COPD.

In the two 12-week Combivent Respimat studies, a total of 831 COPD patients were exposed to Combivent Respimat (485 for 20/100 mcg and 345 for 40/200 mcg, respectively). Additionally, a total of 900 COPD patients were exposed to ipratropium Respimat or placebo Respimat in these two 12-week studies. In the 6-month study for ipratropium Respimat, a total of 415 COPD patients were exposed to ipratropium Respimat or placebo Respimat. The safety evaluation included adverse events, vital signs, physical examination, clinical laboratory tests, and ECG.

There were 12 deaths in the three clinical studies (eight in the two 12-week studies and four in the 6-month study). The death cases are reviewed in Section 7.1.1. It appears that the deaths were not test drug related. All death cases were contributed to concomitant serious diseases, conditions, or accidents. The vital signs, physical examination, clinical laboratory tests, and ECG did not revealed safety signals in the three clinical studies.

The common adverse events were respiratory system disorders, accounting for the majority of adverse event cases in all three clinical studies. The single most common adverse event in two 12-week studies was COPD exacerbation. For the 6-month study, COPD exacerbation was the second most common adverse event (22.8%), next to cases of upper respiratory tract infection (28.3%). Other common adverse events were cough, dyspnea, bronchitis, sinusitis, and headache. These adverse events were not unexpected in COPD population, and were similar in incidence across the treatment groups including placebo group.

The patients in the 6-month study had a higher incidence of pharyngitis (10.5%) compared to that of the two 12-week studies (3.6% and 4.1%). Noticeably, the incidence of pharyngitis in the 6-month study was not evenly distributed in treatment groups. The patients in the ipratropium Respimat 40 mcg group had the highest incidence of pharyngitis (16.4%), and the patients with Respimat device (ipratropium Respimat 20, 40 mcg and placebo Respimat combined) had more pharyngitis (12.3%) than that of the patients with MDI device (7.4%, placebo MDI and Atrovent MDI 36 mcg combined). This could be a potential safety concern that long term use of Respimat may be related to high incidence of pharyngitis and, therefore, affect the acceptance of the COPD population to the proposed drug product.

In a tele-conference on March 11, 2009, the Applicant was informed that long term (one year) safety and patient acceptability data are needed to support the proposed drug product. The Applicant subsequently submitted a protocol to conduct a one year safety and patient acceptability study protocol for Combivent Respimat (20/100 mcg) Inhalation Spray on May 18, 2009.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen for Combivent Respimat (20/100 mcg) Inhalation Spray is "One inhalation (20/100 mcg) four times a day. Patients may take additional inhalations as needed." This regimen and choice of dose is supported by the data from the pivotal study.

1.3.5 Drug-Drug Interactions

There are no drug interaction studies conducted with Combivent Respimat and other medications commonly used in the treatment of COPD. COPD patients in clinical studies for Combivent Respimat were permitted to be on stabilized therapy with low dose of oral corticosteroids, orally inhaled corticosteroids, theophylline preparations, mucolytic agents, leukotriene receptor antagonists, and as needed albuterol inhalation. No interactions were observed between these drugs and Combivent Respimat.

1.3.6 Special Populations

There were no studies in special populations for Combivent Respimat (20/100 mcg) Inhalation Spray to review. Because Combivent Respimat (20/100 mcg) Inhalation Spray and Combivent Inhalation Aerosol MDI contain the same active ingredients, language regarding pregnancy, labor and delivery, and nursing mothers is taken from the approved Combivent Inhalation Aerosol MDI labeling for the Combivent Respimat (20/100 mcg) Inhalation Spray labeling. No differences in efficacy were observed in geriatric patients. Although patients of 65 years of age and older had a slightly higher frequency of adverse events than patients of less than 65 years of age, no dose adjustment is proposed.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Combivent inhalation spray is a combination of ipratropium bromide and albuterol sulfate. Ipratropium bromide is an anti-cholinergic bronchodilator chemically related to atropine. Ipratropium bromide is a white to off-white crystalline substance freely soluble in water and methanol, slightly soluble in ethanol, and insoluble in lipophilic solvent such as ether, chloroform, and fluorocarbons. Albuterol sulfate is a relatively selective $beta_2$ adrenergic bronchodilator. Albuterol is the official generic name in the United States. In Europe albuterol is officially called salbutamol that is the name used in this NDA submission. Albuterol is a white to off-white crystalline substance freely soluble in water and slightly soluble in ethanol, chloroform, and ether.

The drug product Combivent Respimat (20/100 mcg) Inhalation Spray consists of a sterile aqueous inhalation solution of ipratropium bromide and albuterol sulfate in a 4.5 mL cartridge and a Respimat inhaler. Excipients include water for injection, benzalkonium chloride, edetate disodium and hydrochloric acid. Respimat inhaler is an oral inhalation device that uses mechanical energy to generate a slow moving aerosol cloud of medication. The cartridge with the inhalation solution and the Respimat inhaler are supplied as two entities in one package. Prior to first use, the patient inserts the cartridge into the device and prime the inhaler. Each inhalation delivers 20 mcg ipratropium bromide/100 mcg albuterol (base) per spray from the mouthpiece.

2.2 Currently Available Treatment for Indications

There are several drug classes available for relief of bronchospasm in patients with COPD. These include beta-adrenergic agents, anti-cholinergic agents, combination beta agonists/ anti-cholinergics, methylxanthines, and combination corticosteroid/long-acting beta agonists. Table 1 listed currently available drugs in the United States for treatment of COPD.

Table 1 Currently available drugs for treatment of COPD

Trade name	Generic name	Drug class	Formulation
Ventolin and others	albuterol	Short-acting β-agonist	MDI, Inhalation solution
Serevent Diskus	salmeterol	Long-action β-agonist	DPI
Foradil Aerolizer	formoterol	Long-action β-agonist	DPI
Brovana	formoterol	Long-action β-agonist	Inhalation solution
Atrovent	ipratropium	Short-acting anticholinergic	MDI, Inhalation solution*
Spiriva HandiHaler	tiotropium	Long-action anticholinergic	DPI
Many brands	theophylline	methylxanthine	Tablet/capsule/injectable
Combivent	Ipratropium/albuterol	Combination product	MDI
Duoneb	Ipratropium/albuterol	Combination product	Inhalation solution
Advair Diskus	Fluticasone/salmeterol	Combination product	DPI

DPI: dry powder inhaler; MDI: metered dose inhaler
* Ipratropium bromide inhalation solutions are also available as generic drug products.

2.3 Availability of Proposed Active Ingredient in the United States

Ipratropium bromide is currently marketed as Atrovent inhalation aerosol HFA MDI (NDA 21-527) and as an active ingredient of combinations of Duoneb inhalation solution (NDA 20-950) and Combivent inhalation aerosol MDI (20-291). Multiple generic inhalation solution drug products are also approved for ipratropium bromide as single ingredient drug products and in combination with albuterol. Albuterol sulfate is currently marketed as Ventolin HFA MDI (NDA 20-983), Proair HFA MDI (NDA 21-457), Proventil HFA MDI (NDA20-503), and is available as an active ingredient of combinations of Duoneb inhalation solution (NDA 20-950) and Combivent inhalation aerosol MDI (20-291). No major safety concerns have been identified post approval for ipratropium bromide and albuterol sulfate products.

2.4 Important Issues With Pharmacologically Related Products

Ipratropium bromide is a short-acting, anticholinergic bronchodilator that is approved for use in patients with COPD. Ipratropium bromide has proved to be relatively safe in the COPD patient population. According to the product label for Atrovent HFA, 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.

Albuterol is approved for use in patients with obstructive airway disease including asthma and COPD. Albuterol is a commonly used short-acting $beta_2$ adrenergic bronchodilator that has proved to be safe in patient with obstructive airway disease. According to the product label for Ventolin HFA, the product, like all other sympathomimetic agents, should be used with caution in patients with underlying cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Immediate hypersensitivity reactions may occur after administration of albuterol sulfate inhalation aerosol, as demonstrated by cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

2.5 Presubmission Regulatory Activity

Combivent Respimat (20/100 mcg) Inhalation Spray was developed to replace the currently marketed Combivent Inhalation Aerosol CFC MDI that is currently the only ipratropium/albuterol MDI marketed in the United State, although several ipratropium/albuterol solutions are available for use with a nebulizer. Because of the ongoing CFC phase out of CFC-containing medications in response to the U.S. agreement with the global treaty for removal of substances that damage the ozone layer (i.e. the Montreal Protocol), the proposed Combivent Respimat is important to the patients who are using Combivent CFC-MDI that will eventually become unavailable after the rule is finalized.

Combivent Inhalation Aerosol CFC-MDI (NDA 20-291) was approved October 24, 1996. The approved dosage of Combivent Inhalation Aerosol CFC-MDI is ipratropium bromide 36 mcg/albuterol sulfate 206 mcg (delivered as two inhalations of 18/103 mcg) four times daily for patients with COPD. (b) (4)

(b) (4). In the last 7 - 8 years the Applicant has had several interactions with the Agency over the study design and endpoints of the clinical trials for Combivent Respimat. A Special Protocol Assessment of the pivotal clinical trial for Combivent Respimat submitted and reviewed by the Division in 2001 [IND 57,948, Special Protocol Assessment, Medical Officer Review, Raymond F. Anthracite, M. D., November 7, 2001]. The pivotal clinical trial (Study 1012.46) and the planned NDA submission were further discussed in a pre-NDA meeting on September 24, 2003 [IND 57,948, Pre-NDA Package Review, Carol Bosken, M. D., September 30, 2003; IND 57,948, Pre-NDA Meeting Minutes, October 24, 2003].

The clinical trial (Study 1012.46) was completed in 2004. Study 1012.46 was a Phase 3, randomized, double-blind, 12-week, parallel group study in 1,148 patients with COPD. In this study, there were five study medications including both Respimat and CFC placebos: (1) Combivent Respimat 40/200 mcg, (2) Combivent CFC 36/206 mcg, (3) ipratropium Respimat 40 mcg, (4) placebo Respimat, and (5) placebo CFC all administered four times daily. The primary efficacy endpoint was FEV_1 AUC_{0-6} at study day 85. All active treatments were superior to placebo. In addition, there was a numerical separation of Ipratropium Respimat from Combivent Respimat from the 4 hour time point which reached statistical significance at the FEV_1 AUC_{6-8} hour interval. The study results demonstrated that the ipratropium Respimat mono-therapy (treatment 3) comparator produced better FEV_1 values than the Combivent Respimat (treatment 1) at the end of an 8-hour dosing interval on study days 29, 57 and 85, thus not showing the combination was superior to the individual active ingredients. PK data showed that, despite similar nominal doses, there were higher drug exposures from the Respimat device than from the CFC MDI. (b) (4)

The Applicant therefore developed a lower dosage form of Combivent Respimat (20/100 mcg). Since December 2005 the Division and the Applicant have discussed the study protocol several times [IND 57,948, Meeting Minutes, January 9, 2006; IND 57,948, Meeting Minutes, May 11, 2006; and IND 57,948, Biometrics Review, Feng Zhou, June, 12, 2006]. The proposed study (Study 1012.56) was similar in study design and endpoints to the Study 1012.46 except for the decreased delivering doses of ipratropium and albuterol. The Division agreed that the study would be a randomized, double-blind, double-dummy, parallel-group, active-control, 12-week study in approximately 1,500 patients with COPD. The patients would be randomized 1:1:1 to receive (1) Combivent Respimat 20/100 mcg plus placebo Combivent CFC-MDI, (2) Combivent CFC-MDI 36/206 mcg plus placebo Combivent Respimat, and (3) ipratropium bromide Respimat 20 mcg plus placebo Combivent CFC-MDI, all administered four times daily. The agreed upon co-primary endpoints were:

(1) Non-inferiority of Combivent Respimat 20/100 mcg to Combivent CFC-MDI 36/206 mcg in FEV_1 AUC from 0 to 6 hours at Day 85,
(2) Superiority of Combivent Respimat 20/100 mcg to ipratropium bromide Respimat 20 mcg in FEV_1 AUC from 0 to 4 hours at Day 85 (to assess the albuterol contribution to the combination product), and
(3) Non-inferiority of Combivent Respimat 20/100 mcg to ipratropium bromide Respimat 20 mcg in FEV_1 AUC from 4 to 6 hours at Day 85.

The non-inferiority margin would be 50 ml for the lower limit of the confidence interval.
In a pre-NDA meeting on January 16, 2008, the Division accepted the Applicant's plan to submit the NDA with only one pivotal clinical study 1012.56 to support the efficacy of Combivent

Respimat with reservations: "The Division does have reservations regarding your plan to perform a single "pivotal" clinical trial especially since previous studies have failed to demonstrate that the combination is superior to each of its components. However, if efficacy findings are robust, a single trial may be sufficient to establish efficacy." [IND 57,948, Pre-NDA Meeting Minutes, February 1, 2008]

2.6 Other Relevant Background Information

Respimat, as a novel inhalation drug delivering device, has not been approved for any drug product in the United States. The long term safety and patient acceptability are unknown. There were no long term (one year) safety studies in this NDA submission. In a tele-conference on March 11, 2009, the Applicant was informed that long term (one year) safety and patient acceptability data are needed to support the proposed drug product. Subsequently, the Applicant submitted a study protocol under IND 57,948 on May 18, 2009, to conduct a one year safety and patient acceptability study for the proposed drug product. The proposed study is entitled "One-year, randomized, open-label safety and patient acceptability study of Combivent (ipratropium bromide/salbutamol) (20/100 mcg) Respimat inhalation spray in comparison to Combivent inhalation aerosol (36/206 mcg) in adults with chronic obstructive pulmonary disease (COPD)." Comments to the study protocol have been conveyed to the Applicant.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The product Combivent Respimat consists of a sterile aqueous inhalation solution of ipratropium bromide and albuterol sulfate in a 4.5 mL cartridge and a Respimat inhaler. Respimat inhaler is a novel oral inhalation device that uses mechanical energy to generate a slow moving aerosol cloud of medication. The cartridge with the inhalation solution and the Respimat inhaler are supplied as two entities in one package. Prior to first use, the patient inserts the cartridge into the device and primes the inhaler.

The cartridge that contains the drug solution consists of (b) (4)

an aluminum cylinder (b) (4) and a tamper protection seal. (b) (4)

Being a novel device, the Respimat inhaler was developed with several interim versions. For Combivent Respimat, two versions of the device are of importance: (1) the Respimat version A4 – it has been used in the phase 3 clinical study (1012.46), delivering 40 mcg of ipratropium bromide and 200 mcg of albuterol per actuation. (2) the Respimat version A5, which is intended for the commercial product; it has been used in primary stability studies and in phase 3 trial 1012.56, delivering 20 mcg ipratropium bromide/100 mcg albuterol (base) per spray from the mouthpiece. (b) (4)

(b) (4) The Respimat A5 inhaler is the final inhaler intended to be marketed.

Functionality and in use studies indicate that the devices were fairly robust. In the Combivent Respimat clinical phase 3 trials 1012.46 and 1012.56 approximately 10,600 Respimat A4 and A5 inhalers were used by patients. Only four out of 35 suspected malfunctioning inhalers could be confirmed as relevant in trial 1012.46. This is confirmed in trial 1012.56 where no malfunctioning inhalers were reported.

In the pivotal study 1012.56, 100 normally functioning Combivent Respimat inhalers were collected from patients at 37 study sites in the United States when the dose indicator reached the 30 dose remaining mark from 120 doses available for each inhaler. These inhalers were tested for the shape of spray plume, dose accuracy, and particle size distribution. All the sprays from the collected inhalers exhibited a normal cone-shaped spray plume. The mean value of the metered spray volume was 99% of the target value of (b) (4) The fine particle fraction (b) (4) of the released spray as determined by laser diffraction remained unchanged from the results at batch release.

In a 6-month safety study for ipratropium Respimat (244.2484), 30 Respimat devices that had been used by patients in the study for 20 weeks were collected. Each device had been released for 30 months and been used for 20 weeks (600 puffs and five cartridges) in the study. The devices were tested with new cartridges containing 0.833% fenoterol hydrobromide test solution. The Applicant stated that the actuation mode of the devices simulated actual patient use. There were no changes in the testing parameters observed in the Respimat devices collected from patients that had been released for 30 months and been used for 600 puffs and five cartridges in the study compared to the initial results of the device batch release.

The inhalation solution in an unopened cartridge is sterile. (b) (4) manufacturing has been chosen and has been assured by validation. (b) (4) In addition to sterility testing of the unopened cartridge, (b) (4) test was also performed and validated to assure microbial control.

Detailed CMC information can be found in ONDQA Review [NDA 21-747 N-000, Chemistry Review, Alan C. Schroeder, Ph. D., June 4, 2009].

3.2 Animal Pharmacology/Toxicology

This application was submitted under Section 505(b)(2) of the Food, Drug & Cosmetic Act, which permits that the submission relies on the Agency's previous pre-clinical and clinical findings to support the approval of the propose drug product.

There were no new animal pharmacology data in this submission. There no new genetic toxicity data, carcinogenicity data, reproductivity toxicology data in this submission. The relevant toxicology data for albuterol and ipratropium had been reviewed and considered previously in

setting acceptable specifications in other products [NDA 21-747 N-000, Pharmacology and Toxicology Review, Luqi Pei, Ph. D., April 14, 2009].

The application included general toxicity study data of a single-dose study in rats, repeated-dose studies in rats and dogs for 2 and 13weeks. The LD_{50} of ipratropium was estimated to be 1,766 and 1,074 mg/kg in oral doses in males and females, respectively. The inhalation of up to 1,328 µg/kg/day of albuterol in rats for 14 days did not show any significant toxicity. The inhalation of up to 584 µg/kg/day albuterol in dogs for 14 days showed dose-dependent increases in heart rate and myocardial necrosis. The maximum recommended human daily inhalation dose (MRHID) was 14.4 µg/kg/day and 2.4 µg/kg/day for albuterol sulfate and ipratropium bromide, respectively. The proposed dosage for Combivent Respimat (ipratropium bromide 20 mcg/albuterol sulfate100 mcg) Inhalation Spray was one spray four times daily. This proposed dose for Combivent Respimat Inhalation Spray was lower than that of the currently marketed Combivent CFC MDI, and was only a small portion of the MRHID. The toxicity studies for excipients were included in the submission. No treatment-related effects were observed.

Overall, the pharmacology and toxicology review team concluded that the application has submitted adequate nonclinical safety data to support registration of Combivent Respimat Inhalation Sprays, the available nonclinical data are considered supportive of the intended use of Combivent Respimat Inhalation Sprays, and the approval of the application is recommended from the nonclinical perspective [NDA 21-747, Pharmacology and Toxicology Review, Luqi Pei, Ph. D., 04/14/2009].

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The source of data for this review is the clinical studies contained in the application. The pivotal efficacy and safety data were from one pivotal study 1012.56. The application also included clinical studies conducted in (b) (4) a higher strength formulation of Combivent Respimat. (b) (4) This review included the pivotal efficacy and safety study and four major supportive studies. More detailed description of these studies follow below.

1. The pivotal study 1012.56 was entitled "A comparison of ipratropium bromide/albuterol delivered by the Respimat inhaler to Combivent Inhalation Aerosol and ipratropium bromide delivered by the Respimat in a 12-week, double-blind, safety and efficacy study in adults with chronic obstructive pulmonary disease." The specific objectives of this study were to (1) demonstrate non-inferiority (between 0-6 hours) of Combivent Respimat 20/100 mcg and Combivent CFC-MDI 36/206 mcg on Day 85, (2) demonstrate the superiority (between 0-4 hours) of Combivent Respimat 20/100 mcg over ipratropium Respimat 20 mcg on Day 85, and (3) demonstrate the non-inferiority (between 4-6 hours) of Combivent Respimat 20/100 mcg over ipratropium Respimat 20 mcg on Day 85. In addition, the steady state pharmacokinetics (PK) of the study medication was evaluated in a subgroup of patients over one dosing interval after 4 weeks of therapy.

2. Study 1012.46 was a Phase 3, randomized, double-blind, 12-week, parallel group study in about 1,118 patients with COPD. There were five study medications including both Respimat and CFC placebos in this study: (1) Combivent Respimat 40/200 mcg, (2) Combivent CFC MDI 36/206 mcg, (3) ipratropium Respimat 40 mcg, (4) placebo Respimat, and (5) placebo CFC all administered four times daily. The primary efficacy endpoint was FEV_1 AUC_{0-6} at study day 85. The ipratropium Respimat mono-therapy ipratropium Respimat 40 produced better FEV_1 values than that of the combinations Combivent Respimat 40/200 and Combivent CFC MDI 36/206 from 4 hours post-dosing till the end of the 8-hour period. PK data showed that, despite similar nominal doses, there were higher drug exposures from the Respimat device than from the CFC MDI. (b) (4) The Applicant therefore developed a lower dosage form of Combivent Respimat (20/100 mcg) and conducted the pivotal study 1012.56.

3. Study 244.2484 was a randomized, double-blind within device, placebo and active controlled, parallel group study. The test agent was ipratropium bromide Respimat at 20 and 40 mcg doses. The active comparator was ipratropium bromide CFC at 36 mcg. The drugs were given four times daily for 24 weeks. Subjects had to be >40 years old, had a clinical diagnosis of COPD, a ≥10 pack-year smoking history, and a FEV_1 ≤65%. The patients had a mean age of 65.8 and a mean FEV_1 of 1.01 L. The primary outcome was FEV_1 AUC_{0-6} change from baseline on Day 85.

4. Study 244.2447 was a randomized, double-blind within device, placebo and active controlled, 8-treatment, 4-period, single-dose study. The test agent was ipratropium bromide Respimat at 10, 20, 40, 80, & 160 mcg doses. The active comparator was ipratropium bromide CFC at 18 & 36 mcg. Subjects had to be >40 years old, had a clinical diagnosis of COPD, a ≥10 pack-year smoking history, and a FEV_1 ≤65%. In addition, they had to demonstrate reversibility to ipratropium of ≥15%. The patients had a mean age of 63.5 and a mean FEV_1 of 1.03 L. The primary outcome variable was FEV_1 AUC_{0-6} change from baseline.

5. Study 243.7 was a randomized, double-blind within device, placebo and active controlled, 7-period, dose crossover study. The test agent was albuterol Respimat at 25, 50, 100, & 200 mcg doses. The active comparator was albuterol CFC MDI at 90 & 180 mcg. Subjects had to be >40 years old, had a clinical diagnosis of COPD, a ≥10 pack-year smoking history, and a FEV_1 ≤65%. In addition, they had to demonstrate reversibility to albuterol of ≥15%. The patients had a mean age of 64.2 and a mean FEV_1 of 1.05 L. The primary outcome was FEV_1 AUC_{0-6} change from baseline.

4.2 Tables of Clinical Studies

Table 2 List of clinical studies reviewed in this application

Study #	Study type	Treatment groups	Treatment duration	Study design	Number of subjects	Diagnosis, age of subjects
1012.56	**Pivotal efficacy and safety study**	**Combivent R* 20/100 Ipratropium 20 Combivent MDI 18/103**	**Multiple-dose, 12 weeks**	**Randomized, multi-national, double-blinded, placebo-, active-controlled**	**1460**	**COPD 64.1 years (mean age)**

1012.46	Supportive efficacy and safety study	Combivent R* 40/200 Ipratropium R 40 Combivent MDI 36/206 Placebo R Placebo MDI	Multiple-dose, 12 weeks	Randomized, double-blinded, placebo-, active-controlled	1118	COPD 64.2 years (mean age)
244.2484	6-month safety study for ipratropium Respimat	Ipratropium R* 20, 40 Atrovent MDI 36 Placebo R* Placebo MDI	Multiple-dose, 6 months	Randomized, double-blinded, placebo-, active-controlled	646	COPD 65.8 years (mean age)
244.2447	Ipratropium dose-selection study	Ipratropium R* 10, 20, 40, 80, 160 Atrovent MDI 18, 36 Placebo R*	Single dose	Randomized, double-blinded, placebo-, active-controlled	116	COPD 63.5years (mean age)
243.7	Albuterol dose-selection study	Albuterol R* 25, 50, 50 , 100, 200 Ventolin MDI 90, 180 Placebo R*	Single dose	Randomized, double-blinded, placebo-, active-controlled	62	COPD 64.2 years (mean age)

* Respimat

4.3 Review Strategy

The clinical review focused on five clinical trials: the pivotal phase 3 efficacy and safety study (1012.56), a 12-week supportive efficacy and safety study (1012.46) for Combivent Respimat (20/200 mcg) Inhalation Spray, a 6-month safety study (244.2484) for ipratropium Respimat, a ipratropium bromide dose ranging study (244.2447), and a albuterol sulfate dose ranging study (243.7). (b) (4)

Reviews of the individual studies were based primarily on the study reports prepared by the Applicant. The Applicant's summary data tables were also reviewed in detail.

4.4 Data Quality and Integrity

A request for DSI consultation was submitted. There was only a single pivotal trial to support the efficacy of this NDA application. The trial was designed with three co-primary endpoints, two of which were based on demonstration of non-inferiority to active treatment controls. Because in a non-inferiority trial the lack of difference is the measure of the efficacy outcome, certain factors such as poor compliance, missing data, and errors in randomization (mix up of study treatment arms) may make the investigational drug more likely to appear to be efficacious. Therefore, the quality of trial conduct is critical to the validity of the inferences drawn in non-inferiority trials. Of the pivotal study 1012.56, there were 179 study sites worldwide and 87 study sites inside the United States. We requested a DSI audit of four study sites in the United States, based on the enrollment of large numbers of study subjects in these sites. In choosing sites for audit, no outliers were identified with regard to financial disclosure, protocol violations, or site specific efficacy. There were no specific data irregularities revealed during the review of this application. The inspection of the four study sites showed that the audited subjects exist, met the eligibility criteria, received assigned study medications, adhered to the protocol, and

signed informed consent documents. The data from these sites appear acceptable for use in support of the NDA. [NDA 21-747 N-000, Clinical Inspection Summary, Susan D. Thompson, M. D., Good Clinical Practice Branch II, DSI, April 3, 2009]

4.5 Compliance with Good Clinical Practices

The Applicant stated that the clinical trials were conducted in compliance with the principles laid down in the Declaration of Helsinki (1996 Version), in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), and in accordance with applicable regulatory requirements [Volume 5.19, Section 5.3.5.1]. The Applicant also provided debarment certification [Volume 1.1, Section 1.3.3].

4.6 Financial Disclosures

The Applicant provided financial disclosures for investigators participating in the pivotal study 1012.56 and the phase 3 study 1012.46 [Volume 1.1, Section 1.3.4]. The majority of investigators did not have financial interests requiring disclosure. There were a total of 7 investigators with financial interests totaling >$25,000. Of these, 4 investigators were in study 1012.46 and 3 were in the pivotal study 1012.56 .

Reviewer comment:
The financial disclosure forms of the investigators who claimed financial interests revealed that all 7 investigators have been participating in speaker activities for Boehringer Ingelheim, and received honoraria for their speeches and lectures about COPD and BI's products that were not related to drugs in the study.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

In the pivotal study 1012.56, pharmacokinetic data were obtained from 162 COPD patients at study sites in the United States. The PK samples were collected after 4 weeks of treatment according to the protocol. Table 3 listed PK parameters for ipratropium and albuterol in these patients. Detailed information can be found in the Clinical Pharmacology Review [NDA 21-747 N-000, Clinical Pharmacology Review, Partha Roy, Ph. D., June 2, 2009].

Briefly, in the 162 patients the ipratropium systemic exposure in three treatment groups was comparable, as evaluated by AUC_{0-6} and Cmax. Plasma albuterol PK parameters were obtained in 108 patients. In the patients (n=52) who received Combivent Respimat (20/100 mcg) Inhalation Spray the albuterol AUC_{0-6} and Cmax were approximately 25% lower than in the patients (n=56) who received Combivent Inhalation Aerosol MDI 36/206 mcg treatment. Since Combivent Respimat is an inhalation spray intended for local effect in the pulmonary tract, the pharmacokinetic profile is primarily useful for safety determination. With the comparable systemic exposure for ipratropium and lower systemic exposure for albuterol comparing to the approved drug product Combivent CFC-MDI, the test drug product Combivent Respimat

(20/100 mcg) Inhalation Spray should not pose additional systemic safety problems comparing to the approved and marketed drug product.

Table 3 Plasma PK parameters for ipratropium and albuterol in patients, study 1012.56

PK parameter	Combivent Respimat 20/100 mcg (A) N=52	Combivent CFC-MDI 36/206 mcg (B) N=56	Ipratropium Respimat 20 mcg (C) N=54	Ratio of means	
				A/B	A/C
Ipratropium					
AUC_{0-6} (h.pg/mL)					
Mean	127.51	122.59	115.42	1.04	1.10
(90% CI)	(110.24, 147.48)	(106.97, 140.50)	(100.57, 132.47)		
Cmax (pg/mL)					
Mean	33.46	33.80	35.11	0.99	0.95
(90% CI)	(28.94, 38.69)	(29.40, 38.86)	(30.54, 40.37)		
Cmin (pg/mL)					
Mean	15.25	16.08	14.84	0.95	1.03
(90% CI)	(13.76, 16.92)	(14.56, 17.76)	(13.43, 16.39)		
Albuterol					
AUC_{0-6} (h.ng/mL)					
Mean	4.09	5.52	---	0.74	---
(90% CI)	(3.54, 4.72)	(4.82, 6.34)	---		
Cmax (ng/mL)					
Mean	0.91	1,20	---	0.76	---
(90% CI)	(0.79, 1.04)	(1.05, 1.37)	---		
Cmin (ng/mL)					
Mean	0.43	0.60	---	0.71	---
(90% CI)	(0.36, 0.52)	(0.51, 0.72)	---		

(Source: Volume 5.19, Section 5.3.5.1, p147-150)

5.2 Pharmacodynamics

No new pharmacodynamic data was included in this submission. Since Combivent Respimat is an inhalation spray intended for local effect in the pulmonary tract, pharmacodynamic relationships for efficacy with regard to blood levels are not informative. In the pivotal study 1012.56, a therapeutic response was defined as to achieve a FEV_1 value of at least 115% of the corresponding test-day baseline value at any time during the first 2 hours after administration of study medication. Similar numbers of the patients (74% to 79%) in the Combivent Respimat 20/100 mcg) Inhalation Spray group and the Combivent Inhalation Aerosol MDI 36/206 mcg group were responders in all test days. In the ipratropium Respimat 20 mcg group, 63% to 66% of patients were responders. With regards to safety, there was no difference in adverse event profile for patients who received Combivent Respimat 20/100 mcg) Inhalation Spray, Combivent Inhalation Aerosol MDI 36/206 mcg, or the ipratropium Respimat 20 mcg.

5.3 Exposure-Response Relationships

Exposure-response relationships were evaluated in two dose ranging studies. For ipratropium bromide the dose ranging study 244.2447 compared the bronchodilation effect of five ipratropium Respimat doses (10, 20, 40, 80, and 160 mcg) with Atrovent Inhalation Aerosol doses (18 and 36 mcg) to identify the ipratropium Respimat doses that were comparable to approved Atrovent Inhalation Aerosol doses. Both the 20 mcg and 40 mcg doses of ipratropium Respimat were showed similar bronchodilation effect in COPD patients to Atrovent Inhalation

Aerosol 36 mcg. For albuterol sulfate the dose ranging study 243.7 compared the bronchodilation effect of four salbutamol Respimat doses (25, 50, 100, and 200 mcg) with Ventolin Inhalation Aerosol doses (90 and 180 mcg) to identify the albuterol Respimat doses that were comparable to approved Ventolin Inhalation Aerosol doses. Both the 50 mcg and 100 mcg doses of albuterol Respimat were comparable to 90 mcg dose of Ventolin Inhalation Aerosol, and 200 mcg dose of albuterol Respimat was comparable to 90 mcg and 180 mcg doses of Ventolin Inhalation Aerosol for bronchodilation effect in COPD patients. [see Section 6.1.1.1 and 6.1.1.2]

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is stated as "Combivent Respimat is indicated for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator."

6.1.1 Methods

Efficacy of Combivent Respimat 20/100 mcg Inhalation Spray was assessed in one pivotal study (1012.56) entitled "A comparison of ipratropium bromide/salbutamol delivered by the Respimat inhaler to Combivent Inhalation Aerosol and ipratropium bromide delivered by the Respimat in a 12-week, double-blind, safety and efficacy study in adults with chronic obstructive pulmonary disease." The study evaluated the FEV1 at the end of the treatment period as the primary efficacy measurement. The study was intended to demonstrate the non-inferiority of Combivent Respimat 20/100 mcg comparing to Combivent Inhalation Aerosol 36/206 mcg between 0 to 6 hours post dosing, the superiority of Combivent Respimat 20/100 mcg comparing to ipratropium Respimat 20 mcg between 0 to 4 hours post dosing, and the non-inferiority of Combivent Respimat 20/100 mcg comparing to ipratropium Respimat 20 mcg between 4 to 6 hours post dosing.

Reviewer comment:
In a pre-NDA meeting on January 16, 2008, the Division accepted the Applicant's plan to submit the NDA with only one pivotal clinical study 1012.56 to support the efficacy of Combivent Respimat with reservations: "The Division does have reservations regarding your plan to perform a single "pivotal" clinical trial especially since previous studies have failed to demonstrate that the combination is superior to each of its components. However, if efficacy findings are robust, a single trial may be sufficient to establish efficacy." [IND 57,948, Pre-NDA Meeting Minutes, February 1, 2008]

6.1.1.1 Dose selection for ipratropium bromide

Dose selection for the ipratropium component was based on the dose ranging study 244.2447. The study was a single-dose, randomized, double-blinded, placebo controlled, crossover study in COPD patients to characterize the dose response of single inhalation of ipratropium bromide delivered via the Respimat inhaler. The doses of ipratropium bromide included in the study were 10, 20, 40, 80, and 160 mcg. Two doses (18 and 36 mcg) of an approved ipratropium bromide

inhalation aerosol product, Atrovent MDI, were also included in the study. The primary efficacy endpoint was the FEV_1 AUC change from 0 to 6 hours post-dosing.

Table 4 summarized the mean FEV_1 AUC_{0-6} change from baseline for treatment groups and the comparison of mean FEV_1 AUC_{0-6} change between ipratropium Respimat doses and Atrovent Inhalation Aerosol 36 mcg. The ipratropium 10 mcg had a lowest mean FEV_1 AUC_{0-6} change in active treatment groups and ipratropium 20 and 40 mcg had a same mean FEV_1 AUC_{0-6} change. The ipratropium 160 mcg had a largest mean FEV_1 AUC_{0-6} change than all other active treatments. The Applicant pre-set a dose comparison criterion that a dose is considered comparable only if the 90% confidence interval for the difference is completely contained in the interval between -50 mL to +50 mL. The ipratropium Respimat 20 mcg and 40 mcg were considered equivalent to the Atrovent Inhalation Aerosol 36 mcg dose based on this criterion.

Table 4 Mean FEV_1 AUC_{0-6} change (liters) from baseline of treatment groups and differences between ipratropium Respimat and Atrovent Inhalation Aerosol groups

Treatment	N	Mean FEV_1 AUC_{0-6} change	Treatment difference (90% CI)	
			Compared to Atrovent 18 mcg	Compared to Atrovent 36 mcg
Ipratropium Respimat 10 mcg	58	0.16	0.019 (-0.012, 0.051)	-0.025 (-0.055, 0.006)
Ipratropium Respimat 20 mcg	60	0.19	0.051 (0.020, 0.082)	0.007 (-0.024, 0.037)
Ipratropium Respimat 40 mcg	58	0.19	0.045 (0.013, 0.077)	0.001 (-0.030, 0.032)
Ipratropium Respimat 80 mcg	54	0.23	0.088 (0.057, 0.121)	0.045 (0.014, 0.076)
Ipratropium Respimat160 mcg	51	0.26	0.118 (0.086, 0.150)	0.074 (0.042, 0.106)
Atrovent MDI 18 mcg	54	0.14	--------	--------
Atrovent MDI 36 mcg	58	0.19	--------	--------
Placebo Respimat	57	0.05	--------	--------

(Source: Volume 5.10, Section 5.3.4.2, page50-51)

The dose response curve of mean FEV_1 AUC_{0-6} change from baseline for the eight treatment groups is shown in Figure 1. All active treatments showed significantly higher mean FEV_1 AUC_{0-6} change than that of the placebo group. The ipratropium Respimat 20 mcg and 40 mcg were considered equivalent to the Atrovent Inhalation Aerosol 36 mcg dose. The dose response curves for the two Atrovent Inhalation Aerosol doses (18 and 36 mcg) and for the five ipratropium Respimat doses (10, 20, 40, 80, and 160 mcg) are shown below.

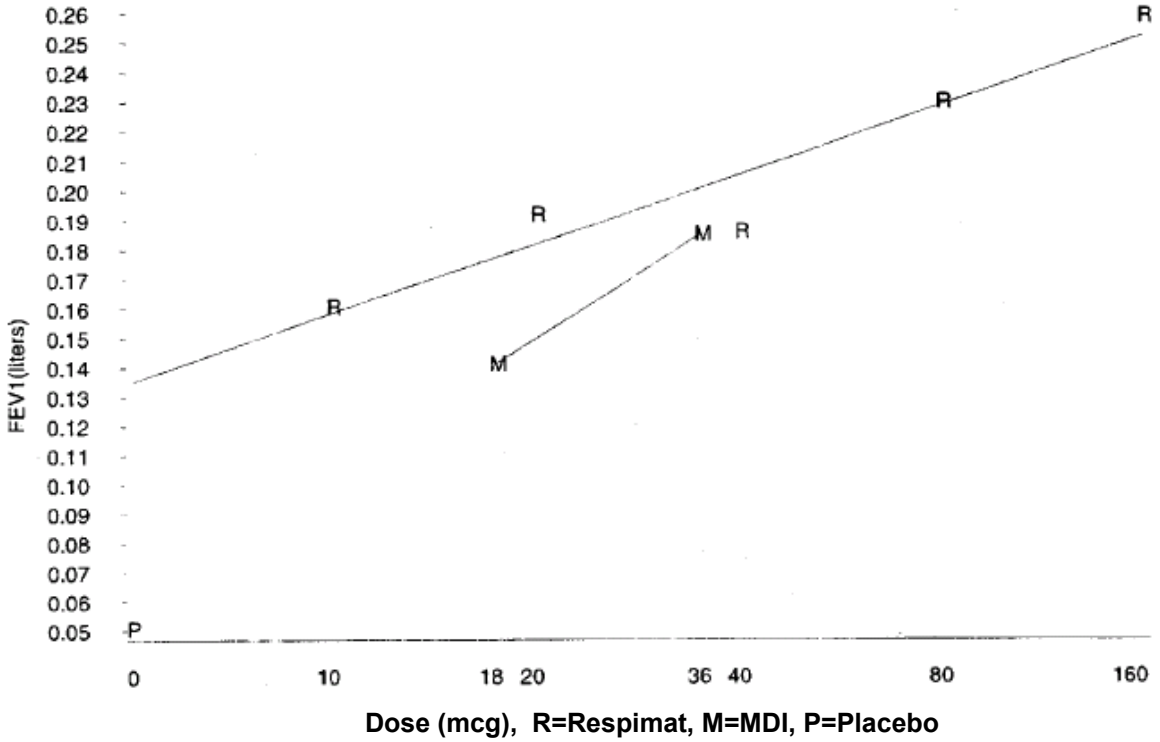

Figure 1 **Dose response curve of mean FEV_1 AUC_{0-6} change from baseline of treatment groups** (Volume 5.10, Section 5.3.4.2, page49)

Conclusion

This single-dose study compared the bronchodilation effect of five ipratropium Respimat doses (10, 20, 40, 80, and 160 mcg) with Atrovent Inhalation Aerosol doses (18 and 36 mcg) to identify the ipratropium Respimat doses that are comparable to approved Atrovent Inhalation Aerosol doses. The results showed that both 20 mcg and 40 mcg doses of ipratropium Respimat are comparable to approved dose of Atrovent Inhalation Aerosol 36 mcg for bronchodilation effect in COPD patients.

6.1.1.2 Dose selection for albuterol

Dose selection for the albuterol component was based on the dose ranging study 243.7. The study was a single-dose, randomized, double-blinded, placebo controlled, crossover study in COPD patients to characterize the dose response of single inhalation of albuterol delivered via the Respimat inhaler. The doses of albuterol included in the study were 25, 50, 100, and 200 mcg. Two doses (90 and 180 mcg) of an approved albuterol inhalation aerosol product, Ventolin MDI, were also included in the study. The primary efficacy endpoint was the FEV_1 AUC change from 0 to 6 hours post-dosing.

Table 5 summarized the mean FEV_1 AUC_{0-6} change from baseline for seven treatment groups and the comparison of mean FEV_1 AUC_{0-6} change between albuterol Respimat doses and Ventolin Inhalation Aerosol 90 mcg and 180 mcg treatment groups. The albuterol Respimat 25 mcg had the smallest mean FEV_1 AUC_{0-6} change in active treatment groups and the albuterol Respimat 50 and 100 mcg had the similar mean FEV_1 AUC_{0-6} change. The Applicant pre-set a

dose comparison criterion that a dose is considered comparable only if the 90% confidence interval for the difference is completely contained in the interval between -50 mL to +50 mL. The dose response curve of mean FEV_1 AUC_{0-6} change from baseline for the seven treatment groups is shown in Figure 2. All active treatments showed significantly higher mean FEV_1 AUC_{0-6} change than that of the placebo group. The albuterol Respimat 50 mcg and 100 mcg were considered therapeutically comparable to the Ventolin Inhalation Aerosol 90 mcg dose. The albuterol Respimat 200 mcg was considered therapeutically comparable to the Ventolin Inhalation Aerosol 90 mcg and 180 mcg doses.

Table 5 Mean FEV_1 AUC_{0-6} change (in liters) from baseline of treatment groups and differences between albuterol Respimat and Ventolin Inhalation Aerosol groups

Treatment	N	Mean FEV_1 AUC_{0-6} change	Treatment difference (90% CI)	
			Compared to Ventolin 90 mcg group	Compared to Ventolin 180 mcg group
Salbutamol Respimat 25	59	0.091	-0.041 (-0.064, -0.018)	-0.077 (-0.100, -0.053)
Salbutamol Respimat 50	59	0.117	-0.016 (-0.039, 0.008)	-0.051 (-0.075, -0.028)
Salbutamol Respimat 100	56	0.127	-0.006 (-0.029, 0.017)	-0.041 (-0.064, -0.018)
Salbutamol Respimat 200	58	0.144	0.012 (-0.012, 0.035)	-0.024 (-0.047, 0.000)
Ventolin 90	56	0.132	---	---
Ventolin 180	59	0.168	---	---
Placebo Respimat	56	0.027	---	---

(Source: Volume 5.13, Section 5.3.4.2, page55-56)

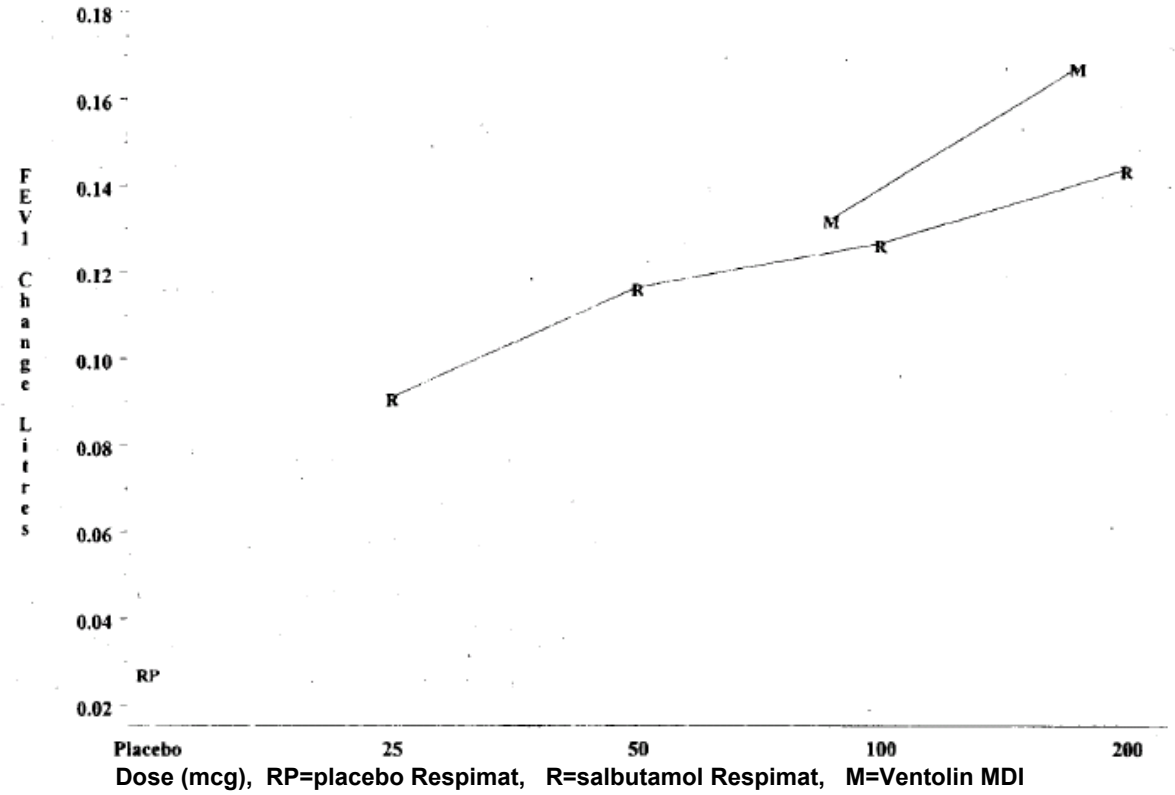

Figure 2 **Dose response curve of mean FEV_1 AUC_{0-6} change from baseline of treatment groups** (Source: Volume 5.13, Section 5.3.4.2, page54)

Conclusion

This single-dose study compared the bronchodilation effect of four salbutamol Respimat doses (25, 50, 100, and 200 mcg) with Ventolin Inhalation Aerosol doses (90 and 180 mcg) to identify the albuterol Respimat doses that are comparable to approved Ventolin Inhalation Aerosol doses. The dose response curves can be drawn for the four salbutamol Respimat doses and for the two Ventolin Inhalation Aerosol doses. The dose equivalence comparisons show that both 50 mcg and 100 mcg doses of albuterol Respimat are comparable to 90 mcg dose of Ventolin Inhalation Aerosol, and 200 mcg dose of albuterol Respimat is comparable to 90 mcg and 180 mcg doses of Ventolin Inhalation Aerosol for bronchodilation effect in COPD patients.

6.1.2 General Discussion of Endpoints

The primary efficacy measurement for the pivotal study (1012.56) was FEV_1 response after 12-week treatment (on test day 85). Pulmonary function tests were performed at baseline (i.e., pre-treatment, performed 15 ± 10 minutes prior to test drug administration) and were repeated at 15, 30, and 60 minutes and 2, 3, 4, 5, and 6 hours after the drug administration. PFTs from 15 minutes to 2 hours were performed within ± 5 minutes of the specified time points, and PFTs from 3-6 hours were performed within ± 10 minutes of the scheduled time point. Spirometry was performed according to ATS criteria. The highest FEV_1 and FVC of three maneuvers were recorded regardless of whether they came from the same or different maneuvers. For each patient, PFTs started at approximately the same time of the day.

The area under the curve (AUC) of the FEV_1 change from the test day baseline was used as the primary efficacy endpoints. There were three co-primary efficacy end points in this trial:

(1) FEV_1 AUC change from 0 to 6 hours post-dosing divided by 6 (FEV_1 AUC_{0-6}) was designed to determine the non-inferiority of Combivent Respimat 20/100 mcg compared to Combivent Inhalation Aerosol 36/206 mcg over the period of 0 to 6 hours post-treatment on test day 85. The non-inferiority criterion has been set as the difference of the two treatments in mean FEV_1 AUC_{0-6} change is not statistically significant and the 95% confidence interval of the difference is less than 50 mL.

As noted, Combivent Respimat has been developed to replace currently marketed Combivent Inhalation Aerosol, a CFC-containing product. The first co-primary efficacy endpoint is to determine if Combivent Respimat is efficaciously comparable to Combivent Inhalation Aerosol in the treatment of COPD patients.

(2) FEV_1 AUC change from 0 to 4 hours post-dosing divided by 4 (FEV_1 AUC_{0-4}) was designed to determine the superiority of Combivent Respimat 20/100 mcg compared to ipratropium Respimat 20 mcg over the period of 0 to 4 hours post-treatment on test day 85. The superiority criterion has been set as the difference of the two treatments in mean FEV_1 AUC_{0-4} change to be statistically significant ($p<0.05$) and the 95% confidence interval of the difference is more than 50 mL.

The second co-primary efficacy endpoint is designed to show the contribution of the albuterol component of this combination drug product. Albuterol is a short acting β agonist, with its bronchodilation effect persisting for about 3 to 4 hours. Within the first

4 hours post-dosing, Combivent Respimat 20/100 mcg should be superior to ipratropium Respimat 20 mcg alone in the treatment of COPD patients.

(3) FEV_1 AUC change from 4 to 6 hours post-dosing divided by 2 (FEV_1 AUC_{4-6}) was designed to determine the non-inferiority of Combivent Respimat 20/100 mcg compared to ipratropium Respimat 20 mcg over the period of 4 to 6 hours post-treatment on test day 85. The non-inferiority criterion has been set as the difference of the two treatments in mean FEV_1 AUC_{4-6} change is not statistically significant and the 95% confidence interval of the difference is less than 0.05 liters.

The third co-primary efficacy endpoint is designed to show the efficacy of the ipratropium component of this combination drug product. When the effect of albuterol fades after 4 hours of administering the combination product, the brochodilation effect of Combivent Respimat 20/100 mcg should be comparable to that of ipratropium Respimat 20 mcg alone in the treatment of COPD patients.

Reviewer comments:
FEV_1 is a well-accepted, validated, reproducible efficacy measurement and has been the basis of approval of the majority of medications for asthma and COPD. FEV_1 change from the test day baseline at the end of the dosing interval has been used as the primary efficacy variable to support the efficacy of Combivent Inhalation Aerosol (NDA 20-291). The use of FEV_1 response after 12-week treatment (on test day 85) as the primary efficacy measurement is appropriate.

The development program of Combivent Respimat utilizes a non-inferiority design in comparing the efficacy of the test product with that of the approved product Combivent Inhalation Aerosol. To meet the non-inferiority criterion, the difference in FEV_1 changes of two treatments should have no statistical significance and the 95% confidence interval of the difference should be less than 0.05 liters. Likewise, to meet the superiority criterion, the difference in FEV_1 changes of two treatments should be statistically significant and the 95% confidence interval of the difference should be more than 0.05 liters.

Combivent Respimat is a combination product including albuterol and ipratropium. The study design of this trial was not a typical 2x2 factorial design to test the efficacy of each component in the combination. However, measuring the FEV_1 change during different time post-dosing enables us to evaluate the contribution of the two components to the efficacy of this combination product. The second co-primary endpoint measures FEV_1 AUC change from 0 to 4 hours post-dosing of the combination product compared to ipratropium Respimat, which evaluates the efficacy contribution of the albuterol component in the combination. The third co-primary endpoint measures FEV_1 AUC change from 4 to 6 hours post-dosing of the combination product, which evaluates if ipratropium component works as well as an ipratropium alone product (ipratropium Respimat).

The secondary efficacy endpoints in this pivotal trial included:

(1) FEV_1 AUC on Days 1, 29, and 57 (AUC_{0-6}, AUC_{0-4}, and AUC_{4-6})
(2) Peak FEV_1 in the 2-hour interval after treatment on Days 1, 29, 57 and 85
(3) Peak FEV_1 response (change from test-day baseline) on Days 1, 29, 57 and 85
(4) Onset of therapeutic FEV_1 response on Days 1, 29, 57 and 85
(5) Duration of therapeutic FEV_1 response on Days 1, 29, 57 and 85
(6) Time to peak FEV_1 response on Days 1, 29, 57 and 85

(7) FVC AUC_{0-6} and peak on Days 1, 29, 57 and 85
(8) Trough peak expiratory flow rate (PEFR) measured by the patient at home once a day (weekly mean) during the treatment period
(9) Individual FEV_1 and FVC measurements at each measurement time
(10) Amount of β agonist therapy used (i.e., weekly mean number of salbutamol doses during day and, separately, at night) as rescue medication during the treatment period
(11) Rescue medication usage during the treatment period
(12) Daily symptom scores (weekly mean) over the treatment period, and
(13) Physician's global evaluation on Days 1, 29, 57 and 85

Reviewer comment:
The therapeutic response was determined based on FEV_1 change at the end of the treatment period as the primary efficacy endpoint. The listed secondary efficacy measurements are not well characterized and validated (such as symptom scores, physician's global evaluation, and amount of β agonist used) or not sensitive enough to evaluate the therapeutic response (such as FVC and patient-measured PEFR) in COPD patients. Also, the Applicant employed multiple comparisons under different names for the same set of measurements (such as peak FEV_1, peak FEV_1 response, therapeutic FEV_1 response, onset, duration, and time to peak FEV_1 response). The statistical robustness of these multiple comparisons is questionable. Therefore, these secondary efficacy endpoints were only evaluated for trends as supportive evidence for the primary efficacy endpoints.

6.1.3 Study Design

This pivotal trial was a three-treatment, 12-wcek, randomized, multi-national, parallel-group, double-blind, double-dummy, active controlled study. There were 1,480 male or female COPD patients aged 40 or older randomized into following three treatment groups:

(1) Combivent Respimat (ipratropium bromide 20 mcg/albuterol 100 mcg) one inhalation 4 times daily plus placebo Combivent CFC-MDI
(2) Ipratropium bromide Respimat (ipratropium bromide 20 mcg) one inhalation 4 times daily plus placebo Combivent CFC-MDI
(3) Combivent CFC-MDI (ipratropium bromide 36 mcg/albuterol 206 mcg) two inhalations of 18 mcg/103 mcg 4 times daily plus placebo Combivent Respimat

After an initial screening visit, patients entered a 2-week baseline run-in period in which they were given Atrovent HFA-MDI (18 mcg ipratropium bromide per actuation) and albuterol HFA-MDI as needed. All patients had to have a diagnosis of COPD and must have had the following spirometric criteria at Visit 1 (screening) and Visit 2 (start of treatment): a clinical diagnosis of COPD, ≥10 pack-year smoking history, a relatively stable, moderate to severe airway obstruction with pre-bronchodilator FEV ≤65% of predicted normal and FEV_1/FVC ratio ≤70%. Patients with narrow angle glaucoma, symptomatic prostatic hypertrophy or bladder neck obstruction were excluded. Patients who successfully completed this phase were randomized into the double-blind study treatment groups. There were more male patients (65.4%) than females. The majority of patients were Caucasian (89%). African and Asian Americans were 5.3% and 5.6% of the study subjects, respectively. The average age of the patients was 64.1 years, with the range from 40 to 89 years old. There were 52.4% and 47.6% of the patients aged <65 years and

≥65 years, respectively. The enrolled patients had a mean baseline FEV_1 measurement of 1.144 liters and an FEV_1/FVC ratio of 0.448.

The trial was conducted in 179 study sites around the world, among which 87 study sites were within the United States.

