

## ORIGINAL ARTICLE

# Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

Huib A.M. Kerstjens, M.D., Michael Engel, M.D., Ronald Dahl, M.D.,  
Pierluigi Paggiaro, M.D., Ekkehard Beck, M.D., Mark Vandewalker, M.D.,  
Ralf Sigmund, Dipl.Math., Wolfgang Seibold, M.D., Petra Moroni-Zentgraf, M.D.,  
and Eric D. Bateman, M.D.

## ABSTRACT

**BACKGROUND**

Some patients with asthma have frequent exacerbations and persistent airflow obstruction despite treatment with inhaled glucocorticoids and long-acting beta-agonists (LABAs).

**METHODS**

In two replicate, randomized, controlled trials involving 912 patients with asthma who were receiving inhaled glucocorticoids and LABAs, we compared the effect on lung function and exacerbations of adding tiotropium (a total dose of 5  $\mu$ g) or placebo, both delivered by a soft-mist inhaler once daily for 48 weeks. All the patients were symptomatic, had a post-bronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>) of 80% or less of the predicted value, and had a history of at least one severe exacerbation in the previous year.

**RESULTS**

The patients had a mean baseline FEV<sub>1</sub> of 62% of the predicted value; the mean age was 53 years. At 24 weeks, the mean ( $\pm$ SE) change in the peak FEV<sub>1</sub> from baseline was greater with tiotropium than with placebo in the two trials: a difference of 86 $\pm$ 34 ml in trial 1 (P=0.01) and 154 $\pm$ 32 ml in trial 2 (P<0.001). The predose (trough) FEV<sub>1</sub> also improved in trials 1 and 2 with tiotropium, as compared with placebo: a difference of 88 $\pm$ 31 ml (P=0.01) and 111 $\pm$ 30 ml (P<0.001), respectively. The addition of tiotropium increased the time to the first severe exacerbation (282 days vs. 226 days), with an overall reduction of 21% in the risk of a severe exacerbation (hazard ratio, 0.79; P=0.03). No deaths occurred; adverse events were similar in the two groups.

**CONCLUSIONS**

In patients with poorly controlled asthma despite the use of inhaled glucocorticoids and LABAs, the addition of tiotropium significantly increased the time to the first severe exacerbation and provided modest sustained bronchodilation. (Funded by Boehringer Ingelheim and Pfizer; ClinicalTrials.gov numbers, NCT00772538 and NCT00776984.)

From the University of Groningen and the Department of Pulmonary Medicine and Tuberculosis, University Medical Center Groningen, and Groningen Research Institute for Asthma and COPD — all in Groningen, the Netherlands (H.A.M.K.); Therapeutic Area Respiratory Diseases, Boehringer Ingelheim Pharma, Ingelheim am Rhein (M.E., P.M.-Z.), the Medical Department, Institut für Gesundheitsförderung, Rüdersdorf Brandenburg (E.B.), and Biostatistics (R.S.) and Clinical Research (W.S.), Boehringer Ingelheim Pharma, Biberach an der Riss — all in Germany; the Department of Respiratory Diseases, Aarhus University Hospital, Aarhus, Denmark (R.D.); CardioThoracic Department, Pulmonary Unit, University Hospital of Pisa, Pisa, Italy (P.P.); Clinical Trials, Clinical Research of the Ozarks, Columbia, MO (M.V.); and the Department of Medicine, University of Cape Town, Cape Town, South Africa (E.D.B.). Address reprint requests to Dr. Kerstjens at the University of Groningen, Department of Pulmonology, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, the Netherlands, or at h.a.m.kerstjens@umcg.nl.

All clinical investigators are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on September 3, 2012, at NEJM.org.

N Engl J Med 2012.

DOI: 10.1056/NEJMoal208606

Copyright © 2012 Massachusetts Medical Society.

A SUBSTANTIAL PROPORTION OF PATIENTS with asthma have poorly controlled disease, with recurring symptoms and exacerbations despite the use of preferred controller drugs (i.e., inhaled glucocorticoids with or without inhaled long-acting beta-agonists [LABAs]). For these patients, alternative treatment options may have substantial limitations, including marginal efficacy, cumbersome routes of administration, side effects, and high cost.<sup>1,2</sup>

The option of adding a second long-acting inhaled bronchodilator in patients with uncontrolled asthma has been supported by results from recent studies that examined the efficacy of tiotropium, a long-acting anticholinergic bronchodilator approved for the treatment of chronic obstructive pulmonary disease (COPD) but not for the treatment of asthma.<sup>3,4</sup> Three studies with durations ranging from 8 to 16 weeks have shown the efficacy of the addition of tiotropium in patients with asthma who were already receiving standard treatment regimens.<sup>5-7</sup> The effect of tiotropium had not been evaluated in long-term clinical trials of sufficient duration and power to permit assessment of key end points, such as exacerbation frequency, in patients with poorly controlled asthma.

We report here the results of two replicate, randomized, placebo-controlled trials, PrimoTina-asthma 1 and PrimoTina-asthma 2 (hereafter referred to as trial 1 and trial 2), in which we studied the efficacy and safety of adding tiotropium delivered by a soft-mist inhaler, as compared with placebo delivered by the same system, to a treatment regimen of glucocorticoids and LABAs. We evaluated the effects on lung function, exacerbation frequency, and other end points during a 48-week period in patients with poorly controlled asthma.

