

# Efficacy and Tolerability of Budesonide/Formoterol Added to Tiotropium in Patients with Chronic Obstructive Pulmonary Disease

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**Rationale:** Budesonide/formoterol and tiotropium are commonly used maintenance treatments for patients with chronic obstructive pulmonary disease. Combining these medications may provide additional benefits.

**Objectives:** To assess the efficacy and tolerability of budesonide/formoterol added to tiotropium in patients eligible for inhaled corticosteroid/long-acting  $\beta_2$ -agonist combination therapy.

**Methods:** In this 12-week, randomized, double-blind, parallel-group, multicenter study, after a 2-week run-in, 660 subjects (75% male; mean age, 62 yr; FEV<sub>1</sub>, 1.1 L; 38% predicted normal), 40 years of age or older, received tiotropium (18  $\mu$ g once daily) plus either budesonide/formoterol (320/9  $\mu$ g) (n = 329) or placebo (n = 331) twice daily.

**Measurements and Main Results:** Clinic predose (primary outcome) and postdose FEV<sub>1</sub>, predose and postdose forced vital capacity and inspiratory capacity, and health status were measured. Other outcomes included daily measurements taken at home (pre- and postdose morning FEV<sub>1</sub> and peak expiratory flow, morning symptoms and activities, and morning reliever use), severe exacerbations, and tolerability. Over the treatment period, budesonide/formoterol plus tiotropium significantly increased predose FEV<sub>1</sub> by 6% (65 ml) and postdose by 11% (123 and 131 ml at 5 and 60 min postdose, respectively) versus tiotropium alone (both  $P < 0.001$ ). Other outcomes all significantly improved with budesonide/formoterol plus tiotropium versus tiotropium alone. The number of severe exacerbations decreased by 62% (rate ratio, 0.38; 95% confidence interval, 0.25–0.57;  $P < 0.001$ ). Both treatments were well tolerated.

**Conclusions:** In patients with chronic obstructive pulmonary disease, budesonide/formoterol added to tiotropium versus tiotropium alone provides rapid and sustained improvements in lung function, health status, morning symptoms and activities, and reduces severe exacerbations.

Clinical trial registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT00496470).

**Keywords:** morning activities; morning symptoms; exacerbations; tiotropium; budesonide/formoterol

The goals of chronic obstructive pulmonary disease (COPD) management guidelines include reducing COPD symptoms, improving both health status and exercise tolerance, and reducing the future risk of exacerbations (1). Inhaled bronchodi-

## AT A GLANCE COMMENTARY

### Scientific Knowledge on the Subject

Evidence from clinical trials indicates that combining an anticholinergic with an inhaled corticosteroid (ICS) and a long-acting  $\beta_2$ -agonist (LABA) may provide clinical benefits additional to those associated with these treatments alone in patients with chronic obstructive pulmonary disease (COPD). However, to date, no studies have specifically investigated the therapeutic benefits of tiotropium combined with budesonide/formoterol.

### What This Study Adds to the Field

Budesonide/formoterol added to tiotropium compared with tiotropium alone was shown to improve overall lung function and daytime and nighttime symptoms and reduce severe exacerbations in patients with COPD eligible for ICS/LABA combination therapy. Significant improvements were also seen in morning lung function, morning symptoms and reliever use, and patients' ability to perform morning activities. This study thus highlights the use of a triple-therapy approach with budesonide/formoterol added to tiotropium in the management of patients with COPD.

lators are central to the symptomatic management of COPD (1). The two principal classes of long-acting bronchodilators are long-acting  $\beta_2$ -agonists (LABAs) and long-acting muscarinic antagonists. These therapies, used alone or in combination, provide a range of benefits including improved lung function (2–5), reduced symptoms (2), a decreased need for reliever therapy (2, 5), a reduction in exacerbations (4, 6), improved exercise tolerance (7), and improved health-related quality of life in patients with COPD compared with placebo (3, 4). For patients with more severe COPD and a history of exacerbations, current guidelines recommend the addition of an inhaled corticosteroid (ICS) to a long-acting bronchodilator (1, 8).

The ICS/LABA combination therapies budesonide/formoterol and salmeterol/fluticasone improve lung function and symptoms, reduce reliever use, and prevent exacerbations compared with placebo or either monotherapy alone (9–13). Furthermore, clinically meaningful improvements in health-related quality of life have been reported with budesonide/formoterol (9, 10, 14) compared with placebo.

The benefits of combining the long-acting muscarinic antagonist tiotropium, once daily, with other COPD medications have also been demonstrated (15–18). Few studies have examined the therapeutic potential of combining tiotropium with ICS/LABA therapy (15, 17–19). This treatment approach is of

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interest because the goal of COPD management is to achieve optimal control, as the possibility of achieving full control, as in asthma, is low with today's treatment armamentarium. Treatment with tiotropium combined with ICS/LABA is therefore an attractive alternative for patients with more severe disease. It is also of interest because corticosteroids have antiinflammatory protective effects (20) and tiotropium and LABAs act through different bronchodilatory mechanisms (21). Those clinical studies that have investigated this treatment approach have examined tiotropium combined with salmeterol/fluticasone (15, 17, 19). However, none has investigated tiotropium combined with budesonide/formoterol, despite there being differences between budesonide/formoterol and salmeterol/fluticasone regarding the onset of bronchodilatory effect (22).

This randomized, double-blind trial was conducted to evaluate the effect of budesonide/formoterol combined with tiotropium on lung function, patient-centered clinical outcomes (symptoms, health-related quality of life, exacerbations, and morning activities), and tolerability in patients with COPD.

Some of the results of these studies have been previously reported in the form of abstracts (23, 24).

## METHODS

### Study Design

This was a 12-week, randomized, double-blind, parallel-group, multicenter study (study NCT00496470; www.clinicaltrials.gov) conducted in 102 centers in 9 countries. Patients with COPD eligible for ICS/LABA combination therapy, with a prebronchodilator FEV<sub>1</sub> not exceeding 50% of the predicted normal value and a history of exacerbations requiring systemic steroids and/or antibiotics, were studied. Details of inclusion and exclusion criteria can be found in the online supplement. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines and approved by independent local research ethics committees. Written, informed consent was obtained from all patients.

Before entering the study, patients stopped their LABA and ICS medication (2 and 4 wk before run-in, respectively). During the 2-week run-in period, all patients used tiotropium (SPIRIVA HandiHaler; Boehringer Ingelheim, Ingelheim, Germany) 18 µg once daily plus

reliever medication. Patients were subsequently randomized to tiotropium 18 µg once daily plus either budesonide/formoterol (Symbicort Turbuhaler; AstraZeneca, Lund, Sweden) 320/9 µg one inhalation twice daily or placebo twice daily (Figure 1). Terbutaline 0.5 mg/inhalation (Bricanyl Turbuhaler; AstraZeneca) was used as needed for symptom relief during the run-in period and throughout the treatment period in both treatment arms. The randomization schedule was computer generated at AstraZeneca. Patients visited the clinic at the beginning and end of the run-in period (Weeks -2 and 0, respectively) and after 1, 6, and 12 weeks of treatment.

