CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Number:	21747
Drug Name:	Combivent Respimat (ipratropium bromide and albuterol sulfate inhalation spray)
Indication(s):	Combivent Respimat is intended to be a propellant-free replacement for Combivent CFC Inhalation Aerosol 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.
Applicant:	Boehringer Ingelheim
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Review Priority:	Standard
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Keywords:

NDA, clinical studies, co-primary, noninferiority

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Study 1012.56 adequately achieves all three co-primary efficacy objectives specified in the protocol. First, Combivent Respimat has been shown to be non-inferior to Combivent CFC-MDI in terms of test day 85 mean FEV_1 AUC_{0-6} (using a prespecified non-inferiority margin of 50 mL for the difference of Combivent Respimat minus Combivent CFC). Second, Combivent Respimat has been shown to be superior to Ipratropium Bromide in terms of test day 85 mean FEV_1 AUC_{0-4}. And third, Combivent Respimat has been shown to be non-inferior to Ipratropium Bromide in terms of test day 85 mean FEV_1 AUC_{4-6} (using a prespecified non-inferiority margin of 50 mL for the difference of Combivent Respimat minus Ipratropium Bromide). These conclusions are consistent with varying missing data imputation schemes and do not appear to differ by age or gender.

1.2 Brief Overview of Clinical Studies

The sponsor has submitted the results of one phase 3 pivotal study to support the regulatory approval of Combivent Respimat as a propellant-free replacement for Combivent CFC Inhalation Aerosol 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.

Study 1012.56, the pivotal study, was titled, "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". As part of this study, subjects were randomly assigned (1:1:1) to the following treatment groups:

(1.) Combivent Respimat (20 mcg ipratropium bromide/100 mcg salbutamol, one inhalation qid) plus placebo Combivent CFC-MDI – referred to in this document as **Combivent Respimat**

(2.) ipratropium bromide (Atrovent) Respimat (20 mcg ipratropium bromide, one inhalation qid) plus placebo Combivent CFC-MDI – referred to in this document as **Ipratropium Bromide**

(3.) Combivent Inhalation Aerosol (CFC-MDI) (36 mcg ipratropium bromide/206 mcg salbutamol, in two inhalations qid) plus placebo Combivent Respimat – referred to in this document as **Combivent CFC-MDI**

The primary objectives of the study were to compare the long-term (12-week) bronchodilator efficacy and safety of Combivent Respimat to Ipratropium Bromide (by demonstrating superiority in mean FEV_1 AUC_{0-4} and noninferiority in mean FEV_1 AUC_{4-6}) and to Combivent CFC-MDI (by demonstrating noninferiority in mean FEV_1 AUC_{0-6}) in patients with chronic obstructive pulmonary disease (COPD).

1.3 Statistical Issues and Findings

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

- Analysis of baseline and demographic factors indicate that the treatment groups were adequately balanced to allow attributing differences between the groups to the effect of treatment assignment. (Section 3.1.2)
- Using the FAS_PFT and FAS_PFT46 analysis sets, the main conclusions of the primary efficacy analyses are as follows.
    - Combivent Respimat is non-inferior to Combivent CFC-MDI in terms of test day 85 mean FEV_1 AUC_{0-6} (using a prespecified non-inferiority margin of -0.05 liters).
    - Combivent Respimat is superior to Ipratropium Bromide in terms of test day 85 mean FEV_1 AUC_{0-4}.
    - Combivent Respimat is non-inferior to Ipratropium Bromide in terms of test day 85 mean FEV_1 AUC_{4-6} (using a prespecified non-inferiority margin of -0.05 liters).

  These conclusions were found to be robust to the choice of the statistical model and are consistent with varying missing data imputation schemes. (Section 3.1.2)
- Twenty-two subjects switched treatment during the study due to errors associated with the reserve medication kits and the interactive-voice-response-system or a site error. Discussion is provided indicating why the conclusions of the primary efficacy analyses for this study remain reliable. (Section 3.1.2)
- A summary of the primary efficacy comparisons by gender and age did not reveal any differing treatment effects in those subgroups. Subgroup analyses by race were not possible as nearly all subjects in this study were white. (Section 4.1)

2. INTRODUCTION

2.1 Overview

The sponsor has submitted the results of one phase 3 pivotal study to support the regulatory approval of Combivent Respimat as a propellant-free replacement for Combivent CFC Inhalation Aerosol 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.

Study 1012.56, the pivotal study, was titled, "A comparison of ipratropium bromide/salbutamol delivered by the Respimat inhaler to Combivent Inhalation Aerosol and impratropium bromide delivered by the Respimat in a 12-week, double-blind, safety and efficacy study in adults with chronic obstructive pulmonary disease". As part of this study, subjects were randomly assigned (1:1:1) to the following treatment groups:

(1.) Combivent Respimat (20 mcg ipratropium bromide/100 mcg salbutamol, one inhalation qid) plus placebo Combivent CFC-MDI – referred to in this document as **Combivent Respimat**

(2.) ipratropium bromide (Atrovent) Respimat (20 mcg ipratropium bromide, one inhalation qid) plus placebo Combivent CFC-MDI – referred to in this document as **Ipratropium Bromide**

(3.) Combivent Inhalation Aerosol (CFC-MDI) (36 mcg ipratropium bromide/206 mcg salbutamol, in two inhalations qid) plus placebo Combivent Respimat – referred to in this document as **Combivent CFC-MDI**

The primary objectives of the study were to compare the long-term (12-week) bronchodilator efficacy (and safety) of Combivent Respimat to Ipratropium Bromide (by demonstrating superiority in mean FEV_1 AUC_{0-4} and noninferiority in mean FEV_1 AUC_{4-6}) and to Combivent CFC-MDI (by demonstrating noninferiority in mean FEV_1 AUC_{0-6}) in patients with chronic obstructive pulmonary disease (COPD).