## METHODS

### PATIENT CHARACTERISTICS

Eligible patients were between the ages of 18 and 75 years and had a 5-year or longer history of asthma that was diagnosed before the age of 40 years. Patients were required to have a score of 1.5 or higher on the Asthma Control Questionnaire 7 (ACQ-7), which consists of seven questions, each scored on a range from 0 (no impairment) to 6 (maximum impairment), with a minimal clinically important difference of 0.5 units<sup>8</sup>; and to have persistent airflow limitation, which was

defined as a post-bronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>) of 80% or less of the predicted value<sup>9</sup> and 70% or less of forced vital capacity (FVC) 30 minutes after the inhalation of four puffs of 100  $\mu$ g of salbutamol or 90  $\mu$ g of albuterol at the screening visit, despite daily therapy with inhaled glucocorticoids ( $\geq$ 800  $\mu$ g of budesonide or the equivalent) and LABAs. Patients were required to have had at least one exacerbation that was treated with systemic glucocorticoids in the previous year and to be either lifelong nonsmokers or to have a smoking history of fewer than 10 pack-years, with no smoking in the year before enrollment.

The main exclusion criteria were a past diagnosis of COPD, serious coexisting illnesses, and concurrent use of anticholinergic bronchodilators. Details of inclusion and exclusion criteria and permitted and excluded concomitant medications are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

### TRIAL DESIGN AND OVERSIGHT

The two replicate trials had a randomized, double-blind, placebo-controlled, parallel-group design, with a 48-week study period. They were conducted between October 2008 and July 2011 in 15 countries (listed in the Supplementary Appendix) and were performed in accordance with the provisions of the Declaration of Helsinki. The protocols were approved by the institutional review board at each participating center. All patients provided written informed consent.

After a 4-week screening period, eligible patients underwent randomization. There were nine visits: a visit at the start of the trial (screening), a visit at randomization (baseline), and seven additional visits during the 48-week treatment period. Full trial protocols, including the statistical analysis plans, are available at NEJM.org.

All the authors had access to all data and vouch for the accuracy and completeness of the data and for the fidelity of the trials to the final protocols; all the authors were involved in the interpretation of the data and in the writing and editing of the manuscript and made the decision to submit the manuscript for publication. Editorial assistance was provided by International Meetings and Science. Representatives of Boehringer Ingelheim designed and conducted the trial with the first author and collected and analyzed the data. Funding for the trials and editorial assistance was provided by Boehringer Ingelheim and Pfizer.

### TRIAL AND CONCOMITANT MEDICATIONS

Patients were randomly assigned to self-administer two puffs of either 2.5  $\mu\text{g}$  (i.e., 5  $\mu\text{g}$ ) of tiotropium or matching placebo each morning using a soft-mist inhaler (Respimat) as add-on therapy to individual pretrial maintenance asthma therapy consisting of high-dose inhaled glucocorticoids and LABAs. Continued use of sustained-release theophylline, leukotriene modifiers, anti-IgE antibody, and oral glucocorticoids ( $\leq 5$  mg per day) was also permitted if the dose of each remained stable for at least 4 weeks before study entry and for the duration of the trial. An open-label metered-dose inhaler of salbutamol (100  $\mu\text{g}$  per puff) or albuterol (90  $\mu\text{g}$  per puff) was provided as rescue medication for use during the trials, but the patients were responsible for supplying their own maintenance medications.

### TRIAL END POINTS

The two coprimary lung-function end points for each trial were the peak  $\text{FEV}_1$  response (within 3 hours after administration of the maintenance and study drugs) and the trough  $\text{FEV}_1$  response at week 24 — both expressed as the change from the baseline  $\text{FEV}_1$ . The baseline  $\text{FEV}_1$  was measured at the time of randomization (during visit 2) in the morning, 10 minutes before the administration of maintenance and trial medications. In a subgroup of patients, serial measurements of  $\text{FEV}_1$  were performed over a 24-hour period at week 24. A prespecified third coprimary end point, the time to the first severe asthma exacerbation (which was defined as a deterioration of asthma necessitating initiation or at least a doubling of systemic glucocorticoids for  $\geq 3$  days),<sup>10</sup> was evaluated from 48-week pooled trial data.

Secondary end points included the peak and trough  $\text{FEV}_1$  and FVC at each treatment visit, as well as the area under the curve for 3 hours after the administration of the maintenance and study drugs. Also included was the time to the first worsening of asthma (prespecified as the time to the first asthma exacerbation), which was defined as either a progressive increase in symptoms (as compared with usual day-to-day asthma symptoms) or a decline of 30% or more in the best morning peak expiratory flow (PEF) from the mean screening morning PEF for 2 or more consecutive days. Patients recorded morning and evening PEF, asthma symptoms (on the European Quality of Life–5 Dimensions questionnaire, a standardized measure of five dimensions of

health status, each rated as “no problems,” “some problems,” or “severe problems”), and medication use in an electronic diary (Asthma Monitor AM3) twice daily. Measurements were recorded daily and analyzed as means of weekly predose values for morning and evening PEF and asthma symptoms. Asthma control and quality of life were assessed with the use of the ACQ-7<sup>8</sup> and the Asthma Quality of Life Questionnaire (AQLQ),<sup>11</sup> respectively. The AQLQ consists of 32 questions addressing asthma-related symptoms and limitation during the preceding 2 weeks. Each item is scored on a scale of 1 (severely impaired) to 7 (no impairment at all); the minimal clinically important difference is 0.5 units. Adverse events, pulse rate, and blood pressure were assessed routinely.

### RANDOMIZATION AND MASKING

After the screening period, patients were randomly assigned in a 1:1 ratio to one of the two study groups. Randomization was performed in blocks of four per center, with no other stratification. The randomization schedule was generated by a validated system (PMX CTM, release 3.3.0 HP2, Propack Data) with the use of a pseudo-random-number generator and a supplied seed number.

