Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD

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ABSTRACT: **This study compared the bronchodilator effects of tiotropium, formoterol and both combined in chronic obstructive pulmonary disease (COPD).**

A total of 71 COPD patients (mean forced expiratory volume in one second (FEV_1) 37% predicted) participated in a randomised, double-blind, three-way, crossover study and received tiotropium 18 μg _q.d._, formoterol 12 μg _b.i.d._ or both combined _q.d._ for three 6-week periods. The end-points were 24-h spirometry (FEV_1, forced vital capacity (FVC)) at the end of each treatment, rescue salbutamol and safety.

Compared with baseline (FEV_1 prior to the first dose in the first period), tiotropium produced a significantly greater improvement in average daytime FEV_1 (0–12 h) than formoterol (127 _versus_ 86 mL), while average night-time FEV_1 (12–24 h) was not different (tiotropium 43 mL, formoterol 38 mL). The most pronounced effects were provided by combination therapy (daytime 234 mL, night-time 86 mL); both differed significantly from single-agent therapies. Changes in FVC mirrored the FEV_1 results. Compared with both single agents, daytime salbutamol use was significantly lower during combination therapy (tiotropium plus formoterol 1.81 puffs·day^{-1}, tiotropium 2.41 puffs·day^{-1}, formoterol 2.37 puffs·day^{-1}). All treatments were well tolerated.

In conclusion, in chronic obstructive pulmonary disease patients, tiotropium _q.d._ achieved a greater improvement in daytime and comparable improvement in night-time lung function compared with formoterol _b.i.d._ A combination of both drugs _q.d._ was most effective and provided an additive effect throughout the 24-h dosing interval.

Chronic obstructive pulmonary disease (COPD) is a progressive disease in patients experiencing increasing symptoms of airflow obstruction with limitations in their daytime physical activity. As the disease progresses, disability can become extreme, with limitations on even modest physical exertion disrupting daily life. Inhaled bronchodilator therapy is central in the treatment of COPD. When symptoms persist and are not adequately controlled with short-acting bronchodilators, recent guidelines recommend regular treatment with mono- or combination therapy of long-acting bronchodilators [1, 2]. In this respect, it is noted that, at present, no data exist on combination maintenance therapy with long-acting bronchodilators.

The currently available long-acting β2-agonists (LABAs) salmeterol or formoterol provide significant increases in lung function for ~12 h and relief of symptoms [3–5]. Recently, the new long-acting anticholinergic tiotropium has become available to clinical practice for the treatment of COPD [6, 7]. In contrast to LABAs, which have a twice-daily dose regimen, once-daily tiotropium maintains bronchodilation over 24 h. The clinical benefit of this once-daily anticholinergic agent has been established in comparative 1-yr clinical studies _versus_ placebo [8] and ipratropium bromide [9], and in two 6-month studies _versus_ salmeterol or placebo [10, 11]. Overall, tiotropium was found to be superior to these active agents in improving lung function.

Up to now, there have been no major clinical studies comparing tiotropium and formoterol in COPD, and a combination therapy of tiotropium

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and an inhaled LABA has not been investigated in depth. As highlighted by TENNANT *et al.* [12], combination therapy of these long-acting agents could provide important benefits, since these drugs have complementary actions on the airways. In this respect, CAZZOLA *et al.* [13] found a trend for additive effects of tiotropium and formoterol in COPD using a single-dose study design. Previously, it has been shown that add-on therapy of formoterol in the morning to maintenance therapy of tiotropium significantly improved the spirometric variables of forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and inspiratory capacity (IC) for >12 h in COPD patients [14]. Add-on therapy with a second formoterol dose in the evening provided a further improvement in average FEV1, FVC and IC during the night-time hours, but not in the FVC and IC values the following morning (*i.e.* measured 12 h after the evening dose of formoterol). The use of rescue salbutamol during the night was very low and not different between treatments, indicating that the impact of the add-on evening formoterol dose was not reflected in the need for reliever medication and that the tiotropium component provided sufficient bronchodilation during the night-time. Once-daily combination therapy would be an attractive option, as it simplifies therapy and could enhance compliance.

Therefore, the purpose of the present study was to compare the bronchodilator effects of tiotropium *q.d.* with formoterol *b.i.d.* during a pharmacodynamic steady state, with serial spirometry over a 24-h observation period. In addition, the bronchodilator effects of a combination therapy of tiotropium and formoterol, administered *q.d.* in separate devices, was compared with those of single-agent therapies.

