

# Tiotropium improves FEV<sub>1</sub> in patients with COPD irrespective of smoking status

J. Moita<sup>a,\*</sup>, C. Bárbara<sup>b</sup>, J. Cardoso<sup>c</sup>, R. Costa<sup>d</sup>, M. Sousa<sup>e</sup>, J. Ruiz<sup>f</sup>, M.L. Santos<sup>g</sup>

<sup>a</sup>*Centro Hospitalar de Coimbra, Pneumology Service, Quinta dos Vales, 3041-853 Coimbra, Portugal*

<sup>b</sup>*Hospital Pulido Valente, Lisbon, Portugal*

<sup>c</sup>*Hospital Santa Marta, Lisbon, Portugal*

<sup>d</sup>*Hospital Fernando Fonseca, Lisbon, Portugal*

<sup>e</sup>*Boehringer Ingelheim, Lisbon, Portugal*

<sup>f</sup>*Boehringer Ingelheim, San Cugat, Spain*

<sup>g</sup>*Pfizer, Porto Salvo, Portugal*

Received 27 October 2006; received in revised form 13 March 2007; accepted 25 April 2007

## Abstract

This study evaluated whether the effect of tiotropium on the change in trough forced expiratory volume in 1 s (FEV<sub>1</sub>), vs. placebo, is affected by smoking status. In a 3-month, double-blind study in 31 centres in Portugal, 311 (289 completed) patients were randomised to tiotropium 18 µg once daily or placebo. Baseline mean (standard deviation (SD)) FEV<sub>1</sub> was 1.11 (0.39) l in the tiotropium group and 1.13 (0.39) l in the placebo group. Patients had an average smoking history of 55 (25.7) pack-years; 80 (26%) were smokers and 224 (74%) were ex-smokers. The primary end-point was change in morning pre-dose (i.e. trough) FEV<sub>1</sub> after 12 weeks. Trough FEV<sub>1</sub> at 12 weeks was significantly improved with tiotropium vs. placebo: the difference in means was 102 ml,  $P = 0.0011$ , 95% confidence interval (CI) (41, 164). The difference in means in smokers was 138 ml,  $P = 0.0105$ , CI (32, 244); in ex-smokers it was 66 ml,  $P = 0.0375$ , CI (3, 129). The difference between smokers and ex-smokers was not statistically significant ( $P = 0.6982$ ) and may be due to greater variability and differences in disease severity. The significant improvement in lung function in patients treated with tiotropium vs. placebo in both smokers and ex-smokers suggests that tiotropium is an effective and well-tolerated therapy in chronic obstructive pulmonary disease (COPD), regardless of smoking status.

© 2007 Elsevier Ltd. All rights reserved.

**Keywords:** Tiotropium; Lung function; FEV<sub>1</sub>; Smoking status; COPD

## 1. Introduction

Cigarette smoking is a major risk factor for the development of chronic obstructive pulmonary disease (COPD) in susceptible individuals worldwide and may account for up to 90% of the risk in developed countries [1–3]. Evidence suggests that the number of years spent as a smoker and amount of cigarettes smoked impacts on the prevalence of respiratory symptoms, exacerbations, rate of decline in lung function (i.e. forced expiratory volume in 1 s [FEV<sub>1</sub>]) and COPD-related mortality [4–7]. Cigarette smoking is thought to exert its effects via increased

inflammation, airway wall fibrosis, destruction of alveolar attachments, and inhibition of repair mechanisms [2,8].

Currently, smoking cessation is the only intervention shown to slow the long-term progression of airflow obstruction as measured by the decline in FEV<sub>1</sub> [1]. However, smoking cessation is far from easy and smoking cessation programmes generally have poor success rates [9–11]. Evidence also suggests that chronic inflammation persists after smoking has stopped [12], which will continue to contribute to lung function decline. Hence, it is important to identify treatments that benefit patients with COPD, despite the fact that they might continue to smoke.

Tiotropium is a once-daily maintenance treatment for COPD that provides 24 h efficacy due to prolonged M<sub>3</sub>-receptor antagonism. It has consistently been shown to

\*Corresponding author. Tel.: +351 239 800 195; fax: +351 239 800 149.  
E-mail address: [joaquimmoita@chc.min-saude.pt](mailto:joaquimmoita@chc.min-saude.pt) (J. Moita).

improve lung function, exercise tolerance and health status, and reduce dyspnoea in patients with COPD [13–15]. Post hoc analysis of two combined 1-yr placebo trials has also provided preliminary evidence to suggest that long-term maintenance treatment with tiotropium once daily may slow the decline in trough (i.e. morning pre-dose) FEV<sub>1</sub> compared with placebo [16]; a possibility that is currently specifically being investigated in a 4-year prospective trial [17].