### STATISTICAL ANALYSIS

For both trials separately, statistical testing of 24-week lung-function results followed a hierarchical sequence. First, the superiority of treatment with tiotropium to treatment with placebo was tested with respect to peak  $\text{FEV}_1$ . If significance was determined, the trough  $\text{FEV}_1$  was tested next. Ordered one-sided hypotheses (alpha of 0.025) underwent analysis on the basis of adjusted means with the use of a restricted-maximum-likelihood-based mixed-effects model with a repeated-measures approach. Analyses included fixed categorical effects of treatment, center, visit, and interaction between treatment and visit, as well as the baseline value of the outcome variable (the pretreatment measure of interest on the day of randomization) and the interaction between baseline and visit measurements. If tiotropium therapy showed superiority with respect to the two primary lung-function end points in each trial, with the type I error rate protected, the third coprimary end point (the time to the first severe exacerbation) was tested on the basis of pooled data after 48 weeks.

For the third coprimary end point, a prespecified interim analysis was performed once

by an independent data monitoring committee when the total number of patients with at least one severe exacerbation in the two trials combined reached 65; as a result, the sample size was increased to approximately 400 patients per trial, as prespecified in the protocols. The method described by Cui et al. was used to calculate the P value for the third coprimary end point.<sup>12</sup> Initial sample-size calculations are provided in the Supplementary Appendix.

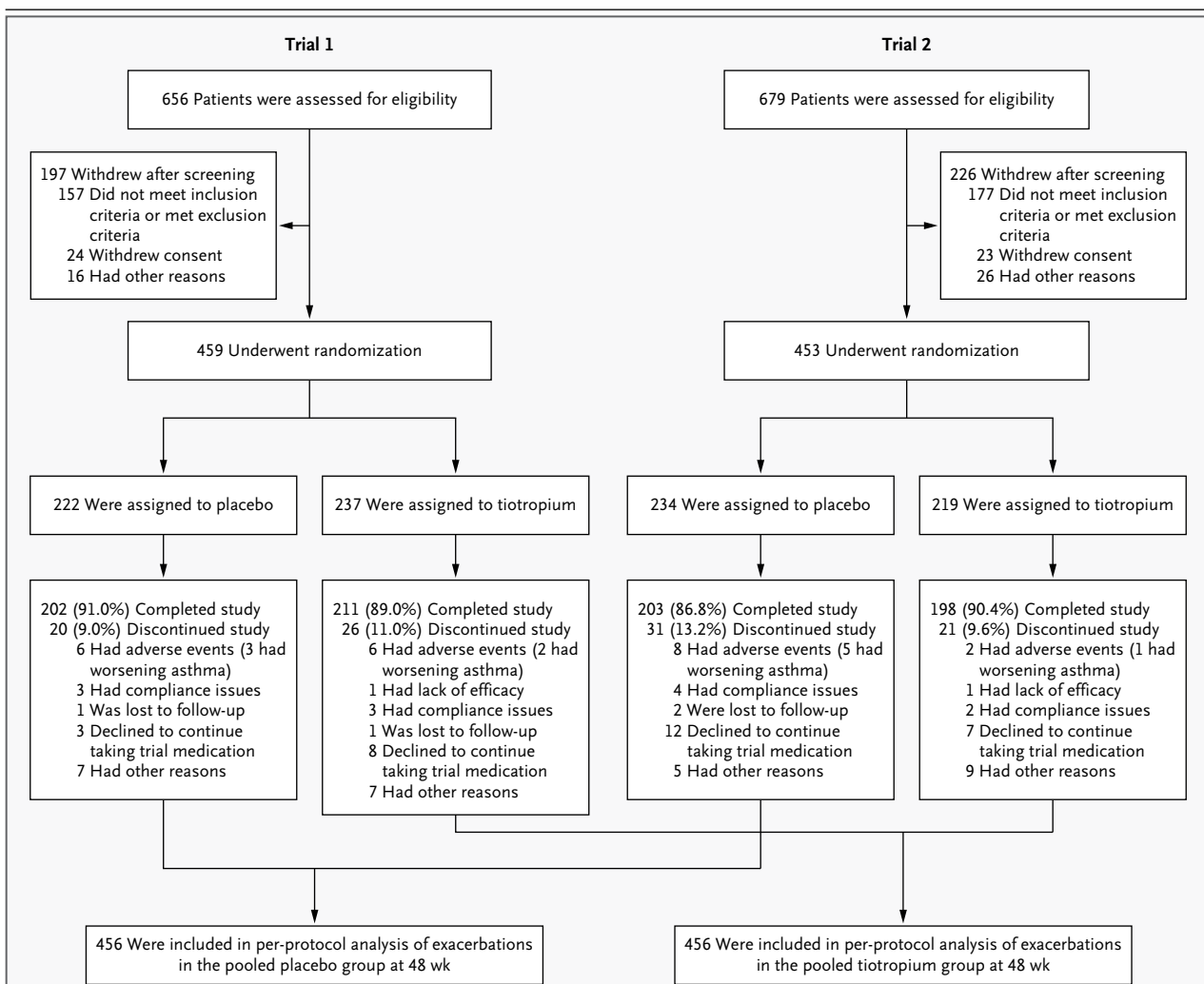
All statistical analyses were prespecified, with the exception of the analyses of subgroups defined according to age and smoking status. Statistical comparisons of secondary end points (also analysis of covariance) were exploratory.

The statistical analyses were performed with the use of SAS software (SAS Institute). Details regarding the statistical analysis plans are provided in the Supplementary Appendix.