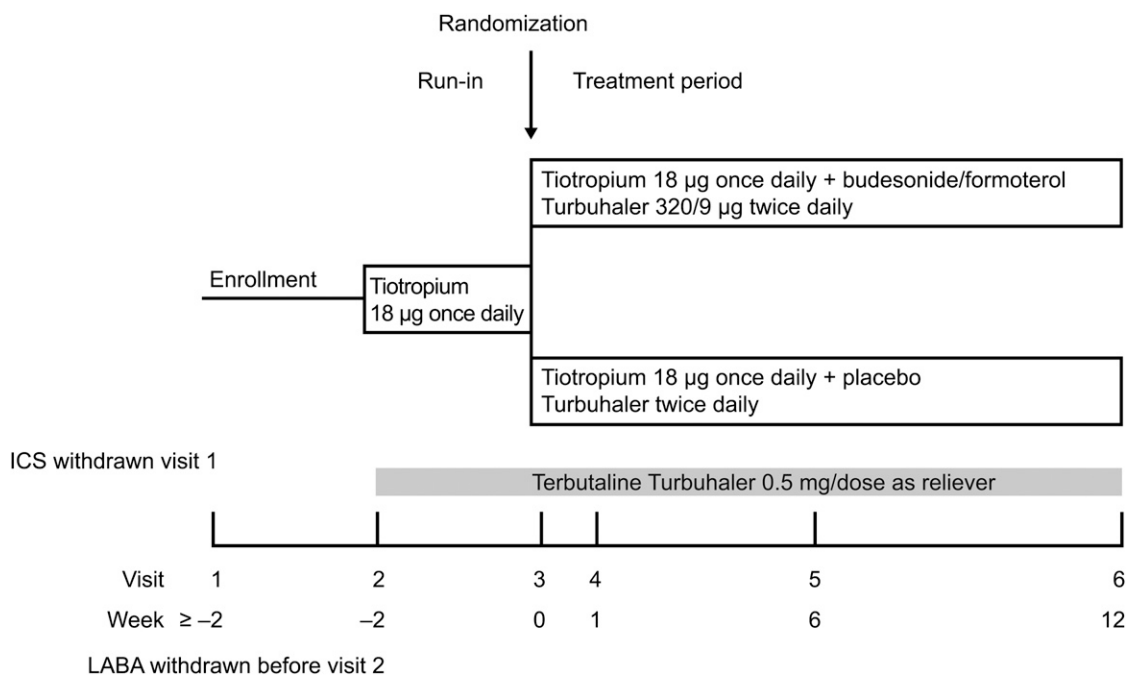
### Outcome Measures

**Clinic assessment of lung function and health status.** The primary efficacy outcome measure was the change in predose FEV<sub>1</sub> from randomization (Week 0) to the full treatment period (mean FEV<sub>1</sub> at 1, 6, and 12 wk of treatment), as assessed by spirometry at each clinic visit. Secondary outcome variables were pre- and postdose spirometry measurements (predose forced vital capacity and inspiratory capacity and posttreatment FEV<sub>1</sub> [5 and 60 min], forced vital capacity [5 and 60 min], and inspiratory capacity [60 min]) and the St. George's Respiratory Questionnaire for COPD (SGRQ-C) (25), assessed at each clinic visit. Clinic measurements were taken before 12:00 noon.

**Morning lung function assessments.** Morning FEV<sub>1</sub> and peak expiratory flow were measured at home (eSense PiKo; PHT Corporation, Geneva, Switzerland), predose and postdose (5 and 15 min), soon after the patient arose from bed (not later than 30 min afterward); all patients were instructed to perform at least three measurements twice daily (morning and evening). The highest measurement at each time period was transmitted wirelessly to an electronic diary (eDiary).

**COPD symptoms and morning activities.** The eDiary was used to record morning symptoms and activities on a daily basis. Breathlessness and chest tightness (assessed by the Global Chest Symptoms Questionnaire) (26), morning activities (assessed by the Capacity of Daily Living during the Morning questionnaire) (26), and COPD symptoms (i.e., breathing, cough, chest tightness, and nighttime awakenings due to COPD symptoms) were recorded. Patients completed the eight-item Capacity of Daily Living during the Morning questionnaire (further details on the questions and scoring can be found in the online supplement) at home at midday after performing all morning activities (washing, drying, dressing, eating breakfast, and walking around the home early and later in the morning).

**Reliever use.** Use of reliever medication (morning [period defined as from rising from bed until midday], day [period defined as from



**Figure 1.** Study protocol. ICS = inhaled corticosteroid; LABA = long-acting  $\beta_2$ -agonist.

rising from bed until going to bed], night [period defined as from going to bed until rising from bed], and total use [determined as the sum of nighttime and daytime measurements]) and study drug was also recorded in the eDiaries. Morning reliever use, as well as all postdose measurements (peak expiratory flow, FEV<sub>1</sub>, Global Chest Symptoms Questionnaire, and Capacity of Daily Living during the Morning questionnaire), were recorded during run-in and Weeks 1, 6, and 12 (for seven consecutive days) of treatment.

**Exacerbations.** The time to first severe exacerbation and the number of severe exacerbations (defined as worsening of COPD leading to treatment with systemic corticosteroids [oral or parenteral] and/or hospitalization/emergency room visits) were recorded. Antibiotic use was also recorded in the medication log, along with the reason for use.

**Tolerability.** Tolerability was assessed at each clinic visit (Weeks -2 to 12) by documenting all adverse events and vital signs.

**Statistical Analysis**

On the basis of a true difference of 6% in the primary variable, FEV<sub>1</sub>, and a residual standard deviation of 0.21 on the logarithmic scale, a total of 280 patients per group were required for 90% power using a 5% significance level and a two-sided *t* test. After an approximate adjustment for a withdrawal rate of about 10%, 620 patients were to be

randomized. All randomized patients with efficacy data pre- and postrandomization were included in the full analysis set for efficacy analyses. The primary variable, change in predose FEV<sub>1</sub> from Week 0 to the average value of FEV<sub>1</sub> for Weeks 1 to 12, expressed as a ratio, was analyzed using a multiplicative analysis of variance model with treatment and country as fixed factors and Week 0 value as a (log-transformed) covariate. The changes in predose forced vital capacity and inspiratory capacity were analyzed in the same way. A descriptive analysis was also made to express spirometry differences on an additive scale. Tolerability analyses were based on patients who received one or more doses of study drug.

For further details of the statistical analyses, see the online supplement.

**RESULTS**

**Study Subjects**

Patient enrollment began in May 2007 and the last subject completed in June 2008. Patient flow is summarized in Figure 2. Baseline characteristics were comparable between the two treatment groups (Table 1), were similar to those of COPD