METHODS
Patients
Patients were male or female outpatients, aged $\geqslant 40$ yrs, and current or ex-smokers with a $\geqslant 10$ pack-yr smoking history. All patients had a diagnosis of COPD [15] and were required to have a baseline FEV1 $\leqslant 60\%$ predicted [16] and a FEV1/FVC $\leqslant 70\%$. Specific exclusion criteria were a current or past diagnosis of asthma, atopy, allergic rhinitis or an elevated blood eosinophil count ($\geqslant 600$ mm^3). Also, patients with any of the following were excluded: a clinically significant medical disorder other than COPD; recent history of myocardial infarction; heart failure or cardiac arrhythmia requiring drug therapy; oxygen therapy; known symptomatic prostatic hypertrophy; and narrow-angle glaucoma. Patients with a respiratory infection or COPD exacerbation in the 6 weeks

prior to screening or during the run-in period were randomised 6 weeks following recovery from the event.

Study design
This was a three-centre, 20-week study consisting of a 2-week run-in period, followed by a randomised, double-blind, double-dummy, crossover design of three 6-week treatment periods. Following the screening visit, eligible patients entered a 2-week run-in period to ensure clinical stability (*i.e.* no exacerbations). Furthermore, this period was used to train the patients in the appropriate daily recording of as-needed use of salbutamol and peak expiratory flow rate (PEFR). Patients who successfully completed this phase were entered into the three 6-week periods, in which they received three treatment regimens in a randomised sequence (table 1). The evening dose of study drug was taken ~12 h after the morning dose of study medication. The patients were allowed to continue the use of inhaled steroids and oral steroids up to the equivalent of 10 mg·day^{-1} prednisone. All inhaled anticholinergic (8 h), short- (8 h) or long-acting inhaled β_2-agonist (48 h) medication use was discontinued at the end of the run-in period (tiotropium was not commercially available in the Netherlands and Belgium at the time of initiation). Theophylline preparations were not allowed for $\geqslant 1$ month prior to the screening visit. Open-label salbutamol was provided at the screening visit, and patients were instructed to use it as-needed for acute symptom relief. The study protocol was approved by the hospital medical ethics committees (Atrium medisch centrum, Heerlen, The Netherlands; Virga Jesse Ziekenhuis, Hasselt, and Ziekenhuis Oost-Limburg, Lanaken, Belgium), and written informed consent was obtained before any study procedure was undertaken.

Measurements
In addition to the qualifying spirometric tests (FEV1 and FVC) at the screening visit (visit 1), the bronchodilator responsiveness was assessed 1 h after inhalation of 4 puffs of salbutamol 100 µg (in order to characterise the study population and not to be used as an inclusion criterion). Subsequently, one spirometric assessment was conducted following the 2-week run-in period (visit 2, *i.e.* randomisation visit), *i.e.* before inhalation of the first dose of randomised study medication, whereas serial measurements were conducted during a 24-h observation period at the end of each 6-week treatment period at the following time points: 10 min prior to the morning dose; 30

TABLE 1	Treatment regimens of the three 6-week treatment periods	
6-week treatment period	**Treatment regimens**	
	Morning dose	**Evening dose**
1	Tiotropium[#] powder capsule 18 µg + formoterol-matched placebo[¶] powder capsule	Formoterol-matched placebo[¶] powder capsule
2	Tiotropium-matched placebo[#] powder capsule + formoterol[¶] powder capsule 12 µg	Formoterol[¶] powder capsule 12 µg
3	Tiotropium[#] powder capsule 18 µg + formoterol[¶] powder capsule 12 µg	Formoterol-matched placebo[¶] powder capsule

[#]: tiotropium (Spiriva®) and tiotropium-matched placebo powder capsule *via* HandiHaler (Boehringer Ingelheim International GmbH, Ingelheim/Rhein, Germany); [¶]: formoterol (Foradil®) and formoterol-matched placebo powder capsule *via* Aerolizer (Novartis Pharma AG, Basel, Switzerland).

and 60 min, and 2, 3, 4, 6, 8, 10 and 12 h after inhalation of the morning dose of study medication; and 30 and 60 min, and 2, 7, 10, 11 and 12 h after inhalation of the evening dose of study medication. Testing started between 08:00 and 10:00 h at the same time of the day, *i.e.* ±30 min maximum difference between the start of the test at the randomisation visit and the tests on subsequent clinic visits. The measurements were performed with a spirometer meeting American Thoracic Society (ATS) criteria [17]. The highest values of FEV1 and FVC from three technically adequate measurements were retained. Vital signs were recorded at the same time intervals as pulmonary function testing. During the 2-week run-in period, as well as during the three 6-week treatment periods, patients recorded daily the as-needed use of salbutamol metered-dose inhaler (MDI) and twice-daily PEFR. PEFR was measured prior to study medication as the best of three manoeuvres, using the Personal Best Peak Flow Meter (Healthscan Products Inc., Cedar Grove, NJ, USA). Use of salbutamol MDI was recorded separately for daytime and night-time. At each scheduled visit to the clinic, details of clinical status, adverse events and withdrawals were recorded. Before entry and at the completion of study participation, patients underwent a medical examination, laboratory testing and a 12-lead ECG recording.

