Efficacy and safety of ipratropium bromide/albuterol delivered via Respimat® inhaler versus MDI

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KEYWORDS
COPD; Respimat® inhaler; Ipratropium bromide; Anticholinergic; Bronchodilator

Summary
We compared the efficacy and safety of ipratropium bromide/albuterol delivered via Respimat® inhaler, a novel propellant-free inhaler, versus chlorofluorocarbon (CFC)-metered dose inhaler (MDI) and ipratropium Respimat® inhaler in patients with COPD.

This was a multinational, randomized, double-blind, double-dummy, 12-week, parallel-group, active-controlled study. Patients with moderate to severe COPD were randomized to ipratropium bromide/albuterol (20/100 mcg) Respimat® inhaler, ipratropium bromide/albuterol MDI [36 mcg/206 mcg (Combivent® Inhalation Aerosol MDI)], or ipratropium bromide (20 mcg) Respimat® inhaler. Each medication was administered four times daily. Serial spirometry was performed over 6 h (0.15 min, then hourly) on 4 test days. The primary efficacy variable was forced expiratory volume in 1 s (FEV1) change from test day baseline at 12 weeks.
Introduction

The effective treatment of patients with airway disease such as chronic obstructive pulmonary disease (COPD) requires efficient delivery of medical aerosols to the lungs. Inhaled bronchodilators, the cornerstone treatment for COPD, are commonly delivered to the lungs via metered dose inhalers (MDI) which utilize chlorofluorocarbons (CFC) or hydrofluoroalkane (HFA) propellants to generate an aerosolized medication. Respimat® inhalation spray is a propellant-free, multi-dose inhaler designed as an alternative to MDIs. It uses mechanical energy from a pretensioned spring to generate a medical aerosol, rather than CFC propellants which contribute to ozone-depletion, with subsequent negative environmental and public health impacts.

The Respimat® inhaler generates a slow moving aerosol over 1.5 s facilitating coordination with inhalation and a fine particle spray (<5.8 μm), improving efficiency of drug delivery to the lungs.1,2 Studies have shown that lung deposition was approximately doubled and oropharyngeal deposition was reduced for Respimat® compared to MDI.1-5 Use of the Respimat® inhaler is independent of inspiratory effort and the device provides the patient with a dose indicator, a locking mechanism that prevents delivery of partial doses; and for ipratropium bromide/albuterol Respimat® inhaler (20/100 mcg), the convenience of single puff dosing.

Clinical studies have established that a combination therapy of ipratropium bromide, an anticholinergic bronchodilator, and albuterol, a β2-adrenergic bronchodilator, results in an additive bronchodilator effect.6,7 Use of the combination therapy also results in improved patient outcomes (fewer Emergency Room visits, hospitalizations and a subsequent reduction in hospital length of stay) and compliance, compared with concomitant use of separate ipratropium and albuterol MDIs.8

The aim of this study was to determine the efficacy and safety of the Respimat® inhaler during combination treatment with ipratropium bromide/albuterol 20 mcg/100 mcg versus ipratropium bromide/albuterol 36 mcg/206 mcg MDI (Combivent® MDI) and the mono-component ipratropium 20 mcg Respimat® inhaler in patients with moderate to severe COPD during a 12-week study period.

Methods

Sample

Male and females aged ≥40 years with COPD (forced expiratory volume in 1 s [FEV1] ≤ 65% predicted normal and FEV1/Forced vital capacity [FVC] ≤ 70%) and a smoking history of ≥10 pack-yrs were included. Patients with a confounding disease that would put the patient at risk because of study participation or potentially influence the results of the study were excluded. Other exclusion criteria included: known hypersensitivity to anticholinergic or beta-agonist therapy; concomitant use of drugs contraindicated with anticholinergic or beta-agonist therapy; elevated blood eosinophil count (≥600/nm3); respiratory infection within 6 weeks prior to screening; regular daytime oxygen therapy; use of antihistamines, oral corticosteroids at unstable doses (i.e. <6 weeks on a stable dose or exceeding the equivalent of prednisone 10 mg daily), initiation of inhaled steroid or change in dose <6 weeks prior to screening; use of beta-blockers, monoamine oxidase (MAO) inhibitors, tricyclic antidepressants <30 days before baseline period or during treatment period. Long-acting and short-acting inhaled anticholinergic agents and long-acting beta agonists were not allowed during the conduct of the study. All patients were provided with albuterol MDI to use as needed.