## RESULTS

### STUDY PATIENTS

Of the 1335 patients who were screened, 912 eligible patients underwent randomization (Fig. 1). A total of 409 patients receiving tiotropium (211 in trial 1 and 198 in trial 2) and 405 patients receiving placebo (202 in trial 1 and 203 in trial 2) completed their respective trial. The primary analyses were performed on the full analysis set,



**Figure 1. Screening, Randomization, and Study Completion.**

A total of five patients in trial 2 were excluded because of compliance issues after randomization: two patients in the placebo group and three patients in the tiotropium group. See the Supplementary Appendix for additional information.

which was defined as all 907 patients who underwent randomization and received at least one dose of a study drug and had at least one on-treatment efficacy measurement (Fig. 1). Baseline characteristics were similar in the two trials and well balanced between the study groups (Ta-

ble 1, and Table S1 in the Supplementary Appendix). Medication used at the time of randomization (visit 2) consisted of inhaled glucocorticoids (median budesonide equipotent dose, 800  $\mu$ g; interquartile range, 800 to 1600) and LABAs, plus additional protocol-approved treatments, as used

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	All Patients (N=912)	Trial 1		Trial 2	
		Tiotropium (N=237)	Placebo (N=222)	Tiotropium (N=219)	Placebo (N=234)
Female sex — no. (%)	551 (60.4)	146 (61.6)	143 (64.4)	127 (58.0)	135 (57.7)
Age — yr	53.0 $\pm$ 12.4	52.9 $\pm$ 12.4	53.9 $\pm$ 12.8	51.4 $\pm$ 12.5 <sup>†</sup>	53.6 $\pm$ 11.7
Body-mass index <sup>‡</sup>	28.2 $\pm$ 6.0	28.2 $\pm$ 5.8	28.1 $\pm$ 6.4	28.2 $\pm$ 5.9	28.2 $\pm$ 5.9
Race — no. (%)§					
White	759 (83.2)	200 (84.4)	187 (84.2)	176 (80.4)	196 (83.8)
Other	153 (16.8)	37 (15.6)	35 (15.8)	43 (19.6)	38 (16.2)
Never smoked cigarettes — no. (%)	692 (75.9)	182 (76.8)	174 (78.4)	158 (72.1)	178 (76.1)
Median age of asthma onset — yr (range)	26 (0–44)	23 (0–40)	26 (0–39)	29 (0–44)	27 (0–39)
Median duration of asthma — yr (range)	28 (5–72)	31 (6–70)	28 (6–68)	26 (5–72)¶	28 (5–69)
Severe exacerbations in past year — no. (%)					
<3	738 (80.9)	201 (84.8)	185 (83.3)	179 (81.7)	173 (73.9)
3–5	128 (14.0)	27 (11.4)	27 (12.2)	30 (13.7)	44 (18.8)
>5	46 (5.0)	9 (3.8)	10 (4.5)	10 (4.6)	17 (7.3)
Use of maintenance oral glucocorticoids — %**	5.3	6.8	5.0	3.7	5.6
Use of omalizumab — %	3.9	2.5	4.5	2.7	6.0
Mean daily no. of puffs of short-acting beta-agonists <sup>††</sup>	3.2	2.8	3.3	3.4	3.3
Use of theophyllines — %	16.7	18.6	21.2	14.2	12.8
Use of leukotriene modifiers — %	22.3	25.3	27.5	16.4	19.7
Use of antihistamines — %	14.7	20.3	16.2	14.2 <sup>†</sup>	8.1
ACQ-7 score <sup>‡‡</sup>	2.6 $\pm$ 0.7	2.7 $\pm$ 0.7	2.7 $\pm$ 0.7	2.6 $\pm$ 0.7	2.6 $\pm$ 0.7
AQLQ score <sup>§§</sup>	4.6 $\pm$ 1.1	4.6 $\pm$ 1.1	4.6 $\pm$ 1.1	4.6 $\pm$ 1.0	4.7 $\pm$ 1.1
Forced expiratory volume in 1 sec					
Value before bronchodilation — liters**	1.603 $\pm$ 0.540	1.596 $\pm$ 0.546	1.558 $\pm$ 0.537	1.659 $\pm$ 0.569	1.598 $\pm$ 0.506
Percent of predicted value before bronchodilation	54.8 $\pm$ 12.4	54.6 $\pm$ 12.2	54.6 $\pm$ 12.2	55.1 $\pm$ 12.8	55.0 $\pm$ 12.6
Percent of predicted value after bronchodilation	62.2 $\pm$ 12.7	61.5 $\pm$ 12.5	62.7 $\pm$ 12.6	62.6 $\pm$ 12.5	62.3 $\pm$ 13.0
Reversibility — ml	217 $\pm$ 217	201 $\pm$ 211	230 $\pm$ 223	228 $\pm$ 206	209 $\pm$ 229
Forced vital capacity — liters**	2.744 $\pm$ 0.900	2.715 $\pm$ 0.923	2.704 $\pm$ 0.912	2.894 $\pm$ 0.909	2.788 $\pm$ 0.851

\* Plus-minus values are means  $\pm$ SD. All values were measured during screening (visit 1), unless otherwise stated. There were no significant differences between the two study groups in either trial unless otherwise indicated.

<sup>†</sup> P<0.05.

<sup>‡</sup> The body-mass index is the weight in kilograms divided by the square of the height in meters.

<sup>§</sup> Race was self-reported.

<sup>¶</sup> P<0.01.

<sup>||</sup> Exacerbations are expressed as the number of courses of glucocorticoids administered during the previous year.

<sup>\*\*</sup> This measurement was performed at the time of randomization (visit 2).

<sup>††</sup> This measurement reports mean use during the final week before randomization (visit 2).

<sup>‡‡</sup> The Asthma Control Questionnaire 7 (ACQ-7) consists of seven questions, each of which is scored on a range from 0 (no impairment) to 6 (maximum impairment).

