

## ARTICLE OPEN

## Tiotropium in patients with moderate COPD naive to maintenance therapy: a randomised placebo-controlled trial

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**BACKGROUND:** The benefits of pharmacotherapy with tiotropium HandiHaler 18 µg for patients with chronic obstructive pulmonary disease (COPD) have been previously demonstrated. However, few data exist regarding the treatment of moderate disease (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II).

**AIMS:** To determine whether tiotropium improves lung function/patient-reported outcomes in patients with GOLD stage II COPD naive to maintenance therapy.

**METHODS:** A randomised 24-week double-blind placebo-controlled trial of tiotropium 18 µg once daily (via HandiHaler) was performed in maintenance therapy-naïve patients with forced expiratory volume in 1 s (FEV<sub>1</sub>)/forced vital capacity (FVC) ratio < 0.7 and post-bronchodilator FEV<sub>1</sub> ≥ 50 and < 80%.

**RESULTS:** A total of 457 patients were randomised (238 tiotropium, 219 placebo; mean age 62 years; FEV<sub>1</sub> 1.93 l (66% predicted)). Tiotropium was superior to placebo in mean change from baseline in post-dose FEV<sub>1</sub> area under the curve from 0 to 3 h (AUC<sub>0-3h</sub>) at week 24 (primary endpoint): 0.19 vs. -0.03 l (least-squares mean difference 0.23 l,  $P < 0.001$ ). FVC AUC<sub>0-3h</sub>, trough and peak FEV<sub>1</sub> and FVC were significantly improved with tiotropium versus placebo ( $P < 0.001$ ). Compared with placebo, tiotropium provided numerical improvements in physical activity ( $P = \text{NS}$ ). Physician's Global Assessment (health status) improved ( $P = 0.045$ ) with less impairment on the Work Productivity and Activity Impairment questionnaire ( $P = 0.043$ ) at week 24. The incidence of exacerbations, cough, bronchitis and dyspnoea was lower with tiotropium than placebo.

**CONCLUSIONS:** Tiotropium improved lung function and patient-reported outcomes in maintenance therapy-naïve patients with GOLD stage II COPD, suggesting benefits in initiating maintenance therapy early.

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## INTRODUCTION

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend maintenance therapy for patients with a post-bronchodilator forced expiratory volume in 1 s (FEV<sub>1</sub>) < 80% of predicted normal and FEV<sub>1</sub>/forced vital capacity (FVC) ratio of < 0.7.<sup>1</sup> However, retrospective studies suggest that maintenance therapy is not typically initiated until individuals experience severe airflow obstruction and significant symptoms.<sup>2,3</sup> The benefits of pharmacotherapy for chronic obstructive pulmonary disease (COPD) have been demonstrated in numerous trials,<sup>4-6</sup> but few data exist regarding the treatment of moderate (GOLD stage II) disease.

Secondary analyses of the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT)<sup>7</sup> and Towards a Revolution in COPD Health (TORCH)<sup>8,9</sup> trials suggested that long-acting bronchodilators reduce the rate of decline of FEV<sub>1</sub> in GOLD stage II COPD. A secondary analysis of patients in the UPLIFT trial previously untreated with other long-acting bronchodilators or inhaled corticosteroids (ICS) also demonstrated acute and long-term benefits of tiotropium therapy.<sup>10</sup> However, many patients received concomitant maintenance therapy (long-acting β<sub>2</sub>-agonists and/or ICS) during the UPLIFT trial; only 38% of patients receiving tiotropium and 27% of patients receiving placebo were maintenance therapy naive at baseline, and < 26% of patients

overall received no long-acting β<sub>2</sub>-agonist and/or ICS.<sup>4</sup> The long-term impact of tiotropium as the first and only maintenance therapy on lung function in moderate COPD is therefore less clear.

The effects of pharmacological interventions on patient-centred outcomes such as physical activity are largely unknown in moderate COPD. In patients with severe COPD (mean FEV<sub>1</sub> 43–44% predicted), tiotropium reduces dynamic hyperinflation and dyspnoea, thereby improving exercise tolerance.<sup>11–13</sup> When combined with pulmonary rehabilitation (in patients with mean FEV<sub>1</sub> 34% predicted), tiotropium improved exercise endurance, dyspnoea and health status.<sup>11</sup> Whether these benefits translate into enhanced physical activity requires further investigation.

Three studies have investigated physical activity in early COPD;<sup>14–16</sup> they did not report concomitant medication status, and patients were recruited from tertiary care. All reported significantly reduced physical activity in these patients. The present trial investigated lung function improvement with tiotropium 18 µg/day administered via HandiHaler as the first and only maintenance therapy in patients with moderate COPD. Furthermore, the effect of tiotropium on physical activity, worker productivity and health status was measured. This study is among the first to use a validated activity monitoring device to assess physical activity during pharmacological intervention in a relatively large COPD population.

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## MATERIALS AND METHODS

### Study design

The study design (Figure 1) and methods have been reported previously.<sup>17</sup> This 24-week randomised parallel-group double-blind placebo-controlled multicentre trial of patients with GOLD stage II COPD previously naïve to maintenance therapy was conducted at 70 centres in 10 countries (ClinicalTrials.gov identifier NCT00523991; study number 205.365).

