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The efficacy of tiotropium administered via Respimat® Soft Mist™ Inhaler or HandiHaler® in COPD patients☆

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Respimat®;
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Summary
Background: Tiotropium, a once daily inhaled anticholinergic delivered via HandiHaler®, provides bronchodilation for >24 h and improves patient-centred outcomes. The Respimat® Soft Mist™ Inhaler (SMI), a novel, propellant-free inhaler, has been developed and proposed as an alternative delivery device for use with tiotropium.
Methods: In a pre-specified, pooled analysis of two 30-week, double-blind, double-dummy, crossover studies, 207 patients with Chronic Obstructive Pulmonary Disease (COPD) were randomised to receive once daily tiotropium 5 μg or 10 μg (aqueous solution delivered via Respimat SMI), tiotropium 18 μg (inhalation powder via HandiHaler) or placebo. The primary endpoint was trough forced expiratory volume in 1 s (FEV_1) response. Forced vital capacity (FVC), peak expiratory flow rate (PEFR), rescue medication use, safety and pharmacokinetics (in a subgroup of patients) were also assessed.
Results: Both tiotropium doses delivered by Respimat SMI were significantly superior to placebo and non-inferior to tiotropium 18 μg HandiHaler on the primary endpoint (all $p < 0.0001$). All active treatments were significantly superior to placebo (all $p < 0.0001$) and both doses of tiotropium Respimat SMI were non-inferior to tiotropium 18 μg HandiHaler on the secondary spirometry variables and rescue medication use. The systemic exposure was similar between tiotropium 5 μg Respimat SMI and tiotropium 18 μg HandiHaler but was higher for tiotropium 10 μg Respimat SMI. All active treatments were well tolerated.

☆ Co-ordinating centres of this multicentre study were the Atrium Medisch Centrum, Heerlen and Spartanburg Clinical Research, USA.

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Conclusions: Tiotropium 5 μg Respimat SMI is comparable with tiotropium 18 μg HandiHaler in terms of efficacy, pharmacokinetics and safety. Respimat SMI is an effective alternative, multi-dose delivery device for tiotropium.

Introduction

A new generation, propellant-free inhaler, known as the Respimat® Soft Mist™ Inhaler (SMI) has been developed for delivering drugs to the lungs in COPD patients.[1] This device is unique in that it uses mechanical energy, in the form of a spring, to generate a fine, slow-moving cloud (the Soft Mist™) for inhalation. Respimat SMI also has a number of benefits. Most notably, it is simple to coordinate and the delivered dose is independent of inspiratory effort; it is therefore not affected by the breathing manoeuvre problems inherent with some other devices, so it is suitable for all patients to use.[2–4]

Previously reported studies have shown that the delivery of ipratropium bromide/fenoterol hydrobromide via Respimat SMI is as safe and effective as delivery from an established metered-dose inhaler (MDI).[5,6] However, Respimat SMI has primarily been developed as an alternative delivery device for use with tiotropium, an established anticholinergic that provides prolonged M_3 receptor blockade. The lung function improvements associated with tiotropium HandiHaler® (the usual delivery vehicle) have been well established in clinical trials of COPD patients.[7–12]

Short-term studies of Respimat SMI have been favourable in a randomised, double-blind-within-device, parallel-group, dose-ranging study, tiotropium 1.25–20 μg Respimat SMI, tiotropium 18 μg HandiHaler or placebo were administered to 202 COPD patients for 3 weeks.[13] This study showed that tiotropium 5 μg Respimat SMI and tiotropium 18 μg HandiHaler improved lung function to a statistically significantly greater extent than placebo. The primary aim of the current studies was to demonstrate non-inferiority of lung function response to either tiotropium 5 μg or 10 μg Respimat SMI compared with tiotropium 18 μg HandiHaler in patients with COPD after 4-week treatment periods.

Methods

Study design

This was a pre-specified pooled analysis of two identical 30-week, multicentre, randomised, placebo-controlled, double-blind, double-dummy, crossover studies. These trials were designed to assess the efficacy and tolerability of two doses of tiotropium (5 μg or 10 μg) delivered via Respimat SMI (Boehringer Ingelheim, Ingelheim am Rhein, Germany) and one dose of tiotropium (18 μg) delivered via HandiHaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany) in patients with COPD. One study (#205.249) was conducted at 11 centres in the United States (10 centres) and Canada (one centre), and one study (#205.250) was conducted at two centres, one in the Netherlands and one in Belgium.[14] The studies were conducted in accordance with the Declaration of Helsinki (1996), and were approved by the relevant Independent Ethics Committees.