Communication with the sponsor regarding this study is documented under IND 32529 and 57948. Pertinent parts of the statistical portion of those communications are summarized herein.

- In response to questions posed by the sponsor and responded to by the Division in advance of a type C meeting held on December 21, 2005, the Division agreed that the proposed efficacy comparisons and endpoints were acceptable; however, the Division indicated that all three of the proposed comparisons were necessary for demonstration of effectiveness. That is the following comparisons should be considered co-primary with each having to achieve a 5% level of significance.
    - Non-inferiority of Combivent Respimat to Combivent CFC-MDI in FEV_1 AUC_{0-6}
    - Superiority if Combivent Respimat to Atrovent Respimat monotherapy in FEV_1 AUC_{0-4}
    - Non-inferiority of Combivent Respimat to Atrovent Respimat monotherapy in FEV_1 AUC_{4-6}.

- At the type C meeting held on December 21, 2005, the sponsor suggested the use of a clinical threshold of 50 ml for the non-inferiority analyses described above, stating that this threshold had been used previously in other pivotal clinical trials. The Division agreed that this was a reasonable approach but requested that the sponsor provide justification for this threshold in the NDA.

- The requirement to formally demonstrate noninferiority (rather than "comparability") and the use of a noninferiority margin of 50 mL was at the request of the sponsor revisited in a type B meeting with the sponsor on April 26, 2006. The outcome of this discussion remained unchanged from the suggestions from the Division that have been described in the previous two bullets.

- Ultimately, the sponsor apparently agreed to these recommendations (i.e., the co-primary analyses, the use of a formal non-inferiority test, and a non-inferiority margin of 50 mL) in that study 1012.56 was designed with these objectives.

- Regarding calculation of FEV_1 AUC_{0-x} values for the primary efficacy comparisons, in a faxed communication dated June 23, 2006, the Division cautioned that in order to account for the possibility that the FEV_1 might drop below it's baseline value, the FEV_1 AUC_{0-x} defined as the area under the response curve and above baseline from zero to x hours and then divided by x hours should be reduced by the portion of the AUC (if any) that falls below test-day baseline (for further explanation of this calculation, the reader is referred to Figure 1). This was discussed with the sponsor at a brief teleconference on July 18, 2006. The sponsor agreed to this definition and inquired whether test-day baseline could be used and the Division agreed. The sponsor implemented this definition in both the protocol and the study report.

2.2 Data Sources

At the request of the Division, analysis data sets for study 1012.56 were submitted electronically. The following data sets were utilized in the review of this study.

basco.xpt
eindpft.xpt
esumpft.xpt
popu.xpt

All submitted data sets were found to be adequately documented and organized.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design (Study 1012.56)

Study 1012.56 was a three-treatment, parallel group, double-dummy, double-blind, multi-center, 12-week study in adults with chronic obstructive pulmonary disease. The primary objectives of the study were to compare the long-term (12-week) bronchodilator efficacy of Combivent Respimat to Ipratropium Bromide (by demonstrating superiority in mean FEV_1 AUC_{0-4} and noninferiority in mean FEV_1 AUC_{4-6}) and to Combivent CFC-MDI (by demonstrating noninferiority in mean FEV_1 AUC_{0-6}) in patients with chronic obstructive pulmonary disease (COPD). Among other criteria, eligible patients were to have a diagnosis of COPD and have the following spirometric criteria at visits 1 and 2: a relatively stable, moderate to severe airway obstruction with prebronchodilator $FEV_1 \leq 65\%$ of predicted normal and $FEV_1 \leq 70\%$ of forced vital capacity. In total, the protocol specified six inclusion and 28 exclusion criteria for enrollment in this study.

Eligible subjects underwent a two-week run-in period during which all patients received Atrovent HFA-MDI at a dosage of two puffs four times a day and salbutamol HFA-MDI (or CFC-MDI if HFA-MDI was not available) as needed. After the run-in period, subjects were randomly assigned (1:1:1) to the following treatments to be received throughout the 12-week treatment period

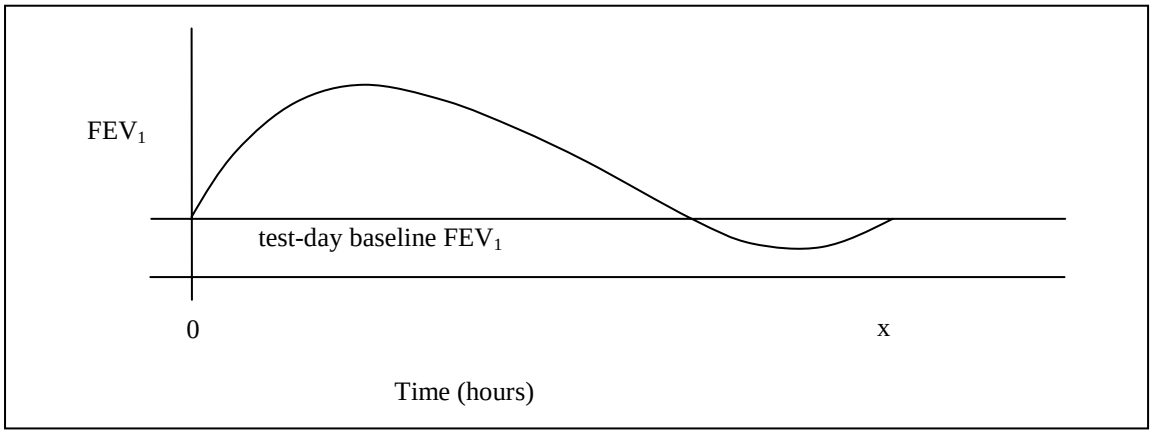
(1.) Combivent Respimat (20 mcg ipratropium bromide/100 mcg salbutamol, one inhalation qid) plus placebo Combivent CFC-MDI – referred to in this document as **Combivent Respimat**
(2.) ipratropium bromide (Atrovent) Respimat (20 mcg ipratropium bromide, one inhalation qid) plus placebo Combivent CFC-MDI – referred to in this document as **Ipratropium Bromide**
(3.) Combivent Inhalation Aerosol (CFC-MDI) (36 mcg ipratropium bromide/206 mcg salbutamol, in two inhalations qid) plus placebo Combivent Respimat – referred to in this document as **Combivent CFC-MDI**