Study design

A multinational (13 countries), multi-national (179 centers), randomized, double-blind, double-dummy, parallel design, active controlled non-inferiority study was performed to compare efficacy and safety of orally inhaled ipratropium bromide/albuterol 20 mcg/100 mcg Respimat® inhaler with ipratropium bromide/albuterol 36 mcg/206 mcg MDI (Combivent® MDI) and ipratropium bromide 20 mcg Respimat® inhaler in patients with moderate-to-severe COPD.

Following an initial screening visit and a 2-week run-in phase with ipratropium bromide MDI (two actuations of 17 mcg, 4 times daily) and albuterol MDI as needed, eligible patients were randomized to receive ipratropium bromide/albuterol (1 actuation of 20 mcg/100 mcg) Respimat® inhaler plus placebo MDI (2 actuations), ipratropium bromide/albuterol MDI (2 actuations of 18 mcg/103 mcg)
plus placebo Respimat® inhaler (1 actuation), or ipratropium bromide Respimat® inhaler (1 actuation of 20 mcg) plus placebo MDI (2 actuations) for 12 weeks (Fig. 1). All formulations were taken four-times daily: arising, mid-day, early evening, before retiring. The double-dummy design ensured that all patients handled both inhalers equally often and prevented both investigators and patients from differentiating active drug from placebo, despite the different inhaler devices.

Ipratropium bromide/albuterol inhalation solution (20 mcg/100 mcg), placebo inhalation solution, and ipratropium bromide inhalation solution (20 mcg) cartridges were supplied by Boehringer Ingelheim Pharma GmbH & Co., Ingelheim, Germany. Respimat® inhalers were provided by Boehringer Ingelheim Micro Part, Dortmund, Germany. Ipratropium bromide/albuterol sulfate inhalation aerosol (18/103 mcg through the mouth piece) and placebo inhalation aerosol were supplied by Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT. The studies took place in November 2006–April 2008 and were conducted in accordance with the Declaration of Helsinki (1996) and GCP. All patients provided written informed consent prior to participation in the study and the study was approved by the institutional ethics review boards used by participating investigators. The study was sponsored by Boehringer Ingelheim.

Efficacy endpoints

The three co-primary endpoints in this study included FEV1 change from test-day baseline at Day 85 for: (1) ipratropium bromide/albuterol Respimat® inhaler vs. ipratropium bromide/albuterol MDI (AUC0–6 h) to show non-inferiority, (2) ipratropium bromide/albuterol Respimat® inhaler vs. ipratropium bromide Respimat® inhaler (AUC 0–4 h) to show superiority of the combination of the anticholinergic and beta-agonist agents to the mono-component, and (3) ipratropium bromide/albuterol Respimat® inhaler vs. ipratropium bromide Respimat® inhaler (AUC4–6 h) to show non-inferiority to the mono-component. Change from test-day baseline is the post-dose FEV1 compared to pre-dose value on the same test day. The latter endpoint analysis was chosen to assure that there was no difference in bronchodilator efficacy even 4–6 h after drug administration between the combination therapy of ipratropium bromide/albuterol Respimat® compared to the monotherapy of ipratropium bromide Respimat®. Pulmonary function tests (PFT) were conducted 15 min pre-treatment, 15, 30, 60 min, and 2, 3, 4, 5, 6 h after drug administration at the end of the 2-week baseline period, Day 29, 57, and 85. Spirometry was performed in accordance with American Thoracic Society criteria.9,10

Secondary endpoints included FEV1 at Day 1, 29, 57, peak FEV1 (maximum FEV1 value within the first 2 h after study drug administration), peak FEV1 response (the maximum change in FEV1 from test-day baseline within the first 2 h after study drug administration), time to peak FEV1 response, median time to onset of a therapeutic response, median duration of therapeutic response, FVC AUC0–4, AUC0–4, AUC4–6, and peak FVC response (maximum change in FVC from test-day baseline within the first 2 h after study drug administration) on Day 1, 29, 57, 85. For the purpose of this study, a therapeutic response during the 6-h PFT day was considered to have been achieved if a FEV1 measurement of at least 1.15 times the pre-dose value was recorded at any time during the first 2 h of observation. Termination of therapeutic response was defined as the first fall below 1.15 times pre-dose FEV1, on two consecutive measurements after therapeutic response.