Following screening and a 2-week run-in period, eligible patients were randomised to four 4-week treatment periods (Fig. 1). The treatments were tiotropium 5 μg (two actuations of 2.5 μg) Respimat SMI plus one inhalation of placebo HandiHaler; tiotropium 10 μg (two actuations of 5 μg) Respimat SMI plus one inhalation of placebo HandiHaler; tiotropium 18 μg HandiHaler plus two inhalations of placebo Respimat SMI; or two inhalations of placebo Respimat SMI plus one inhalation of placebo HandiHaler. All doses were administered in the morning between 07:00 and 10:00 h, and Respimat SMI doses were administered before the HandiHaler dose. Each treatment period was separated by a 4-week washout period.

Subjects

Patients were males or females aged $\geq$40 years with a diagnosis of COPD (pre-bronchodilator forced expiratory volume in 1 s [FEV_1] $\leq$ 60% predicted normal[15] and FEV_1/forced vital capacity [FVC] $\leq$ 70%) and were current or ex-smokers with >10 pack-year smoking history. Patients with significant diseases other than COPD, or those with a history of asthma or allergic rhinitis, were excluded, as were pregnant or nursing women and pre-menopausal women not using adequate contraception. Patients with a respiratory infection or COPD exacerbation were also excluded. Patients taking regular daytime oxygen therapy, β-blocker medications, cromolyn sodium, nedocromil sodium, anti-leukotrienes or oral corticosteroids at unstable doses were excluded. All patients provided written informed consent to participate.

Medication restrictions

Prior to the screening visit, short-acting anticholinergics and short-acting β agonists were not permitted for 8 h, long-acting β agonists were not permitted for 48 h, and short-acting theophylline was not permitted for 24 h. Patients were required to stop using tiotropium HandiHaler 4 weeks prior to inclusion. Some medications were allowed during the study if they were stabilised for at least 6 weeks prior to and during the study. These included oral and inhaled corticosteroids, mucolytic agents and salbutamol, which could be used by the patients as rescue medication during each of the 4-week treatment periods. Inhaled short-acting or long-acting β agonists were allowed during the washout periods, but were not permitted for 8 h and 48 h, respectively, prior to clinic visits, and short-acting theophylline could be used as long as there was a 24-h washout prior to clinic visits.

