

## ARTICLE

# Efficiency of Ipratropium Bromide and Albuterol Deposition in the Lung Delivered via a Soft Mist Inhaler or Chlorofluorocarbon Metered-Dose Inhaler

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The propellant-free Combivent Respimat Soft Mist Inhaler (CVT-R) was developed to replace the chlorofluorocarbon-propelled Combivent metered-dose inhaler (CVT-MDI). This steady-state pharmacokinetic (PK) substudy evaluated drug lung-delivery efficiency, using data from two phase III safety and efficacy trials. PK parameters were obtained from well-controlled population PK analyses. Area under the plasma concentration–time curve (AUC), maximum observed plasma concentration ( $C_{max}$ ), and minimum observed plasma concentration ( $C_{min}$ ) showed systemic exposure to ipratropium bromide and albuterol delivered via the CVT-R was proportional to ex-mouthpiece delivered dose. Although the labeled dose of ipratropium bromide in the CVT-R was half that in the CVT-MDI, the systemic exposure was comparable. No PK interaction for the ipratropium bromide and albuterol Respimat drug components was demonstrated. Ipratropium bromide alone resulted in similar exposure to the combination of ipratropium bromide and albuterol. These results show that CVT-R delivers drug more efficiently to the lung than CVT-MDI.

*Clin Transl Sci* (2016) 9, 105–113; doi:10.1111/cts.12387; published online on 6 March 2016.

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Effective pharmacologic treatment of patients with COPD requires efficient delivery of appropriate drugs to the lungs.

### WHAT QUESTION DID THIS STUDY ADDRESS?

This study addresses the efficiency of ipratropium bromide and albuterol deposition in the lung delivered via a soft mist inhaler (CVT-R) compared with a CFC metered-dose inhaler (CVT-MDI).

### WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

The results presented show the relative efficiency

of drug deposition in the lungs for ipratropium bromide plus albuterol sulfate and ipratropium bromide alone, when delivered via a Respimat inhaler compared with CVT-MDI.

### HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

Lung deposition based on pharmacokinetic data from CVT-R is approximately two times as efficient as the older CVT-MDI, allowing the CVT-R to deliver a similar dose of drug to patients compared with the CVT-MDI, with similar effects.

Effective pharmacologic treatment of patients with chronic obstructive pulmonary disease (COPD) requires efficient topical delivery of appropriate active drugs to the lungs. Short-acting anticholinergic and  $\beta_2$ -agonist bronchodilators are commonly used in COPD treatment, either alone or in combination.<sup>1</sup> The short-acting anticholinergic ipratropium bromide is indicated for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.<sup>2</sup> Short-acting  $\beta_2$  bronchodilators, such as albuterol, are also used for the management of acute bronchospasm in asthma<sup>3</sup> and for treatment of stable COPD in patients requiring additional symptomatic relief; they may be provided as a standing dose or on an as-needed basis.<sup>1</sup>

Combining short-acting bronchodilators with different mechanisms of action increases the degree of bronchodi-

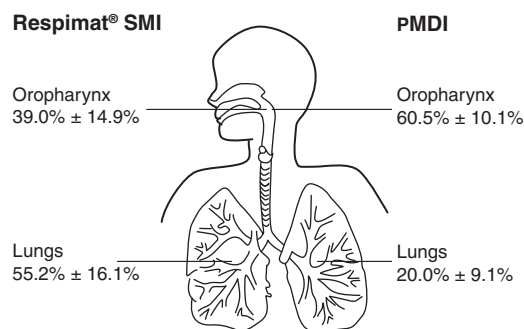
lation, with equivalent or fewer side effects compared with increasing the dose of a single bronchodilator.<sup>1</sup> In a 12-week, double-blind, randomized, parallel-group trial in patients with moderately severe, stable COPD, ipratropium bromide 21  $\mu$ g and albuterol sulfate 120  $\mu$ g combined in a metered-dose inhaler (MDI) and delivered as two puffs, four times daily, gave greater and more sustained improvement in forced expiratory volume in 1 s ( $FEV_1$ ) compared with either drug alone.<sup>4</sup> Additionally, adults with COPD treated with ipratropium bromide and albuterol sulfate combined in a single inhaler compared with two separate inhalers had lower respiratory-related healthcare use and charges, and greater treatment compliance.<sup>5</sup>

In 1996, the US Food and Drug Administration (FDA) approved Combivent Inhalation Aerosol MDI (CVT-MDI);

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Received 27 October 2015; accepted 12 January 2016; published online on 6 March 2016. doi:10.1111/cts.12387



**Figure 1** Mean  $\pm$  SD percentage deposition in patients ( $n = 43$ ) following inhalation with the Respimat Soft Mist Inhaler (Respimat SMI) or a pressurized metered-dose inhaler (pMDI). Data are derived from Brand *et al.*,<sup>7</sup> Boehringer Ingelheim International GmbH,<sup>8</sup> and data from Boehringer Ingelheim Clinical Trial Report 260.2706, Doc No. U97-0056. The Respimat SMI data are presented as percentage of ex-mouthpiece delivered dose and the pMDI data as percentage of ex-valve metered dose.

Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) for use in COPD. This was the only short-acting bronchodilator that delivered both ipratropium bromide and albuterol in a single delivery device. Pressurized MDIs (pMDIs) have been used since the 1950s to deliver inhaled drugs; however, they have several limitations. First, aerosol clouds produced by pMDIs have a high velocity and short duration. In a study by Hochrainer *et al.*,<sup>6</sup> the mean velocity of an aerosol cloud 10 cm from the nozzle was 2.0–8.4 m/s and the mean cloud duration was 0.15–0.36 s. These characteristics result in high oropharyngeal deposition of the ex-valve dose, with only a small proportion ( $\sim 20\%$ ) of the drug actually reaching the target site, i.e., lungs (**Figure 1**; Brand *et al.*,<sup>7</sup> Boehringer Ingelheim International GmbH,<sup>8</sup> and data from Boehringer Ingelheim Clinical Trial Report 260.2706, Doc No. U97-0056). Second, because the aerosol cloud is fast moving, users are less able to synchronize device actuation and inspiration to receive maximal lung deposition and thus drug benefit.<sup>6,9</sup> Therefore, patient education is required, and ensuring the use of the correct technique can be particularly challenging for the elderly and infirm. Lastly, conventional pMDIs rely on chlorofluorocarbon (CFC) propellants for drug delivery. Since CFCs harm the environment by depleting the Earth's ozone layer, the use of CFC-containing inhalers has been phased out under the terms of the Montreal Protocol on Substances that Deplete the Ozone Layer international agreement.<sup>10</sup> On 13 April 2010, the FDA announced that in the United States, seven MDIs containing CFCs would be phased out on specified dates up to a final date of December 2013;<sup>11</sup> this included the CVT-MDI.

The impending phase-out of CFC-pMDIs served as a stimulus to develop a new generation, propellant-free inhaler which, when compared with the CFC-pMDIs, would provide improved lung deposition, be easier for patients to use, and be preferred by patients. To replace the CVT-MDI, the ipratropium bromide/albuterol Respimat Soft Mist inhaler (CVT-R; Boehringer Ingelheim, Ingelheim, Germany) was developed.

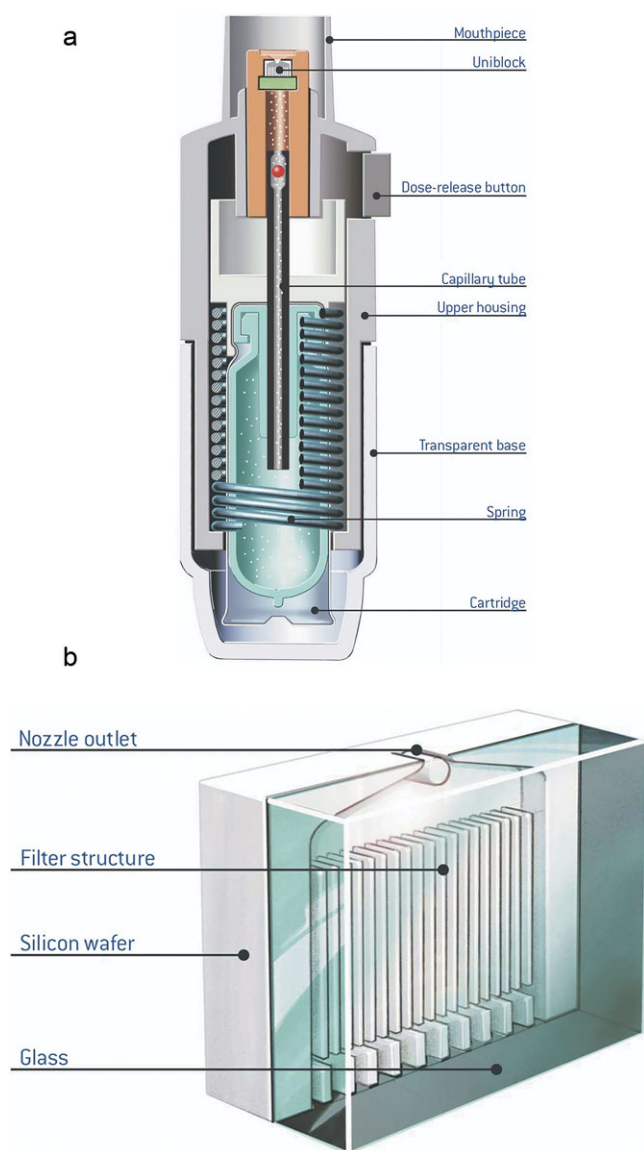
The Respimat inhaler was first launched in Europe in 2004 to deliver ipratropium bromide and the long-acting

$\beta_2$ -agonist bronchodilator, fenoterol hydrobromide (Berodual Respimat), and in 2007 to deliver tiotropium (Spiriva Respimat) for the treatment of patients with COPD; this device has since been used in a large number of patients with COPD.<sup>12–17</sup> Compared with pMDIs, the Respimat inhaler has also been shown to be preferred by patients.<sup>17,18</sup>

The Respimat inhaler delivers active drug in an aqueous solution by generating a slow-moving aerosol cloud with a longer mean duration (1.5 s vs. 0.15–0.36 s) and a slower velocity (0.8 m/s vs. 2.0–8.4 m/s) than pMDIs,<sup>6</sup> allowing patients more time to synchronize actuation with inhalation more effectively. To enhance lung penetration, the Respimat inhaler was designed to aerosolize the metered dose with droplets mostly within the respirable size range  $>1 \mu\text{m}$  to  $<5.8 \mu\text{m}$ .<sup>19,20</sup> This high fine-droplet fraction (around 66%)<sup>21</sup> is almost double that reported for most pMDIs and dry powder inhalers,<sup>22</sup> and enhances deposition of drug deep into the airways. The proportion of the ex-mouthpiece delivered dose deposited in the lungs from the Respimat inhaler compared with most hydrofluoroalkane (HFA)- or CFC-MDIs (ex-valve metered dose) is reported to be about two to three times greater (**Figure 1**). Ex-valve metered dose is the amount of drug expelled from the inhaler valve on actuation and ex-mouthpiece delivered dose is the amount of drug expelled from the inhaler valve on actuation minus drug deposited in the inhaler between actuation and expulsion from the mouthpiece.