Safety endpoints

Adverse and serious adverse events were monitored throughout the 2 week baseline and 12 week treatment period. Pulse rate and blood pressure were measured at baseline and on each test day (Day 1, 29, 57, 85). Each patient at baseline and on the test day (Day 1, 29, 57, 85). At baseline and end-of-study (week 12) physical examination and electrocardiogram were also recorded.

Statistical analysis

The three co-primary endpoints were analyzed using analysis of covariance (ANCOVA) with fixed effects for treatment and pooled investigator site and day 1 baseline as a covariate. Using a standard deviation of 180 mL for each of the three co-primary endpoints, the sample size of 400 patients per treatment group provided a 97% chance of rejecting each of the three null hypotheses. Treated

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**Figure 1** Overall scheme of the study design. During the 2 week baseline run-in phase, all patients took ipratropium MDI at a dosage of 17 mcg, two actuations q.i.d. and albuterol MDI as needed. During the 12 week treatment period, patients took study medication q.i.d.: on arising, mid-day, early evening, and before retiring. PFT, pulmonary function test; q.i.d., four times daily; *1 actuation; † 2 actuations; ‡ as needed.
patients from the full analysis set who had valid baseline PFT data and ≥4 time points of PFT data during the first 3 h after the study drug administration on at least 1 test day were included in the AUC0–6 and AUC0–4 efficacy analysis. As a subset of the analysis set for the AUC0–6 and AUC0–4 efficacy analysis, treated patients who had all 3 PFT data at 4, 5, 6 h after drug administration on at least 1 of the last 3 test days were included in the AUC4–6 efficacy analysis.

ANCOVA model was also used to analyze secondary endpoints. Onset and duration of therapeutic response and time to peak FEV1 response were summarized by simple medians. Safety analyses were summarized descriptively. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.1. In order to see combined occurrence rates of medically related adverse events, multiple MedDRA preferred terms were combined into a more meaningful single clinical pre-defined collapsed term. Randomized patients from the treated set who received ≥1 dose of study medication were included in the safety analysis.

Results

Patient disposition and characteristics

A total of 2462 patients signed informed consent and were enrolled in the study. One thousand four hundred and eighty patients were randomized and received treatment, and 1460 were evaluable (98.6%) (Fig. 2). Baseline characteristics were comparable among randomized treatment groups (Table 1). The mean age of the treated patient population was 64.1 years; 65.4% of the treated patients were male and 89.0% were white. The mean duration of COPD was 8.4 years. All patients were current smokers (n = 600, 41.1%) or ex-smokers (n = 860, 58.9%) with a mean percent predicted FEV1 of 41.4% and mean FEV1/FVC of 44.8% at screening. The percentages of patients taking any pulmonary medication were balanced across the three treatment groups. Most frequently used classes of concomitant pulmonary medications at the time of screening were inhaled short-acting beta agonists (62%), inhaled corticosteroids (44%), inhaled short-acting anticholinergic agents (38%), inhaled long-acting beta agonists (31%). Less frequently used were: methylxanthines (10%), inhaled long-acting anticholinergic agents (9%), and oxygen (4%). Long-acting inhaled anticholinergic agents and long-acting beta agonists were not allowed during the conduct of the study. The withdrawal rates were similar for the three treatment groups (12.6% ipratropium Respimat® inhaler; 11.2% ipratropium bromide/albuterol MDI; 9.9% ipratropium bromide/albuterol Respimat® inhaler).