The protocol specified that pulmonary function testing was to be conducted at baseline and at weeks 4, 8, and 12 during the treatment period. At each of these visits, pulmonary function test was to be done at -15 (pre-treatment), 15, 30, 60 minutes, 2, 3, 4, 5, and 6 hours after study drug administration.

The primary efficacy endpoints for this study were obtained at day 85 and are as follows
(1.) mean FEV_1AUC_{0-4} (for demonstration of superiority of Combivent Respimat over Ipratropium Bromide)
(2.) mean FEV_1AUC_{4-6} (for demonstration of noninferiority of Combivent Respimat and Ipratropium Bromide)
(3.) mean FEV_1AUC_{0-6} (for demonstration of noninferiority of Combivent Respimat and Combivent CFC-MDI)

As illustrated in Figure 1, AUC_{0-x} was defined as the area between test-day baseline FEV_1 and the FEV_1 curve, from 0 to x hours divided by x hours. If any component of AUC fell below test-day baseline, this negative AUC component was subtracted from the positive AUC component. AUC was calculated using the trapezoidal rule.

Figure 1: Illustration for calculation of FEV_1 AUC $_{0-x}$



The primary efficacy analyses were comparisons of FEV_1 AUC across treatment groups using an analysis of covariance (ANCOVA) model with fixed effects for treatment and pooled investigator site, and test-day-1-baseline as a covariate. The following three null hypotheses (corresponding to each of the primary objectives of the study) were each tested, with a one-sided α=0.025.

H_0: Combivent Respimat FEV_1 AUC_{0-4} = Ipratropium Bromide FEV_1 AUC_{0-4}
(i.e., for demonstration of superiority of Combivent Respimat over Ipratropium Bromide for FEV_1 AUC_{0-4})

H_0: Ipratropium Bromide FEV_1 AUC_{4-6} - Combivent Respimat FEV_1 $AUC_{4-6} \geq 50$
(i.e., for demonstration of noninferiority of Combivent Respimat and Ipratropium Bromide for FEV_1 AUC_{4-6})

H_0: Combivent CFC-MDI FEV_1 AUC_{0-6} - Combivent Respimat FEV_1 $AUC_{0-6} \geq 50$
(i.e., for demonstration of noninferiority of Combivent Respimat and Combivent CFC-MDI for FEV_1 AUC_{0-6})

The primary efficacy analyses were to be conducted using the protocol-defined full analysis set (FAS), which consisted of all randomized patients with baseline data and data for at least six of the seven time points in the first three hours after treatment. Imputation of missing spirometry data occurred as specified in the protocol and detailed further in the statistical analysis plan, as described below.

For within visit imputation:

- Test day baseline missing: The baseline for the previous test day (including the pre-dose PFT measurement at the screening visit if the test day 1 baseline is missing) is carried forward.
- Missing "middle" observations: Linear interpolation between the two adjacent measurements was used to estimate missing spirometry measurements occurring between two available measurements.
- Missing measurements at the end of the time profile:
    - For values at the end of the profile that were missing because rescue medication was taken, the minimum observed FEV_1 value on that test day (even if it was the pre-dose value) was used as the estimate.
    - For values at the end of the profile that were missing for reasons unrelated to the patient's response to treatment, the last available value was used as the estimate.
    - For values at the end of the profile that were missing for unknown reasons, the observed minimum PFT value on that test-day (even if it was the pre-dose value) is used as the estimate.

  Note: An additional sensitivity analysis was conducted for the primary efficacy endpoints in which the missing values at the end of the profiles were imputed by the minimum observed FEV_1 value on that test day (even if it was the pre-dose value), regardless of the reason for missing data.

For between visit imputation:

- Last visit carried forward is used to account for early withdrawals, i.e., all the serial observations for the missing visits are imputed by the serial observations in the previous visit.