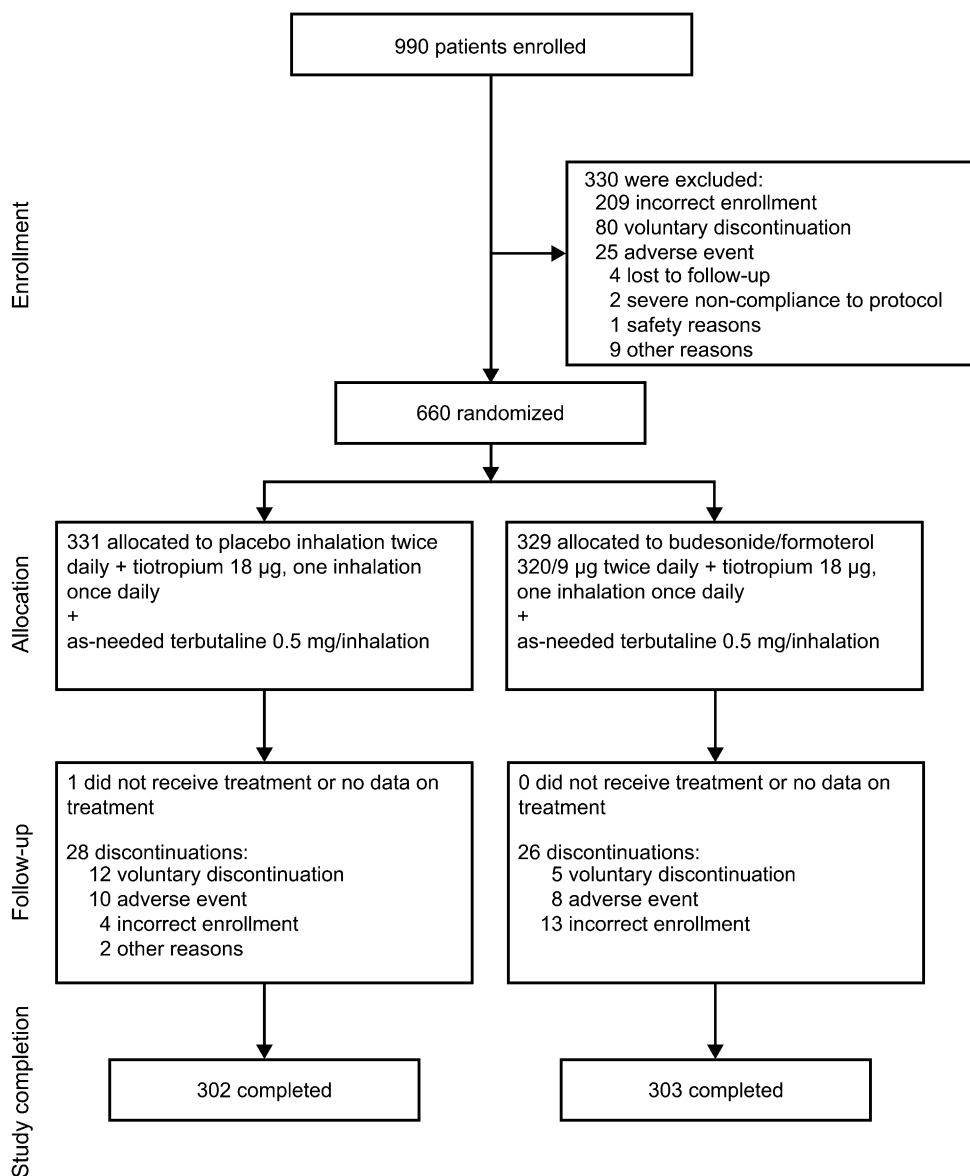


Figure 2. Patient flow.

**TABLE 1. PATIENT\* DEMOGRAPHICS AND BASELINE CHARACTERISTICS**

| Characteristic  | PBO + TIO<br>(n = 331) | BUD/FORM + TIO<br>(n = 329) |
|---|------------------------|-----------------------------|
| Male, n (%)   | 245 (74)               | 251 (76)                    |
| Age, yr (range)   | 62.5 (41–82)           | 62.4 (40–85)                |
| BMI, kg/m <sup>2</sup>                                    | 26.3 (5.0)             | 26.4 (5.4)                  |
| Time since diagnosis (yr),<br>median (range)              | 5.7 (0.2–52.6)         | 5.7 (0.3–43.4)              |
| Previous smokers, n (%)                                   | 178 (54)               | 192 (58)                    |
| Smoking history (pack-years),<br>median (IQR)             | 38 (11)                | 36 (12)                     |
| Medications used at entry, n (%)                          |                        |                             |
| ICS   | 199 (60)               | 219 (67)                    |
| Anticholinergics <sup>†</sup>                             | 257 (78)               | 247 (75)                    |
| LAMA  | 180 (54)               | 168 (51)                    |
| SAMA  | 112 (34)               | 96 (29)                     |
| LABA  | 249 (75)               | 254 (77)                    |
| SABA  | 198 (60)               | 183 (56)                    |
| LABA + ICS*   | 126 (38)               | 148 (45)                    |
| LABA + LAMA*  | 134 (40)               | 133 (40)                    |
| LABA + LAMA + ICS*  | 122 (37)               | 130 (40)                    |
| Mucolytics  | 15 (5)                 | 10 (3)                      |
| Xanthines   | 82 (25)                | 83 (25)                     |
| FEV <sub>1</sub> , L                                      | 1.1 (0.3)              | 1.1 (0.3)                   |
| FVC, L  | 2.36 (0.71)            | 2.41 (0.70)                 |
| FEV <sub>1</sub> , % PN                                   | 37.7 (8.5)             | 38.1 (8.7)                  |
| FEV <sub>1</sub> reversibility, % PN                      | 5.2 (7.0)              | 5.9 (7.5)                   |
| Reliever use, no. inhalations/24 h                        | 4.4 (3.3)              | 4.1 (2.8)                   |
| Symptom scores (scale, 0–4)                               |                        |                             |
| Breathlessness  |                        |                             |
| Mean (SD)   | 1.8 (0.6)              | 1.7 (0.6)                   |
| Median  | 1.8                    | 1.8                         |
| Chest tightness   |                        |                             |
| Mean (SD)   | 1.5 (0.7)              | 1.4 (0.7)                   |
| Median  | 1.5                    | 1.4                         |
| Cough   |                        |                             |
| Mean (SD)   | 1.8 (0.8)              | 1.8 (0.8)                   |
| Median  | 1.7                    | 1.8                         |
| Nighttime awakenings                                      |                        |                             |
| Mean (SD)   | 1.0 (0.7)              | 0.9 (0.7)                   |
| Median  | 1.0                    | 1.0                         |
| Mean exacerbations last year,<br>n (range)                | 1.4 (1–5)              | 1.4 (1–7)                   |
| Treatment with antibiotics at<br>last exacerbation, n (%) | 285 (86)               | 283 (86)                    |

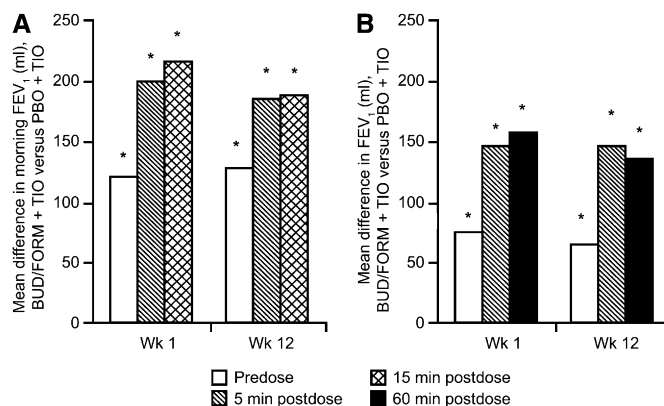
*Definition of abbreviations:* BMI = body mass index; BUD/FORM = budesonide/formoterol; ICS = inhaled corticosteroid; IQR = interquartile range; LABA = long-acting  $\beta_2$ -agonist; LAMA = long-acting muscarinic antagonist; PBO = placebo; SABA = short-acting  $\beta_2$ -agonist; SAMA = short-acting muscarinic antagonist; PN = predicted normal; TIO = tiotropium.

Data are expressed as means (SD) unless otherwise indicated.

\* Medications were not mutually exclusive and data are presented separately.

<sup>†</sup> LAMA or SAMA, separately or in combination.

patient populations in other major budesonide/formoterol studies (9, 10), and comparable to those in previous salmeterol/fluticasone studies (12, 27, 28). Of the 660 patients randomized, approximately 25% were classified, by postbronchodilator FEV<sub>1</sub>, as being at GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage II (FEV<sub>1</sub> 50–80% predicted), 64% GOLD stage III (FEV<sub>1</sub> 30–50% predicted), and 11% GOLD stage IV (FEV<sub>1</sub> < 30% predicted); one patient had no value for FEV<sub>1</sub> percent predicted normal. For the safety and efficacy analyses, 659 patients were analyzed (in an intention-to-treat analysis; 1 patient did not receive any study drug). Similar withdrawal rates were seen for both treatment groups ( $P = 0.785$ ): 7.9% in the budesonide/formoterol added to tiotropium arm and 8.5% in the tiotropium-alone arm. Treatment compliance, which was recorded by patients in their



**Figure 3.** Change in FEV<sub>1</sub> measurements (A) at home (at bedside), from run-in to Weeks 1 and 12, and (B) at the clinic, from randomization (Week 0) to the full treatment period (the average value of data for Weeks 1, 6, and 12), using an additive analysis of variance model. BUD/FORM = budesonide/formoterol; PBO = placebo; TIO = tiotropium. \* $P < 0.001$  BUD/FORM + TIO versus PBO + TIO.

eDiary (yes/no response to intake of medication), was also similar (mean compliance per 24 h = 96% in both groups).