Spirometry

Comparable bronchodilation was achieved with ipratropium bromide/albuterol Respimat® inhaler and ipratropium bromide/albuterol MDI as shown by FEV1 change from test-day baseline from 0–6, 0–4 and 4–6 h at 12 weeks, respectively (Fig. 3A).
On test Day 85, the ipratropium bromide/albuterol Respimat® inhaler group was non-inferior to the ipratropium bromide/albuterol MDI group at 0–6 h, and was superior to the ipratropium Respimat® inhaler group with a difference of 0.047 l (P < 0.0001) at 0–4 h in favor of ipratropium bromide/albuterol Respimat® inhaler. At 4–6 h, the bronchodilation achieved with ipratropium bromide/albuterol Respimat® inhaler was non-inferior to that achieved with the mono-component ipratropium Respimat® inhaler (Fig. 3B).

Ipratropium bromide/albuterol Respimat® inhaler significantly improved FEV1 compared with the mono-component ipratropium Respimat® inhaler at 0–4 and 0–6 h on all test days. (Fig. 4)

The results from the secondary FEV1 and FVC endpoints were consistent with the primary FEV1 data. Peak FEV1, peak FEV1 response (Fig. 5), and peak FVC response were comparable between ipratropium bromide/albuterol Respimat® inhaler and ipratropium bromide/albuterol MDI and superior to ipratropium Respimat® inhaler (<0.0001) on all test days. The median time to onset of therapeutic response occurred approximately 13 min after study drug administration for both ipratropium bromide/albuterol Respimat® inhaler and ipratropium bromide/albuterol MDI. The overall median time to a peak response was comparable across the three treatment groups: 60 min after study drug administration on all test days for ipratropium bromide/albuterol Respimat® inhaler and MDI; 2 h after study drug administration for ipratropium Respimat® inhaler on test Days 1 and 29 and 60 min on test Days 57 and 85. Median duration of a therapeutic response was comparable between ipratropium bromide/albuterol Respimat® inhaler (165–189 min) and MDI (172–219 min) overall test days, which was longer compared with ipratropium Respimat® inhaler (70–122 min). Seventy-six percent (n = 358), 74% (n = 357) and 63% (n = 295) of patients treated with ipratropium bromide/albuterol Respimat® inhaler and MDI and ipratropium Respimat® inhaler, respectively, had an FEV1 increase ≥15% above their baseline on Day 85 and within the first 2 h after study drug administration.

Safety

Exposure across treatment groups was similar with a mean of 80.1 days. The total incidence of adverse events was comparable across treatment groups (Table 2). Respiratory events were the most frequently reported adverse events and were predominately comprised of COPD exacerbations. There were no differences among the treatment groups in the frequency of potential anticholinergic class adverse events (2.1% ipratropium Respimat® inhaler, 2.0% ipratropium bromide/albuterol MDI, 1.6% ipratropium bromide/albuterol Respimat® inhaler). The majority of these events were dry mouth (0.7%) and tremor (0.3%). The highest frequency of possible beta-agonist-related adverse events occurred in the ipratropium Respimat® inhaler group (9.1%), whereas both ipratropium bromide/albuterol groups were comparable (7.2% and 7.5% ipratropium bromide/albuterol Respimat® inhaler and MDI, respectively, non-