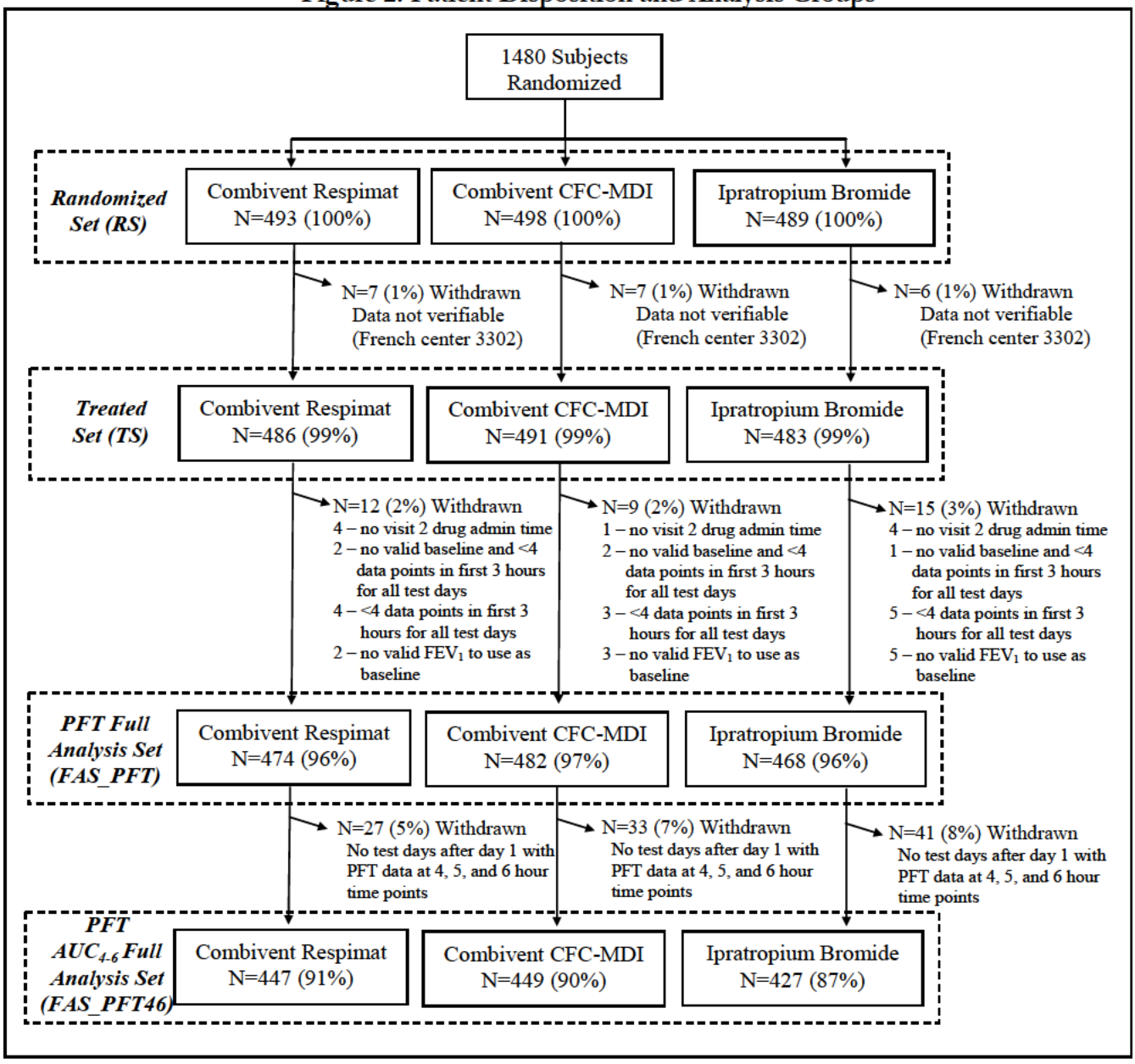
  Note: An additional sensitivity analysis for the primary efficacy analysis including only observed data was conducted.

3.1.2 Results (Study 1012.56)

One thousand four hundred eighty patients were randomized (1:1) into study 1012.56, 493 to receive Combivent Respimat, 498 to receive Combivent CFC-MDI, and 489 to receive Ipratropium Bromide. One center, center number 3302, a French center, was excluded from all analyses since according to the sponsor the accuracy of the recorded data could not be verified against source documentation. As described in Figure 2, two separate analysis sets were developed from the remaining patients for conducting the primary efficacy analyses, the *PFT Full Analysis Set* (FAS_PFT) and the *PFT AUC4-6 Full Analysis Set* (FAS_PFT46). The FAS_PFT was used for analyses designed to demonstrate the noninferiority of Combivent Respimat and Combivent CFC-MDI for FEV_1 AUC_{0-6} and the superiority of Combivent Respimat over Ipratropium Bromide in FEV_1 AUC_{0-4}. The FAS_PFT46 was used for analyses designed to demonstrate the noninferiority of Combivent Respimat and Ipratropium Bromide in FEV_1 AUC_{4-6}. The FAS_PFT included patients in the "treated set" 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). The FAS_PFT46 included patients in the 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 (Days 29, 57, and 85).

The FAS_PFT and FAS_PFT46 were not protocol specified. The protocol specified analysis set to be used for the primary efficacy analysis was referred to as the full analysis set (FAS) and was to consist of all randomized patients with baseline data and data for at least six of the seven time points in the first three hours after treatment. The sponsor does not address this discrepancy in the study report but presumably the non-protocol specified approach to development of two analysis sets for the primary efficacy analyses was used to allow more subjects to be included in the analyses of FEV_1 AUC_{0-6} and FEV_1 AUC_{0-4} while excluding subjects without sufficient data in the 4 to 6 hour time frame only in the analysis of the FEV_1 AUC_{4-6}. Also of note is that the exclusions from the FAS_PFT and FAS_PFT46 sets were fairly low and balanced across treatment groups, with the largest proportion of patients being excluded only from the FAS_PFT46 set. The post-hoc definitions for the FAS_PFT and FAS_PFT46 sets are similar to that of the protocol specified FAS in that for inclusion in the analysis, they require data at a minimum number of time points. In conclusion, although not ideal since these methods were not protocol specified, this approach does not seem unreasonable and is unlikely to have caused any significant biases in the by-treatment-group comparisons.

Figure 2: Patient Disposition and Analysis Groups



Demographic and other baseline characteristics, including pre-bronchodialator screening FEV_1, for the treated set were provided by the sponsor in the clinical study report and are summarized in Table 1. Overall, 65% of the subjects were male and 89% of the subjects were white. The average age among subjects was 64 years, the average smoking history was 53 pack years, the mean COPD duration was 8.4 years, and the mean screening FEV_1 was 2.59 liters. As would be expected due to the random treatment assignment, the three treatment groups were well-balanced with respect to all baseline demographic characteristics.