The primary endpoint was the FEV<sub>1</sub> area under the curve from 0 to 3 h (AUC<sub>0–3h</sub>) post-dose response at week 24 (final visit). The objective was to evaluate the difference between treatment with tiotropium 18 µg once daily via HandiHaler plus p.r.n. salbutamol versus placebo once daily via HandiHaler plus p.r.n. salbutamol on the FEV<sub>1</sub> AUC<sub>0–3h</sub> post-dose response at week 24. Response was defined as change from baseline in pre-dose FEV<sub>1</sub> to 3 h post-dose at week 24 (final visit).

Secondary outcome measures included other FEV<sub>1</sub> and FVC parameters, physical activity and energy expenditure, physician's and patient's global assessments of health status and work productivity.

Safety evaluations included the assessment of adverse events (AEs), serious adverse events (SAEs) and COPD exacerbations.

### Patients

Inclusion and exclusion criteria are summarised in Table 1. All patients provided signed informed consent, consistent with the International Conference on Harmonisation—Good Clinical Practice Guidelines<sup>18</sup> prior to study participation. Co-morbidities present at baseline were based on self-report and/or analysis of available medical records.

### Randomisation and interventions

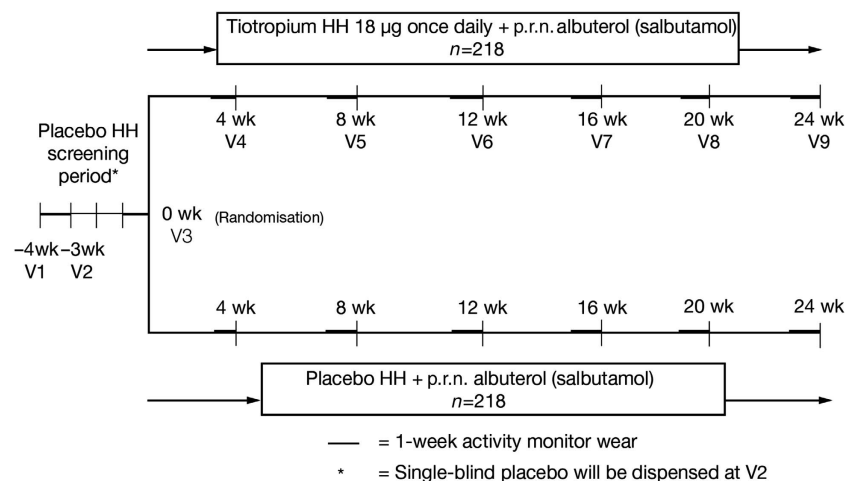
After screening, patients entered a one-month run-in period. During screening, all patients received single-blinded placebo from week –3 (screening phase) until week 0 (baseline, randomisation). During the active double-blind treatment phase, patients were randomised in a 1:1 ratio to tiotropium bromide 18 µg or placebo once daily via HandiHaler, self-administered in the morning for 24 weeks. Open-label salbutamol p.r.n. was permitted as rescue medication during the screening and treatment periods.

Prohibited medications during the six months before and throughout the study (including screening) were: long-acting β<sub>2</sub>-agonists; short-acting β<sub>2</sub>-agonists (except salbutamol after visit 1); oral β<sub>2</sub>-agonists; ICS; ICS/long-acting β<sub>2</sub>-agonist combinations; oral corticosteroids; theophylline; leukotriene antagonists; all open-label anticholinergics (including ipratropium, tiotropium, combinations of these and oxitropium). Temporary oral corticosteroids for up to two weeks during the study treatment period were permitted for acute exacerbations.

### Procedures and outcome measures

Spirometry was performed at week –4 (screening phase), at week 0 (baseline/randomisation) and at weeks 8, 16 and 24 (end of study) in accordance with American Thoracic Society criteria.<sup>19</sup>

Physical activity levels were measured using a validated activity monitor, the SenseWear Armband (BodyMedia, Pittsburgh, PA, USA, using software version 6.1).<sup>20</sup> Physical activity and energy expenditure (over time, using predefined activity metabolic equivalent task (MET) as determined by the activity monitor) included average time/day spent in light, moderate or higher intensity (≥ 3 METs) activity and number of steps/day. We also reported physical activity levels for age-appropriate MET levels according



**Figure 1.** Study design. V1–V9 Study Visit 1 to 9. V1 and V2 were scheduled 4 and 3 weeks prior to randomisation. HH, HandiHaler.

**Table 1.** Patient inclusion and exclusion criteria

| Inclusion criteria  | Exclusion criteria   |
|---|--|
| <ul style="list-style-type: none"> <li>• Male or female</li> <li>• Age 40–80 years</li> <li>• Smoking history ≥ 10 pack-years</li> <li>• Diagnosis of COPD (GOLD stage II): post-bronchodilator FEV<sub>1</sub>/FVC ratio &lt; 0.7; FEV<sub>1</sub> ≥ 50 and &lt; 80% of predicted normal; MRC dyspnoea score ≥ 2</li> <li>• Ability to: demonstrate compliance with HandiHaler, a salbutamol MDI, and the activity monitor; perform acceptable PFTs; an exercise stress test; follow study procedures</li> </ul> | <ul style="list-style-type: none"> <li>• Prior maintenance medication (LABAs, inhaled or systemic corticosteroids, theophylline, leukotriene receptor antagonists) within six months prior to screening</li> <li>• Current chronic treatment with systemic steroids</li> <li>• Diagnosis of asthma</li> <li>• History of cystic fibrosis</li> <li>• Upper and/or lower respiratory tract infection or COPD exacerbation in six weeks prior to, or during, screening</li> </ul> |

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LABA, long-acting β<sub>2</sub>-agonist; MDI, metered-dose inhaler; MRC, Medical Research Council; PFTs, pulmonary function tests.

to Haskell and Pollock (for subjects aged 40–64 years, light intense activity is 2.5–4.4 METs and moderate intense activity is 4.5–5.9 METs; for subjects aged 65–79 years, the levels are 2.0–3.5 and 3.6–4.7 METs, respectively).<sup>21</sup>

Physician's global assessment<sup>22</sup> reflected the physician's opinion of the patient's overall clinical condition (based on need for concomitant medication, number and severity of exacerbations since last visit, cough and dyspnoea severity, and ability to exercise). The patient's global assessment reflected the patient's opinion of their own overall condition. Both assessments occurred at weeks 0, 12 and 24.