The rationale for performing this trial was based on a meta-analysis from seven clinical trials with the shorter-acting anticholinergic, ipratropium, in patients with moderate to severe COPD, which suggested that the improvement in baseline lung function in ipratropium-treated patients was greater in ex-smokers than in smokers [18]. The aim of this study, entitled ‘Spiriva<sup>®</sup> Assessment of FEV<sub>1</sub> (SAFE)’, was to evaluate whether the effect of tiotropium on the change in trough FEV<sub>1</sub> is affected by smoking status.

## 2. Methods

### 2.1. Study design

This was a randomised, double-blind, parallel-group, placebo-controlled, 3-month study conducted in 31 centres in Portugal. The study (#205.282) was designed to determine whether the effect of tiotropium on trough FEV<sub>1</sub> in patients with COPD was affected by smoking status. The study was approved by regulatory and ethics committees at all centres.

### 2.2. Subjects

Males or females aged  $\geq 40$  years with a diagnosis of COPD (FEV<sub>1</sub>  $\leq 70\%$  of predicted and FEV<sub>1</sub>/forced vital capacity (FVC)  $\leq 70\%$  [19]) and a smoking history of  $\geq 10$  pack-years were eligible for inclusion.

Patients were asked about their smoking status on the first visit. Smoking status consisted of two categories: smokers and ex-smokers (0 cigarettes/day).

Patients were not included if they had a history of asthma, allergic rhinitis, atopy, myocardial infarction, unstable arrhythmia, or if they had any clinically significant disease that might put the patient at risk because of study participation. Patients with  $\geq 3$  exacerbations of COPD in the preceding year or an exacerbation or lower respiratory tract infection within the 6 weeks prior to randomisation were also excluded.

Concomitant use of prn salbutamol MDI (100  $\mu\text{g}/\text{puff}$ ; withheld for at least 6 h prior to each clinic visit), long-acting  $\beta_2$ -agonists and continued use of theophylline preparations (excluding 24 h preparations) (both withheld for at least 24 h prior to each clinic visit) were allowed during the study period. Concomitant use of mucolytics, orally inhaled corticosteroids, minimal doses of oral corticosteroids (equivalent to prednisone  $\leq 10$  mg/day or

$\leq 20$  mg/alternate days) were allowed if the dosage was stabilised for at least 6 weeks before the study. Temporary increases in the dose of theophylline preparation of  $\leq 7$  days or addition/increased dose of oral steroids for  $\leq 2$  weeks were allowed for the treatment of an exacerbation during the study period. If appropriate, scheduled visits were postponed for at least 1 week, but not more than 2 weeks. Use of antibiotics was not restricted. Short-acting anticholinergics, oral  $\beta_2$ -agonists, antileukotrienes, and other investigational drugs were not allowed during the study.

### 2.3. Assessments

After a 2-week run-in period, patients were randomised to receive tiotropium 18  $\mu\text{g}$  once daily, delivered via the HandiHaler<sup>®</sup> device (Boehringer Ingelheim, Ingelheim am Rhein, Germany), or placebo for 12 weeks. FEV<sub>1</sub> and FVC were measured on test days at 10 min ( $\pm 5$  min) prior to administration of study drug (trough). Measurements were performed in triplicate using a Datspир 120C spirometer (Sibelmed, Barcelona, Spain) in accordance with American Thoracic Society criteria [20].

The primary end-point was the change in trough FEV<sub>1</sub> after 12 weeks of treatment. Trough FEV<sub>1</sub> was measured 24 h after the previous dose of study drug on Day 1 (randomisation) as well as after 6 and 12 weeks of treatment. Secondary end-points included trough FEV<sub>1</sub> after 6 weeks of treatment, trough FVC after 6 and 12 weeks of treatment, assessment of COPD symptoms, Physician’s Global Evaluation, Quality of Life Questionnaire (EQ-5D) and use of daytime and nighttime rescue medication (salbutamol MDI 100  $\mu\text{g}/\text{puff}$ ). Rescue medication use, cigarette consumption and drug compliance were recorded in patient diary cards. Adverse events were collected throughout the study.