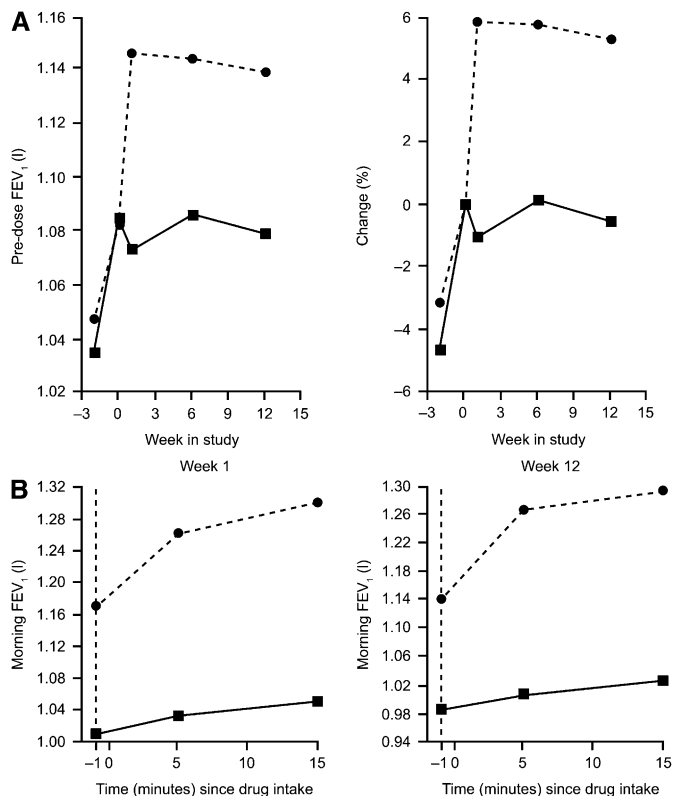
#### Clinical Assessment of Lung Function and Health Status

**Lung function.** Treatment with budesonide/formoterol added to tiotropium improved FEV<sub>1</sub> to a greater extent than tiotropium alone (Figures 3 and 4). Over the course of the treatment period, the increase in predose FEV<sub>1</sub> was 6% higher ( $P < 0.001$ ) at clinic visits in the budesonide/formoterol added to tiotropium group, corresponding to an absolute difference of 65 ml compared with tiotropium alone. Budesonide/formoterol added to tiotropium also increased postdose FEV<sub>1</sub> versus tiotropium alone, by 123 and 131 ml at 5 and 60 minutes postdose, respectively. Improvements in predose and postdose forced vital capacity and inspiratory capacity were also seen with budesonide/formoterol added to tiotropium compared with tiotropium alone (Table 2). Budesonide/formoterol added to tiotropium had a rapid onset of effect that was faster than that of tiotropium alone, and the improvement in FEV<sub>1</sub> was sustained over the course of the study (Figure 4A; and see Figure E1 in the online supplement).

**Health status.** Over the study period, SGRQ-C total score improved by 3.8 units with budesonide/formoterol added to tiotropium compared with 1.5 units with tiotropium alone (mean difference,  $-2.3$ ; 95% confidence interval [CI]:  $-4.23$ ,  $-0.32$ ;  $P = 0.023$ ). Improvements in SGRQ-C total score by more than 4 units were seen in 49.5 and 40.0% of patients in the budesonide/formoterol added to tiotropium and tiotropium-alone arms, respectively ( $P = 0.016$ ); a similar proportion of patients in each arm had a deterioration in SGRQ-C total score by more than 4 units (27.6 and 29.7%, respectively).

#### Morning Lung Function Assessments

Similar to the clinic lung function results, lung function measurements at home (measured by PiKo spirometer) showed significant improvements in pretreatment and posttreatment (5 and 15 min) morning FEV<sub>1</sub> and peak expiratory flow with budesonide/formoterol added to tiotropium compared with tiotropium alone after 1 week of treatment. The improvements in FEV<sub>1</sub> were maintained to Week 12 (all  $P < 0.001$ ). The improvements in FEV<sub>1</sub> from baseline to the last week of treatment corresponded to differences of 128, 185, and 186 ml predose, 5 minutes postdose, and



**Figure 4.** Change in lung function. (A) Pre-dose FEV<sub>1</sub> at the clinic: visit geometric means and percentage mean change from baseline. (B) Onset of effect, measured by FEV<sub>1</sub> at bedside in the morning at Weeks 1 and 12. BUD/FORM = budesonide/formoterol; PBO = placebo; TIO = tiotropium. Circles represent BUD/FORM + TIO; squares represent PBO + TIO. The graphs illustrate absolute pre- and postdose values at Weeks 1 and 12. The onset was calculated as change from predose to 5 and 15 minutes postdose, corresponding to differences between treatments of 70 and 90 ml, respectively, at Week 1 and 100 ml at both time points at Week 12 in favor of budesonide/formoterol added to tiotropium versus tiotropium alone ( $P < 0.001$ ).

15 minutes postdose, respectively (Figure 3 and Table 3). There was also a significantly more rapid onset of improvements in lung function as measured 5 and 15 minutes postdose, with budesonide/formoterol added to tiotropium compared with tiotropium alone, shortly after rising in the morning (Figure 4).

**COPD Symptoms and Morning Activities**

Treatment differences were demonstrated in all COPD symptom scores (breathlessness, nighttime awakening, chest tightness, and cough) from run-in to full treatment period (day and night) in favor of budesonide/formoterol added to tiotropium (all  $P < 0.001$ ) (Table 3). There were also significant improvements in morning symptoms predose and 5 and 15 minutes postdose, as compared with tiotropium alone (Table 3). Significant improvements in morning activities (total score and for individual questions) were also seen with budesonide/formoterol added to tiotropium versus tiotropium alone at Week 12 (Table 3). Changes in total morning activity score were more apparent after 1 week of treatment in the budesonide/formoterol added to tiotropium arm than in the tiotropium-alone arm (mean difference, 0.074;  $P = 0.027$ ); these improvements were sustained (Figure 5 and Table 3) and continued to improve over the study period (Figure 5).

**TABLE 2. TREATMENT COMPARISONS FOR SPIROMETRY VARIABLES MEASURED AT CLINIC VISITS OVER TREATMENT PERIOD**

|                           | Mean Treatment Difference | Geometric Mean |           | Treatment Comparison Ratio (95% CI) |
|---------------------------|---------------------------|----------------|-----------|-------------------------------------|
|                           |                           | Run-in         | Treatment |                                     |
| <b>FEV<sub>1</sub>, L</b> |                           |                |           |                                     |
| Predose                   |                           |                |           |                                     |
| PBO + TIO                 | 0.065                     | 1.08           | 1.08      | 1.06 (1.04–1.09)*                   |
| BUD/FORM + TIO            |                           | 1.08           | 1.15      |                                     |
| 5 min postdose            |                           |                |           |                                     |
| PBO + TIO                 | 0.123                     | 1.08           | 1.13      | 1.11 (1.09–1.13)*                   |
| BUD/FORM + TIO            |                           | 1.08           | 1.25      |                                     |
| 60 min postdose           |                           |                |           |                                     |
| PBO + TIO                 | 0.131                     | 1.08           | 1.17      | 1.11 (1.09–1.14)*                   |
| BUD/FORM + TIO            |                           | 1.08           | 1.30      |                                     |
| <b>FVC, L</b>             |                           |                |           |                                     |
| Predose                   |                           |                |           |                                     |
| PBO + TIO                 | 0.053                     | 2.34           | 2.35      | 1.03 (1.00–1.05)†                   |
| BUD/FORM + TIO            |                           | 2.32           | 2.40      |                                     |
| 5 min postdose            |                           |                |           |                                     |
| PBO + TIO                 | 0.157                     | 2.34           | 2.45      | 1.07 (1.05–1.09)*                   |
| BUD/FORM + TIO            |                           | 2.33           | 2.61      |                                     |
| 60 min postdose           |                           |                |           |                                     |
| PBO + TIO                 | 0.160                     | 2.34           | 2.53      | 1.07 (1.05–1.09)*                   |
| BUD/FORM + TIO            |                           | 2.33           | 2.70      |                                     |
| <b>IC, L</b>              |                           |                |           |                                     |
| Predose                   |                           |                |           |                                     |
| PBO + TIO                 | 0.064                     | 1.96           | 1.99      | 1.03 (1.01–1.06)‡                   |
| BUD/FORM + TIO            |                           | 1.97           | 2.07      |                                     |
| 60 min postdose           |                           |                |           |                                     |
| PBO + TIO                 | 0.110                     | 1.96           | 2.13      | 1.05 (1.03–1.08)*                   |
| BUD/FORM + TIO            |                           | 1.98           | 2.26      |                                     |

*Definition of abbreviations:* BUD/FORM = budesonide/formoterol; CI = confidence interval; IC = inspiratory capacity; PBO=placebo; TIO = tiotropium

Mean treatment difference values from an additive analysis. Treatment comparisons for spirometry variables measured at the clinic, placebo added to tiotropium versus BUD/FORM added to tiotropium.