<table>
<thead>
<tr>
<th>Variablea</th>
<th>Ipratropium bromide/albuterol Respimat® inhaler (n = 486)</th>
<th>Ipratropium bromide/albuterol MDI (n = 491)</th>
<th>Ipratropium Respimat® inhaler (n = 483)</th>
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</thead>
<tbody>
<tr>
<td>Male [N (%)]</td>
<td>316 (65.0)</td>
<td>322 (65.6)</td>
<td>317 (65.5)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.8</td>
<td>64.23</td>
<td>63.4</td>
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<tr>
<td>Current smoker [N (%)]</td>
<td>211 (43.4)</td>
<td>188 (38.3)</td>
<td>201 (41.6)</td>
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<td>Smoking history (pack-years)</td>
<td>51.7</td>
<td>52.4</td>
<td>55.4</td>
</tr>
<tr>
<td>COPD duration (years)</td>
<td>8.2</td>
<td>8.6</td>
<td>8.5</td>
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<tr>
<td>FEV1 (L)</td>
<td>1.154 (0.418)</td>
<td>1.162 (0.426)</td>
<td>1.117 (0.416)</td>
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<tr>
<td>FVC (L)</td>
<td>2.617 (0.823)</td>
<td>2.600 (0.802)</td>
<td>2.559 (0.811)</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>41.5 (12.3)</td>
<td>41.9 (12.5)</td>
<td>40.9 (12.7)</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>44.7 (10.6)</td>
<td>45.3 (11.1)</td>
<td>44.3 (10.6)</td>
</tr>
<tr>
<td>FEV1 (L reversibility at 30 min following 400 µg albuterol)</td>
<td>0.217</td>
<td>0.216</td>
<td>0.217</td>
</tr>
<tr>
<td>Patients taking pulmonary medication at screening (&gt;25%) [N(%)]</td>
<td>389 (80)</td>
<td>393 (80)</td>
<td>390 (80.7)</td>
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<tr>
<td>β-adrenergics, short acting</td>
<td>301 (61.9)</td>
<td>296 (60.3)</td>
<td>301 (62.3)</td>
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<tr>
<td>β-adrenergics, long acting</td>
<td>153 (31.5)</td>
<td>138 (28.1)</td>
<td>160 (33.1)</td>
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<tr>
<td>Inhaled steroids</td>
<td>214 (44.0)</td>
<td>215 (43.8)</td>
<td>218 (45.1)</td>
</tr>
<tr>
<td>Anticholinergics, short acting</td>
<td>197 (40.5)</td>
<td>179 (36.5)</td>
<td>180 (37.3)</td>
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<tr>
<td>Patients taking concomitant pulmonary medication (&gt;25%) during 12 weeks</td>
<td>246 (50.6)</td>
<td>233 (47.5)</td>
<td>242 (50.1)</td>
</tr>
<tr>
<td>Inhaled steroids</td>
<td>187 (38.5)</td>
<td>185 (37.7)</td>
<td>188 (38.9)</td>
</tr>
</tbody>
</table>

There were no noticeable differences among the three treatment groups. FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

a Mean (SD) unless otherwise stated.
The percentage of patients who discontinued due to an adverse event, with a higher frequency occurring in the ipratropium bromide/albuterol Respimat inhaler (3.5%) and ipratropium Respimat inhaler (2.9%). Lower respiratory events were the most frequent (ipratropium bromide/albuterol Respimat inhaler: 2.7%, ipratropium bromide/albuterol MDI: 3.7%, ipratropium Respimat inhaler: 2.3%) with COPD exacerbations accounting for the majority of events (ipratropium bromide/albuterol Respimat inhaler: 2.3%, ipratropium bromide/albuterol MDI: 2.6%, ipratropium Respimat inhaler: 1.7%).

Three deaths occurred on treatment in the ipratropium bromide/albuterol Respimat inhaler group: one from pneumonia, one from a COPD exacerbation with respiratory failure, and one with an unknown cause. There was one homicide-related death in the MDI group, and two deaths in the ipratropium bromide Respimat inhaler group: one from brain cancer and one from small cell lung cancer. None of the deaths were considered related to study treatment. There were no clinically significant differences in vital signs for all treatment groups.

Discussion

The aim of our study was to determine the efficacy and safety of ipratropium bromide/albuterol delivered via the Respimat inhaler compared with this bronchodilator combination delivered by MDI and with ipratropium alone via the Respimat inhaler. Test drugs were administered four times daily in patients with moderate to severe COPD over a 12-week study period. Since we included ipratropium in all three treatment arms, our study was not designed to evaluate the efficacy or safety of this drug. Rather, we were interested in evaluating its combination with albuterol delivered via this novel delivery device.

Previous dose-ranging studies and a Phase III trial indicated that a higher dose of ipratropium bromide/albuterol administered via the Respimat inhaler (40 mcg/200 mcg) was also more effective than the monotherapy of ipratropium bromide (40 mcg) Respimat inhaler but provided minimal additional bronchodilator effect over the ipratropium bromide/albuterol Respimat inhaler 20/100 mcg dose chosen for our study. Additionally the 40/200 mcg dose was equivalent in bronchodilator activity to that of the MDI (36 mcg/206 mcg) formulation, a goal of the formulation, since the Respimat inhaler is intended as an alternative to the MDI.