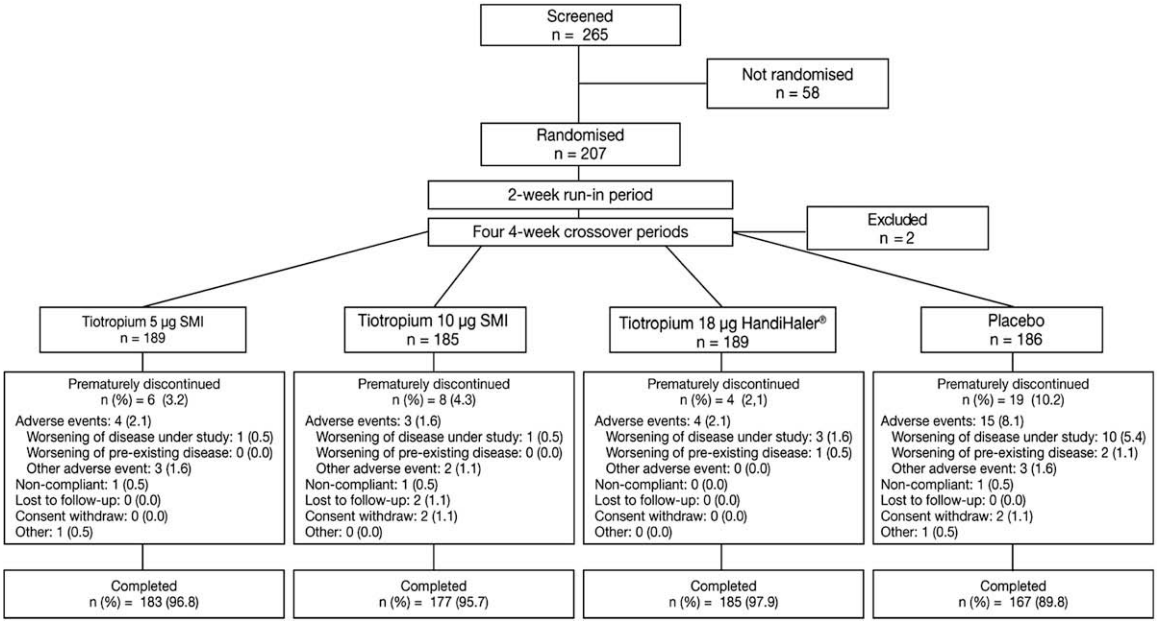

Figure 1 Study design and patient disposition. SMI, Soft Mist™ Inhaler.

Assessments

Spirometry was performed in accordance with American Thoracic Society criteria.[16] Assessments were conducted at the beginning of each period (till 3 h post-dosing), and at the end of each 4-week treatment period; these measurements were performed over a 12-h observation period, with readings taken at −10 min and 15, 30 min, 1, 2, 3, 4, 6, 8, 10 and 12 h after inhalation of the morning dose of study medication. Testing always started between 07:00 and 10:00 h and at the same time of the day; the maximum difference between the start of the test at the randomisation visit and the tests on subsequent clinic visits was ±30 min. The highest values of FEV_1 and FVC from three technically acceptable measurements were retained. Patients also recorded daily the number of occasions they used salbutamol metered-dose inhaler (MDI) and twice-daily (morning [pre-medication] and bedtime) peak-expiratory flow rates (PEFR) during the 2-week baseline period as well as during the four 4-week treatment periods.

Pharmacokinetics

Blood and urine samples were collected from a subset of 98 patients on the pulmonary function test days at the end of each 4-week treatment period. Tiotropium concentrations were determined by a validated HPLC-MS/MS assay. Blood was collected pre-dose (within <1 h) and 10 min (±5 min), 60 min (±20 min), and 6 h (±2 h) post-dose. Urine samples were collected pre-dose and over the time intervals 0—2 and 2—12 h post-dose. To avoid contamination, these samples were taken in a separate room from where priming of the Respimat SMI or drug inhalation took place. Plasma vials were stored closed and only opened if necessary for the procedure. Study personnel and patients were instructed to wear gloves and to wash hands prior to collection, handling of the samples and after inhalation. Systemic exposure to tiotropium at steady state (ss) was determined using plasma concentration—time profiles, maximum drug plasma concentration ($C_{max,ss}$), and the area under the concentration—time curve of tiotropium in plasma over the time interval 0—6 h ($AUC_{0-6,ss}$) and 0—12 h ($AUC_{\tau,ss}$). Furthermore, the amount/fraction of tiotropium excreted in urine over the time interval 0—2 h ($Ae_{0-2,ss}$/$fe_{0-2,ss}$) and 0—12 h ($Ae_{0-12,ss}/fe_{0-12,ss}$) at steady state was determined.

Safety assessments

Adverse events were collected throughout the study period and assigned to treatment from the first dose of a period up to 30 days after discontinuation of medication for that period or start of study medication for the next period, whichever comes first. Vital signs were measured at the first and last days of each 4-week period up to 3 h post-dose at the same time intervals as pulmonary function testing. Routine laboratory tests and 12-lead electrocardiogram (ECG) were assessed at the start of the 2-week run-in period and at the end of the last 4-week treatment period.

Statistical analysis

The primary efficacy endpoint was trough FEV_1 response defined as the change in FEV_1 from period baseline (Day 1) to the end of each 4-week treatment period (Day 29). Secondary clinic spirometric endpoints included trough and peak FVC, FVC $AUC_{(0-12h)}$, peak FEV_1 and FEV_1 $AUC_{(0-12h)}$ at Day 29, and the time to therapeutic response (defined as an increase in $FEV_1 \geq 15\%$ from baseline within 2 h after the first dose). For continuous endpoints (FEV_1, FVC, PEFR, and rescue medication use), an analysis of covariance (ANCOVA) with terms for centre, patients within centre, period,

Table 1 Baseline characteristics of the study population ($n = 205$).