Table 1: Demographic and Baseline Characteristics (Treated Set)

Demographic/ Baseline Characteristic		Combivent Respimat N=486	Combivent CFC-MDI N=491	Ipratropium Bromide N=483	Total N=1460
Gender (N (%))	Male	316 (65%)	322 (66%)	317 (66%)	955 (65%)
	Female	170 (35%)	169 (34%)	166 (34%)	505 (35%)
Race (N (%))	White	430 (89%)	442 (90%)	428 (89%)	1300 (89%)
	Black	27 (6%)	25 (5%)	26 (5%)	78 (5%)
	Asian	29 (6%)	24 (5%)	29 (6%)	82 (6%)
Age (years)	Mean (st dev)	64 (9)	64 (9)	64 (9)	64 (9)
Height (cm)	Mean (st dev)	170 (9)	169 (9)	169 (10)	169 (9)
Weight (kg)	Mean (st dev)	78 (20)	78 (19)	77 (21)	78 (20)
Alcoholic history (N (%)) *	Non-drinker	223 (46%)	232 (47%)	223 (46%)	678 (46%)
	Average consumption	263 (54%)	258 (53%)	260 (54%)	781 (54%)
	Excessive consumption	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
Smoking history (N (%))	Exsmoker	275 (57%)	303 (62%)	282 (58%)	860 (59%)
	Smoker	211 (43%)	188 (38%)	201 (42%)	600 (41%)
Smoking history (pack years)	Mean (st dev)	52 (28)	52 (27)	55 (28)	53 (28)
	Median (range)	45 (11 to 175)	47 (10 to 225)	49 (12 to 161)	47 (10 to 225)
COPD duration (years)	Mean (st dev)	8 (6)	9 (7)	9 (6)	8 (6)
	Median (range)	7 (<1 to 40)	7 (<1 to 50)	7 (<1 to 43)	7 (<1 to 50)
FEV1 (liters)	Missing	12	17	18	47
	Mean (st dev)	1.2 (.4)	1.2 (.4)	1.1 (.4)	1.1 (.4)

*Average consumption = drinks alcohol but should not interfere with participation in trial, Excessive consumption = drinks alcohol and could interfere with participation in trial
Source: Study 1012.56, clinical study report, tables 11.2:1 and 11.2:1, with modifications in format.

All primary efficacy analyses were conducted using the statistical procedures specified in the protocol and described in section 3.1.1 of this document. The three co-primary efficacy results are given in Table 2.

Table 2: Three Co-Primary Efficacy Analysis[1] – By-Treatment Group Differences in Day 85 FEV_1 AUC_{0-x}			
I. Noninferiority Analysis of FEV_1 AUC_{0-6} using FAS_PFT Analysis Set			
	Combivent Respimat	**Combivent CFC-MDI**	**By-Treatment Group Difference and 95% CI**
Sample Size	474	482	
Least Squares Means[2] (liters)	0.145	0.149	-0.003 (-0.022, 0.015)
II. Superiority Analysis of FEV_1 AUC_{0-4} using FAS_PFT Analysis Set			
	Combivent Respimat	**Ipratropium Bromide**	**By-Treatment Group Difference and 95% CI**
Sample Size	474	468	
Least Squares Means[2] (liters)	0.189	0.142	0.047 (0.028, 0.066)
III. Noninferiority Analysis of FEV_1 AUC_{4-6} using FAS_PFT46 Analysis Set			
	Combivent Respimat	**Ipratropium Bromide**	**By-Treatment Group Difference and 95% CI**
Sample Size	447	427	
Least Squares Means[2] (liters)	0.056	0.073	-0.017 (-0.039, 0.005)

1. As specified in the protocol, test days entirely missing were imputed by carrying the last test day forward and missing data within a test day were imputed by carrying either the lowest or last value forward. The lowest value was used when within-test-day-data were missing due to use of recue medication or for an unknown reason. The last value was carried forward when the reason for the missing within-test-day-data was unrelated to the subject's treatment response.
2. Least squares means are from analysis of covariance (ANCOVA) models with terms for treatment, test-day baseline, and pooled center (as a fixed effect). Separate ANCOVA models were fit for each endpoint.
Source: Study 1012.56, clinical study report, tables 11.4.1.1: 2 through 11.4.1.1: 4, with modifications in format.

The results in Table 2 provide evidence that all three co-primary objectives of this study have been achieved. First, as displayed in section I of Table 2, the primary efficacy analysis demonstrates that Combivent Respimat is non-inferior to Combivent CFC-MDI in terms of test day 85 mean FEV_1 AUC_{0-6} as evidenced by the prespecified non-inferiority margin, -0.05 liters, falling below the lower limit of the 95% confidence interval for the mean difference between treatment groups for this endpoint. Second, as displayed in section II of Table 2, Combivent Respimat is superior to Ipratropium Bromide in terms of test day 85 mean FEV_1 AUC_{0-4} as evidenced by the 95% confidence interval for the mean difference between treatment groups for this endpoint including only positive values (i.e., excludes zero). Finally, as displayed in section III of Table 2, Combivent Respimat has been demonstrated to be non-inferior to Ipratropium Bromide in terms of test day 85 mean FEV_1 AUC_{4-6}, as evidenced by the prespecified non-inferiority margin, -0.05 liters, falling below the lower limit of the 95% confidence interval for the mean difference between treatment groups for this endpoint.

Sensitivity analyses to address the impact of the missing data imputation for the primary efficacy analyses are provided in Tables 3 and 4. These sensitivity analyses lead to conclusions that are qualitatively consistent with the primary efficacy results for the three co-primary efficacy objectives.