Pharmacokinetic data from our study has shown comparable ipratropium bromide systemic exposure for all three investigational treatments of this trial, and less systemic exposure for albuterol with ipratropium bromide/albuterol Respimat inhaler (20 mcg/100 mcg) than that with ipratropium bromide/albuterol MDI (36/206 mcg).

The 20 mcg dose of ipratropium with 100 mcg of albuterol maintained the 1:5 ratio of ipratropium bromide to albuterol Respimat inhaler group (2.5%) compared with ipratropium bromide/albuterol MDI (4.3%) and ipratropium Respimat inhaler (5.0%). COPD exacerbations (2.7%) accounted for the majority of lower respiratory system disorder leading to treatment discontinuation.

A total of 64 patients (4.4%) experienced ≥1 serious adverse event, with a higher frequency occurring in the ipratropium bromide/albuterol MDI arm (6.7%) versus ipratropium bromide/albuterol Respimat inhaler (3.5%) and ipratropium Respimat inhaler (2.9%). Lower respiratory events were the most frequent (ipratropium bromide/albuterol Respimat inhaler: 2.7%, ipratropium bromide/albuterol MDI: 3.7%, ipratropium Respimat inhaler: 2.3%) with COPD exacerbations accounting for the majority of events (ipratropium bromide/albuterol Respimat inhaler: 2.3%, ipratropium bromide/albuterol MDI: 2.6%, ipratropium Respimat inhaler: 1.7%).

The percentage of patients who discontinued due to an adverse event was lower in the ipratropium bromide/albuterol Respimat inhaler group: ipratropium bromide/albuterol Respimat inhaler (3.7%), ipratropium bromide/albuterol MDI (6.9%), ipratropium Respimat inhaler (6.8%). Lower respiratory system disorders were the most frequent adverse event leading to treatment discontinuation (3.9%) and occurred with the lowest frequency in the ipratropium bromide/albuterol Respimat inhaler group (2.5%) compared with ipratropium bromide/albuterol MDI (4.3%) and ipratropium Respimat inhaler (5.0%). COPD exacerbations (2.7%) accounted for the majority of lower respiratory system disorder leading to treatment discontinuation.

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albuterol in the currently marketed product ipratropium bromide/albuterol Respimat\textsuperscript{R} inhaler, ipratropium bromide/albuterol MDI, and ipratropium Respimat\textsuperscript{R} inhaler (20 mcg) has been shown to be clinically comparable to ipratropium bromide MDI (36 mcg Atrovent\textsuperscript{R} CFC Inhalation Aerosol).\textsuperscript{13}

Our results indicate that after 12 weeks of treatment equivalent bronchodilation was achieved with ipratropium bromide/albuterol via Respimat\textsuperscript{R} inhaler and ipratropium bromide/albuterol via MDI. Additionally, the bronchodilator combination via Respimat\textsuperscript{R} inhaler produced greater bronchodilation than ipratropium alone administered by this inhaler. Albuterol and ipratropium delivered by Respimat\textsuperscript{R} inhaler and MDI also had similar efficacy in peak FEV\textsubscript{1} response, median time to onset of therapeutic response, median duration of therapeutic response, and percentage of patients who achieved a therapeutic response within two hours of administration. The fixed combination treatment via either Respimat\textsuperscript{R} inhaler or MDI reduced the median time to onset of therapeutic response and median time to peak response and prolonged the median duration of therapeutic response compared to ipratropium alone given

Figure 4 Mean FEV\textsubscript{1} (l) response between 0—6 h post-dose following treatment with ipratropium bromide/albuterol Respimat\textsuperscript{R} inhaler, ipratropium bromide/albuterol MDI, and ipratropium Respimat\textsuperscript{R} inhaler on test Day 1, 29, 57, and 85. Data are expressed as change from baseline. Missing data were imputed by carrying either the lowest or last value forward depending on why the data were missing. Means (SE) were adjusted for treatment baseline and pooled centre (fixed). A separate ANCOVA was fitted for each time point and test day. FEV\textsubscript{1}, forced expiratory volume. Standard error was comparable across treatment groups and time points ranging from 0.007 to 0.009 l.