\*  $P < 0.001$ .

†  $P = 0.021$ .

‡  $P = 0.020$ .

**Reliever Use**

Significant improvements in morning, nighttime, and daytime reliever use were also seen with budesonide/formoterol added to tiotropium (Table 3). These effects were seen after the first week of treatment and were stable over time. Reduction of morning reliever medication use accounted for 80% of the total daytime reduction, despite the morning constituting approximately one third of the total daytime hours.

**Exacerbations**

Severe exacerbations were experienced by 25 patients (7.6%) in the budesonide/formoterol added to tiotropium group and 61 patients (18.5%) in the tiotropium-alone group. Budesonide/formoterol added to tiotropium decreased the rate of severe exacerbations by 62% (Figure 6 and Table 4) (rate ratio, 0.38; 95% CI, 0.25–0.57;  $P < 0.001$ ) and decreased the number of hospitalizations/emergency room visits by 65% (rate ratio, 0.35; 95% CI, 0.16–0.78;  $P = 0.011$ ) compared with tiotropium alone (Table 4). Time to first severe exacerbation (hazard ratio, 0.39; 95% CI, 0.24–0.62;  $P < 0.001$ ) and time to first hospitalization/emergency room visit (hazard ratio, 0.39; 95% CI, 0.17–0.89;  $P = 0.026$ ) were also prolonged by budesonide/formoterol added to tiotropium compared with tiotropium alone. In addition, 57 patients (19 [6%] in the budesonide/formoterol added to tiotropium arm and 38 [12%] in the tiotropium arm) required a prescription of antibiotics for the reason “exacerbation of

**TABLE 3. TREATMENT COMPARISONS FOR MORNING PEAK EXPIRATORY FLOW, RELIEVER USE, AND MORNING ACTIVITIES/SYMPTOMS FROM RUN-IN PERIOD TO LAST WEEK OF TREATMENT\***

|   | Adjusted Mean Change |                | Mean Difference: BUD/FORM +<br>TIO versus PBO + TIO<br>(95% CI) | P Value |
|---|----------------------|----------------|---|---------|
|   | PBO + TIO            | BUD/FORM + TIO |   |         |
| Morning FEV <sub>1</sub> , L            |                      |                |   |         |
| Predose                                 | -0.074               | 0.054          | 0.128 (0.078–0.179)   | <0.001  |
| 5 min postdose                          | -0.026               | 0.159          | 0.185 (0.134–0.237)   | <0.001  |
| 15 min postdose                         | 0.016                | 0.202          | 0.186 (0.126–0.246)   | <0.001  |
| Morning PEF, L/min                      |                      |                |   |         |
| Predose                                 | -8.19                | 3.85           | 12.0 (6.08–18.0)  | <0.001  |
| 5 min postdose                          | -2.39                | 15.3           | 17.7 (11.1–24.3)  | <0.001  |
| 15 min postdose                         | 2.53                 | 20.5           | 18.0 (11.0–25.0)  | <0.001  |
| Reliever use, mean no. of inhalations   |                      |                |   |         |
| Morning                                 | -0.080               | -0.480         | -0.400 (-0.564, -0.236)   | <0.001  |
| Nighttime                               | 0.075                | -0.237         | -0.313 (-0.456, -0.169)   | <0.001  |
| Daytime (including morning)             | -0.141               | -0.649         | -0.508 (-0.772, -0.244)   | <0.001  |
| GCSQ (scale, 0–4)                       |                      |                |   |         |
| Predose                                 |                      |                |   |         |
| Breathlessness                          | -0.036               | -0.184         | -0.148 (-0.238, -0.058)   | 0.001   |
| Chest tightness                         | -0.029               | -0.119         | -0.090 (-0.181, 0.001)  | 0.051   |
| 5 min postdose                          |                      |                |   |         |
| Breathlessness                          | -0.222               | -0.365         | -0.144 (-0.244, -0.043)   | 0.005   |
| Chest tightness                         | -0.169               | -0.273         | -0.104 (-0.204, -0.004)   | 0.042   |
| 15 min postdose                         |                      |                |   |         |
| Breathlessness                          | -0.310               | -0.495         | -0.185 (-0.286, -0.085)   | <0.001  |
| Chest tightness                         | -0.231               | -0.352         | -0.121 (-0.216, -0.025)   | 0.014   |
| CDLM (scale, 0–5) <sup>†</sup>          |                      |                |   |         |
| Total score                             | 0.083                | 0.264          | 0.180 (0.090–0.270)   | <0.001  |
| Separate CDLM questions                 |                      |                |   |         |
| Wash yourself                           | 0.125                | 0.298          | 0.174 (0.061–0.287)   | 0.003   |
| Dry yourself                            | 0.046                | 0.256          | 0.210 (0.097–0.322)   | <0.001  |
| Get dressed                             | 0.108                | 0.298          | 0.189 (0.075–0.304)   | 0.001   |
| Eat breakfast                           | 0.034                | 0.173          | 0.140 (0.019–0.260)   | 0.023   |
| Walk around early                       | 0.128                | 0.261          | 0.133 (0.021–0.246)   | 0.020   |
| Walk around later                       | 0.140                | 0.278          | 0.138 (0.039–0.238)   | 0.006   |
| Time to finish morning activities       | 0.945                | 1.01           | 1.07 (0.955–1.19)   | 0.258   |
| COPD symptoms <sup>‡</sup> (scale, 0–4) |                      |                |   |         |
| Breathlessness                          | -0.039               | -0.181         | -0.142 (-0.214, -0.069)   | <0.001  |
| Nighttime awakenings                    | -0.027               | -0.184         | -0.157 (-0.222, -0.092)   | <0.001  |
| Chest tightness                         | -0.053               | -0.195         | -0.142 (-0.212, -0.072)   | <0.001  |
| Cough                                   | -0.088               | -0.250         | -0.161 (-0.238, -0.084)   | <0.001  |

*Definition of abbreviations:* BUD/FORM = budesonide/formoterol; CDLM = Capacity of Daily Living during the Morning questionnaire; CI = confidence interval; COPD = chronic obstructive pulmonary disease; GCSQ = Global Chest Symptoms Questionnaire; PBO = placebo; PEF = peak expiratory flow; TIO = tiotropium

\* Mean treatment difference in change from run-in to final week (Week 12).

<sup>†</sup> From a multiplicative analysis of variance.

<sup>‡</sup> COPD symptoms; change from run-in to full treatment period.

COPD” (Table 4). There was no statistically significant correlation between exacerbation rates and ICS use at study entry (interaction analysis; Table 4).