### 2.4. Statistical analysis

For the primary end-point, the comparison between tiotropium and placebo was assessed via an analysis of covariance (ANCOVA) model, with treatment and centre as fixed effects, and mean trough FEV<sub>1</sub> baseline as covariate. The primary end-point was also stratified according to smoking status (smokers and ex-smokers), which was added to the ANCOVA model as a fixed effect. The least square mean (LSM) for FEV<sub>1</sub> response was computed and compared for each treatment group, stratified by smoking status. The secondary spirometry measures were also analysed using a similar ANCOVA model. The COPD symptoms and global evaluation by investigator were analysed only descriptively. The EQ-5D questionnaire was evaluated following EuroQol Group Enterprise conventions [22]. Descriptive statistics were used for safety variables.

Efficacy analyses were performed using the full analysis set (FAS), which included all patients who received at least

one dose of treatment and had at least a baseline value and who did not change smoking status during the trial. The safety analysis set (SAS) included all patients who received at least one dose of treatment and had one safety evaluation after treatment.

To detect a difference of 130 ml with 90% power based on a SD of 215 ml, 59 patients were required in each treatment group. In order to obtain 59 ex-smokers in the placebo group, based on assumed ratio of smokers to ex-smokers of 3:2, a total of 148 patients were required in each treatment group.

### 3. Results

#### 3.1. Subjects

A total of 335 patients were screened and 311 were randomised to treatment. Seven patients changed their smoking status during the 12 weeks after randomisation, and were excluded from the study. A total of 304 patients were included in the full analysis set (tiotropium: 144; placebo: 160) (Table 1). The baseline characteristics for the remaining 304 patients were comparable across treatment groups (Table 1).

Patients had a mean smoking history of 55 pack-years, and 80 (26%) were smokers and 224 (74%) were ex-smokers. A greater proportion of ex-smokers (27%) had very severe disease (defined as FEV<sub>1</sub>/FVC < 70% and FEV<sub>1</sub> < 30% predicted) compared with smokers (19%). In the tiotropium treatment group, the study was unable to provide smoker and ex-smoker groups with comparable baseline characteristics for smoking history and FEV<sub>1</sub>. Compared with ex-smokers in the tiotropium group, smokers in the tiotropium group had a higher pack-year smoking history (5.6 pack-years) and a higher FEV<sub>1</sub> (0.20 L). The percentage completing the study according to protocol was high at 92.9% (289/311) (Table 2).

#### 3.2. Efficacy assessments

In the overall group population, tiotropium significantly improved the mean trough FEV<sub>1</sub> at 12 weeks compared with placebo, with a mean difference of 102 ml ( $P = 0.001$ ) (Table 3).

Compared with placebo, tiotropium significantly improved mean trough FEV<sub>1</sub> after 12 weeks in both smokers and ex-smokers though the variability was greater with smokers (Fig. 1). At study end, the mean difference between the tiotropium and placebo groups was 138 ml ( $P = 0.011$ ) in the smokers group, and 66 ml ( $P = 0.038$ ) in the ex-smokers group. The difference between smokers and ex-smokers was not statistically significant ( $P = 0.698$ ).

A similar trend was also observed for trough FEV<sub>1</sub> at 6 weeks. The mean difference between the tiotropium and placebo groups was 94 ml (95% CI: 154, 34;  $P = 0.022$ ). The difference between treatment groups was 121 ml (95% CI: 226, 15;  $P = 0.025$ ) for smokers and 67 ml

Table 2  
Disposition of patients

	Tiotropium	Placebo	Total
Patients randomised (%)	147 (100.0)	164 (100.0)	311 (100.0)
Completed study according to protocol	136 (92.5)	153 (93.3)	289 (92.9)
Reasons for premature discontinuation			
Unexpected worsening of COPD			
Unexpected worsening of other pre-existing condition	1 (0.7)	2 (1.2)	3 (1.0)
Lost to follow-up	5 (3.4)	4 (2.4)	9 (2.9)
Consent withdrawn (not due to adverse event)	0 (0.0)	1 (0.6)	1 (0.3)
Other adverse events <sup>a</sup>	3 (2.0)	2 (1.2)	5 (1.6)
Other reasons	1 (0.7)	2 (1.2)	3 (1.0)

<sup>a</sup>Tiotropium: cardio-respiratory arrest, chest pain, dry mouth, sudden death; Placebo: rash, dry mouth, tremor, nausea and vomiting, constipation, weakness.