Statistical analysis

The planned sample size was 60 completed patients. Assuming a standard deviation of 140 mL for paired differences as observed in other trials [18, 19], this sample size provides a power of 90% to detect a true difference of 60 mL in average FEV1 over 24 h (type I error rate: 0.05), resulting in an overall power for the first four comparisons (combination *versus* single agents) of ⩾80%.

The primary efficacy end-points were the average FEV1 over the first 12 h (0–12 h) and over the full 24-h observation period (0–24h) on the last day of each 6-week period of randomised treatment. The average FEV1 was calculated as the area under the curve from zero time to 12 or 24 h (or 12–24 h), respectively, using the trapezoidal rule divided by the corresponding duration (*i.e.* 12 or 24 h) to give the result in litres. The pre-dose FEV1 value was assigned to zero time and defined as the measurement before administration of the last morning dose of study drug at the end of each 6-week treatment period. Secondary end-points were trough and peak FEV1, as well as FEV1 values at individual time points. Trough was defined as the value measured at the end of the 24-h observation period at the end of each 6-week treatment period, *i.e.* ~24 and 12 h after the last morning, respectively, evening dose of study medication. The peak FEV1 was the highest FEV1 reading observed within 3 h after inhalation of the morning study medication. Average, trough and peak responses were defined as the change from the baseline FEV1 value, which was the measurement obtained on visit 2 (randomisation visit) prior to the first morning dose of randomised study medication. Analogous definitions were used for FVC-based parameters. Patient diary-based end-points were twice-daily PEFRs (morning and evening) and as-needed salbutamol use (daytime and night-time). To eliminate possible carry-over effects, the data obtained in the first 3 weeks of each 6-week treatment period were discarded [20, 21]; the mean of observations obtained in the last 3 weeks of each treatment period were calculated and used to compare the treatment regimens. The run-in period was used for training purposes; diary data recorded in this period were not used for the analysis.

For all end-points, adjusted means for the three treatments were calculated using a fixed-effects ANOVA model with terms for centre, patients within centre, treatment and period, as specified in the study protocol. All patients with on-treatment data available were included in the analysis (safety: n=74; diary and spirometric end-points: n=71 and n=69, respectively). No period effect could be detected, whereas centre and patient were found significant (F-test p<0.05) for the primary and most of the secondary end-points. Sensitivity analysis did not reveal a treatment by centre interaction. For the primary end-points, treatment means were compared in a pre-specified order to control type-I error rate (fixed sequence testing). For other end-points, no adjustments for multiple comparisons were utilised. In order to include the same patients at each time point in the spirometric summaries, missing values were estimated using other values recorded for the patient on that 24-h pulmonary function test day. Randomly missing trough values were estimated by the value obtained as a test day pre-dosing reading and *vice versa*. The linear interpolation between two adjacent measurements was used to estimate the middle missing spirometric measurements, and the last observation carried forward method was applied if no subsequent measurement was available. Values that were missing for reasons related to the patient's treatment response, *e.g.* shortness of breath and use of rescue medication, were estimated using the minimum observed spirometric measurement on a specific test day. For diary end-points, similar rules were applied.

RESULTS

A total of 74 patients were randomised to treatment and eight patients prematurely discontinued the study. One patient withdrew informed consent and seven patients discontinued due to adverse events. Three patients discontinued the study in the first 3 weeks of the first treatment period and, therefore, had no efficacy data that could be used for the comparison of treatment arms (fig. 1). The demographics and baseline characteristics of the 71 patients included in the efficacy analysis are presented in table 2.

Lung function

The mean±SE baseline FEV1 at the start of the treatment periods was 1.019±0.03 L. After 6 weeks of treatment with tiotropium *q.d.*, formoterol *b.i.d.* or tiotropium plus formoterol *q.d.*, the pre-dose values were 1.127±0.01 L, 1.091±0.01 L or 1.134±0.01 L, respectively, and the difference between the combination and formoterol was significant (p<0.05).