<sup>§§</sup> The Asthma Quality of Life Questionnaire (AQLQ) consists of 32 questions addressing asthma-related symptoms and limitations during the preceding 2 weeks. Each item is scored on a scale of 1 (severely impaired) to 7 (no impairment).

before the trial (Table S1 in the Supplementary Appendix). Glucocorticoids and LABAs, as well as most pulmonary medications, were continued throughout the trial, as detailed in Methods.

#### PRIMARY END POINTS

##### Lung Function

Airflow obstruction was significantly reduced with the addition of tiotropium, as compared with the addition of placebo. At 24 weeks, the mean ( $\pm$ SE) difference between the tiotropium group and the placebo group in the change in the adjusted peak FEV<sub>1</sub> from baseline in the first 3 hours after the administration of tiotropium was  $86\pm34$  ml in

trial 1 ( $P=0.01$ ) and  $154\pm32$  ml in trial 2 ( $P<0.001$ ) (Table 2 and Fig. 2A and 2B). The between-group difference in change from baseline in the trough FEV<sub>1</sub> at 24 weeks was also significantly greater for patients in the tiotropium group than for those in the placebo group:  $88\pm31$  ml in trial 1 ( $P=0.01$ ) and  $111\pm30$  ml in trial 2 ( $P<0.001$ ).

##### Severe Exacerbations

The time to the first exacerbation (the primary end point) was increased by 56 days with tiotropium as compared with placebo (282 days vs. 226 days, representing the time until at least 25% of the patients [first quartile] had a first severe

**Table 2.** Mean Difference between Tiotropium and Placebo in the Change from Baseline to Week 24 and Week 48 in the Two Trials.\*

Measure and Week	Trial 1		Trial 2	
	No. of Patients	Difference in Change mean (95% CI)	No. of Patients	Difference in Change mean (95% CI)
<b>Forced expiratory volume in 1 sec</b>				
Peak at 0–3 hr (ml)				
24 wk†	428	86 (20 to 152)‡	423	154 (91 to 217)§
48 wk	417	73 (5 to 140)‡	403	152 (87 to 217)§
Trough (ml)				
24 wk†	428	88 (27 to 149)¶	422	111 (53 to 169)§
48 wk	417	42 (–21 to 104)	402	92 (32 to 151)¶
<b>Forced vital capacity</b>				
Peak (ml)				
24 wk	428	89 (6 to 173)‡	423	94 (10 to 177)‡
48 wk	417	125 (40 to 210)¶	403	114 (29 to 200)¶
Trough (ml)				
24 wk	428	136 (58 to 214)§	422	106 (25 to 186)¶
48 wk	417	111 (31 to 190)¶	402	71 (–12 to 153)
<b>Peak expiratory flow  </b>				
Morning (liters/min)				
24 wk	414	21.5 (12.7 to 30.4)§	407	23.3 (14.5 to 32.1)§
48 wk	369	20.3 (11.3 to 29.4)§	378	14.0 (5.1 to 22.9)¶
Evening (liters/min)				
24 wk	413	22.0 (13.0 to 30.9)§	405	29.9 (20.7 to 39.1)§
48 wk	369	22.6 (13.5 to 31.7)§	377	24.5 (15.1 to 33.8)§

\* All differences are calculated as the adjusted mean change from baseline, as measured at randomization (visit 2), for tiotropium minus placebo. Baseline was defined as the measurement obtained before any study or maintenance medication was administered. Values for forced expiratory volume in 1 second and forced vital capacity have been adjusted for treatment, center, visit, baseline value, and interactions between treatment and visit and between baseline value and visit.

† This category was a coprimary end point in the two trials.

‡  $P<0.05$ .

§  $P<0.001$ .

¶  $P<0.01$ .

|| All values are means of weekly measurements of peak expiratory flow.



exacerbation), corresponding to a reduction of 21% in risk (hazard ratio, 0.79; 95% confidence interval [CI], 0.62 to 1.00;  $P=0.03$ ) (Fig. 2C). (Since less than 50% of the patients had a severe exacerbation, the median time to the first severe exacerbation cannot be calculated.)

