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APPLICATION NUMBER:

021747Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	21747, SDN 20
Submission Date	April 08, 2011
Brand Name	Combivent® Respimat®
Generic Name	Ipratropium bromide/Albuterol sulfate
Primary Reviewer	Partha Roy, Ph.D.
Team Leader (Acting)	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Pulmonary, Allergy & Rheumatology Products
Sponsor	Boehringer Ingelheim
Submission Type	Resubmission - Class 2
Dosage Form	Inhalation Aerosol
Strength	20 mcg ipratropium bromide (monohydrate) / 100 mcg albuterol base (120 mcg albuterol sulfate) per inhalation
Route of Administration	Oral Inhalation
Proposed Indication	Treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator

Background

A New Drug Application (NDA) for Combivent (NDA 21747) was originally submitted to the Food and Drug Administration (FDA) by (b) (4) on October 08, 2008. Following completion of the review, the FDA took a Complete Response action on August 07, 2009. The Agency concluded that the clinical program did 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 had been demonstrated, there was no data beyond 12 weeks to support long-term use of the product in patients with COPD.

Review Summary

From a clinical pharmacology perspective, the original submission was deemed acceptable (refer to Clinical Pharmacology review by Dr. Partha Roy dated 06/02/2009). In the first cycle of review, initial labeling review was already completed by core disciplines and initial labeling edits and comments were communicated in the Complete Response letter. Clinical Pharmacology had the following comment following the initial review of the submitted label.

In the proposed label under section 12.3, the sponsor had the following statement:

(b) (4)

This reviewer suggested revision of the proposed statement as shown below was communicated to the sponsor in the complete response action letter:

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

In response to FDA's suggestion, the sponsor had the following response in this resubmission supporting the proposed language.

BI Response: (b) (4)

Following review of the above-mentioned material, this reviewer concludes the following:

1. (b) (4)
2. (b) (4)

Therefore based on the above conclusions, this reviewer recommends deleting (indicated by deletion) the following sentence completely from the label:
(b) (4)

The label is still under active negotiation at the time of writing this review and hence final agreement on this issue has not been reached yet. Please refer to the Action Letter for final agreed upon labeling language.

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

/s/

PARTHA ROY
08/24/2011

SURESH DODDAPANENI
08/24/2011

CLINICAL PHARMACOLOGY REVIEW

NDA:	21-747
Type:	505(b)(2)
Brand Name:	COMBIVENT® RESPIMAT®
Generic Name:	ipratropium bromide/albuterol sulfate
Drug Class:	combination anticholinergic / beta$_2$-adrenergic bronchodilator
Indication:	Treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator
Dosage Form:	Inhalation Aerosol
Strength:	20 mcg ipratropium bromide (monohydrate) / 100 mcg albuterol base (120 mcg albuterol sulfate) per inhalation
Route of Administration:	Oral Inhalation
Dosing regimen:	1 inhalation 4 times daily
Applicant:	Boehringer Ingelheim
OCP Division:	Clinical Pharmacology 2
Clinical Division:	Pulmonary and Allergy Products (OND-570)
Submission Date:	October 08, 2008
Reviewer:	Partha Roy, Ph.D.
Team Leader (Acting):	Sally Choe, Ph.D.

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1 Executive Summary

1.1 Background

COMBIVENT RESPIMAT is a combination inhaled product containing ipratropium bromide and albuterol (a.k.a salbutamol) sulfate in a sterile inhalation solution in the Respimat inhaler. It has been developed as a propellant-free replacement for COMBIVENT Inhalation Aerosol, which uses chlorofluorocarbon (CFC) propellants in a pressurized metered dose inhaler (pMDI), in preparation for the eventual removal of the Essential Use Status of COMBIVENT® Inhalation Aerosol. COMBIVENT RESPIMAT Inhalation Spray is indicated for use in COPD patients who are on a regular aerosol bronchodilator, who continue to have evidence of bronchospasm, and who require a second bronchodilator.

The main objectives of this NDA are to demonstrate 1) comparable bronchodilator efficacy and safety of the new COMBIVENT RESPIMAT with the currently marketed COMBIVENT CFC-MDI, and 2) superior efficacy of the COMBIVENT drug combination over ipratropium bromide alone, both delivered by the RESPIMAT inhaler. COMBIVENT CFC-MDI 18/103 mcg is dosed as two inhalations four times a day, and thus each delivered dose (2 inhalations) contains 36 mcg of ipratropium bromide and 206 mcg of albuterol sulfate resulting in a total daily delivered dosage of 144 mcg of ipratropium bromide and 824 mcg of albuterol sulfate.

According to the sponsor, the RESPIMAT inhaler is a multi-dose, oral inhalation device that uses mechanical energy instead of a propellant gas to generate a slow moving cloud of medication from a metered volume of drug solution. Each actuation from the COMBIVENT RESPIMAT inhaler delivers 20 mcg of ipratropium bromide and 100 mcg of albuterol base in 11.4 μL of solution from the mouthpiece. The dose of COMBIVENT RESPIMAT is one inhalation four times a day.

This review focuses on the following three clinical pharmacology aspects of the development program: 1) final dose selection of COMBIVENT RESPIMAT, 2) evaluation of comparative systemic exposure of ipratropium and albuterol delivered from the CFC-MDI device vs. RESPIMAT device, and 3) assessment of age and gender effects on pharmacokinetics (PK) of these drugs.

1.2 Recommendation

The Office of Clinical Pharmacology /Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA21-747 submitted on October 08, 2008 and finds it acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.3 Summary of Clinical Pharmacology Findings

Dose Selection

Dose selection for the Phase 3 COMBIVENT RESPIMAT clinical program was based on the efficacy and pharmacokinetic (PK) results from the dose-ranging studies conducted with single-ingredient RESPIMAT products, ipratropium RESPIMAT and albuterol

RESPIMAT. Dose selection was primarily based on two Phase 2, single-dose, dose-response studies in patients with COPD, namely ipratropium RESPIMAT Trial 244.2447 and albuterol RESPIMAT Trial 243.7 with additional information from other trials.

In Trial 244.2447, a Phase 2, dose-response study in COPD patients, single doses of 20 mcg and 40 mcg of ipratropium bromide administered with the RESPIMAT inhaler were both comparable in FEV_1 response to single dose of 36 mcg of ipratropium CFC-MDI. In addition, mean total amounts of drug excreted in urine from ipratropium RESPIMAT 10 mcg and 20 mcg were found to be comparable to ipratropium CFC-MDI 18 mcg and 36 mcg, respectively, while RESPIMAT 40 mcg resulted in twice the urinary amount of drug compared to that of 36 mcg CFC-MDI.

In Trial 243.7, a Phase 2, dose-response study in COPD patients, single doses of albuterol RESPIMAT 50, 100 and 200 mcg differed little for bronchodilatory effect, indicating that all these doses are at the top of the dose response curve. Based on the ratios of mean amount of albuterol excreted in urine, CFCMDI 90 mcg dose was comparable to albuterol RESPIMAT 50 mcg while the CFCMDI 180 mcg dose was comparable to albuterol RESPIMAT 200 mcg with minimal difference between albuterol RESPIMAT 100 and 200 mcg doses.

Based on these single-ingredient trials and keeping with the 1:5 ratio of ipratropium bromide to albuterol found in COMBIVENT CFC-MDI, the dose combination of 40 mcg of ipratropium bromide and 200 mcg of albuterol was chosen for subsequent testing in the Phase 3 trial 1012.46, which was initially intended to be the pivotal safety and efficacy trial.

The efficacy results from Trial 1012.46 concluded that the FEV_1 response of COMBIVENT RESPIMAT (AUC_{0-6h}) was comparable to COMBIVENT CFC-MDI 36/206 mcg on Test Day 1 with slightly higher lung-function responses in the RESPIMAT 40/200 mcg group on subsequent test days. The PK evaluations revealed considerably higher steady state systemic exposures [peak plasma drug concentration (Cmaxss), area under the plasma drug concentration-time curve (AUCss), urinary drug excretion] for both drug components with the RESPIMAT inhaler in comparison to the CFC-MDI inhaler in the range of 2.8 to 4.6-fold greater exposures for ipratropium and 1.26 to 1.62 greater exposures for albuterol.

The efficacy and PK results from this 1012.46 trial prompted selection of a lower combination dose of COMBIVENT RESPIMAT (20 mcg of ipratropium bromide and 100 mcg of albuterol) for testing in the pivotal Phase 3 trial 1012.56. COMBIVENT RESPIMAT 20/100 mcg also maintains the 1: 5 ratio of ipratropium bromide to albuterol consistent with the reference marketed product COMBIVENT CFC-MDI (36 mcg of ipratropium and 180 mcg of albuterol base). Therefore, the selection of the 20 mcg dose of ipratropium with 100 mcg of albuterol in the RESPIMAT device for further testing in the pivotal Phase 3 trial (1012.56) appears reasonable. The PK results from the trial 1012.56 demonstrated comparable systemic exposures for ipratropium between COMBIVENT RESPIMAT 20/100 mcg and COMBIVENT CFC-MDI 36/206 mcg

treatments while for albuterol, systemic exposure from COMBIVENT RESPIMAT 20/100 mcg was less than that from COMBIVENT CFC-MDI 36/206 mcg, indicating no additional drug burden from the proposed product compared to the currently marketed product. The efficacy results of this pivotal trial are further discussed in the Medical Officer's Review.