The Work Productivity and Activity Impairment (WPAI) questionnaire<sup>23,24</sup> was administered at baseline and at all subsequent visits. The WPAI is a six-item self-administered instrument that is novel in COPD research and is easy to complete by patients.

### Statistical analysis

All efficacy analyses, except physical activity endpoints, were performed using the full analysis set population (all randomised patients receiving  $\geq 1$  dose of study drug, with FEV<sub>1</sub> at baseline and  $\geq 1$  measurement after baseline). Missing data from early withdrawal due to worsening COPD were replaced by the least favourable prior observation. Other missing values were replaced by the corresponding time point at the most recent non-missing visit. Details about these analyses and calculation of sample size are contained in the Supplementary Materials and Methods.

Physical activity endpoints were assessed using the activity evaluable set, defined as all full analysis set patients with physical activity data available for  $\geq 12$  weeks.

Continuous data were summarised as means  $\pm$  s.d. or as geometric mean and corresponding 95% confidence interval (CI); categorical data were summarised as counts and percentages. Continuous efficacy endpoints (change from baseline) were assessed using an analysis of covariance model with terms for treatment group, investigator site and baseline value. Analysis of categorical endpoints was performed using Cochran–Mantel–Haenszel tests with investigator site as the stratification variable. All hypotheses were tested using a type I error rate of 0.05 and statistical tests were two-sided.

WPAI scores were analysed by analysis of covariance models, with terms for treatment group, investigator site and baseline value. No data imputation was performed for missing patient-reported outcome (PRO) values.

## RESULTS

### Patient disposition

The trial was conducted between April 2007 and July 2010 and included 457 randomised patients (238 tiotropium, 219 placebo);

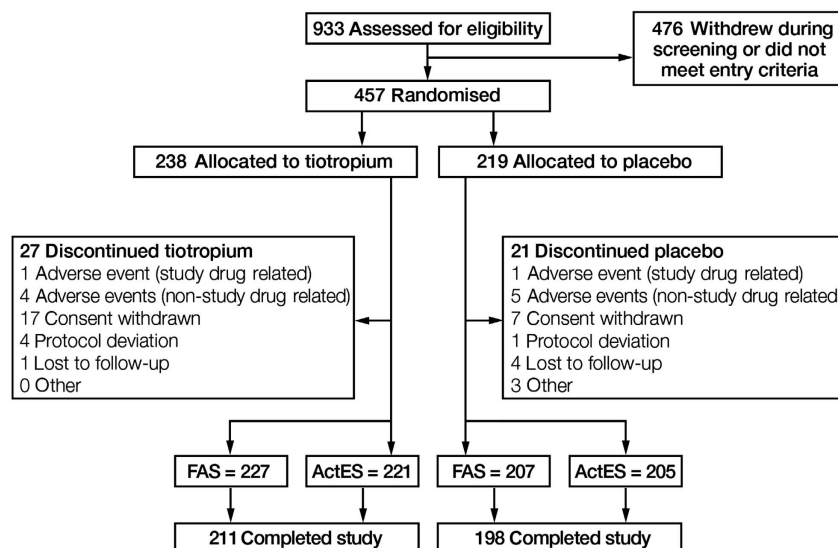
Figure 2). The baseline characteristics and demographics of the patients in the two groups were generally comparable (Table 2). The mean age was 62 years, 68% were men and mean post-bronchodilator FEV<sub>1</sub> was 1.93 l (66% predicted). Use of prior and concomitant drug treatments was generally balanced between the groups. Of the 48 patients who discontinued (27 in the tiotropium group, 21 in the placebo group, not significant; Figure 2), only 15 met the inclusion criteria for the activity evaluable set and were included in the activity analysis set population (eight receiving tiotropium, seven receiving placebo). Discontinued patients in both groups were much less active at baseline (by number of steps, age-appropriate light, moderate or higher activity and moderate or higher activity (>3 METs)) than those who completed the study. Mean duration of wearing the activity monitor was comparable between those who completed the study and those who discontinued (mean 17.1 vs. 16.8 h;  $P=0.771$ ). Baseline co-morbidities by system organ class are presented in Table 3.

The WPAI score for activity impairment due to health at baseline was similar in the tiotropium and placebo groups ( $28 \pm 22$  and  $25 \pm 21\%$ , respectively). Altogether, 41% of patients in the tiotropium group and 37% in the placebo group were employed; there was no difference in the degree of impairment while working. The percentage of work time missed due to ill health at baseline was low (tiotropium group  $2.7 \pm 12\%$ ; placebo group  $5.5 \pm 19\%$ ).