Variables[a]	
Age (y)	64 (8)
Male, *n* (%)	147 (72)
Ex-smoker, *n* (%)	128 (62)
Smoking history (pack-years)	51 (32)
Duration of COPD (y)	10 (8)
FEV_1 (L)	1.05 (0.38)
FEV_1 (% predicted)	37 (12)
FVC (L)	2.54 (0.86)
FEV_1/FVC (%)	42 (10)
FEV_1 30 min after 400 μg salbutamol (L)	1.3 (0.4)
FEV_1 reversibility (change from pre-dose, L)	0.2 (0.1)
FEV_1 reversibility (% change from pre-dose)	19.9 (14.3)
Patients taking pulmonary medication at baseline, *n* (%)	176 (86)
Anticholinergics, long-acting (tiotropium), *n* (%)	1 (<1)
Anticholinergics, short-acting, *n* (%)	104 (51)
β-Adrenergics, long-acting, *n* (%)	93 (45)
β-Adrenergics, oral, *n* (%)	1 (<1)
β-Adrenergics, short-acting, *n* (%)	118 (58)
Steroids, inhaled, *n* (%)	112 (55)
Steroids, oral, *n* (%)	2 (<1)
Xanthines, *n* (%)	11 (5)

[a] Mean (SD) unless otherwise stated.

period baseline and treatment was performed. A retrospective analysis was performed to evaluate the potential additive effect (FEV_1) of concomitantly inhaled glucocorticosteroid (iCS) use. The effect of concomitant iCS use was assessed by adding terms for iCS use, patients within iCS use and the interaction treatment by iCS use to the model and removing the terms centre and patients within centre. Time to therapeutic response, the percentage of patients achieving therapeutic response and all safety variables were analysed using descriptive statistics. Type I error was preserved by a stepwise procedure that tested each tiotropium Respimat SMI dose (5 μg and 10 μg), first for superiority over placebo, and then for non-inferiority (defined as a response within 50 mL for the primary endpoint) compared with tiotropium HandiHaler.

The Full Analysis Set (FAS), which consisted of all treatment periods where baseline data and post-treatment data were available, was used for the analyses. Missing trough FEV_1 values at the end of a treatment period were imputed by the lowest recorded value on the first test day (even if it was baseline). Treated patients were included in the safety analysis. However, two patients from study #205.249 were excluded from all efficacy and safety analyses, because it was unclear which treatment they used in which period (this was a patient error as these two patients shared the same dwelling and mixed up their medication).

The sample size was calculated individually for each study; a sample size of 64 patients was required to demonstrate non-inferiority within 0.05 L with a power of 90% for at least one dose. A one-sided significance level (p) of 0.025 was assumed for the primary analyses, with a two-sided p of 0.05 for all secondary endpoints.

The pharmacokinetic analysis for tiotropium was carried out by non-compartmental analysis of the plasma and urine concentration time data using the WinNonlin® software program (Professional, Pharsight Corporation, Mountain View, CA). AUC was calculated using the linear up/log-down rule. Any plasma concentrations below the limit of quantification (LOQ) were replaced by half the LOQ (i.e., 1.25 pg/mL) to avoid a potential bias of the mean. For tiotropium 10 μg Respimat SMI, tiotropium 5 μg Respimat SMI, and tiotropium 18 μg HandiHaler, about 13%, 35%, and 42% of the plasma concentrations were replaced by half the LOQ, respectively; mainly pre-dose samples and, to a lesser extent, samples taken 6 h after inhalation were affected. The replacement of concentrations that were below LOQ was not applied to the urinary excretion data.

Results

Population

A total of 207 patients were randomised to treatment in studies #205.249 ($n = 131$) and #205.250 ($n = 76$). The baseline characteristics for the patients ($n = 205$) included in the efficacy and safety analyses are shown in Table 1. The majority of patients were male (72%), ex-smokers (62%) with a mean COPD duration of 10 years, and mean FEV_1 was 37% of predicted normal. Pharmacokinetic data were obtained from 98 patients (72 men and 26 women aged

Table 2a Mean (SE) trough FEV_1 response[a] (L) at the end of the 4-week treatment period (Day 29).

Treatment difference	Mean (SE)	95% CI	*p* value	
			Non-inferiority	Superiority
Day 29 (vs. placebo)				
Tiotropium 5 μg SMI	0.126 (0.013)	[0.100—0.152]	—	<0.0001
Tiotropium 10 μg SMI	0.127 (0.013)	[0.101—0.153]	—	<0.0001
Tiotropium 18 μg HH	0.097 (0.013)	[0.071—0.123]	—	<0.0001
Day 29 (vs. tiotropium 18 μg HH)				
Tiotropium 5 μg SMI	0.029 (0.013)	[0.004—0.055]	<0.0001	—
Tiotropium 10 μg SMI	0.031 (0.013)	[0.005—0.056]	<0.0001	—

[a] Adjusted for centre, patient (within centre), period, period baseline and treatment.
HH, HandiHaler®; SMI, Soft Mist™ Inhaler.