The 24-h FEV1 profiles for the three treatments are presented in figure 2. Following inhalation of the morning dose of tiotropium or formoterol, the improvements in FEV1 were comparable between the two bronchodilators until 8 h after dosing. From 8 to 12 h, post-dose tiotropium provided a significantly greater improvement in FEV1 compared with formoterol in the range of 0.064 L (p<0.002) to 0.081 L (p=0.0001). After inhalation of the second (evening) formoterol
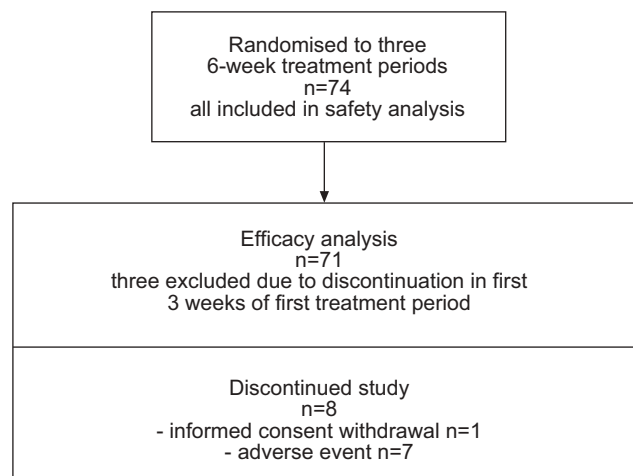
FIGURE 1. Flow diagram of the three-centre, randomised, double-blind (double-dummy), crossover study with three 6-week treatment periods. The diagram presents information on the number of patients who were randomised to treatment, included in the efficacy analysis and the number discontinued in the study.
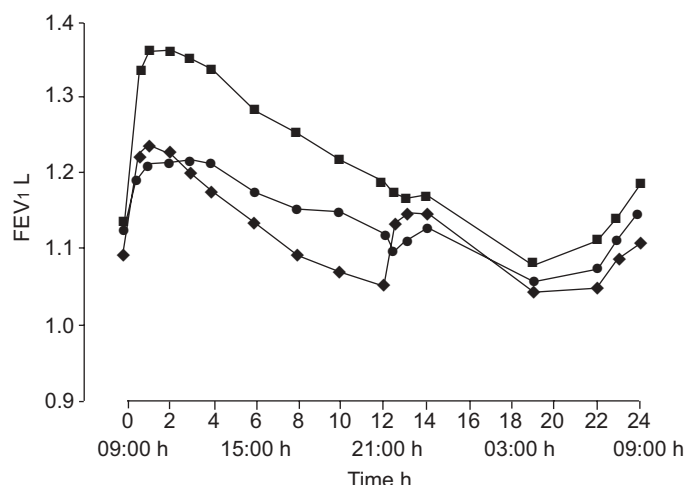
FIGURE 2. Mean forced expiratory volume in one second (FEV_1; adjusted for period, centre and patient within centre) before and during 24 h after the inhalation of tiotropium *q.d.* (●), formoterol *b.i.d.* (◆), and tiotropium plus formoterol *q.d.* (■) at the end of the 6-week treatment periods.

TABLE 2	Demographics and characteristics of the study population
Variable	
Subjects n	71[#]
Males/females	56/15
Age yrs	64.9±9.4
Smoking history pack-yrs	37.7±20.3
Duration of disease yrs	10.9±7.2
FEV_1 L	1.04±0.29
FEV_1 % pred	37.2±8.6
FVC L	2.79±0.68
FEV_1/FVC %	37.9±7.9
FEV_1 reversibility[¶]	
L	0.18±0.15
% baseline	18.0±15.3
% pred	6.4±5.3
COPD severity[+]	
Moderate	20 (28)
Severe	44 (62)
Very severe	7 (10)
Respiratory medication use	
Any pulmonary medication	71 (100.0)
Inhaled anticholinergics	59 (83.1)
Inhaled β-adrenergics	68 (95.8)
Inhaled steroid	63 (88.7)
Oral steroid	2 (2.8)

Data are presented as n, mean±SD and n (%). FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease. [#]: patients included in efficacy analysis; [¶]: response to 4 puffs of salbutamol 100 μg (Ventolin® metered dose inhaler; GlaxoSmithKline B.V., Zeist, the Netherlands; and GlaxoSmithKline s.a./n.v., Genval, Belgium); [+]: according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [1].

dose, no significant differences were observed between tiotropium and formoterol during the night-time, except, at the 24-h measurement (trough value), tiotropium was again superior to formoterol by 0.042 L (p<0.05). The mean average, peak and trough responses for the single drugs, as well as the combination regimen, derived from the 24-h FEV_1 time–response profiles are shown in table 3.