### Lung function

Figure 3a shows the mean pre-dose FEV<sub>1</sub> (raw values in litres) at time 0 and the mean post-dose FEV<sub>1</sub> for up to 3 h post-dose in the tiotropium and placebo groups at baseline and the last visit (week 24). For the primary endpoint of mean change from baseline in FEV<sub>1</sub> AUC<sub>0–3h</sub> at week 24, tiotropium was superior to placebo ( $0.19 \pm 0.27$  vs.  $-0.03 \pm 0.22$  l; least-squares (LS) mean difference 0.23 l; 95% CI, 0.18–0.27;  $P < 0.001$ ; Figure 3b). The corresponding mean change from baseline to week 24 values for FVC AUC<sub>0–3h</sub> were  $0.23 \pm 0.47$  l for tiotropium and  $-0.06 \pm 0.37$  l for placebo (LS mean difference tiotropium versus placebo 0.31 l; 95% CI, 0.24–0.38;  $P < 0.001$ ; Figure 3c).

Figure 3d presents trough FEV<sub>1</sub> at all visits in both groups. After 24 weeks, the mean change from baseline in trough FEV<sub>1</sub> favoured tiotropium ( $0.08 \pm 0.27$  vs.  $-0.05 \pm 0.22$  l with placebo; LS mean



**Figure 2.** Patient disposition. ActES, activity evaluable set; FAS, full analysis set.

**Table 2.** Patient baseline characteristics

| Characteristic   | Tiotropium (n = 238) |                           | Placebo (n = 219) |                           |
|--|----------------------|---------------------------|-------------------|---------------------------|
| Age, years   | 61.2 ± 8.2           |                           | 62.3 ± 8.6        |                           |
| Male, %  | 69.7                 |                           | 67.1              |                           |
| Height, cm   | 171.4 ± 8.2          |                           | 170.5 ± 8.3       |                           |
| Weight, kg   | 79.7 ± 16.6          |                           | 83.2 ± 20.1       |                           |
| BMI, kg/m <sup>2</sup>                                       | 27.0 ± 4.9           |                           | 28.5 ± 5.9        |                           |
| Current smoker, %  | 61.7                 |                           | 57.0              |                           |
| Smoking history, pack-years                                  | 44.0 ± 22.4          |                           | 43.9 ± 34.9       |                           |
| <i>Pre-bronchodilator</i>                                    |                      |                           |                   |                           |
| FEV <sub>1</sub> , l   | 1.75 ± 0.44          |                           | 1.70 ± 0.44       |                           |
| FVC, l   | 3.25 ± 0.79          |                           | 3.17 ± 0.84       |                           |
| <i>Post-bronchodilator</i>                                   |                      |                           |                   |                           |
| FEV <sub>1</sub> , l   | 1.95 ± 0.44          |                           | 1.90 ± 0.43       |                           |
| FEV <sub>1</sub> , % predicted                               | 65.6 ± 8.2           |                           | 65.8 ± 8.2        |                           |
| FVC, l   | 3.53 ± 0.80          |                           | 3.41 ± 0.87       |                           |
| FEV <sub>1</sub> /FVC  | 0.6 ± 0.1            |                           | 0.6 ± 0.1         |                           |
| <i>WPAI</i>  |                      |                           |                   |                           |
| Activity impairment due to health, % <sup>a</sup>            | 28.0 ± 22.3          |                           | 25.4 ± 21.4       |                           |
| Patients employed, %   | 41                   |                           | 37                |                           |
| Impairment while working due to health, % <sup>b</sup>       | 21.1 ± 21.1          |                           | 17.2 ± 20.2       |                           |
|  | <i>Median</i>        | <i>GM (95% CI)</i>        | <i>Median</i>     | <i>GM (95% CI)</i>        |
| <i>Activity<sup>c</sup></i>                                  |                      |                           |                   |                           |
| Steps, number/day  | 6,748.7              | 6,374.5 (5,889.2–6,899.9) | 6,901.8           | 6,433.3 (5,950.7–6,955.0) |
| Time in moderate or higher (≥3 METs), min/day                | 86.8                 | 77.2 (67.9–87.7)          | 73.8              | 68.6 (59.6–78.9)          |
| Time in age-appropriate moderate or higher activity, min/day | 24.7                 | 20.62 (16.85–25.22)       | 20.6              | 19.28 (15.77–23.57)       |

Data are mean ± s.d. unless specified otherwise.

Abbreviations: BMI, body mass index; CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; GM, geometric mean; METs, metabolic equivalents; WPAI, Work Productivity and Activity Impairment questionnaire with outcomes expressed as impairment percentages (higher numbers indicate greater impairment and less productivity; i.e., worse outcomes).

<sup>a</sup>n = 433.

<sup>b</sup>n = 164.

<sup>c</sup>Median values.

difference 0.14 l; 95% CI, 0.09–0.18;  $P < 0.001$ ). Similarly, mean trough FVC at week 24 was higher with tiotropium than with placebo ( $0.10 \pm 0.42$  vs.  $-0.10 \pm 0.37$  l; LS mean difference 0.21; 95% CI, 0.14–0.28;  $P < 0.001$ ; Figure 3e).

At week 24 the mean increase from baseline in peak FEV<sub>1</sub> was significantly higher with tiotropium than with placebo ( $0.28 \pm 0.27$  vs.  $0.04 \pm 0.23$  l; LS mean difference 0.24 l; 95% CI, 0.19–0.29;  $P < 0.001$ ). The mean change from baseline in peak FVC was also higher with tiotropium than with placebo ( $0.41 \pm 0.59$  vs.  $0.08 \pm 0.38$  l; LS mean difference 0.33 l; 95% CI, 0.24–0.42;  $P < 0.001$ ).