6.1.4 Efficacy Findings

6.1.4.1 Primary Efficacy Endpoint

Table 6 summarized the results of the evaluation for three co-primary efficacy endpoints. On test day 85, the Combivent Respimat 20/100 mcg group had a mean FEV_1 AUC_{0-6} change from test day baseline of 0.145 liters compared to 0.149 liters for the Combivent CFC-MDI 36/206 mcg group. Although the result was slightly in favor numerically of the Combivent CFC-MDI 36/206 mcg group with a difference of 0.003 liters in the mean FEV_1 AUC_{0-6} change from same day baseline, this difference is not statistically significant (95% CI: -0.022 to 0.015 liters), and the upper limit of the 95% confidence interval of the difference for the change in FEV_1 AUC was 0.015 liters (less than 0.05). The pre-set criterion of non-inferiority was met and the Combivent Respimat 20/100 mcg was considered non-inferior to Combivent CFC-MDI 36/206 mcg, because the difference of the two treatments in mean FEV_1 AUC_{0-6} change was not statistically significant and the 95% confidence interval of the difference was less than 0.05 liters.

The Combivent Respimat 20/100 mcg group had a 0.189 liter mean change in FEV_1 AUC_{0-4}, and the ipratropium Respimat 20 mcg group had a 0.142 liter mean change in FEV_1 AUC_{0-4} from test day baseline on test day 85. The difference of the mean change in FEV_1 AUC_{0-4} from test day baseline was 0.047 liter, with a p-value of <0.0001 and 95% CI from 0.028 to 0.066 liters. The result showed that Combivent Respimat 20/100 mcg was superior to ipratropium Respimat 20 mcg in the mean changes in FEV_1 AUC_{0-4} from test day baseline. This demonstrated the efficacy contribution of albuterol in this combination product.

Albuterol is a short acting β agonist, with its bronchodilation effect persisting for about 3 to 4 hours. The FEV_1 AUC_{4-6} was design to measure the efficacy of ipratropium component of the combination product. The Combivent Respimat 20/100 mcg group had a mean FEV_1 AUC_{4-6} change from test day baseline of 0.056 liters compared to 0.073 liters for the ipratropium Respimat 20 mcg group on test day 85. The difference in the mean change in FEV_1 AUC_{4-6} between two groups was 0.017 liters. The difference was slightly in favor numerically of the ipratropium Respimat 20 mcg group, but this difference was not statistically significant (95% CI: -0.039 to 0.005 liters). Also the 95% confidence interval of the difference is less than 0.05 liters. The result demonstrates that the Combivent Respimat 20/100 mcg is non-inferior to ipratropium Respimat 20 mcg in the mean change in FEV_1 AUC_{4-6} from test day baseline.

Table 6 Summary of co-primary efficacy endpoints – mean FEV_1 AUC change on test day 85

Efficacy endpoint	Treatment comparison	N	Mean (SE) (in liters)	Treatment difference (in liters)	
				Mean (SE)	95% CI
FEV_1 AUC_{0-6}	Combivent Respimat 20/100 Combivent CFC-MDI	474 482	0.145 (0.007) 0.149 (0.007)	-0.003 (0.010)	-0.022, 0.015
FEV_1 AUC_{0-4}	Combivent Respimat 20/100 ipratropium Respimat 20	474 468	0.189 (0.007) 0.142 (0.007)	0.047* (0.010)	0.028, 0,066
FEV_1 AUC_{4-6}	Combivent Respimat 20/100 ipratropium Respimat 20	447 427	0.056 (0.008) 0.073 (0.008)	-0.017 (0.011)	-0.039, 0.005

* P<0.0001

Figure 3 graphically summarized the three co-primary efficacy endpoints. The Figure demonstrated that Combivent Respimat 20/100 mcg was non-inferior to Combivent CFC-MDI 36/206 mcg in mean FEV_1 AUC_{0-6} change, superior to ipratropium Respimat 20 mcg in mean changes in FEV_1 $AUC_{0-4,}$ and non-inferior to ipratropium Respimat 20 mcg in mean change in FEV_1 AUC_{4-6} from test day baseline.

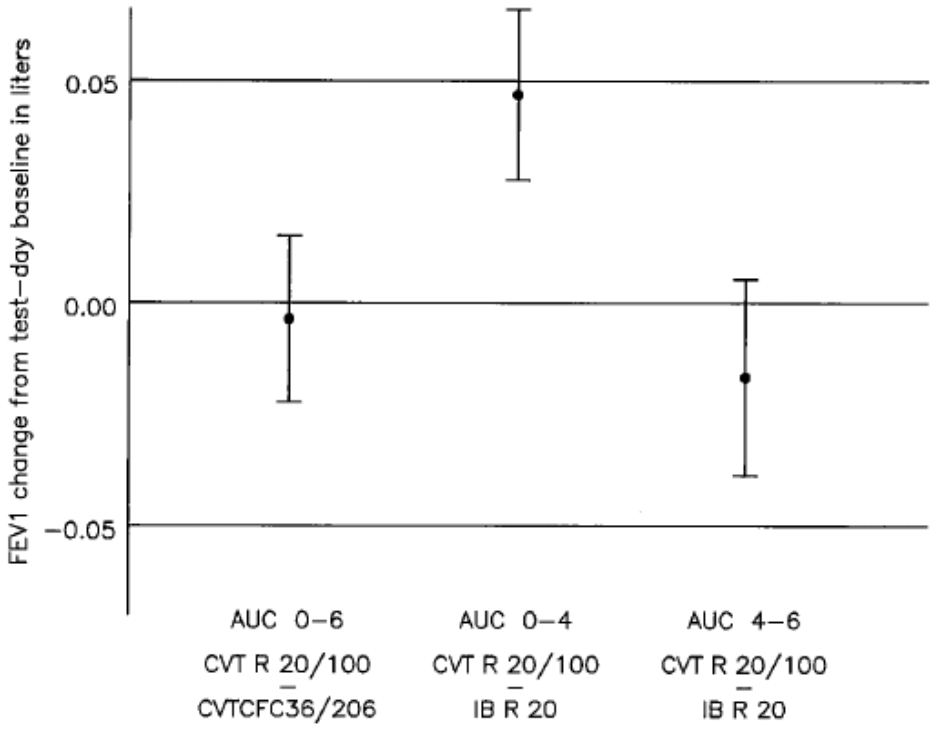

Figure 3 **Summary of three co-primary efficacy endpoints: mean changes in FEV_1 AUC from test day baseline and the 95% confidence intervals for three treatment groups on test day 85** (Source: Volume 5.19, Section 5.3.5.1, p 106)

Serial FEV_1 measurements (change from test-day baseline) on test-days 1, 29, 57 and 85 are shown in Figure 4. On all test day measurements Combivent Respimat (20/100 mcg) was shown to be non-inferior to Combivent Inhalation Aerosol (36/206 mcg) in terms of mean FEV_1 AUC_{0-6}. In addition, the mean FEV_1 AUC_{0-4} for Combivent Respimat (20/100 mcg), was superior to that of ipratropium bromide while the mean FEV_1 AUC $_{4-6}$ for Combivent Respimat (20/100 mcg) was non-inferior to that of ipratropium bromide.

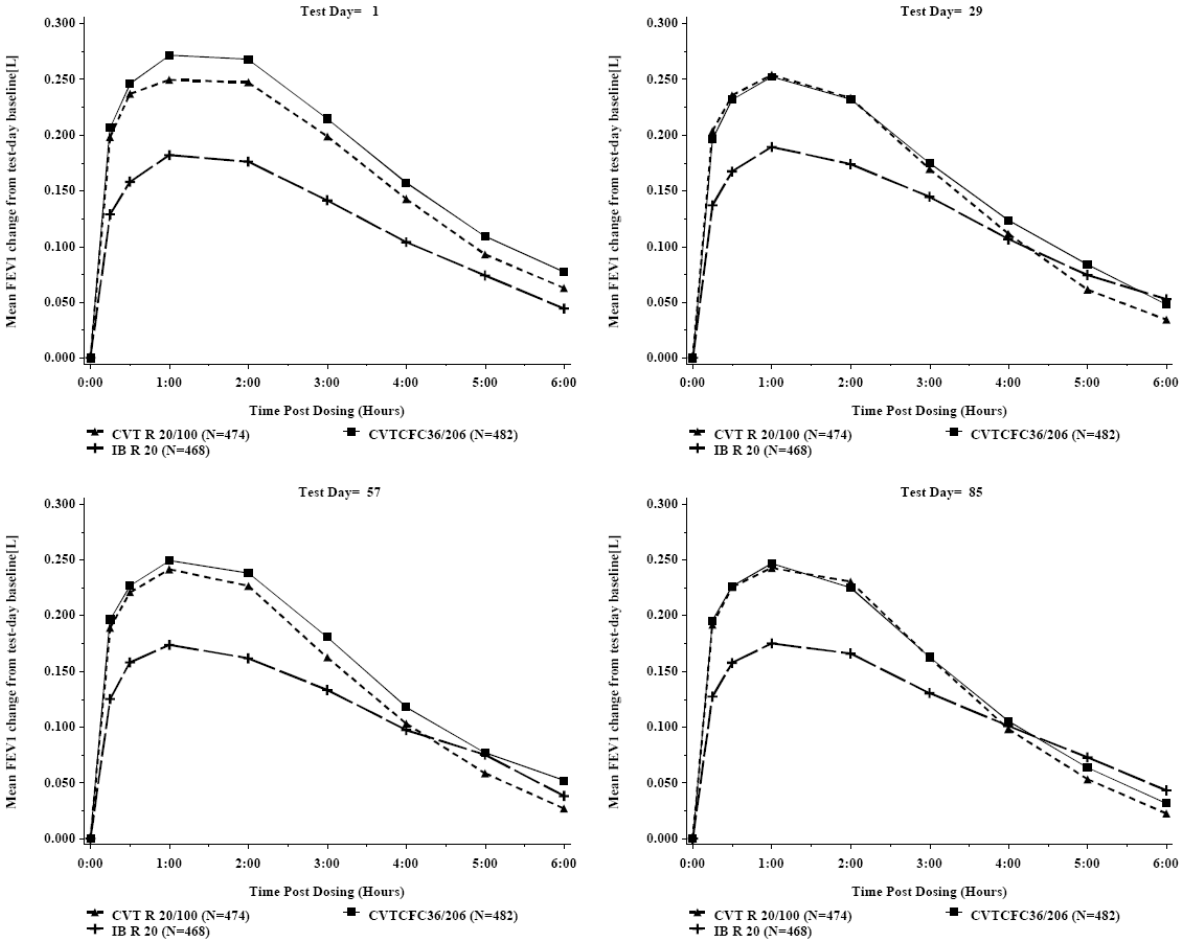

Figure 4 **Time profile of FEV_1 change on day 1, 29, 57, and 85**
(Source: Volume 5.19, Section 5.3.5.1, p 100)

Subgroup analyses were performed for different gender groups and patients over 65 years of age versus those under 65 years of age. In this 12-week study no differences in FEV_1 AUC change from test day baseline were identified within males versus females or in patients over 65 years of age versus those under 65 years of age. There were too few African-American subjects to adequately assess differences in effects in that population.

6.1.4.2 Secondary Efficacy Endpoint

Peak FEV_1 and peak FEV_1 response

The peak FEV_1 was the maximum FEV_1 value recorded within the first 2 hours after administration of study medications. Table 7 showed the peak FEV_1 measurements of three treatment groups on test days 1, 29, 57, and 85. The Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg groups were similar in peak FEV_1 on all test days. The Combivent Respimat 20/100 mcg group was numerically superior to the ipratropium Respimat 20 mcg group in peak FEV_1 on all test days. The differences in peak FEV_1 between these two groups were 0.065, 0.061, 0.053, and 0.066 liters in favor of the Combivent Respimat 20/100 mcg group. The Combivent CFC-MDI 36/206 mcg group was also numerically superior to the ipratropium Respimat 20 mcg group in peak FEV_1 on all test days. The differences in peak

FEV_1 between these two groups were 0.085, 0.056, 0.062, and 0.058 liters, in favor of the Combivent CFC-MDI 36/206 mcg group. These results demonstrated that the test drug Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg were comparable and both drugs were superior to ipratropium Respimat 20 mcg at maximum FEV_1 value measured within 2 hours post-dosing on all test days.

Table 7 Peak FEV_1 on test day 1, 29, 57, and 85

Test Day	Combivent Respimat 20/100 mcg (A)		Combivent MDI 36/206 mcg (B)		Ipratropium Respimat 20 mcg (C)		Treatment difference		
Peak FEV_1	Mean	SE	Mean	SE	Mean	SE	A-B	A-C	B-C
Day 1	1.4164	0.008	1.4365	0.008	1.3511	0.008	-0.020	0.065	0.085
Day 29	1.4065	0.011	1.4016	0.011	1.3458	0.011	0.005	0.061	0.056
Day 57	1.3952	0.011	1.4038	0.011	1.3417	0.011	-0.009	0.053	0.062
Day 85	1.4043	0.012	1.3965	0.012	1.3383	0.012	0.008	0.066	0.058

(Source: Volume 5.29, Section 5.3.5.1, p 676-687)

Peak FEV_1 response was defined as the maximum change of FEV_1 from test day baseline within the first 2 hours after administration of study medications. Figure 5 showed that the test drug Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg were comparable and both drugs were superior to ipratropium Respimat 20 mcg at peak FEV_1 response on all test days.

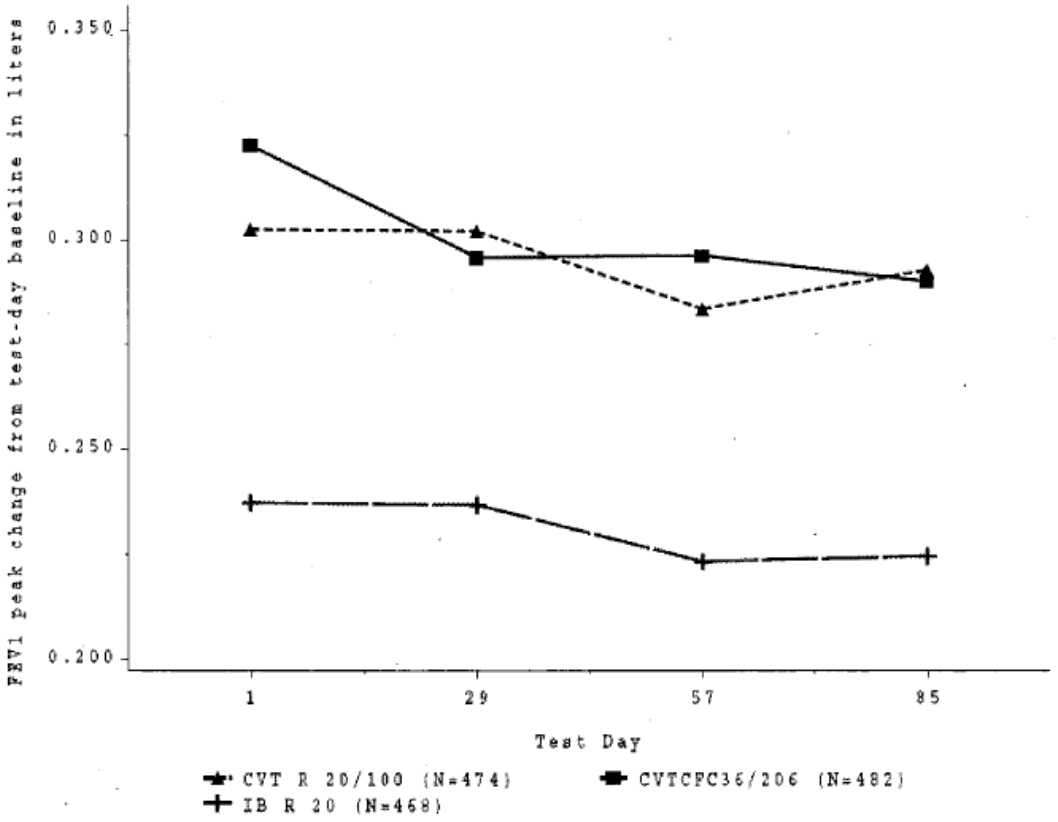

Figure 5 **Peak FEV_1 response on test day 1, 29, 57, and 85**
(Source: Volume 5.19, Section 5.3.5.1, p110)

Onset of therapeutic FEV_1 response and time to peak FEV_1

A therapeutic response was defined as to achieve a FEV_1 value of 115% of the corresponding test-day baseline value during the first 2 hours after administration of study medication. The onset of the therapeutic response was the median time in minutes from the study medication administration to the achievement of the first therapeutic response. The time to peak FEV_1 was the median time in minutes from the study medication administration to the peak FEV_1 measurement.

As shown in Table 8, the median time to onset of the therapeutic FEV_1 response were comparable between the Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg groups on all test days. The median time to onset of the therapeutic FEV_1 response is 12 to 13 minutes after the administration of study medication for these two treatment groups. In contrast the ipratropium Respimat 20 mcg group had a relatively longer median time to onset of the therapeutic FEV_1 response on all four test days. This result demonstrated that albuterol component of the combination drug product contributed to the quick onset of the therapeutic FEV_1 response. The median time to peak FEV_1 was the same in the three treatment groups on all test days, with the exception for the ipratropium Respimat 20 mcg group on test day 1.

Table 8 Onset of therapeutic FEV_1 response and time to peak FEV_1 on test day 1, 29, 57, and 85

Test Day	Combivent Respimat 20/100 mcg		Combivent MDI 36/206 mcg		Ipratropium Respimat 20 mcg	
	Onset of therapeutic FEV_1 response*	Time to peak FEV_1#	Onset of therapeutic FEV_1 response	Time to peak FEV_1	Onset of therapeutic FEV_1 response	Time to peak FEV_1
Day 1	13	60	12	60	28	120
Day 29	12	60	13	60	27	60
Day 57	13	60	12	60	29	60
Day 85	12	60	13	60	27	60

* Median time in minutes, time to onset of therapeutic FEV_1 response (15% above the test day baseline)
# Median time in minutes, time to peak FEV_1
(Source: Volume 5.19, Section 5.3.5.1, p302)

Rescue medication use

All patients were given albuterol MDI as rescue medication in this 12-week study. The day time and night time rescue medication use (as mean puffs of albuterol inhalation) during treatment period was compared to that at study baseline. Table 9 showed the data of day time and night time rescue medication use in the study. For all three treatment groups the mean of the day time rescue albuterol use was decreased during treatment period compared to the study baseline. However, the mean of the night time rescue albuterol use was slightly increased during treatment period compared to that of the study baseline.

Table 9 Rescue medication use as mean puffs of albuterol inhalation in day and night time at baseline and during treatment period

Test Day	Combivent Respimat 20/100 mcg		Combivent MDI 36/206 mcg		Ipratropium Respimat 20 mcg	
	Baseline	Treatment period	Baseline	Treatment period	Baseline	Treatment period
Day time	2.597	2.300	2.605	2.191	2.624	2.456
Night time	0.970	0.977	0.938	0.977	0.995	0.997

(Source: Volume 5.19, Section 5.3.5.1, p123-127)

Other secondary efficacy endpoints (PEFR, symptom score, physician global evaluation) also showed that treatment groups of Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg had generally better results than that of ipratropium Respimat group. Detailed evaluation of secondary efficacy endpoints can be found in Appendices 10.1.1.

Efficacy results in supportive study 1012.46

The Applicant conducted a 12-week efficacy and safety study for a higher dose formulation (Combivent Respimat 40/200 mcg). In this randomized, double-blind, placebo and active controlled study, patients with COPD received one of the three active treatments (Combivent Respimat 40/200 mcg, ipratropium Respimat 40 mcg, and Combivent CFC MDI 36/206 mcg) or a placebo. The primary efficacy endpoint was the mean FEV_1 AUC_{0-6} on test day 85. The results of this study showed that the Combivent Respimat 40/200 mcg group had the mean FEV_1 AUC_{0-6} value of 1.281 liters, compared to the mean FEV_1 AUC_{0-6} value of 1.148 liters in placebo group on test day 85. The difference between the Combivent Respimat 40/200 mcg group and the placebo was statistically significant ($p<0.0001$). The study demonstrated that the Combivent Respimat 40/200 mcg was efficacious in COPD treatment. However, the study 1012.46 failed to demonstrate the contribution of the individual component albuterol and ipratropium to the combination product. Detailed discussion about the supportive efficacy and safety study 1012.46 can be found in Appendices 10.1.2.

Device satisfaction

In the pivotal study 1012.56, the patient satisfaction with Respimat device was assessed by a 10-item questionnaire administered at the end of the study. The objective of the questionnaire was to compare the patient satisfaction to Respimat and MDI inhaler. Because of the double-dummy study design that was used in this study, every patient used both a Respimat inhaler and a MDI throughout the study. The response to the questions were on a scale of 1 to 7, defined as 1=very dissatisfied, 2=dissatisfied, 3=somewhat dissatisfied, 4=satisfied/dissatisfied, 5=somewhat satisfied, 6=satisfied, and 7=very satisfied. The data showed that more patients rated very satisfaction with Respimat than with MDI across the 10 questions. The mean scores were numerically higher with Respimat than with MDI for every question, which meant that patients were more satisfied with Respimat inhaler than with MDI in all aspects of the device. More information regarding the patient device satisfaction in the pivotal study can be found in Appendices 10.1.1.

6.1.5 Clinical Microbiology

The inhalation solution in an unopened cartridge was sterile and (b) (4) (b) (4) (b) (4) manufacturing has been chosen and has been assured by validation. In addition to sterility testing of the unopened cartridge, the (b) (4) test was also performed and validated to assure microbial control. In the sterility testing, 20 test cartridges were negative for bacterial growth while the positive control cartridges were strongly positive. (b) (4) manufacturing

operation and the environmental microbial monitoring were adequate. The microbiology review team recommends an approval action on the basis of product quality microbiology.

Detailed information can be found in the Product Quality Microbiology Review [NDA 21-747 N-000, Product Quality Microbiology Review, Bryan S. Riley, Ph. D., June 22, 2009].

6.1.6 Efficacy Conclusions

The results of the pivotal clinical trial 1012.56 support the efficacy of Combivent Respimat (20/100 mcg) Inhalation Spray in patients with COPD. Pulmonary function in patients with COPD, as evaluated as FEV_1 AUC change from test day baseline, was shown to be positively impacted by treatment with Combivent Respimat 20/100 mcg Inhalation Spray and by Combivent CFC MDI 36/206 mcg alike. The primary efficacy endpoints demonstrated that Combivent Respimat (20/100 mcg) Inhalation Spray is efficaciously non-inferior to Combivent CFC MDI 36/206 mcg, superior to ipratropium bromide 20 mcg during 0 to 4 hours post-dosing, and non-inferior to ipratropium bromide 20 mcg during 4 to 6 hours post-dosing. The superiority of Combivent Respimat 20/100 mcg Inhalation Spray to ipratropium bromide 20 mcg during 0 to 4 hours post-dosing demonstrated the efficacious contribution of albuterol component in the combination product. The study results are robust. Based on the agreement between the Applicant and the Division in pre-NDA meetings, the efficacy data from this 12-week trial are sufficient to form the basis of approval for Combivent Respimat 20/100 mcg inhalation spray for the proposed indication in patients with COPD.

In the development program of Combivent Respimat Inhalation Spray, the Applicant conducted a 12-week efficacy and safety study for a higher dose formulation of Combivent Respimat (40/200 mcg). In this randomized, double-blind, placebo and active controlled study, patients with COPD received one of the three active treatments (Combivent Respimat 40/200 mcg, ipratropium Respimat 40 mcg, and Combivent CFC MDI 36/206 mcg) or a placebo. The primary efficacy endpoint was the mean FEV_1 AUC_{0-6} on test day 85. The results of this study showed that the Combivent Respimat 40/200 mcg group had a significantly greater FEV_1 AUC_{0-6} value on all test days compared to the placebo group ($p<0.0001$). However, the study 1012.46 failed to demonstrate the contribution of the individual active ingredients albuterol and ipratropium in the combination product. The study 1012.46 provided the supportive evidence that the Respimat was an effective device to deliver the Combivent, and that Combivent Respimat Inhalation Spray, in appropriate dosages, was efficacious in COPD treatment.

7 INTEGRATED REVIEW OF SAFETY

This safety review included safety information from five clinical trials, focusing on two 12-week studies for Combivent Respimat (1012.56 ad 1012.46) and one 6-month study for ipratropium Respimat (244.2484). The two single-dose studies for ipratropium Respimat (244.2447) and albuterol Respimat (243.7) were just briefly summarized because these two single-dose studies did not reveal any new safety signals.

The safety data from two 12-week efficacy and safety studies for Combivent Respimat in patients with COPD did not identify new safety signals. In the 6-month safety study for ipratropium Respimat in patients with COPD, however, the groups with Respimat (including 40

mcg, 20 mcg, and placebo Respimat) appeared having a high incidence of pharyngitis (12.3%) versus groups with MDI (7.4%).

7.1 Methods and Findings

7.1.1 Deaths

A total of 11 deaths occurred during the three clinical trials: six deaths in Study 1012.56, one death in study 1012.46, and four deaths in study 244.2484. No death occurred in two single-dose studies for ipratropium Respimat (244.2447) and albuterol Respimat (243.7).

7.1.1.1 Deaths in study 1012.56

As part of the serious adverse events six deaths were reported during the 12-week treatment period of the study (3, 1, and 2 deaths in the Combivent Respimat 20/100 mcg group, Combivent CFC-MDI 36/206 mcg group, and ipratropium Respimat 20 mcg group, respectively). Brief case descriptions for six deaths follow below:

Combivent Respimat 20/100 mcg group
Patient 48325 was a 73 years old male patient. After receiving the treatment medication Combivent Respimat 20/100 mcg for 62 days, the patient suffered with a pneumonia that resulted in hospitalization for 4 days. He was treated with antibiotics, corticosteroids, and symptomatic therapy and discharged. Ten days later the patient was re-admitted to the hospital for severe pneumonia. The treatment medication was discontinued at his second hospitalization. The patient died 11 days after the second hospitalization. No autopsy was performed and the cause of death was reported as pneumonia.
Patient 46632 was a 69 years old female patient. The patient experienced an episode of severe COPD exacerbation on the 29th day of receiving Combivent Respimat 20/100 mcg. The trial medication was discontinued at that time and the patient was hospitalized. The patient then experienced respiratory failure that resulted in death on 18th day of hospitalization. Treatment received included Amoxiclav, Solu-medrol, Isoptin SR. Autopsy was not performed.
Patient 47864 was a 62 years old male patient who was hospitalized for COPD exacerbation after receiving Combivent Respimat 20/100 mcg for 45 days. The patient was admitted to hospital on September 16, 2007 and COPD exacerbation was diagnosed. He was treated with Atrovent, Begalin (Sultamicillin tosylate) and Salospir (aspirin) tablets. Study medication was continued. The patient recovered and was discharged 2 days after the admission. The patient was reported died from unknown cause on 26 days after the discharge. No Autopsy was performed.

Combivent CFC-MDI 36/206 mcg group
Patient 45826 was a 75 years old male patient. The patient was murdered at home by a thief during a robbery on 19th day of receiving Combivent CFC-MDI 36/206 mcg. The cause of dead was traumatic. Autopsy was not performed.

Ipratropium Respimat 20 mcg group
Patient 43616 was a 64 years old female patient. The patient was admitted into the hospital for stroke evaluation due to gait and strength changes along with poor balance on the 29th day of

ipratropium Respimat 20 mcg administration. The patient had also noted a 15-20 pound weight loss in the last six months. Her evaluation included an MRI a CT of the head with findings including metastatic cancer of the brain and numerous largely cystic lesions present throughout the right and left cerebral and cerebellar hemispheres. The event of stroke was ruled out and the events were considered serious. The patient received treatment included dexamethasone and radiation therapy with no significant changes. The patient died 74 days later with the primary diagnosis of malignant brain cancer. No autopsy was performed.

Patient 45559 was an 86 years old male patient. The patient had noticed blood in the sputum for the past several years. On the 7th day of treatment medication administration the patient was evaluated by a physician due to increased blood in sputum and mild chest pain. Chest X-ray, CT scan, bronchoscopy, and bronchial washing confirmed the diagnosis of small cell carcinoma in the left lung. The patient died 67 days later with the diagnosis of small cell carcinoma. No autopsy will be performed. The patient had received ipratropium Respimat 20 mcg treatment for 27 days.

In addition to the six deaths during the study period, there were four deaths that occurred either pre- or post-treatment. The post-treatment period was defined as after midnight the day of the last dose of the study drug. One patient (45324) died of a cerebrovascular accident before randomization (pre-treatment) and never received study therapy. Three patients (44145, 44596, and 45593) had an event resulting in death which began post-treatment. Patient 44145, randomized to Combivent CFC-MDI, died of sudden death approximately 3 weeks post last dose of study treatment. Patient 44596, randomized to ipratropium Respimat, had a reported term "death" 2 days after the last day of study drug. Patient 45593, randomized to Combivent CFC-MDI, had a COPD exacerbation which began 2 days post study, and resulted in death 4 days after the start of the COPD exacerbation.

7.1.1.2 Death in study 1012.46

One death (gastrointestinal hemorrhage) occurred during the treatment period to a patient randomized to the Combivent Respimat 40/200 mcg group. The patient (41791) was on study medication for 46 days. This 77 years old female patient was randomized to Combivent Respimat 40/200 mcg group on 28 March 2003. On 12 May 2003 the patient experienced an acute GI bleed and died. The patient received unspecified treatment for the event. The patient was concomitantly on aspirin, Fosamax and ibuprofen.

Another patient's death (41656) was reported by the field monitor approximately six months after the patient had dropped out of the study due to the complain of shortness of breath. This patient had been randomized to the Combivent Respimat group 40/200 mcg group and was on the study medication for only 6 days. The reported cause of death was a mass in the anterior left lateral ascending aorta.

7.1.1.3 Deaths in study 244.2484

There were 4 deaths reported for this study. Two occurred during the treatment period and two after the study completion. The four death cases appear to be not study medication related.

Patient 1689, a 67 years old male, was randomized to Atrovent MDI 36 mcg group. The patient had completed two months in the study and developed pneumonia when on a visit to Cuba. The

patient was admitted to a hospital in Cuba, treated with i.v. antibiotics, and died in the hospital 13 days later.

Patient 2093, a 77 years old male patient, was randomized to MDI placebo and had completed two months of treatment when developed cold symptoms. The patient then suffered a myocardial infarction and was found dead by his spouse two days later. The patient entered the study with a history of coronary heart disease and was being treated for hypertension and elevated cholesterol. The study screening ECG showed right bundle branch block with occasional ventricular and atrial contractions.

Patient 1863, a 60 years old male, was randomized to ipratropium Respimat 20 mcg group. The patient had completed over two months of treatment when noticed a lump on his neck. The patient was diagnosed with metastatic adenocarcinoma and discontinued from the study. The patient received chemotherapy for the carcinoma and subsequently died from the carcinoma three months after the study discontinuation.

Patient 1582, a 59 year old male, was randomized to ipratropium Respimat 40 mcg group. The patient had completed the study and experienced a tricyclic overdose and cardiac arrest six and a half weeks later.

Reviewer comment:
It appears that all the 11 deaths in the studies are not test drug products related. All the deaths were attributed to concomitant serious diseases, conditions, or accidents.

7.1.2 Other Serious Adverse Events

7.1.2.1 Serious adverse events (SAEs) in study 1012.56

SAEs occurred in a total of 64 patients (4.4%) across all treatment groups (Table 10). The highest frequency of SAEs was in the Combivent CFC-MDI 36/206 mcg group (6.7%), followed by the Combivent Respimat 20/100 mcg group (3.5%), and the ipratropium Respimat 20 mcg group (2.9%). Similar to the pattern in general adverse events, the most frequently occurred SAE was COPD exacerbation in all treatment groups (2.2%). The frequency of COPD exacerbation as SAE across treatment groups was similar for three treatment groups, with the lowest at the ipratropium Respimat 20 mcg group (1.7%), and 2.3 % and 2.6% at Combivent Respimat 20/100 mcg group and Combivent CFC-MDI 36/206 mcg group, respectively.

Table 10 Serious adverse event frequency and percentage in primary system organ class and preferred term[1] by treatment groups, study 1012.56

SAEs	Total (%)	Combivent Respimat 20/100 N (%)	Combivent CFC-MDI 36/206 N (%)	Ipratropium Respimat 20 N (%)
Total treated patients	1460 (100)	486 (100)	491 (100)	483 (100)
Patients with any SAE	64 (4.4)	17 (3.5)	33 (6.7)	14 (2.9)
Death during the trial[2]	6 (0.4)	3 (0.6)	1 (0.2)	2 (0.4)
Cardiac disorders	3 (0.2)	1 (0.2)	2 (0.4)	0
Gastrointestinal disorders	3 (0.2)	0	3 (0.6)	0
General conditions	3 (0.2)	1 (0.2)	0	2 (0.4)

Infections & infestations	3 (0.2)	3 (0.6)	0	0
Injury	3 (0.2)	1 (0.2)	2 (0.4)	0
Musculoskeletal & connective tissue disorders	1 (0.1)	0	1 (0.2)	0
Neoplasms	6 (0.4)	1 (0.2)	3 (0.6)	2 (0.4)
Nervous system disorders	3 (0.2)	0	2 (0.4)	1 (0.2)
Lower respiratory system disorders	42 (2.9)	13 (2.7)	18 (3.7)	11 (2.3)
COPD exacerbation	32 (2.2)	11 (2.3)	13 (2.6)	8 (1.7)
Pneumonia	11 (0.8)	2 (0.4)	5 (1.0)	4 (0.8)
Other respiratory disorders	4 (0.3)	0	3 (0.6)	1 (0.2)
Vascular disorders	2 (0.1)	0	1 (0.2)	2 (0.1)

1 MedDRA version 10.1
2 death cases were described in detail in 7.1.1.3 above
(Source: Volume 5.19, Section 5.3.5.1, p167-169; Volume 5.20, Section 5.3.5.1, p387-389)

7.1.2.2 Serious adverse events (SAEs) in study 1012.46

SAEs occurred in a total of 33 patients (3.0%) across all treatment groups (Table 11). The highest frequency of SAEs was in the Placebo CFC-MDI 36/206 mcg group (5.1%), followed by the ipratropium Respimat 40 mcg group (3.6%). Combivent Respimat 40/200 mcg group had a similar frequency of SAEs (2.3%) to the placebo Respimat group (2.4%). The most frequently occurred SAE was COPD exacerbation in all treatment groups (0.9%). The frequency of COPD exacerbation as SAE was zero in the placebo Respimat group and similar in the rest of the treatment groups.

Table 11 Serious adverse event frequency and percentage in primary system organ class and preferred terms[1] by treatment groups, study 1012.46

SAEs	**Total (%)**	**Combivent Respimat 40/200 N (%)**	**Combivent MDI 36/206 N (%)**	**Ipratropium Respimat 40 N (%)**	**Placebo Respimat N (%)**	**Placebo CFC-MDI N (%)**
Total treated patients	1118	345	180	252	165	176
Patient with any SAE	33 (3.0)	8 (2.3)	3 (1.7)	9 (3.6)	4 (2.4)	9 (5.1)
Death during the trial[2]	1 (0.1)	1 (0.3)	0	0	0	0
Cardiac disorders	4 (0.4)	1 (0.3)	0	1 (0.4)	2 (1.2)	0
Gastrointestinal disorders	1 (0.1)	1 (0.3)	0	0	0	0
General conditions	3 (0.3)	0	0	1 (0.4)	1 (0.6)	1 (0.6)
Infections & infestations	1 (0.1)	0	0	1 (0.4)	0	0
Injury	1 (0.1)	0	0	1 (0.4)	0	0
Metabolism and nutrition disorders	2 (0.2)	0	1 (0.6)	0	0	1 (0.6)
Neoplasms	2 (0.2)	0	1 (0.6)	1 (0.4)	0	0
Nervous system disorders	4 (0.4)	1 (0.3)	0	1 (0.4)	0	2 (1.1)
Lower respiratory system disorders	16 (1.4)	5 (1.4)	1 (0.6)	3 (1.2)	1 (0.6)	6 (3.4)
COPD exacerbation	10 (0.9)	4 (1.2)	1 (0.6)	3 (1.2)	0	2 (1.1)
Pneumonia/bronchitis	6 (0.5)	1 (0.3)	0	0	1 (0.6)	4 (2.3)
Other respiratory disorders	1 (0.1)	0	0	1 (0.4)	0	0
Vascular disorders	3 (0.3)	0	1 (0.6)	2 (0.8)	0	0

1 MedDRA version 7.0
2 death cases were described in detail in 7.1.1.3 above
(Source: Volume 5.65, Section 5.3.5.1, p136, 138)

7.1.2.3 Serious adverse events (SAEs) in study 244.2484

SAEs occurred in a total of 63 patients (9.8%) across all treatment groups (Table 12). The highest frequency of SAEs was in the placebo Respimat group (13.8%), followed by the Atrovent 36 mcg group (11.9%), and the placebo MDI group (10.2%). Ipratropium Respimat 20 and 40 mcg groups had similar frequencies of SAEs. The most frequently occurred SAE was COPD exacerbation in all treatment groups. The frequency of COPD exacerbation as SAE across treatment groups was similar for the treatment groups, with the lowest at the ipratropium Respimat 20 mcg group (3.3%), and the highest in placebo Respimat group (5.2%).

Table 12 Serious adverse event frequency and percentage in primary system organ class and preferred terms[1] by treatment groups, study 244.2484

SAEs	Placebo Respimat N (%)	Ipratropium Respimat 20 N (%)	Ipratropium Respimat 40 N (%)	Placebo MDI N (%)	Atrovent MDI 36 N (%)
Total treated	58 (100)	180 (100)	177 (100)	59 (100)	172 (100)
Patients with any SAE	8 (13.8)	15 (8.3)	15 (8.5)	6 (10.2)	19 (11.9)
Death in the trial[2]	0	1 (0.6)	1 (0.6)	1 (1.7)	1 (0.6)
General disorders	0	1 (0.6)	2 (1.1)	1 (1.7)	1 (0.6)
Cardiovascular disorders	0	2 (1.1)	1 (0.6)	1 (1.7)	0
Gastrointestinal disorders	2 (3.4)	2 (1.1)	2 (1.1)	0	4 (2.3)
Heart rate & rhythm disorders	0	0	1 (0.6)	1 (1.7)	0
Myo- endo- peri-cardial & valve disorders	1 (1.7)	2 (1.1)	0	1 (1.7)	3 (1.7)
Neoplasm	1 (1.7)	2 (1.1)	1 (0.6)	0	1 (0.6)
Respiratory system disorders	3 (5.2)	7 (3.9)	9 (5.1)	3 (5.1)	11 (6.4)
COPD exacerbation	3 (5.2)	6 (3.3)	7 (4.0)	3 (5.1)	7 (4.1)
Pneumonia	0	2 (1.1)	3 (1.7)	0	5 (2.9)
Anemia, microcytic	1 (1.7)	0	0	0	0
Hernia, inguinal	0	0	1 (0.6)	0	0
Thrombophlebitis	0	1 (0.6)	0	0	0
Vision disorder	0	0	0	0	1 (0.6)

1 WHO-coded body system and preferred term
2 death cases were described in detail in 7.1.1.3 above
(Source: Volume 5.6, Section 5.3.4.2, page 131-135)

Reviewer comment:
The serious adverse events were occurred at similar frequencies across treatment groups including placebo treatment. The most frequently occurred SAE was COPD exacerbation in all treatment groups. It is common in patients with COPD to have fluctuations in symptom severity as a natural course of the disease. Therefore, COPD exacerbation, counted as an adverse event, may not constitute a true AE in the real sense. It appears that there were no new safety signals revealed in evaluating SAEs in the clinical trials.

7.1.3 Dropouts and Other Significant Adverse Events

A total of 198 patients dropped out from three of the clinical studies due to adverse events. There were dropouts of 85 patients (5.8%), 65 patients (5.8%), and 48 (7.4%) due to adverse

events in study 1012.56, 1012.46, and 244.2484, respectively. The summary of patients with adverse events leading to withdrawal from the clinical studies is listed in Table 13. The rates of withdrawal due to adverse events were similar across the treatment and placebo groups in all three studies. It appears that the dropout rates due to adverse events were correlated to the duration of the study, and had no relation with the different test drugs in three clinical studies. Two 12-week studies (1012.56 and 1012.46) had a same dropout rate due to adverse events, while the 6-month study (244.2484) had a higher dropout rate due to adverse events. The common adverse events leading to withdrawal across treatment groups and clinical studies were respiratory system disorders. COPD exacerbation in turn was the single most common reason of withdrawal from the clinical studies. Other adverse events that lead to withdrawal from the studies were not a new safety signal for the test drugs in patients with COPD.

Table 13 Dropouts from the study 1012.56, 1012.46, and 244.2484 due to adverse events

	12-week studies		6-month study
	Study 1012.56	**Study 1012.46**	**Study 244.2484**
Total patients treated	1460	1118	646
Patients with AEs leading to withdrawal	85 (5.8)	65 (5.8)	48 (7.4)
Respiratory system disorders	63 (4.3)	58 (5.2)	27 (4.2)
COPD exacerbation	39 (2.7)	25 (2.2)	20 (3.1)
Dyspnea	9 (0.6)	18 (1.6)	4 (0.6)
Pneumonia	8 (0.5)	4 (0.4)	4 (0.6)
Upper respiratory tract infection	3 (0.2)	1 (0.1)	
Cough	2 (0.1)	2 (0.2)	
General conditions	5 (0.3)	2 (0.2)	4 (0.6)
Nervous system disorders	5 (0.3)	2 (0.2)	1 (0.2)
Cardiovascular disorders	7 (0.5)	3 (0.3)	5 (0.8)
Gastrointestinal disorders		3 (0.3)	2 (0.3)
Heart rate & rhythm disorders			3 (0.5)
Musculoskeletal system disorders	1 (0.1)	2 (0.2)	1 (0.2)
Psychiatric disorders	6 (0.4)	1 (0.1)	3 (0.5)
Neoplasms	1 (0.1)	1 (0.1)	4 (0.6)
Injury & poisoning	3 (0.2)	2 (0.2)	
Infections and infestations	3 (0.2)		
Metabolism disorders	1 (0.1)		
Renal & urinary disorders	1 (0.1)		
Skin and subcutaneous disorders	3 (0.2)		
Eye disorder	1 (0.1)		
Investigations*		3 (0.3)	

* Including drug screening positives and blood pressure increases.
(Source: Volume 2.3, Section 2.7.4, pages 93-95)

7.1.4 Other Search Strategies

No other search strategies were used in this application.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All adverse events were recorded by patients in the patient daily record. At each visit after review of the patient's diary record and discussion with the patient, the adverse events and

information concerning the onset, duration, intensity, severity, and action taken were collected on the Case Report Form (CRF).

COPD exacerbations were reported as AEs. A COPD exacerbation was defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea, and chest tightness) having a duration of three or more days requiring treatment with an antibiotic and/or systemic steroids with or without hospital admission. This information along with the duration and medication used was recorded on the CRF.

Serious adverse events (SAEs) were recorded on the Serious Adverse Event Form and reported by fax to the Local Clinical Monitor as soon as site personnel were aware of the event. A narrative summary of SAEs was forwarded to the Clinical Monitor within 5 working days of notification. Additionally, serious adverse events and all events leading to death, regardless of their relationship to drug, that occurred within 14 days after the subject left the trial were reported as a serious adverse event.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were classified according to different systems for three clinical studies. Different MedDRA dictionary versions were used for the 12-week studies, version 10.1 for study 1012.56 and version 7.0 for study 1012.46. WHO-coded body system and preferred term was used to classify adverse events for the 6-month study 244.2484. Although it is difficult to combine and compare the AEs from all three clinical studies because of the different classification system used in different studies, the AE categorization and preferred terms in each study was appropriate to classify the AEs in the patients with COPD.

7.1.5.3 Incidence of common adverse events

The overall adverse event incidences were similar across treatment and placebo groups in each of the three clinical studies. The 6-month study had a higher adverse event incidence (85.3%) than that of two 12-week studies (47.3% and 47.2%). The common adverse events were respiratory system disorders, accounting for the majority of adverse event cases in all three clinical studies. The single most common adverse event in two 12-week studies was COPD exacerbation (12.7% and 8.9% for study 1012.56 and 1012.46, respectively). For the 6-month study, COPD exacerbation was the second most common adverse event (22.8%), next to cases of upper respiratory tract infection (28.3%). It appears that the overall adverse event incidence and especially the incidence of COPD exacerbation in the three clinical studies were correlated to the duration of the study treatment, and had no relation with the different test drug products. Two 12-week studies (1012.56 and 1012.46) had similar overall adverse event incidences and the incidences of COPD exacerbation. The overall adverse event incidence in the 12-week studies did not reveal new safety signals for the test drug products in patients with COPD.

The 6-month study had a doubled or nearly doubled overall adverse event incidence and the incidence of COPD exacerbation compared to that in 12-week studies. The patients had a much higher incidence of upper respiratory tract infection (28.3%) compared to that of the two 12-week studies (3.7% and 5.0% for study 1012.56 and 1012.46, respectively). It is unclear what caused the high incidence of upper respiratory tract infection in the 6-month study.

The patients in the 6-month study also had a much higher incidence of pharyngitis (10.5%) compared to that of the two 12-week studies (3.6% and 4.1% for study 1012.56 and 1012.46, respectively). Noticeably, the incidence of pharyngitis in the 6-month study was not evenly distributed in treatment groups. The patients in ipratropium Respimat 40 mcg group had a highest pharyngitis incidence (16.4%), and the patients with Respimat device (ipratropium Respimat 20, 40 mcg and placebo Respimat combined) had more pharyngitis (12.3%) than that of the patients with MDI device (7.4%, placebo MDI and Atrovent MDI 36 mcg combined).

7.1.5.4 Common adverse event tables

Table 14 Adverse event frequency and percentage (≥2%) in preferred terms[1] by treatment groups, study 1012.56

Adverse event	Total (%)	Combivent Respimat 20/100 N (%)	Combivent CFC-MDI 36/206 N (%)	Ipratropium Respimat 20 N (%)
Total treated patients	1460	486	491	483
Patients with any AE	691 (47.3)	222 (45.7)	254 (51.7)	215 (44.5)
Respiratory system disorders				
COPD exacerbation	186 (12.7)	72 (14.8)	64 (13.0)	50 (10.4)
Nasopharyngitis	53 (3.6)	18 (3.7)	15 (3.1)	20 (4.1)
Upper respiratory tract inf	54 (3.7)	17 (3.5)	19 (3.9)	18 (3.7)
Bronchitis	38 (2.6)	14 (2.9)	17 (3.5)	7 (1.4)
Cough	32 (2.2)	13 (2.7)	10 (2.0)	9 (1.9)
Dyspnea	37 (2.5)	11 (2.3)	12 (2.4)	14 (2.9)
Sinusitis	24 (1.6)	5 (1.0)	13 (2.6)	6 (1.2)
Nervous system disorders				
Headache	39 (2.7)	13 (2.7)	10 (2.0)	16 (3.3)
Musculoskeletal & connective tissue disorders				
Arthralgia	15 (1.0)	2 (0.4)	10 (2.0)	3 (0.6)

1 MedDRA version 10.1
(Source: Volume 5.20, Section 5.3.5.1, pages 378-383)

Table 15 Adverse event frequency and percentage (≥3%) in preferred terms[1] by treatment groups, study 1012.46

Adverse event	Total (%)	Combivent Respimat 40/200 N (%)	Combivent MDI 36/206 N (%)	Ipratropium Respimat 40 N (%)	Placebo Respimat N (%)	Placebo CFC-MDI N (%)
Total treated patients	1118	345	180	252	165	176
Patients with any AE	528 (47.2)	167 (48.4)	74 (41.1)	121 (48.0)	87 (52.7)	79 (44.9)
Nervous system disorders	73 (6.5)	20 (5.8)	12 (6.7)	12 (4.8)	17 (10.3)	12 (6.8)
Headache	40 (3.6)	11 (3.2)	6 (3.3)	5 (2.0)	9 (5.5)	9 (5.1)
Dizziness	17 (1.5)	2 (0.6)	3 (1.7)	4 (1.6)	7 (4.2)	1 (0.6)
Lower respiratory system disorders	235 (21.0)	77 (21.3)	30 (16.7)	49 (19.4)	47 (28.5)	32 (18.2)
Bronchitis	44 (3.9)	14 (4.1)	7 (3.9)	12 (4.8)	6 (3.6)	5 (2.8)
COPD exacerbation	100 (8.9)	34 (9.9)	12 (6.7)	21 (8.3)	20 (12.2)	13 (7.4)
Cough	30 (2.7)	8 (2.3)	5 (2.8)	6 (2.4)	7 (4.2)	4 (2.3)
Dyspnea	51 (4.1)	14 (4.1)	8 (4.4)	7 (2.8)	15 (9.1)	7 (4.0)
Upper respiratory system disorders	171 (15.2)	56 (16.2)	29 (16.1)	42 (16.7)	19 (11.5)	25 (14.2)
Pharyngitis	46 (4.1)	13 (3.8)	8 (4.4)	14 (5.6)	3 (1.8)	8 (4.5)
Upper respiratory tract inf	56 (5.0)	20 (5.8)	10 (5.6)	15 (6.0)	6 (3.6)	5 (2.8)

1 MedDRA version 7.0.

(Source : Volume 2.3, Section 2.7.4, page 60)

Table 16 Adverse event frequency and percentage (≥3%) in preferred terms[1] by treatment groups, study 244.2484

Adverse event	Total* N (%)	Placebo Respimat N (%)	Ipratropium Respimat 20 N (%)	Ipratropium Respimat 40 N (%)	Placebo MDI N (%)	Atrovent MDI 36 N (%)
Total treated patients	646 (100)	58 (100)	180 (100)	177 (100)	59 (100)	172 (100)
Patients with any AE	535 (82.8)	49 (84.5)	150 (83.3)	152 (85.9)	43 (72.9)	141(82.0)
General disorders	267 (41.3)	24 (41.4)	77 (42.8)	73 (41.2)	22 (37.3)	71 (41.3)
Accident, Household	41 (6.3)	3 (5.2)	13 (7.2)	13 (7.3)	4 (6.8)	8 (4.7)
Back pain	20 (3.1)	2 (3.4)	3 (1.7)	7 (4.0)	2 (3.4)	6 (3.5)
Fall	22 (3.4)	0	7 (3.9)	8 (4.5)	1 (1.7)	6 (3.5)
Fatigue	21 (3.3)	4 (6.9)	7 (3.9)	5 (2.8)	0	5 (2.9)
Headache	121 (18.7)	11 (19.0)	38 (21.1)	33 (18.6)	8 (13.6)	31 (18.0)
Pain	24 (3.7)	2 (3.4)	6 (3.3)	7 (4.0)	2 (3.4)	7 (4.1)
Influenza-like sympt.	50 (7.7)	9 (15.5)	9 (5.0)	11 (6.2)	8 (13.6)	13 (7.6)
Nervous system disorders	82 (12.7)	5 (8.6)	21 (11.7)	27 (15.3)	8 (13.6)	21 (12.2)
Dizziness	43 (6.7)	1 (1.7)	14 (7.8)	13 (7.3)	4 (6.8)	11 (6.4)
Gastro-intestinal system disorders	138(21.4)	14 (24.1)	43 (23.9)	44 (24.9)	5 (8.5)	32 (18.6)
Abdominal pain	27 (4.2)	3 (5.2)	10 (5.6)	11 (6.2)	0	3 (1.7)
Diarrhea	20 (3.1)	5 (8.6)	5 (2.8)	7 (4.0)	1 (1.7)	2 (1.2)
Dyspepsia	24 (3.7)	0	6 (3.3)	12 (6.8)	1 (1.7)	5 (2.9)
Gastroenteritis	16 (2.5)	2 (3.4)	5 (2.8)	6 (3.4)	1 (1.7)	2 (1.2)
Mouth dry	22 (3.4)	2 (3.4)	10 (5.6)	6 (3.4)	0	4 (2.3)
Nausea	31 (4.8)	5 (8.6)	9 (5.0)	10 (5.6)	2 (3.4)	5 (2.9)
Muscular-skeletal system disorders	50 (7.7)	5 (8.6)	17 (9.4)	11 (6.2)	3 (5.1)	14 (8.1)
Myalgia	21 (3.3)	3 (5.2)	5 (2.8)	7 (4.0)	1 (1.7)	5 (2.9)
Respiratory system disorders	398(61.6)	41 (70.7)	107 (59.4)	117 (66.1)	31 (52.5)	102 (59.3)
Bronchitis	35 (5.4)	5 (8.6)	10 (6.6)	11 (6.2)	1 (1.7)	8 (4.7)
COPD exacerbation	147(22.8)	15 (25.9)	42 (23.3)	38 (21.5)	12 (20/3)	40 (23.3)
Cough	56 (8.7)	5 (8.6)	17 (9.4)	14 (7.9)	7 (11.9)	13 (7.6)
Dyspnea	45 (7.0)	5 (8.6)	9 (5.0)	10 (5.6)	5 (8.5)	16 (9.3)
Pharyngitis	68 (10.5)	5 (8.6)	17 (9.4)	29 (16.4)	5 (8.5)	12 (7.0)
Pneumonia	26 (4.0)	3 (5.2)	6 (3.3)	5 (2.8)	0	12 (7.0)
Rhinitis	31 (4.8)	2 (3.4)	9 (5.0)	7 (4.0)	4 (6.8)	9 (5.2)
Sinusitis	19 (2.9)	4 (6.9)	4 (2.2)	5 (2.8)	0	6 (3.5)
Upper resp tract inf	183(28.3)	17 (29.3)	46 (25.6)	55 (31.1)	13 (22.0)	52 (30.2)
Vision disorders	38 (5.9)	3 (5.2)	6 (3.3)	13 (7.3)	2 (3.4)	14 (8.1)

1 WHO-coded body system and preferred term

* Some total numbers were slightly different from the sums of the 5 treatment groups because it included adverse events reported at the screening visit and, in a few cases, adverse events reported after the 6-month treatment period.

(Source: Volume 2.3, Section 2.7.4, pages 62-65)

Reviewer comment:

It is noticeable that the patients in the 6-month study had much higher incidences of upper respiratory tract infection, COPD exacerbation, and pharyngitis compared to those of the patients in the two 12-week studies. Furthermore, the incidence of pharyngitis in the 6-month

study was not evenly distributed in treatment groups. The patients in ipratropium Respimat 40 mcg group had a highest pharyngitis incidence (16.4%), and the patients with Respimat device (ipratropium Respimat 20, 40 mcg and placebo Respimat combined) had more pharyngitis (12.3%) than that of the patients with MDI device (7.4%, placebo MDI and Atrovent MDI 36 mcg combined). This may potentially be a safety signal in patients who are expected to use Combivent Respimat regularly. Since there is no Respimat device approved in the United States, a well designed long term safety study is necessary to address this potential safety issue and the long term patient acceptance to Combivent Respimat.

7.1.6 Less Common Adverse Events

There were no safety signals revealed in less common adverse events in the three clinical studies in patients with COPD.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

For the three clinical studies, laboratory testing included routine blood chemistry, hematology, and urinalysis. Chemistry included CO_2, alkaline phosphatase, LDH, SGOT, SGPT, glucose, calcium, chloride, uric acid, urea nitrogen, creatinine, total protein, albumin, and total bilirubin. Hematology included hemoglobin, hematocrit, red blood cell count, white blood cell count including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) total eosinophil count and platelet count. The urinalysis includes specific gravity, pH, glucose, protein, and hemoglobin. A serum pregnancy test will be conducted at the screening visit in all women of child-bearing potential.