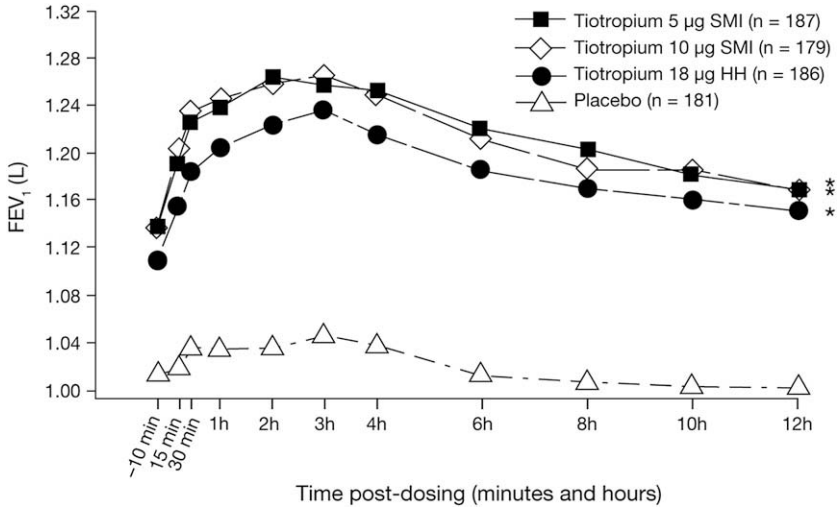

Figure 2 Mean FEV_1 (L) response* following treatment with tiotropium 5 or 10 µg Respimat® SMI, tiotropium 18 µg HandiHaler® or placebo at pharmacodynamic steady state (Day 29). *Adjusted for centre, patient (within centre), period, period baseline and treatment. Tiotropium treatments were statistically significantly different from placebo ($p < 0.0001$) at all post-dose time points. SMI, Soft Mist™ Inhaler; HH, HandiHaler®.

between 41 and 87 years; 2 Afro-Americans and 96 Caucasians). Patient withdrawals are shown in Fig. 1.

Efficacy assessments

Both tiotropium Respimat SMI doses were significantly superior to placebo and non-inferior to tiotropium 18 µg HandiHaler on the primary endpoint (trough FEV_1 response on Day 29; Table 2a). Furthermore, the study also showed that the mean trough FEV_1 response on Day 29 was 29 mL higher for tiotropium 5 µg ($p < 0.03$) and 31 mL higher for tiotropium 10 µg Respimat SMI ($p < 0.02$) compared with tiotropium 18 µg HandiHaler. During the 12-h observation period on Day 29, the FEV_1 time—response (expressed as mean values at each time point) was significantly increased following treatment with tiotropium 5 µg Respimat SMI, tiotropium 10 µg Respimat SMI and tiotropium 18 µg HandiHaler when compared with placebo (Fig. 2).

The percentage of patients achieving therapeutic response on Day 1 with the Respimat SMI was 64% (tiotropium 5 µg) and 72% (tiotropium 10 µg) compared with 57% (tiotropium 18 µg HandiHaler) and 22% (placebo). On Days 1 and 29, all active treatments were significantly superior to placebo on the secondary spirometry endpoints (Tables 2b and 3), and both doses of tiotropium (5 µg and 10 µg) Respimat SMI were numerically superior to tiotropium 18 µg HandiHaler on the secondary endpoints (Table 3).

Pharmacokinetics

Systemic exposure was similar between tiotropium 5 µg Respimat SMI and tiotropium 18 µg HandiHaler, whereas the systemic exposure of tiotropium 10 µg Respimat SMI was higher compared with the other treatments (Fig. 3 and Table 4). The amount of drug excreted in urine was higher in the tiotropium 5 µg Respimat SMI group compared with the tiotropium 18 µg HandiHaler group by about 26% in the time interval 0—12 h post-dose (see Table 4). The amount of drug excreted after treatment with tiotropium 10 µg Respimat SMI was twice as high when compared with tiotropium 5vµg Respimat SMI (Table 4).