Compared with the individual components, the once-daily tiotropium plus formoterol treatment performed significantly better during the first 12-h period after inhalation of the morning dose. The additional improvement in FEV_1 *versus* tiotropium ranged from 0.070 L (p=0.001) to 0.151 L (p<0.0001), whereas improvements compared with formoterol *b.i.d.* ranged 0.110–0.164 L (p<0.0001). During the night-time (12–24 h), the combination regimen provided a significantly greater bronchodilation of 0.053 L (p<0.01) compared with formoterol 7 h after the evening dose (*i.e.* 19 h after the morning dose of the combination at ~04:00 h), which gradually increased to 0.079 L (p<0.001) at the end of the 24-h observation period. The significant difference *versus* tiotropium observed during the daytime was sustained until 13 h after the morning dose (0.060 L; p<0.02). During the night-time, the combination regimen remained numerically superior until the end of the observation period.

The mean±SE baseline FVC at the start of the treatment periods was 2.631±0.08 L. The pre-dose values after the 6-week treatment period with tiotropium, formoterol or tiotropium plus formoterol were 2.793±0.03 L, 2.671±0.03 L or 2.790±0.03 L, respectively; the difference between the combination regimen and formoterol, as well as that between tiotropium and formoterol, was significant (p<0.002). The 24-h FVC profiles are depicted in figure 3, and the mean average, peak and trough responses for the three treatments derived from the FVC time–response curves are shown in table 3. The results for FVC closely reflected those obtained for FEV_1. During the daytime, tiotropium provided a substantially longer duration of bronchodilation, as reflected by significant

TABLE 3	Average, peak and trough response in forced expiratory volume in one second (FEV$_1$) and forced vital capacity (FVC), and the comparison between treatment regimens				
Variable	Average[#]			Peak	Trough
	0–12 h	0–24 h	12–24 h		
FEV$_1$ response L					
T	0.127±0.01	0.085±0.01	0.043±0.01	0.220±0.01	0.100±0.02
F	0.086±0.01	0.062±0.01	0.038±0.01	0.223±0.01	0.059±0.02
T+F	0.234±0.01	0.160±0.01	0.086±0.01	0.354±0.01	0.138±0.02
T+F *versus* T	0.107 (0.072–0.142)	0.075 (0.042–0.108)	0.043 (0.008–0.079)	0.134 (0.094–0.175)	0.037 (-0.005–0.079)
p-value	<0.0001	<0.0001	<0.02	<0.0001	0.08
T+F *versus* F	0.147 (0.112–0.182)	0.098 (0.065–0.131)	0.048 (0.013–0.084)	0.131 (0.090–0.171)	0.079 (0.037–0.121)
p-value	<0.0001	<0.0001	<0.01	<0.0001	<0.0005
T *versus* F	0.040 (0.006–0.075)	0.023 (-0.010–0.056)	0.005 (-0.030–0.041)	-0.004 (-0.044–0.036)	0.042 (0.000–0.083)
p-value	<0.03	0.17	0.77	0.86	<0.05
FVC response L					
T	0.234±0.02	0.155±0.02	0.076±0.03	0.430±0.03	0.157±0.03
F	0.147±0.02	0.091±0.02	0.036±0.03	0.437±0.03	0.083±0.03
T+F	0.414±0.02	0.274±0.02	0.133±0.03	0.678±0.03	0.234±0.03
T+F *versus* T	0.180 (0.117–0.242)	0.118 (0.057–0.180)	0.057 (-0.013–0.127)	0.249 (0.169–0.328)	0.078 (0.002–0.153)
p-value	<0.0001	0.0002	0.11	<0.0001	<0.05
T+F *versus* F	0.267 (0.204–0.330)	0.182 (0.120–0.244)	0.097 (0.027–0.168)	0.242 (0.161–0.322)	0.151 (0.076–0.227)
p-value	<0.0001	<0.0001	<0.01	<0.0001	<0.001
T *versus* F	0.088 (0.025–0.150)	0.064 (0.003–0.125)	0.040 (-0.029–0.110)	-0.007 (-0.086–0.072)	0.074 (-0.001–0.148)
p-value	<0.01	<0.05	0.25	0.86	0.054

Data are presented as mean±SE and mean (95% confidence interval), unless otherwise stated. Means are adjusted for period, centre and patient within centre. T: tiotropium *q.d.*; F: formoterol *b.i.d.*; T+F: tiotropium plus formoterol *q.d.*[#]: the average was calculated as the area under the curve from zero time to 12 or 24 h (or 12–24 h), respectively, using the trapezoidal rule divided by the corresponding duration (*i.e.* 12 or 24 h) to give the result in litres.