#### Physical activity

Figure 4 summarises the overall changes in physical activity levels from baseline in both treatment groups (moderate or higher intensity activity/day (using age-appropriate METs) and mean number of steps/day). While physical activity levels were higher numerically in the tiotropium group than in the placebo group, they were not statistically significantly different between groups at any time point. From baseline to week 24, the mean number of minutes/day in light activity increased slightly in the tiotropium and placebo groups (baseline means  $102.6 \pm 74.13$  and  $98.7 \pm 73.23$  min; week 24 means  $111.4 \pm 81.71$  min and  $101.4 \pm 79.85$  min, respectively). The proportion of patients classified as inactive ( $< 6,000$  steps/day) was lower with tiotropium than with placebo (significant at week 12) (see Supplementary

Table S1). While similar trends were observed at all other visits, the differences did not reach statistical significance.

#### Global health assessments and WPAI scores

At baseline, 58.1 and 58.9% of patients in the two groups received a physician's global assessment of 'good' (Table 4); patients in the tiotropium group were classified as 'excellent' less frequently than in the placebo group (7.5 vs. 11.1%). However, at week 24, patients treated with tiotropium were more frequently classified by their physician as 'excellent' than those in the placebo group (18.1 vs. 10.9%) and were less frequently classified as 'poor/fair' compared with the placebo group (19.0 vs. 25.4%), signifying improved health status with tiotropium compared with placebo ( $P = 0.045$  at week 24). The trends were similar for the patient's global assessment (Table 4); however, the between-group difference was significant only at week 12 in favour of tiotropium ( $P = 0.01$ ).

After 24 weeks the baseline WPAI score improved by  $2.1 \pm 22\%$  in the tiotropium group but deteriorated by  $5.6 \pm 20\%$  in the placebo group (LS mean difference for tiotropium versus placebo  $-3.76$ ; 95% CI,  $-7.39$  to  $-0.13$ ;  $P = 0.043$ ); patients receiving tiotropium also tended to experience less impairment while working than those in the placebo group (LS mean difference  $-5.88\%$ ; 95% CI,  $-12.1$  to  $0.35$ ;  $P = 0.064$ ). The percentage of work time missed due to ill health at week 24 was not significantly different between the two groups (LS mean difference for



**Table 3.** Concomitant diagnoses at baseline by system organ class

| <i>MedDRA preferred term</i>                         |                   |                |
|--|-------------------|----------------|
| <i>Medical history</i>                               | <i>Tiotropium</i> | <i>Placebo</i> |
| Number of patients                                   | 238 (100)         | 219 (100)      |
| Number of patients with $\geq 1$ disease or syndrome | 190 (79.8)        | 179 (81.7)     |
| Blood and lymphatic system disorders                 | 0 (0.0)           | 2 (0.9)        |
| Cardiac disorders                                    | 30 (12.6)         | 24 (11.0)      |
| Congenital, familial and genetic disorders           | 0 (0.0)           | 1 (0.5)        |
| Ear and labyrinth disorders                          | 2 (0.8)           | 9 (4.1)        |
| Endocrine disorders                                  | 16 (6.7)          | 13 (5.9)       |
| Eye disorders  | 12 (5.0)          | 12 (5.5)       |
| Gastrointestinal disorders                           | 41 (17.2)         | 43 (19.6)      |
| General disorders and administration site conditions | 1 (0.4)           | 2 (0.9)        |
| Hepatobiliary disorders                              | 5 (2.1)           | 1 (0.5)        |
| Immune system disorders                              | 22 (9.2)          | 17 (7.8)       |
| Infections and infestations                          | 4 (1.7)           | 7 (3.2)        |
| Injury poisoning and procedural complications        | 1 (0.4)           | 4 (1.8)        |
| Investigations                                       | 4 (1.7)           | 5 (2.3)        |
| Metabolism and nutritional disorders                 | 69 (29.0)         | 86 (39.3)      |
| Musculoskeletal and connective tissue disorders      | 72 (30.3)         | 64 (29.2)      |
| Neoplasms benign, malignant, unspecified             | 0 (0.0)           | 0 (0.0)        |
| Nervous system disorders                             | 23 (9.7)          | 28 (12.8)      |
| Psychiatric disorders                                | 32 (13.4)         | 22 (10.0)      |
| Renal and urinary disorders                          | 6 (2.5)           | 10 (4.6)       |
| Reproductive system and breast disorders             | 18 (7.6)          | 20 (9.1)       |
| Respiratory, thoracic and mediastinal disorders      | 16 (6.7)          | 8 (3.7)        |
| Skin and subcutaneous tissue disorders               | 11 (4.6)          | 11 (5.0)       |
| Social circumstances                                 | 3 (1.3)           | 3 (1.4)        |
| Surgical and medical procedures                      | 6 (2.5)           | 3 (1.4)        |
| Vascular disorders                                   | 105 (44.1)        | 118 (53.9)     |

Data shown as number (%) of patients.

tiotropium versus placebo  $-2.33\%$ ; 95% CI,  $-7.39$  to  $2.73$ ;  $P=0.363$ ).

### Safety

Overall, AEs were infrequent for both groups and most were not considered treatment related (Table 5). Few patients experienced exacerbations recorded as AEs, and the incidence was lower in the tiotropium group than in the placebo group (odds ratio 0.42; 95% CI, 0.21–0.84). There was also a lower incidence of cough, bronchitis, and dyspnoea in the tiotropium group. No SAEs were considered related to study drug (see Supplementary Table S2), and patients recovered from all events. There were no deaths.