Table 2b Mean (SE) peak FEV_1 response[a] (L) on Day 1.

Treatment difference	Mean (SE)	95% CI	*p* value	
			Non-inferiority	Superiority
Day 1 (vs. placebo)				
Tiotropium 5 µg SMI	0.140 (0.010)	[0.121—0.159]		<0.0001
Tiotropium 10 µg SMI	0.165 (0.010)	[0.146—0.185]		<0.0001
Tiotropium 18 µg HH	0.108 (0.010)	[0.089—0.127]		<0.0001
Day 1 (vs. tiotropium 18 µg HH)				
Tiotropium 5 µg SMI	0.032 (0.010)	[0.013—0.051]	0.0009	
Tiotropium 10 µg SMI	0.057 (0.010)	[0.038—0.076]	<0.0001	

[a] Adjusted for centre, patient (within centre), period, period baseline and treatment.
HH, HandiHaler®; SMI, Soft Mist™ Inhaler.

Table 3 Comparison between 4-week tiotropium treatment regimens in average, peak (FEV_1, FVC) and trough response (FVC), PEFR (morning and evening) and rescue medication use.

Variables	Treatment differences (vs. placebo)			Treatment differences (vs. tiotropium 18 μg HH)	
	Tiotropium 5 μg SMI	Tiotropium 10 μg SMI	Tiotropium 18 μg HH	Tiotropium 5 μg SMI	Tiotropium 10 μg SMI
Peak FEV_1 (L)[a]	0.215* (0.013)	0.219* (0.013)	0.185* (0.013)	0.030** (0.013)	0.034** (0.013)
FEV_1 (L) $AUC_{(0-12h)}$[a]	0.199* (0.012)	0.195* (0.012)	0.167* (0.012)	0.031** (0.011)	0.028** (0.011)
Trough FVC (L)[a]	0.232* (0.030)	0.263* (0.030)	0.210* (0.030)	0.022 (0.030)	0.053 (0.030)
FVC (L) $AUC_{(0-12h)}$[a]	0.359* (0.025)	0.369* (0.025)	0.338* (0.025)	0.021 (0.024)	0.031 (0.024)
Peak FVC (L)[a]	0.405* (0.031)	0.410* (0.031)	0.395* (0.031)	0.010 (0.030)	0.016 (0.030)
Weekly morning PEFR (L/min)[a]	19.8* (2.1)	21.5* (2.1)	16.8* (2.1)	3.0 (2.1)	4.7** (2.1)
Weekly evening PEFR (L/min)[a]	23.7* (2.2)	24.1* (2.2)	19.6* (2.2)	4.0 (2.1)	4.5** (2.2)
24-h rescue medication use (number of occasions)[a]	−1.1* (0.1)	−1.1* (0.1)	−0.9* (0.1)	−0.2 (0.1)	−0.2 (0.1)

Adjusted for centre, patient (within centre), period, period baseline and treatment. AUC, area under FEV_1 time—response curve; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEFR, peak expiratory flow rate; SMI, Soft Mist™ Inhaler; HH, HandiHaler®.
[a] Mean (SE); *$p < 0.0001$; **$p < 0.05$.

Safety assessments

The incidence of adverse events is summarised in Table 5. The most common adverse events were COPD exacerbations (9.6% [tiotropium 5 μg]; 10.9% [tiotropium 10 μg]; 11.2% [tiotropium 18 μg]; 13.0% [placebo]) and nasopharyngitis (7.5% [tiotropium 5 μg]; 8.2% [tiotropium 10 μg]; 5.9% [tiotropium 18 μg]; 8.2% [placebo]). The incidence of dyspnoea exacerbated was more common in the placebo group, whereas dry mouth occurred slightly more frequently in the tiotropium 10 μg Respimat SMI group.

Discontinuations due to adverse events were low and similar in the active treatment groups: 4/187 (2.1%; tiotropium 5 μg Respimat SMI); 3/183 (1.6%; tiotropium 10 μg Respimat SMI); and 4/187 (2.1%; tiotropium 18 μg HandiHaler). Discontinuations in the placebo group were higher (15/184 [8.2%]). Eight patients discontinued an intermediate treatment period but continued with the next period and completed the trial. In total, 26 patients experienced a serious adverse event including four deaths (one COPD exacerbation, one cardiac arrest [tiotropium 5 μg Respimat SMI], one cerebrovascular accident [tiotropium 18 μg HandiHaler], one cardiorespiratory arrest [placebo]); however, none of these was considered to be related to study medication. There were no clinically meaningful changes in blood pressure or pulse rate measured up to 3 h post-dose. There were no clinically relevant changes in routine laboratory tests measured from the run-in period to the study end.