Comparative Bioavailability

Comparative bioavailability at steady-state was assessed in the pivotal Phase 3 trial 1012.56 where PK analyses were conducted on the steady-state concentrations of plasma ipratropium and albuterol and 0 to 6 hour renal excretion of the test drugs over one dosing interval after 4 weeks of therapy for a subset of 162 patients from U.S. sites. PK measures (Cmaxss, AUCss, and amount of drug renally excreted over one dosing interval at steady state) were summarized descriptively (Table 1). PK comparability of the COMBIVENT RESPIMAT 20/100 mcg (n = 52) to the marketed reference, COMBIVENT CFC MDI 36/206 mcg (n = 56), as well as to the ipratropium RESPIMAT 20 mcg monotherapy (n = 54), was evaluated.

For ipratropium, the two combination products (Respimat and CFC MDI) were found to be comparable for all PK measures with ratios very close to unity (Table 1). Ipratropium systemic exposure (Cmax and AUC) was also found to be comparable between COMBIVENT RESPIMAT 20/100 mcg and ipratropium RESPIMAT 20 mcg indicating lack of any effect of albuterol on the systemic exposure of ipratropium bromide.

For albuterol, the systemic exposure following COMBIVENT RESPIMAT 20/100 mcg dosing was about 25% less than the systemic exposure following dosing with the marketed reference, COMBIVENT CFC-MDI 36/206 mcg (Table 1).

Table 1. Summary of plasma PK parameters (geometric mean with 90% confidence interval) for ipratropium and albuterol at steady-state

Treatment	AUC pg*h/mL (IPT) ng*h/mL (ALB)	Cmax pg/mL (IPT) ng/mL (ALB)	Cmin pg/mL (IPT) ng/mL (ALB)
Ipratropium (IPT)			
CVT Respimat 20/100 mcg (n = 52)	127.51 (110.24 – 147.48)	33.46 (28.94 – 38.69)	15.25 (13.76 – 16.92)
CVT CFC-MDI 36/206 mcg (n = 56)	122.59 (106.97 – 140.50)	33.80 (29.40 – 38.86)	16.08 (14.56 – 17.76)
IPT Respimat 20 mcg (n = 54)	115.42 (100.57 – 132.47)	35.11 (30.54 – 40.37)	14.84 (13.43 – 16.39)
CVT Respimat / CVT CFC-MDI	***1.04***	***0.99***	***0.95***
Albuterol (ALB)			
CVT Respimat 20/100 mcg (n = 52)	4.09 (3.54 – 4.72)	0.91 (0.79 – 1.04)	0.43 (0.36 – 0.52)
CVT CFC-MDI 36/206 mcg (n = 56)	5.52 (4.82 – 6.34)	1.20 (1.05 – 1.37)	0.60 (0.51 – 0.72)
CVT Respimat / CVT CFC-MDI	***0.74***	***0.76***	***0.71***

As supportive data, comparison of total amount of drugs collected in urine from the COMBIVENT RESPIMAT 20/100 mcg to the marketed reference, COMBIVENT CFC-MDI 36/206 mcg and the mono-component ipratropium RESPIMAT 20 mcg is presented in Table 2. Urine PK results are generally supportive of the plasma data showing comparable amount of urinary ipratropium between the two Combivent formulations while the amount of albuterol in urine was less from the RESPIMAT device compared to that of the CFC MDI device.

In conclusion, the comparability of the ipratropium systemic exposure between the proposed COMBIVENT RESPIMAT 20/100 mcg and the marketed reference, COMBIVENT CFC-MDI 36/206 mcg and less systemic exposure for albuterol from the RESPIMAT device compared to the marketed CFC-MDI device demonstrates that the dose combination of 20/100 mcg chosen for COMBIVENT RESPIMAT should not pose any additional systemic drug burden for both drug components compared to the marketed product. Therefore, the proposed product is not expected to exhibit any systemic safety concern that is not already experienced with the marketed CFC-MDI product.

Table 2. Ratios of the amount (mcg) of ipratropium and albuterol collected in the urine between treatments at steady-state (Trial 1012.56).

Treatment	Ae(0-2h)	Ae(0-6h)
Ipratropium (IPT)		
CVT Respimat / CVT CFC-MDI	***1.08***	***1.18***
IPT Respimat / CVT Respimat	***0.97***	***0.91***
Albuterol (ALB)		
CVT Respimat / CVT CFC-MDI	***0.72***	***0.86***

Ae(0-2h): amount of drug excreted in 2 hours; Ae(0-6h): amount of drug excreted in 6 hours

Effect of age and gender

For both ipratropium and albuterol, gender had minimal effect on systemic exposure following repeated administration of COMBIVENT RESPIMAT 20/100 mcg in the Trial 1012.56. However, for both drugs, patients 65 years of age or older exhibited higher systemic exposures than their younger (< 65 years) counterparts. At steady state, AUC estimates for patients ≥ 65 years were 58% and 66% higher than those for patients < 65 years for ipratropium and albuterol, respectively. The Cmax and urinary excretion (Ae(0-6h)) data also supported this trend. Given similar age effect observed with the marketed Combivent CFC-MDI product in the Trial 1012.56, this difference in systemic exposure between young and elderly patients does not warrant a dose adjustment for the elderly group. Since both drugs are primarily eliminated via kidney, it is not surprising to observe higher systemic exposure in elderly patients, a finding consistent with widely accepted phenomenon of renal impairment with age.

2 QUESTION BASED REVIEW

2.1 General Attributes/Background

2.1.1 What was the sponsor's initial regulatory plan for introducing the RESPIMAT device in the US market?

The sponsor, Boehringer Ingelheim (BI) Pharmaceuticals (b) (4) This submission is intended to switch COMBIVENT from a CFC to a non-CFC inhaler (i.e. RESPIMAT) in line with the ongoing CFC phase out of CFC containing medications in response to the global treaty for removal of substances that damage the ozone layer.

2.1.2 What are the highlights of the formulation and the product/device?

COMBIVENT RESPMAT Inhalation Spray consists of the drug combination of ipratropium bromide and albuterol sulfate in a sterile aqueous solution in the RESPIMAT inhaler. It has been developed as a propellant-free replacement for Combivent Inhalation Aerosol, which uses chlorofluorocarbon (CPC) propellants in a pressurized metered dose inhaler (MDI), in anticipation of the eventual removal of the Essential Use Status of COMBIVENT Inhalation Aerosol.

According to the sponsor, the RESPIMAT inhaler is a hand-held, pocket-sized, oral inhalation device that uses mechanical energy to generate a slow moving cloud ("soft mist") of medication from a metered volume of drug solution. The COMBIVENT sterile aqueous solution is contained in a specifically designed 4.5 mL (b) (4) plastic container crimped into an aluminum cylinder for use with the COMBIVENT RESPIMAT inhaler. Excipients include water for injection, benzalkonium chloride, edetate disodium and hydrochloric acid. The cartridge is only intended for use with the COMBIVENT RESPIMAT inhaler. The plastic container system holds multiple doses of solution that are expelled mechanically. Twisting the base of the inhaler compresses a spring that transfers a metered volume (b) (4) of formulation from the drug cartridge to the dosing chamber. When the inhaler is actuated, the spring is released (b) (4) to form the slow-moving aerosol mist. Each actuation of the inhaler provides a delivered dose (from the mouthpiece) of 20 mcg of ipratropium bromide and 100 mcg of albuterol (which is equivalent to 120 mcg of albuterol sulfate). The inhaler is intended for oral inhalation only and is discarded after

use with one cartridge. The inhaler and cartridge have been developed to deliver 120 metered actuations, which is equivalent to four actuations a day for a supply of 30 days.

2.1.3 What are the proposed mechanism of action and therapeutic indications?

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 beta$_2$-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.

COMBIVENT RESPIMAT Inhalation Spray is indicated for use in patients with COPD who are on a regular aerosol bronchodilator, who continue to have evidence of bronchospasm and who require a second bronchodilator.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

COMBIVENT RESPIMAT is intended for oral inhalation only. Each actuation of the COMBIVENT RESPIMAT inhaler provides a delivered dose of 20 mcg of ipratropium bromide and 100 mcg of albuterol base (which is the molar equivalent to 120 mcg of albuterol sulfate) from the mouthpiece. The intended dosage of COMBIVENT RESPIMAT is four inhalations a day, and thus the proposed total daily delivered dosage is 80 mcg of ipratropium bromide and 400 mcg of albuterol.

2.2 General Clinical Pharmacology

2.2.1 What clinical studies were submitted in this NDA?

Table 3 lists all the clinical trials included in this NDA. Two Phase 3 trials (the supportive trial 1012.46 with COMBIVENT RESPIMAT 40/200 mcg and the pivotal trial 1012.56 with COMBIVENT RESPIMAT 20/100 mcg) were the key trials conducted to provide three critical safety and efficacy comparisons:

1. COMBIVENT RESPIMAT compared with COMBIVENT CFC-MDI to establish a comparability to the 40/200 mcg dose in Trial 1012.46 and non-inferiority to the 20/100 mcg dose in Trial 1012.56.
2. COMBVIENT RESPIMAT (401200 mcg or 20/100 mcg) compared with ipratropium RESPIMAT (40 mcg or 20 mcg) to establish superiority of the drug combination over the single drug ipratropium bromide (Trials 1012.46 and 1012.56).

3. COMBIVENT RESPIMAT 40/200 mcg compared with placebo RESPIMAT to establish the superiority of COMBIVENT over placebo (Trial 1012.46).