differences compared with formoterol, from 6 h following the morning dose until the end of the first 12-h dosing interval; the differences ranged from 0.116 L (p<0.005) to 0.183 L (p<0.0001). During the second 12-h dosing interval (night-
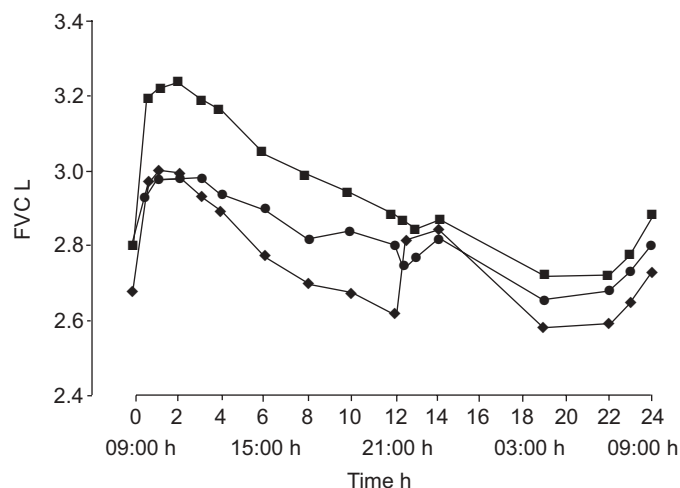
FIGURE 3. Mean forced vital capacity (FVC; adjusted for period, centre and patient within centre) before and during 24 h after inhalation of tiotropium *q.d.* (●), formoterol *b.i.d.* (◆), and tiotropium plus formoterol *q.d.* (■) at the end of the 6-week treatment periods.

time), differences in favour of tiotropium were observed from 7 h post-evening dosing until the end of the observation period, *i.e.* on the next morning, which ranged from 0.070 L (p=0.075) at 19 h to 0.087 L (p<0.05) at 22 h.

The combination regimen was superior to the individual components during the first 12 h of the 24-h period; the largest difference *versus* tiotropium was obtained 30 min after the morning dose (0.278 L; p<0.0001) and *versus* formoterol at 8 h post-dosing (0.292 L; p<0.0001). Throughout the night-time period, combination therapy provided a greater improvement in FVC compared with single-agent therapy. The difference between the combination and formoterol reached statistical significance from 7 h following the evening dose (~04:00 h), until the end of the second 12-h time interval (range 0.125–0.151 L).

PEFR and as-needed salbutamol use
Morning and evening PEFR data are presented in table 4. With respect to morning PEFR, the combination regimen was superior to formoterol by a statistically significant difference of 9.2 L·min^{-1} (p<0.02). In line with the clinic spirometry results, a statistically significant higher evening PEFR was achieved with the combination compared to tiotropium (9.8 L·min^{-1}; p<0.01), as well as formoterol (17.1 L·min^{-1}; p<0.0001). Tiotropium was numerically superior to formoterol in both morning (2.8 L·min^{-1}) and evening PEFR (7.3 L·min^{-1}).

TABLE 4	Three-weekly morning/evening peak flow and number of puffs per day of salbutamol		
	Tiotropium	Formoterol	Tiotropium and formoterol
Peak flow L·min^{-1}			
Morning	262±2.6	259±2.6	268±2.5[#]
Evening	274±2.8	266±2.8	283±2.6[¶]
Salbutamol *p.r.n.*			
Daytime	2.41±0.14	2.37±0.14	1.81±0.13[+]
Night-time	0.56±0.05	0.52±0.05	0.52±0.05

Data are presented as mean±SE. [#]: p<0.02 *versus* formoterol; [¶]: p<0.01 *versus* tiotropium and p<0.0001 *versus* formoterol; [+]: p<0.003 *versus* tiotropium plus formoterol. Means are adjusted for period, centre and patient within centre.

Use of daytime rescue salbutamol was significantly reduced during treatment with the combination regimen (p<0.01; table 4); no difference was found between the single drugs. Use of reliever medication was generally less during the night-time, and no differences were found between the three treatment periods.

Safety

Seven patients discontinued the study prematurely due to an adverse event: one patient when on tiotropium (due to impaired balance), one patient during the formoterol period (due to a COPD exacerbation), and five during treatment with the combination (two patients due to a COPD exacerbation, two due to angina pectoris and one patient due to lung cancer). The events leading to discontinuation were classified as not related to the study drug.