Table 3 contains analyses of the "completed set"(CS) where subjects whose missing data were imputed with last-observation-carried-forward methods in the primary efficacy analysis are excluded allowing assessment of the efficacy data without the impact of the LOCF methods (but with the possible bias associated with exclusion of a large group of subjects based on a post-randomization characteristic). Eighty-three subjects originally included in the FAS_PFT46 were excluded from the CS due to early discontinuation (did not stay on study medication up to and including day 85) and 31 subjects were excluded due to day 85 six hour PFT data missing for reasons unrelated to treatment response. As with the primary efficacy analyses, within-test-day-data missing due to rescue medication use or for an unknown reason continued to be imputed with the lowest value for that subject for that day.

There were 22 subjects who switched treatment during the study due to errors associated with the reserve medication kits and the interactive-voice-response-system or a site error. For the efficacy analyses, the sponsor grouped these patients under the first treatment they used at the randomization visit; however, all efficacy data for these subjects from the point the subject received a different treatment onwards were excluded and normal imputation rules for missing data were applied. These errors are expected to have had little impact on the overall primary efficacy results in that they occurred in a small proportion of subjects (i.e., less than 2% of subjects). The consistency in the analyses presented in Table 2 (including these subjects as described above) and Table 3 (excluding these subjects completely) lend support for this.

Table 3: "Completed Set" (CS) Sensitivity Analysis[1]: Co-Primary Efficacy Analysis – By-Treatment Group Differences in Day 85 FEV_1 AUC_{0-x}

I. Noninferiority Analysis of FEV_1 AUC_{0-6} using CS Analysis Set			
	Combivent Respimat	**Combivent CFC-MDI**	**By-Treatment Group Difference and 95% CI**
Sample Size	412	410	
Least Squares Means[2] (liters)	0.145	0.152	-0.006 (-0.027, 0.0143)
II. Superiority Analysis of FEV_1 AUC_{0-4} using CS Analysis Set			
	Combivent Respimat	**Ipratropium Bromide**	**By-Treatment Group Difference and 95% CI**
Sample Size	412	387	
Least Squares Means[2] (liters)	0.191	0.139	0.052 (0.031, 0.073)
III. Noninferiority Analysis of FEV_1 AUC_{4-6} using CS Analysis Set			
	Combivent Respimat	**Ipratropium Bromide**	**By-Treatment Group Difference and 95% CI**
Sample Size	412	387	
Least Squares Means[2] (liters)	0.054	0.068	-0.014 (-0.037, 0.009)

1. Subjects whose missing data were imputed with last-observation-carried-forward methods in the primary efficacy analysis are excluded from this "completed set". That is 83 subjects were excluded from the completed set due to early discontinuation (did not stay on study medication up to and including day 85) and 31 subjects were excluded due to day 85 six hour PFT data missing for reasons unrelated to treatment response. Within-test-day-data missing due to rescue medication use or for an unknown reason were imputed with the lowest value for that day.
2. Least squares means are from analysis of covariance (ANCOVA) models with terms for treatment, test-day baseline, and pooled center (as a fixed effect). Separate ANCOVA models were fit for each endpoint.
Source: Study 1012.56, Statdocs 6.2.20 through 6.2.22, with modifications in format.

Table 4 contains analyses of the FAS_PFT and FAS_PFT46 sets where as with the primary efficacy analyses, test days that were entirely missing were imputed by carrying the last test day forward but unlike the primary efficacy analyses, missing data within a test day were imputed by carrying the lowest value for that test day forward regardless of the reason for the missing data. This sensitivity analysis allows one to address the impact in the primary efficacy analysis of carrying the last value forward when the reason for the missing within-test-day-data was unrelated to the subject's treatment response.

Table 4: Lowest Observed Value Imputed Sensitivity Analysis[1]: Co-Primary Efficacy Analysis – By-Treatment Group Differences in Day 85 FEV_1 AUC_{0-x}			
I. Noninferiority Analysis of FEV_1 AUC_{0-6} using FAS_PFT Analysis Set			
	Combivent Respimat	**Combivent CFC-MDI**	**By-Treatment Group Difference and 95% CI**
Sample Size	474	482	
Least Squares Means[2] (liters)	0.143	0.145	-0.002 (-0.021, 0.016)
II. Superiority Analysis of FEV_1 AUC_{0-4} using FAS_PFT Analysis Set			
	Combivent Respimat	**Ipratropium Bromide**	**By-Treatment Group Difference and 95% CI**
Sample Size	474	468	
Least Squares Means[2] (liters)	0.186	0.140	0.046 (0.027, 0.065)
III. Noninferiority Analysis of FEV_1 AUC_{4-6} using FAS_PFT46 Analysis Set			
	Combivent Respimat	**Ipratropium Bromide**	**By-Treatment Group Difference and 95% CI**
Sample Size	447	427	
Least Squares Means[2] (liters)	0.055	0.071	-0.015 (-0.037, 0.007)

1. Test days entirely missing were imputed by carrying the last test day forward and missing data within a test day were imputed by carrying the lowest value for that test day forward regardless of the reason for the missing data.
2. Least squares means are from analysis of covariance (ANCOVA) models with terms for treatment, test-day baseline, and pooled center (as a fixed effect). Separate ANCOVA models were fit for each endpoint.
Source: Study 1012.56, Statdocs 6.2.24 through 6.2.26, with modifications in format.

Additional analyses of the primary efficacy endpoints employing slight variations in the ANCOVA model (e.g., inclusion of center as a random effect and inclusion of the treatment by center interaction) were conducted by both the sponsor and this reviewer and indicate that the qualitative conclusions supported by Table 2 are robust against these variations in the ANCOVA model.