The Respimat inhaler is a hand-held, pocket-sized device, which holds a 4-week supply of drug solution in a cartridge. The cartridge is an aluminum cylinder with a double-walled, plastic bag inside, which collapses as medication is withdrawn (**Figure 2a**). Doses of drug solution are expelled mechanically through a uniblock by the energy released from a tensioned spring rather than by propellants. The uniblock is built on a silicon wafer and consists of a filter structure with two very fine outlet nozzles. The cartridge and dosing chamber are connected by a capillary tube, which has a non-return valve. When the base of the inhaler is twisted 180°, the spring is compressed and medication is drawn up through the capillary tube into the dosing chamber. When the dose release button is actuated, the energy from the tensioned spring is released, which forces the micro-piston into the dosing chamber and, as a consequence, a measured dose of drug solution is forced through the uniblock (**Figure 2b**). The two fine jets of drug solution collide at a precise angle and their impact aerosolizes the liquid to produce a slow-moving aerosol cloud.<sup>21</sup>

CVT-R was approved in the United States by the FDA in October 2011, and is indicated for use in patients with COPD, who are on a regular aerosol bronchodilator, and continue to have evidence of bronchospasm and require a second bronchodilator.<sup>23</sup> In a randomized, double-blind, placebo- and active-controlled study, ZuWallack *et al.*<sup>16</sup> demonstrated that ipratropium bromide 20  $\mu\text{g}$ /albuterol 100  $\mu\text{g}$  CVT-R (CVT-R 20/100) administered four times daily for 12 weeks provided equivalent bronchodilator efficacy and comparable safety to ipratropium bromide 36  $\mu\text{g}$ /albuterol sulfate 206  $\mu\text{g}$  CVT-MDI (CVT-MDI 36/206), and that lung function was significantly improved compared with the single-component ipratropium bromide 20  $\mu\text{g}$  Respimat inhaler (I-R 20).



**Figure 2** Schematic drawing of (a) the Respimat Soft Mist Inhaler and (b) the uniblock. Respimat Soft Mist Inhaler ©2013 Boehringer Ingelheim.

Ferguson *et al.*,<sup>17</sup> in an open-label, 1-year study evaluating patient satisfaction, device use, and long-term safety of CVT-R compared with CVT-MDI or the free combination of ipratropium bromide HFA pMDI and albuterol sulfate HFA pMDI, showed comparable efficacy and safety, but greater patient satisfaction with CVT-R compared with the other treatments.

Measurements of systemic concentrations of inhaled drugs are only indirectly reflective of the local deposition in the lungs, because a significant proportion of actuated doses are swallowed. Systemic concentrations of an inhaled drug therefore reflect the release of the active moiety from the pharmacologic site in the lungs, the mucociliary and absorptive clearances of excess drug from the lungs, and the absorption of the swallowed portion from the gastrointestinal tract. The oral fraction of albuterol is readily absorbed (50%

oral bioavailability) and undergoes significant gastrointestinal first-pass metabolism.<sup>24</sup> On the other hand, ipratropium bromide is minimally absorbed following oral administration (~2% oral bioavailability),<sup>25</sup> making it a suitable marker of total lung deposition.

The results presented here show the relative efficiency of drug deposition in the lungs for ipratropium bromide plus albuterol and ipratropium bromide alone, when delivered via a Respimat inhaler compared with CVT-MDI.

## METHODS

### Clinical trials

Study patients were selected from two phase III, 12-week, multicenter, randomized, parallel group, double-blind, active-controlled clinical trials, which evaluated efficacy and safety of ipratropium bromide and albuterol in patients with COPD. Study patients were outpatient males and females, aged  $\geq 40$  years, with a diagnosis of COPD ( $FEV_1 \leq 65\%$  predicted normal and  $FEV_1/\text{forced vital capacity [FVC]} \leq 70\%$ ), and a smoking history of  $> 10$  pack-years.

Trial 1 (BI code 1012.46) was conducted between October 2002 and March 2004 and Trial 2 (BI code 1012.56; ClinicalTrials.gov identifier NCT00400153<sup>16</sup>) between November 2006 and April 2008. Trial 1 was blinded within-device and had three active treatment groups and two placebo groups, and Trial 2 used a double-dummy design, with three active treatment groups. Treatments were delivered via a single actuation per dose for CVT-R and via two actuations per dose for CVT-MDI; for both inhalers the doses are given as delivered ex-mouthpiece; full details of the treatment regimens are given in **Table 1**. In both trials, each formulation was used four times daily. In Trial 2, the Respimat-delivered placebo was inhaled prior to two inhalations of CVT-MDI active treatment. Doses of CVT-R in Trial 2 were half those in Trial 1.

Respimat inhalers were supplied by Steag MicroParts (Dortmund, Germany) in Trial 1 and Boehringer Ingelheim Micro Part (Dortmund, Germany) in Trial 2. Inhalation solution cartridges for use with the Respimat inhaler were supplied by Boehringer Ingelheim Pharma (Ingelheim, Germany). CVT-MDIs were supplied by Boehringer Ingelheim Pharmaceuticals (Danbury, CT).

The pharmacokinetic (PK) substudy population was from specific study sites where PK studies could be performed. For PK analyses, patient identification was blinded. PKs of the component drugs were evaluated at steady state during one dosing interval after 4 weeks of therapy (day 29).

Both trials were carried out in compliance with the protocols according to the principles of the Declaration of Helsinki (1996 version), the International Conference on Harmonisation (ICH), Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and local regulatory requirements. The study was approved by the Institutional Review Board / Independent Ethics Committee used by each investigator. All subjects were informed verbally and in writing by the investigator of the nature of the study drugs to be administered. Written informed consent was obtained from all patients prior to initiation of any study-related procedure. The trials were conducted 4 years apart.

**Table 1** Treatment regimes

Trial	Treatment	Delivery system	
		Respimat inhaler <sup>a</sup>	MDI <sup>b</sup>
1	1	Ipratropium bromide 40 µg and albuterol 200 µg (equivalent to 240 µg albuterol sulfate) – ex-mouthpiece dose	—
	2	—	Ipratropium bromide 36 µg and albuterol sulfate 206 µg (equivalent to 180 µg albuterol base) <sup>c</sup> – ex-mouthpiece dose (Ipratropium bromide 42 µg and albuterol sulfate 240 µg – ex-valve)
	3	Ipratropium bromide 40 µg – ex-mouthpiece dose	—
	4	Placebo	—
	5	—	Placebo
2	1	Ipratropium bromide 20 µg and albuterol 100 µg (equivalent to 120 µg albuterol sulfate) – ex-mouthpiece dose	Placebo
	2	Placebo	Ipratropium bromide 36 µg and albuterol sulfate 206 µg <sup>c</sup> – ex-mouthpiece dose (Ipratropium bromide 42 µg and albuterol sulfate 240 µg – ex-valve)
	3	Ipratropium bromide 20 µg – ex-mouthpiece dose	Placebo

Abbreviation: MDI, metered-dose inhaler.