Table 3. 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				
244.1504	Phase II	Ipratropium RESPIMAT	Cumulative doses	COPD
244.1505	Phase II (pilot)	Ipratropium RESPIMAT	Cumulative doses	COPD
244.2489	Phase II	Ipratropium RESPIMAT	Multiple doses	COPD
243.3	Phase II	Salbutamol RESPIMAT	Cumulative doses	Asthma
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
215.1357	Phase IIIb	A5 RESPIMAT	Multiple doses	Asthma/COPD
Deposition Trials				
260.2706	Phase I	Fenoterol	Single doses	Healthy volunteers
215.1364	Phase IV	Ipratropium/fenoterol	Single doses	COPD
215.1365	Phase IV	Ipratropium/fenoterol	Single doses	COPD

There are four supporting trials involving single ingredient products that provided data to support dose selection in Phase 3 trials. Particularly, dose selection of each drug component in COMBIVENT RESPIMAT was based on two Phase 2, single-dose, crossover, dose-response studies in patients with COPD: Trial 244.2447 (supporting

ipratropium dose) and Trial 243.7 (supporting albuterol dose). Therefore, this review focuses on Trials 1012.56, 1012.46, 244.2447 and 243.7.

2.2.2 What clinical pharmacology study data contribute to the assessment of efficacy and safety of COMBIVENT RESPIMAT?

The primary efficacy variable in the pivotal efficacy studies was the change from baseline in average pre-dose and 1-hour post-dose FEV_1 over the treatment period. Since systemic absorption of inhaled drugs is the result of pulmonary and gastrointestinal absorption, and because there is uncertainty about the site of absorption along the respiratory tract/airways, plasma concentrations cannot be correlated to efficacy (FEV_1). Therefore, plasma concentrations can only be related to systemic safety.

2.2.3 What is the basis for dose selection for pivotal Phase 3 studies as well as final dosing recommendation?

Dose selection for the Phase 3 COMBIVENT RESPIMAT clinical program was based on the efficacy and PK results of the individual dose-ranging studies for ipratropium RESPIMAT and albuterol RESPIMAT. (b) (4) . Dose selection of the drug components in COMBIVENT RESPIMAT was primarily based on two Phase 2, single-dose, dose-response trials in patients with COPD, namely ipratropium RESPIMAT Trial 244.2447 and albuterol RESPIMAT Trial 243.7. For the ipratropium dose, further support was provided by another Phase 2, 6-month Trial 244.2484 and the cumulative dose response Trial 244.1504 in patients with COPD. For the albuterol dose, additional support was provided by the Phase 2, single dose, dose-response Trial 243.2 and the Phase 2, cumulative dose Trial 243.3 in patients with asthma. Refer to the Medical Officer Review for additional details.

In Trial 244.2447, the Phase 2, single dose, dose-response study in COPD patients of 40 years and older, all seven active treatments (i.e., ipratropium RESPIMAT 10, 20, 40, 80, and 160 mcg and ipratropium CFC-MDI 18 and 36 mcg) were found to be more efficacious than placebo RESPIMAT. Ipratropium RESPIMAT doses (i.e., 10, 20, 40, 80, and 160 mcg) revealed a pattern of increasing efficacy with increasing doses. Single doses of 20 mcg and 40 mcg of ipratropium bromide administered with the RESPIMAT inhaler had comparable FEV_1 responses to that of single dose of 36 mcg of ipratropium CFC-MDI. Plots describing adjusted mean changes in FEV_1 from baseline were similar for these three treatments for the entire testing period of 0 to 8 hours. In addition, equivalence tests (two treatments were considered equivalent if the 90% confidence interval for the treatment difference was completely within the equivalence region of ±0.05 L) on adjusted means for average FEV_1 AUC_{0-6} showed that both the 20 mcg and 40 mcg RESPIMAT doses were statistically equivalent to the CFC-MDI 36 mcg dose (Table 4).

Table 4. Equivalence assessment for adjusted mean FEV_1 AUC_{0-6h} following single dose administration of ipratropium.

Treatment Contrast	Treatment Difference	90% Confidence Interval	p-value for Equivalence Test[1,2]
Ipratropium RESPIMAT 10 mcg vs. ipratropium CFC-MDI 36 mcg	-0.025	-0.055, 0.006	0.088
Ipratropium RESPIMAT 20 mcg vs. ipratropium CFC-MDI 36 mcg	0.007	-0.024, 0.037	0.009
Ipratropium RESPIMAT 40 mcg vs. ipratropium CFC-MDI 36 mcg	0.001	-0.030, 0.032	0.005
Ipratropium RESPIMAT 80 mcg vs. ipratropium CFC-MDI 36 mcg	0.045	0.014, 0.076	0.387
Ipratropium RESPIMAT 160 mcg vs. ipratropium CFC-MDI 36 mcg	0.074	0.042, 0.106	0.890

Source Data: Appendix 15.9.2, STATDOC 4.1.4 (U97-3209).

1 Test of differences in least-squares means, adjusted for center, patient within center, treatment, and visit.

2 Null hypothesis of treatment difference: > 0.05 liters.

In comparison to the ipratropium CFC-MDI 36 mcg dose, the ipratropium RESPIMAT 20 mcg dose resulted in almost 2-fold greater median unchanged drug excreted in urine over 24 hours while the ipratropium RESPIMAT 40 mcg dose resulted in about 2.5-fold as much (Table 5). On the other hand, mean total amounts of drug excreted in urine were found to be about 25% greater from ipratropium RESPIMAT 10 mcg and 20 mcg compared to ipratropium CFC-MDI 18 mcg and 36 mcg, respectively (Table 5), which is considered sufficiently comparable between these dose strengths (10 mcg to 18 mcg and 20 mcg to 36 mcg) delivered from two inhaler devices such as RESPIMAT and CFC-MDI.

Table 5. Amount of ipratropium excreted unchanged in urine during 24 hours after single dose administration

Test Drug	N	Median (mcg)	Percent (of mean) Excreted	Mean ± SE (mcg)
Ipratropium RESPIMAT 10 mcg	13	2.83	26.8	2.7 ± 0.3
Ipratropium RESPIMAT 20 mcg	13	3.96	20.8	3.9 ± 0.7
Ipratropium RESPIMAT 40 mcg	15	5.06	16.1	6.5 ± 1.3
Ipratropium RESPIMAT 80 mcg	13	6.54	9.6	7.7 ± 1.2
Ipratropium RESPIMAT 160 mcg	14	16.28	10.4	16.7 ± 1.9
Ipratropium CFC-MDI 18 mcg	12	1.59	10.9	2.1 ± 0.6
Ipratropium CFC-MDI 36 mcg	13	2.04	9.3	3.1 ± 0.7

In Trial 243.7, a Phase 2, single dose, dose-response study in COPD patients, all six active treatments (i.e. albuterol RESPIMAT 25, 50, 100, or 200 mcg and albuterol CFC-MDI 90 mcg or 180 mcg) were more efficacious than the placebo treatment. Albuterol RESPIMAT doses (i.e., 25 mcg, 50 mcg, 100 mcg, and 200 mcg) showed a pattern of increasing efficacy with increasing doses. Therapeutic equivalence tests (two treatments were considered equivalent if the 90% confidence interval for the treatment difference was completely within the equivalence region of ±0.05 L) for average FEV_1 ($AUC_{0\text{-}6h}$) indicated that albuterol RESPIMAT doses of 50 mcg, 100 mcg and 200 mcg were statistically equivalent to albuterol CFC-MDI 90 mcg dose while only the albuterol RESPIMAT 200 mcg dose was statistically equivalent to the albuterol CFC-MDI 180 mcg dose. Several secondary endpoints indicated that the albuterol RESPIMAT 100 and 200 mcg doses differed little for bronchodilatory effect, indicating that both these doses are at the top of the dose response curve.

Table 6. Equivalence assessment for adjusted mean FEV_1 $AUC_{0\text{-}6h}$ following single dose administration of albuterol.

Treatment Contrast	Treatment Difference (L)	90% Confidence Interval	p-value for Equivalence Test
Salbutamol CFC-MDI 90 mcg versus:			
Salbutamol RESPIMAT 25 mcg	-0.041	-0.64, -0.018	> 0.05
Salbutamol RESPIMAT 50 mcg	-0.016	-0.039, 0.008	0.0080
Salbutamol RESPIMAT 100 mcg	-0.006	-0.029, 0.017	0.0008
Salbutamol RESPIMAT 200 mcg	0.012	-0.012, 0.035	0.0036
Salbutamol CFC-MDI 180 mcg versus:			
Salbutamol RESPIMAT 25 mcg	-0.077	-0.100, -0.053	> 0.05
Salbutamol RESPIMAT 50 mcg	-0.051	-0.075, -0.028	> 0.05
Salbutamol RESPIMAT 100 mcg	-0.041	-0.064, -0.018	> 0.05
Salbutamol RESPIMAT 200 mcg	-0.024	-0.047, 0.000	0.0325

Source Data: Appendix 15.9.2, STATDOC 4.1 (U97-3214).

Notes:

The table shows differences in least-squares means, adjusted for center, patient within center, and visit.
Null hypothesis of treatment difference: (RESPIMAT - VENTOLIN) > 0.05 liters.

The amount of albuterol excreted in the first 30 minutes following inhalation is assumed to be a representation of the total albuterol absorbed systemically that has not undergone gastrointestinal absorption or in other words, via inhalation absorption. Based on the ratios of mean and median amount excreted for the albuterol dose, the RESPIMAT device doses of 100 mcg and 200 mcg gave comparable amounts excreted in urine over the first 30 minutes as the comparable CFC-MDI doses of 90 mcg and 180 mcg, respectively (Table 7). The corresponding plasma concentration data in Table 8 illustrates similar results.