Secondary endpoints for this study that were derived from FEV_1 included FEV_1 AUC_{0-x} measures on test days 1, 29, and 57; peak FEV1 and peak change from test-day baseline FEV1 within the first two hours of study drug administration on days 1, 29, 57, and 85; time to onset of therapeutic response (achievement of ≥15% increase in FEV_1 within first 2 hours), and duration of therapeutic response for FEV_1. In addition, graphical displays of the mean FEV_1 for each treatment group over six hours on test days 1, 29, 57, and 85 were provided by the sponsor. Secondary endpoints derived from forced vital capacity (FVC) included FVC AUC_{0-x} on test days 1, 29, 57, and 85 and peak FVC on test days 1, 29, 57, and

85. Other secondary endpoints were obtained through patient diaries and included morning peak expiratory flow rate, nighttime and daytime rescue medication use, and patient symptom scores. Finally site physicians provided a "global evaluation" of each patient. The results of these endpoints were generally consistent with those of the primary efficacy analysis.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

A summary of the primary efficacy analyses by gender and age are given in Tables 5 and 6. Subgroup analyses by race are not presented as nearly all (i.e., approximately 90%) of the subjects in this study were white. These analyses did not reveal any differing treatment effects in the subgroups examined.

Table 5: Three Co-Primary Efficacy Analysis by Gender[1] – By-Treatment Group Differences in Day 85 FEV_1 AUC_{0-x}			
Males			
I. Noninferiority Analysis of FEV_1 AUC_{0-6} using FAS_PFT Analysis Set			
	Combivent Respimat	**Combivent CFC-MDI**	**By-Treatment Group Difference and 95% CI**
Sample Size	308	317	
Least Squares Means[2] (liters)	0.158	0.161	-0.004 (-0.030, 0.013)
II. Superiority Analysis of FEV_1 AUC_{0-4} using FAS_PFT Analysis Set			
	Combivent Respimat	**Ipratropium Bromide**	**By-Treatment Group Difference and 95% CI**
Sample Size	308	310	
Least Squares Means[2] (liters)	0.198	0.149	0.048 (0.022, 0.074)
III. Noninferiority Analysis of FEV_1 AUC_{4-6} using FAS_PFT46 Analysis Set			
	Combivent Respimat	**Ipratropium Bromide**	**By-Treatment Group Difference and 95% CI**
Sample Size	290	282	
Least Squares Means[2] (liters)	0.062	0.078	-0.016 (-0.047, 0.015)
Females			
I. Noninferiority Analysis of FEV_1 AUC_{0-6} using FAS_PFT Analysis Set			
	Combivent Respimat	**Combivent CFC-MDI**	**By-Treatment Group Difference and 95% CI**
Sample Size	166	165	
Least Squares Means[2] (liters)	0.117	0.133	-0.016 (-0.045, 0.014)
II. Superiority Analysis of FEV_1 AUC_{0-4} using FAS_PFT Analysis Set			
	Combivent Respimat	**Ipratropium Bromide**	**By-Treatment Group Difference and 95% CI**
Sample Size	166	158	
Least Squares Means[2] (liters)	0.164	0.124	0.040 (0.008, 0.072)
III. Noninferiority Analysis of FEV_1 AUC_{4-6} using FAS_PFT46 Analysis Set			
	Combivent Respimat	**Ipratropium Bromide**	**By-Treatment Group Difference and 95% CI**
Sample Size	157	145	
Least Squares Means[2] (liters)	0.037	0.064	-0.027 (-0.062, 0.008)

1. As specified in the protocol, test days entirely missing were imputed by carrying the last test day forward and missing data within a test day were imputed by carrying either the lowest or last value forward. The lowest value was used when within-test-day-data were missing due to use of recue medication or for an unknown reason. The last value was carried forward when the reason for the missing within-test-day-data was unrelated to the subject's treatment response.

2. Least squares means are from analysis of covariance (ANCOVA) models with terms for treatment, test-day baseline, and pooled center (as a fixed effect). Separate ANCOVA models were fit for each endpoint.

Source: Reviewer analyses

Table 6: Three Co-Primary Efficacy Analysis by Age[1] – By-Treatment Group Differences in Day 85 FEV_1 AUC_{0-x}			
Age < 65 years			
I. Noninferiority Analysis of FEV_1 AUC_{0-6} using FAS_PFT Analysis Set			
	Combivent Respimat	**Combivent CFC-MDI**	**By-Treatment Group Difference and 95% CI**
Sample Size	246	249	
Least Squares Means[2] (liters)	0.147	0.146	0.002 (-0.028, 0.031)
II. Superiority Analysis of FEV_1 AUC_{0-4} using FAS_PFT Analysis Set			
	Combivent Respimat	**Ipratropium Bromide**	**By-Treatment Group Difference and 95% CI**
Sample Size	246	248	
Least Squares Means[2] (liters)	0.193	0.156	0.037 (0.007, 0.068)
III. Noninferiority Analysis of FEV_1 AUC_{4-6} using FAS_PFT46 Analysis Set			
	Combivent Respimat	**Ipratropium Bromide**	**By-Treatment Group Difference and 95% CI**
Sample Size	232	227	
Least Squares Means[2] (liters)	0.058	0.075	-0.016 (-0.053, 0.020)
Age ≥65 years			
I. Noninferiority Analysis of FEV_1 AUC_{0-6} using FAS_PFT Analysis Set			
	Combivent Respimat	**Combivent CFC-MDI**	**By-Treatment Group Difference and 95% CI**
Sample Size	228	233	
Least Squares Means[2] (liters)	0.142	0.155	-0.012 (-0.041, 0.016)
II. Superiority Analysis of FEV_1 AUC_{0-4} using FAS_PFT Analysis Set			
	Combivent Respimat	**Ipratropium Bromide**	**By-Treatment Group Difference and 95% CI**
Sample Size	228	220	
Least Squares Means[2] (liters)	0.184	0.130	0.054 (0.026, 0.082)
III. Noninferiority Analysis of FEV_1 AUC_{4-6} using FAS_PFT46 Analysis Set			
	Combivent Respimat	**Ipratropium Bromide**	**By-Treatment Group Difference and 95% CI**
Sample Size	215	200	
Least Squares Means[2] (liters)	0.052	0.079	-0.026 (-0.058, 0.005)