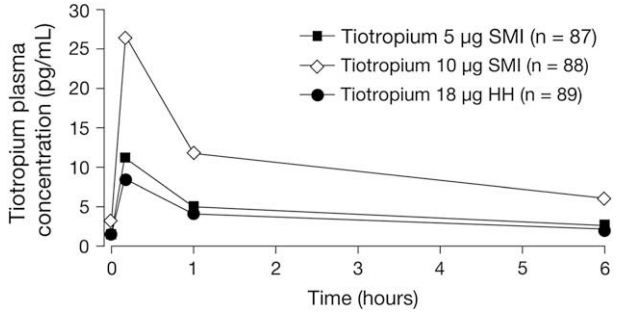

Figure 3 Geometric mean tiotropium plasma concentration—time profiles on Day 29 following once daily inhalation of tiotropium in COPD patients. SMI, Soft Mist™ Inhaler; HH, HandiHaler®.

Discussion

This study assessed the efficacy and safety of tiotropium delivered via Respimat SMI or HandiHaler in the treatment of COPD. The results showed that tiotropium 5 μg and 10 μg Respimat SMI were non-inferior to tiotropium 18 μg HandiHaler on the primary endpoint (trough FEV_1 response) ($p < 0.0001$); furthermore, the mean trough FEV_1 response on Day 29 was around 30 mL (approximately 1% predicted in FEV_1) higher for tiotropium 5 μg and 10 μg Respimat SMI than tiotropium 18 μg HandiHaler. Both delivery vehicles provided rapid and sustained improvements in pulmonary parameters; the FEV_1 (expressed as mean values at each time point) on the last day was improved within the first 30 min of treatment (compared to test day baseline) and was maintained over the 12-h post-dose period (Fig. 2). Although FEV_1 was not measured over a 24-h period, the 12-h observation period and trough were sufficient to show that lung function efficacy was maintained even after 24 h; furthermore, rescue medication use over the 24-h period was extremely low for all active treatments. All three active treatments were well tolerated compared with placebo.

The pharmacokinetic subgroup analysis revealed that the systemic exposure was similar between tiotropium 5 μg Respimat SMI and tiotropium 18 μg HandiHaler as shown by similar plasma AUC and C_{max} values at steady state. The systemic exposure following administration of tiotropium 10 μg Respimat SMI was higher compared with the other treatments. This finding was not unexpected, given that tiotropium Respimat SMI delivers a higher fine-particle dose

Table 4 Pharmacokinetic parameters for tiotropium treatment regimens.

Pharmacokinetic parameter	*n*	Tiotropium 5 μg SMI	Tiotropium 10 μg SMI	Tiotropium 18 μg HH
		gMean (gCV [%])		
$AUC_{0-6,ss}$ (pg h/mL)	87/88/89	26.4 (76.7)	61.9 (80.7)	21.7 (73.0)
$AUC_{t,ss}$ (pg h/mL)	87/88/89	64.7 (59.2)	146 (74.5)	55.9 (56.6)
$C_{max,ss}$ (pg/mL)	87/88/89	11.5 (95.6)	26.4 (95.8)	8.49 (99.1)
$Ae_{0-2h,ss}$ (ng)	84/82/82	171 (86.1)	352 (91.7)	116 (98.9)
$Ae_{0-12h,ss}$ (ng)	82/82/81	530 (68.6)	1090 (84.2)	421 (69.9)

Ae_{t1-t2}, amount of analyte eliminated in urine over time; AUC, area under the concentration–time curve of the analyte in plasma over time; C_{max}, maximum measured concentration of the analyte in plasma; SMI, Soft Mist™ Inhaler; HH, HandiHaler®; SS, at steady state; t_{max}, time to maximum concentration of the analyte in plasma.

(i.e., the amount of drug in the lungs). However, the higher systemic exposure observed with tiotropium 10 μg Respimat SMI was not reflected in the primary endpoint as tiotropium 5 μg Respimat SMI was comparable. This may be indicative of a dose–response plateau, and taken together with the higher incidence of dry mouth observed with tiotropium 10 g Respimat SMI, is further support for use of the lower (5 μg) dose with Respimat SMI.