## DISCUSSION

### Main findings

Our results provide insight into the long-term effects of tiotropium in patients with moderate COPD who are naïve to respiratory maintenance therapy. The main finding is that the primary endpoint was met, with tiotropium plus p.r.n. salbutamol significantly improving the FEV<sub>1</sub> AUC<sub>0–3h</sub> post-dose response in synchrony with other lung function improvements after 24 weeks. Additionally, tiotropium had a positive impact on secondary endpoints relevant to COPD patients. The study also suggested that optimising pharmacotherapy may improve aspects of physical activity, but the results are inconclusive. Tiotropium was well tolerated and safety was consistent with previous data.<sup>4,7</sup>

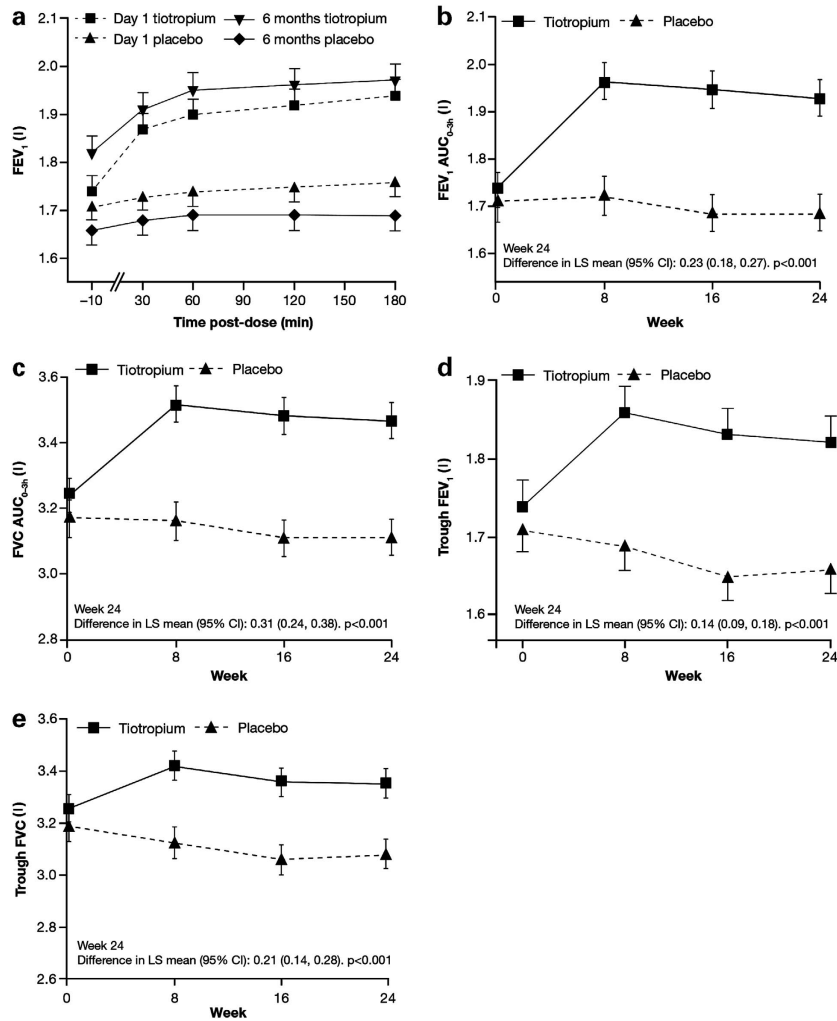
### Strengths and limitations of this study

This study has a number of unique characteristics. First, it targeted a patient population with moderate COPD receiving first maintenance respiratory therapy or matching placebo. Unlike other trials, the patients represented the entire range of GOLD stage II COPD (post-bronchodilator FEV<sub>1</sub>  $\geq 50$  to  $< 80\%$  predicted); FEV<sub>1</sub> was 300–350 ml, approximately 7% predicted larger than for GOLD stage II patients recruited in the UPLIFT and TORCH trials.<sup>4,9</sup> Moreover, many patients (39%) were employed and most were still engaged in physical activity, with baseline levels corresponding to those of other GOLD stage II patient cohorts.<sup>15,25</sup> This suggests that the study population represents the milder end of the GOLD stage II disease spectrum, making it particularly interesting for clinicians. Dyspnoea was measured only during the screening period using the Medical Research Council dyspnoea scale, not baseline dyspnoea index. The Clinical COPD Questionnaire and the Chronic Respiratory Disease Questionnaire were completed only at baseline for phenotyping and therefore could not be used as an outcome measure in the present trial. The effects of tiotropium on health-related quality of life in patients comparable to those in the present trial, however, is available in a sub-analysis of the UPLIFT trial<sup>10</sup> and was not attempted to be replicated in the present study.