1. As specified in the protocol, test days entirely missing were imputed by carrying the last test day forward and missing data within a test day were imputed by carrying either the lowest or last value forward. The lowest value was used when within-test-day-data were missing due to use of recue medication or for an unknown reason. The last value was carried forward when the reason for the missing within-test-day-data was unrelated to the subject's treatment response.
2. Least squares means are from analysis of covariance (ANCOVA) models with terms for treatment, test-day baseline, and pooled center (as a fixed effect). Separate ANCOVA models were fit for each endpoint.
Source: Reviewer analyses

4.2 Other Special/Subgroup Populations

No other subgroups of interest were identified in the course of this review.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

- Analysis of baseline and demographic factors indicate that the treatment groups were adequately balanced to allow attributing differences between the groups to the effect of treatment assignment. (Section 3.1.2)
- Using the FAS_PFT and FAS_PFT46 analysis sets, the main conclusions of the primary efficacy analyses are as follows.
    - Combivent Respimat is non-inferior to Combivent CFC-MDI in terms of test day 85 mean FEV_1 AUC_{0-6} (using a prespecified non-inferiority margin of -0.05 liters).
    - Combivent Respimat is superior to Ipratropium Bromide in terms of test day 85 mean FEV_1 AUC_{0-4}.
    - Combivent Respimat is non-inferior to Ipratropium Bromide in terms of test day 85 mean FEV_1 AUC_{4-6} (using a prespecified non-inferiority margin of -0.05 liters).

  These conclusions were found to be robust to the choice of the statistical model and are consistent with varying missing data imputation schemes. (Section 3.1.2)
- Twenty-two subjects switched treatment during the study due to errors associated with the reserve medication kits and the interactive-voice-response-system or a site error. Discussion is provided indicating why the conclusions of the primary efficacy analyses for this study remain reliable. (Section 3.1.2)
- A summary of the primary efficacy comparisons by gender and age did not reveal any differing treatment effects in those subgroups. Subgroup analyses by race were not possible as nearly all subjects in this study were white. (Section 4.1)

5.2 Conclusions and Recommendations

Study 1012.56 adequately achieves all three co-primary efficacy objectives specified in the protocol. First, Combivent Respimat has been shown to be non-inferior to Combivent CFC-MDI in terms of test day 85 mean FEV_1 AUC_{0-6} (using a prespecified non-inferiority margin of 50 mL for the difference of Combivent Respimat minus Combivent CFC). Second, Combivent Respimat has been shown to be superior to Ipratropium Bromide in terms of test day 85 mean FEV_1 AUC_{0-4}. And third, Combivent Respimat has been shown to be non-inferior to Ipratropium Bromide in terms of test day 85 mean FEV_1 AUC_{4-6} (using a prespecified non-inferiority margin of 50 mL for the difference of Combivent Respimat minus Ipratropium Bromide). These conclusions are consistent with varying missing data imputation schemes and do not appear to differ by age or gender.

The following recommendations are being made for the Clinical Studies section of the Combivent labeling.

- The clinical studies section of the sponsor's proposed label describes the results of study 1012.56 using general statements regarding the efficacy comparisons of Combivent Respimat and Combivent CFC-MDI versus placebo. It currently is not limited to the planned primary efficacy endpoints or comparisons. This should be revised to describe the primary efficacy variables and comparisons specifically. This recommendation is being made in order to limit the claims to those that have been rigorously pre-defined, studied, and critically evaluated.
  - The sponsor proposes the phrase (b) (4) to described the comparison of Combivent Respimat and Combivent CFC-MDI. This should be replaced by an accurate account of the comparisons between these treatment groups citing that these were non-inferiority comparisons and describing the specific efficacy endpoints which were involved.
  - Similarly, the superiority comparison of Combivent Respimat to Ipratropium Bromide should include a description of the endpoint analyzed.
  - (b) (4) . However, this was not part of the co-primary efficacy analyses for this study and should not be included.
- (b) (4) This should be revised to indicate that the treatment effects for Combivent Respimat were not observed to be different in any of these subgroups. (b) (4)
- The sponsor proposes text indicating (b) (4) . The term (b) (4) is not well defined from a statistical perspective. Citing actual data to represent the onset of action for Combivent Respimat is preferable to using this descriptor. As requested by the FDA medical division, the onsets of action analyses given by the sponsor in the summary of clinical efficacy were verified as part of this statistical review.
  - Onset of action was calculated as follows. On test days, spirometry was recorded prior to inhaling randomized treatment and at ¼, ½, 1, 2, 3, 4, 5, and 6 hours after inhalation. A therapeutic response was considered to have been achieved if an FEV1 measurement of at least 1.15 times the test-day baseline FEV1 value was recorded at any time during the first 2 hours of observation. Onset of therapeutic response was defined as the linear interpolation of the time of the first therapeutic response and the time of the observation just prior to the first therapeutic response (even if that was the pre-dose observation). If no therapeutic response was achieved then the onset was flagged with the value 361 minutes. The median onset of action among all subjects is reported.

- The sponsor proposes the following statement, [redacted] The contribution of ipratropium bromide was not studied in study 1012.56 as there was not an albuterol sulfate only treatment group. The contribution of albuterol sulfate was studied but will be described in the label as part of the primary efficacy results. Therefore the sponsor's proposed sentence should be deleted.
- The sponsor proposes to include a statement indicating [redacted] between Combivent Respimat and Combivent CFC-MDI. [redacted] and thus should not be included in labeling unless specific selected endpoints are of significant clinical importance and their inclusion can be justified from that perspective. If any of these endpoints are included, the term [redacted] should not be used since from a statistical perspective, that term is not well-defined.

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