Table 1  
Demographic and baseline characteristics (full analysis set)

	Tiotropium ( $n = 144$ )		Placebo ( $n = 160$ )	
	Non-smokers	Smokers	Non-smokers	Smokers
Patients ( $n$ )	104	40	120	40
Males (%)	97	93	95	93
Age (years) <sup>a</sup>	65.7 ± 8.6	61.6 ± 9.8	65.7 ± 9.0	64.0 ± 7.2
Duration of COPD (years) <sup>a</sup>	14.0 ± 10.9	9.4 ± 6.8	13.7 ± 10.5	12.3 ± 8.5
Smoking history (pack-years) <sup>a</sup>	54.3 ± 27.1	59.9 ± 23.4	54.3 ± 26.7	55.3 ± 17.3
Duration of smoking cessation (year) <sup>a</sup>	9.1 ± 9.8	0.0 ± 0.0	10.2 ± 10.4	0.0 ± 0.0
Median (range) duration of smoking cessation (years)	5.6 (0.0–51.0)	0.0 ± 0.0	6.1 (0.0–55.0)	0.0 ± 0.0
FEV <sub>1</sub> (L) <sup>a</sup>	1.06 ± 0.37	1.26 ± 0.42	1.13 ± 0.40	1.15 ± 0.40
FEV <sub>1</sub> (% predicted) <sup>a</sup>	38.4 ± 12.8	44.4 ± 13.9	42.3 ± 15.3	40.4 ± 14.5
FVC (L) <sup>a</sup>	2.42 ± 0.76	2.68 ± 0.73	2.52 ± 0.69	2.54 ± 0.71
FEV <sub>1</sub> /FVC (%) <sup>a</sup>	44.4 ± 11.0	47.9 ± 13.7	45.2 ± 11.5	46.7 ± 13.4

<sup>a</sup>Mean (SD); FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 3  
Trough FEV<sub>1</sub> and FVC response (tiotropium–placebo) for change from baseline values at 12 weeks by smoking status

	FEV <sub>1</sub>			FVC		
	Difference, LSM (ml)	95% CI	P-value	Difference, LSM (ml)	95% CI	P-value
All patients	102	41, 164	0.0011	164	58, 270	0.0024
Smokers	138	32, 244	0.0105	158	23, 341	0.0870
Ex-smokers	66	3, 129	0.0375	170	62, 278	0.0021

LSM, least square means; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity. \*Differences between smoking groups were not significant ( $P = 0.6982$  for FEV<sub>1</sub> and  $P = 0.5220$  for FVC).

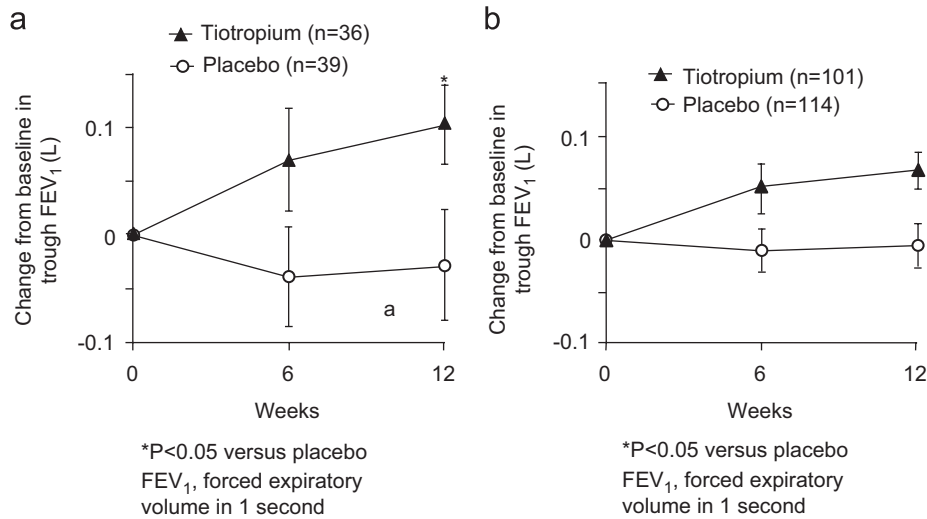


Fig. 1. Mean change in trough FEV<sub>1</sub> during the 12-week study by treatment group and smoking status: (a) smokers and (b) ex-smokers.