Table 7. Amount of albuterol excreted unchanged in urine within the first 30 minutes (inhalation absorption only) after single dose administration

Test Drug	N	Median (mcg)	Percent (of mean) Dose	Mean ± SD (mcg)
Salbutamol RESPIMAT 25 mcg	12	0.7	3	1.3 ± 1.5
Salbutamol RESPIMAT 50 mcg	15	2.2	4	3.5 ± 3.1
Salbutamol RESPIMAT 100 mcg	19	3.8	4	5.6 ± 5.2
Salbutamol RESPIMAT 200 mcg	20	5.1	3	6.2 ± 3.9
Salbutamol CFC-MDI 90 mcg	16	3.2	4	3.7 ± 3.3
Salbutamol CFC-MDI 180 mcg	19	7.3	4	7.1 ± 4.8

Table 8. Median plasma albuterol concentrations at 30 minutes following Inhalation administration of albuterol treatments

Treatment	N	Concentration (ng/mL) at 30 min
RESPIMAT, 25 mcg	30	Baseline
RESPIMAT, 50 mcg	28	0.5
RESPIMAT, 100 mcg	29	0.72
RESPIMAT, 200 mcg	28	1
CFC MDI, 90 mcg	29	0.69
CFC MDI, 180 mcg	27	0.99

Based on these single-ingredient trials and the intended conservation of the 1:5 ratio of ipratropium bromide to albuterol that is found in COMBIVENT CFC-MDI as well as the marketed mono-products, the dose combination of 40 mcg of ipratropium bromide and 200 mcg of albuterol was chosen for testing in the Phase 3 trial 1012.46, a 3-month, multiple dose, placebo-controlled study initially determined to be the pivotal safety and efficacy trial comparing COMBIVENT RESPIMAT 40/200 mcg with COMBIVENT CFC-MDI 36/206 mcg and ipratropium RESPIMAT 40 mcg (1:1 dose ratio of each component RESPIMAT to CFC-MDI) in patients with COPD.

The efficacy results from Trial 1012.46 concluded that the FEV_1 response of COMBIVENT RESPIMAT ($AUC_{0\text{-}6h}$) was comparable to COMBIVENT CFC-MDI 36/206 mcg on Test Day 1 with slightly higher lung-function responses in the RESPIMAT 40/200 mcg group on subsequent test days. The PK evaluations also revealed higher steady state exposures for both drug components with the RESPIMAT inhaler in comparison with comparable doses for the CFC-MDI inhaler in the range of 2.8 to 4.6 greater exposures for ipratropium and 1.26 to 1.62 greater exposures for albuterol (see Table 9).

Table 9. Comparison of geometric mean ratios for albuterol (a.k.a salbutamol) and ipratropium systemic exposure from the treatments in Trial 1012.46.

	Salbutamol	Ipratropium	
	COMBIVENT RESPIMAT (40/200 mcg)/COMBIVENT CFC-MDI (36/206mcg)	COMBIVENT RESPIMAT (40/200 mcg)/COMBIVENT CFC-MDI (36/206mcg)	Ipratropium RESPIMAT (40 mcg)/ COMBIVENT RESPIMAT (40/200 mcg)
AUC_{0-8}	1.42	4.62	1.03
C_{max}	1.62	3.14	0.87
Ae_{0-2}	1.26	3.50	0.87
Ae_{0-8}	1.33	2.80	0.90

The efficacy as well as PK results from this 1012.46 trial prompted selection of a lower combination dose of COMBIVENT RESPIMAT (20 mcg of ipratropium bromide and 100 mcg of albuterol) for testing in the subsequent Phase 3 trial 1012.56. This dose combination (20/100 mcg) is expected to exhibit a better match for systemic exposure with COMBIVENT CFC-MDI 36/206 mcg than the 40/200 mcg dose combination. In addition, 40/200 mcg compared to COMBIVENT CFC-MDI 36/206 mcg did not yield significantly greater efficacy relative to 20/100 mcg (Tables 4 and 6), indicating a shallow dose response curve. This dose combination also maintains the 1: 5 ratio of ipratropium bromide to albuterol consistent with the reference marketed product COMBIVENT CFC-MDI (36 mcg of ipratropium and 180 mcg of albuterol base). Based on the results discussed above, this reviewer finds the Phase 3 dose selection strategy acceptable.

The pivotal trial 1012.56 evaluated the comparability of COMBIVENT RESPIMAT 20/100 mcg with COMBIVENT CFC-MDI 36/206 mcg and the superiority of COMBIVENT RESPIMAT 20/100 mcg in relation to ipratropium RESPIMAT 20 mcg. The results from this trial demonstrated that following chronic inhalation administration (day 85), COMBIVENT RESPIMAT 20/100 mcg had comparable efficacy to COMBIVENT CFC-MDI 36/206 mcg with respect to FEV1 AUC0-6h, superior efficacy to the mono-component ipratropium RESPIMAT 20 mcg with respect to FEV1 AUC0-4h and comparable efficacy to ipratropium RESPIMAT 20 mcg with respect to FEV1 AUC4-6h. In addition, the PK results demonstrated comparable systemic exposures for ipratropium following all treatments while for albuterol, systemic exposure from COMBIVENT RESPIMAT was less than that from the marketed reference, COMBIVENT CFC-MDI 36/206 mcg, indicating no additional drug burden from the proposed product compared to the currently marketed product. The efficacy results of this pivotal trial are further discussed in the Medical Officer's Review.

2.3 Intrinsic Factors

2.3.1 What is the effect of age and gender on the systemic exposure of ipratropium bromide and albuterol and thereby any impact on efficacy and/or safety?

Based on the PK measures obtained from trial 1012.56, gender had minimal effect on systemic exposure on both ipratropium and albuterol (Table 10) following repeated administration of COMBIVENT RESPIMAT 20/100 mcg. However, for both drugs, patients who were 65 years of age or older exhibited higher systemic exposures than those from their younger counterparts. At steady state, AUC estimates for patients ≥ 65 years were 58% (ipratropium) and 66% (albuterol) higher than that for patients < 65 years. The Cmax and Ae(0-6) data also supported this trend. This age effect observed with COMBIVENT RESPIMAT in the 1012.56 trial is consistent with the PK results observed from 56 patients using the marketed product COMBIVENT CFC-MDI 36/206 mcg from the same trial.

In addition, PK data from the supporting Phase 3 trial 1012.46, also supported the conclusion of age effect on the pharmacokinetics of ipratropium and albuterol, with the exception of ipratropium Cmax (Table 11). Higher systemic ipratropium exposures in patients aged 65 years and older were also observed following inhalation administration of the monoproduct ipratropium RESPIMAT (data not shown). Since this difference in systemic exposure between young and elderly patients has been observed with the marketed COMBIVENT CFC-MDI product where no dose adjustment was recommended in elderly patients, this age effect observed with COMBIVENT RESPIMAT also does not warrant a dose adjustment for this patient group.

Table 10. Effect of age and gender on steady-state PK (geometric mean, range) of ipratropium and albuterol following administration of COMBIVENT RESPIMAT 20/100 mcg

Subgroup	AUC pg*h/mL (IPT) ng*h/mL (ALB)	Cmax pg/mL (IPT) ng/mL (ALB)	Ae(0-6) (mcg)
Ipratropium (IPT)			
Female (n = 25)	123 (55 – 578)	31.7 (10.7 – 192)	1.27 (0.20 – 6.8)
Male (n = 26)	131 (65 – 390)	35.4 (12.5 – 87)	2.05 (0.14 – 23.7)
Age < 65y (n = 29)	105 (55 – 278)	30.1 (10.7 – 79.3)	1.48 (0.14 – 6.8)
Age ≥ 65y (n = 22)	166 (65 – 578)	38.5 (10.7 – 192)	1.9 (0.43 – 23.7)
Albuterol (ALB)			
Female (n = 25)	4.2 (1.68 – 25.3)	0.93 (0.31 – 5.55)	26.4 (2.31 – 191)
Male (n = 26)	4.0 (1.16 – 19.0)	0.89 (0.34 – 3.63)	42.6 (10.8 – 355)
Age < 65y (n = 29)	3.3 (1.16 – 13.9)	0.74 (0.31 – 2.88)	29.2 (2.31 – 156)
Age ≥ 65y (n = 22)	5.4 (1.38 – 25.3)	1.19 (0.34 – 5.55)	41.7 (6.58 – 355)

Ae(0-6h): amount of drug excreted in 6 hours

Table 11. Effect of age on steady-state PK (geometric mean, range) of ipratropium (IPT) and albuterol (ALB) following administration of COMBIVENT RESPIMAT 40/200 mcg in Trial 1012.46.

Drug	**N**	**Dose** (mcg)	**Group**	**AUC** pg*h/mL (IPT) ng*h/mL (ALB)	**Cmax** pg/mL (IPT) ng/mL (ALB)	**Ae(0-8)** mcg
IPT	29	40	<65y	273.4	87.5	4.3
	19	40	≥65y	310.7	82.3	5.7
ABT	29	200	<65y	7.7	1.51	53.3
	19	200	≥65y	9.6	2.02	70.1

2.4 Extrinsic Factors

2.4.1 Does the presence of albuterol affect the PK of ipratropium bromide and vice versa?

Ipratropium and albuterol have been already combined in the approved COMBIVENT Inhalation Aerosol (CFC MDI product). Under the original submission for NDA 20291

S000 for COMBIVENT Inhalation Aerosol, the PK interaction had been evaluated in a crossover study in healthy subjects comparing bioavailability of COMBIVENT CFC-MDI to the two active components administered individually and the conclusion was that the co-administration of ipratropium bromide and albuterol sulfate did not significantly alter the systemic absorption of either component, indicating lack of any PK interaction between these two drugs.