<sup>a</sup>Total doses are from one actuation.

<sup>b</sup>Total doses are from two actuations.

<sup>c</sup>Each actuation = ipratropium bromide 18 µg and albuterol sulfate 103 µg.

### Pharmacokinetic sampling

On day 29, 10-ml blood samples were drawn into heparinized tubes at trough (pretreatment), 5, 15, 30, and 60 min and 2, 4, and 8 h (Trial 1 second trough) or 6 h (Trial 2 second trough) after inhalation of the treatment. Sampling was carried out after each corresponding pulmonary function test.

### Sample handling and bioanalytical assays

See **Supplementary Methods 1**.

### Pharmacokinetic modeling

The steady-state PKs of albuterol and ipratropium bromide in plasma and urine following administration from the inhaled devices were characterized using noncompartmental methods with the PK and statistical software program WinNonlin v. 5 (Pharsight, Mountain View, CA). Primary parameters of interest included the maximum observed plasma concentration ( $C_{max}$ ), minimum observed plasma concentration ( $C_{min}$ ), and area under the plasma concentration–time curve (AUC), estimated using a model-independent trapezoidal method. The amount of unchanged drug excreted into urine at 0–2 h and over the entire 8-h (Trial 1) or 6-h (Trial 2) collection period was evaluated for each device.

### Statistical analysis

The PK end points for Trial 1 were  $AUC_{0-8}$ ,  $C_{max}$ ,  $C_{min}$ , amount of urine excretion at 0–2 h and 0–8 h and for Trial 2 were  $AUC_{0-6}$ ,  $C_{max}$ ,  $C_{min}$ , amount of urine excretion at 0–2 h and 0–6 h. All end points were measured at steady state. PK geometric means of the end points were summarized descriptively with 90% confidence intervals (CIs). PK equivalence of Respimat inhaler-delivered ipratropium bromide and albuterol at the 40 µg / 200 µg (Trial 1) or 20 µg / 100 µg

(Trial 2) dose combinations were compared with: (i) the corresponding dose of Respimat inhaler-delivered ipratropium bromide (monocomponent) and (ii) CVT-MDI 36/206.