(95% CI: 124, 10;  $P = 0.021$ ) for ex-smokers. There was no evidence of tachyphylaxis (Fig. 1).

The mean change from baseline in trough FEV<sub>1</sub> was generally higher in smokers than in ex-smokers.

Tiotropium significantly improved mean trough FVC after 12 weeks compared with placebo ( $P = 0.019$ ) (Table 3). Improvements compared with placebo occurred in both smokers and ex-smokers, though they were significant only in ex-smokers. However, the difference between responses to tiotropium in smokers and ex-smokers was not statistically significant ( $P = 0.535$ ).

Compared with placebo, patients in the tiotropium group used fewer doses of daytime and nighttime rescue medication during the study. This difference tended to increase over the 12-week treatment period. The difference in daytime usage between placebo and tiotropium was significant at weeks 2, 6, 8, 11 and 12 ( $P < 0.05$ ). The magnitude of the reduction in daytime rescue medication use with tiotropium compared with placebo tended to be greater in smokers than ex-smokers in the latter 6 weeks of treatment (Fig. 2). Similar trends were seen with nighttime rescue medication.

COPD symptoms, global evaluation by the investigator and the EQ-5D showed no differences between treatment groups.

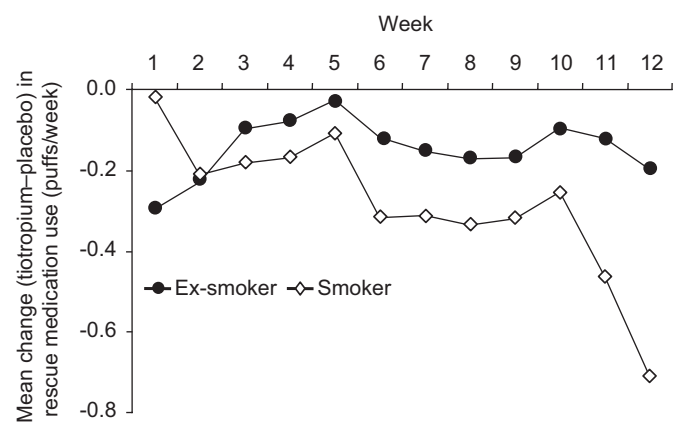


Fig. 2. Mean change (tiotropium–placebo) in daytime rescue medication use in smokers and ex-smokers.

### 3.3. Safety assessment

The proportion of patients experiencing at least one adverse event during the study was 11.6% in the tiotropium group and 15.9% in the placebo group. Six patients (4.1%) in the tiotropium group and three patients (1.8%) in the placebo group experienced a serious adverse event, including two deaths (both in the tiotropium group),

Table 4  
Adverse event profile

	Tiotropium	Placebo
Patients ( <i>n</i> ) <sup>a</sup>	147	164
Serious adverse events	6 (4.1)	3 (1.8)
Patients with adverse events	17 (11.6)	26 (15.9)
Cardiac disorders	2 (1.4)	1 (0.6)
Eye disorders	0 (0.0)	1 (0.6)
Gastrointestinal disorders	3 (2.0)	2 (1.2)
General disorders	6 (4.1)	5 (3.0)
Infections and infestations	1 (0.7)	1 (0.6)
Musculoskeletal and connective tissue disorders	1 (0.7)	2 (1.2)
Nervous system disorders	1 (0.7)	5 (3.0)
Lower respiratory system disorders (excluding exacerbations)	3 (2.0)	6 (3.7)
Exacerbations	6 (4.1)	6 (3.7)
Upper respiratory system disorders	4 (2.7)	4 (2.4)
Skin and subcutaneous disorders	0 (0.0)	1 (0.6)

Data are presented as *n* (%) unless otherwise indicated.

<sup>a</sup>Analysis includes all 311 patients (i.e., including the seven patients who changed their smoking status during the trial).

but none of these nine events was considered to be related to study medication.

Respiratory system disorders were distributed in three different groups: lower (including COPD exacerbations), upper and other. The results showed that the most commonly reported adverse events in both the tiotropium and placebo groups were: lower respiratory disorders (18.3% and 20.1%, respectively); and upper respiratory disorders (5.4% and 4.9%, respectively) (Table 4).

#### 4. Discussion

The aim of this study was to determine whether the effect of inhaled tiotropium on lung function in patients with COPD was affected by smoking status. The primary outcome of this study showed that there was a significant improvement in trough FEV<sub>1</sub> after 12 weeks' treatment with tiotropium compared with placebo, irrespective of smoking status. These data were supported, at least in part, by the secondary outcomes.