The impact of tiotropium HandiHaler on patient-centred outcomes, such as health-related quality of life,[7–9] exercise endurance time,[17,18] and the response to pulmonary rehabilitation,[19] has been well established. Given that there were comparable lung function improvements between tiotropium Respimat SMI and tiotropium HandiHaler. It is likely that tiotropium (5 μg and 10 μg) Respimat SMI will have comparable benefits to tiotropium HandiHaler for patient-centred outcomes, although these are not examined in the current study.

In a published safety analysis of 19 randomised trials, which included 4435 tiotropium- and 3384 placebo-treated patients, tiotropium was found to be consistently well tolerated.[20] Overall, dyspnoea, dry mouth, COPD exacerbations and upper respiratory tract infections were the most commonly reported adverse events associated with tiotropium. In the current study, given that tiotropium 5 μg Respimat SMI provides comparable lung function improvements and systemic exposure to tiotropium 18 μg HandiHaler, it is assumed that it will provide the same clinical efficacy in terms of patient-related outcomes, with a comparable safety profile. Our study shows that, in general, the incidences of adverse events were comparable between tiotropium 5 μg Respimat SMI and tiotropium 18 μg HandiHaler, for example, both had a low incidence of dry mouth (1.1%).

Recent controlled long-term studies in COPD have demonstrated that fixed-dose combination therapy of a long-acting beta-agonist (LABA) with an inhaled glucocorticosteroid (iCS) is more effective in improving lung function compared to its single components.[21–24] In order to evaluate a potential additive effect of tiotropium and concomitant use of iCS, a retrospective analysis was performed. Irrespective of whether tiotropium was inhaled as dry powder or as soft-mist inhaler no difference was found in response between the subgroup with ($n = 121$) or without ($n = 84$) concomitant use of iCS in terms of trough FEV_1 and the average FEV_1 AUC_{0-12h} on Day 29. Of note, each of the present individual studies was designed differently compared to the prospective studies conducted to evaluate combination therapy of an LABA and iCS. Therefore, it is mandatory to design a prospective clinical study to evaluate the benefit of combined tiotropium and iCS therapy in COPD.

In conclusion, this study shows that, for patients with moderate-to-very-severe COPD, tiotropium delivered via Respimat SMI is effective in improving lung function and is well tolerated compared with tiotropium delivered via HandiHaler and placebo; these lung function improvements are consistent with those observed with Respimat SMI in previous studies.[13,25] Given that the systemic exposure was similar between tiotropium 5 μg Respimat SMI and tiotropium 18 μg HandiHaler, these findings support the use of the lower dose of 5 μg with Respimat SMI, as this dose may offer the best efficacy-to-safety profile. Previous studies have also shown that Respimat SMI allows relative dose reduction compared with other devices such as ipratropium/fenoterol pMDI.[5] Tiotropium administered from the multidose Respimat inhaler generates an aqueous aerosol with a delivered dose that is independent of the

Table 5 Adverse events reported in ≥3% of patients.

	Tiotropium 5 μg SMI ($n = 187$)	Tiotropium 10 μg SMI ($n = 183$)	Tiotropium 18 μg HH ($n = 187$)	Placebo ($n = 184$)
Total, *n* (%)	73 (39.0)	79 (43.2)	64 (34.2)	91 (49.5)
Dry mouth	2 (1.1)	6 (3.3)	2 (1.1)	1 (0.5)
Nasopharyngitis	14 (7.5)	15 (8.2)	11 (5.9)	15 (8.2)
COPD exacerbation	18 (9.6)	20 (10.9)	21 (11.2)	24 (13.0)
Dyspnoea exacerbated	10 (5.3)	6 (3.3)	7 (3.7)	22 (12.0)

patient's inspiratory effort. Because of the Respimat's increased efficiency it allows reduction in the nominal dose of tiotropium and offers to prescribers and COPD patients an alternative formulation to the dry powder with similar efficacy and safety.

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Declaration of disclosures/Conflicts of interest for each person

Dr. Piet Cornelissen, Dr. Juliane Platz and Achim Mueller are all employees of Boehringer Ingelheim (the sponsor). There are no other conflicts of interest.

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