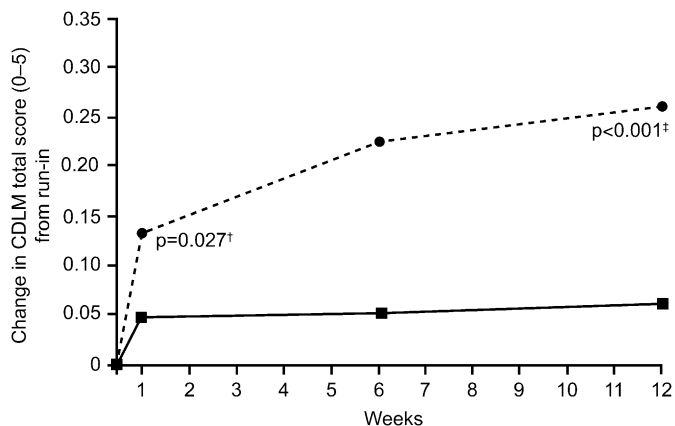
### Tolerability

Both treatment regimens were well tolerated and the overall incidence and severity of adverse events were comparable between groups (Table 5). The incidence of pharmacologically predictable adverse events related to treatment was rare and comparable across treatment groups. There were three cases of pneumonia within each treatment group (<1%). One serious adverse event (pleuritic pain) in the budesonide/formoterol added to tiotropium group was considered causally related to the study drug, as assessed by the investigator. One death occurred (lung neoplasm) on budesonide/formoterol added to tiotropium, but was judged by the investigator as not causally related. Discontinuations due to adverse events were rare in both groups (8 [2%] with budesonide/formoterol added to tiotropium compared with 10 [3%] with tiotropium alone).

### DISCUSSION

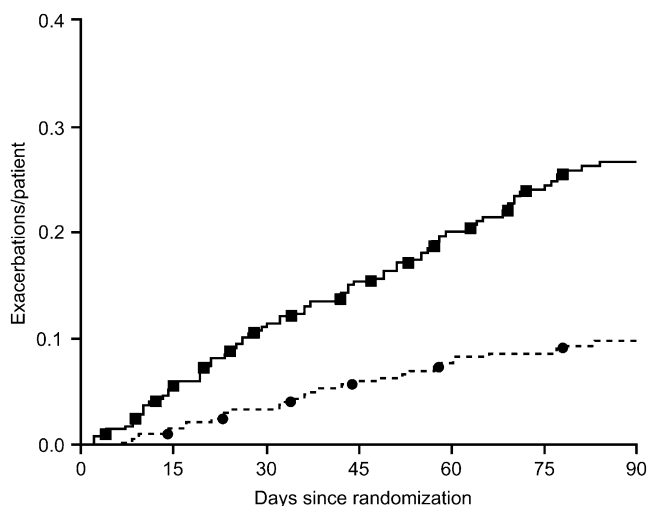
The aims of COPD management include reducing symptoms and improving patient health status as well as reducing future risk of exacerbations and progression of the disease. This is the first clinical study to directly evaluate the clinical efficacy of combining budesonide/formoterol with tiotropium in patients with COPD. This treatment approach was associated with marked improvements in various assessments at the clinic and at home in the morning compared with tiotropium alone. In addition, a significant 62% reduction was seen in severe exacerbations. Budesonide/formoterol added to tiotropium was well tolerated.

Our data showing significant improvements in clinic lung function with budesonide/formoterol added to tiotropium compared with tiotropium alone are consistent with previous findings in two studies investigating the triple inhaled therapy approach using salmeterol/fluticasone plus tiotropium (15, 17). Both studies showed that prebronchodilator FEV<sub>1</sub> improved with tiotropium combined with ICS/LABA over tiotropium alone (15, 17) and tiotropium plus salmeterol (17). These effects



**Figure 5.** Change in morning activities (absolute scores) over treatment period. BUD/FORM = budesonide/formoterol; CDLM = Capacity of Daily Living during the Morning questionnaire; PBO = placebo; TIO = tiotropium. Circles represent BUD/FORM + TIO; squares represent PBO + TIO. CDLM score at run-in: BUD/FORM + TIO, 4.09; PBO + TIO, 4.13. †Treatment comparison from randomization to first week of treatment. ‡Treatment comparison from randomization to last week of treatment.

on prebronchodilator FEV<sub>1</sub> are in line with the contribution of budesonide added to formoterol (9, 10, 29, 30). Importantly, we found that morning FEV<sub>1</sub> and peak expiratory flow measured at home (soon after the patient arose from bed) were significantly improved with budesonide/formoterol added to tiotropium compared with tiotropium alone. The improvements in morning FEV<sub>1</sub> reached a difference of 185 ml 5 minutes postdose, which were greater than the clinic recordings (made before 12:00 noon). This may be a reflection of the early morning trough, giving higher “room for improvement” as compared with the later part of the day. The rapid onset of bronchodilatory effect of budesonide/formoterol, as previously documented, is be-



**Figure 6.** Mean number of severe exacerbations per patient versus time. BUD/FORM = budesonide/formoterol; PBO = placebo; TIO = tiotropium. Circles represent BUD/FORM + TIO; squares represent PBO + TIO. Poisson regression: rate ratio, 0.38 (95% CI, 0.25–0.57;  $P < 0.001$ ). Total number of events: BUD/FORM + TIO (n = 329), 31; PBO + TIO (n = 330), 82. Patients with one or more severe exacerbations: BUD/FORM + TIO (n = 329), 25; PBO + TIO (n = 330), 61.

**TABLE 4. OCCURRENCE OF SEVERE EXACERBATIONS**

|   | PBO + TIO        | BUD/FORM + TIO | Treatment Comparison of Ratio (95% CI); P Value |
|---|------------------|----------------|---|
| All severe exacerbations                    |                  |                |   |
| Rate, events/patient/3 mo                   | 0.326            | 0.124          | 0.38 (0.25–0.57); <0.001                        |
| Hospitalizations/ER treatment               |                  |                |   |
| Rate, events/patient/3 mo                   | 0.080            | 0.028          | 0.35 (0.16–0.78); 0.011                         |
| Subgroup analysis, all severe exacerbations | Stratum Variable |                |   |
| Rate, events/patient/3 mo*                  | ICS at entry     | Yes            | 0.33 (0.19–0.55); <0.001                        |
|   |                  | No             | 0.49 (0.25–0.96); 0.038                         |
| Patients prescribed antibiotics, n (%)      |                  |                |   |
| Exacerbation of COPD                        | 38 (12)          | 19 (6)         |   |
| COPD (not exacerbation related)             | 10 (3)           | 8 (2)          |   |
| Other (non-COPD related)                    | 59 (18)          | 50 (15)        |   |

Definition of abbreviations: BUD/FORM = budesonide/formoterol; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ER = emergency room; ICS = inhaled corticosteroid; PBO = placebo; TIO = tiotropium.

\* Interaction analysis,  $P = 0.26$ .

lieved to be attributable mostly to the rapid onset of effect of the LABA component, formoterol (31), but the addition of budesonide may also contribute (9, 32).

There are methods for assessing symptoms and activities in clinical trials, but it was anticipated that measurement of

**TABLE 5. SUMMARY OF ADVERSE EVENTS\***

|  | PBO + TIO | BUD/FORM + TIO |
|--|-----------|----------------|
| No. (%) of patients with an adverse event in each category     |           |                |
| Any adverse event  | 82 (25)   | 81 (25)        |
| Serious adverse events   |           |                |
| Leading to death   | 0         | 1† (<0.5)      |
| Other than death   | 14 (4)    | 9 (3)          |
| Discontinuations due to an adverse event‡                      | 10 (3)    | 8 (2)          |
| Other significant adverse events                               | 0         | 0              |
| Most frequently reported adverse events                        |           |                |
| COPD   | 20 (6)    | 13 (4)         |
| Nasopharyngitis  | 12 (4)    | 7 (2)          |
| Bronchitis   | 4 (1)     | 3 (1)          |
| Hypertension   | 2 (1)     | 5 (2)          |
| Upper respiratory tract infection (bacterial)                  | 4 (1)     | 3 (1)          |
| Pharmacologically predictable adverse events,§ patient no. (%) |           |                |
| Dysphonia/aphonia  | 0         | 4 (1)          |
| Palpitations   | 1 (<0.5)  | 1 (<0.5)       |
| Oral candidiasis   | 1 (<0.5)  | 1 (<0.5)       |
| Cough  | 1 (<0.5)  | 0              |
| Dyspnea  | 0         | 1 (<0.5)       |
| COPD exacerbations   | 1 (<0.5)  | 0              |
| Dry mouth  | 0         | 1 (<0.5)       |
| Pleuritic pain   | 0         | 1 (<0.5)       |

Definition of abbreviations: BUD/FORM = budesonide/formoterol; COPD = chronic obstructive pulmonary disease; PBO = placebo; TIO = tiotropium.