Laboratory tests were performed in study 1012.56 at the screening visit only. There were no analyses of laboratory values for study 1012.56. In study 1012.46, clinical laboratory tests were conducted on all patients at the screening visit, and repeated after 4 weeks of therapy and at the end of patient participation. In study 244.2484, clinical laboratory tests were conducted on all patients at the screening visit, and repeated after 12 weeks of therapy and at the end of patient participation. An abnormal laboratory value at the end of treatment was to be recorded as an adverse event if it was not associated with an already reported adverse event symptom or diagnosis. Clinical laboratory values were assessed as individual patient marked changes and as mean changes from baseline. The results of clinical laboratory tests did not indicate any clinically important findings and relevant differences among the treatment groups.

7.1.7.2 Additional analyses and explorations

No additional analyses or explorations of laboratory values were conducted.

7.1.7.3 Special assessments

No special laboratory assessments were conducted.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs consisted of blood pressure and pulse rate. Blood pressure and pulse rate were measured and recorded at each clinical visit in the three clinical studies. The results of vital sign evaluation did not indicate any clinically relevant differences in mean changes and marked changes among the treatment groups in the three clinical studies.

7.1.8.2 Additional analyses and explorations

No additional analyses or explorations of vital signs were conducted.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

A standard 12-lead ECG was to be performed on all patients at the screening visit and repeated at the end of the treatment period for all patients in the 12-week and 6-month studies. The ECG was to be performed prior to the test-day pre-dose PFT. All ECGs were interpreted by the investigator or other qualified site personnel. Follow up ECGs were also performed on all patients discontinuing early. All abnormal ECG findings at baseline were recorded as concomitant medical diagnoses. Any new abnormal finding or worsening of a baseline condition detected at a follow up ECG was recorded as an adverse event.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

In the pivotal study 1012.56 for Combivent Respimat, ECGs were performed at screening and the end of the trial or upon early discontinuation. In the 12-week study 1012.46 for Combivent Respimat, ECGs were performed at screening, first visit during the study, at 4 week and the end of the trial or upon early discontinuation. In the 6-month study for ipratropium Respimat, ECGs were performed at screening, 12 week, and the end of the trial or upon early discontinuation.

7.1.9.3 Standard analyses and explorations of ECG data

There were no clinically important ECG changes in two 12-week studies for Combivent Respimat (1012.56 and 1012.46). In the 6-month study for ipratropium Respimat, 12 out of 646 treated patients (0.19%, 12/646) had clinical significant finding in ECG either at the 12-week visit or at the end of the trial. These patients were distributed across the five treatment groups (2 patients in Respimat placebo, 3 patients in ipratropium Respimat 20 mcg, 2 patients in ipratropium Respimat 40 mcg, 2 patients in MDI placebo, and 3 patients in Atrovent MDI).

In the Respimat placebo group, two patients had significant changes in their ECG at the final visit. One patient had sinus tachycardia. This patient discontinued from the study due to a diagnosis of prostate cancer. Another patient had sinus bradycardia at the final visit, which was

not treated and resolved three days later. All ECG findings appear to not be directly related to the study medications.

There were 3 patients who had significant findings in the final ECG in the ipratropium Respimat 20 mcg group. One patient had atrial fibrillation at the final visit ECG. This patient had been treated by a cardiologist and had three ER visits for chest pain with shortness of breath. One patient had a mild atrial fibrillation in the ECG at the 12-week and final visits. This patient was followed by a general practitioner and received no treatment for the atrial fibrillation. Another patient had a left bundle branch block in the final visit ECG. This patient had no cardiac symptoms and was followed by a general practitioner.

In the ipratropium Respimat 40 mcg group, one patient had mild and intermittent atrial fibrillation in the final visit ECG. Another patient had premature ventricular contractions in the final visit ECG. This patient had a history of hypertension and screening ECG showed non-specific ST segment - T wave changes and evidence of an old inferior lateral wall myocardial infarction. Both patients were followed by general practitioners.

Two patients in the MDI placebo group had clinically relevant changes in the 12-week visit ECG. One patient with a history of hypertension had premature ventricular contractions. Another patient had an ECG examination after a car accident. The ischemic change was noted.

There were three patients with ECG findings in the Atrovent MDI 36 mcg group. One patient with a history of hypertension had a first degree heart block in the 12-week ECG. Another patient had an episode of atrial fibrillation. The event was moderate in intensity. One patient had experienced a myocardial infarction two months after the randomization and was recorded as having an abnormal ECG on the final visit.

Reviewer comment:
Tachycardia would be a cardiovascular adverse event of anti-cholinergics, if any. Tachycardia was not observed in the two 12-week studies with Combivent Respimat or in the 6-month study with ipratropium Respimat. The ECG findings in the 6-month study with ipratropium Respimat were similar across all treatment groups including the placebos. These ECG findings during a 6-month period in COPD patients revealed no safety signals for the test drug.

7.1.9.4 Additional analyses and explorations

No additional analyses or explorations of vital signs were conducted.

7.1.10 Immunogenicity

Since albuterol and ipratropium are small molecules, immunogenicity is not a concern; thus, immunogenicity was not evaluated as part of this application.

7.1.11 Human Carcinogenicity

Carcinogenicity studies in animals did not suggest carcinogenic potential for ipratropium and albuterol. In the two 12-week studies (1012.56 and 1012.46) a total of eight patients had adverse events of benign or malignant neoplasm. These included four in Combivent CFC MDI 36/206

mcg group, two in ipratropium Respimat 20 mcg group, one in ipratropium Respimat 40 mcg group, and one in Combivent Respimat 20/100 mcg group. There were five patients had adverse events of benign or malignant neoplasm in 6-month study (244.2484), including two in ipratropium Respimat 40 mcg group, one in ipratropium Respimat 20 mcg group, one in ipratropium CFC MDI 36 mcg group, and one in placebo MDI group. Given the older age of the patients enrolled in these studies, the scattered neoplasm cases are not unexpected. No safety signals were revealed in evaluating these neoplasm cases.

7.1.12 Special Safety Studies

No special safety studies were conducted in this application

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Ipratropium bromide and albuterol sulfate are not controlled substances and have no known abuse potential. No withdrawal effects were reported in any of the clinical studies in this NDA submission.

7.1.14 Human Reproduction and Pregnancy Data

No clinical data are available for pregnancies exposed to tiotropium or for nursing females. Because COPD is a disease that generally occurs only in older patients with a significant smoking history, clinical trials only enrolled patients greater than 40 years of age.

7.1.15 Assessment of Effect on Growth

COPD is a disease that generally occurs only in the older adult population. Therefore, an assessment of effect on growth does not apply to this application.

7.1.16 Overdose Experience

In the Combivent Respimat development program, no cases of drug overdose were reported. In the dose ranging study 244.2447, single dose of ipratropium bromide was administered to COPD patients via Respimat at doses of 10, 20, 40, 80, and 160 mcg. There were no cases of over dose reported in the study. In the dose ranging study 243.7, single dose of albuterol sulfate was administered to COPD patient via Respimat at doses of 25, 50, 100, and 200 mcg. There were no cases of over dose reported in the study.

7.1.17 Postmarketing Experience

At the time of the NDA, post-marketing experience was not available with Combivent Respimat since Combivent Respimat is not approved for marketing in any country. However, Combivent as a fixed dose combination of ipratropium bromide and albuterol sulfate has been marketed in Europe since March 22, 1994, and in the United States since October 24, 1996. There are two formulations of Combivent on the world market for patients with COPD, including Combivent Inhalation Aerosol delivered with a MDI inhaler and Combivent Inhalation Solution delivered with unit dose vials (UDV). Only Combivent Inhalation Aerosol MDI has been marketed in the United States.

The Applicant provided post-marketing experience report for Combivent, covering the period from March 22, 1994 until January 31, 2008. The estimated worldwide patient exposure to Combivent was 15,285,146 patient-years (14,561,253 patient-years for Combivent Inhalation Aerosol MDI and 723,893 patient-years for Combivent UDV, respectively). This estimation was from sales data ((b) (4) actuations for MDI and (b) (4) vials for UDV), assuming all wholesale products were dispended to patients, all patients treated with Combivent Inhalation Aerosol MDI consumed eight metered doses per day and all patients treated with Combivent UDV used 4 vials per day.

A total of 5,023 adverse events by MedDRA System Organ Class (SOC) were reported to the Applicant, accounting for 32.86 adverse events per 100,000 patient-years exposure. The most common adverse events by SOC was general disorder including drug ineffective (8 per 100,000 patient-years), followed by respiratory, thoracic, and mediastinal disorders (7.55 per 100,000 patient-years), and nervous system disorders (6.7 per 100,000 patient-years).

A total of 520 serious adverse events were reported to the Applicant, accounting for 3.4 SAEs per 100,000 patient-years exposure. The most common SAEs were respiratory, thoracic, and mediastinal disorder (0.95 per 100,000 patient-years). There were 74 fatalities reported during the period from March 22, 1994 until January 31, 2008, accounting for 0.48 deaths per 100,000 patient-years exposure.

Reviewer comment:
The post marketing adverse events for Combivent Inhalation Aerosol and Combivent UDV did not reveal evidence of any specific safety signals related to Combivent use in COPD patients.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Safety data were primarily provided by three clinical studies: two 12-week studies for Combivent Respimat and one 6-month study for ipratropium Respimat. The three studies are summarized in Table 17 below.

Table 17 Summary of Combivent Respimat program clinical studies used to support safety

Study #	Study type	Treatment groups	N	Treatment duration	Study design	Diagnosis, age of subjects
1012.56	Pivotal efficacy and safety study	Combivent R* 20/100 Ipratropium 20 Combivent MDI 18/103	486 483 491	Multiple-dose, 12 weeks	Randomized, multi-national, double-blinded, placebo-, active-controlled	COPD 64.1 years (mean age)
1012.46	Safety study	Combivent R* 40/200 Ipratropium R* 40 Combivent MDI 36/206	345 252 180	Multiple-dose, 12 weeks	Randomized, double-blinded, placebo-, active-	COPD 64.2 years (mean age)

		Placebo R* Placebo MDI	165 176		controlled	
244.2484	Long-term safety study for ipratropium Respimat	Ipratropium R* 20 Ipratropium R* 40 Atrovent MDI 36 Placebo R* Placebo MDI	180 177 172 58 59	Multiple-dose, 6 months	Randomized, double-blinded, placebo-, active-controlled	COPD 65.8 years (mean age)

* Respimat

7.2.1.2 Demographics

Demographics and basic characteristics of patients in study 1012.56

Patients' baseline demographic information is summarized in Table 18. Overall, 65% and 34.6% of the treated patients were males and females, respectively. In terms of race or ethnic groups, 89% of the patients were white. The African American and Asian were 5.3% and 5.6% of the study patients, respectively. The average age of the patient population was 64 years, with the range from 40 to 89 years old. Over 50% of the patients were in the range from 40 to 64 years old. The average smoking history was 53 pack-years, and the mean COPD duration was 8.4 years. The three treatment groups were comparable with respect to the baseline demographic characteristics.

The study population was relatively balanced across treatment groups at baseline in the PFT evaluation. The overall mean baseline (pre-bronchodilator screening) FEV_1 was 1.144 liters. The ipratropium Respimat 20 mcg group had a slightly lower mean baseline FEV_1 value than that of other two treatment groups (1.117 vs. 1.154 and 1.162, respectively). But the percent of predicted FEV_1 values were comparable among the three treatment groups. All treatment groups were comparable in baseline FVC value, and the overall mean ratio of FEV_1/FVC was 44.8%.

Table 18 Summary of demographics for patients, study 1012.56

Demographics and baseline PFT	**Total** **N (%)**	**Combivent Respimat 20/100** **N (%)**	**Combivent MDI 36/206** **N (%)**	**Ipratropium Respimat 20** **N (%)**
Total treated	1460	486	491	483
Sex Male	955 (65.4)	316 (65.0)	322 (65.6)	317 (65.6)
Female	505 (34.6)	170 (35.9)	169 (34.4)	166 (34.4)
Race White	1300 (89.0)	430 (88.5)	442 (90.0)	428 (88.6)
Black	78 (5.3)	27 (5.6)	25 (5.1)	26 (5.4)
Asian	82 (5.6)	29 (6.0)	24 (4.9)	29 (6.0)
Age Mean (years)	64.1	63.8	64.2	64.3
Min	40	40	40	40
Max	88	86	88	87
Smoking history(pack-years)				
Mean	53.2	51.7	52.4	55.4
SD	27.5	27.7	27.1	27.6
Median	47.0	45.0	47.0	49.0
COPD duration (yrs) Mean	8.4	8.2	8.6	8.5
SD	6.3	6.1	6.5	6.4
Screening FEV_1 (L) Mean	1.144	1.154	1.162	1.117
SD	0.42	0.418	0.426	0.416
% predicted FEV_1 Mean	41.4	41.5	41.9	40.9
SD	12.5	12.3	12.5	12.7

FEV_1/FVC (%)	**Mean**	44.8	44.7	45.3	44.3
	SD	10.8	10.6	11.1	10.6

(Source: Volume 5.19, Section 5.3.5.1, p94-97, 260-268)

Demographics and basic characteristics of patients in study 1012.46

A total of 1118 patients were randomized and took at least one dose of study medication. There were 345 patients in the Combivent Respimat 40/200 mcg group, 180 patients in the Combivent CFC-MDI 36/206 mcg group, 165 in the placebo Respimat group, 176 in the placebo CFC-MDI group and 252 patients in the ipratropium Respimat 40 mcg group.

Table 19 summarized the demographics and baseline characteristics of the patient population. The demographic information was comparable across treatment groups. Overall, 65% of the patients were male, over 90% of the patients were white. The average age was 64.2 years, the mean COPD duration was 9.3 years. All treatment groups were comparable in screening FEV_1 and FVC. The overall mean FEV_1 was 1.13 liters, the percent of predicted FEV_1 was 41.6%, and the FEV_1/ FVC ratio was 48.4%.

Table 19 Summary of demographics for patients, study 1012.46

Demographics and baseline PFT	**Total N (%)**	**Combivent Respimat 40/200 N (%)**	**Combivent MDI 36/206 N (%)**	**Ipratropium Respimat 40 N (%)**	**Placebo (Respimat&MDI) N (%)**
Total treated	1118	345	180	252	341
Sex Male	727 (65.0)	226 (65.5)	105 (58.3)	162 (64.3)	234 (68.6)
Female	391 (35.0)	119 (34.5)	74 (41.7)	90 (35.7)	107 (31.4)
Race White	1034 (92.5)	312 (90.4)	169 (93.9)	233 (92.5)	320 (93.8)
Black	82 (7.3)	32 (9.3)	11 (6.1)	19 (7.5)	21 (5.9)
Asian	1 (0.2)	1 (0.3)	0	0	1 (0.3)
Age (yrs) Mean	64.2	64.6	63.8	64.0	64.1
SD	9.3	9.2	8.7	9.3	9.6
Smoking history (pack-years) Mean	58.8	58.2	59.0	58.7	59.4
SD	32.7	31.1	30.0	31.7	36.2
COPD duration (yrs) Mean	9.26	9.44	8.82	9.00	9.51
SD	7.78	7.77	7.68	7.56	8.03
Screening FEV_1 (L) Mean	1.126	1.130	1.116	1.120	1.132
SD	0.443	0.437	0.428	0.447	0.455
% predicted FEV_1 Mean	41.553	41.732	41.749	41.458	41.3340
SD	13.673	13.284	13.346	13.807	14.178
FEV_1/FVC(%) Mean	48.391	48.655	48.677	48.625	47.801
SD	11.130	10.740	11.370	11.263	11.317

(Source: Volume 5.65, Section 5.3.5.1, p 93-95)

Demographics and basic characteristics of patients in study 244.2484

Patients' baseline demographic information and baseline pulmonary function test were summarized in Table 20. A total of 646 patients were randomized into five treatment groups at a ratio 1 to 3 for 2 placebo groups and 3 active treatment groups. Overall, 57% and 43% of the treated patients were males and females, respectively. In terms of race or ethnic groups, 98% of the patients were white. The African Americans and Asians were only 1% each of the study

patients. The average age of the patient population was 65.8 years. Over 60% of the patients were in the range from 61 to 75 years old. The average smoking history was 49.5 pack-years, and the mean COPD duration was 7.7 years. The five treatment groups were comparable with respect to the baseline demographic characteristics and baseline pulmonary function test.

Table 20 Summary of demographics for patients, study 244.2484

Demographics and baseline PFT	Total (%)	Placebo Respimat N (%)	Ipratropium Respimat 20 N (%)	Ipratropium Respimat 40 N (%)	Placebo MDI N (%)	Atrovent MDI 36 N (%)
Total treated	646 (100)	58 (100)	180 (100)	177 (100)	59 (100)	172 (100)
Sex Male	371 (57)	33 (57)	101 (66)	92 (52)	40 (68)	105 (61)
Female	275 (43)	25 (43)	79 (44)	85 (48)	19 (32)	67 (39)
Race White	636 (98)	55 (95)	178 (99)	177 (100)	59 (100)	167 (97)
Black	4 (1)	1 (2)	1 (0.5)	0	0	2 (1)
Asian	6 (1)	3 (3)	1 (0.5)	0	0	3 (2)
Age Mean(yrs)	65.8	64.5	66.4	65.1	64.8	66.6
SD	8.5	8.0	8.4	8.7	8.6	8.7
Min (yrs)	41	48	41	43	47	43
Max (yrs)	90	77	90	83	82	89
40 - 60 yrs	174 (27)	19 (33)	39 (22)	51 (29)	20 (34)	45 (26)
61 - 75 yrs	399 (62)	36 (62)	120 (67)	110 (62)	33 (56)	100 (58)
>75 yrs	73 (11)	3 (5)	21 (11)	16 (9)	6 (10)	27 (16)
Smoking history Pack-years						
Mean	49.5	48.5	51.3	49.8	45.5	49.1
SD	24,6	21.4	25.2	25.8	25.9	23.5
COPD duration (years) Mean	7.7	7.1	7.7	7.9	7.8	7.5
SD	6.2	4.9	6.1	6.8	7.3	5.6
Screening FEV_1 (liters) Mean	1.01	1.00	1.00	0.99	1.05	1.03
SD	0.42	0.41	0.40	0.47	0.45	0.40
% predicted FEV_1 Mean	40.38	39.34	40.77	39.72	40.01	41.14
SD	13.81	14.16	14.10	14.18	13.19	13.30
FEV_1/FVC Mean	0.48	0.48	0.48	0.47	0.48	0.48
SD	0.12	0.12	0.12	0.12	0.12	0.12

(Source: Volume 5.6, Section 5.3.4.2, page 77-79)

7.2.1.3 Extent of exposure (dose/duration)

Extent of exposure for study 1012.56

A total of 1,460 patients received at least one dose of study medication.
Four hundred eighty six patients (486) received Combivent Respimat 20/100 mcg, 491 received Combivent CFC-MDI 36/206 mcg and 483 received Ipratropium Respimat 20 mcg. Approximately 90% of patients in all three groups were exposed to the treatment medication for more than 70 days. The mean and median exposure days for all treatment groups are 80.1 and 85 days, respectively. The total patient exposure days for Combivent Respimat 20/100 mcg, Combivent CFC-MDI 36/206 mcg, and Ipratropium Respimat 20 mcg were 39,091, 39,698, and 38,093, respectively. The exposure to trial medications was considered adequate to assess the efficacy and short term safety. Table 21 lists the total and group exposure to the trial medications.

Table 21 Exposure to trial medications, study 1012.56

Exposure	Total	Combivent Respimat 20/100	Combivent CFC-MDI 36/206	Ipratropium Respimat 20
Total treated patients	1460	486	491	483
Treatment duration: days (%)				
0 day	8 (0.5)	4 (0.8)	2 (0.4)	2 (0.4)
12-14 days	26 (1.8)	7 (1.4)	7 (1.4)	12 (2.5)
15-42 days	74 (5.1)	24 (4.9)	21 (4.3)	29 (6.0)
43-70 days	50 (3.4)	16 (3.3)	17 (3.5)	17 (3.5)
>70 days	1302 (89.2)	435 (89.5)	444 (90.4)	423 (87.6)
Exposure (days) Sum	116882	39091	39698	38093
Mean	80.1	80.4	80.9	78.9
Median	85.0	85.0	85	85

(Source: Volume 5.19, Section 5.3.5.1, p157)

Extent of exposure for study 1012.46

A total of 345 patients received Combivent Respimat 40/200 mcg, 252 patients received ipratropium Respimat 40 mcg and 180 patients received Combivent CFC-MDI 36/206 mcg. One hundred sixty-five patients received Respimat placebo and 176 patients received Placebo CFC-MDI. The mean exposure for all five groups was 78.9 days; the median exposure was 85 days. The active Combivent groups had very similar exposure. The ipratropium Respimat group had the highest mean exposure of 83.3 days and the placebo Respimat group had the lowest mean exposure of 72.1 days. Table 22 summarized the exposure by treatment group.

Table 22 Exposure to trial medications, study 1012.46

Exposure	Total (%)	CVT Respimat 40/200 N (%)	CVT CFC-MDI 36/206 N (%)	Ipratr. Respimat 40 N (%)	Placebo Respimat N (%)	Placebo MDI N (%)
Total treated patients	1118	345	180	252	165	176
Treatment duration: days (%)						
1 -14 days	46 (4.1)	13 (3.8)	2 (1.1)	2 (0.8)	14 (8.5)	15 (8.5)
15-42 days	63 (5.6)	14 (4.1)	12 (6.7)	8 (3.2)	18 (10.9)	11 (6.3)
43-70 days	36 (3.2)	10 (2.9)	7 (3.9)	8 (3.2)	7 (4.2)	4 (2.3)
>70 days	973 (87.0)	308 (89.3)	159 (88.3)	234 (92.9)	126 (76.4)	146 (83.0)
Exposure (days) Mean	78.9	79.8	80.9	83.3	72.1	75.2
SD	21.7	20.0	17.8	14.5	28.9	26.9
Median	85	85	85	85	85	85

(Source: Volume 5.65, Section 5.3.5.1, p134)

Extent of exposure for study 244.2484

A total of 646 patients were randomized into five treatment groups and received at least one dose of study medication. One hundred eighty (180) patients received ipratropium Respimat 20 mcg, 177 patients received ipratropium Respimat 40 mcg, and 172 patients received Atrovent MDI 36 mcg. Fifty-eight (58) patients and 59 patients received Respimat placebo and MDI placebo, respectively. About 90% of patients in all five groups exposed to the treatment for more than 84 days and more than 30% of patients in all treatment groups exposed to the treatment fro more than 169 days. The average exposure days for patients in this study was about 152 days. Table 23 listed the total and group exposure to the treatment dedication.

Table 23 Exposure to trial medications, study 244.2484

Exposure	Total (%)	Placebo Respimat N (%)	Ipratropium Respimat 20 N (%)	Ipratropium Respimat 40 N (%)	Placebo MDI N (%)	Atrovent MDI 36 N (%)
Total treated	646 (100)	58 (100)	180 (100)	177 (100)	59 (100)	172 (100)
Treatment days (%)						
1	3 (0.5)	1 (1.7)	0	0	0	2 (1.2)
2-30	32 (5.0)	5 (8.6)	8 (4.4)	6 (3.4)	7 (11.9)	6 (3.5)
31-84	40 (6.2)	3 (5.2)	9 (5.0)	10 (5.6)	4 (6.8)	14 (8.1)
85-169	352 (54.5)	31 (53.4)	103 (57.2)	98 (55.4)	30 (50.8)	90 (52.3)
>169	219 (33.9)	18 (31.0)	60 (33.3)	63 (35.6)	18 (30.5)	60 (34.9)
Average exp. days	152	146	155	155	142	150

(Source : Volume 5.6, Section 5.3.4.2, page 88-91 ; Volume 5.10, page 116)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Two dose ranging studies for ipratropium Respimat (244.2447) and albuterol Respimat (243.7) in this submission were reviewed. Safety data collected from these two single dose studies included adverse event, vital signs, clinical laboratory tests, physical examination, and ECG. No safety signals revealed from these two studies. Details regarding the individual study can be found in Section 10 Appendices.

7.2.2.2 Postmarketing experience

At the time of the NDA, post-marketing experience was not available with Combivent Respimat since Combivent Respimat is not approved for marketing in any country. However, Combivent as a fixed dose combination of ipratropium bromide and albuterol sulfate has been marketed in Europe since March 22, 1994, and in the United States since October 24, 1996. There are two formulation of Combivent on the world market for patients with COPD, including Combivent Inhalation Aerosol delivered with a MDI inhaler and Combivent Inhalation Solution delivered with unit dose vials (UDV). Only Combivent Inhalation Aerosol MDI has been marketed in the United States.

The Applicant provided post-marketing experience report for Combivent, covering the period from March 22, 1994 until January 31, 2008. The post marketing experience for Combivent are described in Section 7.1.17.

7.2.3 Adequacy of Overall Clinical Experience

Overall, 2,578 COPD patients participated in two 12-week Combivent Respimat studies. A total of 831 COPD patients were exposed to Combivent Respimat (485 for 20/100 mcg and 345 for 40/200 mcg, respectively). Additionally, a total of 900 COPD patients were exposed to ipratropium Respimat or placebo Respimat in these two 12-week studies. In the 6-month study for ipratropium Respimat, a total of 646 COPD patients participated in the study, and 415 COPD patients were exposed to ipratropium Respimat or placebo Respimat. It appears that the overall

clinical experience is adequate to evaluate the efficacy and short term safety of the proposed drug product Combivent Respimat (20/100 mcg) Inhalation Spray. However, there are no long term (one year) studies for any Respimat inhaler to evaluate its safety and patient acceptability. As a replacement of Combivent MDI that has been broadly used by patients with COPD, Combivent Respimat (20/100 mcg) Inhalation Spray is expected to be used regularly in COPD patient population. Long term study of at least 200 patients for one year is needed to evaluated the long term safety and patient acceptability of the proposed drug product [Guidance fro Industry Points to Consider: Clinical Development Program for MDI and DPI Drug Products. September 19, 1994].

Reviewer comment:
In a tele-conference on March 11, 2009, the Applicant was informed that long term (one year) safety and patient acceptability data are needed to support the proposed drug product. The Applicant subsequently submitted a one year safety and patient acceptability study protocol for Combivent Respimat (20/100 mcg) Inhalation Spray on May 18, 2009.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal or in vitro testing was submitted as part of this application.

7.2.5 Adequacy of Routine Clinical Testing

For the majority of patients in the phase 3 studies, physical examination vital signs and routine clinical testing including blood chemistry, hematology, urinalysis, and ECG were performed at screening baseline and at the end of the study. Given the clinical experience obtained from Combivent Inhalation Aerosol, it appears adequate to monitoring the clinical testing as presented in the application. The evaluation of clinical testing did not indicate any clinically important findings and relevant differences among the treatment groups.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

A workup for metabolic, clearance, and interactions was not conducted as part of this application since the same chemical entities (ipratropium bromide and albuterol sulfate) are already marketed as a combination drug product (Combivent Inhalation Aerosol MDI) or individual drug product (Atrovent MDI for ipratropium bromide and Ventolin MDI for albuterol sulfate).

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Adverse events have been adequately assessed as part of the Combivent Respimat development program. See Section 7.2.3 for discussions of common adverse events, serious adverse events including deaths.

7.2.8 Assessment of Quality and Completeness of Data

No concerns regarding data quality were identified during the review. The clinical follow up was adequate in all of the studies. Protocol violations were infrequent in the clinical studies. DSI audit has been requested, and the final report of DSI audit is not available at the time of finalization of this primary review.

7.2.9 Additional Submissions, Including Safety Update

There are no additional submissions for this application. No safety update is available because the proposed drug product is not marketed and there was no additional data from clinical studies pending at the time of submission. In a pre-NDA meeting on January 16, 2008, the Division agreed that "a four-month safety update is not required for the Combivent Respimat NDA" [IND 57,948, Pre-NDA Meeting Minutes, February 8, 2008].

As the result of the discussion with the Division regarding the need of a long term safety and patient acceptability study to support the proposed drug product, the Applicant submitted a study protocol under IND 57,948 on May 18, 2009. The proposed study is entitled "One-year, randomized, open-label safety and patient acceptability study of Combivent (ipratropium bromide/salbutamol) (20/100 mcg) Respimat inhalation spray in comparison to Combivent inhalation aerosol (36/206 mcg) in adults with chronic obstructive pulmonary disease (COPD)." Comments to the study protocol have been conveyed to the Applicant.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

An increased number of pharyngitis was observed in the 6-month study for ipratropium Respimat compared to MDI and controls. The patients in ipratropium Respimat 40 mcg group had a highest pharyngitis incidence (16.4%), and the patients with Respimat device (ipratropium Respimat 20, 40 mcg and placebo Respimat combined) had more pharyngitis (12.3%) than that of the patients with MDI device (7.4%, placebo MDI and Atrovent MDI 36 mcg combined). This may potentially be a safety signal in COPD patients who are expected to use Combivent Respimat regularly. A long term (one year) study to evaluate the safety and patient acceptability of the proposed drug product Combivent Respimat is warranted.

Other adverse events were not unexpected for COPD patient population. Across the studies as a whole, the most common adverse events were in the respiratory system, including COPD exacerbation, dyspnea, nasopharyngitis, and upper respiratory tract infections.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

In general, the data from the clinical studies included in this review were evaluated as individual study data. The study design and study duration, the dose of the test drug administered in the studies, and the comparators were different among the clinical studies; as such, pooling data from these different clinical studies was not acceptable.

7.4.2 Explorations for Predictive Factors

It is noticeable that the patients in the 6-month study for ipratropium Respimat had much higher incidences of upper respiratory tract infection, COPD exacerbation, and pharyngitis compared to those of the patients in the two 12-week studies for Combivent Respimat. Most of these respiratory system adverse events were similar across the treatment groups (including placebo) in the study. The higher incidence of respiratory system disorders observed in a 6-month study than that in two 12-week studies could be just a reflection of the course of the treated disease (COPD). However, the incidence of pharyngitis in the 6-month study was not evenly distributed in treatment groups. The patients with Respimat (ipratropium Respimat 20, 40 mcg and placebo Respimat combined) had more pharyngitis (12.3%) than that of the patients with MDI device (7.4%, placebo MDI and Atrovent MDI 36 mcg combined). Thus, the long term use of Respimat may potentially be a predictive factor for pharyngitis in COPD patients. Since there is no Respimat device approved in the United States, a well designed long term safety study is necessary to address this potential safety issue and the long term patient acceptance to Combivent Respimat.

7.4.3 Causality Determination

No plausible causal relationship between the adverse events and the test drug product could be drawn from the available data. As noted above, additional data from long term studies are needed to determine if the long term use of Respimat could be related to high incidence of pharyngitis, and if so, what the mechanism might be.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimen for Combivent Respimat (20/100 mcg) Inhalation Spray is “One inhalation (20/100 mcg) four times a day. Patients may take additional inhalations as required; however, the total number of inhalations should not exceed six in 24 hours.” This regimen and choice of dose is supported by the data from the pivotal study.

8.2 Drug-Drug Interactions

There are no drug interaction studies conducted with Combivent Respimat and other medications commonly used in the treatment of COPD. COPD patients in clinical studies for Combivent Respimat were permitted for stabilized therapy with low dose of oral corticosteroids, orally inhaled corticosteroids, theophylline preparations, mucolytic agents, leukotriene receptor antagonists, and as needed albuterol inhalation. No interactions were observed between these drugs and Combivent Respimat. The Applicant stated that "Combivent Respimat has been used concomitantly with other drugs, including those commonly used in the treatment of COPD (e.g., sympathomimetic bronchodilators, methylxanthines, and steroids) without adverse drug reactions." [Volume 3.3, Section 2.7.4, page 127]

8.3 Special Populations

There were no studies in special populations for Combivent Respimat (20/100 mcg) Inhalation Spray to review. Because Combivent Respimat (20/100 mcg) Inhalation Spray and Combivent Inhalation Aerosol MDI contain the same active ingredients, language regarding pregnancy, labor and delivery, and nursing mothers is taken from the approved Combivent Inhalation Aerosol MDI labeling for the Combivent Respimat (20/100 mcg) Inhalation Spray labeling. No differences in efficacy were observed in geriatric patients. Although patients of 65 years of age and older had a slightly higher frequency of adverse events than patients of less than 65 years of age, no dose adjustment is proposed.

8.4 Pediatrics

COPD is a disease of older adult patients. The studies in children would be impossible or highly impractical. The Applicant requested waiver under PREA for the proposed drug product. This reviewer recommends the waiver be granted to Combivent Respimat (20/100 mcg) Inhalation Spray.

8.5 Advisory Committee Meeting

An Advisory Committee Meeting was not held for this NDA. The two active ingredients in this drug product (ipratropium bromide and albuterol sulfate) are well studied molecules, and the combination of the two active ingredients has been accepted in the United States and abroad.

8.6 Literature Review

There is no literature review included in this NDA submission. The Applicant has not published the data from clinical trials of the Combivent Respimat development program.

8.7 Postmarketing Risk Management Plan

The Applicant did not submit a post-marketing risk management plan.

8.8 Other Relevant Materials

No other relevant materials were used in this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

9.1.1 Efficacy conclusion

The efficacy of the proposed drug product Combivent Respimat (20/100 mcg) Inhalation Spray was evaluated in one pivotal study (1012.56) and supported by efficacy data from a supportive study (1012.46). From an efficacy perspective, the results of the pivotal study are sufficient to support approval of Combivent Respimat (20/100 mcg) Inhalation Spray for the indication of the treatment in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator, who continue to have evidence of bronchospasm, and who require a second bronchodilator.

The results of the pivotal clinical trial 1012.56 support the efficacy of Combivent Respimat (20/100 mcg) Inhalation Spray in patients with COPD. Pulmonary function in patients with COPD, as evaluated as FEV_1 AUC change from test day baseline, was shown to be positively impacted by treatment with Combivent Respimat (20/100 mcg) Inhalation Spray and by Combivent CFC MDI 36/206 mcg alike. The primary efficacy endpoints demonstrated that Combivent Respimat (20/100 mcg) Inhalation Spray is efficaciously non-inferior to Combivent CFC MDI 36/206 mcg, superior to ipratropium bromide 20 mcg during 0 to 4 hours post-dosing, and non-inferior to ipratropium bromide 20 mcg during 4 to 6 hours post-dosing. The superiority of Combivent Respimat 20/100 mcg Inhalation Spray to ipratropium bromide 20 mcg during 0 to 4 hours post-dosing demonstrated the efficacious contribution of albuterol component in the combination product. The study results are robust. Based on the agreement between the Applicant and the Division in pre-NDA meetings, the efficacy data from this 12-week trial are sufficient to form the basis of approval for Combivent Respimat 20/100 mcg inhalation spray for the proposed indication in patients with COPD.

In the development program of Combivent Respimat Inhalation Spray, the Applicant conducted a 12-week efficacy and safety study for a higher dose formulation of Combivent Respimat (40/200 mcg). In this randomized, double-blind, placebo and active controlled study, patients with COPD received one of the three active treatments (Combivent Respimat 40/200 mcg, ipratropium Respimat 40 mcg, and Combivent CFC MDI 36/206 mcg) or a placebo. The primary efficacy endpoint was the mean FEV_1 AUC_{0-6} on test day 85. The results of this study showed that the Combivent Respimat 40/200 mcg group had a significantly greater FEV_1 AUC_{0-6} value on all test days compared to the placebo group ($p<0.0001$). However, the study 1012.46 failed to demonstrate the contribution of the individual ingredients albuterol and ipratropium to the combination product. The study 1012.46 provided the supportive evidence that the Respimat was an effective device to deliver the Combivent, and that Combivent Respimat Inhalation Spray, in appropriate dosages, was efficacious in COPD treatment.

9.1.2 Safety conclusion

The safety data submitted in the Combivent Respimat (20/100 mcg) Inhalation Spray clinical program are not sufficient to support approval. Safety data were evaluated from the pivotal study, a 12-week study for Combivent Respimat 40/200 mcg, and a 6-month study for ipratropium Respimat. There are no studies for any Respimat inhaler to evaluate its long term safety and patient acceptability. As a replacement of Combivent MDI that has been broadly used by patients with COPD, Combivent Respimat (20/100 mcg) Inhalation Spray is expected to be used regularly in COPD patient population. Long term studies for one year is needed to evaluate the long term safety and patient acceptability of the proposed drug product. The Applicant has proposed a one year study to evaluate the safety and patient acceptability of the proposed drug product in patients with COPD.

In two 12-week Combivent Respimat studies, a total of 831 COPD patients were exposed to Combivent Respimat (485 for 20/100 mcg and 345 for 40/200 mcg, respectively). Additionally, a total of 900 COPD patients were exposed to ipratropium Respimat or placebo Respimat in these two 12-week studies. In the 6-month study for ipratropium Respimat, a total of 415 COPD patients were exposed to ipratropium Respimat or placebo Respimat. The safety evaluation included adverse events, vital signs, physical examination, clinical laboratory tests, and ECG.

There were 12 deaths in the three clinical studies (eight in the two 12-week studies and four in the 6-month study). The death cases were reviewed in Section 7.1.1. It appears that the deaths were not test drug related. All death cases were contributed to concomitant serious diseases, conditions, or accidents. The vital signs, physical examination, clinical laboratory tests, and ECG did not revealed safety signals in the three clinical studies.

The common adverse events were respiratory system disorders, accounting for the majority of adverse event cases in all three clinical studies. The single most common adverse event in two 12-week studies was COPD exacerbation. For the 6-month study, COPD exacerbation was the second most common adverse event (22.8%), next to cases of upper respiratory tract infection (28.3%). Other common adverse events were cough, dyspnea, bronchitis, sinusitis, and headache. These adverse events were not unexpected in COPD population, and were similar in incidence across the treatment groups including placebo group.

The patients in the 6-month study had a higher incidence of pharyngitis (10.5%) compared to that of the two 12-week studies (3.6% and 4.1%). Noticeably, the incidence of pharyngitis in the 6-month study was not evenly distributed in treatment groups. The patients in ipratropium Respimat 40 mcg group had a highest pharyngitis incidence (16.4%), and the patients with Respimat device (ipratropium Respimat 20, 40 mcg and placebo Respimat combined) had more pharyngitis (12.3%) than that of the patients with MDI device (7.4%, placebo MDI and Atrovent MDI 36 mcg combined). This could be a potential safety concern that long term use of Respimat may be related to high incidence of pharyngitis and, therefore, affect the acceptance of COPD population to the proposed drug.

There are no studies for any Respimat inhaler to evaluate its long term safety and patient acceptability. In a tele-conference on March 11, 2009, the Applicant was informed that long term (one year) safety and patient acceptability data are needed to support the proposed drug product. The Applicant subsequently submitted a

protocol to conduct a one year safety and patient acceptability study protocol for Combivent Respimat (20/100 mcg) Inhalation Spray on May 18, 2009.

9.2 Recommendation on Regulatory Action

The clinical recommendation for this application is a "complete response" action.

The efficacy of Combivent Respimat (20/100 mcg) Inhalation Spray is demonstrated by a 12-week pivotal clinical study and supported by another 12-week study in patients with chronic obstructive pulmonary disease (COPD). The safety data submitted in the Combivent Respimat (20/100 mcg) Inhalation Spray clinical program are not sufficient to support approval. To support this application, long term assessment is required to evaluate the safety and patient acceptability of the proposed drug product.

9.3 Recommendation on Postmarketing Actions

This section does not apply as the recommended regulatory action is complete response.

9.3.1 Risk Management Activity

This section does not apply as the recommended regulatory action is complete response.

9.3.2 Required Phase 4 Commitments

This section does not apply as the recommended regulatory action is complete response.

9.3.3 Other Phase 4 Requests

This section does not apply as the recommended regulatory action is complete response.

9.4 Labeling Review

A full labeling review was conducted. The proposed label is in the new Physicians Labeling Rule (PLR) format. Changes have been made throughout the label to comply with the PLR format. Since COMBIVENT is a combination of a short-acting beta agonist (albuterol) and an anti-cholinergic, the approved package inserts for combination products in PLR format (i.e. SYMBICORT and ADVAIR DISKUS) and short-acting beta$_2$-agonists in PLR format (i.e. VENTOLIN HFA) were compared, and formatting and language were adapted from these labels for consistency where appropriate. The headings in the Full Prescribing information Table of Contents have been revised to comply with the heading changes throughout the labeling. The Patient Instructions for Use is not being reviewed at this time.

The FDA-proposed revisions to the Applicant's draft labeling for COMBIVENT RESPIMAT are attached below. These revisions were sent to the Applicant on June 18, 2008. In the revised labeling, FDA insertions are underlined and deletions are strike-out. Comments to explain the FDA edits are provided throughout the package insert where appropriate, and areas where data are needed are indicated with "XXX." A revised label from the Applicant is expected by July, 15, 2009.

(b) (4)

30 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

9.5 Comments to Applicant

Deficiency comment regarding the need for a long term safety and patient acceptability study will be conveyed to the Applicant in the action letter.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study 1012.56

This is a 12-week efficacy and safety study for Combivent Respimat (20/100 mcg) versus Combivent CFC-MDI (36/206 mcg) and Ipratropium Respimat (20 mcg) in patients with chronic obstructive pulmonary disease (COPD).

Table 24 Summary of study 1012.56

Protocol #	1012.56
Title	A comparison of ipratropium bromide/salbutamol delivered by the Respimat inhaler to Combivent Inhalation Aerosol and ipratropium bromide delivered by the Respimat in a 12-week, double-blind, safety and efficacy study in adults with chronic obstructive pulmonary disease
Study dates	Study initiated: November 15, 2006 Study completed: April 4, 2008 Date of study report: August 8, 2008
Sites	There were 179 study sites around the world, among which 87 study sites were within the United States
IRB	A list of 96 Institutional Review Boards (IRB) is provided [Volume 5.24, Section 5.3.5.1, Content 16.1.3, pages 3-28]. There are 10 IRBs that covered multiple study sites. The final original study protocol was approved in writing by the IRBs before enrollment of any subject into the study. Subsequent protocol amendments were also approved by the IRBs.
Ethics	The study report states that the study was performed in compliance with the ethical principles that have their origin in the Declaration of Helsinki (1996 Version), in accordance with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), and in accordance with applicable regulatory requirements.
Source references	Unless otherwise indicated, all source references are to: Study report 1012.56 and related information [Volume 5.19 – 5.64, Section 5.3.5.1]

10.1.1.1 Protocol

10.1.1.1.1 Objectives

Primary Objectives:

(1) demonstrate non-inferiority (between 0-6 hours) of Combivent Respimat 20/100 mcg and Combivent CFC-MDI 36/206 mcg on Day 85,

(2) demonstrate the superiority (between 0-4 hours) of Combivent Respimat 20/100 mcg over ipratropium Respimat 20 mcg on Day 85, and
(3) demonstrate the non-inferiority (between 4-6 hours) of Combivent Respimat 20/100 mcg over ipratropium Respimat 20 mcg on Day 85.

Secondary objectives: None declared in the protocol. However, the steady state pharmacokinetic properties of the study medication were evaluated in a subgroup of patients over one dosing interval after 4 weeks of therapy.

10.1.1.1.2 Protocol Amendments

The original protocol was dated August 2, 2006. Four amendments were made after the study initiated on November 15, 2006.

The first amendment (December 19, 2006) was made to add a word "multinational" to the methodology section from original "three-treatment, 12-week, randomized, parallel design, double-blind, double-dummy, active-controlled" to "three-treatment, 12-week, multinational, randomized, parallel design, double-blind, double-dummy, active-controlled." The amendment also clarified specific stopping rules for patients.

The second amendment (December 14, 2006) was made for studies in France only. The amendment was made according to request by French Ethic Committee to mention specifically in the inclusion or exclusion section that the following patients can not be enrolled into the study: in situations of social brittleness (private people of freedom by a court order or administrative, people hospitalized without assent, and allowed people in medical or social establishment at other ends of research), and with major incompetents or out of state to express their assent.

The third amendment (May 7, 2007) was made for studies in Brazil only. The amendment clarified the clinical assessment to identify patients currently on Spiriva who may desire to and be appropriate for participation in the study. The original statement "Patients taking Spiriva should have their Spiriva discontinued after signing the informed consent" was changed to "Any patient currently on Spiriva, who desires to participate in 1012.56 trial, must be fully evaluated by the pulmonologist to assess whether or not a change from a long acting anticholinergic to a short acting anticholinergic would be clinically appropriate. After such evaluation, if the patient is to participate in the trial, he/she should have Spiriva discontinued after signing the informed consent."

The fourth amendment (August 22, 2007) was made for studies in Korea and Taiwan only. The amendment was to create a paper diary for patients in Korea and Taiwan who were not able to use the e-diary.

10.1.1.1.3 Summary of Study Design

This is a three-treatment, 12-week, randomized, parallel design, double-blind, double dummy, active controlled study.

The initial screening visit will be followed by a 2-week baseline run-in period. All patients will receive Atrovent inhalation aerosol (2 puffs, four times per day) and salbutamol MDI (used

PRN) during the 2-week baseline period. After the baseline period, patients will be randomized into the 12-week double-blind treatment period in which they will receive one of the three treatments.

10.1.1.1.4 Population

A sufficient number of patients (approximately 1,440) would be randomized to ensure that a minimum of 1,200 patients of either sex, 40 years of age or older, with a diagnosis of COPD would complete the 12-week study. Each study site is expected to enter approximately 10 patients with a minimum enrollment of two patients per month at each site in order to meet the required timeline.

Enrollment is expected to be completed within 9 months after study initiation and would end when the trial clinical monitor (TCM) has determined that at least 1,200 patients would complete the study. At least eighteen (all in the United States) of the 180 study sites would participate in the pharmacokinetic profiling. Sufficient numbers of patients would be randomized to ensure that a minimum of 120 patients complete the pharmacokinetic portion of-the trial. A log would be kept of all patients screened for study enrollment and document the reasons for exclusion for each subject not entered.

Patients who fail to complete all pulmonary function test-days and/or all of the testing as required in the protocol, would not be considered complete. These patients may not be re-enrolled at a later date and not be replaced. A record would be kept of all patients who fail to complete the study and the reasons would be reported and included in the study analysis.

Inclusion criteria:

- Patients must have a diagnosis of COPD and must meet the following spirometric criteria at Visit 1 (Screening) and Visit 2: Patients must have relatively stable, moderate to severe airway obstruction with pre-bronchodilator FEV_1 ≤65% of predicted normal values and FEV_1/FVC ≤70%.
    - Predicted normal values are calculated following European Coal and Steel Community (ECSC) equations:

  Males: FEV_1 predicted (L) = 4.30 x (height (inch)/39.37) - 0.029 x age (yr) - 2.49
  Females: FEV_1 predicted (L) = 3.95 x (height (inch)/39.37) - 0.025 x age (yr) - 2.60
  Or
  Males: FEV_1 predicted (L) = 4.30 x (height (meter)) - 0.029 x age (yr) - 2.49
  Females: FEV_1 predicted (L) = 3.95 x (height (meter)) - 0.025 x age (yr) - 2.60
- Male or female patients 40 years of age or older.
- Patients must have a smoking history of more than ten pack-years. A pack-year is defined as the equivalent of smoking one pack of 20 cigarettes per day for a year.
- Patients must be able to perform pulmonary function tests and maintain records during the study period as required in the protocol.
- Patients must be able to be trained in the proper use of an MDI and the Respimat inhaler.
- All patients must sign an Informed Consent Form prior to participation in the trial.

Exclusion criteria:

- Patients with significant diseases other than COPD would 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 relevant abnormal baseline hematology, blood chemistry or urinalysis. If the abnormality defines a disease listed as an exclusion criterion, the patient is excluded.
- All patients with an AST (SGOT) >80 lU/L, ALT (SGPT) >80 lU/L, bilirubin >2.0 mg/dL or creatinine >2.0 mg/dL would be excluded regardless of the clinical condition. Repeat laboratory evaluation would not be conducted in these subjects.
- Patients who have a total blood eosinophil count $\geq 600/mm^3$. A repeat eosinophil count will not be conducted in these patients.
- Patients with a recent history (i.e., one year or less) of myocardial infarction.
- Patients with a recent history (i.e., three years or less) of heart failure or patients with any cardiac arrhythmia requiring drug therapy.
- Patients with a history of cancer, other than treated basal cell carcinoma, within the last five years.
- Patients with a history of life-threatening pulmonary obstruction, or a history of cystic fibrosis or clinically evident bronchiectasis
- Patients who have undergone thoracotomy with pulmonary resection. Patients with a history of a thoracotomy for other reasons should be evaluated as per exclusion criteria.
- Patients with a history of asthma or allergic rhinitis.
- Patients with a history of and/or active alcohol or drug abuse.
- Patients with known active tuberculosis.
- Patients with an upper or lower respiratory tract infection or COPD exacerbation in the 6 weeks prior to the Screening Visit (Visit 1) or during the baseline period.
- Patients with known symptomatic prostatic hypertrophy or bladder neck obstruction.
- Patients with known narrow-angle glaucoma.
- Patients with current significant psychiatric disorders.
- Patients who regularly use daytime oxygen therapy for more than 1 hour per day and in the investigator's opinion would be unable to abstain from the use of oxygen therapy.
- Use of cromolyn sodium or nedocromil sodium less than 30 days prior to the baseline period or during the treatment period.
- Patients who are being treated with antihistamines for any excluded allergic conditions.
- Patients using oral corticosteroid medication at unstable doses (i.e., less than 6 weeks on a stable dose) or at a dose in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day.
- Initiation of inhaled steroid use, or new dosage, less than 6 weeks prior to the Screening Visit (Visit 1) or during the baseline period.
- Use of β-blocker medications, MAO inhibitors or tricyclic antidepressants less than 30 days prior to the baseline period or during the treatment period. Beta blocker eye medications for treatment of non-narrow angle glaucoma are allowed.
- Patients who have had changes in their therapeutic plan within the last 6 weeks prior to the Screening Visit (Visit 1) or during the baseline period.

- Pregnant or nursing women or women of childbearing potential not using a medically approved means of contraception (i.e., oral or injectable contraceptives, intrauterine devices or diaphragm with spermicide, or Norplant).
- Patients with known hypersensitivity to anticholinergic drugs, any other component of the ipratropium bromide/salbutamol Respimat solution or the ipratropium bromide/salbutamol MDI components.
- Previous participation in this study. (The patient cannot re-enroll into this study.)
- Patients who are currently participating in another study.
- Patients who have taken an investigational drug within 1 month or 6 half lives (whichever is greater) prior to the screening.

10.1.1.1.5 Study Treatment

There are three treatment groups in this study, as listed in Table 25. A double-dummy blind was used in the study. Placebo Combivent CFC-MDI was administered with treatments Combivent Respimat and ipratropium bromide (Atrovent) Respimat. Placebo Combivent Respimat was use with Combivent CFC-MDI. Each patient received the same number of inhalation puffs from test drug and placebo.

Table 25 Study treatments, Study 1012.56

Treatment A **Experimental product**	Combivent Respimat (20/100 mcg) Inhalation Spray one puff Batch Number: B06300048 with Respimat inhaler B063000461 plus placebo Combivent CFC-MDI 2 puffs ; 4 times daily
Treatment B **Reference Product**	Ipratropium bromide (Atrovent) Respimat 20 mcg one puff Batch Number: B063000477 with Respimat inhaler B063000461 plus placebo Combivent CFC-MDI 2 puffs ; 4 times daily
Treatment C **Reference Product**	Combivent CFC-MDI (18/103 mcg) two puffs (delivered dose 36/206 mcg), Batch number: B063000475 plus placebo Combivent Respimat 1 puff; 4 times daily

The Applicant states that the administered dose for the Combivent Respimat (ipratropium 20 mcg/salbutamol 100 mcg) was selected based on plasma and urine pharmacokinetic data from Respimat studies 244.2447 and 243.7 (see reviews in the Appendices below). The results of these 2 studies suggested that the lung exposure achieved with these doses would most closely match that of the currently marketed Combivent CFC-MDI (ipratropium 36 mcg/salbutamol 206 mcg).

10.1.1.1.6 Conduct

Refer to the following flow chart (Table 26) for an overview of procedures to be performed at each visit.

Table 26 Study 1012.56 flow chart (Volume 5.19, Section 5.3.5.1, Study protocol 1012.56, page 69)

Trial period	**Screening & baseline**			**Randomized period**		
Visit	0	1	2	3	4	5*
Test day	-30	-14	1	2	3	4
Weeks on therapy	-4	-2	0	4	8	12

Day	-30	-14	1(±5)	29(±5)	57(±5)	85(±5)
Informed consent[1]	X					
Demographics		X				
Medical history		X				
MDI training		X	X			
Respimat inhaler training			X			
Physical examination (with vital signs)		X				X[2]
12-lead ECG		X				X[2]
Laboratory tests (8 hour fasting blood and urine)		X				
Serum pregnancy test[5]		X				
Medication washout/compliance assessment		X	X	X	X	X
Screening PFT (FEV_1 & FVC), seated		X[3]	X[3]			
Reversibility test (albuterol MDI)		X				
Inclusion/exclusion criteria		X				
Dispense e-diary/peak flow meter[6] **training**		X				
Dispense daily patient record		X	X	X	X	
Dispense albuterol MDI		X	X[4]	X[4]	X[4]	
Dispense Atrovent MDI		X				
Review e-diary/peak flow meter/patient record			X	X	X	X
Randomization			X			
Dispense investigational drugs			X	X	X	
6-hour PFT[7]			X	X	X	X
Vital signs (seated)[8]			X	X	X	X
PK-plasma sample & urine collection[9]				X		
Smoking status		X				X[2]
COPD background characteristics		X				
Physician's global evaluation			X	X	X	X
Adverse events		X	X	X	X	X[2]
Concomitant therapy		X	X	X	X	X[2]
Patient device questionnare[10]						X[2]
Conclusion of patient participation						X[2]

* Visit 5 was also the end of the study visit

1 Informed consent must be signed prior to participation in the trial, which includes medication washout and restrictions

2 To be completed by all patients including those who discontinue early

3 FEV_1 must be ≤65% of predicted normal and FEV_1/FVC ≤70%

4 To be dispensed as needed throughout the trial

5 Serum pregnancy test on females of child-bearing potential

6 eDiary/peak flow meter incorporates the electronic patient diary and peak flow meter into one portable electronic instrument. The patient diary and peak expiratory flow rate data collected through the instrument during a clinical trial can be downloaded into a computer.

7 PFT done at -15 (pre-treatment), 15, 30, 60 minutes, and 2, 3, 4, 5, and 6 hours post drug administration

8 Seated vitals to be done during first 3 hours at same time-intervals as PFT

9 PK-Plasma and Urine Samples will be collected only at a subset of designated sites participating in pharmacokinetic testing. (Blood drawn at pre-treatment, 5, 15, and 30 minutes, and 1, 2, 4, and 6 hours post drug administration. Three urine samples (pre-treatment, 0-2, and 2-6 hours post drug administration

10 The patient device questionnaire will only be administered at the participating sites in the US

The initial screening visit would be followed by a 2-week baseline run-in period. All patients would receive Atrovent MDI (2 puffs, four times per day) and salbutamol MDI (used PRN) during the 2-week baseline period. In any country where an HFA formulation is not available, Atrovent CFC-MDI or salbutamol CFC-MDI may be used instead. After the baseline period, patients would be randomized to receive one of three treatments. The patient should take the study medication four times daily at appropriately spaced intervals: upon arising, mid-day, early evening, and prior to retiring.