#### KEY PRESPECIFIED SECONDARY END POINTS

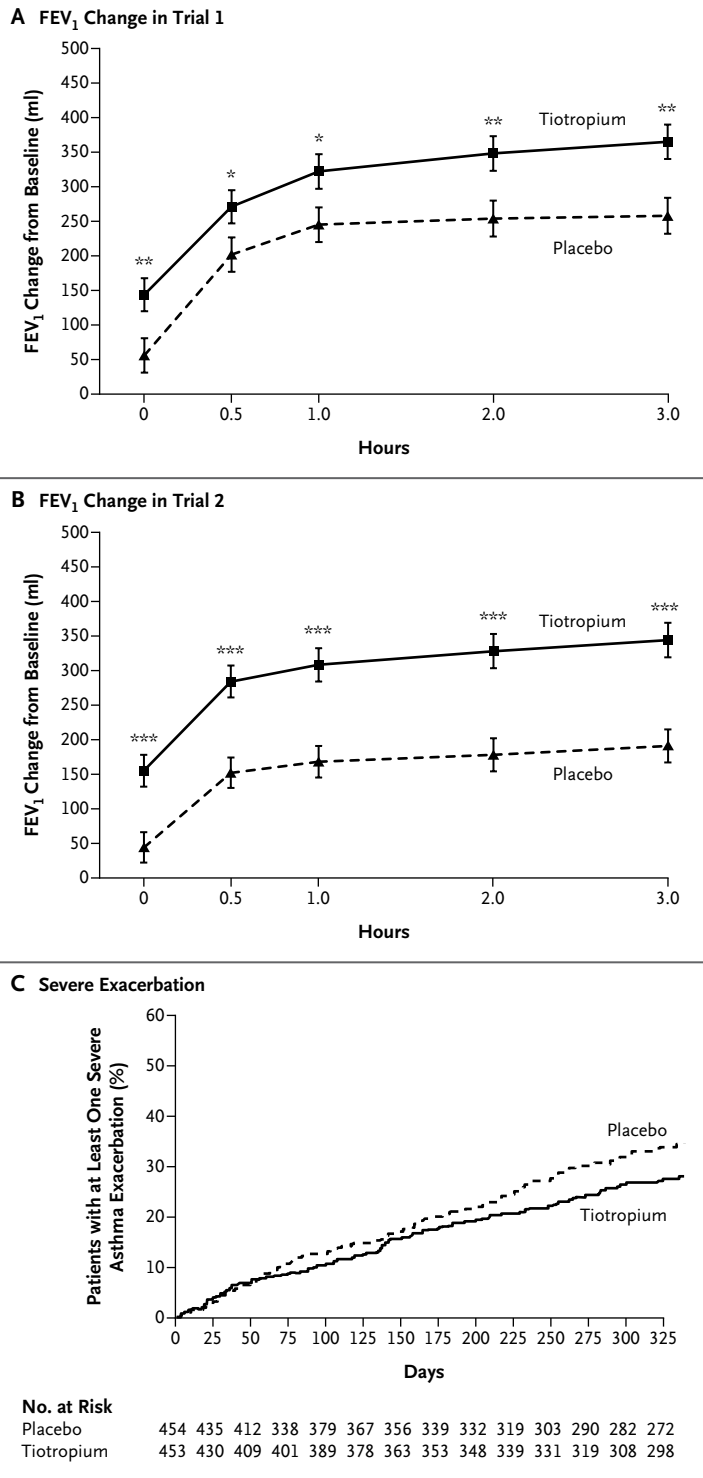
At week 24, there was significant improvement in spirometric measurements among patients in the tiotropium group, as compared with those in the placebo group (Table 2). In a subgroup of patients in whom 24-hour spirometry was performed, the improvement in FEV<sub>1</sub> was maintained over the full day (Fig. S1A and S1B in the Supplementary Appendix). Improvements in peak FEV<sub>1</sub> were sustained over the 48-week period (Fig. S1C and S1D in the Supplementary Appendix). There were also significantly greater improvements in weekly morning and evening PEF values in the tiotropium group; these improvements were also sustained over the full trial period (Fig. S1E through S1H in the Supplementary Appendix).

In the tiotropium group, 122 of 453 patients (26.9%) had at least 1 severe exacerbation, as compared with 149 of 454 patients (32.8%) in the placebo group (Table S2 in the Supplementary Appendix). The total number of severe exacerbations per patient-year was significantly lower in the tiotropium group than in the placebo

group (0.53 vs. 0.66,  $P=0.046$ ) (Table S2 in the Supplementary Appendix). There were 16 patients hospitalized for asthma in the tiotropium group, as compared with 20 patients in the placebo group. The median time to the first worsening

#### Figure 2. Lung Function and Severe Exacerbations.

The mean changes in lung function from baseline to 24 weeks, as measured by the forced expiratory volume in 1 second (FEV<sub>1</sub>) for 3 hours after the administration of the study and maintenance drugs, are shown for trial 1 (Panel A) and trial 2 (Panel B). The baseline FEV<sub>1</sub> was defined as the measurement obtained at randomization (visit 2) before the administration of study and maintenance medications. At subsequent visits during the study period, this measurement was followed immediately by the administration of maintenance and study medications. For Panels A and B, 0 hour denotes the first measurement, taken between 7 and 10 a.m., which was the trough effect of tiotropium or placebo administered 24 hours earlier. Panel C shows the cumulative number of severe exacerbations, with a risk reduction of 21% (hazard ratio, 0.79;  $P=0.03$  in pooled analysis). One asterisk indicates  $P<0.05$ ; two asterisks,  $P<0.01$ ; and three asterisks,  $P<0.001$ . The I bars represent standard errors. Data have been adjusted for treatment, study center, visit, baseline measurement, and the interactions between treatment and visit and between baseline values and visit.



of asthma was increased with the addition of tiotropium (315 days, vs. 181 days with placebo), with a reduction of 31% in risk (hazard ratio, 0.69; 95% CI, 0.58 to 0.82;  $P < 0.001$ ) (Fig. S2 and Table S2 in the Supplementary Appendix).

There were improvements in scores on the ACQ-7 in the two study groups (Fig. S3A and S3B in the Supplementary Appendix). At week 24, the mean difference in scores between the tiotropium group and the placebo group was significant only in trial 2 ( $-0.13$  [ $P = 0.06$ ] and  $-0.2$  [ $P = 0.003$ ] in trials 1 and 2, respectively) (Table S3 in the Supplementary Appendix). The minimal clinically important difference for the ACQ-7 score was not achieved in either trial.

Significant differences in the AQLQ score between the tiotropium group and the placebo group were seen at 24 weeks in trial 2 (0.18 units,  $P = 0.02$ ), but in trial 1 the difference (0.04 units) was not significant (Fig. S3C and S3D and Table S3 in the Supplementary Appendix). The minimal clinically important difference of 0.5 for the AQLQ score was not achieved in either trial.

There were small and nonsignificant between-group differences in the number of symptom-free days, as recorded in the AM3 electronic diary. The use of rescue medication was similar in the two study groups; the adjusted mean difference in puffs per day (weekly mean in the 7 days before week 24, tiotropium minus placebo) was  $-0.09$  in trial 1 and  $-0.26$  in trial 2 (Table S3 in the Supplementary Appendix). Between-group differences in other secondary end points were also not significant.