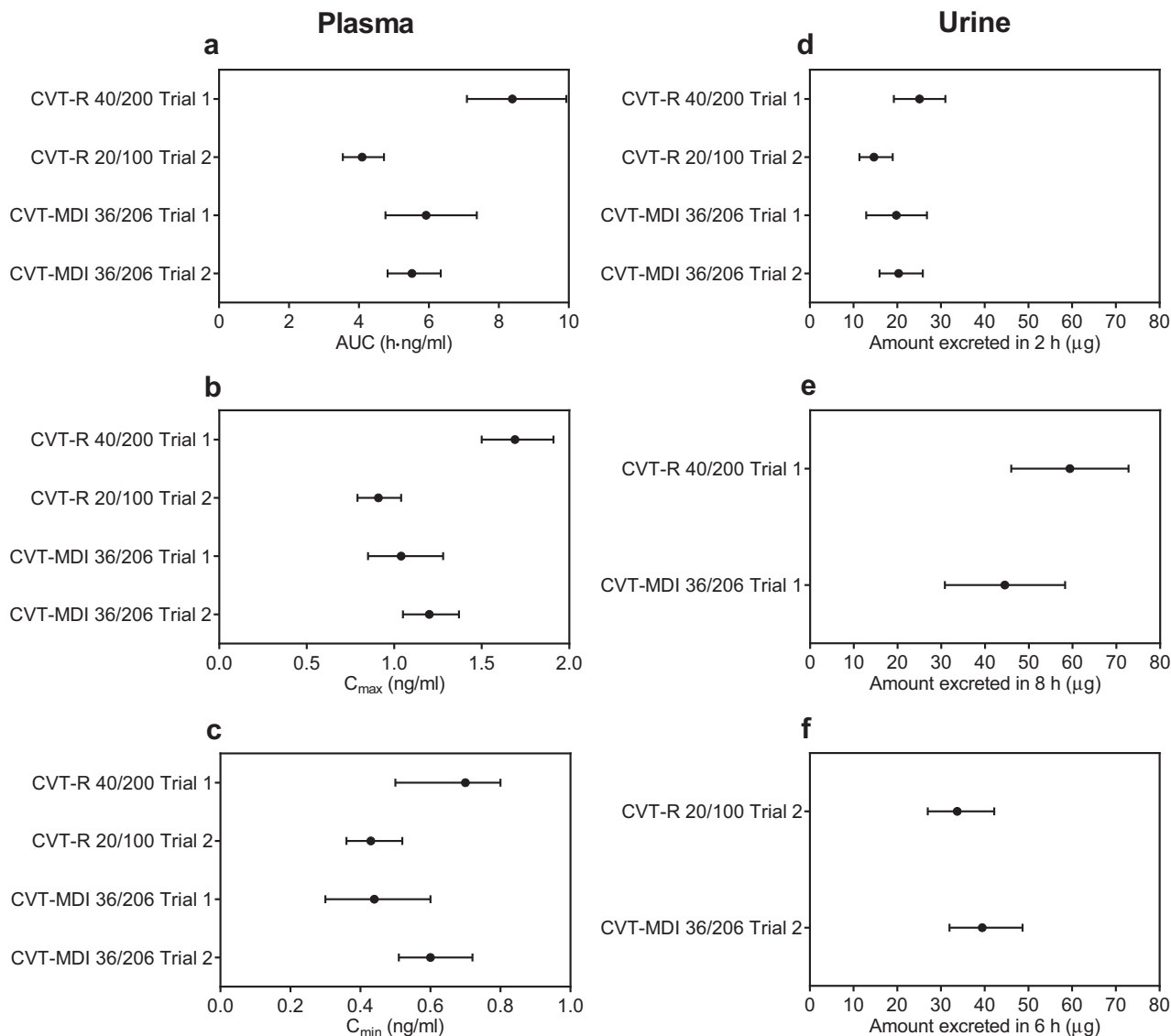
## RESULTS

Trial 1 randomized 1,118 patients, all of whom received treatment, and Trial 2 randomized 1,480 patients, of whom 1,460 received treatment. The PK substudy population included 278 patients (Trial 1,  $n = 116$  and Trial 2,  $n = 162$ ). Demographic and clinical data for the patients in the main trials and in the PK substudies are presented in **Supplementary Tables S1** and **S2**.

In Trial 1, ipratropium bromide and albuterol concentrations in plasma were determined from 1,264 specimens and in urine from 190 specimens. In Trial 2, ipratropium bromide and albuterol concentrations in plasma were determined from 1,247 specimens and in urine from 435 specimens. For both substudies, plasma PKs and urinalysis data for albuterol and ipratropium bromide are shown in **Figures 3** and **4**, respectively (see also **Supplementary Tables S3** and **S4**). Geometric mean ratios (GMRs) for PK parameters are shown in **Tables 2** and **3**. A GMR of 1 denotes systemic exposure equivalence.

In Trial 1, GMRs of the amount of albuterol excreted in urine over 0–2 h and 0–8 h for ipratropium bromide 40 µg/albuterol 200 µg CVT-R (CVT-R 40/200) compared with CVT-MDI 36/206 were 1.26 and 1.33, respectively, and for ipratropium bromide excretion were 3.50 and 2.80, respectively. The GMRs for ipratropium bromide excretion in urine over 0–2 h and 0–8 h for ipratropium bromide 40 µg Respimat inhaler (I-R 40) compared with CVT-R 40/200 were 0.87 and 0.90, respectively.





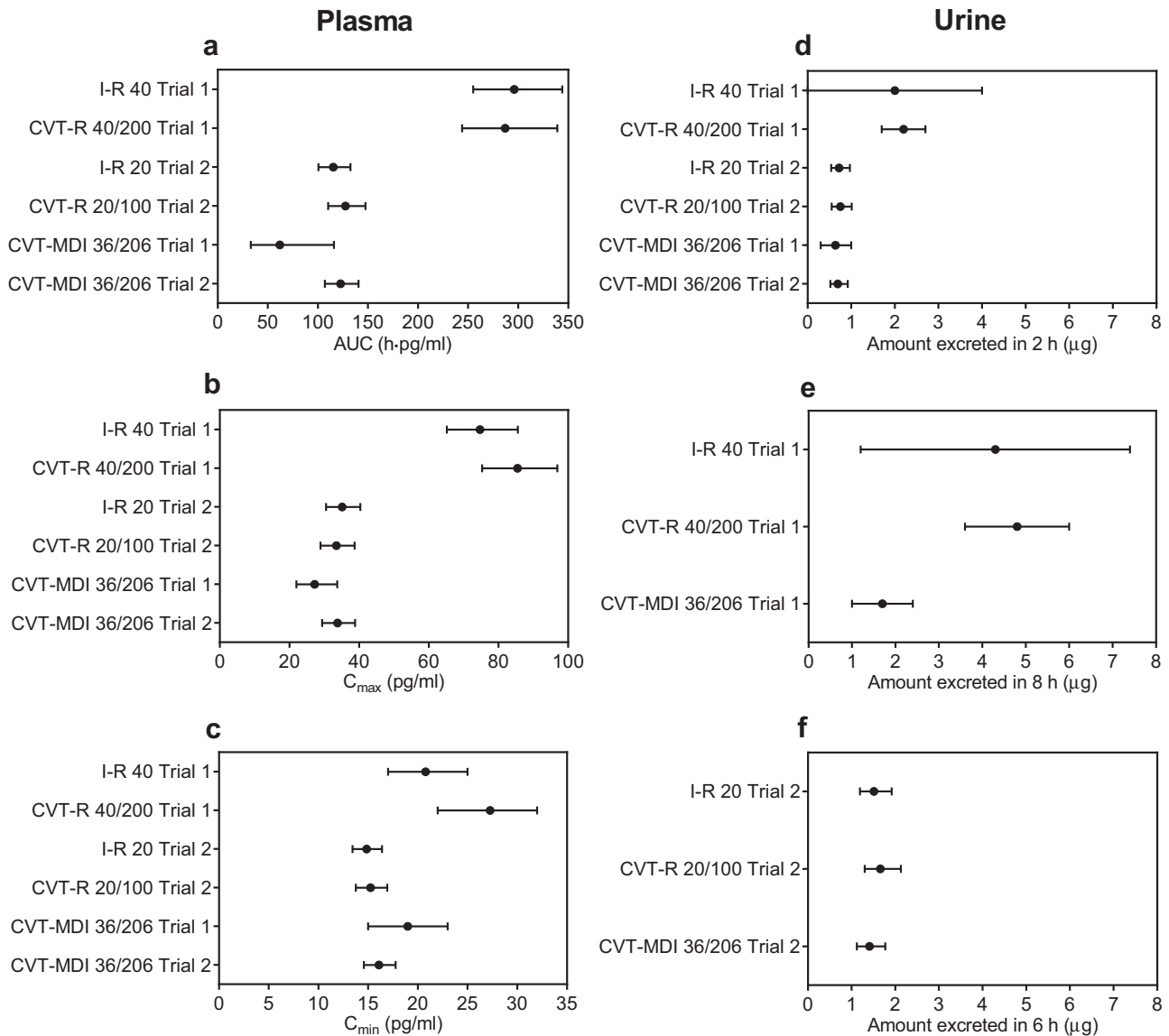
**Figure 3** Pharmacokinetic parameters (geometric means and 90% confidence intervals) for albuterol in plasma ([a] area under the plasma concentration–time curve [AUC; AUC<sub>0–8h</sub> for Trial 1 and AUC<sub>0–6h</sub> for Trial 2], [b] steady-state maximum observed plasma concentration [C<sub>max</sub>], and [c] minimum observed concentration [C<sub>min</sub>], and (d–f) the amount excreted in urine (over 2, 8, and 6 h, respectively). CVT, Combivent; R, Respimat; I, ipratropium; MDI, metered-dose inhaler. CVT-MDI 36/206, ipratropium bromide 36 μg / albuterol sulfate 206 μg CVT-MDI; CVT-R 20/100, ipratropium bromide 20 μg / albuterol 100 μg CVT-R; CVT-R 40/200, ipratropium bromide 40 μg / albuterol 200 μg CVT-R; I-R 20; ipratropium bromide 20 μg Respimat; I-R 40, ipratropium bromide 40 μg Respimat.