The use of short-acting bronchodilators for symptomatic relief provides an indication of the degree of dyspnoea experienced by the patient. Tiotropium reduced daytime and nighttime rescue medication compared with placebo during the study, and the difference between active treatment and placebo tended to increase over the 12-week treatment period. Subgroup analysis suggests that the mean response to tiotropium for reduction of daytime use of rescue medication was significantly greater in smokers compared with ex-smokers. However, though a trend was evident at other time points, this result may be related to greater variability within these subgroups and differences in disease severity.

There have been few studies specifically analysing the relationship between bronchodilators and smoking status.

A meta-analysis of seven trials in moderate to severe COPD has suggested that the bronchodilator response to the anticholinergic ipratropium may be greater in ex-smokers compared with smokers [18]. Examination of the subgroup of ex-smokers in these trials showed them to have a baseline FEV<sub>1</sub> of about 20% less than smokers. Hence, the authors of the meta-analysis suggested that the greater response with ipratropium in ex-smokers might be related to more severe impairment of lung function. This result could have relevance in the interpretation of the Lung Health Study, which suggested no sustained additional effect of ipratropium on the reduced rate of decline in lung function as a result of a smoking cessation programme [21]. The Lung Health Study recruited only current smokers, which, in addition to the reported use of an average of two doses of ipratropium per day rather than the prescribed 3–4 doses per day, could have limited the effect of ipratropium compared with that which may occur in long-term ex-smokers.

Ideally, interventions in COPD need to be effective in both smokers and ex-smokers, particularly as many patients find it difficult to stop smoking. However, smoking cessation must be viewed as the most important therapeutic intervention for those who continue to smoke and should be encouraged with the latest advances in treating nicotine addiction whenever feasible. Bronchodilators are considered first-line maintenance therapy in the management of symptomatic COPD [1]. Hence, the results of the current study showing beneficial effects of tiotropium treatment on lung function in both smokers and ex-smokers are encouraging. A trend for greater responses with tiotropium in smokers, which is in contrast to the findings with ipratropium, may be suggested from some data in this trial. Data from smokers showed greater variability than data from ex-smokers and a greater proportion of ex-smokers had more severe disease than smokers, both of which may account for the lack of statistical significance between groups. More severe disease in ex-smokers was also shown in patients recruited in 1-year study trials with tiotropium [16]. In this case, the authors speculated that patients with more rapidly progressing disease are more likely to have the incentive to stop smoking successfully compared with those with more gradual disease progression.

There are several limitations to the current study. First, according to the protocol, the proportions of smokers and ex-smokers were expected to be 60% and 40%, respectively. However, the proportions were modified to 32% smokers and 68% ex-smokers in order to achieve at least 85% statistical power in the analyses of smokers. Due to enrolment difficulties the ratio of smokers to ex-smokers became more disproportionate. As seven patients changed their smoking status during the study and were excluded from the analyses, a total of 80 smokers were included in the trial (26.3% instead of the expected 32%; 40 smokers per treatment arm), with this ratio the statistical power in the analyses of smokers was 75%. Consequently, the

proportion of smokers available for analysis was lower than planned in the protocol, which may have increased the variability in the data in the smokers subgroup. Second, as smoking abstinence was not verified by saliva cotinine or expired carbon monoxide some patients may have been misclassified. Third, the duration of 12 weeks may not be representative of the long-term effects of maintenance treatment with tiotropium in patients with COPD stratified by smoking status. Hence, further data from large, long-term trials with tiotropium, such as the ongoing, 4-year understanding potential long-term impacts on function with tiotropium (UPLIFT) trial [17] are required to confirm these results.

In summary, tiotropium significantly improved lung function in both smokers and ex-smokers compared with placebo. This, combined with a favourable safety profile from this trial, suggests that tiotropium is an effective and well-tolerated therapy in COPD, regardless of smoking status.

### Acknowledgements

The authors wish to acknowledge the following investigators for their contributions to the study.

Drs. Maria de La Saete Valente, Ricardo Nascimento, Carlos Boavida, Ulisses Brito, Conceição Antunes, João Roque Dias, Dias Pereira, Teresa Cardoso, Reis Ferreira, Jorge Roldão Viera, Abílio Reis, Aida Coelho, Sousa Barros, Carlos Alves, Amaral Marques Ph.D., Paula Simão, José Vieira, Bugalho de Almeida Ph.D., Olga Freitas, Paula Duarte, João de Almeida, Mariano Machado, Luís Goes, Simões Torres, Maria Manuel Machado, Júlio Gomes, Luís Oliveira.