Each dose of study medication consists of one inhalation from the Respimat device plus two inhalations from the MDI. When a patient is randomized to receive a treatment, the appropriate medication kit would be selected which includes two Respimat inhalers, two cartridges, and two MDIs every 4 weeks (28 days). One inhaler would be considered the primary inhaler to use and the other one the spare inhaler. The spare Respimat inhaler and cartridge should be used only if necessary, (e.g. the first one malfunctions, is lost or the patient must schedule the next visit at greater than 30 days). Two new MDI canisters would also be dispensed (one primary and one a spare). The spare canister would be used after the first 21 days (3 weeks) until the next scheduled test day. Any malfunctioning Respimat inhaler would be returned directly to Boehringer Ingelheim. In addition, at selective USA sites, approximately 10% of devices would be collected at completion of the study for internal characterization.

The patient is to return for visits with all inhalers (Respimat devices, cartridges, and MDIs) that were dispensed at the previous visit. If this visit is scheduled within 30 days of the previous visit, the Respimat and MDI inhalers being actively used by the patient would be used to administer test-drug before the pulmonary function testing at this visit. All malfunctioning inhalers were to be returned to Boehringer Ingelheim for evaluation and testing.

All clinical supplies should be stored in a locked, secure cabinet. Combivent inhalation aerosol, CFC-MDI must be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Avoid excessive humidity. The Respimat inhalers should be stored between 15°C and 25°C. Avoid freezing.

The patient enter in the e-Diary/Peak Flow Meter the number of puffs of investigational drug taken and number of puffs of salbutamol inhalation aerosol taken. The investigator/study staff would download and review these records with the patient at each study visit to assess treatment compliance.

The patient device questionnaire would be administered at the end of the study in the subjects of the United States. The questionnaire consists of 10 questions designed to evaluate the subjects' satisfaction and confidence in the inhalers used in the trial. The subjects are to respond to the questions on a scale of 1 to 7, defined as 1=very dissatisfied, 2=dissatisfied, 3=somewhat dissatisfied, 4=satisfied/dissatisfied, 5=somewhat satisfied, 6=satisfied, and 7=very satisfied. The 10 questions are as following:

Q1. How satisfied are you with the overall feeling of inhaling medicine?
Q2. How satisfied are you with the feeling that the inhaled dose goes to the lung?

Q3. How satisfied are you that you can tell the amount of medicine left?
Q4. How satisfied are you with the inhaler works reliably?
Q5. How satisfied are you with the ease of inhaling a dose from the inhaler?
Q6. How satisfied are you with the instructions for use?
Q7. How satisfied are you that the inhaler is durable?
Q8. How satisfied are you with using the inhaler?
Q9. How satisfied are you with the speed of medicine coming out of the inhaler?
Q10. Overall, how satisfied are you with the inhaler?
[Volume 5.51, Section 5.3.5.1, pp 2218 – 2286]

The patients at the 37 study sites in the United States participated in the end-of-use Respimat inhaler testing. One hundred normally functioning Combivent Respimat inhalers were collected from patients when the dose indicator reached the 30 dose remaining mark from 120 doses available for each inhaler. The patients who returned the Respimat inhaler for the end-of-use testing received a new Respimat inhaler, and the study continued following the protocol. The inhaler testing included the shape of spray plume, dose accuracy, and particle size distribution.

10.1.1.1.7 Allowed and Disallowed Medications

Administration of rescue medications can occur during the study period. If a rescue medication at any point during the 6-hour pulmonary function testing as deemed necessary by the investigator, the patient would not complete the remainder of the pulmonary function test-day and the obtained (incomplete) PFT data would be recorded. The patient will return for the next scheduled visit. Information regarding the rescue medication administration, such as time of rescue medication, total dose of salbutamol inhalation aerosol used and the name and dosage of any additional rescue medication would be recorded on the rescue medication page in the CRF.

The following medications are allowed to control acute exacerbations as medically necessary during the treatment period:

- PRN albuterol inhalation aerosol (MDI) (provided by Boehringer Ingelheim and to be recorded on the Patient Daily Record)
- Temporary increases in the dose of theophylline preparations of up to 7 days each are allowed during the 12-week study. If the increases or additions occur prior to pulmonary function testing days, the testing would be postponed for at least 2, but not more than 7 days after the last increased or additional dose is given.
- Temporary increases in the dose or addition of, oral steroids of up to 7 days each are allowed during the 12-week study. Pulmonary function testing should not occur within 7 days of the last administered dose of an increase or addition. Pulmonary function testing may be postponed up to 14 days to meet this restriction.
- The use of antibiotics is not restricted and may be used as medically necessary for exacerbations and other infections.

The following medications are allowed if stabilized for at least 6 weeks prior to and throughout the 12 week study period:

- Oral corticosteroids would be allowed only if the patient is stabilized on minimal doses of steroids (i.e., 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.
- Anti-leukotrienes or leukotriene receptor antagonists only if prescribed for conditions other than asthma or excluded allergic conditions.

The following medications are not allowed for at least 48 hours prior to the beginning of the baseline period and not allowed throughout the study period:

- Oral β-adrenergics or long-acting β-adrenergics such as salmeterol (Serevent) and formoterol (Oxis, Foradil)

The following medications are not allowed for at least 1 month prior to the beginning of the baseline period and throughout the study period:

- All other investigational drugs.
- Long-acting anticholinergic drugs (e.g. Spiriva)
- All β-blockers, MAO inhibitors, tricyclic antidepressants
- Cromolyn sodium/nedocromil sodium

The following medications are allowed prior to the study, but not allowed during the baseline period or the treatment period:

- Short-acting anticholinergic drugs including, Atrovent Inhalation Aerosol and Atrovent Inhalation Solution by oral inhalation and for use in treating a common cold, Atrovent Nasal Spray 0.06%
- Additional Combivent Inhalation Aerosol or combination ipratropium bromide/salbutamol sulfate solution for nebulization

10.1.1.1.8 Discontinuations

Randomized patients who fail to complete all test-days and all of the tests in the protocol would not be considered complete, may not be enrolled at a later date and will not be replaced. A record is kept for all patients who fail to complete all test-days and their reasons for discontinuation. A final physical examination would be conducted on all discontinued patients. All safety information collected from discontinued patients would be included in the safety analysis of the study.

The Applicant states that the trial would be discontinued at any study site for the following reasons:

- Failure to meet expected enrolment goals,
- Emergence of any efficacy/safety information that could significantly affect continuation of the trial or any other administrative reasons,
- Violation of GCP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

10.1.1.1.9 Safety Evaluation

Safety evaluation included (1) all adverse events during the treatment period, (2) pulse rate (PR) and blood pressure (BP) in conjunction with spirometry, (3) physical examination, and (4) electrocardiogram (ECG) at the screening and end of the treatment.

All adverse events would be recorded on the adverse event CRF page after review of the Patient Daily Record, the e-Diary/Peak Flow Meter and discussions with the patient. Information concerning the onset, duration, intensity, severity, medication taken, action taken with study medication and causality of the adverse event would be collected on the CRF page. Where relevant (e.g., paradoxical bronchospasm) the temporal relationship (minutes) between the onset of an adverse event and the time of drug administration would be recorded in the comment section of the adverse event CRF page.

Information on COPD exacerbations would also be reported on the adverse event CRF page. COPD exacerbation is defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea, and chest tightness) having a duration of three or more days requiring treatment with an antibiotic and/or systemic steroids with or without hospital admission. This information along with the duration and medication used is recorded on the CRF. Such events are usually acute worsening of the underlying disease and do not include expected fluctuations in symptoms present in stable patients at the time of enrolment.

Serious adverse events are also recorded on the Serious Adverse Event form and must be reported by fax to the Local Clinical Monitor as soon as site personnel are aware of the event. A narrative summary of the adverse event would be forwarded to the Clinical Monitor within 5 working days of notification. The temporal relationship of all serious adverse events would be recorded on the CRF and in the adverse event narrative. Every attempt should be made to collect discharge summaries for each hospitalization to provide further details. Additionally, serious adverse events and all events leading to death, regardless of their relationship to drug, that occur within 14 days after the subject leaves the trial must be reported as a serious adverse event.

Pulse rate and blood pressure are measured and recorded during the first 3 hours at the same time intervals as pulmonary function testing. Measurements would always be obtained before pulmonary function testing with the patient seated and rested for a minimum of 5 minutes.

Clinical laboratory testing would be conducted on all patients at the Screening Visit (Visit 1). Laboratory specimens (blood and urine) would be collected in the morning with the patient having fasted for at least 8 hours. The patient may have a light snack after blood collection on the pulmonary function test-days. Hematology testing would include hemoglobin, hematocrit, erythrocytes, platelets, total leukocyte count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and absolute eosinophil count. Serum chemistry testing includes albumin, alkaline phosphatase, calcium, CO_2, chloride, creatinine, glucose, inorganic phosphorus, LDH, potassium, AST (SGOT), ALT (SGPT), sodium, total bilirubin, total protein, uric acid and urea nitrogen. The urinalysis includes specific gravity, pH, glucose, protein, and hemoglobin. A serum pregnancy test will be conducted at the screening visit in all women of child-bearing potential. A central laboratory would perform all clinical laboratory tests.

Comments should be given for each value considered clinically relevant (for instance, outside the reference range or if any value that differs importantly from previous ones). If the baseline laboratory evaluation is repeated, only the most recent results are used for evaluation of patient participation.

A standard l2-lead electrocardiogram (ECG) and one minute rhythm strip would be performed on all patients at Visit 1 (Screening) and Visit 5 (the end of the study) or early discontinuation. All electrocardiograms should be performed prior to pulmonary function. The interpretation of the ECG would be performed by the investigator or a qualified designee. The purpose of the baseline ECG is to obtain information about the patient's baseline condition that may have not been elicited in obtaining the medical history; therefore, any significant findings from this examination are recorded on the Medical History/Concomitant Diagnoses page. The purpose of the Visit 5 ECG is to find any new condition or worsening on baseline condition that should be reported as an adverse event.

10.1.1.1.10 Pharmacokinetic Measurements

Approximately 18 of the sites would be designated to participate in the pharmacokinetic profiling. Approximately 150 patients would participate in the PK profiling in order to obtain 120 completed patients. Blood samples would be collected on Visit 3, 10 mL each with heparin, at the following eight time-points: trough (pre-treatment), 5, 15, 30, and 60 minutes and 2, 4, and 6 hours (second trough) after inhalation of test drug. When applicable, this would be done immediately after each corresponding pulmonary function test. Three urine samples would be collected on Visit 3 at pre-dosing, 0 to 2 hours and 2 to 6 hours post-dosing.

10.1.1.1.11 Efficacy

Primary Efficacy Endpoints:
There were three co-primary efficacy endpoints:

(1) Mean FEV_1 over 0 to 6 hours post-dose, defined as the AUC of the change from test day baseline in FEV_1 over 0 to 6 hours post-dose divided by 6 hours (FEV_1 AUC_{0-6}). The primary comparison was to determine the non-inferiority of Combivent Respimat 20/100 mcg compared to Combivent Inhalation Aerosol 36/206 mcg over the period of 0 to 6 hours post-treatment on test day 85. The non-inferiority criterion has been set as the difference of the two treatments in mean FEV_1 AUC_{0-6} change is not statistically significant and the 95% confidence interval (CI) of the difference is less than 50 mL.

(2) Mean FEV1 over 0 to 4 hours post-dose, defined as the AUC of the change from test day baseline in FEV_1 over 0 to 4 hours post-dose divided by 4 hours (FEV_1 AUC_{0-4}). The primary comparison was to determine the superiority of Combivent Respimat 20/100 mcg compared to ipratropium Respimat 20 mcg over the period of 0 to 4 hours post-treatment on test day 85. The superiority criterion has been set as the difference of the two treatments in mean FEV_1 AUC_{0-4} change is statistically significant and the 95% confidence interval of the difference is more than 50 mL.

(3) Mean FEV_1 over 4 to 6 hours post-dose, defined as the AUC of the change from test day baseline in FEV_1 over 4 to 6 hours post-dose divided by 2 hours (FEV_1 AUC_{4-6}). The primary comparison was to determine the non-inferiority of Combivent Respimat 20/100 mcg compared to ipratropium Respimat 20 mcg over the period of 4 to 6 hours post-treatment on test day 85. The non-inferiority criterion has been set as the difference of the two treatments in mean FEV_1 AUC_{4-6} change is not statistically significant and the 95% confidence interval of the difference is less than 50 mL.

The primary criterion for evaluation is measurement of the FEV_1 obtained during pulmonary function testing. Pulmonary function test-days would be scheduled at screening (Visit 1), at the end of the 2-week baseline period (Visit 2), and every 4 weeks thereafter (Visits 3, 4 and 5). Pulmonary function tests (PFTs) would be performed using standardized spirometry equipment provided by the sponsor and calibrated by study staff on all test days. Equipment and techniques should conform to American Thoracic Society (ATS) criteria. PFTs should be performed with the patient in a seated position having abstained from medications as specified. The best of three efforts would be defined as the highest FEV_1 and the highest FVC each obtained on any of three efforts meeting the ATS criteria (with a maximum of five attempts). The highest FEV_1 and FVC would be selected regardless of whether they come from different spirometric maneuvers or the same maneuver. For each patient, pulmonary function testing would always start at approximately the same time of the day.

At Visit 1, all patients would be required to perform a reversibility test using salbutamol MDI. Pulmonary function tests would be conducted in triplicate at baseline and repeated at 30 minutes following four inhalations of salbutamol inhalation aerosol (MDI). The salbutamol MDI used for the reversibility test would be given to the patient for rescue during the 2-week run-in period.

During the pulmonary function test-days on Visits 2-5, FEV_1 and FVC would be obtained at baseline (i.e., pre-treatment, performed 15 ± 10 minutes prior to test drug administration) and be repeated at 15, 30, and 60 minutes and 2, 3, 4, 5, and 6 hours after the drug administration. Measurements from 15 minutes to 2 hours would be performed within ±5 minutes of the specified time points. Measurements made from 3-6 hours would be performed within ± 10 minutes of the scheduled time point.

<u>Secondary Efficacy Endpoints:</u>
Secondary efficacy endpoints of the study included:

(1) FEV_1 AUC on Days 1, 29, and 57 (AUC_{0-6}, AUC_{0-4}, and AUC_{4-6}),
(2) Peak FEV_1 in the 2-hour interval after treatment on Days 1, 29, 57 and 85,
(3) Peak FEV_1 response (change from test-day baseline) on Days 1, 29, 57 and 85,
(4) Onset of therapeutic FEV_1 response on Days 1, 29, 57 and 85,
(5) Duration of therapeutic FEV_1 response on Days 1, 29, 57 and 85,
(6) Time to peak FEV_1 response on Days 1, 29, 57 and 85,
(7) FVC AUC_{0-6} and peak on Days 1, 29, 57 and 85,
(8) Trough peak expiratory flow rate (PEFR) measured by the patient at home once a day (weekly mean) during the treatment period,
(9) Individual $FEV_1$1 and FVC measurements at each measurement time,

(10) Amount of β agonist therapy used (i.e., weekly mean number of salbutamol doses during day and, separately, at night) as rescue medication during the treatment period,
(11) Concomitant medication usage during the treatment period,
(12) Daily symptom scores (weekly mean) over the treatment period, and
(13) Physician's global evaluation on Days 1, 29, 57 and 85.

10.1.1.1.12 Statistical Plan

Three Null Hypotheses:

(1) ipratropium bromide/salbutamol 20 mcg/100 mcg delivered by the Respimat inhaler and Combivent MDI 36 mcg/200 mcg (FEV_1 AUC_{0-6})

Ho: The difference in mean response as determined by FEV_1 AUC_{0-6} between patients treated with Combivent Respimat and patients treated with Combivent MDI after 12 weeks of treatment is at least 50 mL in favor of Combivent MDI.

To demonstrate the non-inferiority (between 0-6 hours) of Combivent Respimat and Combivent MDI over the 6 hour observation period the null hypothesis will be tested using a 1-sided test with $\alpha = 0.025$.

(2) ipratropium bromide/salbutamol 20 mcg/l00 mcg delivered by the Respimat inhaler versus ipratropium bromide 20 mcg delivered by the Respimat inhaler (FEV_1 AUC_{0-4})

Ho: There is no difference in mean response as determined by FEV_1 AUC_{0-4} between patients treated with Combivent Respimat and patients treated with Atrovent Respimat after 12 weeks of treatment.

To demonstrate the superiority (between 0-4 hours) of Combivent Respimat over Atrovent Respimat the null hypothesis will be tested using a 2-sided test with $\alpha = 0.05$.

(3) ipratropium bromide/salbutamol 20 mcg/l00 mcg delivered by the Respimat inhaler and ipratropium bromide 20 mcg delivered by the Respimat inhaler (FEV_1 AUC_{4-6})

Ho: The difference in mean response as determined by FEV_1 AUC_{4-6} between patients treated with Combivent Respimat and patients treated with Atrovent Respimat after 12 weeks of treatment is at least 50 mL in favor of Atrovent Respimat.

To demonstrate the non-inferiority between 4-6 hours of Combivent Respimat over Atrovent Respimat the null hypothesis will be tested using a 1-sided test with $\alpha = 0.025$.

Determination of Sample Size:
Based on the previous study (1012.46), the standard deviation (SD) for Day-85 FEV_1 AUC_{0-6} corrected for Test Day 1 baseline is around 162 mL. It is expected that the SD for FEV_1 AUC_{0-4} and FEV_1 AUC_{4-6} would be slightly greater, e.g. 180 mL. If there is no difference between Combivent Respimat and Combivent MDI in AUC_{0-6}, the AUC_{0-4} for Combivent Respimat is expected to be 50 mL above that for ipratropium Respimat, and no difference is expected

between Combivent Respimat and ipratropium Respimat in AUC_{4-6}. Using an SD of 180 mL for each of the 3 endpoints, the sample size of 400 patients per treatment group provides 97% chance of rejecting each of the 3 null hypotheses and the power for rejecting all three null hypotheses will be at least 0.97x0.97x0.97 =91%.

Analysis Set:
The primary analysis would be the comparison of FEV_1 AUC across treatment groups using ANCOVA with fixed effects for treatment and investigator site. Day-l baseline would be used as the covariate. Treatment-by-investigator site interaction would be evaluated by adding this term to the model but would be excluded from the model in the final analysis. The primary comparison would be for Day 85. The analysis would be repeated for the observation periods 0 to 6 hours (FEV_1 AUC_{0-6}), 0 to 4 hours (FEV_1 AUC_{0-4}), and 4 to 6 hours (FEV_1 AUC_{4-6}), respectively. The analysis would be performed on the full analysis set (FAS) consisting of all randomized patients with baseline data and post-treatment data for the first 3 hours on any test day (Days 1, 29, 57, or 85). Endpoint analysis (last observation carried forward) would be used to account for early withdrawals. The impact of carrying the last observation forward would be assessed by also analyzing the available data set without imputation. The timing and reasons for all patient withdrawals would be listed by treatment group in the final report.

All the secondary endpoints with the exception of onset, duration and time to peak response, and those related to COPD exacerbations would be analyzed in the same way as in the primary analysis. Data available prior to first dose would be used as baseline. Onset, duration of therapeutic response and time to peak FEV_1 response would be summarized by simple medians over the treatment groups. The number (%) of patients with at least one COPD exacerbation during the treatment period would be provided by treatment group. The number of exacerbations and length (duration of exacerbation) would be summarized for each treatment by ratio estimators (total number of events or event days divided by total extent of exposure over the treatment group).

10.1.1.2 Results

10.1.1.2.1 Description of the study population

Summary of Patients and Analysis Set
A total of 1,480 patients were randomized and are included in the randomized set (RS).
Eight analysis sets are created, and the definitions are summarized in Table 27.

- The treated set (TS) includes all randomized patients' who were documented to have taken at least one actuation of the randomized treatment. Twenty randomized patients from a French study centre, who took the randomized treatment, are excluded from TS because accuracy of recorded data could not be verified against source documentation. The TS consisted of 1,460 randomized patients distributed across the following geographic regions: USA (N=867), Europe (UK, France, Greece, South Africa, Turkey, and New Zealand) (N=259), Latin America (Argentina) (N=139), CEE (Poland, Russia, and Ukraine) (N=115) and Asia (Korea and Taiwan) (N=80).

- The full analysis data set (FAS) includes all treated patients of the TS who were documented to have taken at least one actuation of the BI investigational drug, irrespective of whether they also took the placebo used for blinding. For this study, TS and FAS have the same number of patients.
- The PFT full analysis data set (FAS _ PFT) includes patients in FAS who had valid baseline PFT data and had at least four out of the five time points PFT data during the first three hours after the administration of study medication on at least one of the four test days (Days 1, 29, 57, and 85). With this definition, the total number of patients included in FAS_PFT is 1,424, 97.5% of TS and 96.2% of RS. The FAS_PFT is used for analyzing FEV_1 AUC_{0-6} (change from test-day baseline), FEV_1 AUC_{0-4} (change from test-day baseline), FVC AUC_{0-6} (change from test-day baseline), and FVC AUC_{0-4} (change from test-day baseline).
- The PFT AUC_{4-6} full analysis data set (FAS _PFT46) includes patients in FAS _PFT who had all three PFT data at 4, 5, and 6 hours after drug administration on at least one of the test Days 29, 57, and 85. With this definition, 101 patients were excluded from the FAS_PFT46 due to incomplete data between 4 and 6 hours after drug administration, because spirometry was discontinued due to rescue medication use, shortness of breath, or other COPD symptoms. The total number of patients included in FAS_PFT46 is 1,323, 92.9% of FAS_PFT and 90.6% of TS. The FAS_PFT46 is used for analyzing FEV_1 AUC_{4-6} (change from test-day baseline) and FVC AUC_{4-6} (change from test-day baseline).
- The diary full analysis data set (FAS_DRY) consists of patients in FAS who were included in at least one diary data endpoint analysis (PEFR, rescue medication use, or symptom scores). Therefore the number of patients included in the efficacy analyses for different diary data endpoints may be different. For a patient to be included in FAS_DRY, four observations during the 14-day run-in period and four observations during the randomized period would be needed. By this definition, the total number of patients included in FAS_DRY is 1,399, 95.8% of FAS and TS.
- The pharmacokinetic set (PK) includes patients in FAS whose blood and/or urine samples were collected at Visit 3 according to protocol. By this definition, only 162 patients are included in PK, 11.1 % of TS.
- The per-protocol set (PPS) includes patients without important protocol violations. The important protocol violations for exclusion included: pre-bronchodilator FEV_1 >65% of predicted normal at Visit 2 pre-dose, pre-bronchodilator FEV_1 >70% of FVC at Visit 2 pre-dose, total blood eosinophil count ≥600/mm, improper medication wash-out on test days during the randomized treatment period, and invalid/unacceptable or missing FEV_1 measurement at time point -15 minutes at Visit 2 and at -5 minutes at Visit 1 (screening visit). There are 1,400 patients included in PPS, 98.3% of FAS_PFT.
- The completed set (CS) consists of patients in FAS _PFT46 who took the randomized treatment according to protocol, completed all four test days and had PFT data at 6 hours after treatment administration on the last test day (Day 85 or discontinued early on Day 85 due to rescue medication use, shortness of breath, or other COPD symptoms). By this definition, the total number of patients included in CS is 1,209, 91.4% of FAS_PFT46 and 82.8% of TS.

Table 27 Number of patients included in each analysis set for all randomized patients

Analysis set	Total N (% of RS)	Combivent Respimat 20/100 N (% of RS)	Combivent MDI 36/206 N (% of RS)	Ipratropium Respimat 20 N (% of RS)
Randomized set (RS)	1480 (100)	493 (100)	498 (100)	489 (100)
Treated set (TS)	1460 (98.7)	486 (98.6)	491 (98.6)	483 (98.8)
Full analysis set (FAS)	1460 (98.7)	486 (98.6)	491 (98.6)	483 (98.8)
PFT analysis set (FAS_PFT)	1424 (96.2)	474 (96.2)	482 (96.8)	468 (95.7)
PFT AUC_{4-6} analysis set (FAS PFT46)	1323 (89.4)	447 (90.7)	449 (90.2)	427 (87.3)
Completed set (CS)	1209 (81.4)	412 (83.6	410 (82.3)	387 (79.1)
Per protocol set (PPS)	1400 (94.6)	463 (93.9)	475 (95.4)	462 (94.5)
Diary analysis set (FAS DRY)	1399 (94.5)	474 (96.2)	470 (94.4)	455 (93.1)
Pharmacokinetic set (PK)	162 (10.9)	52 (10.6)	56 (11.2)	54 (11.0)

Source: Volume 5.19, Section 5.3.5.1, p 92-94.

Demographics and Baseline Characteristics

Patients' baseline demographic information is summarized in Table 28. Overall, 65% and 34.6% of the treated patients are males and females, respectively. In terms of race or ethnic groups, 89% of the patients are white. The African American and Asian are 5.3% and 5.6% of the study patients, respectively. The average age among TS patient population is 64 years, with the range from 40 to 89 years old. Over 50% of the patients are in the range from 40 to 64 years old. The average smoking history is 53 pack-years, and the mean COPD duration is 8.4 years. The three treatment groups are comparable with respect to the baseline demographic characteristics.

Table 28 Summary of demographics for patients in treated set

Demographics		Total N (%)	Combivent Respimat 20/100 N (%)	Combivent MDI 36/206 N (%)	Ipratropium Respimat 20 N (%)
Total treated (TS)		1460	486	491	483
Sex	Male	955 (65.4)	316 (65.0)	322 (65.6)	317 (65.6)
	Female	505 (34.6)	170 (35.9)	169 (34.4)	166 (34.4)
Race	White	1300 (89.0)	430 (88.5)	442 (90.0)	428 (88.6)
	Black	78 (5.3)	27 (5.6)	25 (5.1)	26 (5.4)
	Asian	82 (5.6)	29 (6.0)	24 (4.9)	29 (6.0)
Age	Mean (years)	64.1	63.8	64.2	64.3
	Median (years	64	64	64	64
	Min	40	40	40	40
	Max	88	86	88	87
	<40 years	0	0	0	0
	40 - 64 years	765 (52.4)	253 (52.1)	254 (51.7)	258 (53.4)
	65 – 74 years	513 (35.1)	182 (37.4)	168 (34.2)	163 (33.7)
	≥74 years	182 (12.5)	51 (10.5)	69 (14.1)	62 (12.8)
Height Mean (cm)		169.3	169.8	169.4	168.8
Weight Mean (kg)		77.8	78.2	77.9	77.3
Alcohol history					
Non-drinker		678 (46.4)	223 (45.9)	232 (47.3)	223 (46.2)
Average consumption[1]		781 (53.5)	263 (54.1)	258 (52.5)	260 (53.8)
Excessive consumption[2]		1 (0.1)	0	1 (0.2)	0
Smoking history					
Ex-smoker		860 (58.9)	275 (56.6)	303 (61.7)	282 (58.4)
Current smoker		600 (41.1)	211 (43.4)	188 (38.3)	201 (41.6)

Smoking history(pack-years)					
Mean		53.2	51.7	52.4	55.4
SD		27.5	27.7	27.1	27.6
Median		47.0	45.0	47.0	49.0
COPD duration (yrs)	**Mean**	8.4	8.2	8.6	8.5
	SD	6.3	6.1	6.5	6.4
	Median	7.0	7.0	7.0	7.0
	Min	0.1	0.1	0.1	0.1
	Max	50	40	50	43

1 Average consumption = drinks alcohol but not interfere with participation in the trial
2 Excessive consumption = drinks alcohol and could interfere with participation in the trial
(Source: Volume 5.19, Section 5.3.5.1, p94-96, 260-261; Volume 5.37, section 5.3.5.1, p3-100)

The study population is relatively balanced across treatment groups at baseline in the PFT evaluation. Patients' baseline (pre-bronchodilator screening) FEV_1 values are summarized in Table 29. The overall mean baseline FEV_1 for the treatment set is 1.144 liters. The ipratropium Respimat 20 mcg group has a slightly lower mean baseline FEV_1 value than that of other two treatment groups (1.117 vs. 1.154 and 1.162, respectively). But the percent of predicted FEV_1 values are comparable among the three treatment groups.

All treatment groups are comparable in baseline FVC value. The overall mean baseline FVC is 2.59 liters, and FEV_1/FVC is approximately 44.8%. The FEV_1 recorded 30 minutes after inhaling 400 mcg of albuterol are also summarized in Table 5. The mean reversibility in liters is similar for the three treatment groups with FEV_1 changes of 0.217, 0.216, and 0.217 liters for Combivent Respimat, Combivent CFC-MDI, and ipratropium Respimat, respectively.

Table 29 Baseline (pre-bronchodilator screening) spirometry data for patients in treated set

Spirometry		**Total**	**Combivent Respimat 20/100**	**Combivent MDI 36/206**	**Ipratropium Respimat 20**
Total treated (TS)		1460	486	491	483
FEV_1 (liters)	**N**	1413	474	474	465
	Mean	1.144	1.154	1.162	1.117
	SD	0.42	0.418	0.426	0.416
	Median	1.074	1.085	1.072	1.053
% predicted FEV_1[1]	**N**	1413	474	474	465
	Mean	41.4	41.5	41.9	40.9
	SD	12.5	12.3	12.5	12.7
	Median	40.8	40.9	41.2	40.2
FVC (liters)	**N**	1413	474	474	465
	Mean	2.592	2.617	2.600	2.559
	SD	0.812	0.823	0.802	0.811
	Median	2.502	2.505	2.569	2.442
FEV_1/FVC (%)	**N**	1413	474	474	465
	Mean	44.8	44.7	45.3	44.3
	SD	10.8	10.6	11.1	10.6
	Median	43.8	43.7	44.2	43.6
FEV_1 change[2] (liters)	**N**				
	Mean	1383	461	466	456
	SD	0.216	0.217	0.216	0.217
	Median	0.175	0.170	0.190	0.162
	Min	0.196	0.205	0.189	0.196

	Max	-0.374 1.256	-0.374 1.141	-0.219 1.256	-0.168 0.842
FEV_1 change[2] (%)	**N** **Mean** **SD** **Median** **Min** **Max**	1383 20.3 16.1 17.9 -28.2 120	461 19.9 15.4 17.4 -28.2 81.3	466 19.9 17.1 17.4 -16.3 120	456 21.9 15.7 19.0 -9.9 86.4

1 Predicted FEV_1 value was calculated by the European Coal and Steel Community (ECSC) formula.
2 Measured 30 minutes after inhaling 400 mcg of albuterol.
(Source: Volume 5.19, Section 5.3.5.1, p 96-97, 268)

Discontinuations

A total of 2,462 patients signed consent forms and were enrolled into the trial. Approximately 60% of the enrolled patients fulfilled inclusion and exclusion criteria, and were randomized to treatment. Twenty of the randomized patients from a French study site (#3302) were excluded from the treated set (TS) because accuracy of recorded data could not be verified against the source documentation, leaving 1,460 patients which comprise the TS. Final disposition and reasons for prematurely discontinued from trial medication are summarized in Table 30.

Of the 1,460 treated patients, 486 received Combivent Respimat 20/100 mcg, 491 received Combivent CFC-MDI 36/206 mcg and 483 were in the ipratropium Respimat 20 mcg group. One hundred sixty four (164) (11.2%) of the randomized patients prematurely discontinued the trial before the final visit. Overall, 53 patients (3.6% of TS) discontinued from the study prematurely due to the study disease worsening. The number of premature discontinuation of study medications due to other adverse events were 35 (2.4 of TS). There were 33 patients refused continuation of medication, accounting for 2.3% of TS. The withdrawal rates for the three treatment groups are similar: 48 patients (9.9%) in the Combivent Respimat 20/100 mcg group, 55 patients (11.2%) in the Combivent CFC-MDI 36/206 mcg group, and 61 patients (12.6%) in the ipratropium Respimat 20 mcg group.

Table 30 Disposition of enrolled patients and reasons for discontinuation

Patients	**Total**	**Combivent Respimat 20/100**	**Combivent CFC-MDI 36/206**	**Ipratropium Respimat 20**
Randomized set (RS)	1480	493	498	489
Not treated*	20	7	7	6
Treated set (TS)	1460	486	491	483
Completed (% of TS)	1296 (88.8)	438 (90.1)	436 (88.8)	422 (87.4)
Prematurely discontinued trial medication (% of TS)	164 (11.2)	48 (9.9)	55 (11.2)	61 (12.6)
Adverse events due to study disease worsening#	53 (3.6)	14 (2.9)	19 (3.9)	20 (4.1)
Adverse events due to other conditions#	35 (2.4)	5 (1.0)	15 (3.0)	15 (3.1)
Non-compliance	20 (1.4)	7 (1.4)	4 (0.8)	9 (1.9)
Lost to follow-up	7 (0.5)	2 (0.4)	1 (0.2)	4 (0.8)
Refused to continue	33 (2.3)	12 (2.5)	11 (2.2)	10 (2.1)
Other	16 (1.1)	8 (1.6)	5 (1.0)	3 (0.6)

* 20 patients from one French study site were excluded from the TS because the accuracy of recorded data could not be verified against source documentation.
# Combined AE terms
(Source: Volume 5.19, Section 5.3.5.1, p 90)

Reviewer comment:
The withdrawal rate of the trial is small (3.6%) and similar across three treatment groups. The withdrawals will not have a significant impact on the results of the trial.

Protocol Deviations

Important protocol violations (PV) are defined as deviations from the protocol-defined inclusion criteria that could potentially alter the analyses, or that would put the patient at risk. Deviations from the pre-specified spirometry criteria are deemed important protocol violations. In total, 43 patients (2.9%) have important protocol violations, approximately equally distributed across treatment groups. Among those patients with protocol violations, fifteen patients (1.0%) have eosinophil values $\geq 600/mm^3$, 15 (1.0%) have invalid/unacceptable or missing the pre-dose spirometry measure at Visit 1, and 14 (1.0%) have FEV_1 >65% of predicted normal value or $FEV_1/FVC > 70\%$. Since the overall number of PV is small, the potential impact on the trial result is considered minor.

Reviewer comments:
The patients with PV were not excluded from the analysis. Since the overall number of PV was small compared to the total treated population of 1460, the potential impact on the trial result was considered minor.

For the 15 patients who had invalid/unacceptable or missing the pre-dose spirometry measure at Visit 1, the Applicant does not provide further details. Without the clinical visit day pre-dose spirometry data (test day baseline), the efficacy evaluation is impossible in these patients. At the first glance, this might cause an analytical error. However, the primary endpoint to evaluate the efficacy is the FEV_1 change from test day baseline at visit 5 (Day 85). It will not affect the efficacy evaluation that 15 patients missed the test day baseline spirometry data at visit 1.

Compliance

At the first visit, an electronic instrument called eDiary/Peak Flow Meter was dispersed to each patient. This instrument is a hand-hold computer that incorporates the electronic patient diary function into a peak flow meter. The patient diary and peak expiratory flow rate data collected through the instrument during a clinical trial can be downloaded and reviewed by investigators. Patients entered in the eDiary/Peak Flow Meter the number of actuations of investigational drug taken. The investigator/study staff downloaded and reviewed these records with the patient at each study visit to assess treatment compliance. Patient compliance is evaluated using the weekly mean number of actuations of study medication per day during the randomized period. The overall percentage compliance is calculated as the percentage of actual number of actuations of study medication during the 12-week randomized period out of the total number of actuations of study medication each patient should have taken during the same period (Table 31). The overall mean number of actuations of active study medication taken per day for the

Respimat group (one inhalation 4 times per day) is 3.5. The overall mean number of actuations of active study medication taken per day for the Combivent CFC-MDI 36/206 group (two puffs 4 times per day) is 6.5. Most of the patients are 80% to 120% compliant with the trial medication.

Table 31 Trial medication compliance recorded during the 12-week study (1012.56)

Treatment group	**Combivent Respimat 20/100**		**Combivent CFC-MDI 36/206**		**Ipratropium Respimat 20**	
Trial medication[1]	Respimat	MDI	Respimat	MDI	Respimat	MDI
Treated set (TS)	486	486	491	491	483	483
Patients recorded compliance	439	439	457	457	438	438
Number of puffs per day: Mean	3.5	6.4	3.5	6.5	3.5	6.4
SD	0.94	1.9	0.99	1.9	0.95	1.9
Percentage compliance[2]						
<50%	26	53	36	52	31	55
50% - <80%	76	86	73	90	65	81
80% - ≤120%	325	300	333	315	331	302
>120%	12	0	16	0	11	0

1 The full daily dose was 4 puffs of Respimat and 8 puffs of MDI.
2 Percentage compliance was calculated as the number of puffs the patient actually took divided by the number the patient should have taken during the treatment period.
(Source: Volume 5.19, Section 5.3.5.1, p 281)

10.1.1.2.2 Efficacy

10.1.1.2.2.1 Primary Efficacy Endpoints

Three co-primary efficacy endpoints are used to demonstrate the contribution of both components of Combivent Respimat:

(1) Comparison of AUC between test-day baseline FEV_1 and the FEV_1 change from test day baseline curve from 0 to 6 hours (FEV_1 AUC_{0-6}) divided by six at Day 85 (the end of the treatment period), for comparison of Combivent Respimat 20/100 mcg to Combivent CFC-MDI 36/206 mcg
(2) Comparison of AUC between test-day baseline FEV_1 and the FEV_1 change from test-day baseline curve from 0 to 4 hours (FEV_1 AUC_{0-4}) divided by four at Day 85 (the end of the treatment period), for comparison of Combivent Respimat 20/100 mcg to ipratropium Respimat 20 mcg
(3) Comparison of AUC between test-day baseline FEV_1 and the FEV1 change from test-day baseline curve from 4 to 6 hours (FEV_1 AUC_{4-6}) divided by two at Day 85 (the end of the treatment period), for comparison of Combivent Respimat 20/100 mcg to ipratropium Respimat 20 mcg

Table 32 Baseline FEV_1 value (liters) for patients in PFT full analysis set on test days[1]

Treatment	**Combivent Respimat 20/100 N=474**		**Combivent CFC-MDI 36/206 N=482**		**Ipratropium Respimat 20 N=468**	
FEV_1 value	Mean	SE	Mean	SE	Mean	SE
Test Day 1[2]	1.123	0.019	1.123	0.019	1.096	0.019
Test day 29	1.014	0.009	1.106	0.009	1.109	0.009
Test day 57	1.112	0.010	1.108	0.010	1.118	0.010
Test day 85	1.112	0.010	1.106	0.010	1.114	0.010

1 Measured prior to the test day drug administration.
2 As the study baseline value.
(Source: Volume 5.19, Section 5.3.5.1, p 99, 285)

Table 32 lists the baseline FEV_1 values on test day 1, 29, 57, and 85. The data shows that the baseline FEV_1 values are comparable across the three treatment groups and among test days.

Table 33 shows that on test day 85, the Combivent Respimat 20/100 mcg group had a mean FEV_1 AUC_{0-6} change from same day baseline of 0.145 liters compared to 0.149 liters for the Combivent CFC-MDI 36/206 mcg group. Although the result is slightly in favor of the Combivent CFC-MDI 36/206 mcg group with a difference of 0.003 liters in the mean FEV_1 AUC_{0-6} change from same day baseline, this difference is not statistically significant (95% CI: -0.022 to 0.015 liters). The criterion of non-inferiority had been pre-set as that the upper limit of the 95% confidence interval of the difference for the change in FEV_1 AUC should be no more than 0.05 liters in comparing the two treatments in the trial. The Combivent Respimat 20/100 mcg is considered non-inferior to Combivent CFC-MDI 36/206 mcg, because the difference of the two treatments in mean FEV_1 AUC_{0-6} change is not statistically significant and the 95% confidence interval of the difference was less than 0.05 liters.

Table 33 Mean differences in FEV_1 AUC_{0-6} (in liter) from test day baseline between Combivent Respimat 20/100 mcg and Combivent MDI 36/206 mcg for patients in PFT full analysis set

Treatment	Combivent Respimat 20/100 mcg (A) N=474		Combivent CFC-MDI 36/206 mcg (B) N=482		Treatment difference (A-B)		
FEV_1 value	Mean	SE	Mean	SE	Mean	SE	95% CI
Day 1	0.173	0.008	0.189	0.008	-0.016	0.010	-0.036, 0.004
Day 29	0.154	0.007	0.161	0.007	-0.007	0.010	-0.026, 0.013
Day 57	0.146	0.007	0.160	0.007	-0.014	0.010	-0.033, 0.005
Day 85[1]	0.145	0.007	0.149	0.007	-0.003	0.010	-0.022, 0.015

1 Co-primary efficacy endpoint
(Source: Volume 5.19, Section 5.3.5.1, p 101)

To demonstrate the second co-primary efficacy endpoint, Table 34 shows the mean changes in FEV_1 AUC_{0-4} from test day baseline. On test day 85, the Combivent Respimat 20/100 mcg group had a 0.189 liter mean change in FEV_1 AUC_{0-4} from test day baseline, and the ipratropium Respimat 20 mcg group had a 0.142 liter mean change in FEV_1 AUC_{0-4} from test day baseline. The difference of the mean change in FEV_1 AUC_{0-4} from test day baseline is 0.047 liter (SE 0.010), with a p value of <0.001. Also the Figure 1 shows that the upper limit of the 95% confidence interval of the change in FEV_1 AUC_{0-4} is greater than the pre-set superiority criterion of 0.05 liters. The result demonstrates that Combivent Respimat 20/100 mcg is statistically superior to the ipratropium Respimat 20 mcg in the mean changes in FEV_1 AUC_{0-4} from test day baseline.

Table 34 Mean differences in FEV_1 AUC_{0-4} (in liter) from test day baseline between Combivent Respimat 20/100 mcg and Ipratropium Respimat 20 mcg for patients in PFT full analysis set

Treatment	Combivent Respimat 20/100 (A) N=474		Ipratropium Respimat 20 (C) N=468		Treatment difference (A-C)			
FEV_1 value	Mean	SE	Mean	SE	Mean	SE	95% CI	p-value
Day 1	0.211	0.008	0.149	0.008	0.061	0.010	0.040, 0.083	<0.001
Day 29	0.197	0.008	0.153	0.008	0.044	0.010	0.024, 0.065	<0.001
Day 57	0.188	0.007	0.141	0.007	0.047	0.010	0.027, 0.067	<0.001
Day 85[1]	0.189	0.007	0.142	0.007	0.047	0.010	0.028, 0.066	<0.001

1 Co-primary efficacy endpoint
(Source: Volume 5.19, Section 5.3.5.1, p 103)

Albuterol is a short acting β agonist, with its bronchodilation effect persisting for about 3 to 4 hours. The FEV_1 AUC_{4-6} is measuring the efficacy of ipratropium component of the combination product. The efficacy measured after 4 hours of the Combivent Respimat 20/100 mcg group should be comparable to that in the ipratropium Respimat 20 mcg group. The third co-primary efficacy endpoint, the mean change in FEV_1 AUC_{4-6} from test day baseline, is shown in Table 35. The Combivent Respimat 20/100 mcg group has a mean FEV_1 AUC_{4-6} change from same day baseline of 0.056 liters compared to 0.073 liters for the ipratropium Respimat 20 mcg group. The difference in the mean change in FEV_1 AUC_{4-6} from test day baseline between two groups is 0.017 liters (SE 0.011). The difference is slightly in favor of the ipratropium Respimat 20 mcg group, but this difference is not statistically significant (95% CI: -0.039 to 0.005 liters). Also the 95% confidence interval of the difference is less than 0.05 liters. The result demonstrates that the Combivent Respimat 20/100 mcg is non-inferior to the ipratropium Respimat 20 mcg in the mean change in FEV_1 AUC_{4-6} from test day baseline.

Table 35 Mean differences in FEV_1 AUC_{4-6} (in liter) from test day baseline between Combivent Respimat 20/100 mcg and Ipratropium Respimat 20 mcg for patients in PFT AUC_{4-6} analysis set

Test Day	Combivent Respimat 20/100 (A) N=447		Ipratropium Respimat 20 (C) N=427		Treatment difference (A-C)		
FEV_1 value	Mean	SE	Mean	SE	Mean	SE	95% CI
Day 1	0.100	0.008	0.074	0.009	0.026	0.012	0.003, 0.049
Day 29	0.068	0.008	0.078	0.008	-0.010	0.011	-0.032, 0.012
Day 57	0.063	0.008	0.073	0.008	-0.011	0.011	-0.033, 0.011
Day 85[1]	0.056	0.008	0.073	0.008	-0.017	0.011	-0.039, 0.005

1 Co-primary efficacy endpoint
(Source: Volume 5.19, Section 5.3.5.1, p 104)

The three co-primary efficacy endpoints are graphically demonstrated in Figure 6. The test drug Combivent Respimat 20/100 mcg is non-inferior to Combivent CFC-MDI 36/206 mcg because the difference in the FEV_1 AUC_{0-6} change for two treatments is small and the 95% confidence interval of the difference was less than the pre-set non-inferior criterion of 0.05 liters. The Figure also demonstrates that the test drug Combivent Respimat 20/100 mcg is superior to ipratropium Respimat 20 mcg within 4 hours post-dosing, as evaluated by the FEV_1 AUC_{0-4} change from same day baseline and this result shows the efficacious contribution of albuterol to the combination product. The Figure again demonstrates that the test drug Combivent Respimat 20/100 mcg is non-inferior to ipratropium Respimat 20 mcg during 4 to 6 hours post-dosing, as

evaluated by the FEV_1 AUC_{4-6} change from same day baseline. These results show the contribution of each component, albuterol and ipratropium, of the combination product.

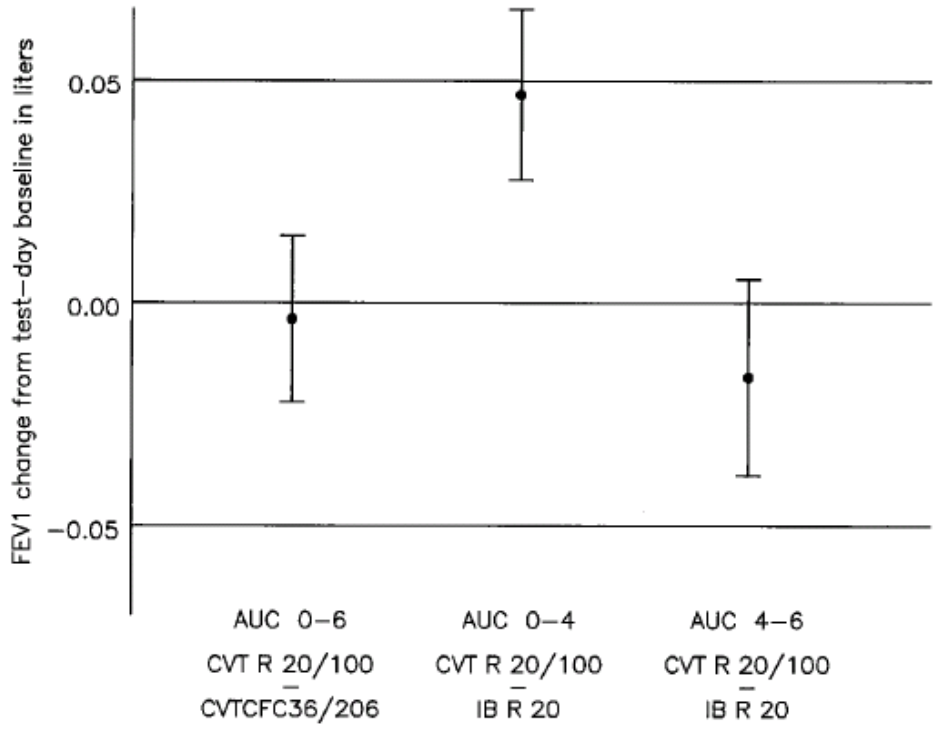

Figure 6 **Summary of three primary efficacy endpoints: mean changes in FEV_1 AUC from test day baseline and the 95% confidence intervals for three treatment groups on test day 85** (Source: Volume 5.19, Section 5.3.5.1, p 106)

Figure 7 shows the FEV_1 AUC change time profiles from 0 to 6 hours post-dosing on test days 1, 29, 57, and 85 in the study 1012.56. The result on test day 85 again shows the three co-primary efficacy endpoints. The Figure 11(D) demonstrates that on test day 85 the test drug Combivent Respimat 20/100 mcg and Combivent CFC-MDI 36/206 mcg have an overlapped FEV_1 AUC change time profile from 0 to 6 hours post-dosing. Both the Combivent Respimat 20/100 mcg and Combivent CFC-MDI 36/206 mcg are superior to ipratropium Respimat 20 mcg in FEV_1 AUC change from 0 to 4 hours post-dosing, which demonstrates the contribution of albuterol component of the combination product. Three treatments have a similar FEV_1 AUC change from 4 to 6 hours post-dosing.

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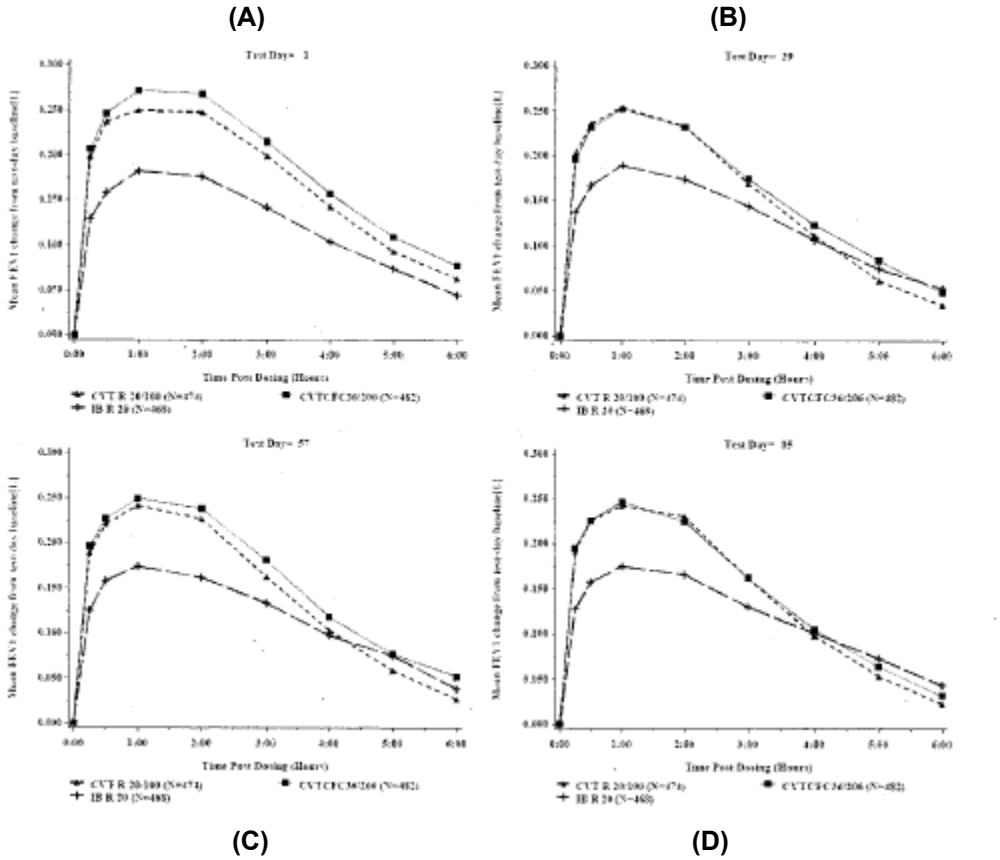


Figure 7 **Mean FEV_1 (change from test-day baseline, in liters) time profile from 0 to 6 hours on day 1 (A), 29(B), 57(C), and 85(D) for patients PFT full analysis set** (Source: Volume 5.19, Section 5.3.5.1, p 100)

10.1.1.2.2.2 Secondary Efficacy Endpoints

FEV_1 AUC on Days 1, 29, and 57 (AUC_{0-6}, AUC_{0-4}, and AUC_{4-6})

As shown in the Tables 33, 34, and 35, the FEV_1 AUC changes on test days 1, 29, and 57 are the same as that on test day 85. The mean changes from test day baselines in FEV_1 AUC_{0-6} are comparable in the Combivent Respimat 20/100 mcg group and the Combivent CFC-MDI 36/206 mcg group (Table 9). The mean changes from test day baselines in FEV_1 AUC_{0-4} are significantly larger in the Combivent Respimat 20/100 mcg group than that in the ipratropium Respimat 20 mcg group (Table 10). Table 11 shows that on test days 29, and 57, mean changes from test day baselines in FEV_1 AUC_{4-6} are comparable in the Combivent Respimat 20/100 mcg group and the ipratropium Respimat 20 mcg group and on test days 1, the Combivent Respimat 20/100 mcg group has a better mean change in FEV_1 AUC_{4-6} from the test day baseline than that in the ipratropium Respimat 20 mcg group (mean: 0.026 liters, 95% CI: 0.003 to 0.049 liters). Overall the FEV_1 AUC changes on test days 1, 29, and 57 support the conclusion of primary

efficacy endpoint evaluation: the test drug Combivent Respimat 20/100 mcg is non-inferior to Combivent CFC-MDI 36/206 mcg as evaluated by the changes from the test day baseline of FEV_1 $AUC_{0-6.}$ Compared with ipratropium Respimat 20 mcg the test drug Combivent Respimat 20/100 mcg is superior within 4 hours post-dosing and non-inferior during 4 to 6 hours post-dosing, as evaluated by the changes from the test day baseline of FEV_1 AUC_{0-4} and $AUC_{4-6,}$ respectively.

Peak FEV_1 in the 2-hour interval after treatment on Days 1, 29, 57 and 85

The peak FEV_1 is the maximum FEV_1 value recorded within the first 2 hours after administration of study medications. Table 36 shows the peak FEV_1 values of the three treatment groups on test days 1, 29, 57, and 85. The Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg groups are comparable in peak FEV_1 on all test days. The differences in peak FEV_1 between these two groups are 0.020 and 0.009 liters on Test Days 1 and 57, with small numeric differences in favor of the Combivent CFC-MDI 36/206 mcg group; and 0.005 and 0.008 liters on Test Days 29 and 85, with small numeric differences in favor of the Combivent Respimat 20/100 mcg group. The differences in peak FEV_1 on all test days between the two groups are not statistically significant. The Combivent Respimat 20/100 mcg group is superior to the ipratropium Respimat 20 mcg group in peak FEV_1 on all test days. The differences in peak FEV_1 between these two groups are 0.065, 0.061, 0.053, and 0.066 liters in favor of the Combivent Respimat 20/100 mcg group. The Combivent CFC-MDI 36/206 mcg group is also superior to the ipratropium Respimat 20 mcg group in peak FEV_1 on all test days. The differences in peak FEV_1 between these two groups are 0.085, 0.056, 0.062, and 0.058 liters, in favor of the Combivent CFC-MDI 36/206 mcg group. These results demonstrate that the test drug Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg are comparable and both drugs are superior to ipratropium Respimat 20 mcg at maximum FEV_1 value measured within 2 hours post-dosing on all test days.