In Trial 1, an overall higher exposure for albuterol was obtained with CVT-R 40/200 in comparison with CVT-MDI 36/206. Although the study was not powered to show a PK difference, GMRs of means for AUC<sub>0–8</sub> and steady-state C<sub>max</sub> were 1.42 and 1.62, respectively. An overall higher exposure for ipratropium bromide was obtained with the Respimat inhaler than for CVT-MDI 36/206 regardless of the presence of albuterol. When comparing CVT-R 40/200 with CVT-MDI 36/206, AUC<sub>0–8</sub> and C<sub>max</sub> GMRs for ipratropium bromide exposure were 4.62 and 3.14, respectively.

In Trial 2, over 0–6 h, when mean albuterol urine excretion for CVT-R 20/100 was compared with the mean for CVT-MDI 36/206, the GMR was 0.86. Over 0–2 h and 0–6 h,

ipratropium bromide urine excretion levels were comparable between treatments (CVT-R 20/100, CVT-MDI 36/206, and I-R 20). Over 0–6 h, when mean ipratropium bromide urine excretion for CVT-R 20/100 was compared with the mean for CVT-MDI 36/206, the GMR was 1.18 and for I-R 20 compared with CVT-R 20/100 it was 0.91.

In Trial 2, comparable ipratropium bromide levels were found in plasma following the three treatments. When comparing I-R 20 with CVT-R 20/100, GMRs for AUC<sub>0–6</sub> and C<sub>max</sub>, were 0.91 and 1.05, respectively, indicating that the presence of albuterol did not adversely affect ipratropium bromide deposition, absorption, or elimination. For ipratropium bromide, GMRs for AUC<sub>0–6</sub> and C<sub>max</sub> for comparisons of



**Figure 4** Pharmacokinetic parameters (geometric means and 90% confidence intervals) for ipratropium bromide in plasma (**[a]** area under the plasma concentration–time curve [AUC; AUC<sub>0–8h</sub> for Trial 1 and AUC<sub>0–6h</sub> for Trial 2], **[b]** steady-state maximum observed plasma concentration [C<sub>max</sub>], and **[c]** minimum observed concentration [C<sub>min</sub>]), and (**d–f**) the amount excreted in urine (over 2, 8, and 6 h, respectively). CVT, Combivent; R, Respimat, I, ipratropium; MDI, metered-dose inhaler. CVT-MDI 36/206, ipratropium bromide 36 μg / albuterol sulfate 206 μg CVT-MDI; CVT-R 20/100, ipratropium bromide 20 μg / albuterol 100 μg CVT-R; CVT-R 40/200, ipratropium bromide 40 μg / albuterol 200 μg CVT-R; I-R 20; ipratropium bromide 20 μg Respimat; I-R 40, ipratropium bromide 40 μg Respimat.

CVT-R 20/100 with CVT-MDI 36/206 were 1.04 and 0.99, respectively. These GMRs were achieved despite the Respimat inhaler-delivered doses of ipratropium bromide being around half that in CVT-MDI 36/206. Therefore, the efficiency of ipratropium bromide delivery to the lungs was around two fold better with the Respimat inhaler compared with CVT-MDI 36/206. In Trial 2, systemic exposure for albuterol was lower for CVT-R 20/100 compared with CVT-MDI 36/206; the GMRs for AUC<sub>0–6</sub> and C<sub>max</sub> were 0.74 and 0.76, respectively. For the Respimat inhaler, administration of study drugs in Trial 2, which were at half the dose ex-valve of those in Trial 1, resulted in around half the systemic exposure in Trial 2 compared with Trial 1.

Comparing the results of these two studies demonstrates the PK linearity of plasma (AUC and C<sub>max</sub>) exposure and urine excretion rate for ipratropium bromide and albuterol when delivered via the Respimat inhaler.

When CVT-R treatment was compared with the monocomponent I-R, systemic exposure to ipratropium bromide was similar within trials, indicating that albuterol did not affect the absorption and elimination of ipratropium bromide.

## DISCUSSION

The CVT-R was developed as an alternative to the CVT-MDI, a formulation that could no longer be marketed in the United

**Table 2** Comparison of pharmacokinetic parameter geometric mean ratios for albuterol

Trial		AUC <sub>0-8</sub> (Trial 1) AUC <sub>0-6</sub> (Trial 2)	C <sub>max</sub>	C <sub>min</sub>	Amount excreted in urine in 0-2 h	Amount excreted in urine in 0-8 h (Trial 1) and 0-6 h (Trial 2)
1	CVT-R (ipratropium bromide 40 µg / albuterol 200 µg) vs. CVT-MDI (ipratropium bromide 36 µg / albuterol sulfate 206 µg)	1.42	1.62	1.59	1.26	1.33
2	CVT-R (ipratropium bromide 20 µg / albuterol 100 µg) vs. CVT-MDI (ipratropium bromide 36 µg / albuterol sulfate 206 µg)	0.74	0.76	0.71	0.72	0.86

Abbreviations: AUC, area under the plasma concentration–time curve; C<sub>max</sub>, maximum observed plasma concentration; C<sub>min</sub>, minimum observed plasma concentration; CVT, Combivent; MDI, metered-dose inhaler; R, Respimat inhaler.