Within the present submission, ipratropium systemic exposure (Cmax and AUC) at steady state (trial 1012.56) were found to be comparable between COMBIVENT RESPIMAT 20/100 mcg (combination) and Ipratropium RESPIMAT 20 mcg (alone) indicating that albuterol did not have any effect on the systemic exposure of ipratropium bromide (Table 12). The urine data presented in Table 12 also supported the conclusion reached from the plasma data.

Table 12. Plasma and urine PK parameters (geometric mean with 90% confidence interval) for ipratropium between ipratropium/albuterol combination (COMBIVENT RESPIMAT) and ipratropium alone (ipratropium RESPIMAT) at steady-state (trial 1012.56)

Treatment	**AUC pg*h/mL (IPT) ng*h/mL (ALB)**	**Cmax pg/mL (IPT) ng/mL (ALB)**	**Cmin pg/mL (IPT) ng/mL (ALB)**
Plasma			
CVT Respimat 20/100 mcg (n = 52)	127.51 (110.24 – 147.48)	33.46 (28.94 – 38.69)	15.25 (13.76 – 16.92)
IPT Respimat 20 mcg (n = 54)	115.42 (100.57 – 132.47)	35.11 (30.54 – 40.37)	14.84 (13.43 – 16.39)
	Amt excreted in 2 hrs (mcg)	**Amt excreted in 6 hrs (mcg)**	
Urine			
CVT Respimat 20/100 mcg (n = 52)	0.75 (0.55 – 1.01)	1.66 (1/30 – 2.13)	
IPT Respimat 20 mcg (n = 54)	0.72 (0.54 – 0.97)	1.51 (1.19 – 1.92)	

2.5 General Biopharmaceutics

2.5.1 What is the relative bioavailability of ipratropium bromide and albuterol delivered in combination from COMBIVENT RESPIMAT compared to the marketed product COMBIVENT CFC MDI in COPD patients?

The sponsor requested a biowaiver for a dedicated comparative bioavailability study, which would not be needed for a locally acting drug product like COMBIVENT RESPIMAT. Steady-state PK assessments of ipratropium and albuterol were conducted for both the

COMBIVENT drug products in two Phase 3 trials along with several supporting clinical trials where comparative PK data was determined for RESPIMAT and CFC-propelled inhalers at the doses evaluated in the pivotal clinical trial.

Relative bioavailability at steady-state was assessed in the pivotal Phase 3 trial 1012.56 where PK analyses were conducted on the steady-state concentrations of plasma ipratropium and albuterol and 0 to 6 hour renal excretion of the test drugs over one dosing interval after 4 weeks of therapy for a subset of 162 patients from U.S. sites. PK comparability of the COMBIVENT RESPIMAT 20/100 mcg (n = 52) to the marketed reference, COMBIVENT CFC MDI 36/206 mcg (n = 56), as well as ipratropium RESPIMAT 20 mcg monotherapy (n = 54), was evaluated.

For ipratropium, the two combination products (RESPIMAT and CFC MDI) were found to be comparable for all PK measures with ratios very close to unity (Table 12). For albuterol, the systemic exposure obtained for albuterol following COMBIVENT RESPIMAT 20/100 mcg dosing was about 25% less than the systemic exposure following dosing with the marketed reference, COMBIVENT CFC-MDI 36/206 mcg (Table 13).

Table 13. Summary of plasma PK parameters (geometric mean with 90% confidence interval) for ipratropium and albuterol at steady-state

Treatment	AUC pg*h/mL (IPT) ng*h/mL (ALB)	Cmax pg/mL (IPT) ng/mL (ALB)	Cmin pg/mL (IPT) ng/mL (ALB)
Ipratropium (IPT)			
CVT Respimat 20/100 mcg (n = 52)	127.51 (110.24 – 147.48)	33.46 (28.94 – 38.69)	15.25 (13.76 – 16.92)
CVT CFC-MDI 36/206 mcg (n = 56)	122.59 (106.97 – 140.50)	33.80 (29.40 – 38.86)	16.08 (14.56 – 17.76)
IPT Respimat 20 mcg (n = 54)	115.42 (100.57 – 132.47)	35.11 (30.54 – 40.37)	14.84 (13.43 – 16.39)
CVT Respimat / CVT CFC-MDI	***1.04***	***0.99***	***0.95***
Albuterol (ALB)			
CVT Respimat 20/100 mcg (n = 52)	4.09 (3.54 – 4.72)	0.91 (0.79 – 1.04)	0.43 (0.36 – 0.52)
CVT CFC-MDI 36/206 mcg (n = 56)	5.52 (4.82 – 6.34)	1.20 (1.05 – 1.37)	0.60 (0.51 – 0.72)
CVT Respimat / CVT CFC-MDI	***0.74***	***0.76***	***0.71***

As supportive data, comparison of total amount of drugs collected in urine from the COMBIVENT RESPIMAT 20/100 mcg to the marketed reference, COMBIVENT CFC-MDI 36/206 mcg and the mono-component ipratropium RESPIMAT 20 mcg is presented

in Table 14. Urine PK results are generally supportive of the plasma data showing comparable amount of ipratropium collected in urine between the two COMBIVENT formulations while the amount of albuterol in urine was less from RESPIMAT device compared to that from CFC MDI device.

In conclusion, the comparable systemic exposure of ipratropium between COMBIVENT RESPIMAT 20/100 mcg and the marketed reference, COMBIVENT CFC-MDI 36/206 mcg and less exposure of albuterol from COMBIVENT RESPIMAT 20/100 mcg than that from the marketed reference should not pose any additional systemic safety concerns that are not already experienced with the marketed CFC-MDI product.

Table 14. Amount of ipratropium and albuterol collected in urine (geometric mean with 90% confidence interval) at steady-state.

Treatment	Ae(0-2h) (mcg)	Ae(0-6h) (mcg)
Ipratropium (IPT)		
CVT Respimat 20/100 mcg (n = 52)	0.75 (0.55 – 1.01)	1.66 (1/30 – 2.13)
CVT CFC-MDI 36/206 mcg (n = 56)	0.69 (0.52 – 0.92)	1.41 (1.12 – 1.77)
IPT Respimat 20 mcg (n = 54)	0.72 (0.54 – 0.97)	1.51 (1.19 – 1.92)
CVT Respimat / CVT CFC-MDI	***1.08***	***1.18***
IPT Respimat / CVT Respimat	***0.97***	***0.91***
Albuterol (ALB)		
CVT Respimat 20/100 mcg (n = 52)	14.68 (11.35 – 18.97)	33.73 (26.98 – 42.17)
CVT CFC-MDI 36/206 mcg (n = 56)	20.31 (15.95 – 25.86)	39.42 (31.93 – 48.66)
CVT Respimat / CVT CFC-MDI	***0.72***	***0.86***

Ae(0-2h): amount of drug excreted in 2 hours; Ae(0-6h): amount of drug excreted in 6 hours

2.6 Analytical Section

2.6.1 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes. All bioanalytical assays fulfilled the regulatory criteria [refer to the FDA guidance for industry "Bioanalytical Method Validation (Final-May 2001)] of not exceeding 15%

(20% for the lowest QC samples) for precision and accuracy during pre-study and in-study validation runs. Study samples were analyzed in runs containing calibrators and quality control samples, as recommended in the FDA guidance.

Ipratropium in Plasma

Ipratropium concentrations were determined using a validated LC/MS/MS assay method. Ipratropium and a stable isotope (b) (4) in plasma (250 µL) were extracted using ion-pairing with potassium iodide followed by methylene chloride with an extraction recovery of >93%. Final analysis was done by LC/MS/MS using positive ion Turbo Ionspray with multiple reaction monitoring. The calibration range was 10 pg/mL to 5000 pg/mL. The linearity of the assay was established with an average correlation coefficient of >0.99 from multiple standard curves.

For study 1012.56, intra-assay and inter-assay precision and accuracy were within 7%. Stability in thawed matrix stored at room temperature was tested for 24 hours before extraction, with the result of less than a 5% difference from original. Re-injection stability for 96 hours at room temperature showed less than a 2% difference from original as well, for three different concentrations. Long-term stability of plasma stored below -20°C was evaluated to 643 days and was within 15% of original values.

Ipratropium in Urine

Ipratropium concentrations were determined using a validated LC/MS/MS assay method. Ipratropium and a stable isotope (b) (4)) in urine (250 µL) were extracted using ion-pairing with potassium iodide followed by methylene chloride with an extraction recovery of 46-60%. Final analysis was done by LC/MS/MS using positive ion Turbo Ionspray with multiple reaction monitoring. The calibration range was 0.1 ng/mL to 100 ng/mL. The linearity of the assay was established with an average correlation coefficient of >0.999 from multiple standard curves.

For study 1012.56, intra-assay and inter-assay precision and accuracy were within 9%. Stability in thawed matrix stored at room temperature was tested for 24 hours before extraction, with the result of less than a 3% difference from original. Re-injection stability for 51 hours at room temperature showed less than a 5% difference from original as well, for three different concentrations. Long-term stability of plasma stored below -20°C was evaluated to 649 days and was within 1% of original values.

Albuterol in Plasma

Albuterol concentrations were determined using a validated LC/MS/MS assay method. Albuterol and its internal standard (b) (4) in plasma (100 µL) were extracted using solid phase extraction (SPE) in a Waters Oasis MCX 96-well plate with a final recovery of >85%. Final analysis was done by LC/MS/MS, using positive ion Turbo Ion Spray with multiple reaction monitoring. The range of the standard curve was validated from 50 pg/mL to 5000 pg/mL. The linearity of the assay was demonstrated with an average

correlation coefficient of >0.99 from multiple standard curves.