Table 36 Peak FEV_1 (least square mean in liters) in the 2-hour interval after treatment on Day 1, 29, 57, and 85 for patients in PFT full analysis set

Test Day	Combivent Respimat 20/100 (A) N=474		Combivent MDI 36/206 (B) N=482		Ipratropium Respimat 20 (C) N=468		Treatment difference		
Peak FEV_1	Mean	SE	Mean	SE	Mean	SE	A-B	A-C	B-C
Day 1	1.4164	0.008	1.4365	0.008	1.3511	0.008	-0.020	0.065*	0.085*
Day 29	1.4065	0.011	1.4016	0.011	1.3458	0.011	0.005	0.061*	0.056*
Day 57	1.3952	0.011	1.4038	0.011	1.3417	0.011	-0.009	0.053*	0.062*
Day 85	1.4043	0.012	1.3965	0.012	1.3383	0.012	0.008	0.066*	0.058*

* Difference with p-value <0.001. (Source: Volume 5.29, Section 5.3.5.1, p 676-687)

Peak FEV_1 response (change from test-day baseline) on Days 1, 29, 57 and 85

The peak FEV_1 response is the maximum change of FEV_1 from the test-day baseline within the first 2 hours after administration of study medications. Tables 27, 28, and 39 list the peak FEV_1 response of the three treatment groups on test days 1, 29, 57, and 85. The Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg groups are comparable in FEV_1 peak response on all

test days. The differences in FEV_1 peak response between these two groups are 0.020 and 0.013 liters on Test Days 1 and 57, with small numeric differences in favor of the Combivent CFC-MDI 36/206 mcg group; and 0.006 and 0.003 liters on Test Days 29 and 85, with small numeric differences in favor of the Combivent Respimat 20/100 mcg group (Table 13). The Combivent Respimat 20/100 mcg is superior to the ipratropium Respimat 20 mcg in FEV_1 peak response on all test days. The differences between the two groups in the FEV_1 peak response are 0.065, 0.065, 0.060, and 0.068 liters, in favor of the Combivent Respimat 20/100 mcg group (Table 14). The Combivent CFC-MDI 36/206 mcg is superior to the ipratropium Respimat 20 mcg in FEV_1 peak response on all test days. The differences in FEV_1 peak response between these two groups are 0.085, 0.059, 0.073, and 0.066 liters in favor of the Combivent CFC-MDI 36/206 mcg group (Table 15).

Table 37 Peak FEV_1 response (change from test-day baseline, mean in liters) in the 2-hour interval after treatment between Combivent Respimat 20/100 mcg and Combivent MDI 36/206 mcg for patients in PFT full analysis set

Test Day	Combivent Respimat 20/100 (A) N=474		Combivent MDI 36/206 (B) N=482		Treatment difference (A-B)		
FEV_1 change	Mean	SE	Mean	SE	Mean	SE	95% CI
Day 1	0.302	0.008	0.323	0.008	-0.020	0.011	-0.042, 0.002
Day 29	0.302	0.008	0.296	0.008	0.006	0.011	-0.015, 0.028
Day 57	0.284	0.008	0.296	0.008	-0.013	0.011	-0.033, 0.008
Day 85	0.293	0.008	0.290	0.008	0.003	0.011	-0.018, 0.024

(Source: Volume 5.19, Section 5.3.5.1, p111)

Table 38 Peak FEV_1 response (change from test-day baseline, mean in liters) in the 2-hour interval after treatment between Combivent Respimat 20/100 mcg and Ipratropium Respimat 20 mcg for patients in PFT full analysis set

Test Day	Combivent Respimat 20/100 mcg (A) N=474		Ipratropium Respimat 20 mcg (C) N=468		Treatment difference (A-C)		
FEV_1 change	Mean	SE	Mean	SE	Mean	SE	95% CI
Day 1	0.302	0.008	0.237	0.008	0.065	0.011	0.043, 0.087
Day 29	0.302	0.008	0.237	0.008	0.065	0.011	0.044, 0.087
Day 57	0.284	0.008	0.223	0.008	0.060	0.011	0.040, 0.081
Day 85	0.293	0.008	0.225	0.008	0.068	0.011	0.047, 0.089

(Source: Volume 5.19, Section 5.3.5.1, p112)

Table 39 Peak FEV_1 response (change from test-day baseline, mean in liters) in the 2-hour interval after treatment between Combivent MDI 36/206 mcg and Ipratropium Respimat 20 mcg for patients in PFT full analysis set

Test Day	Combivent CFC-MDI 36/206 (B) N=482		Ipratropium Respimat 20 (C) N=468		Treatment difference (B-C)		
FEV_1 change	Mean	SE	Mean	SE	Mean	SE	95% CI
Day 1	0.323	0.008	0.237	0.008	0.085	0.011	0.063, 0.108
Day 29	0.296	0.008	0.237	0.008	0.059	0.011	0.037, 0.081
Day 57	0.296	0.008	0.223	0.008	0.073	0.011	0.052, 0.094
Day 85	0.290	0.008	0.225	0.008	0.066	0.011	0.044, 0.087

(Source: Volume 5.29, Section 5.3.5.1, p665-675)

Figure 8 demonstrates that the test drug Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg are comparable and both drugs are superior to ipratropium Respimat 20 mcg at the peal FEV_1 response measured within 2 hours post-dosing on all test days. This figure also graphically shows the efficacious contribution of albuterol in the combination product. The difference in the peak FEV_1 response between Combivent Respimat 20/100 mcg, the Combivent CFC-MDI 36/206 mcg (the upper two lines) and ipratropium Respimat 20 mcg (the lower line) is the contribution of albuterol in the combination product.

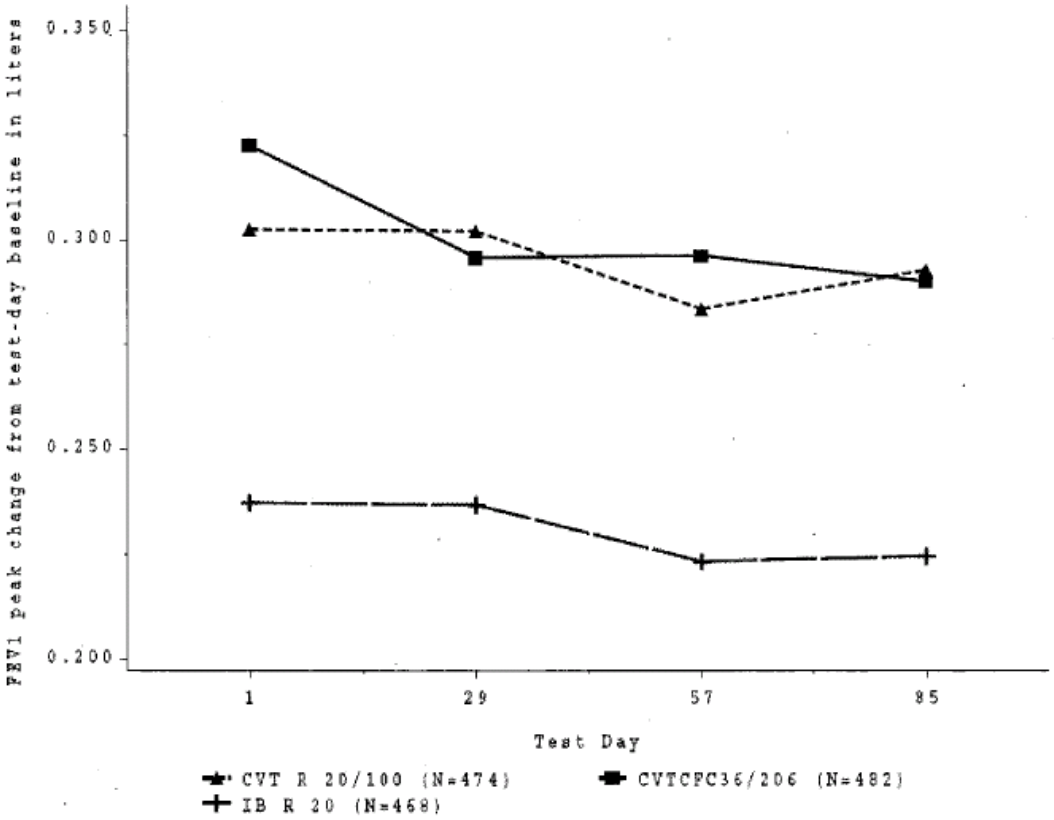


Figure 8 **Peak FEV_1 response (change from test-day baseline, mean in liters) in the 2-hour interval after treatment on test-days for patients in PFT full analysis set**
(Source: Volume 5.19, Section 5.3.5.1, p110)

Onset and duration of therapeutic FEV_1 response on Days 1, 29, 57 and 85

A therapeutic response is defined as to achieve a FEV_1 value of at least 115% of the corresponding test-day baseline value at any time during the first 2 hours after administration of study medication. The time to onset of the therapeutic response is the time from the study medication administration to the achievement of the first therapeutic response. The duration of a therapeutic response is defined as the time interval between the onset and the termination of the therapeutic response.

As shown in Table 40, the median time to onset of the therapeutic response within the first 2 hours after administration of study medication are comparable between the Combivent Respimat

20/100 mcg and the Combivent CFC-MDI 36/206 mcg groups on all test days. The median time to onset of the therapeutic response is 12 to 13 minutes after the administration of study medication for these two treatment groups. In contrast the ipratropium Respimat 20 mcg group has a relatively longer median time to onset of the therapeutic response on all four test days. The median times to onset of a therapeutic response are from 27 to 29 minutes over all test days for the ipratropium Respimat 20 mcg group. The Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg groups have a comparable duration of the therapeutic response over all test days, with a range from 165 to 189 minutes for the Combivent Respimat 20/100 mcg group and a range from 172 to 219 minutes for the Combivent CFC-MDI 36/206 mcg group. The ipratropium Respimat 20 mcg group presents the shortest duration of a therapeutic response among the three treatment groups on all four test days, with a range from 70 to 122 minutes. The Applicant also measured the time when the peak FEV_1 response observed on each test day. Overall, the time to peak FEV_1 response is 60 minutes for the Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg groups on all test days. For the ipratropium Respimat 20 mcg group the time to peak response is 120 minutes on test days 1 and 29, and then reduced to 60 minutes on test days 57 and 85.

Similar numbers of the patients (74% to 79%) in the Combivent Respimat 20/100 mcg and the Combivent CFC-MDI 36/206 mcg groups have the FEV_1 value increased at least 15% above the test day baseline on four test days. In the ipratropium Respimat 20 mcg group less patients (63% to 66%) had the FEV_1 value increased at least 15% above the test day baseline on four test days.

These results shows that the test drug Combivent Respimat 20/100 is comparable to Combivent CFC-MDI 36/206 mcg in onset, duration, and time to peak FEV_1 response on all test days. The ipratropium Respimat 20 mcg group has a longer time to onset of the therapeutic response, short duration of the therapeutic response and longer time to peak FEV_1 response.

Table 40 Onset, duration, and time to peak of therapeutic FEV_1 response (median in minutes) on test-days for patients in PFT full analysis set

Test day & treatment	N	Time to onset of 15% above test-day baseline[4]	Time to peak FEV_1 response	Duration of 15% increase	Number of patients with 15% above test-day baseline (%)
Test Day 1					
Treatment A[1]	474	13	60	189	375 (79.1)
Treatment B[2]	482	12	60	219	385 (79.9)
Treatment C[3]	468	28	120	104	300 (64.1)
Test Day 29					
Treatment A[1]	474	12	60	170	374 (78.9)
Treatment B[2]	482	13	60	178	377 (78.2)
Treatment C[3]	468	27	120	122	311 (66.5)
Test Day 57					
Treatment A[1]	474	13	60	165	354 (74.7)
Treatment B[2]	482	12	60	194	374 (77.6)
Treatment C[3]	468	29	60	84	300 (64.1)
Test Day 85					
Treatment A[1]	474	12	60	168	358 (75.5)
Treatment B[2]	482	13	60	172	357 (74.1)
Treatment C[3]	468	27	60	70	295 (63.0)

1 Treatment A: Combivent Respimat 20/100 mcg

2 Treatment B : Combivent CFC-MDI 36/206 mcg
3 Treatment C : Ipratropium Respimat 20 mcg
4 15% crease above test-day baseline had to occur within 2 hours of treatment administration.
(Source: Volume 5.19, Section 5.3.5.1, p302)

Weekly mean morning peak expiratory flow rate (PEFR) during the treatment period

Morning peak expiratory flow rate (PEFR) (recorded in the morning prior to the administration of trial and/or rescue medication) is used as a secondary endpoint for both the efficacy and the safety analyses. Table 41 shows that the baseline morning PEFR values are approximately 197, 199, and 195 liters for the Combivent Respimat 20/100 mcg, the Combivent CFC-MDI 36/206 mcg, and the ipratropium Respimat 20 mcg groups, respectively. The baseline morning PEFR values are comparable across all three treatment groups. The overall weekly mean morning PEFR values during the treatment period are approximately 192, 191, and 190 liters for the Combivent Respimat 20/100 mcg group, the Combivent CFC-MDI 36/206 mcg group, and the ipratropium Respimat 20 mcg group, respectively. The weekly mean morning PEFR values during the treatment period are comparable across all three treatment groups and slightly lower than that at the baseline.

Table 41 Weekly mean morning PEFR (liters/minute) at baseline and during treatment period for patients in Diary Full Analysis Set (FAS DRY)

	Combivent Respimat 20/100 (A) N=441	Combivent MDI 36/206 (B) N=444	Ipratropium Respimat 20 (C) N=426	Treatment difference	
				A-B	A-C
PEFR value	Mean (SE)	Mean (SE)	Mean (SE)	Mean, SE (95% CI)	Mean, SE (95% CI)
Baseline	196.68 (3.96)	198.64 (3.82)	194.78 (2.24)	--	--
Treatment period	191.95 (1.51)	190.29 (1.53)	189.51 (1.55)	1.63, 2.07 (-2.40, 5.71)	2.44, 2.087 (-1.66, 6.53)

(Source: Volume 5.29, Section 5.3.5.1, p133-136)

Mean numbers of albuterol puffs during day and at night as rescue medication at baseline and during the treatment period

The numbers of albuterol puffs during daytime and at night as rescue medication at baseline and during the treatment period are evaluated. These data were collected from the patient daily records and presented as the weekly average per day (averaged for each week and expressed per day). The week prior to randomization is specified as the baseline. All patients were given Atrovent HFA inhalation aerosol 2 puffs four times per day and albuterol MDI PRN during the 2-week baseline period. Table 42 shows the mean numbers of albuterol puffs during day and at night as rescue medication at baseline and during the treatment period. All treatment groups are comparable in the night-time and daytime rescue medication use at baseline. The average baseline night-time rescue medication use is one actuation per night and the average baseline daytime rescue medication use is approximately 2.6 actuations per day for the three treatment groups. The overall averages of rescue albuterol use at night and during daytime in the treatment period are comparable for the three treatment groups. The patients used approximately one actuation per night during the treatment period. The overall average of the rescue albuterol use

during daytime in the treatment period is slightly less than that of the baseline, ranging from 2.2 to 2.5 puffs per day.

Table 42 Mean number of albuterol puffs during day and night time at baseline and during the treatment period for patients in Diary Full Analysis Set (FAS_DRY)

Treatment	N	Baseline Mean, SE	Treatment period Mean, SE	Treatment difference A-B Mean (95% CI)	Treatment difference A-C Mean (95% CI)
Night time					
Treatment A[1]	471	0.970, 0.066	0.977, 0.047	0 (-0.126, 0.125)	-0.020 (-0.146,0.106)
Treatment B[2]	467	0.938, 0.070	0.977, 0.047		
Treatment C[3]	454	0.995, 0.068	0.997, 0.048		
Day time					
Treatment A[1]	453	2.597, 0.138	2.300, 0.089	0.109 (-0.128,0.346)	-0.155 (-0.395, 0.084)
Treatment B[2]	458	2.605, 0.146	2.191, 0.089		
Treatment C[3]	438	2.624, 0.082	2.456, 0.090		

1 Treatment A: Combivent Respimat 20/100 mcg
2 Treatment B : Combivent CFC-MDI 36/206 mcg
3 Treatment C : Ipratropium Respimat 20 mcg
(Source: Volume 5.19, Section 5.3.5.1, p123-127)

Daily symptom scores (weekly mean) over the treatment period

Each morning, patients rated their night-time symptom as related to the previous night's sleep. In the evening, patients rated their daytime COPD symptoms including coughing, wheezing, chest tightness or breathlessness. The night-time and daytime symptom scores are defined as the followings:

Night-time:
0 = no symptoms;
1 = slept well, but some symptoms;
2 = woke once because of symptoms;
3 = woke several times (2 or 3 times) because of symptoms;
4 = woke most of the night (4 or more times) because of symptoms.

Daytime:
0 = no symptoms;
I = occasional wheezing, chest tightness, breathlessness or coughing;
2 = frequent wheezing, chest tightness, shortness of breath or coughing without interfering with normal activities;
3 = wheezing, chest tightness/shortness of breath or coughing for most of the day, which interfered to some extent with normal activities;
4 = symptom prevented the patient from attending work and engaging in all normal activities.

Table 43 shows the baseline night-time and daytime symptom scores of the patients in all three treatment groups. All treatment groups are comparable in the night-time and daytime symptom scores at baseline. The overall baseline night-time symptom score is slightly below one (slept

well, but some symptoms) and the overall baseline daytime symptom score is just above one (occasional wheezing, chest tightness, breathlessness or coughing). The mean night-time and daytime symptom scores for all three treatment groups are approximately 0.9 and 1.0, respectively. The mean night-time and daytime symptom scores are comparable among three treatment groups.

Table 43 Mean night time and daytime symptom scores at baseline and during the treatment period for patients in Diary Full Analysis Set (FAS_DRY)

Treatment	N	Baseline Mean, SE	Treatment period Mean, SE	Treatment difference A-B Mean (95% CI)	Treatment difference A-C Mean (95% CI)
Night time					
Treatment A[1]	471	0.822, 0.040	0.922, 0.023	0.008 (-0.055, 0.071)	0.065 (0.002, 0.128)
Treatment B[2]	467	0.824, 0.040	0.914, 0.024		
Treatment C[3]	454	0.894, 0.042	0.922, 0.023		
Day time					
Treatment A[1]	452	1.040, 0.042	1.015, 0.022	0.013 (-0.046, 0.072)	0.016 (-0.044,0.075)
Treatment B[2]	456	1.004, 0.040	1.002, 0.022		
Treatment C[3]	437	1.031, 0.040	0.999, 0.022		

1 Treatment A: Combivent Respimat 20/100 mcg
2 Treatment B : Combivent CFC-MDI 36/206 mcg
3 Treatment C : Ipratropium Respimat 20 mcg
(Source: Volume 5.19, Section 5.3.5.1, p128-132)

Physician's global evaluation

The physician made a global evaluation at each visit prior to pulmonary function testing. The evaluation was based on the need for concomitant medication, number and severity of exacerbation since the last visit, severity of coughing, ability to exercise, amount of wheezing, etc. The evaluations would be entered as scores in the CRF as poor (scores 1 and 2), fair (scores 2 and 4), good (scores 5 and 6), and excellent (scores 7 and 8).

Table 44 showed the physician global evaluation scores at baseline and during the treatment period. All patients were in fair to good condition at baseline and during the treatment period. The Combivent Respimat 20/100 mcg group has comparable physician global evaluation scores as compared with the Combivent CFC-MDI 36/206 mcg and the ipratropium Respimat 20 mcg groups.

Table 44 Physician global evaluation scores and treatment differences for patients in treated set

Test day and treatment	N	Physician global evaluation scores Mean, SE	Treatment difference A-B Mean (95% CI)	Treatment difference A-C Mean (95% CI)
Baseline Treatment A[1]	480	4.829, 0.058		
Treatment B[2]	487	4.807, 0.057	---*	---*
Treatment C[3]	481	4.805, 0.060		
Day 29 Treatment A[1]	480	4.936, 0.041	0.077 (-0.034, 0.187)	-0.054 (-0.165, 0.056)
Treatment B[2]	487	4.859, 0.041		
Treatment C[3]	481	4.990, 0.041		

Day 57	**Treatment A[1]**	480	4.971, 0.045	0.006 (-0.115, 0.127)	-0.069 (-0.190, 0.053)
	Treatment B[2]	487	4.965, 0.045		
	Treatment C[3]	481	5.040, 0.046		
Day 85	**Treatment A[1]**	480	5.115, 0.048	0.097 (-0.031, 0.225)	0.018 (-0.111, 0.146)
	Treatment B[2]	487	5.018, 0.048		
	Treatment C[3]	481	5.097, 0.048		

* Data not provided in the submission
1 Treatment A: Combivent Respimat 20/100 mcg
2 Treatment B : Combivent CFC-MDI 36/206 mcg
3 Treatment C : Ipratropium Respimat 20 mcg
(Source: Volume 5.19, Section 5.3.5.1, p136-139)

Subgroup Analyses

The Test Day 85 FEV_1 (change from test-day baseline) between 0 and 6 hours were examined for the following subgroups:

- Gender (male vs. female)
- Age (<65 years vs. ≥65 years)
- Using steroid (inhaled or oral) at randomization (yes vs. no)
- Disease severity (FEV_1 ≥50% predicted, 35% ≤ FEV_1 <50% predicted, and FEV_1 <35% predicted) at screening
- Reversibility to albuterol 400 mg inhalation at screening
- Smoking history (current smokers vs. ex-smokers)

The study shows that the patients of male, <65 years old, and having screening FEV_1 ≥50% have slightly higher test day baseline FEV_1 compared with those of females, ≥65 years old, and screening FEV_1 <50%. However, the test day baseline FEV_1 values are similar across the three treatment groups in all subgroups.

All subgroups show that response to the Combivent Respimat 20/100 mcg group is similar to that of the Combivent CFC-MDl 36/206 mcg group from 0 to 6 hours post-dosing. During 0 to 4 hours post-dosing all subgroups show a higher FEV_1 change in the groups taking Combivent Respimat 20/100 mcg and Combivent CFC-MDl 36/206 mcg than that of the group taking ipratropium Respimat 20 mcg. Then the FEV1 changes from the test day baseline for all three treatment groups are similar during 4 to 6 hours post-dosing. after administration of randomized treatment. These results of sub-group analyses demonstrate that the age, gender, disease severity, steroid using, and smoking status have no apparent effect on the FEV_1 change from test day baseline after the administration of the 3 test drugs.

Inhaler testing

One hundred normally functioning Combivent Respimat inhalers were collected from patients at 37 study sites in the United States when the dose indicator reached the 30 dose remaining mark from 120 doses available for each inhaler. These inhalers were tested for the shape of spray plume, dose accuracy, and particle size distribution. All the sprays from the collected inhalers exhibited a normal cone-shaped spray plume. The mean value of the metered spray volume was 99% of the target value of (b) (4) The fine particle fraction (b) (4) of the released spray as determined by laser diffraction remained unchanged from the results at batch release. More

information regarding inhaler testing can be found in ONDQA Review [NDA 21-747 N-000, Chemistry Review, Alan C. Schroeder, Ph. D., June 4, 2009].

Device Satisfaction

The patient satisfaction with device was assessed by a 10-item questionnaire administered at the end of the study. The objective of the questionnaire was to compare the patient satisfaction to Respimat and MDI inhaler. Because of the double-dummy study design that was used in this study, every patient used both a Respimat and a MDI throughout the study. The response to the questions were on a scale of 1 to 7, defined as 1=very dissatisfied, 2=dissatisfied, 3=somewhat dissatisfied, 4=satisfied/dissatisfied, 5=somewhat satisfied, 6=satisfied, and 7=very satisfied.

The response to the questionnaire was summarized in Table 45. The data showed that more patients rated very satisfaction with Respimat than with MDI across the 10 questions. The mean scores were numerically higher with Respimat than with MDI for every question, which meant that patients were more satisfactory with Respimat than with MDI in all aspects of the device.

Table 45 Device satisfaction: frequency of "very satisfied" rating and overall rating scores

Question	Respimat (N=835)		MDI (N=834)	
	% of very satisfied	Mean scores	% of very satisfied	Mean scores
Overall feeling of inhaling medicine	35.7	5.81	19.5	5.41
Feeling that the inhaled dose goes to the lung	36.3	5.81	16.7	5.33
Tell the amount of medicine left	52.9	6.18	15.7	4.57
Inhaler works reliably	48.0	6.19	28.4	5.68
Ease of inhaling a dose	46.6	6.15	30.3	5.73
Instructions for use	47.8	6.28	36.8	6.05
Durability of inhaler	49.7	6.28	36.1	6.01
Using the inhaler	45.7	6.13	30.0	5.75
Speed of medicine coming out of the inhaler	48.3	6.12	31.7	5.72
Overall satisfaction with device	49.7	6.10	28.8	5.64

(Source: Volume 5.20, Section 5.3.3.1, pages 361-67)

10.1.1.2.3 Safety

10.1.1.2.3.1 Exposure

A total of 1,460 patients were randomized and received at least one dose of study medication. Four hundred eighty six patients (486) received Combivent Respimat 20/100 mcg, 491 received Combivent CFC-MDI 36/206 mcg and 483 received Ipratropium Respimat 20 mcg. About 90% of patients in all three groups expose to the treatment medication for more than 70 days. The mean and median exposure days for all treatment groups are 80.1 and 85 days, respectively. The total patient exposure days for Combivent Respimat 20/100 mcg, Combivent CFC-MDI 36/206 mcg, and Ipratropium Respimat 20 mcg are 39091, 39698, and 38093, respectively. The

exposure to trial medications is considered adequate to assess the safety and efficacy. Table 46 lists the total and group exposure to the trial medications.

Table 46 Exposure to trial medications in Treatment Set

Exposure	Total	Combivent Respimat 20/100	Combivent CFC-MDI 36/206	Ipratropium Respimat 20
Total treated patients	1460	486	491	483
Treatment duration: days (%)				
1 day	8 (0.5)	4 (0.8)	2 (0.4)	2 (0.4)
12-14 days	26 (1.8)	7 (1.4)	7 (1.4)	12 (2.5)
15-42 days	74 (5.1)	24 (4.9)	21 (4.3)	29 (6.0)
43-70 days	50 (3.4)	16 (3.3)	17 (3.5)	17 (3.5)
>70 days	1302 (89.2)	435 (89.5)	444 (90.4)	423 (87.6)
Exposure (days) Sum	116882	39091	39698	38093
Mean	80.1	80.4	80.9	78.9
Median	85.0	85.0	85	85

(Source: Volume 5.19, Section 5.3.5.1, p157)

10.1.1.2.3.2 Adverse Events

The adverse events that occurred more than 1% of the treatment population are listed in Table 47 below. The total patients with adverse events in the study are 691, accounted for 47.3% of the total study population. Overall, the incidence of adverse events is comparable across the three treatment groups, with slightly higher frequencies in the Combivent CFC-MDI treated patients. Lower respiratory system disorders are the most frequently reported events (20.6%), followed by upper respiratory system disorders (13.8%), gastrointestinal disorders (5.9%), musculoskeletal and connective tissue disorders (5.7%), nervous system disorders (5.6%), and general and administration site conditions (5.5%). These events are similar in frequencies in three treatment groups. The most frequently reported adverse events, lower respiratory system disorders, are essentially equivalent in the Combivent Respimat and Combivent CFC-MDI groups (21.6% and 21.8%, respectively) and slightly lower in the ipratropium Respimat group (18.4%). These lower respiratory system events are primarily COPD exacerbations, which occurred in similar frequencies in the Combivent Respimat 20/100 mcg (14.8%) and Combivent CFC-MDI 36/206 mcg (13.0%) treatment groups and at a slightly lower frequency in the ipratropium Respimat 20 mcg (10.4%) treatment group.

In total, 85 patients (5.8%) discontinued participation in the trial during the treatment period due to adverse events. The Combivent Respimat 20/100 mcg group has the lowest frequency of the discontinuation from serious adverse events (3.7%) among three treatment groups. The frequencies are essentially equal in the Combivent CFC-MDI 36/206 mcg group and ipratropium Respimat 20 mcg treatment groups (6.9% and 6.8%, respectively). Similar to the pattern of general adverse events, the majority of events that led to discontinuation in this trial are lower respiratory system disorders. Overall, 57 patients (3.9%) discontinued due to a lower respiratory event; 2.5%, 4.3%, and 5.0% in the Combivent Respimat 20/100 mcg, Combivent CFC-MDI 36/206 mcg, and ipratropium Respimat 20 mcg, respectively. Also similar to the general adverse event pattern, the primary lower respiratory event leading to discontinuation is COPD exacerbation (2.7%). The frequency of COPD exacerbation leading to treatment discontinuation across treatment groups is similar for three treatment groups, with the lowest at Combivent

Respimat 20/100 mcg (1.6%) and 3.1 % and 3.3% at Combivent CFC-MDI 36/206 mcg, and ipratropium Respimat 20 mcg, respectively. Other respiratory events causing discontinuation are dyspnea (0.6%), pneumonia (0.5%), and upper respiratory tract infection (0.2%). All other respiratory events leading to discontinuation occurred in 0.1% or less across all treatment groups.

Table 47 Adverse event frequency and percentage (>1%)[1] in preferred terms[2] in Treated Set

Exposure	Total (%)	Combivent Respimat 20/100 N (%)	Combivent CFC-MDI 36/206 N (%)	Ipratropium Respimat 20 N (%)
Total treated patients	1460 (100)	486 (100)	491 (100)	483 (100)
Patients with AEs	691 (47.3)	222 (45.7)	254 (51.7)	215 (44.5)
AEs leading to treatment discontinuation	85 (5.8)	18 (3.7)	34 (6.9)	33 (6.8)
Lower respiratory system disorders	57 (3.9)	12 (2.5)	21 (4.3)	24 (5.0)
COPD exacerbation	39 (2.7)	8 (1.6)	15 (3.1)	16 (3.3)
Dyspnea	9 (0.6)	1 (0.2)	4 (0.8)	4 (0.8)
Pneumonia	8 (0.5)	2 (0.4)	4 (0.8)	2 (0.4)
Upper respiratory tract inf.	3 (0.2)	2 (0.4)	1 (0.2)	0
Gastrointestinal disorders	86 (5.9)	19 (3.9)	40 (8.1)	27 (5.6)
Diarrhea	17 (1.2)	5 (1.0)	9 (1.8)	3 (0.6)
Nausea	19 (1.3)	4 (0.8)	7 (1.4)	8 (1.7)
General conditions	81 (5.5)	27 (5.6)	30 (6.1)	24 (5.0)
Chest pain	13 (0.9)	3 (0.6)	6 (1.2)	4 (0.8)
Fatigue	19 (1.3)	7 (1.4)	5 (1.0)	7 (1.4)
Edema	17 (1.2)	5 (1.0)	8 (1.6)	4 (0.8)
Musculoskeletal & connective tissue disorders	83 (5.7)	23 (4.7)	31 (6.3)	29 (6.0)
Arthralgia	15 (1.0)	2 (0.4)	10 (2.0)	3 (0.6)
Back pain	22 (1.5)	6 (1.2)	9 (1.8)	7 (1.4)
Nervous system disorders	82 (5.6)	21 (4.3)	28 (5.7)	33 (6.8)
Dizziness	20 (1.4)	6 (1.2)	8 (1.6	6 (1.2)
Headache	39 (2.7)	13 (2.7)	10 (2.0)	16 (3.3)
Lower respiratory system disorders	301 (20.6)	105 (21.6)	107 (21.8)	89 (18.4)
Bronchitis	38 (2.6)	14 (2.9)	17 (3.5)	7 (1.4)
COPD exacerbation	186 (12.7)	72 (14.8)	64 (13.0)	50 (10.4)
Cough	32 (2.2)	13 (2.7)	10 (2.0)	9 (1.9)
Dyspnea	37 (2.5)	11 (2.3)	12 (2.4)	14 (2.9)
Pneumonia	14 (1.4)	2 (0.4)	7 (1.4)	5 (1.0)
Upper respiratory system disorders	202 (13.8)	64 (13.2)	76 (15.5)	62 (12.8)
Influenza	14 (1.0)	3 (0.6)	7 (1.4)	4 (0.8)
Nasal congestion	9 (0.4)	3 (0.6)	6 (1.2)	0
Nasopharyngitis	53 (3.6)	18 (3.7)	15 (3.1)	20 (4.1)
Pharyngolaryngeal pain	19 (1.3)	8 (1.6)	5 (1.0)	6 (1.2)
Sinusitis	24 (1.6)	5 (1.0)	13 (2.6)	6 (1.2)
Upper respiratory tract inf.	54 (3.7)	17 (3.5)	19 (3.9)	18 (3.7)
Skin & subcutaneous tissue disorders	31 (2.1)	10 (2.1)	17 (3.5)	4 (0.8)
Rash	7 (0.5)	1 (0.2)	6 (1.2)	0
Vascular disorders	21 (1.4)	7 (1.4)	5 (1.0)	21 (1.4)
hypertension	15 (1.0)	7 (1.4)	4 (0.8)	15 (1.0)

1 Calculated using total patients of the treatment group as the denominator.
2 MedDRA version 10.1
(Source: Volume 5.20, Section 5.3.5.1, p378-383)

Serious adverse events (SAEs)

SAEs occurred in a total of 64 patients (4.4%) across all treatment groups (Table 48). The highest frequency of SAEs is in the Combivent CFC-MDI 36/206 mcg group (6.7%), followed by the Combivent Respimat 20/100 mcg group (3.5%), and the ipratropium Respimat 20 mcg group (2.9%). Similar to the pattern in general adverse events, the most frequently occurred SAE is COPD exacerbation in all treatment groups (2.2%). The frequency of COPD exacerbation as SAE across treatment groups is similar for three treatment groups, with the lowest at ipratropium Respimat 20 mcg (1.7%), and 2.3 % and 2.6% at Combivent Respimat 20/100 mcg and Combivent CFC-MDI 36/206 mcg, respectively.

Table 48 Serious adverse event frequency and percentage[1] in primary system organ class and preferred term[2] in Treated Set

Exposure	Total (%)	Combivent Respimat 20/100 N (%)	Combivent CFC-MDI 36/206 N (%)	Ipratropium Respimat 20 N (%)
Total treated patients	1460 (100)	486 (100)	491 (100)	483 (100)
Patients with AEs	691 (47.3)	222 (45.7)	254 (51.7)	215 (44.5)
Serious AEs	64 (4.4)	17 (3.5)	33 (6.7)	14 (2.9)
Death during the trial[3]	6 (0.4)	3 (0.6)	1 (0.2)	2 (0.4)
Cardiac disorders	3 (0.2)	1 (0.2)	2 (0.4)	0
Gastrointestinal disorders	3 (0.2)	0	3 (0.6)	0
General conditions	3 (0.2)	1 (0.2)	0	2 (0.4)
Infections & infestations	3 (0.2)	3 (0.6)	0	0
Injury	3 (0.2)	1 (0.2)	2 (0.4)	0
Musculoskeletal & connective tissue disorders	1 (0.1)	0	1 (0.2)	0
Neoplasms	6 (0.4)	1 (0.2)	3 (0.6)	2 (0.4)
Nervous system disorders	3 (0.2)	0	2 (0.4)	1 (0.2)
Lower respiratory system disorders	42 (2.9)	13 (2.7)	18 (3.7)	11 (2.3)
COPD exacerbation	32 (2.2)	11 (2.3)	13 (2.6)	8 (1.7)
Pneumonia	11 (0.8)	2 (0.4)	5 (1.0)	4 (0.8)
Other respiratory disorders	4 (0.3)	0	3 (0.6)	1 (0.2)
Vascular disorders	2 (0.1)	0	1 (0.2)	2 (0.1)

1 Calculated using total patients of the treatment group as the denominator.
2 MedDRA version 10.1
3 In addition to the 6 deaths occurred during the trial period, there were 4 deaths in pre- or post-treatment period. All deaths were considered by the investigator not related to trial medications.
(Source: Volume 5.19, Section 5.3.5.1, p167-169; Volume 5.20, Section 5.3.5.1, p387-389)

Deaths

As part of the serious adverse events six deaths were reported during the 12-week treatment period of the study (3, 1, and 2 deaths in the Combivent Respimat 20/100 mcg group, Combivent CFC-MDI 36/206 mcg group, and ipratropium Respimat 20 mcg group, respectively). None of the deaths is considered related to study drugs. Brief case descriptions for six deaths are as following.

Combivent Respimat 20/100 mcg group

Patient 48325 was a 73 years old male patient. After receiving the treatment medication Combivent Respimat 20/100 mcg for 62 days, the patient suffered with a pneumonia that resulted in hospitalization fro 4 days. He was treated with antibiotics, corticosteroids, and symptomatic therapy and discharged. Ten days later the patient was re-admitted to the hospital for severe pneumonia. The treatment medication was discontinued at his second hospitalization. The patient died 11 days after the second hospitalization. No autopsy was performed and the cause of death was reported as pneumonia. The clinical monitor and the investigator concluded that this case of death was not related to the trial drug.

Patient 46632 was a 69 years old female patient. The patient experienced an episode of severe COPD exacerbation on the 29th day of receiving Combivent Respimat 20/100 mcg. The trial medication was discontinued at that time and the patient was hospitalized. The Patient then experienced respiratory failure that resulted in death on 18th day of hospitalization. Treatment received included Amoxiclav, Solu-medrol, Isoptin SR. Autopsy was not performed. The clinical monitor and the investigator concluded that this case of death was not related to the trial drug.

Patient 47864 was a 62 years old male patient who was hospitalized for COPD exacerbation after receiving Combivent Respimat 20/100 mcg for 45 days. The patient was admitted to hospital on 16 September 2007 and COPD exacerbation was diagnosed. He was treated with Atrovent, Begalin (Sultamicillin tosylate) and Salospir (aspirin) tablets. Study medication was continued. The patient recovered and was discharged 2 days after the admission. The patient was reported died from unknown cause on 26 days after the discharge. No Autopsy was performed. The investigator and clinical monitor judged the events to be unrelated to the study medication.

Combivent CFC-MDI 36/206 mcg group

Patient 45826 was a 75 years old male patient. The patient was murdered at home by a thief during a robbery on 19th day of receiving Combivent CFC-MDI 36/206 mcg. The cause of dead was traumatic. Autopsy was not performed. The clinical monitor and the investigator concluded that the event was not related to the trial drug.

Ipratropium Respimat 20 mcg group

Patient 43616 was a 64 years old female patient. The patient was admitted into the hospital for stroke evaluation due to gait and strength changes along with poor balance on the 29th day of ipratropium Respimat 20 mcg administration. The patient had also noted a 15-20 pound weight loss in the last six months. Her evaluation included an MRI a CT of the head with findings including metastatic cancer of the brain and numerous largely cystic lesions present throughout the right and left cerebral and cerebellar hemispheres. The event of stroke was ruled out and the events were considered serious. The patient received treatment included dexamethasone and radiation therapy with no significant changes. The patient died 74 days later with the primary diagnosis of malignant brain cancer. No autopsy was performed. The clinical monitor and the investigator concluded that the event was not related to the trial drug.

Patient 45559 was an 86 years old male patient. The patient had noticed blood in the sputum for the past several years. On the 7th day of treatment medication administration the patient was evaluated by a physician due to increased blood in sputum and mild chest pain. Chest X-ray, CT scan, bronchoscopy, and bronchial washing confirmed the diagnosis of small cell carcinoma in the left lung. The patient died 67 days later with the diagnosis of small cell carcinoma. No autopsy will be performed. The clinical monitor and the investigator concluded that the event was not related to the trial drug. The patient had received ipratropium Respimat 20 mcg treatment for 27 days.

In addition to the six deaths during the study period, there were four deaths that occurred either pre- or post-treatment. The post-treatment period was defined as after midnight the day of the last dose of the study drug. One patient (45324) died of a cerebrovascular accident before randomization (pre-treatment) and never received study therapy. Three patients (44145, 44596, and 45593) had an event resulting in death which began post-treatment. Patient 44145, randomized to Combivent CFC-MDI, died of sudden death approximately 3 weeks post last dose of study treatment. Patient 44596, randomized to ipratropium Respimat, had a reported term "death" 2 days after the last day of study drug. Patient 45593, randomized to Combivent CFC-MDI, had a COPD exacerbation which began 2 days post study, and resulted in death 4 days after the start of the COPD exacerbation. These 4 deaths were considered by the investigator not related to the trial drugs.

10.1.1.2.3.3 Clinical Laboratory Evaluation

Clinical laboratory tests were conducted on all patients at the Screening Visit only. Therefore, there are no safety analyses of laboratory values.

10.1.1.2.3.4 ECG, Vital Signs, Physical Findings

ECGs and physical examinations were performed at screening (Visit 1) and the end of the trial (Visit 5), or upon early discontinuation. If there was an abnormal finding on physical exam at screening, it was considered a concomitant diagnosis. If there was an abnormal finding at the end of study, it was considered an adverse event.

Pulse rate and blood pressure were measured in the seated position and recorded at baseline and each test day (Day 1, Day 29, Day 57, Day 85) during first 3 hours at same time intervals as PFT. No clinically significant differences in vital signs and ECGs are identified overall or between the treatment groups.

10.1.1.3 Summary and Conclusion

Study 1012.56 is an efficacy and safety study for Combivent Respimat (20/100 mcg) versus Combivent CFC-MDI (36/206 mcg) and ipratropium Respimat (20 mcg) in patients with chronic obstructive pulmonary disease (COPD). The primary objective of this study is to compare the bronchodilator efficacy and safety of the three treatment medications. The study has three co-primary efficacy endpoint: (1) non-inferiority (between 0-6 hours) of Combivent Respimat

20/100 mcg and Combivent CFC-MDI 36/206 mcg on Day 85, (2) superiority (between 0-4 hours) of Combivent Respimat 20/100 mcg over ipratropium Respimat 20 mcg on Day 85, and (3) non-inferiority (between 4-6 hours) of Combivent Respimat 20/100 mcg over ipratropium Respimat 20 mcg on Day 85. The steady state pharmacokinetic parameters following four weeks of therapy are also evaluated.

A total of 1,480 patients with moderate to severe COPD were randomized into treatment groups in this study. Twenty randomized patients in a French study center were excluded because the accuracy of their recorded data could not be verified. Thus, a total of 1,460 patients received the following three treatments: Combivent Respimat (20/100 mcg) Inhalation Spray (N=486); Combivent CFC-MDI 36/206 mcg (N=491); and ipratropium Respimat 20 mcg (N=483). Overall, 65% and 34.6% of the treated patients are males and females, respectively. In terms of race or ethnic groups, 89% of the patients are white. The African American and Asian are 5.3% and 5.6% of the study patients, respectively. The average age among TS patient population is 64 years, with the range from 40 to 89 years old. Over 50% of the patients are in the range from 40 to 64 years old. The average smoking history is 53 pack-years, and the mean COPD duration is 8.4 years. The three treatment groups are comparable with respect to the baseline demographic characteristics.

The study population is relatively balanced across treatment groups at baseline in the PFT evaluation. The overall mean baseline FEV_1 for the treatment set is 1.144 liters. The ipratropium Respimat 20 mcg group has a slightly lower mean baseline FEV_1 value than that of other two treatment groups (1.117 vs. 1.154 and 1.162, respectively). But the FEV_1 percent to the predicted value is comparable among the three treatment groups. All treatment groups are comparable in baseline FVC value. The overall mean baseline FVC is 2.59 liters, and FEV_1/FVC ratio is approximately 44.8%. The mean reversibility in liters responding to 400 mg albuterol inhalation is similar for the three treatment groups with FEV1 changes of 0.217, 0.216, and 0.217 liters for Combivent Respimat, Combivent CFC-MDI, and ipratropium Respimat, respectively. No differences were observed among treatment groups on reversibility to albuterol inhalation.

The blood of 162 and 102 patient sub-samples from study sites in the United States were collected at Visit 3 (study day-29) for ipratropium and albuterol PK parameter evaluation, respectively. The ipratropium systemic exposure in three treatment groups was comparable, as evaluated by AUC_{0-6}, Cmax. In the 52 patients receiving Combivent Respimat 20/100 mcg, the albuterol AUC_{0-6} and Cmax were approximately 75% of those in the 56 patients receiving Combivent CFC-MDI 36/206 mcg treatment. With the comparable systemic exposure for ipratropium and lower systemic exposure for albuterol comparing to the approved drug product Combivent CFC-MDI, the test drug product Combivent Respimat 20/100 mcg should not pose additional safety problems than the approved and marketed drug product.

The total patient exposure days for Combivent Respimat 20/100 mcg, Combivent CFC-MDI 36/206 mcg, and Ipratropium Respimat 20 mcg were 39091, 39698, and 38093, respectively. The mean and median exposure days for all treatment groups were 80.1 and 85 days, respectively. About 90% of patients in all three treatment groups exposed to the treatment

medication for more 70 days. The exposure to trial medications is adequate to assess the short term safety of the test drug product.

The safety evaluation is performed mainly by adverse events during the treatment period. Vital signs were recorded in conjunction with PFT, and physical examination and ECG were evaluated at the screening and end of the treatment. The abnormal physical examination findings are considered as adverse events. The total patients with adverse events in the study are 691, accounting for 47.3% of the total study population. The overall incidence of adverse events is comparable across the three treatment groups. Serious adverse events (SAEs) occurred in a total of 64 patients (4.4%) across all treatment groups. The highest frequency of SAEs is in the Combivent CFC-MDI 36/206 mcg group (6.7%), followed by the Combivent Respimat 20/100 mcg group (3.5%), and the ipratropium Respimat 20 mcg group (2.9%). The most frequently occurred SAE is COPD exacerbation in all treatment groups. There are six deaths reported as serious adverse events during the 12-week treatment period of the study (3, 1, and 2 deaths in the Combivent Respimat 20/100 mcg group, Combivent CFC-MDI 36/206 mcg group, and ipratropium Respimat 20 mcg group, respectively). It appears that all deaths are not treatment drug related. No clinically significant differences in vital signs and ECGs were identified overall or between the treatment groups.

Three co-primary efficacy endpoints are used to demonstrate the contribution of both components to the efficacy of Combivent Respimat 20.100 mcg. The three co-primary efficacy endpoints are: FEV_1 AUC_{0-6}, FEV_1 AUC_{0-4}, and FEV_1 AUC_{4-6} changes from test-day baseline on study day 85. Combivent Respimat 20/100 mcg group has a mean FEV_1 AUC_{0-6} change from same day baseline of 0.145 liters compared to 0.149 liters for the Combivent CFC-MDI 36/206 mcg group on study day 85. Although the result is slightly in favor of the Combivent CFC-MDI 36/206 mcg group with a difference of 0.003 liters in the mean FEV_1 AUC_{0-6} change from same day baseline, this difference is not statistically significant (95% CI: -0.022 to 0.015 liters). The criterion of non-inferiority has been pre-set as that the 95% confidence interval of the difference for the change in FEV_1 AUC should be no more than 0.05 liters in comparing the two treatments in the trial. The Combivent Respimat 20/100 mcg is considered non-inferior to Combivent CFC-MDI 36/206 mcg, because the difference of the two treatments in mean FEV_1 AUC_{0-6} change is not statistically significant and the 95% confidence interval of the difference is less than 0.05 liters. The Combivent Respimat 20/100 mcg group is statistically superior to the ipratropium Respimat 20 mcg in the mean changes in FEV_1 AUC_{0-4} from test day baseline on test day 85. This result shows the contribution of the albuterol part in the combination product, as demonstrated in the superior mean change in FEV_1 AUC_{0-4} from test day baseline. Albuterol is a short acting β agonist, with its bronchodilation effect persisting for about 3 to 4 hours. The bronchodilation effect measured after 4 hours of the Combivent Respimat 20/100 mcg administration should be comparable to that in the ipratropium Respimat 20 mcg group. The third co-primary efficacy endpoint, the mean change in FEV_1 AUC_{4-6} from test day baseline, demonstrates that the Combivent Respimat 20/100 mcg is non-inferior to the ipratropium Respimat 20 mcg in the mean change in FEV_1 AUC_{4-6} from test day baseline on test day 85.

The Applicant has evaluated a group of the secondary efficacy endpoints for the test drug Combivent Respimat 20/100 mcg, including FEV_1 AUC changes on test days 1, 29, and 57 (AUC_{0-6}, AUC_{0-4}, and AUC_{4-6}), peak FEV_1 response and changes from same day baseline, onset

and duration of therapeutic FEV_1 response, forced vital capacity (FVC) AUC, peak expiratory flow rate (PEFR) measured by the patient at home, rescue albuterol use, weekly means of daily symptom scores over the treatment period, and physician's global evaluation. The overall evaluation of the secondary efficacy endpoints supported the conclusion of primary efficacy endpoint evaluation: the test drug Combivent Respimat 20/100 mcg is comparable (non-inferior) to Combivent CFC-MDI 36/206 mcg. The test drug Combivent Respimat 20/100 mcg is superior within 4 hours post-dosing, and non-inferior during 4 to 6 hours post-dosing to the ipratropium Respimat 20 mcg group, respectively.

Support for the test drug Combivent Respimat (20/100 mcg) Inhalation Spray is clearly demonstrated in the trial 1012.56. The inhalation of Combivent Respimat 20/100 mcg in COPD patients shows comparable bronchodilation effect comparing to Combivent CFC-MDI 36/206 mcg during 0 to 6 hours post-dosing. Comparing to ipratropium Respimat 20 mcg, Combivent Respimat 20/100 mcg is statistically superior during 0 to 4 hours post-dosing and non-inferior during 4 to 6 hours post-dosing.

10.1.2 Study 1012.46

This is a 12-week efficacy and safety study for Combivent Respimat (40/200 mcg) versus Combivent CFC-MDI (36/206 mcg) and Ipratropium Respimat (40 mcg) in patients with chronic obstructive pulmonary disease (COPD).

Table 49 Summary of study 1012.46

Protocol #	1012.46
Title	A comparison of ipratropium bromide/salbutamol delivered by the Respimat inhaler to ipratropium bromide Respimat, Combivent Inhalation Aerosol and placebo of each formulation in a 12-week, double-blind, safety and efficacy study in adults with chronic obstructive pulmonary disease
Study dates	Study initiated: October 16, 2002 Study completed: March 29, 2004 Date of study report: October 15, 2004
Sites	There were 150 study sites across the United States [Volume 5.65, Section 5.3.5.1, pages 28-39]
IRB	A list of 33 Institutional Review Boards (IRB) was provided [Volume 5.69, Section 5.3.5.1, Content 16.1.3.1, pages 1452-1471]. The final original study protocol was approved in writing by the IRBs before enrollment of any subject into the study. Subsequent protocol amendments were also approved by the IRBs.
Ethics	The study report states that the study was performed in compliance with the ethical principles that have their origin in the Declaration of Helsinki (1996 Version), in accordance with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), and in accordance with applicable regulatory requirements.
Source references	Unless otherwise indicated, all source references are to: Study report 1012.46 and related information [Volume 5.65 – 5.75, Section 5.3.5.1]

10.1.2.1 Protocol

10.1.2.1.1 Objectives
The primary objectives: (1) to compare the long-term (12-week) bronchodilator efficacy and safety of ipratropium bromide/salbutamol combination administered by the Respimat inhaler (40 mcg/200 mcg) to Combivent CFC-MDI (36/206 mcg) and Placebo formulations of each in patients with COPD, and (2) to show the superiority of Combivent Respimat as compared to ipratropium bromide (40 mcg) Respimat.

Secondary objectives were not declared in the protocol. However, the steady state pharmacokinetics, at selected centers, after four weeks of dosing was characterized.

10.1.2.1.2 Summary of Study Design
This is a 12-week, randomized, double-blind, five-treatment, placebo- and active-controlled parallel group study.

Following an initial screening, patients entered a 2-week baseline period in which they were given Combivent Inhalation Aerosol. They were instructed to take Combivent Inhalation Aerosol as two actuations, four times per day during the 2-week baseline period. The number of actuations of rescue medication (Ventolin HFA-MDI) and trough PEFR measurements were recorded daily. Patients who successfully completed this phase were randomized into the 12-week double-blind treatment period of the study in which they received one of the five treatments.

Beginning with Visit 2, pulmonary function testing was conducted over an 8-hour period following drug administration. Pulmonary function testing was repeated at the same time intervals every 4 weeks for the next 12 weeks. Trough PEFR, daily symptom scores, adverse events and concomitant therapies were tracked from the screening visit through the end of the treatment period.

10.1.2.1.3 Population
A total of 1118 patients of either sex enrolled in this study. The patients were males or females, 40 years of age or older, and with a diagnosis of COPD.

Inclusion criteria:

- Patients must have a diagnosis of COPD and must meet the following spirometric criteria at Visit 1 (Screening) and Visit 2: Patients must have relatively stable, moderate to severe airway obstruction with pre-bronchodilator FEV_1 ≤65% of predicted normal values and FEV_1/FVC ≤70%.
  - Predicted normal values were calculated by following equations:
    Males: FEV_1 predicted (L) = 0.093 x (height (inch)) - 0.032 x age (yr) – 1.343
    Females: FEV_1 predicted (L) = 0.085 x (height (inch)) - 0.025 x age (yr) - 1.692

- Patients must have a smoking history of more than ten pack-years. A pack-year is defined as the equivalent of smoking one pack of 20 cigarettes per day for a year.

- Patients must be able to perform pulmonary function tests and maintain records during the study period as required in the protocol.
- Patients must be able to be trained in the proper use of an MDI and the Respimat inhaler.
- All patients must sign an Informed Consent Form prior to participation in the trial.

Exclusion criteria:

- Patients with significant diseases other than COPD would 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 relevant abnormal baseline hematology, blood chemistry, or urinalysis. If the abnormality defines a disease listed as an exclusion criterion, the patient is excluded.
- All patients with an AST (SGOT) >80 IU/L, ALT (SGPT) >80 IU/L, bilirubin >2.0 mg/dL or creatinine >2.0 mg/dL will be excluded regardless of the clinical condition. Repeat laboratory evaluation would not be conducted in these subjects.
- Patients who have a total blood eosinophil count $\geq 600/mm^3$. A repeat eosinophil count was not conducted in these patients.
- Patients with a recent history (i.e., one year or less) of myocardial infarction.
- Patients with a recent history (i.e., three years or less) of heart failure or patients with any cardiac arrhythmia requiring drug therapy.
- Patients with a history of cancer, other than treated basal cell carcinoma, within the last five years.
- Patients with a history of life-threatening pulmonary obstruction, or a history of cystic fibrosis or clinically evident bronchiectasis.
- Patients who have undergone thoracotomy with pulmonary resection. Patients with a history of a thoracotomy for other reasons should be evaluated as per exclusion criteria.
- Patients with a history of asthma or allergic rhinitis.
- Patients with a history of and/or active alcohol or drug abuse.
- Patients with known active tuberculosis.
- Patients with an upper or lower respiratory tract infection or COPD exacerbation in the 6 weeks prior to the Screening Visit (Visit 1) or during the baseline period.
- Patients with known symptomatic prostatic hypertrophy or bladder neck obstruction.
- Patients with known narrow-angle glaucoma.
- Patients with current significant psychiatric disorders.
- Patients who regularly use daytime oxygen therapy for more than 1 hour per day and in the investigator's opinion will be unable to abstain from the use of oxygen therapy.
- Use of cromolyn sodium or nedocromil sodium less than 30 days prior to the baseline period or during the treatment period.
- Patients who are being treated with antihistamines for any excluded allergic conditions.
- Patients using oral corticosteroid medication at unstable doses (i.e., less than 6 weeks on a stable dose) or at a dose in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day.