**Table 3** Comparison of pharmacokinetic parameter geometric mean ratios for ipratropium bromide

Trial		AUC <sub>0-8</sub> (Trial 1) AUC <sub>0-6</sub> (Trial 2)	C <sub>max</sub>	C <sub>min</sub>	Amount excreted in urine in 0-2 h	Amount excreted in urine in 0-8 h (Trial 1) and 0-6 h (Trial 2)
1	CVT-R (ipratropium bromide 40 µg / albuterol 200 µg) vs. CVT-MDI (ipratropium bromide 36 µg / albuterol sulfate 206 µg)	4.62	3.14	1.44	3.50	2.80
	I-R (ipratropium bromide 40 µg) vs. CVT-R (ipratropium bromide 40 µg / albuterol 200 µg)	1.03	0.87	0.76	0.87	0.90
2	CVT-R (ipratropium bromide 20 µg / albuterol 100 µg) vs. CVT-MDI (ipratropium bromide 36 µg / albuterol sulfate 206 µg)	1.04	0.99	0.95	1.08	1.18
	I-R (ipratropium bromide 20 µg) vs. CVT-R (ipratropium bromide 20 µg / albuterol 100 µg)	0.91	1.05	0.97	0.97	0.91

Abbreviations: AUC, area under the plasma concentration–time curve; C<sub>max</sub>, maximum observed plasma concentration; C<sub>min</sub>, minimum observed plasma concentration; CVT, Combivent; I, ipratropium bromide; MDI, metered-dose inhaler; R, Respimat inhaler.

States after December 2013.<sup>11</sup> CVT-R became available to patients with COPD in the United States in September 2012.

The new-generation delivery system was developed to be more environmentally friendly than pMDIs, but also to be more efficient at drug delivery and easier for patients to use. Since delivery of drug in aqueous solution is droplet size dependent (not drug dependent) via the Respimat inhaler, experience from previous data on other drugs used with this device would be relevant to CVT-R.

Gamma scintigraphy studies suggest that drug delivery to the lung via a Respimat inhaler is ~2.8 times greater than via a pMDI (**Figure 1**<sup>7,8</sup> [and data from Boehringer Ingelheim Clinical Trial Report 260.2706, Doc No. U97-0056]). Following training in correct inhalation techniques, whole-lung deposition, measured by gamma scintigraphy, was higher in patients with COPD administered fenoterol hydrobromide 50 µg / ipratropium bromide 20 µg delivered via a Respimat inhaler than via an HFA pMDI (mean ± SD, 53 ± 17% of delivered dose vs. 21 ± 10% of metered dose).<sup>7</sup> In a study in patients with COPD that compared whole-lung deposition of fenoterol hydrobromide 50 µg / ipratropium bromide 20 µg delivered via a Respimat inhaler or an HFA pMDI, deposition was highest using the Respimat inhaler (mean ± SD, 60.1 ± 16.1% of delivered dose vs. 24.9 ± 6.5% of metered dose).<sup>8</sup> In another study, whole-lung deposition of fenoterol hydro-

bromide was higher in healthy, nonsmoker subjects using a Respimat inhaler compared with subjects using a pMDI (mean ± SD, 50.0 ± 14.7% of delivered dose vs. 11.0 ± 4.9% of metered dose; unpublished data [Boehringer Ingelheim Clinical Trial Report 260.2706, Doc No. U97-0056]).

The two studies reported here examined the comparative efficiency of drug delivery using CVT-R and CVT-MDI. Graphical comparisons of Trials 1 and 2 are presented in **Figure 3** (albuterol) and **Figure 4** (ipratropium). Following analysis of Trial 1 data, it was concluded that the Respimat inhaler delivered more ipratropium and albuterol to the lung and systemic circulation than did the CFC device, following similar ex-mouthpiece delivered doses. Since years of efficacy and safety data were available for CVT-MDI, it was decided that, for a larger safety and efficacy clinical trial (Trial 2), ipratropium and albuterol doses for the Respimat inhaler would be reduced to one-half of those in Trial 1. Based on the geometric means and wide 90% CIs for albuterol and ipratropium, as shown in **Figures 3** and **4**, respectively, for Trial 1, a larger PK sample size was required in Trial 2 to obtain a more precise estimate of lung deposition via systemic drug concentrations and urinary excretion.

Trial 2 was of similar design to Trial 1 (**Table 1**). Both trials used the same CVT-MDI dose (i.e., ipratropium bromide 36 µg and albuterol sulfate 206 µg), but the CVT-R dose in

Trial 2 was half that used in Trial 1. Trial 2 included more than 50 patients in each PK evaluation; this large PK substudy comprised nearly 15% of the COPD population in the safety and efficacy trial. This large PK sample size in the substudy assured both clinical relevance of the PK data and more precise estimates. Comparing the two studies, dose proportionality for CVT-R was demonstrated for both albuterol (**Figure 3**) and ipratropium (**Figure 4**) for AUC,  $C_{\max}$ ,  $C_{\min}$ , and amount excreted in urine in the first 2 h after inhalation. The 90% CIs were smaller in Trial 2 because the sample size was larger. In both trials, ipratropium alone delivered via the Respimat inhaler was consistent with the respective CVT-R dose, indicating neither a physical nor PK interaction was observed.