For study 1012.56, the intra-day assay precision and accuracy were within 5.2%. The inter-day assay precision and accuracy were within 11.5%. Stability in thawed matrix stored at room temperature was tested 24 hours before extraction, with the result of within 5.1 % of original. Re-injection stability for samples stored at 0 to 50°C for 99 hours were within 5.1 % difference from original. Long-term stability of plasma stored below -20°C was evaluated to 425 days and was within an 8% difference of the original values.

Albuterol in Urine

Albuterol amounts in urine were determined using a validated LC/MS/MS assay method. Albuterol and its internal standard (b) (4) were extracted from urine (0.050 mL) with using solid phase extraction (SPE) in a Waters Oasis MCX 96-well plate with a final recovery of 69-74%. Final analysis was done by LC/MS/MS, using positive ion Turbo Ion Spray with multiple reaction monitoring. The calibration range was 1.00 ng/mL to 200 ng/mL. The linearity of the assay resulted in an average correlation coefficient of >0.99 from multiple standard curves.

For study 1012.56, the intra-day and inter-day assay precision and accuracy were within 10%. Stability in thawed matrix stored at room temperature was tested 24 hours before extraction, with the result within 5% of the original value. Re-injection stability for 51 hours at room temperature showed less than 8.4% difference from original as well. Long-term stability of urine stored below -20°C was evaluated to 393 days and was within 10% difference of the original value.

3 Labeling Recommendations

Here are the initial labeling edits (either as strikethrough or edits in blue bold fonts).

Section 12.3

Section 8.5

4 Appendix – Proposed Label

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

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

/s/

Partha Roy
6/2/2009 02:55:04 PM
BIOPHARMACEUTICS

Sally Choe
6/2/2009 03:42:46 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21747**	**Brand Name**	**Combivent® Respimat®**
OCP Division	**II**	**Generic Name**	**Ipratropium Bromide and Albuterol Sulfate**
Medical Division	**570**	**Drug Class**	**Muscarinic antagonist / β-agonist combo**
OCP Reviewer	**Partha Roy, Ph.D.**	**Indication(s)**	**Proposed indication: Use in COPD patients on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator.**
OCP Team Leader (Acting)	**Wei Qiu, Ph. D.**	**Dosage Form**	**Inhalation Aerosol**
		Dosing Regimen	**Each dose (actuation) delivers 20 mcg Ipratropium bromide and 100 mcg Albuterol (i.e. 120 mcg Albuterol Sulfate); 1 inhalation Q.I.D, NTE 6 inhalations per 24 hrs**
Date of Submission	**8 Oct 08**	**Route of Administration**	**Oral Inhalation (Propellant-free MDI)**
Estimated Due Date of OCP Review	**27 May 09**	**Sponsor**	**Boehringer Ingelheim Pharmaceuticals**
PDUFA Due Date	**08 Aug 09**	**Priority Classification**	**S**
Division Due Date	**08 June 09**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**4**		**Assays for 2 drugs in 2 matrices: plasma and urine**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-		**7**		
single dose:	x	3		**3 supporting PK studies with Respimat monoproducts**
multiple dose:	x	4		**2 Phase III studies plus 2 multiple-dose trials with Respimat monoproducts**
Dose proportionality -				
fasting / non-fasting single dose:	x			
fasting / non-fasting multiple dose:	x			
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x			
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request	**x**			
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	**Waiver request**			
Literature References				
Total Number of Studies		**9**		

Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?	**x**	
Comments sent to firm?	None	
QBR questions (key issues to be considered)	**1. What is the relative BA between Combivent Respimat and Combivent CFC-MDI formulations for both the active drug componenets?** **2. Is there any drug-drug interaction by combining these 2 ingredients?** **3. Does age and gender affect the systemic exposure of the two active drug components when delivered from the Respimat device?**	
Other comments or information not included above	**No single dose relative BA study to compare systemic exposure of Ipratropium and Albuterol between Combivent Respimat and Combivent CFC-MDI. The sponsor is requesting biowaiver for such a study, granting such waiver will be a review issue.**	
Primary reviewer Signature	**Partha Roy, Ph.D.**	
Secondary reviewer Signature	**Wei Qiu, Ph.D.**	

INTRODUCTION

Combivent® Respimat® is a combination inhaled product containing Ipratropium Bromide (anticholinergic bronchodilator) and Albuterol Sulfate (β-adrenergic bronchodilator) in a sterile inhalation solution delivered via Respimat® device. It has been developed as a propellant-free replacement for Combivent® Inhalation Aerosol, which uses chlorofluorocarbon (CPC) propellants in a pressurized metered dose inhaler (MDI), in preparation for the eventual removal of the Essential Use Status of COMBIVENT Inhalation Aerosol. The proposed indication of Combivent Respimat is identical to the existing indication for the approved Combivent CFC-MDI product, i.e. use in COPD patients on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator.

The objective of this sNDA is to provide data to demonstrate comparable bronchodilator efficacy and safety of Combivent Respimat and Combivent CFC-MDI and superior efficacy of the Combivent drug combination delivered by the Respimat inhaler device over Ipratropium bromide alone delivered by the Respimat inhaler.

Two formulation strengths of Ipratropium/Albuterol were evaluated in the COPD clinical development program: 20/100 mcg per actuation and 40/200 mcg per actuation, each administered as 1 actuation per dose. However, the applicant is only seeking approval of the combination 20/100 mcg strength.

CLINICAL PHARMACOLOGY PROGRAM

The primary objective of the clinical pharmacology program is to provide comparative PK data for Ipratropium and Albuterol delivered via Combivent Respimat and Combivent CFC-MDI in patients with COPD. Pharmacokinetic data (plasma and urine) on the Combivent Respimat formulation, at two different dosage levels, were evaluated in two Phase III combination drug trials (1012.46 and 1012.56). Several clinical trials of the mono-components (244.2447, 244.2489, 243.7, 243.2, and 243.3), Ipratropium Bromide or Albuterol Sulfate, with the RESPIMAT inhaler provided additional PK information supportive of Phase III dose selection for the two active drugs.

Request for Bioavailability/Bioequivalence Waiver

The Sponsor has requested that the FDA waive Title 21, CFR 320.22 (Criteria for Waiver of Evidence of in vivo Bioavailabi1ity or Bioequivalence) (b) (3) (i), because the drug product in this application is an approved combination formulated as a solution that is inhaled for a local effect rather than a systemic effect. Pharmacodynamic equivalence of Combivent Respimat 20/100 mcg to the marketed Combivent CFC-MDI 36/206 mcg, has been demonstrated by presenting clinical efficacy and safety data in the pivotal Trial 1012.56. In addition, the Sponsor has evaluated the steady state PK of each of the drug components in approximately 265 COPD patients in the two Phase III clinical trials (1012.46 and 1012.56). These evaluations demonstrated the systemic comparability of Ipratropium levels when delivered by the Respimat and CFC-propelled inhalers in the pivotal Trial 1012.56 at the doses selected. Albuterol levels were slightly lower from the Respimat device compared to the CFC-MDI device.

Reviewer's Comments: The efficacy data from study 1012.56 will be critical in determining the clinical relevance of lower exposure for Albuterol from Combivent Respimat 20/100 mcg in comparison to Combivent CFC-MDI 36/206 mcg. Granting of the biowaiver will be based on the quality and robustness of the PK.

SUMMARY OF RESULTS

Pivotal Combivent Respimat Trial 1012.56

Study design: This was a 12-week, randomized, double-blind, double-dummy, active-controlled trial in 1460 COPD patients that compared Combivent Respimat (Ipratropium Bromide 20 mcg and Albuterol 100 mcg) with Combivent CFC-MDI (Ipratropium Bromide 36 mcg and Albuterol Sulfate 206 mcg) and Ipratropium Bromide Respimat 20 mcg. The general trial objectives were to evaluate the long-term bronchodilator efficacy and safety of the three treatment groups. The specific objectives were to demonstrate at test day 85: (1) non-inferiority of Combivent Respimat 20/100 mcg in comparison with Combivent CFC-MDI 36/206 mcg for FEV_1 AUC for 0 to 6 hours, (2) superiority of Combivent Respimat 20/100 mcg to Ipratropium Respimat 20 mcg for FEV_1 AUC for 0 to 4 hours, and (3) non-inferiority of Combivent Respimat 20/100 mcg to Ipratropium Respimat 20 mcg for FEV_1 AUC for 4 to 6 hours.

PK analyses were conducted on the steady state concentrations of plasma Ipratropium and Albuterol and 0 to 6 hour renal excretion of the test drugs over one dosing interval after 4 weeks of therapy. Each patient had eight plasma samples (trough pre-dose, 5, 15, 30, and 60 minutes post-dose, as well as 2, 4, and 6 hours post-dose) and three urine specimens (pre-dose void, 0-2 hours, and 2-6 hours total urine collection) obtained at Visit 3 (Day 29 of dosing). PK endpoints at steady-state (i.e., Cmax, AUC, and amount of drug renally excreted over one dosing interval) were summarized descriptively. PK comparability between three treatments was evaluated. A sufficient number of patients were randomized into the PK substudy to ensure that a minimum of 50 patients per treatment arm completed this portion of the trial.

Results:

A total of 162 patients in U.S. sites were enrolled in the PK sub-study as Combivent Respimat 20/100 mcg (n = 52), Combivent CFC-MDI 36/206 mcg (n = 56), and Ipratropium Respimat 20 mcg (n = 54).