Figure 5 Mean peak FEV\textsubscript{1} (l) response within the first 2 h after administration of ipratropium bromide/albuterol Respimat\textsuperscript{R} inhaler, ipratropium bromide/albuterol MDI, and ipratropium Respimat\textsuperscript{R} inhaler on test Day 1, 29, 57, and 85. Data are expressed as change from baseline after 12 weeks of treatment. FEV\textsubscript{1}, forced expiratory volume in 1 s. Standard error was 0.008 l across treatment groups and time points.
All primary system organ classes are defined by MedDRA with the exception of ‘Respiratory, thoracic and mediastinal disorders’ which includes multiple MedDRA preferred terms.

In this trial and occurred with the highest frequency in the treatment groups. Headache, a class event was observed infrequently and occurred consistent with potential anticholinergic (ipratropium), and were lower respiratory system disorders. Adverse events that caused discontinuation in the trial were mainly of COPD exacerbations. These events occurred at comparable rates in the ipratropium bromide/albuterol MDI and the ipratropium Respimat® inhaler, with slightly higher frequencies in the ipratropium bromide/albuterol MDI (n = 491) compared to the MDI and improved delivery of drug to the lungs consistent with previous studies evaluating drug deposition via Respimat® inhaler. This study indicates that ipratropium bromide/albuterol Respimat® inhaler (20 mcg/100 mcg) delivered by this inhaler had superior efficacy to the mono-component ipratropium delivered by an MDI. Furthermore, the combination delivered by Respimat® inhaler had comparable efficacy and safety to the same drug combination (ipratropium bromide/albuterol) at a dose of 36 mcg/206 mcg delivered by an MDI. A patient assessment questionnaire showed that the majority of patients in the trial preferred the Respimat® inhaler to MDI. This finding is consistent with previous studies demonstrating ease of use, improved patient inhalation technique and patient preference for Respimat® inhaler over MDIs or DPIs. In addition, end of use testing of the Respimat® inhaler demonstrated reliable near end of use performance for dosing behavior for volume accuracy and particle size fraction. Pharmacokinetic analysis showed increased efficiency with a lower dose of ipratropium bromide/albuterol in the Respimat® inhaler compared to the MDI and improved delivery of drug to the lungs consistent with previous studies evaluating drug deposition via Respimat® inhaler. These data demonstrated that Respimat® inhaler is a convenient and reliable inhaler for COPD patients.

In summary, this 12 week study demonstrated that ipratropium bromide/albuterol (20 mcg/100 mcg) delivered by the Respimat® inhaler had comparable efficacy and safety to the same drug combination (ipratropium bromide/albuterol) at a dose of 36 mcg/206 mcg delivered by an MDI. Furthermore, the combination delivered by Respimat® inhaler had superior efficacy to the mono-component ipratropium delivered by this inhaler. This study indicates that ipratropium bromide/albuterol Respimat® inhaler (20 mcg/100 mcg) administered as one inhalation q.i.d. is as effective and safe as the reference MDI (Combivent® MDI) for use in patients with moderate to severe COPD.