#### SUBGROUP ANALYSES

The improvements in peak FEV<sub>1</sub> in the tiotropium group, as compared with the placebo group (measured as the interaction between the subgroup and study treatment), tended to be higher in patients with a lower FEV<sub>1</sub> as a percentage of the predicted value (trial 1,  $P = 0.03$ ; trial 2,  $P = 0.56$ ), in men (trial 1,  $P = 0.09$ ; trial 2,  $P = 0.04$ ), and in former smokers with a history of fewer than 10 pack-years (trial 1,  $P = 0.14$ ; trial 2,  $P = 0.047$ ) in post hoc analysis. However, improvements were independent of other factors that were analyzed, including geographic region, level of reversibility, age (post hoc), body-mass index, allergic status, asthma duration, ACQ-7 score at baseline, and use of systemic glucocorticoids in the year before trial enrollment. Similar results

were observed in the analysis of the time to the first severe exacerbation.

#### ADVERSE EVENTS

Adverse events were reported in 73.5% of patients in the tiotropium group and 80.3% of patients in the placebo group. Among the adverse events reported by at least 2% of patients in any study group, only allergic rhinitis occurred at a significantly higher rate in the tiotropium group; asthma events and insomnia were significantly more common in the placebo group (Table 3). Adverse events were assessed as drug-related in 26 of 456 patients (5.7%) in the tiotropium group, as compared with 21 of 456 patients (4.6%) in the placebo group. Dry mouth was reported by 11 patients: 8 (1.8%) in the tiotropium group and 3 (0.7%) in the placebo group.

Serious adverse events were reported for 77 patients: 37 (8.1%) in the tiotropium group and 40 (8.8%) in the placebo group (Table S4 in the Supplementary Appendix). Of the serious adverse events, 3 events (all in the tiotropium group) were considered to be life-threatening. Two patients had an asthma exacerbation and recovered fully; 1 patient was admitted to the hospital for cerebral infarction. Cardiac adverse events occurred in less than 2% of patients and were well balanced between the study groups. Drug-related cardiac events were reported in 2 patients (0.4%) in the tiotropium group and 1 patient (0.2%) in the placebo group. Changes that were observed in blood pressure and pulse rate and laboratory or electrocardiographic abnormalities were balanced between the study groups. No deaths occurred.

#### DISCUSSION

Tiotropium is the most widely used long-acting bronchodilator worldwide for the treatment of COPD. However, its role as a treatment for asthma has only recently been subject to systematic clinical investigation. The results of these two replicate trials confirm that adding tiotropium once daily provided modest sustained bronchodilation over 24 hours. Adding tiotropium also reduced severe exacerbations and episodes of the worsening of asthma in patients who were symptomatic and had persistent airflow limitation despite the use of inhaled glucocorticoids and LABAs and, in some cases, additional controller drugs.



**Table 3. Adverse Events.\***

Event	Trial 1		Trial 2	
	Tiotropium (N=237)	Placebo (N=222)	Tiotropium (N=219)	Placebo (N=234)
	<i>number of patients (percent)</i>			
Any adverse event	167 (70.5)	170 (76.6)	168 (76.7)	196 (83.8)
Asthma	91 (38.4)	109 (49.1)	91 (41.6)	123 (52.6)
Decreased rate of peak expiratory flow	49 (20.7)	58 (26.1)	44 (20.1)	64 (27.4)
Nasopharyngitis	19 (8.0)	20 (9.0)	32 (14.6)	36 (15.4)
Headache	12 (5.1)	13 (5.9)	17 (7.8)	20 (8.5)
Bronchitis	12 (5.1)	10 (4.5)	13 (5.9)	10 (4.3)
Sinusitis	3 (1.3)	10 (4.5)	13 (5.9)	12 (5.1)
Upper respiratory tract infection	13 (5.5)	6 (2.7)	8 (3.7)	10 (4.3)
Influenza	10 (4.2)	4 (1.8)	10 (4.6)	10 (4.3)
Cough	6 (2.5)	5 (2.3)	7 (3.2)	8 (3.4)
Back pain	3 (1.3)	7 (3.2)	8 (3.7)	5 (2.1)
Oropharyngeal pain	3 (1.3)	5 (2.3)	6 (2.7)	6 (2.6)
Pneumonia	7 (3.0)	1 (0.5)	5 (2.3)	6 (2.6)
Arthralgia	6 (2.5)	2 (0.9)	4 (1.8)	7 (3.0)
Dysphonia	5 (2.1)	4 (1.8)	5 (2.3)	4 (1.7)
Diarrhea	4 (1.7)	4 (1.8)	4 (1.8)	6 (2.6)
Respiratory tract infection	5 (2.1)	5 (2.3)	2 (0.9)	6 (2.6)
Allergic rhinitis	3 (1.3)	2 (0.9)	10 (4.6)	1 (0.4)
Hypertension	2 (0.8)	2 (0.9)	4 (1.8)	8 (3.4)
Insomnia	0	1 (0.5)	2 (0.9)	9 (3.8)

\* The listed events were reported in at least 2% of patients who underwent randomization in trials 1 and 2. Events are described according to preferred term classifications in the *Medical Dictionary for Drug Regulatory Affairs*, version 14.0. A list of all serious adverse events is provided in Table S4 in the Supplementary Appendix.