- Initiation of inhaled steroid use, or new dosage, less than 6 weeks prior to the Screening Visit (Visit 1) or during the baseline period.
- Use of β-blocker medications, MAO inhibitors or tricyclic antidepressants less than 30 days prior to the baseline period or during the treatment period. Beta blocker eye medications for treatment of non-narrow angle glaucoma are allowed.
- Patients who have had changes in their therapeutic plan within the last 6 weeks prior to the Screening Visit (Visit 1) or during the baseline period.
- Pregnant or nursing women or women of childbearing potential not using a medically approved means of contraception (i.e., oral or injectable contraceptives, intrauterine devices or diaphragm with spermicide, or Norplant).
- Patients with known hypersensitivity to anticholinergic drugs, any other component of the ipratropium bromide/salbutamol Respimat solution or the ipratropium bromide/salbutamol MDI components.
- Previous participation in this study. (The patient cannot re-enroll into this study.)
- Patients who are currently participating in another study.

10.1.2.1.4 Study Treatment

There were three treatment groups in this study, as listed in Table 50. All patients randomized to a Respimat device were instructed to take one actuation, four times daily at appropriately spaced intervals: upon arising, mid-day, early evening and prior to retiring. All patients randomized to an MDI device were instructed to take two actuations, four times daily at the same spaced intervals.

Table 50 Study treatments, Study 1012.46

Treatment A **Experimental product**	Combivent Respimat 1 puff of ipratropium bromide 40 mcg/albuterol 200 mcg inhalation solution Lot Number: 203156/203157; 4 times daily
Treatment B **Reference Product**	Ipratropium bromide Respimat 1 puff of ipratropium bromide 40 mcg inhalation solution Lot Number: 204143; 4 times daily
Treatment C **Reference Product**	Combivent CFC-MDI 2 puffs of ipratropium bromide 18 mcg/albuterol 103 mcg inhalation aerosol (delivered dose 36/206 mcg) Lot number: PD-2152/PD-2262; 4 times daily
Treatment D **Placebo**	Placebo Respimat 1 puff Lot number: WE0180199/WE02060127; 4 times daily
Treatment E **Placebo**	Placebo MDI 2 puffs Lot number: 203154; 4 times daily

The Applicant stated that the administered dose for the Combivent Respimat (ipratropium 40 mcg/salbutamol 200 mcg) was selected based on the approved dose of presently marketed Combivent CFC-MDI (ipratropium 18 mcg/albuterol 103 mcg per actuation through the mouthpiece, two actuations four times daily). In addition, previous Respimat studies 244.2447 and 243.7 (see reviews in the Appendices below) suggested that the safety and efficacy profiles were comparable between the Respimat device and MDI device in delivering similar doses of ipratropium and albuterol.

10.1.2.1.5 Conduct

Refer to the following flow chart (Table 51) for an overview of procedures to be done at each visit.

Table 51 Study 1012.46 flow chart (Volume 5.65, Section 5.3.5.1, page 67)

Trial period	**Screening**	**Treatment period (week 0 – 12)**			
Visit	1	2	3	4	5
Test day	-	1	2	3	4
Weeks on therapy	-2	0	4	8	12
Day	-14(±5)	1(±5)	29(±5)	57(±5)	85(±5)
Informed consent[1]	X				
Demographics	X				
Medical history	X				
MDI training	X	X			
Respimat inhaler training		X			
Physical examination (with vital signs)	X				X[2]
12-lead ECG	X	X[3]	X[3]		X[2,3]
Laboratory tests (8 hour fasting blood)	X		X		X[2]
Smoking status	X				X[2]
Medication washout/compliance assessment	X	X	X	X	X
Screening PFT (FEV_1 & FVC), seated	X[4]	X[4]			
Reversibility test (albuterol MDI)	X				
Inclusion/exclusion criteria	X	X			
Dispense peak flow meter	X				
Dispense daily patient record	X	X	X	X	
Dispense albuterol MDI	X	X[5]	X[5]	X[5]	
Dispense Combivent MDI	X				
Review PEFR and daily patient records		X	X	X	X
Randomization		X			
Administrate treatment drugs from new inhaler			X	X	X
Administrate treatment drugs from used inhaler		X			
Dispense investigational drugs		X	X	X	
8-hour PFT		X	X	X	X
Vital signs (seated)		X	X	X	X
Plasma sample and urine collection[6]			X		
COPD background characteristics	X				
Physician's global evaluation		X	X	X	X
Adverse events	X	X	X	X	X
Concomitant therapy	X	X	X	X	X
Patient device questionnaire					X
Provider prescribing rating assessment					X

1 Informed consent must be signed prior to participation in the trial, which includes medication washout and restrictions
2 To be completed by all patients including those who discontinue early
3 ECG performed pre-treatment and 1-hour post-treatment
4 FEV_1 must be ≤65% of predicted normal and FEV_1/FVC ≤70%
5 To be dispensed as needed throughout the trial

6 At study sites participating in pharmacokinetic testing
(Source: Volume 5.65, Section 5.3.5.1, page 67)

The initial screening visit would be followed by a 2-week baseline run-in period. All patients would receive Atrovent MDI (2 puffs, four times per day) and salbutamol MDI (used PRN) during the 2-week baseline period. In any country where an HFA formulation is not available, Atrovent CFC-MDI or salbutamol CFC-MDI may be used instead. After the baseline period, patients would be randomized to receive one of five treatments. All patients randomized to a Respimat device were instructed to take one actuation, four times daily at appropriately spaced intervals: upon arising, mid-day, early evening and prior to retiring. All patients randomized to an MDI device were instructed to take two actuations, four times daily at the same spaced intervals.

Visit 2: Patients received new Respimat inhaler and cartridge or MDI according to the randomization codes. Patients would be trained by the research nurse or physician to prime and use the device correctly. The patient received an additional device that was to be used only if necessary, (e.g., the first one malfunctions, is lost or the patient had to schedule the next visit at greater than 30 days).

Visits 3, 4 and 5: Patient returned with the devices that were dispensed at the previous visit. Prior to test-drug administration, a member of the study site staff reviewed the patient diary. Patients would inhale the test drug before pulmonary function testing at this visit. Patients would receive new devices at visit 3 and 4. If the spare device had been used, the patient received a replacement. At the final visit, patients were questioned about their satisfaction with the Respimat or MDI device and their device preference.

Pulse rate and blood pressure were measured and recorded during the first 3 hours at the same time intervals as pulmonary function testing. Measurements were obtained before pulmonary function testing with the patient seated and rested for a minimum of five minutes.

Clinical laboratory tests were conducted on all patients at the Screening Visit (Visit 1), and repeated after 4 weeks of therapy (Visit 3) and at the end of patient participation. Laboratory specimens (blood and urine) were collected in the morning with the patient having fasted for at least 8 hours. The hematology included hemoglobin, hematocrit, erythrocytes, platelets, total leukocyte count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and absolute eosinophil count. The serum chemistry included albumin, alkaline phosphatase, calcium, $C0_2$, chloride, creatinine, glucose, inorganic phosphorus, LDH, potassium, SGOT, SGPT, sodium, total bilirubin, total protein, uric acid and urea nitrogen. The urinalysis included specific gravity, pH, glucose, protein, and hemoglobin. A serum pregnancy test was conducted at the screening visit in all women of child-bearing potential.

A standard 12-lead electrocardiogram (ECG) was performed on all patients at Visit 1 (baseline, and Visit 2, 3, and 5. All test-day ECGs were to be obtained within 5 minutes of the associated PFT.

A complete physical examination was completed on all patients at screening (Visit 1) and repeated at 12 weeks (Visit 5) or at the end of the trial for patients terminating early. Any

abnormal findings at baseline were recorded on the Medical History/Concomitant Diagnoses CRF page. New clinically significant abnormal findings or worsening of baseline conditions detected at follow-up examination were recorded as adverse events on the appropriate CRF page.

Reviewer comment
In this study patients randomized to a Respimat device were instructed to take one actuation, four times daily and patients randomized to an MDI device were instructed to take two actuations, four times daily. This imbalance of actuation numbers for different devices means the study was not 100% blinded between the Respimat and MDI. However, the blindness within formulation was maintained.

10.1.2.1.6 Allowed and Disallowed Medications
Administration of rescue medications can occur during the study period. Information regarding the rescue medication administration (name and dosage of the rescue medication, time of administration) will be recorded on the rescue medication page in the CRF.

The following medications are allowed to control acute exacerbations as medically necessary during the treatment period:

- PRN albuterol inhalation aerosol (MDI) (provided by Boehringer Ingelheim (BI) and to be recorded on the Patient Daily Record)
- Temporary increases in the dose of theophylline preparations of up to 7 days each are allowed during the 12-week study. If the increases or additions occur prior to pulmonary function testing days, the testing would be postponed for at least 2, but not more than 7 days after the last increased or additional dose is given.
- Temporary increases in the dose or addition of, oral steroids of up to 7 days each are allowed during the 12-week study. Pulmonary function testing should not occur within 7 days of the last administered dose of an increase or addition. Pulmonary function testing may be postponed up to 14 days to meet this restriction.
- The use of antibiotics is not restricted and may be used as medically necessary for exacerbations and other infections.

The following medications are allowed if stabilized for at least 6 weeks prior to and throughout the 12 week study period:

- Oral corticosteroids would be allowed only if the patient is stabilized on minimal doses of steroids (i.e., 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.
- Anti-leukotrienes or leukotriene receptor antagonists only if prescribed for conditions other than asthma or excluded allergic conditions.

The following medications are not allowed for at least 48 hours prior to the beginning of the baseline period and not allowed throughout the study period:

- Oral β-adrenergics or long-acting β-adrenergics such as salmeterol (Serevent) and formoterol (Oxis, Foradil)

The following medications are not allowed for at least 1 month prior to the beginning of the baseline period and throughout the study period:

- All other investigational drugs.
- All β-blockers, MAO inhibitors, tricyclic antidepressants
- Cromolyn sodium/nedocromil sodium

The following medications are allowed prior to the study, but not allowed during the baseline period or the treatment period:

- Short-acting anticholinergic drugs including, Atrovent Inhalation Aerosol and Atrovent Inhalation Solution by oral inhalation and for use in treating a common cold, Atrovent Nasal Spray 0.06%
- Additional Combivent Inhalation Aerosol or combination ipratropium bromide/salbutamol sulfate solution for nebulization

10.1.2.1.7 Discontinuations

Randomized patients who fail to complete all test-days and all of the tests in the protocol would not be considered complete, may not be enrolled at a later date and will not be replaced. A record is kept for all patients who fail to complete all test-days and their reasons for discontinuation. A final physical examination would be conducted on all discontinued patients. All safety information collected from discontinued patients would be included in the safety analysis of the study.

10.1.2.1.8 Safety Evaluations

Safety evaluations included (1) all adverse events during the treatment period, (2) pulse rate (PR) and blood pressure (BP) in conjunction with spirometry, (3) physical examination, clinical laboratory tests, and (4) electrocardiogram (ECG).

All adverse events were recorded on the adverse event CRF page after review of the Patient Daily Record and discussions with the patient. Information concerning the onset, duration, intensity, severity, medication taken, action taken with study medication and causality of the adverse event were collected on the CRF page. Information on COPD exacerbations was also reported on the adverse event CRF page.

10.1.2.1.9 Pharmacokinetic Measurements

Approximately 15% of the randomized patients would be designated for pharmacokinetic evaluations. Thirteen study sites completed pharmacokinetic profiling. At Visit 3, blood samples, 10 mL each with heparin, were drawn at trough (pre-treatment), 5, 15,30 and 60 minutes and 2, 4 and 8 hours (second trough) after inhalation of test drug. When applicable, this was done immediately after each corresponding pulmonary function test. Blood samples were placed in ice and centrifuged and plasma aliquots prepared within 30 minutes after blood collection. Total urine over the 8-hour period following the administration of medication on Visit 3 was collected in two fractions: 0 to 2 hours and 2 to 8 hours. Patients were also instructed to collect a pretreatment void prior to dosing. The total volumes of all fractions were determined and recorded.

10.1.2.1.10 Efficacy

Primary Efficacy Endpoints:
The primary criterion for evaluation was the average FEV_1 AUC_{0-6} on test day 85. Pulmonary function test-days were scheduled at screening (Visit 1), at the end of the 2-week baseline period (Visit 2), and every 4 weeks thereafter (Visits 3, 4, and 5). All pulmonary function tests were conducted while the patient was in a seated position. The tests were done in triplicate, and the largest FEV_1 and the largest FVC were recorded.

At Visit 1, all patients would be required to perform a reversibility test using salbutamol MDI. Pulmonary function tests would be conducted in triplicate at baseline and repeated at 30 minutes following four inhalations of salbutamol inhalation aerosol (MDI). The salbutamol MDI used for the reversibility test would be given to the patient for rescue during the 2-week run-in period.

During the pulmonary function test-days on Visits 2-5, FEV_1 and FVC would be obtained at baseline (i.e., pre-treatment, performed 15 ± 10 minutes prior to test drug administration) and be repeated at 5, 15, 30, and 60 minutes and 2, 3, 4, 5, 6, 7 and 8 hours after the drug administration. Measurements from 15 minutes to 2 hours would be performed within ±5 minutes of the specified time points. Measurements made from 3-8 hours would be performed within ± 15 minutes of the scheduled time point.

Secondary Efficacy Endpoints:
FEV_1 AUC on the test days, FVC, patient daily diary, PEFR, rescue medication use, symptom assessments, physician global evaluation.

10.1.2.1.11 Statistical Plan
To demonstrate the efficacy of the ipratropium bromide/salbutamol l40 mcg/200 mcg delivered by the Respimat inhaler over placebo the following null hypotheses was tested using a 2-sided t-test with $\alpha = 0.05$: no difference in mean response between patients treated with ipratropium bromide/salbutamol 40 mcg/200 mcg delivered by the Respimat inhaler and patients treated with placebo after 12 weeks of treatment.

To establish the superiority of ipratropium bromide/salbutamol 40 mcg/200 mcg delivered by the Respimat inhaler over ipratropium bromide (40 mcg) delivered by the Respimat inhaler the following null hypotheses was tested using a 2-sided t-test with $\alpha = 0.05$: no difference in mean response between patients treated with ipratropium bromide/salbutamol 40 mcg/200 mcg delivered by the Respimat inhaler and patients treated with ipratropium bromide (40 mcg) delivered by the Respimat inhaler after 12 weeks of treatment.

In addition, a test was performed with Combivent Inhalation Aerosol versus placebo to validate the trial. The comparability of ipratropium bromide/salbutamol 40 mcg/200 mcg delivered by the Respimat inhaler and Combivent Inhalation Aerosol was determined based on clinical judgment and not by formal tests of hypotheses.

Safety analyses were descriptive.

It estimated that the standard deviation for FEV_1 AUC_{0-6} ranged from 160 mL to 215 mL. It was expected that if there was no difference between the ipratropium bromide/salbutamol 40 mcg/200 mcg delivered by the Respimat inhaler and the Combivent inhalation aerosol groups, with 300 patients randomly assigned to ipratropium bromide/salbutamol 40 mcg/200 mcg delivered by the Respimat inhaler and 150 patients to Combivent inhalation aerosol, there was a 98% chance that the mean difference between them did not exceed 50 mL (with 215 mL for standard deviation). A total of 300 patients were required in the arm for ipratropium bromide/salbutamol 40 mcg/200 mcg delivered by the Respimat inhaler for collecting adequate safety data. The mean difference between the active groups and placebo was expected to be approximately 150 mL. The power to detect this difference exceeds 99%. To detect a 50 mL difference in mean between ipratropium bromide/salbutamol 40 mcg/200 mcg delivered by the Respimat inhaler (n=300) and ipratropium bromide (40 mcg) delivered by the Respimat inhaler (n=225) at 5% level of significance, the power is 74% with 215 mL standard deviation and 94% with 160 mL standard deviation.

10.1.2.2 Results

10.1.2.2.1 Description of the Study Population
A total of 1118 patients were randomized and took at least one dose of study medication. There were 345 patients in the Combivent Respimat 40/200 mcg group, 180 patients in the Combivent CFC-MDI 36/206 mcg group, 165 in the placebo Respimat group, 176 in the placebo CFC-MDI group and 252 patients in the ipratropium Respimat 40 mcg group. The randomization ratio was 4:3:2:2:2 for Combivent Respimat 40/200: ipratropium Respimat 40: Combivent CFC-MDI 36/206: placebo Respimat: placebo CFC-MDI.

Four analysis sets were created. The PFT full analysis data set (FAS) included all randomized patients who took study medication and had adequate baseline measurements and had at least six out of seven time point data within the first three hours after the administration of study medication on any of the test days (Days 1, 29, 57 or 85). With this definition, eight patients were excluded from the FAS_PFT due to fewer than 6 data points within the first three hours on any test days. Two patients were excluded from FAS_PFT due to invalid baseline values. The total number of patients included in the FAS_PFT was 1108, approximately 99% of the total treated patients.

Table 52 summarizes the study population, the demographics and baseline characteristics of the patient population. The demographic information was comparable across treatment groups. Overall, 65% of the patients were male, over 90% of the patients were white. The average age was 64.2 years, the mean COPD duration was 9.3 years. All treatment groups were comparable in screening FEV_1 and FVC. The overall mean FEV_1 was 1.13 liters, the percent of predicted FEV_1 was 41.6%. The mean FVC was 2.34 1iters, the FEV_1/ FVC was approximately 48.4%.

Table 52 Patient population, the demographics and baseline characteristics

Patient population	Total N (%)	Combivent Respimat 40/200 N (%)	Combivent MDI 36/206 N (%)	Ipratropium Respimat 40 N (%)	Placebo (Respimat&MDI) N (%)
Randomized	1118	345	180	252	341
PFT full analysis set (FAS PFT)	1108 (99.1)*	343 (99.4)*	180 (100)*	250 (99.2)*	335 (98.2)*
Sex Male	727 (65.0)	226 (65.5)	105 (58.3)	162 (64.3)	234 (68.6)
Female	391 (35.0)	119 (34.5)	74 (41.7)	90 (35.7)	107 (31.4)
Race White	1034 (92.5)	312 (90.4)	169 (93.9)	233 (92.5)	320 (93.8)
Black	82 (7.3)	32 (9.3)	11 (6.1)	19 (7.5)	21 (5.9)
Asian	1 (0.2)	1 (0.3)	0	0	1 (0.3)
Age (yrs) Mean	64.2	64.6	63.8	64.0	64.1
SD	9.3	9.2	8.7	9.3	9.6
Smoking history					
Ex-smoker	623 (55.7)	185 (54.5)	92 (51.1)	153 (60.7)	190 (55.7)
Current smoker	495 (44.3)	157 (45.5)	88 (48.9)	99 (39.3)	151 (44.3)
Smoking history (pack-years) Mean	58.8	58.2	59.0	58.7	59.4
SD	32.7	31.1	30.0	31.7	36.2
COPD duration (yrs) Mean	9.26	9.44	8.82	9.00	9.51
SD	7.78	7.77	7.68	7.56	8.03
Screening FEV_1 (L) Mean	1.126	1.130	1.116	1.120	1.132
SD	0.443	0.437	0.428	0.447	0.455
% predicted FEV_1 Mean	41.553	41.732	41.749	41.458	41.3340
SD	13.673	13.284	13.346	13.807	14.178
FEV_1/FVC (%) Mean	48.391	48.655	48.677	48.625	47.801
SD	11.130	10.740	11.370	11.263	11.317

* Percent of the randomized population. (Source: Volume 5.65, Section 5.3.5.1, p 93-95)

10.1.2.2.2 Protocol Deviations and Compliance

Patients excluded from the PFT FAS and patients with important protocol violations were excluded from the per-protocol set (PPS). In total, 20 patients (1.8%) had an $FEV_1 > 65\%$ of the predicted normal. Eight patients (0.7%) had a $FEV_1/FVC > 70\%$ which was a violation of the protocol specified limit. Eighteen patients (1.6%) had baseline blood eosinophil value $\geq 600/mm^3$. There were 1073 patients included in PPS, approximately 97% of the patients included in the FAS_PFT.

Patient compliance was evaluated by monitoring the weekly mean number of actuations of study medication per day during the treatment period. The Overall mean number of actuations of study medication taken per day for all the Respimat groups was 4.0. The overall mean number of actuations of study medication taken per day was 7.5 for the CVT CFC-MDI 36/206 group and 7.7 for the placebo CFC-MDI group.

10.1.2.2.3 Efficacy

The primary efficacy endpoint was FEV_1 AUC_{0-6} on Test Day 85. AUC_{0-6} was defined as the total area under the response curve above zero and from zero to six hours divided by six hours.

The FEV_1 AUC_{0-6} for each treatment group is shown in Table 53. All three active treatment groups show significantly greater FEV_1 AUC_{0-6} values on test day 85 when compared to the placebo group ($p<0.001$). The differences of FEV_1 AUC_{0-6} among the three active treatment groups are not statistically significant. On test day 85, the FEV_1 AUC_{0-6} value of ipratropium Respimat 40 mcg group is numerically greater than that of Combivent Respimat 40/200 mcg and Combivent CFC-MDI 36/206 mcg groups.

Table 53 FEV_1 AUC_{0-6} (liters) on test days

	Combivent Respimat 40/200 mcg N=343		Combivent CFC-MDI 36/206 mcg N=180		Ipratropium Respimat 40 mcg N=250		Placebo (Respimat plus CFC-MDI) N=335	
FEV_1 value	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Day 1	1.329	0.009	1.299	0.013	1.255	0.011	1.121*	0.010
Day 29	1.306	0.011	1.276	0.016	1.292	0.013	1.132*	0.012
Day 57	1.288	0.012	1.276	0.017	1.294	0.014	1.147*	0.012
Day 85	1.281	0.013	1.262	0.017	1.291	0.015	1.148*	0.013

* The placebo group has significantly lower FEV_1 AUC_{0-6} than all three active treatment groups on all test days ($p<0.0001$).

Reviewer comment
In the statistical plan for the evaluation of the primary efficacy endpoint (10.1.2.1.11), two null hypotheses were pre-set for this trial: (1) no difference in mean response between patients treated with ipratropium bromide/salbutamol 40 mcg/200 mcg delivered by the Respimat inhaler and patients treated with placebo after 12 weeks of treatment, and (2) no difference in mean response between patients treated with ipratropium bromide/salbutamol 40 mcg/200 mcg delivered by the Respimat inhaler and patients treated with ipratropium bromide (40 mcg) delivered by the Respimat inhaler after 12 weeks of treatment. The first null hypothesis is rejected at the level of $p<0.0001$. It means that Combivent Respimat 40/200 mcg is superior to placebo. The second null hypothesis is not rejected. It means that Combivent Respimat 40/200 mcg is not superior to single ingredient ipratropium Respimat 40 mcg in COPD treatment. Furthermore, Combivent Respimat 40/200 mg is even numerically inferior to the single ingredient ipratropium Respimat 40 mcg as evaluated by the FEV_1 AUC_{0-6} value on test day 85.

Figure 9 displays the mean FEV_1 time profile from 0 to 8 hours post-dosing for active treatment and placebo groups on all test days. The mean FEV_1 time profile on test day 85 demonstrates (1) all three active treatment groups have greater mean FEV_1 values during 0 to 6 hours post-dosing compared with placebo group; (2) starting at 4 hours post-dosing, ipratropium Respimat 40 mcg group shows a better mean FEV_1 value than Combivent Respimat 40/200 mcg and Combivent CFC-MDI 36/206 mcg groups and this better effect appears increasing along the time during the 4 to 8 hours post-dosing period.

The Applicant also evaluated FEV_1 AUC_{6-8} values for all treatment groups. The FEV_1 AUC_{6-8} was defined as the total area under the response curve above zero and from hour 6 to hour 8 divided by two hours. On Test Day 1, all active treatment groups demonstrated significantly larger FEV_1 AUC_{6-8} values than the placebo group. On Test Days 29, 57 and 85, only the ipratropium Respimat 40 mcg group demonstrated significantly larger FEV_1 AUC_{6-8} than the

placebo group. The Combivent Respimat 40/200 mcg and Combivent CFC-MDI 36/206 mcg groups were comparable in FEV_1 AUC_{6-8} on all test days. The Combivent Respimat 40/200 mcg group presented comparable FEV_1 AUC_{6-8} on Test Day 1 and inferior FEV_1 AUC_{6-8} values on Test Days 29, 57 and 85 to the ipratropium Respimat 40 mcg group.

The secondary efficacy evaluations demonstrate that three active treatment groups are superior to the placebo group and those secondary efficacy endpoints are largely comparable between three active treatment groups.

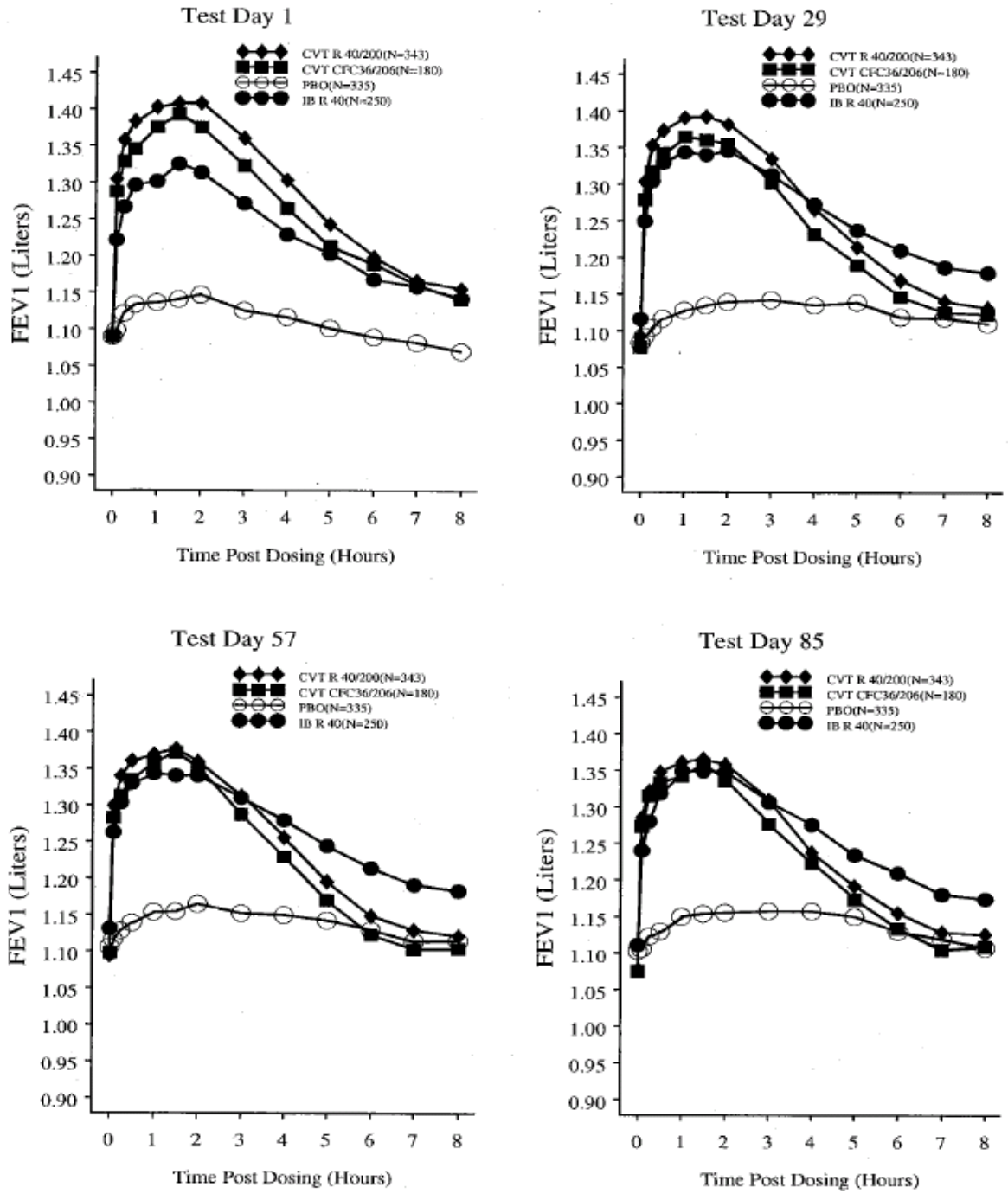


Figure 9 Mean FEV_1 time profile from 0 to 8 hours post-dosing on all test days, study 1012.46

10.1.2.2.4 Safety

10.1.2.2.4.1 Exposure
A total of 1,118 patients were randomized and received at least one dose of study medication.

A total of 345 patients received Combivent Respimat 40/200 mcg, 252 patients received ipratropium Respimat 40 mcg and 180 patients received Combivent CFC-MDI 36/206 mcg. One hundred sixty-five patients received Respimat placebo and 176 patients received Placebo CFC-MDI. The mean exposure for all five groups was 78.9 days; the median exposure was 85 days. The active Combivent groups had very similar exposure. The ipratropium Respimat group had the highest mean exposure of 83.3 days and the Placebo Respimat group had the lowest mean exposure of 72.1 days. The exposure to trial medications is considered adequate to assess the safety and efficacy. Table 54 summarizes the duration of exposure by treatment group.

Table 54 Exposure to trial medications

Exposure	Total (%)	CVT Respimat 40/200 N (%)	CVT CFC-MDI 36/206 N (%)	Ipratr. Respimat 40 N (%)	Placebo Respimat N (%)	Placebo MDI N (%)
Total treated patients	1118	345	180	252	165	176
Treatment duration: days (%)						
1 -14 days	46 (4.1)	13 (3.8)	2 (1.1)	2 (0.8)	14 (8.5)	15 (8.5)
15-42 days	63 (5.6)	14 (4.1)	12 (6.7)	8 (3.2)	18 (10.9)	11 (6.3)
43-70 days	36 (3.2)	10 (2.9)	7 (3.9)	8 (3.2)	7 (4.2)	4 (2.3)
≥70 days	973 (87.0)	308 (89.3)	159 (88.3)	234 (92.9)	126 (76.4)	146 (83.0)
Exposure (days) Mean	78.9	79.8	80.9	83.3	72.1	75.2
SD	21.7	20.0	17.8	14.5	28.9	26.9
Median	85	85	85	85	85	85

(Source: Volume 5.65, Section 5.3.5.1, p134)

10.1.2.2.4.2 Adverse Events

The terms used to report adverse events were classified using the MedDRA 7.0. The overall summary of adverse events is detailed in Table 55. Adverse events were experienced by 528 patients (47.2%) during the trial. Thirty-three patients (3%) experienced at least one serious adverse event (SAE) and there was one death reported during the study. A total of 65 patients (5.8%) experienced an adverse event which resulted in discontinuation from the study medication.

The most frequently occurring adverse events in this study population were respiratory events. Bronchitis, COPD exacerbation, cough, dyspnea, pharyngitis and upper respiratory infection were the most frequently occurring respiratory events. The most commonly occurring adverse event was COPD exacerbation in 100 patients (8.9%). In the active treatment groups, 34 patients (9.9%) in the Combivent Respimat group experienced a COPD exacerbation as compared to 12 patients (6.7%) in the Combivent CFC-MDI group. Lower respiratory system disorders were higher in the Combivent Respimat group (22.3%) as compared to the Combivent CFC-MDI group (16.7%). Upper respiratory system disorders were almost identical between the Combivent Respimat group (16.2%) and the Combivent CFC-MDI group (16.1 %). For other respiratory events, the incidences were fairly consistent across the active treatment groups. The incidence of headache was greater than three percent in every group, except the ipratropium Respimat group, in which it occurred in 5 patients (2.0%). For the other groups, the number of patients with headache was: 11 (3.2%) in the Combivent Respimat group, 6 (3.3%) in the Combivent CFC-MDI group, 9 (5.5%) in the Placebo Respimat group and 9 (5.1 %) in the Placebo CFC-MDI group.

Table 55 Adverse event frequency and percentage in preferred terms[1] by treatment groups

Adverse event	Total (%)	CVT Respimat 40/200 N (%)	CVT MDI 36/206 N (%)	Ipratr. Respimat 40 N (%)	Placebo Respimat N (%)	Placebo CFC-MDI N (%)
Total treated patients	1118	345	180	252	165	176
Patients with AEs	528 (47.2)	167 (48.4)	74 (41.1)	121 (48.0)	87 (52.7)	79 (44.9)
Patients with AEs leading to withdrawal	65 (5.8)	21 (6.1)	7 (3.9)	7 (2.8)	17 (10.3)	13 (7.4)
Patient with SAEs	33 (3.0)	8 (2.3)	3 (1.7)	9 (3.6)	4 (2.4)	9 (5.1)
Death during the trial	1 (0.1)	1 (0.3)	0	0	0	0
Nervous system disorders	73 (6.5)	20 (5.8)	12 (6.7)	12 (4.8)	17 (10.3)	12 (6.8)
Dizziness	17 (1.5)	2 (0.6)	3 (1.7)	4 (1.6)	7 (4.2)	1 (0.6)
Headache	40 (3.6)	11 (3.2)	6 (3.3)	5 (2.0)	9 (5.5)	9 (5.1)
Lower respiratory system disorders	235 (21.0)	77 (21.3)	30 (16.7)	49 (19.4)	47 (28.5)	32 (18.2)
Bronchitis	44 (3.9)	14 (4.1)	7 (3.9)	12 (4.8)	6 (3.6)	5 (2.8)
COPD exacerbation	100 (8.9)	34 (9.9)	12 (6.7)	21 (8.3)	20 (12.2)	13 (7.4)
Cough	30 (2.7)	8 (2.3)	5 (2.8)	6 (2.4)	7 (4.2)	4 (2.3)
Dyspnea	51 (4.1)	14 (4.1)	8 (4.4)	7 (2.8)	15 (9.1)	7 (4.0)
Upper respiratory system disorders	171 (15.2)	56 (16.2)	29 (16.1)	42 (16.7)	19 (11.5)	25 (14.2)
Pharyngitis	46 (4.1)	13 (3.8)	8 (4.4)	14 (5.6)	3 (1.8)	8 (4.5)
Upper respiratory tract inf.	56 (5.0)	20 (5.8)	10 (5.6)	15 (6.0)	6 (3.6)	5 (2.8)

1 MedDRA version 7.0. (Source: Volume 5.65, Section 5.3.5.1, p136, 138)

Reviewer comment
The test drug, Combivent Respimat 40/200 mcg has adverse event profile and incidence comparable to other two active treatment groups and to placebos. There is no new safety signal revealed for the test drug.

Adverse Events Leading to Discontinuation of the Trial

A total of 65 patients (5.8%) experienced an adverse event which resulted in discontinuation from the study medication. The Combivent Respimat group had 21 patients (6.1%) discontinue due to an adverse event and the Combivent CFC-MDI group had 7 patients (3.9%) discontinue due to an adverse event. The Placebo Respimat group had the highest incidence with 17 patients (10.3%) discontinued the trial due to an adverse event. The Placebo CFC-MDI group had 13 patients (7.4%) discontinue due to an adverse event. The ipratropium Respimat group had the lowest incidence of discontinuation due to an adverse event in 7 patients (2.8%).

Lower respiratory system disorders were the most common events leading to discontinuation in 51 patients (4.6%). COPD exacerbation was the most common AE within the lower respiratory system disorders causing discontinuation and was reported by 25 patients (2.2%). The 25 patients were divided among the groups as follows: the Combivent Respimat group had 11 patients (3.2%), the Combivent CFC-MDI group had 3 patients (1.7%), the ipratropium Respimat group had 1 patient (0.4%), the Placebo Respimat group had 5 patients (3.0%), and the Placebo CFC-MDI group had 5 patients (2.8%). Dyspnea was reported to be the AE leading to discontinuation in 18 patients (1.6%). The Placebo Respimat group had the highest

discontinuation rate due to dyspnea (7 patients, 4.2%) and ipratropium Respimat group had the lowest discontinuation rate due to dyspnea (1 patient, 0.4%).

Death
One death (gastrointestinal hemorrhage) occurred during the study to a patient randomized to the Combivent Respimat group. The patient (41791) was on study medication for 46 days. This 77 years old female patient was randomized to Combivent Respimat 40/200 mcg group on 28 March 2003. On (b) (6) the patient experienced an acute GI bleed and died. The patient received unspecified treatment for the event. The patient was concomitantly on aspirin, Fosamax and ibuprofen.

Another patient's death (41656) was reported by the field monitor approximately six months after the patient had dropped out of the study due to the complain of shortness of breath. This patient had been randomized to the Combivent Respimat group 40/200 mcg group and was on the study medication for only 6 days. The reported cause of death was a mass in the anterior left lateral ascending aorta.

Reviewer comment
It appears that the 2 death cases are not test medication related.

Other Serious Adverse Events
Thirty-three patients (3.0%) experienced a serious adverse event (SAE) during the 12-week treatment period of the trial. Three patients reported an SAE during the screening period and went on to successfully complete the study. Eleven patients reported an SAE during the post-study period.

Serious adverse events occurred in similar rates across treatment groups and there were no events occurring in more than 1 % of the overall study population. The highest incidence of SAEs occurred in the placebo groups: 2.4% in the Placebo Respimat group and 5.1 % in the Placebo CFC-MDI group. In the active treatment groups, the ipratropium Respimat group has the highest incidence of SAEs (3.6%) as compared to 2.3% in the Combivent Respimat group and 1.7% in the Combivent CFC-MDI group. None of the SAEs, including the death, were considered to be related to treatment by the investigator.

COPD exacerbations were the most commonly reported SAE in 10 patients (0.9%). The Combivent Respimat group had 4 patients (1.2%) with a COPD exacerbation and the ipratropium Respimat group had 3 patients (1.2%) with a COPD exacerbation that were reported as SAEs. The other three COPD exacerbations reported as SAEs were in the Combivent CFC-MDI group (1 patient, 0.6%) and the Placebo CFC-MDI groups (2 patients, 1.1 %).

10.1.2.2.4.3 Clinical Laboratory Evaluation
Clinical laboratory tests were conducted on all patients at the Screening Visit (Visit 1), and repeated after four weeks of therapy (Visit 3) and at the end of patient participation. Laboratory specimens (blood and urine) were collected in the morning with the patient having fasted for at least 8 hours. The hematology included hemoglobin, hematocrit, erythrocytes, platelets, total leukocyte count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and

basophils), and absolute eosinophil count. The serum chemistry included albumin, alkaline phosphatase, calcium, CO2, chloride, creatinine, glucose, inorganic phosphorus, LDH, potassium, SGOT, SGPT, sodium, total bilirubin, total protein, uric acid and urea nitrogen. The urinalysis included specific gravity, pH, glucose, protein, and hemoglobin. The results of clinical laboratory tests do not indicate any clinically relevant differences among the treatment groups.

10.1.2.2.4.4 Vital Signs, Physical Examination, ECG
Pulse rate and blood pressure were measured and recorded during the first 3 hours at the same time intervals as pulmonary function testing. Measurements were obtained before pulmonary function testing with the patient seated and rested for a minimum of five minutes. No clinically significant differences in vital signs were identified between the treatment groups.

A complete physical examination was completed on all patients at screening (Visit 1) and repeated at 12 weeks (Visit 5) or at the end of the trial for patients terminating early. Any abnormal findings at baseline were recorded on the Medical History/Concomitant Diagnoses CRF page. New clinically significant abnormal findings or worsening of baseline conditions detected at follow-up examination were recorded as adverse events on the appropriate CRF page. There were no clinically significant differences of physical examinations between treatment groups.

A standard 12-lead electrocardiogram (ECG) was performed on all patients at Visit 1 (Screening), and Visit 2, 3 and 5. All test-day ECGs were obtained within 5 minutes of the associated PFT. An outside expert analyzed the ECG data and concluded that there was no evidence of any clinically relevant ECG effects.

10.1.2.3 Summary and Conclusion

Study 1012.46 is an efficacy and safety study for Combivent Respimat (40/200 mcg) versus Combivent CFC-MDI (36/206 mcg) and ipratropium Respimat (40 mcg) in patients with chronic obstructive pulmonary disease (COPD). The primary objectives of this study was (1) to compare the bronchodilator efficacy and safety of ipratropium bromide/salbutamol combination administered by the Respimat inhaler (40 mcg/200 mcg) to Combivent CFC-MDI (36/206 mcg) and Placebo formulations in patients with COPD, and (2) to show the superiority of Combivent Respimat 40 mcg/200 mcg as compared to ipratropium Respimat 40 mcg. The steady state pharmacokinetics over one dosing interval following four weeks of therapy was also investigated.

A total of 1,118 patients with moderate to severe COPD were randomized and received treatment: 345 to the Combivent Respimat 40/200 mcg group, 252 to the Combivent CFC-MDI 36/206 mcg group, and 180 to the ipratropium Respimat 40 mcg group. One hundred sixty-five patients received Respimat placebo and 176 patients received Placebo CFC-MDI. Overall, 65% and 35% of the treated patients are males and females, respectively. In terms of race or ethnic groups, over 90% of the patients are white. The African Americans and Asian account 7.3% and 0.2% of the study patients, respectively. The average age among the patient population is 64.2 years. The average smoking history is 58.2 pack-years, and the mean COPD duration is 9.3

years. The five treatment groups are comparable with respect to the baseline demographic characteristics.

The mean exposure for all five groups was 78.9 days; the median exposure was 85 days. The active Combivent groups had very similar exposure. The ipratropium Respimat group had the highest mean exposure of 83.3 days and the Placebo Respimat group had the lowest mean exposure of 72.1 days. The exposure to trial medications is considered adequate to assess the safety and efficacy.

The safety evaluation is performed mainly by adverse events during the treatment period. Clinical laboratory tests were conducted on all patients at the Screening Visit (Visit 1), and repeated after four weeks of therapy (Visit 3) and at the end of patient participation. Vital signs were recorded in conjunction with PFT. Physical examinations were evaluated at the screening and end of the treatment. The abnormal physical examination findings are considered as adverse events. ECG was performed on all patients at Visit 1 (Screening), and Visit 2, 3 and 5. The total patients with adverse events in the study are 528, accounting for 47.2% of the total study population. The overall incidence of adverse events is comparable across the three treatment groups. Serious adverse events (SAEs) occurred in a total of 33 patients (3%) across all treatment groups. The highest frequency of SAEs is in the placebo CFC-MDI group (5.1%). The most frequently occurred SAE is COPD exacerbation in all treatment groups (10 patients, 0.9%). One death (gastrointestinal hemorrhage) occurred during the 12-week treatment period to a patient randomized to the Combivent Respimat group. It appears that the death was not treatment drug related. No clinically significant differences in vital signs and ECGs were identified overall or between the treatment groups.

The primary efficacy endpoint was FEV_1 AUC_{0-6} on Test Day 85. All three active treatment groups show significantly greater FEV_1 AUC_{0-6} values on test day 85 when compared to the placebo group ($p<0.001$). The differences of FEV_1 AUC_{0-6} among three active treatment groups are not statistically significant. On test day 85, the FEV_1 AUC_{0-6} value of ipratropium Respimat 40 mcg group is numerically greater than that of Combivent Respimat 40/200 mcg and Combivent CFC-MDI 36/206 mcg groups. The mean FEV_1 time profile on test day 85 demonstrates that all three active treatment groups have greater mean FEV_1 values during 0 to 6 hours post-dosing compared with placebo group, and starting at 4 hours post-dosing, ipratropium Respimat 40 mcg group shows a better mean FEV_1 value than Combivent Respimat 40/200 mcg and Combivent CFC-MDI 36/206 mcg groups and this better FEV_1 value appears increasing along the time during the 4 to 8 hours post-dosing period.

The Applicant has evaluated a group of the secondary efficacy endpoints for the test drug Combivent Respimat 40/200 mcg, including FEV_1 AUC on all test days, FVC, patient daily diary, PEFR, rescue medication use, symptom assessment, and physician's global evaluation. The overall evaluation of the secondary efficacy endpoints demonstrate that the three active treatment groups are superior to the placebo group and those secondary efficacy endpoints are largely comparable between the three active treatment groups.

In conclusion, there is no new safety signals revealed for the test drug Combivent Respimat 40/200 mcg in this 12-week study. The Combivent Respimat 40/200 mcg appears to be safe to

the study patients with COPD. However, the efficacy of the test drug is not supported by study 1012.46. The results of the study failed to demonstrate that the Combivent Respimat 40/200 mcg is superior to the single ingredient ipratropium Respimat 40 mcg as evaluated by the primary efficacy endpoint FEV_1 AUC_{0-6} on test day 85.

10.1.3 Study 244.2447

This is a dose ranging study to characterize the dose response profile of single inhalations of ipratropium bromide delivered as an aqueous solution via the Respimat device in patients with chronic obstructive pulmonary disease (COPD).

Table 56 Summary of study 244.2447

Protocol #	244.2447
Title	A dose ranging study of ipratropium bromide inhalation solution delivered via the Respimat device
Study dates	Study initiated: December 28, 1995 Study completed: September 24, 1996 Date of study report: July 31, 1997
Sites	There were 5 study sites in the United States
IRB	A list of two Institutional Review Boards (IRB) is provided [Volume 5.11, Section 5.3.5.1, Content 16.1.3, pages EC1 – EC9]. The two IRBs covered five study sites. The final original study protocol was approved in writing by the IRBs before enrollment of any subject into the study. Subsequent protocol amendment was also approved by the IRBs.
Ethics	The study report states that the study was performed in compliance with the ethical principles that have their origin in the Declaration of Helsinki (1975 Version), in accordance with the Good Clinical Practice (GCP), and in accordance with applicable regulatory requirements.
Source references	Unless otherwise indicated, all source references are to: Study report 244.2447 and related information [Volume 5.10 – 5.13, Section 5.3.4.2]

10.1.3.1 Protocol

10.1.3.1.1 Objectives
The objective of this study was to characterize the dose response profile of single inhalations of ipratropium bromide delivered as an aqueous solution via the Respimat device in patients with chronic obstructive pulmonary disease (COPD) and to indentify the ipratropium Respimat doses which were superior to placebo and which produced comparable bronchodilation effects to Atrovent Inhalation Aerosol (36 mcg, two inhalations of 18 mcg each).

10.1.3.1.2 Summary of Study Design
This is a single dose, randomized, double-blind, placebo-controlled, 8-treatment, 4-period incomplete crossover study.

After the initial screening visit, the patients will be randomized to receive one of eight treatments. The patient will be crossed over to another treatment according to the randomization code after a washout period of 3-7 days. Each patient will receive 4 treatments in this study.

10.1.3.1.3 Population
The Applicant originally planned a sample size of 56 patients for this study. In a protocol amendment prior to the study, the sample size was increased from 56 to 112 patients to assure approximately 90% probability of declaring a true equivalent dose to Atrovent 36 mcg.

Inclusion criteria:

- Patients must have a diagnosis of COPD and must meet the following spirometric criteria at Visit 1 (Screening) and Visit 2: Patients must have relatively stable, moderate to severe airway obstruction with pre-bronchodilator FEV_1 ≤65% of predicted normal values and FEV_1/FVC ≤70%.

    - Predicted normal values were calculated by following equations:
    Males: FEV_1 predicted (L) = 0.093 x (height (inch)) - 0.032 x age (yr) – 1.343
    Females: FEV_1 predicted (L) = 0.085 x (height (inch)) - 0.025 x age (yr) - 1.692

- Patients improve in FEV_1 ≥ 15% within one hour after the inhalation of 36 mcg ipratropium bromide from an MDI device (reversibility test).
- Patients must be 40 years of age or older, having a smoking history of more than ten pack-years. A pack-year is defined as the equivalent of smoking one pack of 20 cigarettes per day for a year.
- Patients must be able to perform pulmonary function tests and maintain records during the study period as required in the protocol.
- Patients must be able to be trained in the proper use of an MDI and the Respimat inhaler.
- All patients must sign an Informed Consent Form prior to participation in the trial.

Exclusion criteria:

- Patients with significant diseases other than COPD would 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 relevant abnormal baseline hematology, blood chemistry or urinalysis. If the abnormality defines a disease listed as an exclusion criterion, the patient is excluded.
- All patients with an AST (SGOT) >80 IU/L, ALT (SGPT) >80 IU/L, bilirubin >2.0 mg/dL or creatinine >2.0 mg/dL will be excluded regardless of the clinical condition. Repeat laboratory evaluation would not be conducted in these subjects.
- Patients with a history of asthma, allergic rhinitis or atopy or who have a total blood eosinophil count ≥600/mm^3. A repeat eosinophil count was not conducted.
- Patients with a recent history (i.e., one year or less) of myocardial infarction.
- Patients with a history of cancer, other than treated basal cell carcinoma, within the last five years.

- Patients with a history of life-threatening pulmonary obstruction, or a history of cystic fibrosis or clinically evident bronchiectasis.
- Patients who have undergone thoracotomy with pulmonary resection. Patients with a history of a thoracotomy for other reasons should be evaluated as per exclusion criteria.
- Patients with a history of and/or active alcohol or drug abuse.
- Patients with known active tuberculosis.
- Patients with an upper or lower respiratory tract infection or COPD exacerbation in the 6 weeks prior to the Screening Visit (Visit 1) or during the baseline period.
- Patients with known symptomatic prostatic hypertrophy or bladder neck obstruction.
- Patients with known narrow-angle glaucoma.
- Patients with current significant psychiatric disorders.
- Patients who regularly use daytime oxygen therapy for more than 1 hour per day and in the investigator's opinion will be unable to abstain from the use of oxygen therapy.
- Use of cromolyn sodium or nedocromil sodium less than 30 days prior to the baseline period or during the treatment period.
- Patients who are being treated with antihistamines for any excluded allergic conditions.
- Patients using oral corticosteroid medication at unstable doses (i.e., less than 6 weeks on a stable dose) or at a dose in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day.
- Initiation of inhaled steroid use, or new dosage, less than 6 weeks prior to the Screening Visit (Visit 1) or during the baseline period.
- Use of β-blocker medications, MAO inhibitors or tricyclic antidepressants less than 30 days prior to the baseline period or during the treatment period. Beta blocker eye medications for treatment of non-narrow angle glaucoma are allowed.
- Patients who have had changes in their therapeutic plan within the last 6 weeks prior to the Screening Visit (Visit 1) or during the baseline period.
- Pregnant or nursing women or women of childbearing potential not using a medically approved means of contraception (i.e., oral or injectable contraceptives, intrauterine devices or diaphragm with spermicide, or Norplant).
- Patients with known hypersensitivity to anticholinergic drugs, any other component of the ipratropium bromide/salbutamol Respimat solution or the ipratropium bromide/salbutamol MDI components.

10.1.3.1.4 Study Treatment

There are eight treatment groups in this study, as listed in Table 57. All treatments are administered through oral inhalation.

Table 57 Study treatments, study 244.2447

Treatment	Lot number	Expiration date
Ipratropium Respima (b) (4) (one puff, 10 mcg)	PD-1611	Dec. 31, 1996
Ipratropium Respimat (b) (4) (one puff, 20 mcg)	PD-1612	Jan. 31, 1997
Ipratropium Respimat (b) (4) (one puff, 40 mcg)	PD-1613	Jan. 31, 1997
Ipratropium Respimat (b) (4) (one puff, 80 mcg)	PD-1614	Jan. 31, 1997
Ipratropium Respimat (b) (4) (one puff, 160 mcg)	PD-1615	Dec. 31, 1996
Placebo Respimat (one puff)	PD-1616	Dec. 31, 1996
Atrovent MDI 0.021 mg (one puff, 18 mcg plus one puff from placebo MDI)	PD-1560 PD-1381	July 31, 1997 Sept. 30, 1996

Atrovent MDI 0.021 mg (two puffs from 2 canisters, 36mcg)	PD-1560	July 31, 1997

(Volume 5.10, Section 5.3.4.2, pages 26-27)

10.1.3.1.5 Conduct

Refer to the following flow chart (Table 58) for an overview of procedures to be performed at each visit.

Table 58 Study 244.2447 flow chart (Volume 5.10, Section 5.3.4.2, page 33)

Trial period	**Screening**	**Treatment period**			
Visit	1	2	3	4	5
Days since last visit	---	3-7	3-7	3-7	3-7
Administration of investigational drugs		X	X	X	X
Demographics	X				
Medical history	X				
Inclusion/Exclusion criteria	X	X			
Informed consent	X				
Physical examination	X				X
Vital signs (seated)	X	X	X	X	X
Laboratory tests (fasting)	X				X
12-lead ECG	X				X
Theophylline level	X	X	X	X	X
Respimat device training	X				
Reversibility test	X				
Randomization		X			
Spirometry (FEV_1 & FVC), seated	X	X	X	X	X
Adverse events	X	X	X	X	X
Concomitant therapy	X	X	X	X	X
PK measurement[1]		X	X	X	X

1 PK measured for patients at two study centers only.

(Source: Volume 5.10, Section 5.3.4.2, page 33)

A complete medical history, physical examination, laboratory evaluation, and a 12-lead ECG was conducted prior to randomization (at Visit 2). The physical examination included measurements of systolic and diastolic blood pressure and pulse rate which were measured with the patient seated and resting for at least five minutes. Patients were instructed on the proper use of the MDI and then performed a reversibility test. A theophylline level was obtained from all patients prior to pulmonary function testing. Patients with theophylline levels higher than 5.0 mcg/mL were rescheduled. If the patient returned two additional times and the theophylline levels remained higher than 5.0 mcg/mL, they were not enrolled in the study. Pulmonary function testing was conducted in the morning between 7:00 a.m.-12:00 noon. FEV_1 and FVC were measured at baseline and FEV 1 was measured at 15, 30 and 60 minutes (± 5 minutes) following drug administration. At the end of the screening visit, the patient was instructed in the use of the Respimat device.

On each test day, patients were required to have baseline FEV_1 within ± 15% of their FEV_1 obtained on the initial test day (Visit 2). If they did not, the test day was to be rescheduled. If after two additional attempts, the patient did not have baseline FEV_1 within ±15% of their FEV_1 obtained on the initial test day (Visit 2), they were to be replaced. FEV_1 and FVC were obtained at baseline (i.e., pretreatment) and repeated at 5, 15, 30, 60, 90 minutes and 2, 3, 4, 5, 6, 7 and 8 hours after drug administration on all test days. The 5 minute measurement was to be performed within ± one minute of the 5 minute time point. Measurements from 15 minutes to 2 hours (inclusive) were to be performed within ± 5 minutes of the specified time points. Measurements made from 3-8 hours were to be performed within ± 15 minutes. Pulse rate and blood pressure were measured and recorded at the same time intervals as pulmonary function testing at baseline and during the first three hours. These variables were measured immediately before pulmonary function testing with the patient seated and rested for at least five minutes. Pharmacokinetics samples were collected from two study sites for the measurement of ipratropium bromide levels. In the final visit (Visit 5), patients had a physical examination, laboratory evaluation, 12-lead ECG examination, and pulmonary function test.

10.1.3.1.6 Safety Evaluation
Safety evaluations included (1) all adverse events during the treatment period, (2) vital signs, and (3) physical examination, laboratory test, and electrocardiogram (ECG) at the screening and the end of the treatment.

10.1.3.1.7 Efficacy
Primary endpoint is the average FEV_1 from 0 to 6 hours (AUC_{0-6}) as determined by dividing the area under the FEV_1 curve above test day baseline from 0 to 6 hours by six.