No relevant differences were seen in the incidence of adverse events between the three treatment periods (table 5). Furthermore, measurements of blood pressure and pulse rate did not reveal any difference between the combination and the single drug periods. The post-study ECG recordings and laboratory safety screen (blood chemistry, haematology and urine analysis) did not indicate any study drug-induced changes from the baseline measurements.

TABLE 5	Adverse events[#]		
Event	Tiotropium	Formoterol	Tiotropium plus formoterol
Total treated n	70	69	71
Total with any adverse events	29 (41.4)	32 (46.4)	27 (38.0)
Nasopharyngitis	9 (12.9)	4 (5.8)	4 (5.6)
Headache	4 (5.7)	1 (1.4)	0 (0.0)
Exacerbation of COPD	4 (5.7)	14 (20.3)	10 (14.1)
Dyspnoea exacerbated	7 (10.0)	12 (17.4)	4 (5.6)

Data are presented as n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease. [#]: occurring in ⩾3% of the patients.

DISCUSSION

The present study is the first to report the combined bronchodilator effects of tiotropium and formoterol in COPD, both drugs once daily, compared with the effects of the individual components tiotropium *q.d.* and formoterol *b.i.d.*, following treatment periods of 6 weeks and including serial spirometric assessments over a 24-h period. The single agents tiotropium and formoterol provided significant improvements in pulmonary function (FEV1 and FVC), with tiotropium being superior to formoterol during the daytime (0–12 h). The most pronounced bronchodilator effects, however, were achieved with the once-daily combination treatment. In terms of the average response during the daytime (0–12 h), as well as during the night-time (12–24 h), the combination regimen was superior to single-agent therapy.

As long-acting bronchodilators are the recommended regular treatments in the management of moderate-to-severe COPD [1, 2], and, as several options exist for mono- or combination therapy with these agents, it is essential to provide healthcare providers with comparative clinical data. Although comparable improvements in peak FEV1 and FVC were achieved following the morning dose of the individual treatment regimens, tiotropium was superior (p<0.05) to formoterol in terms of the average FEV1 and FVC (0–12 h). This was due to a substantially longer duration of action of tiotropium. During the second 12-h dosing interval of formoterol, *i.e.* the night-time period (12–24 h), no significant differences were found between the single drugs. The next morning, *i.e.* 24 h after the last tiotropium dose and 12 h after the last formoterol dose, higher trough FEV1 and FVC values were observed for tiotropium.

In the present COPD population, the most favourable bronchodilation was achieved with the combination treatment. Significantly higher peak and average FEV1 and FVC responses were observed as compared with either component in its recommended posology alone. Particularly, during the relevant period of daily activities (0–12 h), the combination regimen appeared to provide additive bronchodilator effects. The value of a once-daily combination as a therapeutic option is further strengthened by the additive effect during the night-time period of the 24-h dosing interval, as reflected in the superior average FEV1 (12–24 h) response over the components (p<0.02) and the trend for a higher trough FEV1 24-h post-dosing value of the combination compared with formoterol *b.i.d.* (+0.08 L; p=0.0003) or tiotropium *q.d.* (+0.04 L; p=0.081). These findings differ substantially from the results of the recently published acute dosing study of tiotropium, formoterol and its combination over 24 h by CAZZOLA *et al.* [13]. In this study, no statistically significant differences were observed between a single dose of the combination regimen and a single dose of either of the two individual drugs. However, any comparison between the studies is hampered by the fact that, as indicated by CAZZOLA *et al.* [13], their study appeared to be underpowered, and spirometric measurements were not performed in pharmacodynamic steady state and, in addition, were missing during the night-time. As shown previously, optimal bronchodilatory responses by tiotropium are achieved in pharmacodynamic steady state [22], meaning that definitive conclusions on the pulmonary effects of the single drugs in

relation to their combination can only be drawn following maintenance therapy. Furthermore, bronchodilator-induced modifications of the circadian variation in airflow limitation can only be established when the study design includes measurements during the night and the early morning hours when the $FEV1$ values are lowest [23]. Finally, in the current study, it is unlikely that the bronchodilating activity of formoterol was diminished, since long-term studies have shown no tolerance to the bronchodilation effect of formoterol in COPD [24, 25].

Comparing the time course of the $FEV1$ and FVC profiles of the combination regimen with the single agents, it appears that the morning dose of formoterol, in addition to tiotropium, can still provide added efficacy after 12 h (end of dosing interval), whereas formoterol alone had returned to the test-day (morning) baseline. In addition, the average night-time $FEV1$ (12–24 h) differed significantly from monotherapy with tiotropium. These findings suggest a more than additive effect, *i.e.* the combined effect is higher or longer acting than predicted from addition of the components.