For all three treatments, plasma Ipratropium concentrations were low and rapidly dissipated within 4-6 hours, which was consistent with the quaternary structure of the compound and the known short half-life of 90 minutes. In many cases, mean data could not be calculated because the majority of the patients were below the limit of quantitation by 4 and 6 hours. In general, the plasma Ipratropium delivered from Combivent Respimat 20/100 mcg had comparable exposure in both plasma and urine to Ipratropium delivered from either Combivent CFC-MDI 36/206 meg or Ipratropium Respimat 20 mcg (Table below). Albuterol delivered from Combivent Respimat 20/100 mcg had a lower exposure in both plasma and urine than Albuterol delivered from Combivent CFC-MDI 36/206 mcg.

In addition, systemic exposure of Ipratropium Bromide appeared to be unaffected by the presence of Albuterol, since ratios of Ipratropium geometric means for Combivent Respimat 20/100 mcg to Ipratropium Respimat 20 mcg were near 1.0 for all the urine and plasma parameters (Table below).

Patients receiving Combivent Respimat 20/100 mcg who were 65 years and over had higher steady state systemic exposures of Ipratropium (AUC = 166 pg.hr/mL) and Albuterol (AUC = 5.44 ng.hr/mL) than patients who were under 65 years of age having Ipratropium AUC of 105 pg.hr/mL and Albuterol AUC of 3.27 ng.hr/mL. Similar data was also obtained for the Ipratropium Respimat alone arm.

Male and female COPD patients exhibited generally comparable steady-state systemic exposure of both Ipratropium and Albuterol following dosing with Combivent Respimat 40/200 mcg and Combivent CFC-MDI 36/206 mcg.

For further details on PK results from study 1012.56, refer to the copy of the filing slides attached at the end of this document.

Table 3.1.1: 1 Comparison of geometric mean ratios for the systemic exposure of the trial formulations in Trial 1012.56

	Salbutamol	Ipratropium	
	COMBIVENT RESPIMAT (20/100 mcg)/COMBIVENT CFC-MDI (36/206mcg)	COMBIVENT RESPIMAT (20/100 mcg)/COMBIVENT CFC-MDI (36/206mcg)	Ipratropium RESPIMAT (20 mcg)/ COMBIVENT RESPIMAT (20/100 mcg)
AUC_{0-6}	0.74	1.04	0.91
C_{max}	0.76	0.99	1.05
Ae_{0-2}	0.72	1.08	0.97
Ae_{0-6}	0.86	1.18	0.91

Source Data: Tables 11.5.2:1-4 (U08-3368-01).

Note: A ratio of 1.00 indicates equivalent systemic exposure.

Additional Combivent Respimat Phase III Trial 1012.46

Study design: This was a 12-week, randomized, double-blinded (within inhaler), parallel study that compared three active treatment groups and two placebo groups in 1,118 COPD patients. The treatment groups were Combivent Respimat (40 mcg of Ipratropium Bromide and 200 mcg of Albuterol), Combivent CFC-MDI (36 mcg of Ipratropium Bromide and 206 mcg of Albuterol Sulfate), Ipratropium Respimat (40 mcg of Ipratropium Bromide), placebo Respimat, and placebo CFC-MDI. The general objectives of this trial were to evaluate the long-term bronchodilator safety and efficacy of the five treatment groups. Specific objectives were to show the comparability of Combivent Respimat 40/200 mcg to Combivent CFC-MDI 36/206 mcg and the superiority of Combivent Respimat 40/200 mcg to Ipratropium Respimat 40 mcg and to characterize the steady-state PK of component drug products during one dosing interval after 4 weeks of study therapy.

PK analyses were conducted on the steady state concentrations of plasma Ipratropium and Albuterol and 0 to 8 hour renal excretion of the test drugs over one dosing interval after 4 weeks of therapy. PK endpoints at steady-state (i.e., Cmax, AUC, and amount of drug renally excreted over one dosing interval) were summarized descriptively. PK comparability between three treatments was evaluated. PK evaluations were planned for approximately 15% of randomized patients.

Results:

Plasma concentrations of Ipratropium and Albuterol were determined from 109 COPD patients while urine concentrations were determined from 113 COPD patients. Ipratropium delivered from the Combivent Respimat 40/200 mcg exhibited substantially greater systemic exposure in both plasma (4.62:1) and urine (2.80:1) than that delivered from Combivent CFC-MDI 36/206 mcg. Although not to the same extent, Albuterol also had greater systemic exposure from Combivent Respimat 40/200 mcg compared to Combivent CFC-MDI (Table below).

In addition, systemic exposure of Ipratropium Bromide appeared to be unaffected by the presence of Albuterol, since ratios of Ipratropium geometric means for Combivent Respimat 40/200 mcg to Ipratropium Respimat 40 mcg were near 1.0 for all the urine and plasma parameters.

Table 3.1.1: 2 Comparison of geometric mean ratios for the systemic exposure of the trial formulations in Trial 1012.46

	Salbutamol	Ipratropium	
	COMBIVENT RESPIMAT (40/200 mcg)/COMBIVENT CFC-MDI (36/206mcg)	COMBIVENT RESPIMAT (40/200 mcg)/COMBIVENT CFC-MDI (36/206mcg)	Ipratropium RESPIMAT (40 mcg)/ COMBIVENT RESPIMAT (40/200 mcg)
AUC_{0-8}	1.42	4.62	1.03
C_{max}	1.62	3.14	0.87
Ae_{0-2}	1.26	3.50	0.87
Ae_{0-8}	1.33	2.80	0.90

Source Data: Tables 15.5.2: 3 (U04-3126).
Note: A ratio of 1.00 indicates equivalent systemic exposure.

Supporting PK Trials in COPD and asthma patients

Pharmaeokinetie data were collected during five supporting trials, one single dose study of Ipratropium Respimat in COPD patients (Trial 244.2447), one multiple dose study of Ipratropium Respimat in COPD patients (Trial 244.2489), one single dose study of Albuterol Respimat in asthmatic patients (Trial 243.2), one single dose study of Albuterol Respimat in COPD patients (Trial 243.7), and one cumulative dose study of Albuterol Respimat in asthmatic patients (Trial 243.3). In all the trials, the standard dose of the marketed CFC-MDI was included as a comparator.

Overall, these individual dose-ranging studies for Ipratropium Respimat and Albuterol Respimat were important in dose(s) selection for Phase III trials. The studies in COPD patients indicated the following:

1. Ipratropium exhibits generally dose proportional PK across doses of 10 to 160 mcg,
2. Comparable median amount of Ipratropium excreted in urine between Ipratropium RESPlMAT 10 mcg and Ipratropium CFC-MDI 36 mcg,
3. Comparable systemic exposure to Albuterol between Albuterol Respimat 200 mcg and Albuterol CFC-MDI 180 mcg following single-dose administration.
4. Greater (~39%) systemic exposure to Albuterol from Albuterol Respimat compared to Albuterol CFC-MDI at comparable doses following multiple-dose administration and at half the dose from the Respimat device only 26% lower exposure from Respimat compared to CFC-MDI.

The Albuterol Respimat trials in asthma patients provided similar comparisons between the two devices and helped arrive at doses to be tested in the COPD patient population.

NDA 21-747

Combivent® Respimat®

Indication: COPD

Type: 505(b)(2)

Filing Meeting

Clinical Pharmacology

Partha Roy, Ph.D.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

Clinical Pharmacology Decision

- **Fileable**
- No relative BA study between Combivent Respimat and Inhalation Aerosol (CFC-MDI)
- No single-dose comparison
- The sponsor requesting Biowaiver for a relative BA study
- No comments to the sponsor at this time

Combivent Respimat Inhalation Spray Product (not approved or marketed in any other country)

- "Switch": Propellant-free replacement for CFC-containing Combivent Inhalation Aerosol 18/103 mcg (approved 1996)
- Aqueous drug combination of Ipratropium bromide and salbutamol sulfate in a sterile inhalation solution and Respimat inhaler
- Each actuation provides a delivered dose of 20 mcg ipratropium bromide and 100 mg salbutamol base (120 mcg salbutamol sulfate)
- Respimat is a hand-held pocket sized oral inhalation device that uses mechanical energy to generate a slow moving aerosol cloud of medication from a metered volume of solution

Trial 1012.56 (Phase III)

Double-blind, active-controlled, double-dummy, 12-week, parallel study with Q.I.D dosing in 1460 COPD patients

- SS PK in 162 patients on Day 29 of dosing with Combivent Respimat 20/100 mcg (n=52), Combivent CFC-MDI 36/206 mcg (n=56), Ipratropium Respimat 20 mcg (n=54)
- Plasma PK samples at 0 (trough pre-dose), 5, 15, 30 min, 1, 2, 4, and 6 hours post-dose
- Urine: 0-2hrs, 2-6hrs

Trial 1012.56 (Phase III) Plasma PK Results

- Comparable systemic exposure of ipratropium between three treatments
- No effect of salbutamol on Ipratropium PK

Table 4.1.2: 1 Pharmacokinetic parameters (geometric mean with 90% confidence intervals) for ipratropium in plasma. (Trial 1012.56)

Treatment	AUC (h•pg/mL)	Cmax (pg/mL)	Cmin (pg/mL)
COMBIVENT RESPIMAT 20/100 mcg (n = 52)	127.51 [110.24, 147.48]	33.46 [28.94, 38.69]	15.25 [13.76, 16.92]
COMBIVENT CFC-MDI 36/206 mcg (n = 56)	122.59 [106.97, 140.50]	33.80 [29.40, 38.86]	16.08 [14.56, 17.76]
Ipratropium RESPIMAT 20 mcg (n = 54)	115.42 [100.57, 132.47]	35.11 [30.54, 40.37]	14.84 [13.43, 16.39]
	Ratios		
COMBIVENT RESPIMAT 20/100 mcg/ COMBIVENT CFC-MDI 36/206 mcg	1.04	0.99	0.95
Ipratropium RESPIMAT 20 mcg/COMBIVENT RESPIMAT 20/100 mcg	0.91	1.05	0.97

Source Data: U08-3368-01.