The dose response profile of ipratropium bromide delivered via the Respimat device was characterized by least square mean responses of FEV_1 AUC_{0-6}. The comparability of the ipratropium Respimat device doses to the Atrovent Inhalation Aerosol 36 mcg dose was addressed by calculating the 90% confidence intervals for the difference between each ipratropium Respimat device dose and the Atrovent Inhalation Aerosol 36 mcg dose. A dose was considered comparable only if the 90% confidence interval for the difference was completely contained in the interval between -90 mL to +90 mL [Volume 5.10, Section 5.3.4.2, page 40].

Secondary endpoints included peak FEV_1, the onset, duration and time to peak FEV_1 response.

Reviewer comment
The Applicant stated in other parts of the study report that a dose was considered comparable only if the 90% confidence interval for the difference is completely contained in the interval between -50 mL to +50 mL or ±0.05 liter [Volume 5.10, pages 50, 53, 67]. In this review, two doses are considered comparable or equivalence if the 90% CI for the differences are completely contained in the interval between ±0.05 liter (±50 mL).

10.1.3.2 Results

10.1.3.2.1 Demographics and Basic Characteristics of the Study Subjects

Patients' baseline demographic information is summarized in Table 59.

Table 59 Summary of demographics for patients in treated set

Demographics		**Total (%)**
Total treated		116 (100)
Per-protocol set*		113 (97.4)
Sex	**Male**	71 (61.2)
	Female	45 (38.8)
Race	**White**	112 (96.6)
	Black	2 (1.7)
	Asian	2 (1.7)
Age mean (years)		63.5
Height mean (in)		67
Weight mean (lb)		172
Alcohol history	**Non-drinker**	678 (46.4)
	Average consumption[1]	781 (53.5)
	Excessive consumption[2]	1 (0.1)
Smoking history	**Ex-smoker**	48 (41.4)
	Current smoker	68 (58.6)
Smoking history(pack-years)		64.7
COPD duration (years)		10.6
FEV_1 (liters), mean (SD)		1.03 (0.49)
Percent of predicted FEV_1,	Mean (SD)	38 (14)
	Range	12 – 78
FEV_1/FVC (%) Mean (SD)		47 (10)

* Three patients were excluded from the final data set because they missed three of the four visits.
(Source: Volume 5.10, Section 5.3.4.2, page43-46)

Overall mean age for patients was 63.5 ± 9.7 years. Ninety-seven percent of patients were white, 2% were Black and 2% were Asian. The mean baseline FEV_1 for all patients was 1.03 liters and the mean percent of predicted normal FEV_1 was 38%. FEV_1 baseline values ranged from 12% to 78% of predicted normal. Duration of COPD ranged from 1. 5 to 35.5 years, with a mean duration of 10.6 years. There were no significant differences in baseline features between the five study centers in age, race or duration of disease. There were no significant differences in baseline FEV_1 values between the eight treatment groups.

10.1.3.2.2 Efficacy

A total of 116 patients were randomized into 8 treatment groups. Three patients who missed three of the four visits were excluded from the efficacy analysis because they missed three of the four visits. The remaining data set with 113 patients, also called the Per-Protocol data set was used for the efficacy analyses. The Intent-to-Treat (ITT) data set was considered the same as the Per-Protocol data set and all efficacy results were presented for the Per-Protocol data set.

Table 60 summarized the mean FEV_1 AUC_{0-6} change from baseline for eight treatment groups and the comparison of mean FEV_1 AUC_{0-6} change between ipratropium Respimat doses and Atrovent Inhalation Aerosol 36 mcg. The ipratropium 10 mcg had a lowest mean FEV_1 AUC_{0-6} change in active treatment groups and ipratropium 20 and 40 mcg had a came mean FEV_1 AUC_{0-6} change. The ipratropium 160 mcg had a largest mean FEV_1 AUC_{0-6} change than all other

active treatments. The Applicant pre-set a dose comparison criterion that a dose is considered comparable only if the 90% confidence interval for the difference is completely contained in the interval between -50 mL to +50 mL. The ipratropium Respimat 20 mcg and 40 mcg were considered equivalent to the Atrovent Inhalation Aerosol 36 mcg dose.

Table 60 Mean FEV_1 AUC_{0-6} change (liters) from baseline of treatment groups and differences between Respimat and Atrovent Inhalation Aerosol 36 mcg groups

Treatment	N	Mean FEV_1 AUC_{0-6} change	Treatment difference (90% CI)	
			Compared to Atrovent 18 mcg	Compared to Atrovent 36 mcg
Ipratropium Respimat 10 mcg	58	0.16	0.019 (-0.012, 0.051)	-0.025 (-0.055, 0.006)
Ipratropium Respimat 20 mcg	60	0.19	0.051 (0.020, 0.082)	0.007 (-0.024, 0.037)
Ipratropium Respimat 40 mcg	58	0.19	0.045 (0.013, 0.077)	0.001 (-0.030, 0.032)
Ipratropium Respimat 80 mcg	54	0.23	0.088 (0.057, 0.121)	0.045 (0.014, 0.076)
Ipratropium Respimat160 mcg	51	0.26	0.118 (0.086, 0.150)	0.074 (0.042, 0.106)
Atrovent MDI 18 mcg	54	0.14	--------	--------
Atrovent MDI 36 mcg	58	0.19	--------	--------
Placebo Respimat	57	0.05	--------	--------

(Volume 5.10, Section 5.3.4.2, page50-51)

The dose response curve of mean FEV_1 AUC_{0-6} change from baseline for the eight treatment groups is shown in Figure 5. All active treatments showed significantly higher mean FEV_1 AUC_{0-6} change than that of the placebo group. The ipratropium Respimat 20 mcg and 40 mcg were considered equivalent to the Atrovent Inhalation Aerosol 36 mcg dose. It appears that dose response curves can be drawn for the two Atrovent Inhalation Aerosol doses (18 and 36 mcg) and for the five ipratropium Respimat doses (10, 20, 40, 80, and 160 mcg). The secondary efficacy endpoints show similar trend that all active treatment treatments were better than the placebo group.

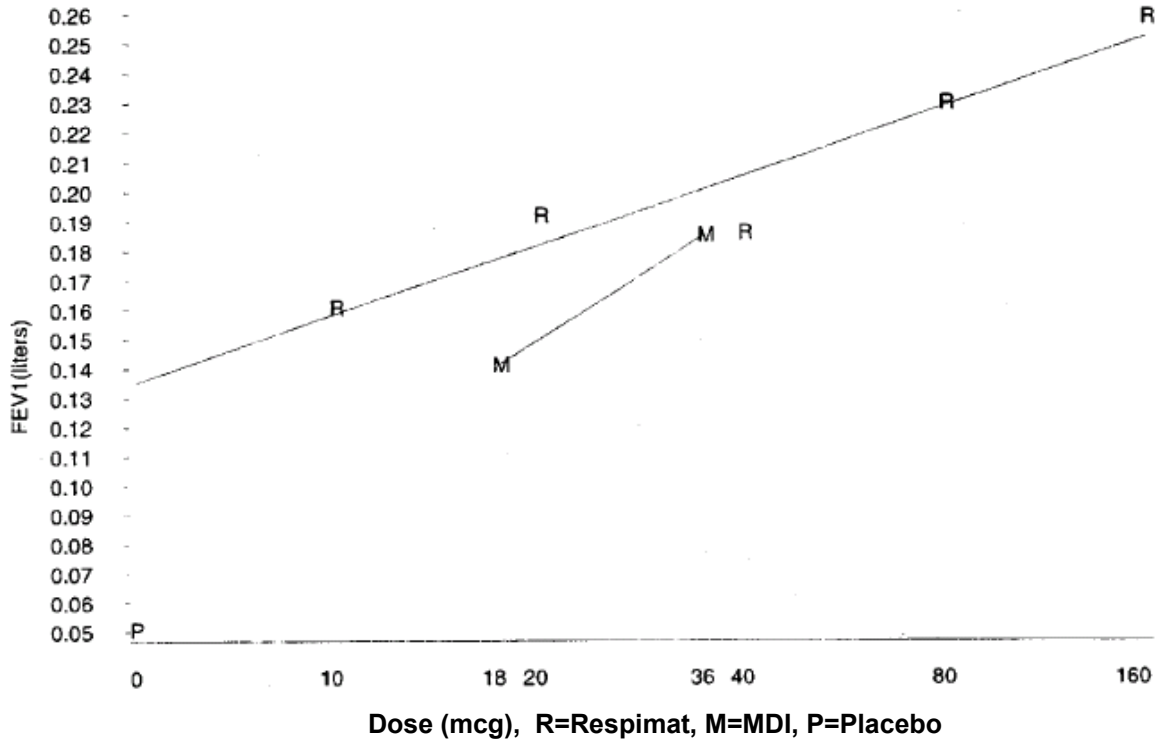


Figure 10 **Dose response curve of mean FEV_1 AUC_{0-6} change from baseline of treatment groups** (Source: Volume 5.10, Section 5.3.4.2, page49)

10.1.3.2.3 Safety Evaluation

Exposure

A total of 116 patients were randomized into 8 treatment groups. All randomized patients were included in the safety evaluation.

Adverse Event

All adverse events occurring on the days of study drug administration have been summarized in Table 61. Overall, the most common adverse event reported during the study was headache, which occurred in six patients. Three patients reported headache at different treatments. One patient reported headache following doses of ipratropium Respimat 10 mcg, 20 mcg, 160 mcg and Atrovent Inhalation Aerosol 36 mcg. One patient reported headache following doses of ipratropium Respimat 80 mcg and Atrovent Inhalation Aerosol 36 mcg. One patient reported headache following doses ipratropium Respimat 20 mcg and Atrovent Inhalation Aerosol 36 mcg.

Table 61 Overall patients (%) with adverse events by treatment groups

Adverse event	Placebo	Ipratropium Respimat					Atrovent MDI	
		10mcg	20mcg	40mcg	80mcg	160mcg	18mcg	36mcg
N	57	58	60	58	54	51	54	58
Patients with AEs	1 (1.8)	3 (5.2)	4 (6.7)	4 (6.9)	1 (1.9)	1 (2.0)	2 (3.7)	4 (6.9)
Headache	0	1 (1.7)	4 (6.7)	2 (3.4)	1 (1.9)	1 (2.0)	0	3 (5.2)
Dizziness	1 (1.8)	1 (1.7)	0	0	0	0	0	1 (1.7)
Gastroenteritis	0	0	0	0	0	0	1 (1.9)	0
Nausea	0	0	0	1 (1.7)	0	0	0	0
Tachycardia	0	0	0	1 (1.7)	0	0	0	0
Respiratory disorder	0	0	0	0	0	0	1 (1.9)	0
Urinary tract infect.	0	1 (1.7)	0	0	0	0	0	0
Vision abnormal	0	0	0	1 (1.7)	0	0	0	0

(Source: Volume 5.10, Section 5.3.4.2, page 64)

Deaths, Serious Adverse Events, and Adverse Events Leading to Withdrawal

There were no deaths during this study. Two patients were discontinued due to an adverse event. One patient experienced an episode of tachycardia 88 minutes after receiving the third treatment drug, ipratropium Respimat 40 mcg. His pulse rate returned to baseline in four and a half hours. The patient was discontinued and received no further treatment. The second patient was discontinued due to a COPD exacerbation during washout period four days after the second treatment day. This 56 years old female patient was hospitalized due to the COPD exacerbation. The event lasted seven days and the patient fully recovered. The patient was discontinued from the study. The event was reported as a serious adverse event. There were no other serious adverse events reported in this study.

Vital Signs, Laboratory Tests, Physical Examinations, and ECG

There was one patient who experienced an episode of tachycardia during the study. The patient was discontinued from the trial due to this adverse event. The tachycardia resolved after four and a half hours. There were no other pulse rate changes that were noteworthy. There were no significant changes in systolic or diastolic blood pressures that warrant discussion. There were no clinically significant laboratory changes during the study. No significant changes in physical findings were reported during the study. There were no significant changes in ECGs.

10.1.3.3 Summary and Conclusion

This single-dose study compared the bronchodilation effect of five ipratropium Respimat doses (10, 20, 40, 80, and 160 mcg) with Atrovent Inhalation Aerosol doses (18 and 36 mcg) to identify the ipratropium Respimat doses that are comparable to approved Atrovent Inhalation Aerosol doses. The dose response curves can be drawn for the five ipratropium Respimat doses and fro two Atrovent Inhalation Aerosol doses. The dose equivalence comparisons show that both 20 mcg and 40 mcg doses of ipratropium Respimat are comparable to approved dose of Atrovent Inhalation Aerosol 36 mcg for bronchodilation effect in COPD patients.

The safety event profile was similar in this single-dose study for ipratropium Respimat and Atrovent Inhalation Aerosol. The incidence of adverse events was similar across all treatment groups. There were no new safety signals revealed for ipratropium inhalation treatment in this study.

10.1.4 Study 243.7

This is a dose ranging study to determine the optimal dose of salbutamol sulfate inhalation solution via the Respimat device in patients with chronic obstructive pulmonary disease (COPD).

Table 62 Summary of study 243.7

Protocol #	243.7
Title	A dose ranging study of salbutamol inhalation solution delivered via the Respimat device inpatients with COPD
Study dates	Study initiated: September 3, 1996 Study completed: March 14, 1997 Date of study report: October 10, 1997
Sites	There were 4 study sites in the United States
IRB	A list of three Institutional Review Boards (IRB) is provided [Volume 5.11, Section 5.3.5.1, Content 16.1.3, pages EC1 – EC9]. The three IRBs covered four study sites. The final original study protocol was approved in writing by the IRBs before enrollment of any subject into the study. Subsequent protocol amendments were also approved by the IRBs.
Ethics	The study report states that the study was performed in compliance with the ethical principles that have their origin in the Declaration of Helsinki (1975 Version), in accordance with the Good Clinical Practice (GCP), and in accordance with applicable regulatory requirements.
Source references	Unless otherwise indicated, all source references are to: Study report 244.2447 and related information [Volume 5.13 – 5.15, Section 5.3.4.2]

10.1.4.1 Protocol

10.1.4.1.1 Objectives
The objective of this study was to determine the optimal dose of salbutamol sulfate inhalation solution via the Respimat device in patients with chronic obstructive pulmonary disease (COPD).

10.1.4.1.2 Summary of Study Design
This is a multi-center, randomized, double-blind, placebo-controlled, 7-treatment crossover study.

Following the initial screening visit, the patients were randomized to receive one of seven treatments including four doses of salbutemol sulfate delivered via Respimat device, Respimat placebo, and two doses of Ventolin Inhalation Aerosol. The patient will be crossed over to another treatment according to the randomization code after a washout period of 3-7 days. In a portion of the patients, plasma and urine salbutemol levels and serum potassium levels were evaluated to assess the pharmacokinetics of salbutemol sulfate delivered via the Respimat device.

10.1.4.1.3 Population
A total of 56 COPD patients were randomized into seven treatment groups.

Inclusion criteria:

- Patients must have a diagnosis of COPD and must meet the following spirometric criteria at Visit 1 (Screening) and Visit 2: Patients must have relatively stable, moderate to severe airway obstruction with pre-bronchodilator FEV_1 ≤65% of predicted normal values and FEV_1/FVC ≤70%.

    - Predicted normal values were calculated by following equations:
    Males: FEV_1 predicted (L) = 0.093 x (height (inch)) - 0.032 x age (yr) – 1.343
    Females: FEV_1 predicted (L) = 0.085 x (height (inch)) - 0.025 x age (yr) - 1.692

- Patients improve in $FEV_1 \geq 15\%$ within one hour after the inhalation of 180 mcg of Ventolin Inhalation Aerosol MDI (reversibility test).
- Patients must be 40 years of age or older, having a smoking history of more than ten pack-years. A pack-year is defined as the equivalent of smoking one pack of 20 cigarettes per day for a year.
- Patients must be able to perform pulmonary function tests and maintain records during the study period as required in the protocol.
- Patients must be able to be trained in the proper use of an MDI and the Respimat inhaler.
- All patients must sign an Informed Consent Form prior to participation in the trial.

Exclusion criteria:

- Patients with significant diseases other than COPD would 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 relevant abnormal baseline hematology, blood chemistry or urinalysis. If the abnormality defines a disease listed as an exclusion criterion, the patient is excluded.
- All patients with an AST (SGOT) >80 IU/L, ALT (SGPT) >80 IU/L, bilirubin >2.0 mg/dL or creatinine >2.0 mg/dL will be excluded regardless of the clinical condition. Repeat laboratory evaluation would not be conducted in these subjects.
- Patients with a history of asthma, allergic rhinitis or atopy or who have a total blood eosinophil count $\geq 600/mm^3$. A repeat eosinophil count was not conducted in these patients.
- Patients with a baseline potassium level below the lower limit of the normal range.
- Patients with a recent history (i.e., one year or less) of myocardial infarction, cardiac failure or arrhythmia requiring drug therapy.
- Patients with a history of cancer within the last five years.
- Patients with a history of life-threatening pulmonary obstruction, or a history of cystic fibrosis or clinically evident bronchiectasis.
- Patients who have undergone thoracotomy with pulmonary resection. Patients with a history of a thoracotomy for other reasons should be evaluated as per exclusion criteria.
- Patients with a history of and/or active alcohol or drug abuse.
- Patients with known active tuberculosis.

- Patients with known symptomatic prostatic hypertrophy or bladder neck obstruction.
- Patients with known narrow-angle glaucoma.
- Patients with current significant psychiatric disorders.
- Patients who regularly use daytime oxygen therapy.
- Patients who are being treated with antihistamines, beta-blockers, MAO inhibitors, tricyclic antidepressants, cromolyn sodium or Nedocromil.
- Patients using oral corticosteroid medication at unstable doses (i.e., less than 6 weeks on a stable dose) or at a dose in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day.
- Initiation of inhaled steroid use, or new dosage, less than 6 weeks prior to the Screening Visit (Visit 1).
- Patients who have had changes in their therapeutic plan within the last 6 weeks prior to the Screening Visit (Visit 1) or during the baseline period.
- Pregnant or nursing women or women of childbearing potential not using a medically approved means of contraception (i.e., oral or injectable contraceptives, intrauterine devices or diaphragm with spermicide, or Norplant).
- Patients with known hypersensitivity to beta-agonist agents.
- Patients who previously participated in this study.

10.1.4.1.4 Study Treatment

There are seven treatment groups in this study, as listed in Table 63. All treatments are administered through oral inhalation.

Table 63 Study treatments, Study 243.7

Treatment	Lot number	Expiration date
Salbutamol Respimat (b) (4) (one puff, 25 mcg)	PD-1650	June 1997
Salbutamol Respimat (b) (4) (one puff, 50 mcg)	PD-1651	June 1997
Salbutamol Respimat (b) (4) (one puff, 100 mcg)	PD-1652	May 1997
Salbutamol Respimat (b) (4) (one puff, 200 mcg)	PD-1653	June 1997
Placebo Respimat (one puff)	PD-1654	August 1997
Ventolin Inhalation Aerosol (one puff, 90 mcg) plus Placebo MDI (one puff)	PD-1656 PD-1659	August 1997 July 1997
Ventolin Inhalation Aerosol (two puffs from 2 canisters, 180 mcg)	PD-1656	August 1997

(Source: Volume 5.13, Section 5.3.4.2, pages 26-27)

10.1.4.1.5 Conduct

Refer to the following flow chart (Table 64) for an overview of procedures to be performed at each visit.

Table 64 Study 243.7 flow chart

Trial period	Screening	Treatment period						
Visit	1	2	3	4	5	6	7	8
Days since last visit	---	3-7	3-7	3-7	3-7	3-7	3-7	3-7
Administration of investigational drugs		X	X	X	X	X	X	X
Demographics	X							

Medical history	X							
Inclusion/Exclusion criteria	X	X						
Informed consent	X							
Physical examination	X							X
Vital signs (seated)	X	X	X	X	X	X	X	X
Laboratory tests (fasting)	X							X
12-lead ECG	X	X	X	X	X	X	X	X
Theophylline level	X	X	X	X	X	X	X	X
Respimat and MDI device training	X							
Reversibility test	X							
Randomization		X						
Spirometry (FEV1 & FVC), seated	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X
PK measurement[1]		X	X	X	X	X	X	X

1 PK measured for patients at two study centers only.
(Source: Volume 5.13, Section 5.3.4.2, page 35)

A complete medical history, physical examination, laboratory evaluation, and a 12-lead ECG were conducted prior to randomization (at Visit 2). The physical examination included measurements of systolic and diastolic blood pressure and pulse rate which were measured with the patient seated and resting for at least five minutes. Patients were instructed on the proper use of the MDI and then performed a reversibility test. A theophylline level was obtained from all patients prior to pulmonary function testing. Patients with theophylline levels higher than 5.0 mcg/mL were rescheduled. If the patient returned two additional times and the theophylline levels remained higher than 5.0 mcg/mL, they were not enrolled in the study. Pulmonary function testing was conducted in the morning between 7:00 a.m.-12:00 noon. FEV_1 and FVC were measured at baseline and FEV 1 was measured at 15, 30 and 60 minutes (± 5 minutes) following drug administration. At the end of the screening visit, the patient was instructed in the use of the Respimat device.

On each test day, patients were required to have baseline FEV_1 within ± 15% of their FEV_1 obtained on the initial test day (Visit 2). If they did not, the test day was to be rescheduled. If after two additional attempts, the patient did not have baseline FEV_1 within ±15% of their FEV_1 obtained on the initial test day (Visit 2), they were to be discontinued. FEV_1 and FVC were obtained at baseline (i.e., pretreatment) and repeated at 5, 15, 30, 60, 90 minutes and 2, 3, 4, 5, 6, 7 and 8 hours after drug administration on all test days. The 5 minute measurement was to be performed within ± one minute of the 5 minute time point. Measurements from 15 minutes to 2 hours (inclusive) were to be performed within ± 5 minutes of the specified time points. Measurements made from 3-8 hours were to be performed within ± 15 minutes. Pulse rate and blood pressure were measured and recorded at the same time intervals as pulmonary function testing at baseline and during the first three hours. These variables were measured immediately before pulmonary function testing with the patient seated and rested for at least five minutes. ECG was performed at baseline and one hour after study drug administration. Pharmacokinetic samples were collected from two study sites for the measurement of albuterol levels. In the final

visit (Visit 5), patients had a physical examination, laboratory evaluation, ECG, and pulmonary function test.

10.1.4.1.6 Safety Evaluation
Safety evaluations included (1) all adverse events during the treatment period, (2) vital signs, (3) 12-lead ECG, and (4) physical examination and laboratory tests at the screening and the end of the treatment.

10.1.4.1.7 Efficacy
Primary endpoint is the average FEV_1 AUC from 0 to 6 hours (AUC_{0-6}) as determined by dividing the area under the FEV_1 curve above test day baseline from 0 to 6 hours by six. The dose response profile of albuterol was characterized by lease square mean FEV_1 $AUC_{0-6.}$

Secondary endpoints included peak FEV_1, the onset, duration and time to peak FEV_1 response. FVC measurements were recorded during the pulmonary function tests.

10.1.4.2 Results

10.1.4.2.1 Demographics and Basic Characteristics of the Study Subjects
Patients' baseline demographic information is summarized in Table 65.

Table 65 Summary of demographics for patients in treated set

Demographics and baseline PFT		Patients (%)
Total randomized		62 (100)
Per-protocol set*		60 (96.8)
Sex	**Male**	42 (67.7)
	Female	20 (32.3)
Race	**White**	59 (95.2)
	Black	2 (3.2)
	Asian	1 (1.6)
Age mean (years)		64.2
Height mean (in)		67.8
Weight mean (lb)		173.4
Alcohol history	**Non-drinker**	678 (46.4)
	Average consumption[1]	781 (53.5)
	Excessive consumption[2]	1 (0.1)
Smoking history	**Ex-smoker**	28 (45.2)
	Current smoker	34 (54.8)
Smoking history(pack-years)		62.7
COPD duration (years)		9.8
FEV_1 (liters), mean (SD)		1.05 (0.45)
Percent of predicted FEV_1,	**Mean (SD)**	37.8 (14.2)
	Range	10.6 – 68.1
FEV_1/FVC (%) Mean (SD)		44.7 (10.4)

* Two patients were excluded from the final data set because they missed at least 2 test days PFT data.
(Source: Volume 5.13, Section 5.3.4.2, page49-50)

A total of 86 patients were screened for the study. Of these, 62 patients were randomized into the study and 55 patients completed the trial. Two of these patients were excluded from the

efficacy analysis because they had insufficient data on at least two test days to characterize the response of the patient to the test dose.

Overall mean age for patients was 64.2 years. Ninety-five percent of patients were white, 3% were Black and 1.6% were Asian. The mean baseline FEV_1 for all patients was 1.05 liters and the mean percent of predicted normal FEV_1 was 37.8%. FEV_1 baseline values ranged from 10.6% to 68% of predicted normal. Duration of COPD ranged from 3 to 31 years, with a mean duration of 9.8 years. There were no significant differences in baseline features between the four study centers in age, race or duration of disease. There were no significant differences in baseline FEV_1 values between the seven treatment groups.

10.1.4.2.2 Efficacy
A total of 62 patients were randomized into seven treatment groups. Two of these patients were excluded from the efficacy analysis because they had insufficient data on at least two test days to characterize the response of the patient to the test dose. The remaining data set with 60 patients, also called the Per-Protocol data set was used for the efficacy analyses. All efficacy results were presented for the Per-Protocol data set.

Table 66 summarized the mean FEV_1 AUC_{0-6} change from baseline for seven treatment groups and the comparison of mean FEV_1 AUC_{0-6} change between salbutamol Respimat doses and Ventolin Inhalation Aerosol 90 mcg and 180 mcg treatment groups. The salbutamol Respimat 25 mcg had a smallest mean FEV_1 AUC_{0-6} change in active treatment groups and ipratropium 20 and 40 mcg had a came mean FEV_1 AUC_{0-6} change. The ipratropium 160 mcg had a largest mean FEV_1 AUC_{0-6} change than all other active treatments. The Applicant pre-set a dose comparison criterion that a dose is considered comparable only if the 90% confidence interval for the difference is completely contained in the interval between -50 mL to +50 mL. The salbutamol Respimat 50 mcg and 100 mcg were considered therapeutically comparable to the Ventolin Inhalation Aerosol 90 mcg dose. The salbutamol Respimat 200 mcg was considered therapeutically comparable to the Ventolin Inhalation Aerosol 90 mcg and 180 mcg doses.

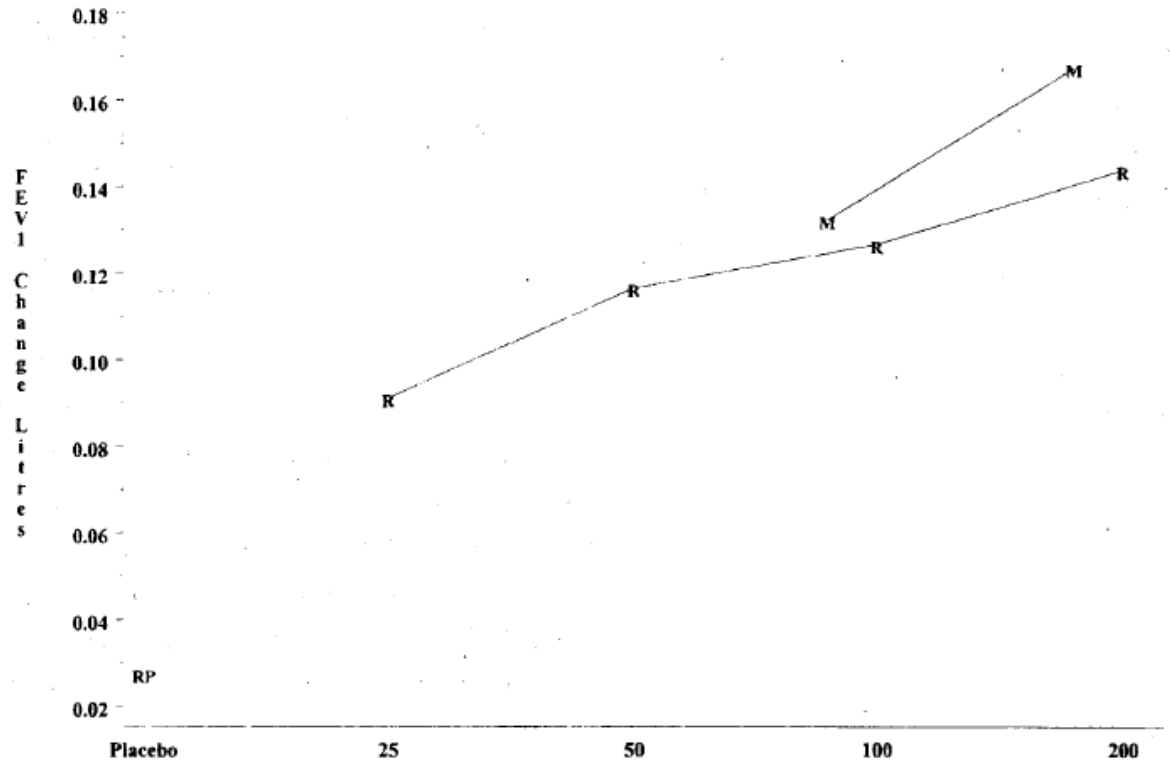
Table 66 Mean FEV_1 AUC_{0-6} change (in liter) from baseline of treatment groups and differences between albuterol Respimat and Ventolin Inhalation Aerosol groups

Treatment	N	Mean FEV_1 AUC_{0-6} change	Treatment difference (90% CI)	
			Compared to Ventolin 90 mcg group	Compared to Ventolin 180 mcg group
Salbutamol Respimat 25	59	0.091	-0.041 (-0.064, -0.018)	-0.077 (-0.100, -0.053)
Salbutamol Respimat 50	59	0.117	-0.016 (-0.039, 0.008)	-0.051 (-0.075, -0.028)
Salbutamol Respimat 100	56	0.127	-0.006 (-0.029, 0.017)	-0.041 (-0.064, -0.018)
Salbutamol Respimat 200	58	0.144	0.012 (-0.012, 0.035)	-0.024 (-0.047, 0.000)
Ventolin 90	56	0.132	---	---
Ventolin 180	59	0.168	---	---
Placebo Respimat	56	0.027	---	---

(Source: Volume 5.13, Section 5.3.4.2, page55-56)

The dose response curve of mean FEV_1 AUC_{0-6} change from baseline for the seven treatment groups is shown in Figure 5. All active treatments showed significantly higher mean FEV_1

AUC_{0-6} change than that of the placebo group. It appears that dose response curves can be drawn for the two Ventolin Inhalation Aerosol doses (90 and 180 mcg) and for the four salbutamol Respimat doses (25, 50, 100, and 200 mcg). The salbutamol Respimat 50 mcg and 100 mcg were considered therapeutically comparable to the Ventolin Inhalation Aerosol 90 mcg dose. The salbutamol Respimat 200 mcg was considered therapeutically comparable to both Ventolin Inhalation Aerosol 90 mcg and 200 mcg doses. The secondary efficacy endpoints show similar trend that all active treatment treatments were better than the placebo group.



Dose (mcg), RP=placebo Respimat, R=salbutamol Respimat, M=Ventolin MDI

Figure 11 Dose response curve of mean FEV_1 AUC_{0-6} change from baseline of treatment groups (Volume 5.13, Section 5.3.4.2, page54)

10.1.4.2.3 Safety Evaluation

Exposure

A total of 62 patients were randomized into seven treatment groups. All randomized patients were included in the safety evaluation.

Adverse Event

All adverse events occurring on the days of study drug administration have been summarized in Table 67. Overall, the most common adverse event reported during the study was headache, which occurred in nine patients. Three patients reported headache at different treatments. One patient reported headache following doses of salbutamol Respimat 25 mcg and 50 mcg and Ventolin Inhalation Aerosol 90 mcg and 180 mcg. One patient reported headache following doses of salbutamol Respimat 50 mcg and 100 mcg. One patient reported headache following doses of Ventolin Inhalation Aerosol 90 mcg and 180 mcg.

Table 67 Overall patients (%) with adverse events by treatment groups

Adverse event	Placebo	Salbutamol Respimat				Ventolin MDI	
		25mcg	50mcg	100mcg	200mcg	90mcg	180mcg
N	60	60	56	58	56	59	57
Patients with AEs	1 (1.7)	3 (5.0)	5 (8.9)	2 (3.4)	1 (1.8)	4 (6.8)	2 (3.5)
Headache	1 (1.7)	1 (1.7)	5 (8.9)	1 (1.7)	1 (1.8)	3 (5.1)	2 (3.5)
Hypertension aggravated	0	1 (1.7)	0	0	0	0	0
Tinnitus	0	1 (1.7)	0	0	0	0	0
Rhinitis	0	0	0	0	0	1 (1.7)	0
ST-T change	0	0	0	1 (1.7)	0	0	0

(Source: Volume 5.13, Section 5.3.4.2, page 71)

Deaths, Serious Adverse Events, and Adverse Events Leading to Withdrawal

There were no deaths during this study. Serious adverse events were reported for two patients in the study. One patient was a 55 years old white female complained nausea and vomiting for 2 weeks and severe headache after receiving salbutamol Respimat 200 mcg dose. The patient was admitted to the hospital and the gastrointestinal and neurology examinations were unremarkable. The patient was discharged 6 days later with a diagnosis of somatization disorder. Concomitant adverse events which were not categorized as serious were ST-T changes (one hour post drug administration of salbutamol Respimat 100 mcg) and vaginal discharge (reported during hospitalization). This patient had been previously diagnosed anxiety disorder. The patient was discontinued from the study and referred to her primary care physician for follow-up care. The second patient, a 72 years old white male, was randomized to Ventolin Inhalation Aerosol 90 mcg group. The patient was admitted into the hospital before the administration of test drug for observation of atrial fibrillation detected during a test day baseline ECG test. The patient was monitored overnight without treatment or reoccurrence of the atrial fibrillation and continued with the trial to complete two additional visits. This patient was discontinued from the study later due to an upper respiratory tract infection. There were no other serious adverse events reported in this study.

Five patients were discontinued from the study due to adverse events. Two of the five patients with serious adverse event are described above. Two patients were discontinued from the study due to a COPD exacerbation and received oral corticosteroid treatment. Another patient was

discontinued because of an upper respiratory infection which resulted in the patient's inability to meet ±15% reproducibility of the baseline FEV_1 value on Visit 6.

Vital Signs, Laboratory Tests, Physical Examinations, and ECG
No significant changes in physical findings were reported during the study. One patient experienced an aggravation of the pre-existing hypertension two hours after received salbutamol Respimat 25 mcg. The patient was asymptomatic throughout the episode and remained to complete the test day. The event was recorded as an adverse event. There were no other significant changes in vital signs during the study. There were no clinically significant laboratory changes during the study. One patient experienced ST-T segment changes one hour post drug administration of salbutamol Respimat 100 mcg. This patient was asymptomatic throughout the episode and had previous ST-T segment changes 6 months prior. The event was recorded as an adverse event. Follow-up ECG and echocardiogram were within normal limits. No other patients experienced clinically significant changes in ECGs.

10.1.4.3 Summary and Conclusion

This single-dose study compared the bronchodilation effect of four salbutamol Respimat doses (25, 50, 100, and 200 mcg) with Ventolin Inhalation Aerosol doses (90 and 180 mcg) to identify the salbutamol Respimat doses that are comparable to approved Ventolin Inhalation Aerosol doses. The dose response curves can be drawn for the four salbutamol Respimat doses and for the two Ventolin Inhalation Aerosol doses. The dose equivalence comparisons show that both 50 mcg and 100 mcg doses of salbutamol Respimat are comparable to 90 mcg dose of Ventolin Inhalation Aerosol, and 200 mcg dose of salbutamol Respimat is comparable to 90 mcg and 180 mcg doses of Ventolin Inhalation Aerosol for bronchodilation effect in COPD patients.

The safety event profile was similar in this single-dose study for salbutamol Respimat and Ventolin Inhalation Aerosol. The incidence of adverse events was similar across all treatment groups. There were no new safety signals revealed for salbutamol Respimat treatment in this study.

10.1.5 Study 244.2484

This is a six-month study to demonstrate the clinical comparability and safety profiles of 2 doses of ipratropium Respimat (20 mcg and 40 mcg) and Atrovent Inhalation Aerosol 36 mcg in patients with chronic obstructive pulmonary disease (COPD).

Table 68 Summary of study 244.2484

Protocol #	244.2484
Title	A six month, double-blind (within formulation), randomized, multiple dose trial to compare the safety and efficacy of 20 mcg and 40 mcg of ipratropium bromide, as delivered by the Respimat device, to 36 mcg Atrovent Inhalation Aerosol (18 mcg x 2 puffs) and respective placebos in adults with chronic obstructive pulmonary disease
Study dates	Study initiated: August 31, 1998 Study completed: October 20, 1999

	Date of study report: October 20, 2000
Sites	There were 36 study sites in Canada
IRB	A list of 23 Institutional Review Boards (IRB) is provided [Volume 5.8, Section 5.3.4.2, page EC1 – EC6]. The two IRBs covered multiple study sites. The final original study protocol was approved in writing by the IRBs before enrollment of any subject into the study. Subsequent protocol amendments were also approved by the IRBs.
Ethics	The study report states that the study was performed in compliance with the ethical principles that have their origin in the Declaration of Helsinki (1996 Version), in accordance with the Good Clinical Practice (GCP), and in accordance with applicable regulatory requirements.
Source references	Unless otherwise indicated, all source references are to: Study report 244.2484 and related information [Volume 5.6 – 5.10, Section 5.3.4.2]

10.1.5.1 Protocol

10.1.5.1.1 Objectives
The objective of this study was to confirm that chronic dosing of 20 mcg and 40 mcg of ipratropium bromide, delivered via the Respimat device, demonstrated clinical comparability and similar safety profiles to the 36 mcg dose of Atrovent Inhalation Aerosol CFC-MDI in patients with chronic obstructive pulmonary disease (COPD). The in-use testing for the proposed life of Respimat device (20 weeks) was also evaluated.

10.1.5.1.2 Summary of Study Design
This is a randomized, double-blind within formulation), placebo-controlled, 5-treatment arms, parallel group design study with a 2-week run-in period and a 6-month treatment period.

Following the initial screening, the patients entered a 2-week run-in period in which the number of puffs of salbutamol inhalation, the home PEFR, and the COPD symptom assessments were recorded daily. The patients who successfully completed this phase were randomized into the 6-month, double-blind treatment period to receive one of five treatments. Pulmonary function tests were performed over 8 hours following drug administration at each visit during the first 12 weeks. This part of the study was designed to demonstrate that ipratropium Respimat was not therapeutically inferior to Atrovent MDI as an effective bronchodilator. Pulmonary function tests were performed over 4 hours following drug administration at each visit during the second 12 weeks. This part of the study was designed to evaluate long term safety of ipratropium Respimat and in-use device performance. PEFR, adverse events, daily symptom scores, and concomitant therapy were recorded throughout the 6-month treatment period.

10.1.5.1.3 Population
A total of 895 COPD patients were screened against the following inclusion/exclusion criteria for entry into the study. Of those screened, 646 patients were eligible and randomized at an active to placebo ratio of 3:1 into one of five treatment arms: Respimat placebo (58 patients), ipratropium Respimat 20 mcg (180 patients), ipratropium Respimat 40 mcg (177 patients), Atrovent CFC MDI (172 patients), and MDI placebo (59 patients).

Inclusion criteria:

- Patients must have a diagnosis of COPD and must meet the following spirometric criteria at Visit 1 (Screening) and Visit 2: Patients must have relatively stable, moderate to severe airway obstruction with pre-bronchodilator FEV_1 ≤65% of predicted normal values and FEV_1/FVC ≤70%.

    - Predicted normal values were calculated following Morris equations[(1)]:
    Males: FEV_1 predicted (L) = 0.0366 x (height in cm) - 0.032 x age (yr) – 1.343
    Females: FEV_1 predicted (L) = 0.0335 x (height in cm) - 0.025 x age (yr) - 1.692

- Patients must be 40 years of age or older, having a smoking history of more than 10 pack-years. A pack-year is defined as the equivalent of smoking one pack of 20 cigarettes per day for a year.
- Patients must be able to perform pulmonary function tests and maintain records during the study period as required in the protocol.
- Patients must be able to be trained in the proper use of an MDI and the Respimat inhaler.
- All patients must sign an Informed Consent Form prior to participation in the trial.

Exclusion criteria:

- Patients with significant diseases other than COPD were excluded. 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.
- Patients with clinically relevant abnormal baseline hematology, blood chemistry or urinalysis. If the abnormality defines a disease listed as an exclusion criterion, the patient was excluded.
- All patients with an AST (SGOT) >80 IU/L, ALT (SGPT) >80 IU/L, bilirubin >34.2 µmol/dL or creatinine >176.8 µmol/dL were excluded regardless of the clinical condition. Repeat laboratory evaluation was conducted in these subjects.
- Patients who had a total blood eosinophil count ≥0.6 GI/L. A repeat eosinophil count was not conducted in these patients.
- Patients with a history of asthma, allergic rhinitis or atopy.
- Patients with a recent history (i.e., one year or less) of myocardial infarction, cardiac failure or arrhythmia requiring drug therapy.
- Patients with a history of cancer within the last five years.
- Patients with a history of life-threatening pulmonary obstruction, or a history of cystic fibrosis or clinically evident bronchiectasis.
- Patients who have undergone thoracotomy with pulmonary resection. Patients with a history of a thoracotomy for other reasons should be evaluated as per exclusion criteria.
- Patients with a history of and/or active alcohol or drug abuse.
- Patients with known active tuberculosis.
- Patients with known symptomatic prostatic hypertrophy or bladder neck obstruction.
- Patients with known narrow-angle glaucoma.
- Patients with current significant psychiatric disorders.

- Patients who regularly use daytime oxygen therapy.
- Patients who are being treated with antihistamines, beta-blockers, cromolyn sodium or Nedocromil.
- Patients using oral corticosteroid medication at unstable doses (i.e., less than 6 weeks on a stable dose) or at a dose in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day.
- Patients who have had changes in their therapeutic plan within the last 6 weeks prior to the Screening Visit (Visit 1) or during the baseline period.
- Pregnant or nursing women or women of childbearing potential not using a medically approved means of contraception (i.e., oral or injectable contraceptives, intrauterine devices or diaphragm with spermicide, or Norplant).
- Patients with known hypersensitivity to anticholinergic drugs or any other components of the Atrovent solution.
- Patients who previously participated in this study.

10.1.5.1.4 Study Treatment

There were five treatment groups in this study, as listed in Table 69. Blinding of the study medications were assured as such the treatments within the same device were indistinguishable. Patients randomized to MDI groups received an indistinguishable Atrovent MDI or placebo MDI. Patients randomized to Respimat groups received a separately packed Respimat device and medication cartridges containing ipratropiun bromide inhalation solution 20 mcg or 40 mcg per spray, or a placebo. Under the supervision of the research nurse or physician, the patient will insert the cartridge into the Respimat device and prime the assembled device 10 times prior to administering the test dose. The Respimat only needs priming when a new cartridge is used or replaced.

Table 69 Study treatments, Study 244.2484

Treatment	Batch number
ipratropium Respimat 20 mcg, one puff 4 times daily	PD-1850
ipratropium Respimat 40 mcg, one puff 4 times daily	PD-1851
Placebo Respimat, one puff 4 times daily	PD-1854
Atrovent CFC MDI 18 mcg, two puffs 4 times daily	PD-1847
Placebo MDI, two puffs 4 times daily	PD-1845

(Source: Volume 5.6, Section 5.3.4.2, page 40-42)

10.1.5.1.5 Conduct

Refer to the following flow chart (Table 70) for an overview of procedures to be performed at each visit.

Table 70 Study 244.2484 flow chart

Trial period	Screening	Treatment 0 -12 wks				Treatment 13-24 wks		
Visit	1	2	3	4	5	6	7	8
Weeks on treatment	---	0	4	8	12	16	20	24
Days	-14	1	29	57	85	113	141	169
Informed consent	X							
Demographics	X							

Medical history	X							
Physical examination	X				X			X
Demographics	X							
Medical history	X							
Vital signs (seated)	X	X	X	X	X	X	X	X
Laboratory tests (fasting)	X				X			X
12-lead ECG	X				X			X
Screening PFT (FEV_1 & FVC), seated	X	X[1]						
Respimat and MDI device training	X							
Inclusion/Exclusion criteria	X	X						
Dispense Peak Flow Meter	X							
Dispense Patient Daily Record	X	X	X	X	X	X	X	
Review PEFR and Patient Daily Record		X	X	X	X	X	X	X
Randomization		X						
Dispense test drugs		X	X	X	X	X	X	
Device performance evaluation		X	X	X	X	X	X	
Administration of test drugs		X	X	X	X	X	X	X
8-hour PFT test[2]		X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X

1 Baseline FEV_1 was required to be ≤65% of predicted, FEV_1/FVC ≤70%, and within ± 15% of FEV_1 at visit 1.
2 4-hour PFT test during 13 to 24-week treatment period
(Source: Volume 5.6, Section 5.3.4.2, page 48)

At the screening visit, all patients were required to sign the informed consent and had a complete medical history, physical examination, laboratory evaluation, pulmonary function test, and a 12-lead ECG. The patients were instructed on the proper use of the MDI and the Respimat device at the screening. Also a peak flow meter and patient daily record were dispensed at the screening visit. Qualified subjects were randomized at visit 2. The test drugs were dispensed to the qualified patients at visit 2.

All patients were required to visit the clinical centers at a schedule in Table 2. On each visit day, pulmonary function testing was conducted in the morning between 7:00 a.m.-10:00 am. FEV_1 and FVC were measured at pre-treatment (baseline) and repeated at 5, 15, 30, 60, 90 minutes and 2, 3, 4, 5, 6, 7 and 8 hours after drug administration on test days during 0 to 12 weeks of the treatment period. During 13 to 24 week of the treatment period, FEV_1 and FVC were measured for 4-hour period post-treatment only. FEV_1 was measured at 15, 30 and 60 minutes (± 5 minutes) following drug administration. At the end of the screening visit, the patient was instructed in the use of the Respimat device. The 5 minute measurement was to be performed within ± one minute of the 5 minute time point. Measurements from 15 minutes to 2 hours (inclusive) were to be performed within ± 5 minutes of the specified time points. Measurements made from 3-8 hours were to be performed within ± 15 minutes. Pulse rate and blood pressure were measured and recorded at the same time intervals as pulmonary function testing at baseline

and during the first three hours. These variables were measured immediately before pulmonary function testing with the patient seated and rested for at least five minutes. A standard 12-lead ECG and one minute rhythm strip were performed on all patients at the screening, at visit 5, and at the conclusion of the patient participation of the study. All patients were required to record the number of puffs of test drug taken each day, daily PEFR, day time and night time COPD symptom scores, and adverse events. The patient records were reviewed at each clinical visit. The COPD symptom scores were composed of 5 symptoms (cough, wheezing, shortness of breath, chest tightness, and sputum production) at a 5-point scale with 0 representing no symptoms, 4 representing the worst symptoms, and 1 to 3 fell in between. The treatment compliance was monitored through the review of the patient record at each visit.

The in-use performance of Respimat devices was evaluated. Thirty Respimat devices that had been used by patients in the study for 20 weeks were collected. Each device had been released for 30 months and been used for 20 weeks (600 puffs and five cartridges) in the study. The devices were tested with new cartridges containing 0.833% fenoterol hydrobromide test solution. The Applicant stated that the actuation mode of the devices simulated actual patient use.

10.1.5.1.6 Safety Evaluation
Safety evaluations included all adverse events during the treatment period, vital signs, ECG, physical examination, and laboratory tests during the treatment period.

10.1.5.1.7 Efficacy
The primary efficacy endpoint was the average FEV_1 AUC from 0 to 6 hours (AUC_{0-6}) as determined by dividing the area under the FEV_1 curve above test day baseline from 0 to 6 hours by six. The primary null hypothesis was that after 12 weeks of treatment at least one of the two ipratropium Respimat doses was not inferior to Atrovent MDI 36 mcg dose in bronchodilation response in COPD patients. The non-inferiority was determined when the 95% confidence interval of the treatment difference in FEV_1 AUC_{0-6} change from test day baseline at test day 85 was above -0.05 liters.

Secondary efficacy endpoints included FEV_1 AUC_{0-6} change from test day baseline at test days 1, 29, and 57, peak FEV_1, the onset, duration and time to peak FEV_1 response. FVC measurements were also recorded during the pulmonary function tests.

10.1.5.2 Results

10.1.5.2.1 Demographics and Basic Characteristics of the Study Subjects
Patients' baseline demographic information and baseline pulmonary function test are summarized in Table 71. A total of 646 patients were randomized into five treatment groups at a ratio 1 to 3 for 2 placebo groups and 3 active treatment groups. Overall, 57% and 43% of the treated patients are males and females, respectively. In terms of race or ethnic groups, 98% of the patients are white. The African Americans and Asians are only 1% each of the study patients. The average age of the patient population was 65.8 years. Over 60% of the patients were in the range from 61 to 75 years old. The average smoking history is 49.5 pack-years, and the mean COPD duration is 7.7 years. The five treatment groups are comparable with respect to the baseline demographic characteristics and baseline pulmonary function test.

Table 71 Summary of demographics and baseline PFT measurement for patients in study 244.2484

Demographics	Total (%)	Placebo Respimat N (%)	Ipratropium Respimat 20 N (%)	Ipratropium Respimat 40 N (%)	Placebo MDI N (%)	Atrovent MDI 36 N (%)
Total treated	646 (100)	58 (100)	180 (100)	177 (100)	59 (100)	172 (100)
Sex Male	371 (57)	33 (57)	101 (66)	92 (52)	40 (68)	105 (61)
Female	275 (43)	25 (43)	79 (44)	85 (48)	19 (32)	67 (39)
Race White	636 (98)	55 (95)	178 (99)	177 (100)	59 (100)	167 (97)
Black	4 (1)	1 (2)	1 (0.5)	0	0	2 (1)
Asian	6 (1)	3 (3)	1 (0.5)	0	0	3 (2)
Age Mean(yrs)	65.8	64.5	66.4	65.1	64.8	66.6
SD	8.5	8.0	8.4	8.7	8.6	8.7
Min (yrs)	41	48	41	43	47	43
Max (yrs)	90	77	90	83	82	89
40 - 60 yrs	174 (27)	19 (33)	39 (22)	51 (29)	20 (34)	45 (26)
61 - 75 yrs	399 (62)	36 (62)	120 (67)	110 (62)	33 (56)	100 (58)
>75 yrs	73 (11)	3 (5)	21 (11)	16 (9)	6 (10)	27 (16)
Height mean(cm)	167.2	167.7	167.0	166.2	168.3	167.9
SD	9.3	9.5	8.2	9.8	9.0	9.8
Weight mean(kg)	73.2	73.3	73.7	71.8	74.4	73.8
SD	17.3	15.8	16.9	17.5	15.1	18.8
Smoking history						
Ex-smoker	384 (59)	30 (52)	104 (58)	103 (58)	41 (69)	106 (62)
Smoker	262 (41)	28 (48)	76 (42)	74 (42)	18 (31)	66 (38)
Pack-years						
Mean	49.5	48.5	51.3	49.8	45.5	49.1
SD	24,6	21.4	25.2	25.8	25.9	23.5
COPD duration						
(years) Mean	7.7	7.1	7.7	7.9	7.8	7.5
SD	6.2	4.9	6.1	6.8	7.3	5.6
Screening FEV_1						
(liters) Mean	1.01	1.00	1.00	0.99	1.05	1.03
SD	0.42	0.41	0.40	0.47	0.45	0.40
% predicted FEV_1						
Mean	40.38	39.34	40.77	39.72	40.01	41.14
SD	13.81	14.16	14.10	14.18	13.19	13.30
FEV_1/FVC Mean	0.48	0.48	0.48	0.47	0.48	0.48
SD	0.12	0.12	0.12	0.12	0.12	0.12

(Source: Volume 5.6, Section 5.3.4.2, page 77-79)

10.1.5.2.2 Efficacy

A total of 646 patients were randomized into five treatment groups. All randomized patients were included in the safety data set. The primary efficacy endpoint was the mean FEV_1 AUC_{0-6} at test day 85. Twenty-two patients were excluded from the efficacy analysis data set. One patient was unable to perform the PFT. Five patients had incomplete pre-dose or post-dose PFT data to obtain the change from test day baseline. Thirteen patients were excluded from the efficacy analysis data set because their test day baseline FEV_1 values were out of the ±15% range of the screening baseline. Two patients withdrew their consent during the study and one patient participated in another clinical trial. A total of 624 patients were analyzed for the efficacy endpoint, accounting for 96.6% of the randomized patients.

Table 72 summarized the mean FEV_1 AUC_{0-6} change from baseline for five treatment groups and the comparison of mean FEV_1 AUC_{0-6} change between ipratropium Respimat doses and Respimat placebo, and between ipratropium Respimat doses and Atrovent MDI 36 mcg. The mean FEV_1 AUC_{0-6} change in all three active treatment groups is significantly greater than that in the two placebo groups. Atrovent MDI 36 mcg group has the largest mean FEV_1 AUC_{0-6} change of 0.155 liters. The ipratropium Respimat 20 mcg and 40 mcg groups have mean FEV_1 AUC_{0-6} changes of 0.134 and 0.143 liters, respectively. Evaluating by the pre-set non-inferiority criterion that the 95% confidence interval of the treatment difference in mean FEV_1 AUC_{0-6} change should be above -0.05 liters, the ipratropium Respimat 20 mcg and 40 mcg were not inferior to Atrovent MDI 36 mcg in bronchodilation response in COPD patients.

Table 72 Mean FEV_1 AUC_{0-6} change (liters) from baseline of treatment groups and differences between ipratropium Respimat and Atrovent Inhalation Aerosol 36 mcg groups

Treatment	N	Mean FEV_1 AUC_{0-6} change	Treatment difference (95% CI)	
			Compared to Atrovent MDI 36 mcg group	Compared to Respimat placebo
Respimat placebo	55	0.057	------	------
Ipratropium Respimat 20	174	0.134	-0.021 (-0.048, 0.006)	0.078 (0.040, 0.117)
Ipratropium Respimat 40	169	0.143	-0.012 (-0.039, 0.015)	0.091 (0.052, 0.129)
MDI placebo	58	0.013	------	------
Atrovent MDI 36	168	0.155	------	------

(Source : Volume 5.6, Section 5.3.4.2, page 88-91 ; Volume 5.10, page 121-122)

10.1.5.2.3 Safety

Exposure

A total of 646 patients were randomized into five treatment groups and received at least one dose of study medication. One hundred eighty (180) patients received ipratropium Respimat 20 mcg, 177 patients received ipratropium Respimat 40 mcg, and 172 patients received Atrovent MDI 36 mcg. Fifty-eight (58) patients and 59 patients received Respimat placebo and MDI placebo, respectively. About 90% of patients in all five groups exposed to the treatment for more than 84 days and more than 30% of patients in all treatment groups exposed to the treatment fro more than 169 days. The average exposure days for patients in this study was about 152 days. Table 73 listed the total and group exposure to the treatment dedication.