Since the CVT-MDI dose was the same in both trials, ipratropium bromide data for  $C_{\max}$ ,  $C_{\min}$  in plasma (**Figure 4b,c**), and amount excreted in urine in the first 2 h after inhalation (**Figure 4d**) were consistent between the two studies. Additionally, there was overlap of CIs for all the parameters for albuterol delivered via CVT-MDI (**Figure 3**). An anomalous finding was a lower  $AUC_{0-8}$  geometric mean estimate and wide 90% CI for ipratropium in Trial 1. Based on this anomalous estimate of a 4.6 GMR (**Table 3**) of AUC, inconsistent with the other parameters ( $C_{\max}$ ,  $C_{\min}$ , amount excreted in the urine in the first 2 h after inhalation) and previous deposition data,<sup>6,7,26</sup> the PK sample size was increased for Trial 2.

The amount excreted in urine over an 8-h period (Trial 1) or a 6-h period (Trial 2) represents the total amount of ipratropium or albuterol absorbed into the systemic circulation via the lung and gut that is not metabolized. As shown in **Figure 4d-f**, ipratropium excretion in Trials 1 and 2 were comparable among CVT-R, CVT-MDI, and I-R, and were consistent with systemic plasma ipratropium parameters (see GMRs in **Table 3**). The same patterns were observed for albuterol (**Figure 3d-f**; **Table 2**). Differences observed in Trials 1 and 2 were due to the difference in CVT-R doses administered and the more robust sampling of the population in Trial 2.

The results of these two studies show that CVT-R 20/100 provided comparable systemic exposure for ipratropium compared with CVT-MDI 36/206, despite the former releasing about one-half of the active ingredient of the latter per ex-mouthpiece delivered dose. This can be explained by the following characteristics of the Respimat inhaler. After each inhaler actuation, the duration of spray is longer for the Respimat inhaler compared with pMDIs (1.5 s vs. 0.15–0.36 s) and the mean velocity is around 4–10 times slower for the Respimat inhaler compared with pMDIs (mean velocity at a 10-cm distance from the nozzle: 0.8 m/s vs. 2.0–8.4 m/s).<sup>6</sup> These two characteristics allow patients time to synchronize actuation with inhalation more effectively. Also, the Respimat inhaler nozzle is optimized to produce a high fine-particle fraction, (i.e., droplets  $<5.8 \mu\text{m}$  in diameter),<sup>19,20</sup> which is small enough to penetrate deep into the lungs.<sup>27</sup>

Plasma ipratropium concentrations or urinary excretion over a dosing interval can be regarded as a "marker" of lung deposition, because its gastrointestinal bioavailability is negligible (~2%).<sup>25</sup> In the present study, ipratropium bromide PKs indicate that half the delivered dose by the Respimat inhaler provides comparable lung doses to the CVT-MDI.

Since the Respimat inhaler was designed to deliver homogeneous droplets ( $<5.8 \mu\text{m}$  in diameter),<sup>19,20</sup> the proportion of lung deposition is unlikely to be different for ipratropium bromide and albuterol. However, with pMDIs, a major proportion of the dose is deposited in the oropharynx (**Figure 1**)<sup>7,8</sup> [and data from Boehringer Ingelheim Clinical Trial Report 260.2706, Doc No. U97-0056] and albuterol is about 50% bioavailable via this route.<sup>28</sup> As a result, CVT-MDI can generate a higher systemic exposure for albuterol, although the lung dose is comparable.

The PK assessments in this substudy of patients from two clinical trials demonstrate that, for both active ingredients, the dose combination of ipratropium bromide 20  $\mu\text{g}$  and albuterol 100  $\mu\text{g}$  chosen for the CVT-R should not pose any further systemic safety burden than the CVT-MDI.

The advantages of these PK analyses are that they included a larger number of participants than are usually included in PK studies. Also, patient demographics for the substudies resemble the population to be treated (i.e., patients with COPD).

Since ipratropium is minimally absorbed from the gastrointestinal tract,<sup>24</sup> ipratropium Respimat data from these two studies demonstrate that ipratropium is a marker of lung deposition and absorption. The dose proportionality of ipratropium observed between Trials 1 and 2 delivered via the Respimat inhaler and the comparability in plasma ipratropium concentrations observed between CVT-MDI and CVT-R delivering half the dose ex-valve of the MDI demonstrates that lung deposition from the Respimat inhaler is approximately two times more efficient than the older CVT-MDI device. This clinical observation in a robust PK population is consistent with smaller deposition imaging studies.<sup>7,8,29</sup>

**Acknowledgments.** The authors thank the patients, investigators, clinicians, and nursing staff who participated in the trials. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE) and were fully responsible for all content and editorial decisions, and were involved at all stages of article development. The authors received no compensation related to the development of the article. This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). Technical assistance and expertise in the calculation and reporting of deposition data from the Respimat inhaler and pMDI were provided by Dr Demetri Pavia. Writing, editorial support, and formatting assistance was provided by Jane M. Gilbert, BSc (Hons) CMPP, of Envision Scientific Solutions which was contracted, and compensated by BIPI for these services.

**Conflict of Interest.** V.R., M.A.C., and C.C.W. are employees of Boehringer Ingelheim Pharmaceuticals Inc.; H.D. is an employee of Boehringer Ingelheim Ltd; and T.R.M. and M.G. were employees of Boehringer Ingelheim Pharmaceuticals, Inc. at the time of the study. The above authors do not stand to gain either directly (bonuses or other) or indirectly (stock ownership) by the availability of Combivent Respimat. R.Z. has received payment for services on speakers' bureaus for Boehringer Ingelheim and Pfizer. His institution has received consultancy fees and grants from Boehringer Ingelheim and payment for services on advisory boards from GlaxoSmithKline.



**Author Contributions.** T.R.M., R.Z., V.R., M.G., and C.C.W. wrote the article; T.R.M., M.A.C., H.D., M.G., and C.C.W. designed the research; T.R.M., R.Z., V.R., H.D., and C.C.W. performed the research; T.R.M., V.R., M.A.C., and H.D. analyzed the data; T.R.M. and V.R. contributed new reagents/analytical tools.

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Supplementary information accompanies this paper on the *Clinical and Translational Science* website. ([http://onlinelibrary.wiley.com/journal/10.1111/\(ISSN\)1752-8062](http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1752-8062))