Serial spirometry was not recorded following the first dose as the acute first-dose effect was not considered relevant for a chronic maintenance therapy, and particularly so for tiotropium, which requires several doses to reach pharmacodynamic steady state [22]. Furthermore, the effect of the combination was tested once daily for both formoterol and tiotropium, although the most commonly used posology for formoterol is twice daily. As COPD is characterised by dyspnoea on exertion mainly during the daytime waking hours, it was hypothesised that the convenient once-daily combination would provide optimal bronchodilation during this relevant period of the day, whereas the sustained 24-h bronchodilator activity of the tiotropium component would provide sufficient bronchodilation during the night-time. This is consistent with the findings by POSTMA *et al.* [23], who demonstrated that the activity of the adrenergic system is most prominent during the day, whereas an increased parasympathetic system activity was found during the night. The hypothesis would be further validated by comparing the need for short-acting bronchodilator rescue medication during the daytime and night-time as a surrogate parameter for additional need for relief from dyspnoea. In this respect, it is interesting to note that previous studies in COPD have also shown less salbutamol consumption during the night-time [26, 27]. In terms of reliever medication, the present data are in agreement with the current authors' previous study on the combination therapy of tiotropium and formoterol [14].

Regular treatment with inhaled glucocorticosteroids is indicated for symptomatic COPD patients with a post-bronchodilator $FEV1$ <50% pred and repeated exacerbations [1]. In order to be eligible for the present study, patients needed to have a pre-bronchodilator $FEV1$ ⩽60% pred. Therefore, it is not surprising that a large proportion of the study population used inhaled glucocorticosteroids concomitantly. Recent studies have demonstrated that the combination of a LABA with an inhaled glucocorticosteroid is more effective than the individual components in improving and maintaining lung function during long-term therapy [28–31].

As controlled prospective clinical data on a combination of tiotropium and an inhaled glucocorticosteroid is not available, the potential additive effect of the inhaled glucocorticosteroids on the lung function improvements found for tiotropium and the combination regimen can only be speculated about. The type and doses of the inhaled glucocorticosteroids varied and were not standardised within the present population. Despite 89% of the patients receiving inhaled glucocorticosteroids, tiotropium provided a greater improvement in daytime lung function and equal improvement in night-time lung function compared with formoterol. In addition, a significant additive bronchodilator effect was achieved with the combination of the two different classes of long-acting bronchodilators, in addition to concomitantly inhaled glucocorticosteroids.

Bronchodilator therapy in COPD may be considered successful if relief from dyspnoea is provided, which should translate into a decrease in the need for an additional bronchodilator. Reduction in rescue need with short-acting β-agonists has been previously demonstrated in patients receiving long-acting bronchodilators [8, 9, 24, 32–34]. In the current study, significantly less as-needed use of salbutamol reflects the bronchodilator-mediated symptomatic benefit of the combination regimen over the single drugs. The reduction in 24-h rescue medication use was due to a reduction during the daytime, the time when patients tend to be active. This finding suggests that optimal bronchodilation during the waking hours could improve the patients' limitations in daytime physical activity. To what extent less use of reliever medication is translated into clinical benefit, such as an improvement in, for instance, exercise performance, remains to be established. Eventually, the goals of treatment in COPD target beyond the optimisation of lung function. The full clinical potential of a combination of tiotropium and a long-acting β-adrenergic over the individual components, in terms of reducing dyspnoea, prevention of COPD exacerbations and the improvement of quality of life, can only be evaluated in larger-scale long-term studies. In particular, these studies have eventually to resolve the question on the therapeutic value of a once-daily combination relative to a combination with twice-daily LABA dosing.

In summary, the current authors have found that once-daily tiotropium provides superior bronchodilation during the daytime as compared with twice-daily formoterol in patients with moderate-to-severe chronic obstructive pulmonary disease; during the night-time, no difference was observed between the two long-acting bronchodilator treatment regimes. A combination of both drugs exhibited additive effects in terms of daytime lung function improvements and sustained improvements during the night compared with the single components, despite the once-daily dosing. As recommended by the Global Initiative for Chronic Obstructive Lung Disease guidelines [1], a combination of two long-acting bronchodilators with different pharmacological mechanisms of action should be considered in all patients with moderate-to-severe chronic obstructive pulmonary disease. In this respect, the present clinical study is the first to support this recommendation for the treatment of moderate-to-severe chronic obstructive pulmonary disease.

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