Table 73 Exposure to trial medications by treatment groups in study 244.2484

Exposure	Total (%)	Placebo Respimat N (%)	Ipratropium Respimat 20 N (%)	Ipratropium Respimat 40 N (%)	Placebo MDI N (%)	Atrovent MDI 36 N (%)
Total treated	646 (100)	58 (100)	180 (100)	177 (100)	59 (100)	172 (100)
Treatment days (%)						
1	3 (0.5)	1 (1.7)	0	0	0	2 (1.2)
2-30	32 (5.0)	5 (8.6)	8 (4.4)	6 (3.4)	7 (11.9)	6 (3.5)
31-84	40 (6.2)	3 (5.2)	9 (5.0)	10 (5.6)	4 (6.8)	14 (8.1)
85-169	352 (54.5)	31 (53.4)	103 (57.2)	98 (55.4)	30 (50.8)	90 (52.3)
>169	219 (33.9)	18 (31.0)	60 (33.3)	63 (35.6)	18 (30.5)	60 (34.9)
Average exp. days	152	146	155	155	142	150

(Source : Volume 5.6, Section 5.3.4.2, page 88-91 ; Volume 5.10, page 116)

Adverse Event

All adverse events occurring during this 6-month study with an incidence of 3% or greater have been summarized in Table 74. Overall, 551 (85.3%) patients randomized to treatment groups experienced at least one adverse event during the study, of which, 150 (83.3%) were in the ipratropium Respimat 20 mcg group, 152 (85.9) were in the ipratropium Respimat 40 mcg group, and 141 (82.0%) were in the Atrovent MDI 36 group. There were 49 (84.5%) and 43 (72.9%) patients in the Respimat placebo group and MDI placebo group reported adverse events during the study, respectively. The overall incidences of adverse events for five treatment groups were similar.

Overall, respiratory system disorders (65.2%) accounted for a majority of adverse events followed by general disorders (45.2%) and the Gastro-intestinal system disorders (24.9%). The most common adverse events in all patients were upper respiratory tract infection (31.6% of patients), COPD exacerbation (23.7%), headache (19.2%), and pharyngitis (11.9%). During treatment with ipratropium Respimat 20 mcg, the most common respiratory system adverse events included upper respiratory tract infection (46 patients, 25.6%), COPD exacerbation (42 patients, 23.3%), pharyngitis and coughing (each 17 patients, 9.4%). The common respiratory system adverse events occurred with ipratropium Respimat 40 mcg included upper respiratory tract infection (55 patients, 31.1 %), COPD exacerbation (38 patients, 21.5%), and pharyngitis (29 patients, 16.4%). In comparison, respiratory system adverse events seen with Atrovent MDI treatment included upper respiratory tract infection (52 patients, 30.2%), COPD exacerbation (40 patients, 23.3%), and dyspnea (16 patients, 9.3%). The incidences of these most common adverse events were similar across the five treatment groups including active treatments and placebos except for pharyngitis. There were more cases of pharyngitis reported in the ipratropium Respimat 40 mcg group (29 patients, 16.4%) than the other treatment groups (7.0-9.4%). The percentage of patients reporting pharyngitis in all Respimat groups (ipratropium Respimat 20 mcg and 40 mcg and Respimat placebo) combined was 12.3% compared with 7.4% in the Atrovent MDI and MDI placebo groups combined.

Table 74 Overall patients (%) with adverse events by treatment groups

Adverse event	Total* N (%)	Placebo Respimat N (%)	Ipratropium Respimat 20 N (%)	Ipratropium Respimat 40 N (%)	Placebo MDI N (%)	Atrovent MDI 36 N (%)
Total treated	646 (100)	58 (100)	180 (100)	177 (100)	59 (100)	172 (100)
Patients with AEs	551 (85.3)	49 (84.5)	150 (83.3)	152 (85.9)	43 (72.9)	141(82.0)
General disorders	292 (45.3)	24 (41.4)	77 (42.8)	73 (41.2)	22 (37.3)	71 (41.3)
Accident, Household	47 (7.3)	3 (5.2)	13 (7.2)	13 (7.3)	4 (6.8)	8 (4.7)
Accident, Vehicular	3 (0.5)	0	1 (0.6)	0	2 (3.4)	0
Back pain	25 (3.9)	2 (3.4)	3 (1.7)	7 (4.0)	2 (3.4)	6 (3.5)
Fall	23 (3.6)	0	7 (3.9)	8 (4.5)	1 (1.7)	6 (3.5)
Fatigue	24 (3.7)	4 (6.9)	7 (3.9)	5 (2.8)	0	5 (2.9)
Fever	14 (2.2)	1 (1.7)	2 (1.1)	6 (3.4)	0	3 (1.7)
Headache	124 (19.2)	11 (19.0)	38 (21.1)	33 (18.6)	8 (13.6)	31 (18.0)
Pain	26 (4.0)	2 (3.4)	6 (3.3)	7 (4.0)	2 (3.4)	7 (4.1)
Influenza-like sympt.	62 (9.6)	9 (15.5)	9 (5.0)	11 (6.2)	8 (13.6)	13 (7.6)
Nervous system disorders	91 (14.1)	5 (8.6)	21 (11.7)	27 (15.3)	8 (13.6)	21 (12.2)
Dizziness	52 (8.0)	1 (1.7)	14 (7.8)	13 (7.3)	4 (6.8)	11 (6.4)

Insomnia	13 (2.0)	0	0	6 (3.4)	2 (2.4)	5 (2.9)
Gastro-intestinal system disorders	161 (24.9)	14 (24.1)	43 (23.9)	44 (24.9)	5 (8.5)	32 (18.6)
Abdominal pain	30 (4.6)	3 (5.2)	10 (5.6)	11 (6.2)	0	3 (1.7)
Diarrhea	24 (3.7)	5 (8.6)	5 (2.8)	7 (4.0)	1 (1.7)	2 (1.2)
Dyspepsia	33 (5.1)	0	6 (3.3)	12 (6.8)	1 (1.7)	5 (2.9)
Gastroenteritis	20 (3.1)	2 (3.4)	5 (2.8)	6 (3.4)	1 (1.7)	2 (1.2)
Mouth dry	30 (4.6)	2 (3.4)	10 (5.6)	6 (3.4)	0	4 (2.3)
Nausea	14 (5.3)	5 (8.6)	9 (5.0)	10 (5.6)	2 (3.4)	5 (2.9)
Vomiting	18 (2.8)	5 (8.6)	5 (2.8)	4 (2.3)	1 (1.7)	3 (1.7)
Muscular-skeletal system disorders	54 (8.4)	5 (8.6)	17 (9.4)	11 (6.2)	3 (5.1)	14 (8.1)
Myalgia	24 (3.7)	3 (5.2)	5 (2.8)	7 (4.0)	1 (1.7)	5 (2.9)
Skeletal pain	11 (1.7)	1 (1.7)	3 (1.7)	1 (0.6)	0	6 (3.5)
Respiratory system disorders	421(65.2)	41 (70.7)	107 (59.4)	117 (66.1)	31 (52.5)	102 (59.3)
Bronchitis	36 (5.6)	5 (8.6)	10 (6.6)	11 (6.2)	1 (1.7)	8 (4.7)
COPD exacerbation	153(23.7)	15 (25.9)	42 (23.3)	38 (21.5)	12 (20/3)	40 (23.3)
Cough	62 (9.6)	5 (8.6)	17 (9.4)	14 (7.9)	7 (11.9)	13 (7.6)
Dyspnea	48 (7.4)	5 (8.6)	9 (5.0)	10 (5.6)	5 (8.5)	16 (9.3)
Epistaxis	14 (2.2)	3 (5.2)	3 (1.7)	2 (1.1)	1 (1.7)	4 (2.3)
Pharyngitis	77 (11.9)	5 (8.6)	17 (9.4)	29 (16.4)	5 (8.5)	12 (7.0)
Pneumonia	27 (4.2)	3 (5.2)	6 (3.3)	5 (2.8)	0	12 (7.0)
Rhinitis	35 (5.4)	2 (3.4)	9 (5.0)	7 (4.0)	4 (6.8)	9 (5.2)
Sinusitis	20 (3.1)	4 (6.9)	4 (2.2)	5 (2.8)	0	6 (3.5)
Upper resp tract inf.	204(31.6)	17 (29.3)	46 (25.6)	55 (31.1)	13 (22.0)	52 (30.2)
Anxiety	18 (2.8)	0	9 (5.0)	3 (1.7)	1 (1.7)	4 (2.3)
Infection	15 (2.3)	2 (3.4)	4 (2.2)	3 (1.7)	0	2 (1.2)
Rash erythematous	3 (0.5)	2 (3.4)	0	0	0	0
Micturition frequency	6 (0.9)	2 (3.4)	1 (0.6)	1 (0.6)	0	1 (0.6)
Vision disorders	40 (6.2)	3 (5.2)	6 (3.3)	13 (7.3)	2 (3.4)	14 (8.1)

* Some total numbers are slightly different from the sums of the 5 treatment groups because it included adverse events reported at the screening visit and, in a few cases, adverse events reported after the 6-month treatment period.

(Volume 5.6, Section 5.3.4.2, pages 121-122)

Deaths, Serious Adverse Events, and Adverse Events Leading to Withdrawal

There were 4 deaths reported for this study. Two occurred during study treatment period and two after the study completion. The four death cases appear to not be related to study medication.

Patient 1689, a 67 years old male, was randomized to Atrovent MDI 36 mcg group. The patient had completed two months in the study and developed pneumonia when on a visit to Cuba. The patient was admitted to a hospital in Cuba, treated with iv antibiotics, and died in the hospital 13 days later.

Patient 2093, a 77 years old male patient, was randomized to MDI placebo and had completed two months of treatment when developed cold symptoms. The patient then suffered a myocardial infarction and was found dead by his spouse two days later. The patient entered the study with a history of coronary heart disease and was being treated for hypertension and

elevated cholesterol. The study screening ECG showed right bundle branch block with occasional ventricular and atrial contractions.

Patient 1863, a 60 years old male, was randomized to ipratropium Respimat 20 mcg group. The patient had completed over two months of treatment when noticed a lump on his neck. The patient was diagnosed with metastatic adenocarcinoma and discontinued from the study. The patient received chemotherapy for the carcinoma and subsequently died from the carcinoma three months after the study discontinuation.

Patient 1582, a 59 year old male, was randomized to ipratropium Respimat 40 mcg group. The patient had completed the study and experienced a tricyclic overdose and cardiac arrest six and a half weeks later.

All serious adverse events reported for this study are listed in Table 75. Overall, there were 72 patients (11.1%) reported serious adverse events. The highest incidence of serious adverse events was in the Respimat placebo group (13.8%). The lowest incidences of serious adverse events were in the ipratropium Respimat 20 mcg and 40 mcg groups (8.3% and 8.5 % respectively). The patients with respiratory system disorders accounted for 36 cases and 50% of all serious adverse events. All of the respiratory system disorders that accounted for serious adverse events were COPD exacerbation (28 patients) or pneumonia (10 patients).

There were 48 patients (7.4%) discontinued from the study due to adverse events during the 6-month treatment period. The Respimat placebo group had the highest percent (10.3%) of patients discontinued due to adverse events. The ipratropium Respimat 20 mcg and 40 mcg groups had the least patients discontinued due to adverse events, accounting for 6.1% and 6.8% of the patients respectively. The Atrovent MDI 36 mcg group and MDI placebo group had comparable percent of patients discontinued due to adverse events (8.1% and 8.5%).

Table 75 Patients (%) with serious adverse events, patients decreased in dose or discontinued from the study due to adverse events by treatment groups

Adverse event	Total* N (%)	Placebo Respimat N (%)	Ipratropium Respimat 20 N (%)	Ipratropium Respimat 40 N (%)	Placebo MDI N (%)	Atrovent MDI 36 N (%)
Total treated	646 (100)	58 (100)	180 (100)	177 (100)	59 (100)	172 (100)
Patients with AEs	72 (11.1)	8 (13.8)	15 (8.3)	15 (8.5)	6 (10.2)	19 (11.9)
General disorders	7 (1.1)	0	1 (0.6)	2 (1.1)	1 (1.7)	1 (0.6)
Accident, Household	1 (0.2)		0	1 (0.6)	0	0
Accident, Vehicular	1 (0.2)		1 (0.6)	0	0	0
Allergic reaction	1 (0.2)		0	0	0	0
Back pain	1 (0.2)		0	0	1 (1.7)	0
Fall	1 (0.2)		0	1 (0.6)	0	0
Edema, Periorbital	1 (0.2)		0	0	0	1 (0.6)
Overdose	1 (0.2)		0	0	0	0
Cardiovascular disorders	4 (0.6)	0	2 (1.1)	1 (0.6)	1 (1.7)	0
Cardiac failure	1 (0.2)		1 (0.6)	0	0	
Cardiac failure, R.	1 (0.2)		0	0	1 (1.7)	
Syncope	2 (0.3)		1 (0.6)	1 (0.6)	0	
Gastro-intestinal						

system disorders	10	(1.5)	2	(3.4)	2	(1.1)	2	(1.1)	0	4 (2.3)
Abdominal pain	1	(0.2)	0		0		0			1 (0.6)
Diverticulitis	2	(0.3)	0		2	(1.1)	0			0
Gastroenteritis	2	(0.3)	1	(1.7)	0		1	(0.6)		0
Gastroesoph. reflux	1	(0.2)	0		0		0			1 (0.6)
GI hemorrhage	3	(0.5)	1	(1.7)	0		0			2 (1.2)
Intestinal obstruct.	1	(0.2)	0		0		1	(0.6)		0
Heart rate & rhythm disorders	3	(0.5)	0		0		1	(0.6)	1 (1.7)	0
Bradycardia	1	(0.2)					1	(0.6)	0	
Cardiac arrest	1	(0.2)					0		0	
Tachycardia	1	(0.2)					0		1 (1.7)	
Myo Endo pericardial & Valve disorders	8	(1.2)	1	(1.7)	2	(1.1)	0		1 (1.7)	3 (1.7)
Aneurysm	2	(0.3)	0		1	(0.6)			0	1 (0.6)
Coronary artery dis.	1	(0.2)	1	(1.7)	0				0	0
Myocardial infarct.	5	(0.8)	0		1	(0.6)			1 (1.7)	2 (1.2)
Neoplasm	6	(0.9)	1	(1.7)	2	(1.1)	1	(0.6)	0	1 (0.6)
Adenocarcinoma	1	(0.2)	0		1	(0.6)	0			0
Bladder carcinoma	2	(0.3)	0		0		1	(0.6)		1 (0.6)
Neoplasm malignant	1	(0.2)	1	(1.7)	0		0			0
Pulm. carcinoma	2	(0.3)	0		1	(0.6)	0			0
Respiratory system disorders	36	(5.6)	3	(5.2)	7	(3.9)	9	(5.1)	3 (5.1)	11 (6.4)
COPD exacerbation	28	(4.3)	3	(5.2)	6	(3.3)	7	(4.0)	3 (5.1)	7 (4.1)
Pneumonia	10	(1.5)	0		2	(1.1)	3	(1.7)	0	5 (2.9)
Anemia, microcytic	1	(0.2)	1	(1.7)	0		0		0	0
Hernia, inguinal	1	(1.7)	0		0		1	(0.6)	0	0
Thrombophlebitis	1	(0.2)	0		1	(0.6)	0		0	0
Vision disorder	1	(0.2)	0		0		0		0	1 (0.6)

* Some total numbers are slightly different from the sums of the 5 treatment groups because it included serious adverse events reported at the screening visit and, in a few cases, serious adverse events reported after the 6-month treatment period.

(Source: Volume 5.6, Section 5.3.4.2, page 131-135)

Vital Signs, Laboratory Tests, Physical Examinations, and ECG

Blood pressure and pulse rate were recorded during the first 3 hours of pulmonary function test at each visit. There were no differences in vital sign changes between treatment groups. Physical examinations and clinical laboratory tests were performed at screening, 12 weeks and at the end of the study. There were no differences in clinical laboratory changes between treatment groups. All changes from the screening baseline in physical examinations were recorded and reported as adverse events.

ECG was performed at screening, 12 weeks and at the end of the study. Twelve patients had clinically significant findings in ECG either at the 12-week visit or the final visit. These patients were distributed across the five treatments (2 patients in Respimat placebo, 3 patients in ipratropium Respimat 20 mcg, 2 patients in ipratropium Respimat 40 mcg, 2 patients in MDI placebo, and 3 patients in Atrovent MDI).

In the Respimat placebo group, two patients had significant changes in their ECG at the final visit. One patient had sinus tachycardia. This patient discontinued from the study due to a

diagnosis of prostate cancer. Another patient had sinus bradycardia at the final visit, which was not treated and resolved three days later. All ECG findings appear not directly related to the study medications.

There were 3 patients who had significant findings in the final ECG in the ipratropium Respimat 20 mcg group. One patient showed atrial fibrillation at the final visit ECG. This patient had been treated by a cardiologist and had three ER visits for chest pain with shortness of breath. One patient had a mild atrial fibrillation in the ECG at the 12-week and final visits. This patient was followed by a general practitioner and received no treatment for the atrial fibrillation. Another patient had a left bundle branch block in the final visit ECG. This patient had no cardiac symptoms and was followed by a general practitioner.

In the ipratropium Respimat 40 mcg group, one patient had mild and intermittent atrial fibrillation in the final visit ECG. Another patient had premature ventricular contractions in the final visit ECG. This patient had a history of hypertension and screening ECG showed non-specific ST segment - T wave changes and evidence of an old inferior lateral wall myocardial infarction. Both patients were followed by general practitioners.

Two patients in the MDI placebo group had clinically relevant changes in the 12-week visit ECG. One patient with a history of hypertension had premature ventricular contractions. Another patient had an ECG examination after a car accident. The ischemic change was noted.

There were three patients with ECG findings in the Atrovent MDI 36 mcg group. One patient with a history of hypertension had a first degree heart block in the 12-week ECG. Another patient had an episode of atrial fibrillation. The event was moderate in intensity. One patient had experienced a myocardial infarction two months after the randomization and was recorded the abnormal ECG on the final visit.

10.1.5.2.4 Performance of Respimat devices

Thirty Respimat devices that had been used by patients in the study for 20 weeks were collected. Each device had been released for 30 months and been used for 20 weeks (600 puffs and five cartridges) in the study. The devices were tested with new cartridges containing 0.833% fenoterol hydrobromide test solution. The Applicant stated that the actuation mode of the devices simulated actual patient use. The main results of the performance test are listed in Table 76. There were no changes in the testing parameters observed in the Respimat devices collected from patients that had been released for 30 months and been used for 600 puffs and five cartridges in the study compared to the initial results of the device batch release.

Table 76 Results of performance test for Respimat devices

Testing parameter	Value	Batch release	Sample devices in this study (N=30)
Uniformity of delivered dose (at the beginning of the first cartridge)	Mean	87%	88%
Uniformity of delivered mass	Mean	(b) (4)	
Uniformity of metered mass	Mean		
Fine particle fraction (cascade impactor)	(b) (4)		
Fine particle fraction (light scattering)	(b) (4)		

(Source: Volume 5.10, Section 5.3.4.2, page LAB19)

10.1.5.3 Summary and Conclusion

This six-month study was conducted to compare the safety and efficacy of repeated administration of two strengths of ipratropium Respimat (20 mcg and 40 mcg) with the standard Atrovent MDI 36 mcg dose in patients with COPD. The results of this study demonstrated that both doses of the ipratropium Respimat were safe and effective in comparison with the metered dose inhaler.

The incidence of all adverse events was similar across all treatment groups except for pharyngitis. The percentage of patients reporting pharyngitis in all Respimat groups (12.3%) was higher than that in the Atrovent MDI and MDI placebo groups combined (7.4%). Other safety parameters showed no significant difference between 5 treatment groups. Overall, the ipratropium Respimat 20 mcg and 40 mcg appeared to be safe in this 6-month study.

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/s/

Xu Wang
7/2/2009 02:45:31 PM
MEDICAL OFFICER

Lydia McClain
7/6/2009 09:04:39 AM
MEDICAL OFFICER
I concur with the recommendation for a Complete Response Action. See CDTL review

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-747	**TRADE NAME:**	COMBIVENT RESPIMAT
APPLICANT/SPONSOR:	Boehringer Ingelheim	**USAN NAME:**	iprotropium bromide and albuterol sulfate inhalation spray
MEDICAL OFFICER:	Xu Wang, M.D., Ph.D.		
TEAM LEADER:	Lydia I Gilbert-McClain, M.D., F.C.C.P.	**CATEGORY:**	Beta 2 agonist, anticholinergic combination
DATE:	11/14/08	**ROUTE:**	Oral inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
10/7/08	10/8/08	NDA 21-747, N-000	100 volumes

RELATED APPLICATIONS

Document Date	Application Type	Comments
02/01/08	IND 57,948	Pre-NDA meeting minutes
05/11/06	IND 57,948	EOP2 meeting minutes
01/09/06	IND 57,948	Type C meeting minutes
10/24/03	IND 57,948	Pre-NDA meeting minutes

REVIEW SUMMARY: This NDA is for Combivent Respimat (ipratropium bromide 20 mcg/albuterol sulfate 100mcg) Inhalation Spray. This product was developed as a propellant-free replacement for Combivent CFC-MDI. The proposed indication is the same as that for Combivent CFC-MDI: for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator, who continue to have evidence of bronchospasm, and who require a second bronchodilator. This NDA has significant public health implications because of the ongoing CFC phase out of CFC-containing medications in response to the US agreement with the global treaty for removal of substances that damage the ozone layer (i.e. the Montreal Protocol). The FDA proposed rule to ban Combivent CFC (and 6 other CFC-containing products) from the market was published and the final rule is targeted to be published in June 2009. Combivent CFC-MDI is currently the only ipratropium/albuterol MDI marketed in the US. Thus the proposed Combivent Respimat is important to patients who are using Combivent CFC-MDI that will eventually become unavailable.

In developing Combivent Respimat a pivotal clinical trial 1012.46 was completed in 2004. The primary efficacy endpoint was FEV1 $AUC_{0\text{-}6}$ at study day 85. The study results demonstrated that the ipratropium Respimat monotherapy produced better FEV1 values than the Combivent Respimat at the end of an 8-hour dosing interval on study days 29, 57 and 85, thus not showing the combination was superior to the individual active ingredients. The Applicant therefore developed a lower dosage form of Combivent Respimat (20/100 mcg) and proposed Study 1012.56 that was similar in study design and endpoints to the Study 1012.46 except for the decreased delivering doses of ipratropiun and albuterol.

Over the last 7 - 8 years, the Applicant has had several interactions over the study designs and endpoints of the clinical trial for Combivent Respimat with the Agency. The Division has agreed on the study design and endpoints of the pivotal study, and accepted the Applicant's plan to submit the NDA with only one pivotal clinical trial 1012.56 to support the efficacy of Combivent Respimat, if efficacy findings of the study are robust. The sponsor has provided a hybrid electronic and paper submission of an eNDA and CTD format. The submission includes all items required for filing and is appropriately indexed to allow review.

The regulatory action recommended from a clinical perspective is "fileable."

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

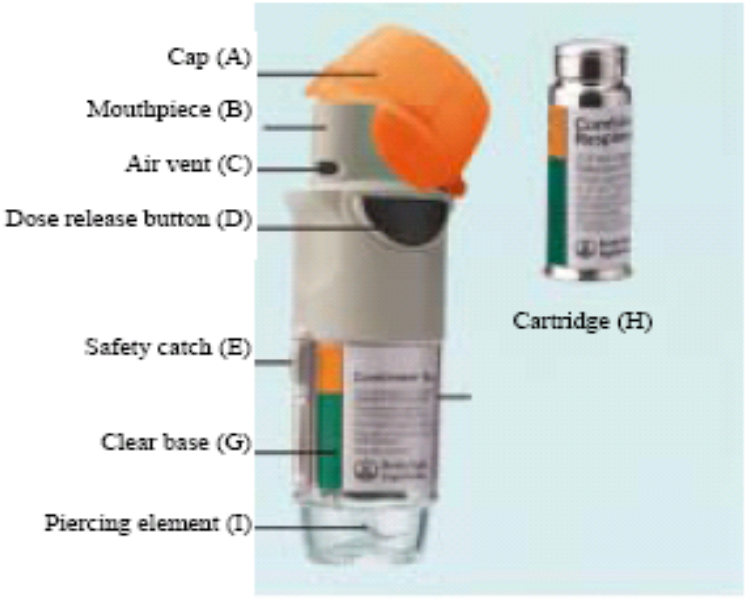
IND/NEW STUDIES:	___	**SAFE TO PROCEED**	___	**CLINICAL HOLD**
NDA/SUPPLEMENTS:	X	**FILEABLE**	X	**NOT FILEABLE**

1. GENERAL INFORMATION AND BACKGROUND

This NDA is a 505(b)(2) application for Combivent Respimat (ipratropium bromide 20 mcg/albuterol sulfate 100mcg) Inhalation Spray. The submission is a 505(b)(2) application because the pharmacology/toxicology data on albuterol was not conducted by or on behalf of the sponsor and the sponsor is relying on the Agency's previous pharmacology toxicology findings in support of the application. This product was developed as a propellant-free replacement for Combivent Inhalation Aerosol CFC-MDI (NDA 20-291, approved October 24, 1996). The proposed labeling indication is the same as that for Combivent Inhalation Aerosol CFC-MDI: for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator, who continue to have evidence of bronchospasm, and who require a second bronchodilator. The proposed dosage is one inhalation (20/100 mcg) four times a day. Patients may take additional inhalations as needed. The total number of inhalations should not exceed six in 24 hours. Summaries of PK studies performed in support of the NDA 20-291 are provided. The sponsor has provided a hybrid electronic and paper submission of an eNDA and CTD format.

The product Combivent Respimat consists of a sterile aqueous inhalation solution of ipratropium bromide and albuterol sulfate in a 4.5 mL cartridge and a Respimat inhaler. Respimat inhaler is an oral inhalation device that uses mechanical energy to generate a slow moving aerosol cloud of medication. The cartridge with the inhalation solution and the Respimat inhaler are supplied as two entities in one package. Prior to first use, the patient inserts the cartridge into the device and prime the inhaler. Each inhalation delivers 20 mcg ipratropium bromide/ 100 mcg albuterol (base) per spray from the mouthpiece. The Combivent Respimat inhaler and the cartridge are shown in Figure 1.

Figure 1: The RESPIMAT inhaler



This NDA has significant public health implications because of the ongoing CFC phase out of CFC-containing medications in response to the U.S. agreement with the global treaty for removal of substances that damage the ozone layer (i.e. the Montreal Protocol). The FDA proposed rule to ban Combivent CFC (and 6 other CFC-containing products) from the market otherwise know as the "Seven Moiety Rule" was published last year and the final rule is targeted to be published in June 2009. The final rule will establish the last date for the removal of the 7 CFC- containing MDI moieties in the US market. Combivent CFC-MDI is currently the only ipratropium/albuterol MDI marketed in the US, although several ipratropium/albuterol solutions are available for use with a nebulizer. Thus the proposed Combivent Respimat is important to the patients who are using Combivent CFC-MDI that will eventually become unavailable after the rule is finalized.

Combivent Inhalation Aerosol CFC-MDI (NDA 20-291) was approved October 24, 1996. The approved dosage of Combivent Inhalation Aerosol CFC-MDI is ipratropium bromide 36 mcg/albuterol sulfate 206 mcg (delivered as two inhalations of 18/103 mcg) four times daily for patients with COPD. (b) (4) In last 7 - 8 years the Applicant has had several interactions over the study design and endpoints of the clinical trials for Combivent Respimat with the Agency. A Special Protocol Assessment of the pivotal clinical trial for Combivent Respimat submitted and reviewed by the Division in 2001 [IND 57,948, Special Protocol Assessment, Medical Officer Review, Raymond F. Anthracite, M. D., November 7, 2001]. The pivotal clinical trial (Study 1012.46) and the planned NDA submission were further discussed in a pre-NDA meeting on September 24, 2003 [IND 57,948, Pre-NDA Package Review, Carol Bosken, M. D., September 30, 2003; IND 57,948, Pre-NDA Meeting Minutes, October 24, 2003].

The clinical trial (Study 1012.46) was completed in 2004. Study 1012.46 was a Phase 3, randomized, double-blind, 12-week, parallel group study in about 1100 patients with COPD. In this study, there were five study medications including both Respimat and CFC placebos: (1) Combivent Respimat 40/200 mcg, (2) Combivent CFC 36/206 mcg, (3) ipratropium Respimat 40 mcg, (4) placebo Respimat, and (5) placebo CFC all administered four times daily. The primary efficacy endpoint was FEV1 AUC_{0-6} at study day 85. All active treatments were superior to placebo. In addition, there was a numerical separation of Ipratropium Respimat from Combivent Respimat from the 4 hour time point which reached statistical significance at the FEV_1 AUC_{6-8} hour interval. The study results demonstrated that the ipratropium Respimat monotherapy (treatment 3) comparator produced better FEV1 values than the Combivent Respimat (treatment 1) at the end of an 8-hour dosing interval on study days 29, 57 and 85, thus not showing the combination was superior to the individual active ingredients. PK data showed that, despite similar nominal doses, there were higher drug exposures from the Respimat device than from the CFC MDI. (b) (4)

The Applicant therefore developed a lower dosage form of Combivent Respimat (20/100 mcg). Since December 2005 the Division and the Applicant have discussed the study protocol several times [IND 57,948, Meeting Minutes, January 9, 2006; IND 57,948, Meeting Minutes, May 11, 2006; and IND 57,948, Biometrics Review, Feng Zhou, June, 12, 2006]. The proposed study (Study 1012.56) was similar in study design and endpoints to the Study 1012.46 except for the decreased delivering doses of ipratropiun and albuterol. The Division agreed that the study would be a randomized, double-blind, double-dummy, parallel-group, active-control, 12-week study in approximately 1500 patients with COPD. The patients would be randomized 1:1:1 to receive (1) Combivent Respimat 20/100 mcg plus placebo Combivent CFC-MDI, (2) Combivent CFC-MDI 36/206 mcg plus placebo Combivent Respimat, and (3) iprotropium bromide Respimat 20 mcg plus placebo Combivent CFC-MDI, all administered four times daily. The agreed upon co-primary endpoints, with each having to achieve a 5% level of significance, were:

(1) Non-inferiority of Combivent Respimat 20/100 mcg to Combivent CFC-MDI 36/206 mcg in FEV1 AUC from 0 to 6 hours at Day 85,
(2) Superiority of Combivent Respimat 20/100 mcg to iprotropium bromide Respimat 20 mcg in FEV1 AUC from 0 to 4 hours at Day 85 (to assess the albuterol contribution to the combination product), and
(3) Non-inferiority of Combivent Respimat 20/100 mcg to iprotropium bromide Respimat 20 mcg in FEV1 AUC from 4 to 6 hours at Day 85.

The non-inferiority margin would be 50 ml for the lower limit of the confidence interval. In a pre-NDA meeting on January 16, 2008, the Division accepted the Applicant's plan to submit the NDA with only one pivotal clinical study 1012.56 to support the efficacy of Combivent Respimat with reservations: "The Division does have reservations regarding your plan to perform a single "pivotal" clinical trial especially since previous studies have failed to demonstrate that the combination is superior to each of its components. However, if efficacy findings are robust, a single trial may be sufficient to establish efficacy." [IND 57,948, Pre-NDA Meeting Minutes, February 1, 2008]

Reviewer comment:
The agreements reached between the Applicant and the Division provided a clear standard in reviewing this NDA for efficacy of the proposed drug product.

2. FOREIGN MARKETING AND REGULATORY HISTORY

Combivent Respimat is not approved in any country. Combivent inhalation aerosol CFC (MDI) has been approved and marketed in the United States October 24, 1996. The Applicant has been marketing Combivent inhalation solution Unit Dose Vial (UDV) in European Union (approved in the United Kingdom on March 22, 1994). In the United States, there are several ipratropium/albuterol inhalation solution products in the market, including DuoNeb by Dey Laboratories (NDA 20-950, approved on March 21, 2001) and several generic forms of ipratropium/albuterol inhalation solution for nebulization.

3. ITEMS REQUIRED FOR FILING AND REVIEWER COMMENTS (21 CFR 314.50)

The following items were included in this submission:

- Form FDA 356h [Volume 1.1, Section 1.1.2]
- Debarment certification [Volume 1.1, Section 1.3.3]
- Financial disclosure statement: From FDA 3454 [Volume 1.1, Section 1.3.4]
- Statements of Good Clinical Practice [Volume 5.19, Section 5.3.5.1, page 29]. The Applicant states that the trial was conducted in compliance with the principles laid down in the Declaration of Helsinki (1996 Version), in accordance with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and in accordance with applicable regulatory requirements.
- There is no Integrated Summary of Efficacy in the submission. This drug product will be supported by a single pivotal study and several supportive studies. In the Pre-NDA meeting on January 16, 2008, the Applicant stated that since there are distinct methodological differences between the pivotal study and supportive studies including dose, method of blinding, inclusion of placebo, and statistical analysis plan, the integration of efficacy data across the studies is scientifically invalid. The Division agreed that the NDA would not contain an integrated efficacy data [IND 57,948, Pre-NDA Meeting Minutes, February 1, 2008].
- There is a Summary of Clinical Safety in the submission [Volume 2.3, Section 2.7.4, pages 1-159]. The Summary of Clinical Safety includes overall safety evaluation and narratives of safety studies, safety results of the phase III and phase II clinical trials, and the post-marketing data. Combivent Respimat is not approved in any country. Combivent inhalation aerosol CFC (MDI) has been approved and marketed in the United States on October 24, 1996. Combivent inhalation solution Unit Dose Vial (UDV) has been approved and marketed in Europe on March 22, 1994. The Applicant submitted Combivent post-marketing data including worldwide Adverse Drug Reactions (ADR) from Spontaneous, Health Authority, literature, Registry, and observational studies from March 22, 1994 to January 31, 2008 [Volume 2.3, Section 2.7.4, pages 129 - 144].
- Proposed labeling and annotated labeling [Volume 1.1, Section 1.14.1.2-3]
- Case report forms for clinical studies are provided as electronic files available at the CDER Electronic Document Room (crf\crftoc.pdf). Individual patient data lists are provided as electronic files available at the CDER Electronic Document Room (crf\datasets\).
- List of referenced DMFs [Volume 1.1, Section 1.4.1]
- Environmental assessment [Volume 1.1, Section 1.12.14]
  - The Applicant has requested a categorical exclusion from this requirement because approval of this NDA would not increase the amount of the active moieties because they are in current use at the same total daily levels for iprotropium bromide and albuterol sulfate. This NDA has been developed as a non-CFC containing product to replace the currently approved product COMBIVENT inhalation Aerosol (NDA 20-291) that contains a CFC-based propellant. The Applicant therefore claims that this NDA represents an additional environmental benefit. [Volume 1.1, Section 1.12.14]
- Request for waiver of pediatric studies [Volume 1.1, Section 1.9.1]
  - The Applicant states that this NDA has been developed as a non-CFC containing product to replace the currently approved product COMBIVENT

inhalation Aerosol (NDA 20-291) for the indication of using in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a secondary bronchodilator. COPD is a progressive chronic respiratory disorder that most often develops in smokers and former smokers in their middle age. COPD is not a disease affecting pediatric patients. The Applicant hereby requests a full waiver of the requirements of 21 CFR 314.55(c)(2) Pediatric Use Information.

4. CLINICAL EFFICACY AND SAFETY STUDIES

This submission includes one pivotal study and several supportive studies. The studies are summarized in the following table.

Table 1.2: 1 List of clinical trials included in the COMBIVENT RESPIMAT NDA

Trial Number	Trial Type	Drug Product	Dosing Regimen	Patient Population
COMBIVENT RESPIMAT Trials				
1012.56	Phase III	COMBIVENT 20/100 mcg	Multiple doses	COPD
1012.46	Phase III	COMBIVENT 40/200 mcg	Multiple doses	COPD
Primary Supporting Trials				
244.2484	Phase III	Ipratropium RESPIMAT	Multiple doses	COPD
244.2447	Phase IIb	Ipratropium RESPIMAT	Single doses	COPD
243.7	Phase IIb	Salbutamol RESPIMAT	Single doses	COPD
243.2	Phase IIb	Salbutamol RESPIMAT	Single doses	Asthma
Other Supporting Trials				
(b) (4)				
Handling Trials				
1012.56	Phase III	A5 RESPIMAT	Multiple doses	COPD
1012.46	Phase III	A4 RESPIMAT	Multiple doses	COPD
244.2484	Phase III	A3 RESPIMAT	Multiple doses	COPD
(b) (4)				
Deposition Trials				
(b) (4)				

The studies are appropriately indexed to allow review. The review will focus on the pivotal study 1012.56, the major supportive study 1012.46, the long-term safety study 244.2484, and two dose-ranging studies 244.2447, and 243.7. More detailed description of these studies follow below.

4.1. Pivotal Study 1012.56

Study 1012.56 is entitled "A comparison of ipratropium bromide/albuterol delivered by the Respimat inhaler to Combivent Inhalation Aerosol and ipratropium bromide delivered by the Respimat in a 12-week, double-blind, safety and efficacy study in adults with chronic obstructive pulmonary disease." The specific objectives of this study were to (1) demonstrate non-inferiority (between 0-6 hours) of Combivent Respimat 20/100 mcg and Combivent CFC-MDI 36/206 mcg on Day 85, (2) demonstrate the superiority (between 0-4 hours) of Combivent Respimat 20/100 mcg over ipratropium Respimat 20 mcg on Day 85, and (3) demonstrate the non-inferiority (between 4-6 hours) of Combivent Respimat 20/100 mcg over ipratropium Respimat 20 mcg on Day 85. In addition, the steady state pharmacokinetics (PK) of the study medication were evaluated in a subgroup of patients over one dosing interval after 4 weeks of therapy.

This study is a three-treatment, 12-wcek, randomized, multi-national, parallel-group, double-blind, double-dummy, active controlled study. There were 1480 male or female COPD patients aged 40 or older randomized into following three treatment groups:

(1) Combivent Respimat (ipratropium bromide 20 mcg/albuterol 100 mcg) one inhalation 4 times daily plus placebo Combivent CFC-MDI, 493 patients (486 treated)
(2) Ipratropium bromide Respimat (ipratropium bromide 20 mcg) one inhalation 4 times daily plus placebo Combivent CFC-MDI, 489 patients (483 treated)
(3) Combivent CFC-MDI (ipratropium bromide 36 mcg/albuterol 206 mcg) two inhalations of 18 mcg/103 mcg 4 times daily plus placebo Combivent Respimat, 498 patients (491 treated)

After an initial screening visit, patients entered a 2-week baseline run-in period in which they were given Atrovent HFA-MDI (18 mcg ipratropium bromide per actuation) and albuterol HFA-MDI as needed. All patients had to have a diagnosis of COPD and must have had the following spirometric criteria at Visit 1 (screening) and Visit 2 (start of treatment): a clinical diagnosis of COPD, ≥10 pack-year smoking history, a relatively stable, moderate to severe airway obstruction with pre-bronchodilator FEV ≤65% of predicted normal and FEV1 ≤70% of FVC. Patients who successfully completed this phase were randomized into the double-blind study treatment groups.

There were three primary efficacy endpoints listed below. The efficacy outcomes are summarized following each efficacy endpoint.

(1) Comparison of AUC between test-day baseline FEV1 and the FEV1 change from test day baseline curve from 0 to 6 hours (FEV1 AUC_{0-6}) divided by six at Day 85 (the end of the treatment period), for comparison of Combivent Respimat 20/100 mcg to Combivent CFC-MDI 36/206 mcg

			Difference	
Treatment	No. of patients	Mean (SE) in L	Mean (SE) in L	95% CI in L
COMBIVENT RESPIMAT 20/100 mcg	474	0.145 (0.007)	-0.003 (0.010)	-0.022, 0.015
COMBIVENT CFC-MDI 36/206 mcg	482	0.149 (0.007)		

(2) Comparison of AUC between test-day baseline FEV1 and the FEV1 change from test-day baseline curve from 0 to 4 hours (FEV1 AUC_{0-4}) divided by four at Day 85 (the end of the treatment period), for comparison of Combivent Respimat 20/100 mcg to ipratropium Respimat 20 mcg

			Treatment difference	
Treatment	No. of patients	Mean (SE) in L	Mean (SE) in L	P-value
COMBIVENT RESPIMAT 20/100 mcg	474	0.189 (0.007)	0.047 (0.010)	<.0001
Ipratropium RESPIMAT 20 mcg	468	0.142 (0.007)		

(3) Comparison of AUC between test-day baseline FEV1 and the FEV1 change from test-day baseline curve from 4 to 6 hours (FEV1 AUC_{4-6}) divided by two at Day 85 (the end of the treatment period), for comparison of Combivent Respimat 20/100 mcg to ipratropium Respimat 20 mcg

			Treatment difference	
Treatment	N	Mean (SE) (L)	Mean (SE) (L)	95% CI (L)
COMBIVENT RESPIMAT 20/100 mcg	447	0.056 (0.008)	-0.017 (0.011)	-0.039, 0.005
Ipratropium RESPIMAT 20 mcg	427	0.073 (0.008)		

The following Figure graphically demonstrated that at day 85, Combivent Respimat 20/100 was non-inferior to Combivent CFC 36/206 in FEV1 AUC_{0-6} and to Ipratropium Respimat 20 in FEV1 AUC_{4-6} (95% CI within the non-inferiority margin of 50 mL). Combivent Respimat 20/100 was also superior to Ipratropium Respimat 20 in FEV1 AUC_{0-4} (95% CI above the margin of 50 mL).

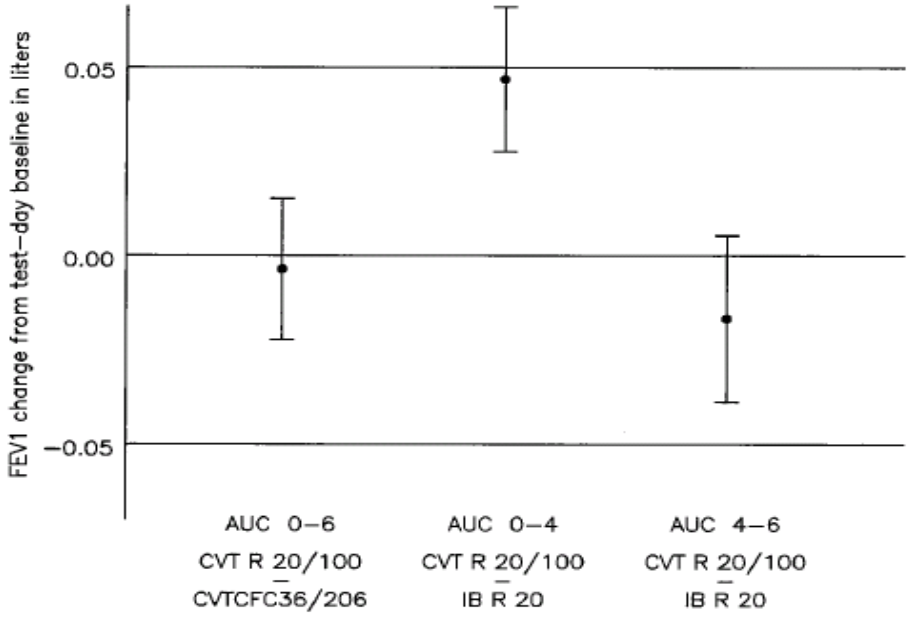


Figure 4:1.5: 1 Day 85 mean treatment differences and 95% confidence intervals, results for the three primary endpoints (Trial 1012.56)

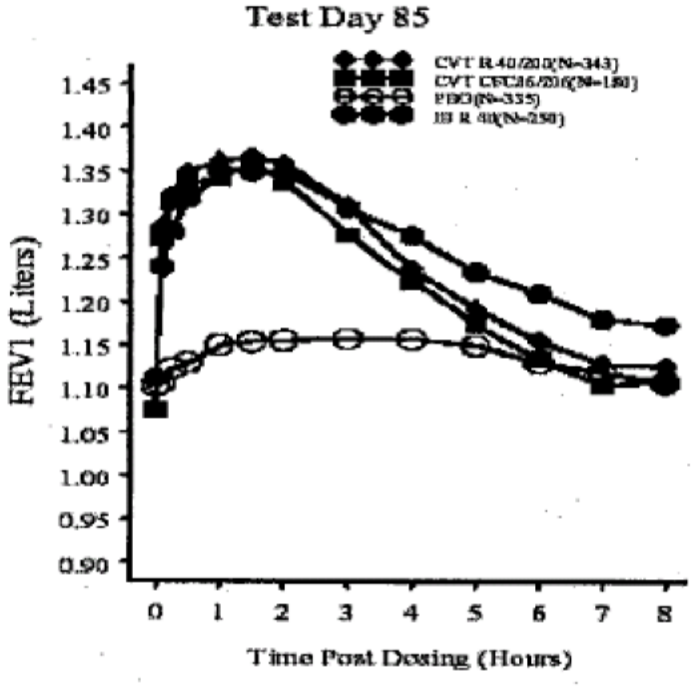
Secondary efficacy endpoints of the study 1012.56 included (1) FEV1 AUC on Days 1, 29, and 57 (AUC_{0-6}, AUC_{0-4}, and AUC_{4-6}), (2) peak FEV1 in the 2-hour interval after treatment on Days 1, 29, 57 and 85, (3) peak FEV1 response (change from test-day baseline) on Days 1, 29, 57 and 85, (4) onset of therapeutic FEV1 response on Days 1, 29, 57 and 85, (5) duration of therapeutic FEV1 response on Days 1, 29, 57 and 85, (6) time to peak FEV1 response on Days 1, 29, 57 and 85, (7) forced vital capacity (FVC) AUC_{0-6} and peak on Days 1, 29, 57 and 85, (8) trough peak expiratory flow rate (PEFR) measured by the patient at home once a day (weekly mean) during the treatment period, (9) individual FEV1 and FVC measurements at each measurement time, (10) amount of beta-agonist therapy used (i.e., weekly mean number of salbutamol doses during day and, separately, at night) as rescue medication during the treatment period, (11) concomitant medication usage, including corticosteroids during the treatment period, (12) daily symptom scores (weekly mean) over the treatment period, (13) number (%) of patients with at least one COPD exacerbation, as well as number and length of COPD exacerbations during the treatment period, and (14) physician's global evaluation on Days 1, 29, 57 and 85.

Safety endpoints were (1) all adverse events during the treatment period, (2) pulse rate (PR) and blood pressure (BP) in conjunction with spirometry, (3) physical examination, and (4) electrocardiogram (ECG) at screening and end of treatment.

4.2. Supportive Study 1012.46

Study 1012.46 was a Phase 3, randomized, double-blind, 12-week, parallel group study in about 1100 patients with COPD. In this study, in order to comply with the combination drug product regulations, there were five study medications including both Respimat and CFC placebos: (1) Combivent Respimat 40/200 mcg, (2) Combivent CFC 36/206 mcg, (3) ipratropium Respimat 40 mcg, (4) placebo Respimat, and (5) placebo CFC all administered four times daily. The primary efficacy endpoint was FEV1 AUC_{0-6} at study day 85. The following Figure 3 showed that at day 85, all active treatments were superior to the placebo in FEV1 AUC_{0-4}. The Ipratropium Respimat monotherapy IB-R 40 produced better FEV1 values that that of the combinations CVT-R 40/200 and CVT-CFC 36/206 from 4 hours post-dosing till the end of the 8-hour period. Thus the trial did not demonstrate the combination was superior to the individual active ingredients. PK data showed that, despite similar nominal doses, there were higher drug exposures from the Respimat device than from the CFC MDI. (b) (4) . The Applicant therefore developed a lower dosage form of Combivent Respimat (20/100 mcg) and conducted the pivotal study 1012.56.

Figure 3: FEV_1 Results Test Day 85



4.3. Long Term Safety Study 244.2484

This is a randomized, double-blind within device, placebo and active controlled, parallel group study. The test agent was ipratropium bromide Respimat at 20 and 40 mcg doses. The active comparator was ipratropium bromide CFC at 36 mcg. The drugs were given four times daily for 24 weeks. Subjects had to be >40 years old, had a clinical diagnosis of COPD, a ≥10 pack-year smoking history, and a FEV1 ≤65%. Of the 646 patients enrolled, 546 completed the study. The patients had a mean age of 65.8 and a mean FEV1 of 1.01 L. The primary outcome was FEV1 AUC_{0-6} change from baseline on Day 85. The safety profiles of the two doses of ipratropium were similar to that of the ipratropium bromide CFC. All treatments were well tolerated. No clinically relevant differences in vital signs or laboratory tests between treatments were observed.

4.4. Ipratropium Dose-Selection Study 244.2447

This is a randomized, double-blind within device, placebo and active controlled, 8-treatment, 4-period, single-dose study. The test agent was ipratropium bromide Respimat at 10, 20, 40, 80, & 160 mcg doses. The active comparator was ipratropium bromide CFC at 18 & 36 mcg. Subjects had to be >40 years old, had a clinical diagnosis of COPD, a ≥10 pack-year smoking history, and a FEV1 ≤65%. In addition, they had to demonstrate reversibility to ipratropium of ≥15%. Of the 116 patients enrolled, 100 completed the study. The patients had a mean age of 63.5 and a mean FEV1 of 1.03 L. The primary outcome variable was FEV1 AUC_{0-6} change from baseline.

4.5. Albuterol Dose-Selection Study 243.7

This is a randomized, double-blind within device, placebo and active controlled, 7-period, dose crossover study. The test agent was albuterol Respimat at 25, 50, 100, & 200 mcg doses. The active comparator was albuterol CFC at 90 & 180 mcg. Subjects had to be >40 years old, had a clinical diagnosis of COPD, a ≥10 pack-year smoking history, and a FEV1 ≤65%. In addition, they had to demonstrate reversibility to albuterol of ≥15%. Of the 62 patients enrolled, 55 completed the study. The patients had a mean age of 64.2 and a mean FEV1 of 1.05 L. The primary outcome was FEV1 AUC_{0-6} change from baseline.

5. BRIEF REVIEW OF PROPOSED LABELING

Proposed labeling and annotated labeling has been included in this submission [Volume 1.1, Section 1.14.1.3, Section 1.14.1.2]. A brief review of proposed labeling was performed. The labeling is in the new PLR format. The clinical trial section contains data from the pivotal trial 1012.56. The safety section contains data from studies 1012.56, 1012. 46, and a 6-month safety study 244.2484. Pre-clinical and post marketing information come from the approved Combivent CFC-MDI labeling.

6. DSI REVIEW/AUDIT

DSI audit will be requested. There is only a single pivotal trial to support the efficacy of this NDA application. The trial was designed with three co-primary endpoints, two of which are based on demonstration of non-inferiority to active treatment. Because in a non-inferiority trial the lack of difference is the measure of the efficacy outcome, certain factors such as poor compliance, missing data, and errors in randomization (mix up of study treatment arms) may make the investigational drug more likely to appear to be efficacious. The quality of trial conduct is critical to the validity of the inferences drawn in non-inferiority trials. The verification of the quality of the trial conduct is specifically important to decision-making. Of the pivotal study 1012.56, there are 179 study sites worldwide and 87 study sites inside the United States. We will request a DSI audit of four study sites in the United States, based on the enrollment of large numbers of study subjects in these sites. Preliminary review of the data did not reveal any specific irregularities.

7. SUMMARY AND RECOMMENDATION

This NDA is a 505(b)(2) application for Combivent Respimat (ipratropium bromide 20 mcg/albuterol sulfate 100 mcg) Inhalation Spray. This product was developed as a propellant-free replacement for Combivent Inhalation Aerosol CFC-MDI (NDA 20-291). The proposed labeling indication is the same as that approved for Combivent Inhalation Aerosol CFC-MDI: for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator, who continue to have evidence of bronchospasm, and who require a second bronchodilator. This NDA has significant public health implications because of the ongoing CFC phase out of CFC-containing medications in response to the US agreement with the global treaty for removal of substances that damage the ozone layer (i.e. the Montreal Protocol). The FDA proposed rule to ban Combivent CFC (and 6 other CFC-containing products) from the market was published last year and the final rule is targeted to be published in June 2009. Combivent CFC-MDI is currently the only ipratropium/albuterol MDI marketed in the US, although several ipratropium/albuterol solutions are available to use with a nebulizer. Thus the proposed Combivent Respimat is important to the patients who are using Combivent CFC-MDI that will eventually be unavailable after the Rule is finalized.

The pivotal clinical trial 1012.46 was completed in 2004. The primary efficacy endpoint was FEV1 AUC_{0-6} at study day 85. The study results demonstrated that the ipratropium Respimat monotherapy produced better FEV1 values than the Combivent Respimat at the end of an 8-hour dosing interval on study days 29, 57 and 85, thus not showing the combination was superior to the individual active ingredients. PK data showed that, despite similar nominal doses, there were higher drug exposures from the Respimat device than from the CFC MDI. (b) (4) . The Applicant therefore developed a lower dosage form of Combivent Respimat (20/100 mcg) and

proposed Study 1012.56 that was similar in study design and endpoints to the Study 1012.46 except for the decreased delivering doses of ipratropiun and albuterol.

In last 7 - 8 years the Applicant has had several interactions over the study designs and endpoints of the clinical trial for Combivent Respimat with the Agency. The Division has agreed on the study design and endpoints of the pivotal study, and accepted the Applicant's plan to submit the NDA with only one pivotal clinical study 1012.56 to support the efficacy of Combivent Respimat, if efficacy findings of the study are robust. The agreements reached between the Applicant and the Division provided a clear standard in reviewing this NDA.

The sponsor has provided a hybrid electronic and paper submission of an eNDA and CTD format. The submission includes all items required for filing and is appropriately indexed to allow review. The regulatory action recommended from a clinical perspective is "fileable."

8. TIME LINE FOR REVIEW

Write-up will be concomitant with the review process. The schedule for review is displayed in Table 2. The pivotal study 1012.56 review will be completed by 01/10/2009. The summary of clinical efficacy review will be completed by 02/15/2009. The review of the safety review and ISS will take place next and will be complete by 03/01/09. Mid cycle review meeting is 03/02/09. Full labeling meeting is 05/11/09. Wrap-up meeting is 05/27/09. The PDUFA goal day is 08/08/09.

Table 2. Proposed schedule for review of NDA 22-279

Milestone	Target Date for Completion
Study 1012.56	01/10/09
Team meeting	01/12/09
Study 1012.46	01/20//09
Study 244.2484	01/25/09
Study 244.2447	01/30/09
Study 243.7	02/05/09
Summary of clinical efficacy	02/15/09
Safety review and ISS	03/01/09
Mid cycle review meeting	03/02/09
Full labeling meeting	05/11/09
Wrap-up meeting	05/27/09
Action Date, 10 months	08/08/09

9. COMMENTS FOR THE SPONSOR

None

Reviewed by:

_____
Xu Wang, M.D., Ph.D.
Medical Officer, Division of Pulmonary and Allergy Products

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Lydia I Gilbert-McClain, M.D., F.C.C.P.
Deputy Director, Division of Pulmonary and Allergy Products

cc: Original NDA 21-747
HFD-570/Division File
HFD-570/ Gilbert-McClain/Division Deputy Director
HFD-570/Wang/Medical Reviewer
HFD-870/Roy/Clinical Pharmacology Reviewer
HFD-580/Schroeder/CMC Reviewer
HFD-570/Pei/Pharmacology/Toxicology Team Leader
HFD-715/Davi/Biometrics Reviewer
HFD-570/Nabavian/CSO

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/s/

Xu Wang
11/18/2008 08:57:40 AM
MEDICAL OFFICER

Lydia McClain
11/18/2008 09:02:13 AM
MEDICAL OFFICER