\* Patients with multiple events in the same category were counted once in the category.

† Lung neoplasm.

‡ Discontinuation of study drug/study due to adverse events.

§ Number (%) of patients who reported adverse events (>1%).

¶ As assessed by the investigator.

morning symptoms, including onset, and of routine morning activities by simple but specific questions was the best way to address "real-life" problems. For this reason, two short questionnaires were used: the Global Chest Symptoms Questionnaire and the Capacity of Daily Living during the Morning Questionnaire (26). Full validation of the two instruments is presently ongoing.

Our finding that morning symptoms are improved by adding budesonide/formoterol to tiotropium is of interest, in light of previous studies reporting that patients with COPD indicate morning as the time when their symptoms particularly are most severe, impacting negatively on social and physical morning activities (33, 34). This may reflect diurnal variations in lung function (33, 35). Significant differences in morning activities were found between the two treatment arms in favor of budesonide/formoterol added to tiotropium. The total score was significantly improved after just 1 week of treatment and, after 12 weeks, improvements in each of the six individual scores were also significant. A therapy that is directed for use at this time of the day and that leads to rapid and sustainable improvements in lung function, symptoms, and activity would clearly be of benefit to patients.

In addition, improvements in daytime symptoms, nighttime awakenings, reliever use, and health-related quality of life were observed. Approximately 50% of patients in the budesonide/formoterol added to tiotropium arm improved their total SGRQ scores by more than four points compared with 40% in the tiotropium-alone group; this four-point difference has been shown to be clinically significant (25). The treatment differences appeared to increase without plateauing during the 12 weeks of treatment, indicating that a longer study is needed to assess maximal treatment differences.

The results of this study also demonstrate a clear benefit of budesonide/formoterol added to tiotropium in reducing the future risk of exacerbations. Relative to tiotropium alone, budesonide/formoterol added to tiotropium reduced the rate of severe exacerbations by 62%. Similar improvements for severe exacerbations have, to our knowledge, not been reported. Aaron and colleagues found that adding salmeterol/fluticasone to tiotropium did not reduce the risk of exacerbations compared with tiotropium alone. It should, however, be noted that the risk for hospitalizations was significantly reduced by salmeterol/fluticasone plus tiotropium compared with the tiotropium-alone arm (33% all causes and 47% respiratory related) (17). Although the use of antibiotics was not part of the definition of exacerbation in the present study, the use of antibiotics for worsening of COPD was lower in the budesonide/formoterol plus tiotropium group (6 vs. 12% in the tiotropium-alone group), indicating that the overall effect on exacerbations was not confounded by differences in antibiotic use between groups. Finally, the withdrawal of ICS treatment during the run-in period from patients who used ICS before study entry might have impacted on the results, particularly effects on exacerbations, as discussed by Suissa and colleagues (36). However, the interaction analysis did not reveal an effect of steroid withdrawal on exacerbation data, and the reduction of exacerbations was comparable between patients who did and did not use steroids before the study.

In this study, the dropout rate was relatively low and similar in both groups. Differential dropout is a problem and is accentuated in placebo-controlled studies where patients receiving placebo have no symptomatic treatment (16, 17, 36). This was overcome in the present study through the use of active symptomatic treatment (all patients received tiotropium after enrollment in the study). In addition, the low dropout rate in our study may be due to the short duration of treatment,

a finding also seen at 3 months in another study (27). Combining tiotropium with budesonide/formoterol was well tolerated, with a tolerability and safety profile similar to that of tiotropium alone. Pneumonia occurred at an incidence of less than 1% in each group, without differences between groups. These data are in line with 6- to 12-month studies showing no increase of pneumonia during treatment with budesonide/formoterol (9, 29, 30).

The major limitation of this study design is the lack of one or two additional arms: a budesonide arm and a formoterol arm. Such a design has the potential to discern the contribution of the two molecules to the overall results of the different end points. With the present design, only speculation about the individual contributions of budesonide and formoterol can be made. On the basis of the different properties of the two molecules, the assumption is that formoterol contributes most to the rapid onset of lung and symptom effects and budesonide contributes most to the risk reduction of exacerbations. However, the effects can also be mutually amplified by both monocomponents. The answers to these speculations can be determined only in a prospective study including all four arms.

The short study duration could also be viewed as a limitation because some of the outcomes need more time to reach the maximal response and show the maximal difference. In addition, results beyond 3 months can only be extrapolated carefully and then based on previous knowledge. In this study, most of the outcome parameters, such as lung function, including the primary outcome, and symptoms, respond quickly to interventions, with sustained effect during the study period. However, morning activities and SGRQ-C did not reach a plateau within the study period and based on previous data (9, 10) the study should last at least 6 months. It could also be argued that the present study was too short to determine effects of treatment on exacerbations. However, it is also plausible that the study shows the true difference between treatments, as longer studies are confounded by differential dropout rates favoring less effective treatments (11, 27). Longer term studies will be required to confirm the sustainability of the results. This study design is a complement to longer and larger studies and should be seen as an alternative that addresses many questions in a faster time frame, cost-effectively and ethically, by not exposing patients to less effective treatment for too long.

In conclusion, budesonide/formoterol added to tiotropium resulted in a rapid and sustained improvement of lung function, both at the clinic and in the home environment, when compared with tiotropium alone, and improved morning symptoms and activities and reduced morning reliever use. The future risk of severe exacerbations was also significantly reduced. The triple-therapy strategy was well tolerated. This study demonstrates the benefits of budesonide/formoterol added to tiotropium in the management of patients with COPD eligible for ICS/LABA combination therapy.

**Conflict of Interest Statement:** T.W. received \$1,001–\$5,000 from AstraZeneca for serving on an advisory board, \$5,001–\$10,000 from Boehringer Ingelheim for serving on a national advisory board, \$1,001–\$5,000 from Novartis for serving on an advisory board, and \$5,001–\$10,000 from MSD for serving on a national and international advisory board, \$5,001–\$10,000 from AstraZeneca in promotional and nonpromotional lecture fees, \$5,001–\$10,000 from Boehringer Ingelheim in promotional and nonpromotional lecture fees, \$1,001–\$5,000 from GlaxoSmithKline in promotional and nonpromotional lecture fees, \$1,001–\$5,000 from Novartis in promotional and nonpromotional lecture fees, and \$5,001–\$10,000 from MSD in promotional and nonpromotional lecture fees. T.W.'s dependent received more than \$100,001 in institutional lecture fees from Novartis; M.M. received \$1,001–\$5,000 from AstraZeneca, \$1,001–\$5,000 from Boehringer Ingelheim-Pfizer, \$1,001–\$5,000 from GlaxoSmithKline, \$1,001–\$5,000 from Ammiral, and \$1,001–\$5,000 from Nycomed in lecture fees, \$1,001–\$5,000 from Bayer Schering, \$5,001–\$10,000 from Boehringer Ingelheim-Pfizer, \$5,001–\$10,000 from GlaxoSmithKline, and \$1,001–\$5,000 from Nycomed for serving on an advisory board, \$10,001–\$50,000 from Boehringer