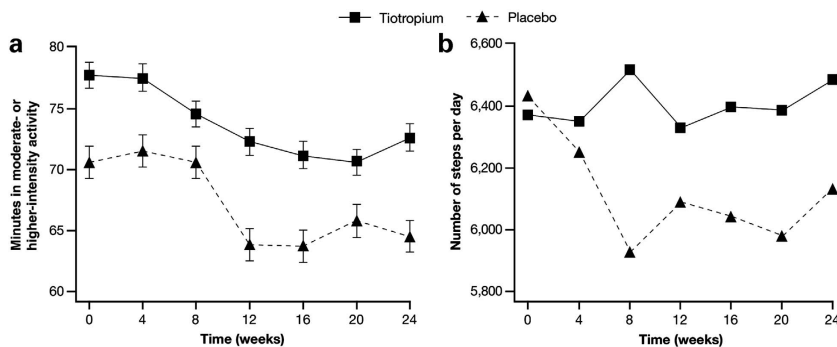
When this study was designed (in 2006/7), physical activity monitoring was in its infancy. We therefore did not include physical activity as a primary endpoint. Today there is more clarity on factors affecting the outcome of such monitoring, number of days of assessment needed, hours/day and validity of activity monitors in COPD.<sup>26–28</sup> We measured physical activity using a validated activity monitor<sup>20,27</sup> as an exploratory endpoint, which allowed for some flexibility in the analysis. Although lung function was improved with tiotropium, this was not readily translated into enhanced physical activity as between-group differences were numerically small and non-significant. This was true despite using individualised activity plans and motivational interviewing techniques (monthly, 20 min, face-to-face consultations).<sup>17</sup> These interventions may have been insufficient to increase physical activity levels notably in the studied time frame and more frequent motivational sessions, proper pulmonary rehabilitation,<sup>29</sup> or selection of inactive patients at baseline may have been more successful. Physical activity levels can also be influenced by other factors such as climate, personality traits and co-morbidities, social environment and regional policy;<sup>30</sup> determining these influences poses a methodological challenge. Nevertheless, integration of activity interventions into routine consultation in pulmonary clinics or even primary care settings may achieve meaningful results. Our study surely calls for better understanding and assessment of physical activity. The 'Physical Activity as a Crucial Patient Reported Outcome in COPD (PROactive)' IMI-JU project aims to do so. It will develop and validate a PRO tool to investigate dimensions of physical activity that are considered essential by patients. Such instruments should help us to understand better the benefits of interventions in enhancing physical activity from a patient perspective.

Interpretation of findings in relation to previously published work To date, only one study has prospectively verified the benefit of tiotropium in patients with moderate COPD not treated with other maintenance pharmacotherapy.<sup>31</sup> However, this was relatively short term (3 months). The absolute difference in trough FEV<sub>1</sub> volumes between tiotropium and placebo in the current study is comparable to the maintenance therapy-naïve cohort in the UPLIFT trial at 6 months (123 ml)<sup>10</sup> and patients with mild disease (FEV<sub>1</sub> 73% predicted) in a Swedish study (118 ml) after 3 months.<sup>31</sup>

Our study is the first prospective multicentre 6 month trial to use physical activity as an outcome measure in maintenance



**Figure 3.** Lung function outcomes (presented as means  $\pm$  s.e.) (a) Pre-dose FEV<sub>1</sub> (raw values in litres) at time – 10 min and post-dose FEV<sub>1</sub> at 30, 60, 90, 120, 150 and 180 min, by treatment group at baseline and last study visit; (b) FEV<sub>1</sub> AUC<sub>0–3h</sub>; (c) FVC AUC<sub>0–3h</sub>; (d) trough FEV<sub>1</sub>; and (e) trough FVC by treatment group during the course of the study. AUC<sub>0–3h</sub>, area under the curve between 0 and 3 h; CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; LS, least squares.



**Figure 4.** Overall physical activity levels (using age-appropriate metabolic equivalents) as shown by (a) mean min/day in moderate- or higher-intensity physical activity and (b) mean number of steps per day in the tiotropium group (solid line) and the placebo group (dashed line).

therapy-naïve patients with COPD. In the maintenance therapy-naïve cohort in the UPLIFT trial, patients receiving tiotropium showed a slower decline in the activity domain of the St George's Respiratory Questionnaire,<sup>10</sup> suggesting that patients receiving bronchodilators may be less likely to become

inactive. Supporting this, there were numerically more active patients (>6,000 steps/day) in the tiotropium group compared with placebo in the present study. However, further exploration of the impact of first-time maintenance therapy on physical activity levels is needed.

**Table 4.** Physician and patient global assessments of overall health status

|                                  | Tiotropium  |             | Placebo     |             | P value |
|----------------------------------|-------------|-------------|-------------|-------------|---------|
|                                  | Baseline    | Week 24     | Baseline    | Week 24     |         |
| <i>Physician's assessment</i>    |             |             |             |             |         |
| Poor/fair                        | 78 (34.4%)  | 41 (19.0%)  | 62 (30.0%)  | 51 (25.4%)  | 0.045   |
| Good                             | 132 (58.1%) | 136 (63.0%) | 122 (58.9%) | 128 (63.7%) |         |
| Excellent                        | 17 (7.5%)   | 39 (18.1%)  | 23 (11.1%)  | 22 (10.9%)  |         |
| <i>Patient's self-assessment</i> |             |             |             |             |         |
| Poor/fair                        | 95 (41.9%)  | 56 (25.9%)  | 72 (35.0%)  | 66 (32.8%)  | 0.086   |
| Good                             | 117 (51.5%) | 128 (59.3%) | 111 (53.9%) | 116 (57.7%) |         |
| Excellent                        | 15 (6.6%)   | 32 (14.8%)  | 23 (11.2%)  | 19 (9.5%)   |         |

Patients and physicians could judge the overall health status as poor, fair, good, or excellent. 'Poor' and 'fair' were pooled. Data are prevalence of the scores with percentages in parentheses.

P values relate to the outcome of the chi-square test.