The authors also wish to acknowledge Dr. José Antunes, Dr. Ana Cristina Bastos, Esmeralda Violas and Conceição Peralta for their work in support of this study and PAREXEL MMS for editorial support in the preparation of this manuscript.

Drs. Joaquim Moita, Cristina Bárbara Ph.D., João Cardoso and Rui Costa were the top recruiters of this study. Drs. Marisa Sousa and Jorge Ruiz are employees of Boehringer Ingelheim, and Dr. Maria Luisa Santos participated in the trial as a clinical trials monitor at Pfizer. This study was funded by Boehringer Ingelheim and Pfizer.

### References

- [1] Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Executive summary. Bethesda, MD: National Institutes of Health. Updated 2005.
- [2] Bartal M. COPD and tobacco smoke. *Monaldi Arch Chest Dis* 2005;63:213–25.
- [3] Fletcher CM, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977;1:1645–8.
- [4] Buist AS. Risk factors for COPD. *Eur Respir Rev* 1996;39:253–8.
- [5] Tashkin PD, Detels R, Simmons M, Liu H, Coulson AH, Sayre J, et al. The UCLA population studies of chronic obstructive respiratory disease: XI. Impact of air pollution and smoking on annual change in forced expiratory volume in one second. *Am J Respir Crit Care Med* 1994;149:1209–17.
- [6] Becklake MR, Laloo U. The ‘healthy smoker’: a phenomenon of health selection? *Respiration* 1990;57:137–44.
- [7] Zalacain R, Sobradillo V, Amilibia J, Barron J, Achotegui V, Pijoan JI, et al. Predisposing factors to bacterial colonization in chronic obstruction pulmonary disease exacerbation. *Eur Respir J* 1999;13:343–8.
- [8] Willemse BWM, ten Hacken NHT, Rutgers B, Lesman-Leegte IGAT, Postma DS, Timen W. Effect of 1-year smoking cessation on airway inflammation in COPD and asymptomatic smokers. *Eur Respir J* 2005;26:835–45.
- [9] Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hugues AR, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340:685–91.
- [10] Tashkin D, Kanner R, Bailey W, Buist S, Anderson P, Nides M, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001;357:1571–5.
- [11] Silagy C, Mant D, Fowler G, Lodge M. Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. *Lancet* 1994;343:139–42.
- [12] Hogg JC. Why does airway inflammation persist after the smoking stops? *Thorax* 2006;61:96–7.
- [13] Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;19:217–24.
- [14] Vincken W, van Noord JA, Greefhorst AP, Bantje TA, Kesten S, Korducki L, et al. On behalf of the Dutch/Belgian Tiotropium Study Group. Improved health outcomes in patients with COPD during 1 yrs treatment with tiotropium. *Eur Respir J* 2002;19:209–16.
- [15] O’Donnell DE, Flüge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004;23:832–40.
- [16] Anzueto A, Tashkin D, Menjoge S, Kesten S. One-year analysis of longitudinal changes in spirometry in patients with COPD receiving tiotropium. *Pulm Pharmacol Ther* 2005;18:75–81.
- [17] Decramer M, Celli B, Tashkin DP, Pauwels RA, Burkhart D, Cassino C, et al. Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: the UPLIFT trial. *COPD* 2004;1:303–12.
- [18] Rennard SI, Serby CW, Ghafouri M, Johnson PA, Friedman M. Extended therapy with ipratropium is associated with improved lung function in patients with COPD. A retrospective analysis of data from seven clinical trials. *Chest* 1996;110:62–70.
- [19] Celli BR, Snider GL, Heffner J, Tiej B, Ziment I, Make B, et al. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;152:77–120.
- [20] American Thoracic Society. Standardization of Spirometry, 1994 Update. *Am J Respir Crit Care Med* 1995;152:1107–36.
- [21] Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. For the Lung Health Study Research Group. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV<sub>1</sub>. The Lung Health Study. *JAMA* 1994;272:1497–505.
- [22] Badia X, Roset M, Montserrat S, Herdman M, Segura A. The Spanish version of EuroQol: a description and its applications. European Quality of Life scale. *Med Clin (Barc)* 1999;112(Suppl):79–85.