Ingelheim, \$1,001–\$5,000 from AstraZeneca, and \$10,001–\$50,000 from Bayer Schering in lecture fees, \$10,001–\$50,000 from Bayer Schering and \$10,001–\$50,000 from Talecris in institutional lecture fees; P.H. received \$1,001–\$5,000 from AstraZeneca, \$5,001–\$10,000 from GlaxoSmithKline, \$1,001–\$5,000 from Boehringer Ingelheim, \$1,001–\$5,000 from Pfizer, and \$1,001–\$5,000 from Actelion for serving on an advisory board, \$1,001–\$5,000 from AstraZeneca, \$1,001–\$5,000 from GlaxoSmithKline, \$1,001–\$5,000 from Boehringer Ingelheim, and \$1,001–\$5,000 from Actelion in lecture fees, \$10,001–\$50,000 from AstraZeneca, more than \$100,001 from GlaxoSmithKline, more than \$100,001 from Boehringer Ingelheim, \$10,001–\$50,000 from Actelion, and \$10,001–\$50,000 from Nycomed in institutional grants, \$10,001–\$50,000 from Eli Lilly in contract research-institutional, \$1,001–\$5,000 from Nycomed for serving on advisory board, and \$10,001–\$50,000 from ZLB Behring in contract research; G.E. is an employee of AstraZeneca, holds a patent Pulmicort Turbuhaler od and Pulmicort RESPules od from AstraZeneca, and holds stock ownership or options from AstraZeneca; S.P. is an employee of AstraZeneca, receiving \$50,001–\$100,001 in compensation, and holds \$50,001–\$100,000 in stock ownership or options in AstraZeneca; T.P. is an employee of AstraZeneca; R.K. received \$1,001–\$5,000 for serving on an advisory board for AstraZeneca.

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**References**

1. Rodriguez-Roisin R, Rabe KF, Anzueto A, Bourbeau J, Calverley P, Casas A, deGuia TS, Fukuchi Y, Hui DSC, Jenkins J, et al.: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for diagnosis, management, and prevention of chronic obstructive pulmonary disease [Internet]. Bethesda, MD: NHLBI; 2008 (Accessed 2009 July 28). Available from: <http://www.goldcopd.com/Guidelineitem.aspx?l1=2&l2=1&intId=2003>
2. Aalbers R, Ayres J, Backer V, Decramer M, Lier PA, Magyar P, Malolepszy J, Ruffin R, Sybrecht GW. Formoterol in patients with chronic obstructive pulmonary disease: a randomized, controlled, 3-month trial. *Eur Respir J* 2002;19:936–943.
3. Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL, Menjoge SS, Serby CW, Witek T Jr. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;19:217–224.
4. Mahler DA, Donohue JF, Barbee RA, Goldman MD, Gross NJ, Wisniewski ME, Yancey SW, Zakes BA, Rickard KA, Anderson WH. Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest* 1999;115:957–965.
5. van Noord JA, Aumann JL, Janssens E, Verhaert J, Smeets JJ, Mueller A, Cornelissen PJ. Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. *Chest* 2006;129:509–517.
6. Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA Jr, Korducki L, Cassino C, Kesten S. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005; 143:317–326.
7. O'Donnell DE, Flüge T, Gerken F, Hamilton A, Webb K, Aguilanin B, Magnussen H. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004;23:832–840.
8. National Institute for Clinical Excellence. Chronic obstructive pulmonary disease (clinical guideline 12). London: National Institute for Clinical Excellence; 2004.

9. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J* 2003;22:912–919.
10. Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, Peterson S, Olsson H. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003;21:74–81.
11. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J; TORCH Investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775–789.
12. Calverley PM, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, Anderson J, Maden C. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;361:449–456.
13. Cazzola M, Hanania NA. The role of combination therapy with corticosteroids and long-acting  $\beta_2$ -agonists in the prevention of exacerbations in COPD. *Int J Chron Obstruct Pulmon Dis* 2006;1: 345–354.
14. Halpin DM, Peterson S, Larsson TP, Calverley PM. Identifying COPD patients at increased risk of mortality: predictive value of clinical study baseline data. *Respir Med* 2008;102:1615–1624.
15. Cazzola M, Ando F, Santus P, Ruggeri P, Di Marco F, Sanduzzi A, D'Amato M. A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. *Pulm Pharmacol Ther* 2007;20:556–561.
16. Tashkin DP, Celli B, Senn S, Burkhardt D, Kesten S, Menjoge S, Decramer M. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1543–1554.
17. Aaron SD, Vandemheen KL, Ferguson D, Maltais F, Bourbeau J, Goldstein R, Balter M, O'Donnell D, McIvor A, Sharma S, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007;146:545–555.
18. Perng DW, Wu CC, Su KC, Lee YC, Perng RP, Tao CW. Additive benefits of tiotropium in COPD patients treated with long-acting  $\beta$  agonists and corticosteroids. *Respirology* 2006;11:598–602.
19. Singh D, Brooks J, Hagan G, Cahn A, O'Connor BJ. Superiority of "triple" therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. *Thorax* 2008;63:592–598.
20. Barnes PJ. How corticosteroids control inflammation: Quintiles Prize Lecture 2005. *Br J Pharmacol* 2006;148:245–254.
21. Bourbeau J, Christodouloupolos P, Maltais F, Yamauchi Y, Olivenstein R, Hamid Q. Effect of salmeterol/fluticasone propionate on airway inflammation in COPD: a randomized controlled trial. *Thorax* 2007; 62:938–943.
22. Lindberg A, Szalai Z, Pullerits T, Radezky E. Fast onset of effect of budesonide/formoterol versus salmeterol/fluticasone and salbutamol in patients with chronic obstructive pulmonary disease and reversible airway obstruction. *Respirology* 2007;12:732–739.
23. Welte T, Miravittles M, Peterson S, Polanowski T, Kessler R. Budesonide/formoterol added to tiotropium improves the management of COPD patients [abstract]. *Am J Respir Crit Care Med* 2009;179:A6192.
24. Welte T, Hartman L, Polanowski T, Hernandez P. Budesonide/formoterol added to tiotropium is well tolerated and reduces risk of severe exacerbations in COPD patients [abstract]. *Am J Respir Crit Care Med* 2009;179:A6188.
25. Jones P, Spencer S, Adie S. The St George's respiratory questionnaire manual, version 2.1. London: St George's Hospital Medical School; 2003.
26. Partridge M, Karlsson N, Stahl E. Development of the Morning Activities and Symptoms Questionnaire (MASQ) for COPD. 251984. *Eur Respir J* 2008;32:814s.
27. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of COPD exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008;177:19–26.
28. Kardos P, Wenker M, Glaab T, Vogelmeier C. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;175:144–149.
29. Tashkin DP, Rennard SI, Martin P, Ramachandran S, Martin UJ, Silkoff PE, Goldman M. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to

- very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. *Drugs* 2008;68:1975–2000.
30. Rennard SI, Tashkin DP, McElhattan J, Goldman M, Silkoff PE. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs* 2009;69:549–565.
  31. Di Marco F, Milic-Emili J, Boveri B, Carlucci P, Santus P, Casanova F, Cazzola M, Centanni S. Effect of inhaled bronchodilators on inspiratory capacity and dyspnoea at rest in COPD. *Eur Respir J* 2003;21:86–94.
  32. Harrison TW, Tattersfield AE. Plasma concentrations of fluticasone propionate and budesonide following inhalation from dry powder inhalers by healthy and asthmatic subjects. *Thorax* 2003;58:258–260.
  33. Partridge M, Karlsson N, Small I. Patient insight into the impact of chronic obstructive pulmonary disease in the morning: an internet survey. *Curr Med Res Opin* 2009;25:2043–2048.
  34. Partridge MR, Karlsson N. Patient insights on the impact of morning symptoms of COPD. Presented at the Sixth International Multi-disciplinary Conference on COPD (COPD6), June 11–13, 2008, Birmingham, UK. P11.
  35. Calverley PM, Lee A, Towse L, van Noord J, Witek TJ, Kelsen S. Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. *Thorax* 2003;58:855–860.
  36. Suissa S, Ernst P, Vandemheen KL, Aaron SD. Methodological issues in therapeutic trials of COPD. *Eur Respir J* 2008;31:927–933.