**Table 5.** Incidence of treatment-emergent AEs (all causality and treatment related;  $\geq 1\%$  in either treatment group) by decreasing cumulative frequency

| MedDRA preferred term                     | All causality |           | Treatment related <sup>a</sup> |           |
|---|---------------|-----------|--------------------------------|-----------|
|   | Tiotropium    | Placebo   | Tiotropium                     | Placebo   |
| Evaluable for AEs                         | 238 (100)     | 219 (100) | 238 (100)                      | 219 (100) |
| COPD (i.e., an exacerbation) <sup>b</sup> | 11 (4.6)      | 24 (11.0) | 0                              | 2 (0.9)   |
| Nasopharyngitis                           | 16 (6.7)      | 11 (5.0)  | 0                              | 0         |
| Upper RTI                                 | 7 (2.9)       | 5 (2.3)   | 0                              | 1 (0.5)   |
| Cough                                     | 4 (1.7)       | 8 (3.7)   | 1 (0.4)                        | 3 (1.4)   |
| Bronchitis                                | 2 (0.8)       | 8 (3.7)   | 0                              | 2 (0.9)   |
| Diarrhoea                                 | 6 (2.5)       | 3 (1.4)   | 0                              | 0         |
| Headache                                  | 2 (0.8)       | 5 (2.3)   | 1 (0.4)                        | 1 (0.5)   |
| Influenza                                 | 4 (1.7)       | 2 (0.9)   | 0                              | 0         |
| RTI                                       | 3 (1.3)       | 3 (1.4)   | 0                              | 0         |
| Rhinitis                                  | 2 (0.8)       | 4 (1.8)   | 0                              | 0         |
| Dry mouth                                 | 3 (1.3)       | 2 (0.9)   | 3 (1.3)                        | 1 (0.5)   |
| Viral RTI                                 | 3 (1.3)       | 2 (0.9)   | 0                              | 0         |
| Hypertension                              | 3 (1.3)       | 2 (0.9)   | 1 (0.4)                        | 0         |
| Arthralgia                                | 2 (0.8)       | 3 (1.4)   | 0                              | 0         |
| Dyspnoea                                  | 0             | 5 (2.3)   | 0                              | 0         |
| Nausea                                    | 3 (1.3)       | 1 (0.5)   | 0                              | 0         |
| Herpes zoster                             | 3 (1.3)       | 1 (0.5)   | 0                              | 0         |
| Chronic bronchitis                        | 1 (0.4)       | 3 (1.4)   | 0                              | 0         |
| Back pain                                 | 0             | 4 (1.8)   | 0                              | 0         |
| Hyperglycaemia                            | 0             | 3 (1.4)   | 0                              | 1 (0.5)   |
| Epistaxis                                 | 0             | 3 (1.4)   | 0                              | 2 (0.9)   |

Data shown as number (%) of patients.

Subjects are counted only once per treatment in each row. Includes data  $\leq 30$  days after last dose of study drug. MedDRA (v13.0) coding dictionary applied.

Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; MedDRA, Medical Dictionary for Regulatory Activities; RTI, respiratory tract infection.

<sup>a</sup>As assessed by the investigator.

<sup>b</sup>The preferred term was COPD; however, since COPD was an inclusion criterion for the study, the investigator entry for this term for all subjects was 'exacerbation of COPD', 'COPD exacerbation', or a similar term.

productivity. Physicians assessed the general health status of tiotropium-treated patients as better than with placebo. Similarly, patients treated with tiotropium rated their own status as 'excellent' more frequently than those receiving placebo. More specific assessment is justified in using validated PRO tools in maintenance-naïve patients. Discrete benefits in favour of tiotropium were also demonstrated by the WPAI, suggesting that treatment with a long-acting bronchodilator may reduce work-related activity impairment in COPD patients, although the clinical significance of changes in WPAI score is unknown.<sup>24,32</sup> How improvements on the WPAI may translate into health economic gains should also be evaluated in future larger scale trials in younger and professionally active COPD patients.

### Conclusions

This study demonstrates that tiotropium enhanced lung function and had a positive impact on PROs in individuals with GOLD stage II COPD disease naïve to maintenance therapy. Tiotropium also reduced COPD symptoms and exacerbations (reported as AEs), supporting the initiation of maintenance therapy earlier in the COPD disease process.

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### CONTRIBUTIONS

All authors were involved in trial design, monitoring of study conduct, approval of statistical analyses, data interpretation and review, writing and decisions regarding publication of the manuscript. All authors had full access to the data and vouch for the accuracy and completeness of the data and analyses.

### COMPETING INTERESTS

TT has received fees as chair of the steering committee from Pfizer, consultancy fees from AstraZeneca and lecture fees from Boehringer Ingelheim, Chiesi and Novartis. FCS has received grants from GlaxoSmithKline, Pfizer, Boehringer Ingelheim, Forest Pharmaceuticals, Actelion, AstraZeneca, NIH and fees for advisory boards from GlaxoSmithKline, AstraZeneca and PneumRx. MD has received fees for advisory boards from Boehringer Ingelheim, GlaxoSmithKline, Nycomed and Altana, consultancy and lectures fees from Boehringer Ingelheim and GlaxoSmithKline, and grants from AstraZeneca. NMS has received consultancy fees from Novartis, Elpen, AstraZeneca and Pfizer, grants from GlaxoSmithKline and Takeda, and lecture fees from Novartis, Elpen, AstraZeneca and Pfizer. CY is an employee of Pfizer and a shareholder. SK, SCS and IMW were

### Implications for future research, policy and practice

In previous trials studying bronchodilator therapy in moderate COPD, health-related quality of life was the only patient-centred outcome to be analysed. The present study investigated the effect of tiotropium on global health status and impairment of worker

employees of Pfizer at the time of the study but are now currently employed by Novartis Pharmaceuticals, East Hanover, NJ, USA.

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