### Table 2

<table>
<thead>
<tr>
<th>System organ class/preferred term</th>
<th>Ipratropium bromide/albuterol Respimat® inhaler (n = 486)</th>
<th>Ipratropium bromide/albuterol MDI (n = 491)</th>
<th>Ipratropium Respimat® inhaler (n = 483)</th>
<th>Total treated (n = 1460)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total with any AE</td>
<td>222 (45.7)</td>
<td>254 (51.7)</td>
<td>215 (44.5)</td>
<td>691 (47.3)</td>
</tr>
<tr>
<td>Lower respiratory disorders</td>
<td>105 (21.6)</td>
<td>107 (21.8)</td>
<td>89 (18.4)</td>
<td>301 (20.6)</td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>72 (14.8)</td>
<td>64 (13.0)</td>
<td>50 (10.4)</td>
<td>186 (12.7)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>14 (2.9)</td>
<td>17 (3.5)</td>
<td>7 (1.4)</td>
<td>38 (2.6)</td>
</tr>
<tr>
<td>Upper respiratory disorders</td>
<td>64 (13.2)</td>
<td>76 (15.5)</td>
<td>62 (12.8)</td>
<td>202 (13.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>18 (3.7)</td>
<td>15 (3.1)</td>
<td>20 (4.1)</td>
<td>53 (3.6)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>17 (3.5)</td>
<td>19 (3.9)</td>
<td>18 (3.7)</td>
<td>54 (3.7)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>21 (4.3)</td>
<td>28 (5.7)</td>
<td>33 (6.8)</td>
<td>82 (5.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (2.7)</td>
<td>10 (2.0)</td>
<td>16 (3.3)</td>
<td>39 (2.7)</td>
</tr>
</tbody>
</table>

There were no noticeable differences among the three treatment groups.

AE, adverse event.

a All primary system organ classes are defined by MedDRA with the exception of ‘Respiratory, thoracic and mediastinal disorders’ which are divided into separate categories of respiratory system disorders, Lower, Upper and Other.

b Collapsed terms include multiple MedDRA preferred terms.

by Respimat® inhaler. Likewise, a higher percentage of patients achieved therapeutic response within the first 2 h after administration of combination study medication via either inhaler versus the mono-component. All secondary spirometry endpoints (FEV₁ and FVC) were consistent with that observed in the primary FEV₁ efficacy endpoints.

The overall adverse event frequencies were comparable across treatment groups, with slightly higher frequencies in the ipratropium bromide/albuterol MDI treated patients. Lower respiratory system events were the most frequently reported events and were comprised mainly of COPD exacerbations. These events occurred at comparable rates in the ipratropium bromide/albuterol groups and a slightly lower frequency in the ipratropium Respimat® inhaler treated patients. The most commonly reported SAE was COPD exacerbation (2.2%), which was distributed evenly across treatment groups; this finding is consistent with previous studies of similar patient groups. There was also a low rate of discontinuation due to adverse events with no notable differences in discontinuation patterns between treatment groups, and the majority of events causing discontinuation in the trial were lower respiratory system disorders. Adverse events consistent with potential anticholinergic (ipratropium) class events were observed infrequently and occurred similarly across all three treatment groups. Headache, consistent with the possible beta agonist class effect of albuterol, was the most commonly reported adverse event in this trial and occurred with the highest frequency in the ipratropium Respimat® inhaler group (the group with no beta agonist administration). Overall, there were no clinically significant differences in the safety profiles among ipratropium bromide/albuterol Respimat® inhaler, ipratropium bromide/albuterol MDI, and the ipratropium Respimat® inhaler. All three treatments were well-tolerated.

### Conflict of interest statement

C. Wood, Y. Zhao and J. Gilly are employees of Boehringer Ingelheim. P. Sachs has received financial support for participation in research activities or speaker’s boards for Boehringer-Ingelheim, GlaxoSmithKline, Pfizer and...
Astra-Zeneca. R. Abrahams has received financial support for participation in research activities or as a speaker for Boehringer-Ingelheim, GlaxoSmithKline, Pfizer, Astra-Zeneca, Novartis, Sepraror, Altana, Bayer, Dey, IVAX, Merck, Adams, Predix, Abbott, TAP, and Byk Gulden. E. Bateman has received financial support for serving on advisory boards, speaking at meetings and for consultancies for Boehringer Ingelheim and Pfizer. R. ZuWallack has received honoraria for speaking for Boehringer Ingelheim and Pfizer, and served as a consultant for Boehringer. Additionally, his institution received an unrestricted grant from Boehringer Ingelheim to conduct a workshop on pulmonary rehabilitation. M.C. De Salvo, F. Fakh, T. Kaelin, C.S. Park, K. Pudi, have no conflicts of interest.

Acknowledgments


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18. "Data on file, Boehringer-Ingelheim".

22. "Data on file, Boehringer-Ingelheim".
23. "Data on file, Boehringer-Ingelheim".