Trial 1012.56 (Phase III) PK Results

- Lower systemic exposure of salbutamol from Respimat vs. CFC
- Hypothesis is that more salbutamol delivered to lungs rather than GI tract

Table 4.1.2: 2 Pharmacokinetic parameters (geometric mean with 90% confidence intervals) for salbutamol in plasma (Trial 1012.56)

Treatment	AUC (h•ng/mL)	Cmax (ng/mL)	Cmin (ng/mL)
COMBIVENT RESPIMAT 20/100 mcg (n = 52)	4.09 [3.54, 4.72]	0.91 [0.79, 1.04]	0.43 [0.36, 0.52]
COMBIVENT CFC-MDI 36/206 mcg (n = 56)	5.52 [4.82, 6.34]	1.20 [1.05, 1.37]	0.60 [0.51, 0.72]
	Ratios		
COMBIVENT RESPIMAT 20/100 mcg/ COMBIVENT CFC-MDI 36/206 mcg	0.74	0.76	0.71

Source Data: U08-3368-01.

Trial 1012.56 (Phase III) Urine PK Results

Table 4.1.1: 1 Pharmacokinetic parameters (geometric mean with 90% confidence intervals) for ipratropium in urine. (Trial 1012.56)

Treatment	Amount Excreted in 2 Hours (mcg)	Amount Excreted in 6 Hours (mcg)
COMBIVENT RESPIMAT 20/100 mcg (n = 52)	0.75 [0.55, 1.01]	1.66 [1.30, 2.13]
COMBIVENT CFC-MDI 36/206 mcg (n = 56)	0.69 [0.52, 0.92]	1.41 [1.12, 1.77]
Ipratropium RESPIMAT 20 mcg (n = 54)	0.72 [0.54, 0.97]	1.51 [1.19, 1.92]
	Ratios	
COMBIVENT RESPIMAT 20/100 mcg/ COMBIVENT CFC-MDI 36/206 mcg	1.08	1.18
Ipratropium RESPIMAT 20 mcg/COMBIVENT RESPIMAT 20/100 mcg	0.97	0.91

Source Data: U01-3368-01.

Table 4.1.1: 2 Pharmacokinetic parameters (geometric mean with 90% confidence intervals) for salbutamol in urine. . (Trial 1012.56)

Treatment	Amount Excreted in 2 Hours (mcg)	Amount Excreted in 6 Hours (mcg)
COMBIVENT RESPIMAT 20/100 mcg (n = 52)	14.68 [11.35, 18.97]	33.73 [26.98, 42.17]
COMBIVENT CFC-MDI 36/206 mcg (n = 56)	20.31 [15.95, 25.86]	39.42 [31.93, 48.66]
	Ratios	
COMBIVENT RESPIMAT 20/100 mcg/ COMBIVENT CFC-MDI 36/206 mcg	0.72	0.86

Source Data: U08-3368-01.

Trial 1012.56 Results: Intrinsic/extrinsic factors on PK

Ipratropium

- Gender has no effect on Ipratropium systemic exposure
- Patients ≥ 65y: 58% higher AUC, 38% higher Cmin, 26% greater Ae(0-6h) compared to <65y olds
- Ex-smokers had 44% higher AUC, 26% higher Cmin, 58% greater Ae (0-6h) compred to current smokers

Salbutamol

- Gender and smoking had minimal effects on salbutamol exposure
- Patients ≥ 65y: 66% higher AUC, 2-fold higher Cmin, 43% greater Ae(0-6h) compared to <65y olds

Trial 1012.46 (Phase III)

Double-blind (within inhaler), placebo-controlled, 12-week, parallel study with Q.I.D dosing in 1118 COPD patients

- SS PK in 109 patients on Day 29 of dosing with Combivent Respimat 40/200 mcg (n=46), Combivent CFC-MDI 36/206 mcg (n=26), Ipratropium Respimat 40 mcg (n=41), placebo Respimat and placebo-CFC
- Plasma PK samples at 0 (trough pre-dose), 5, 15, 30 min, 1, 2, 4, and 8 hours post-dose
- Urine: 0-2hrs, 2-8hrs

Trial 1012.46 (Phase III) Plasma PK Results

- Greater exposure of salbutamol from Respimat vs. MDI
- Significantly greater exposure of ipratropium from Respimat vs. MDI
- No effect of salbutamol on ipratropium PK

Table 4.2.3: 1 Comparison of geometric mean ratios of pharmacokinetic parameters for the trial formulations (Trial 1012.46)

	Salbutamol	Ipratropium	Ipratropium
	COMBIVENT RESPIMAT 40/200 mcg/COMBIVENT CFC-MDI 36/206 mcg	COMBIVENT RESPIMAT 40/200 mcg/COMBIVENT CFC-MDI 36/206 mcg	Ipratropium RESPIMAT 40 mcg/COMBIVENT RESPIMAT 40/200 mcg
AUC_{0-8}	1.42	4.62	1.03
C_{max}	1.62	3.14	0.87
Ae_{0-2}	1.26	3.50	0.87
Ae_{0-8}	1.33	2.80	0.90

Source Data: Tables 15.5.2: 1 and 15.5.2: 2 (U04-3126).
Note: A ratio of 1.00 indicates equivalent systemic exposure

Trial 1012.46 (Phase III) Urine PK Results

- Greater exposure of salbutamol from Respimat vs. MDI
- Significantly greater exposure of ipratropium from Respimat vs. MDI
- No effect of salbutamol on ipratropium PK

Table 4.2.1: 1 Geometric mean amount (mcg) of analytes excreted unchanged in the urine collection intervals after a steady state dose of COMBIVENT or ipratropium (Trial 1012.46)

Treatment	Excretion Interval	Salbutamol (mcg) Geometric Mean (90% CI)	Ipratropium (mcg) Geometric Mean (90% CI)
COMBIVENT RESPIMAT 40 mcg/200 mcg (n = 44)	0-2 hours	25.1 (19.2–31.0)	2.2 (1.7–2.7)
	0-8 hours	59.4 (46.0–72.8)	4.8 (3.6–6.0)
Ipratropium RESPIMAT 40 mcg (n = 39)	0-2 hours	--	2.0 (-0.1–4.0)
	0-8 hours	--	4.3 (1.2–7.4)
COMBIVENT CFC-MDI 36 mcg/206 mcg (n = 26)	0-2 hours	19.8 (12.9–26.8)	0.6 (0.3–1.0)
	0-8 hours	44.5 (30.8–58.3)	1.7 (1.0–2.4)

Supporting PK data

Trial 244.2447: SD, X-over, dose-ranging study of IPT Respimat in COPD pts

- Linear PK from 10-160 mcg based on total drug in urine (Ae)
- Ae: 2.8 mcg (Respimat 10 mcg), 5.1 mcg (Respimat 40 mcg); 2.0 mcg (CFC-MDI 36 mcg)

Trial 2.44.2489: MD, parallel, safety study of IPT Respimat (80 & 160 mcg) in COPD pts

- Dose-dependent increase in IPT exposure
- Half-life: 4-5 hrs; Ae: 10.6 (Respimat 80 mcg); 19.4 (160 mcg)

Trial 243.7: SD, X-over, dose-ranging study of SAL Respimat (25, 50, 100, 200 mcg) and SAL CFC-MDI in COPD pts

- Median plasma level and Ae indicate that Respimat 100 mcg and 200 mcg were comparable to CFC-MDI 90 and 180 mcg, respectively.

Supporting PK data

Trial 243.2: SD, X-over, dose-ranging study of SAL Respimat (25, 50, 100, 200 mcg) and SAL CFC-MDI (90 and 180 mcg) in asthma pts

- Less than dose proportional increase in exposure (Cmax, AUC, Ae) from 25 to 200 mcg
- Based on exposure (Cmax, AUC, Ae), Respimat 100 mcg and 200 mcg were comparable to CFC-MDI 90 and 180 mcg, respectively.
- Higher plasma level within 1-hr pd from Respimat compared to CFC-MDI

Trial 243.3: MD (3-days), X-over, dose-ranging (50-1600 mcg) study of SAL Respimat and SAL CFC-MDI (90-1440 mcg) in asthma pts

- Higher plasma concentrations for Respimat compared to CFC-MDI
- 39% higher conc for Respimat 100 mcg compared to CFC-MDI 90 mcg

Overall PK conclusions

1. Comparable IPT exposure at steady-state between Combivent Respimat 20/100 mcg and Combivent CFC-MDI 36/206 mcg
2. Presence of SAL did not affect IPT exposure in Combivent Respimat
3. SAL exposure significantly lower from Combivent Respimat 20/100 mcg compared to CFC-MDI 36/206 mcg
4. Combivent Respimat 40/200 mcg clearly exceeded the exposure for both drugs from the marketed CFC-MDI 36/206 mcg, hence not the correct dose
5. Generally both drugs exhibit PK linearity when delivered from Respimat device
6. Age and Gender need to be evaluated carefully for higher exposure: Included in the proposed label (under *Geriatric Use* in 8.5 and *Pharmacokinetics* in 12.3)

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/s/

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12/7/2008 08:30:15 AM
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