The improvements in peak FEV<sub>1</sub> in trials 1 and 2 in patients with asthma who received tiotropium (86 ml and 154 ml, respectively) were similar in magnitude to those reported previously by Kerstjens et al.<sup>7</sup> (139 ml) in patients with asthma receiving inhaled glucocorticoids and LABAs. Although the improvements in FEV<sub>1</sub> were relatively small (<10%), it should be noted that these increases were in patients who were already receiving a long-acting bronchodilator and had fixed airflow limitation. The added benefit of combining two long-acting bronchodilators with different modes of action has also been observed in patients with COPD.<sup>13</sup>

Improvements in ACQ-7 and AQLQ scores and other secondary end points in these two replicate trials were small and inconsistent and did not reach the minimal clinically important difference; in light of the fact that episodes of

asthma worsening were reduced significantly, this modest symptomatic benefit was surprising. The reduction in severe exacerbations was also significant: in a post hoc calculation, the number needed to treat in order to prevent one severe exacerbation during the 48-week treatment period was 15. The gains observed in trials 1 and 2, though relatively small, should be viewed in the context of the need for additional treatments for this patient population and the limitations of current alternatives. Leukotriene-receptor antagonists and theophylline have shown little, if any, benefit in this patient population; oral glucocorticoids are associated with severe side effects; and other treatments, such as omalizumab, are suitable only for a subgroup of patients. None of the alternatives have shown benefit across more than a few clinical end points.

We cannot explain the inconsistency in the

results between the two trials. Both trials were performed on several continents in multiple centers, and across the two trials, patient baseline characteristics were similar, and no differences in results according to geographic region were identified in subgroup analyses. A larger placebo response was seen in trial 1 than in trial 2.

In our trials, adverse events and serious adverse events were well balanced between study groups in the two trials. Dry mouth, a typical adverse event with anticholinergic agents, was reported in less than 2% of all patients and was reported more frequently in the tiotropium group than in the placebo group (eight patients vs. three patients) — a finding that is consistent with the known adverse-event profile of tiotropium.

In conclusion, in patients with poorly controlled asthma despite treatment with inhaled glucocorticoids and LABAs, adding tiotropium significantly reduced the risk of episodes of the worsening of asthma and asthma exacerbations requiring treatment with systemic glucocorticoids and provided sustained bronchodilation. The side effects of tiotropium were similar to those previously noted in trials of therapies for COPD.

Supported by Boehringer Ingelheim and Pfizer.

Dr. Kerstjens reports receiving on behalf of his institution consulting fees or honoraria and support from Boehringer Ingelheim for his travel to meetings or for other purposes connected with this clinical study and support from Boehringer Ingelheim, Pfizer, Nycomed, Novartis, Almirall, and Chiesi for his service on advisory boards and from Boehringer Ingelheim, Pfizer, and Nycomed for consulting work; Dr. Engel, being an employee of Boehringer Ingelheim; Dr. Dahl, receiving consulting fees and travel support from Boehringer Ingelheim connected with

this clinical study and receiving on behalf of his institution a grant from Boehringer Ingelheim connected with this clinical study; Dr. Paggiaro, receiving consulting fees from Boehringer Ingelheim in connection with this study, support for service on advisory boards from GlaxoSmithKline, Merck, Novartis, and Takeda/Nycomed, and lecture fees from AstraZeneca, Chiesi, GlaxoSmithKline, Menarini, Novartis, and Takeda/Nycomed and serving on the board of directors for the Global Initiative for Asthma and receiving on behalf of his institution grant support from Boehringer Ingelheim in connection with this clinical study; Dr. Beck, receiving support for participation in review activities and for travel from Boehringer Ingelheim in connection with this study, support from Almirall and Mundipharma for service on advisory boards, and lecture fees from AstraZeneca, Bayer, Novartis, and Takeda/Nycomed and receiving on behalf of his institution grant support related to this clinical study from Boehringer Ingelheim; Dr. Vandewalker, receiving consulting fees, support to participate in review activities, and travel support and receiving on behalf of his institution a grant from Boehringer Ingelheim connected with this clinical study, receiving grant support from Boehringer Ingelheim, and receiving lecture fees from GlaxoSmithKline, AstraZeneca, and Merck; Drs. Sigmund, Seibold, and Moroni-Zentgraf, being employees of Boehringer Ingelheim; Dr. Bateman, receiving consulting fees and support to review results and receiving on behalf of his institution a grant and travel support from Boehringer Ingelheim related to this clinical study, receiving lecture fees from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, ALK-Abelló, Chiesi, Novartis, Pfizer, and Takeda/Nycomed, receiving support for service on advisory boards for Almirall, AstraZeneca, Boehringer Ingelheim, Elevation Pharma, GlaxoSmithKline, Napp Pharma, Novartis, Forest, and Merck, receiving consulting fees from Navigant Consulting, IMS Consulting Group, ALK-Abelló, Almirall, and Hoffmann-La Roche, receiving support for his participation in educational presentations for Indegene Life-systems, and being a member of the Task Force on Severe Asthma of the American Thoracic Society and the European Respiratory Society and an advisory board member for the Global Initiative for Asthma. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all investigators in support of these trials.

## REFERENCES

1. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;170:836-44.
2. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2011 ([http://www.ginasthma.org/uploads/users/files/GINA\\_Report2011\\_May4.pdf](http://www.ginasthma.org/uploads/users/files/GINA_Report2011_May4.pdf)).
3. Matera MG, Cazzola M. Ultra-long-acting beta2-adrenoceptor agonists: an emerging therapeutic option for asthma and COPD? *Drugs* 2007;67:503-15.
4. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1543-54.
5. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010;363:1715-26.
6. Bateman ED, Kornmann O, Schmidt P, Pivovarova A, Engel M, Fabbri LM. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. *J Allergy Clin Immunol* 2011;128:315-22.
7. Kerstjens HA, Disse B, Schröder-Babo W, et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2011;128:308-14.
8. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.
9. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows: official statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:5-40.
10. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59-99.
11. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;47:76-83.
12. Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. *Biometrics* 1999;55:853-7.
13. van Noord JA, Aumann JL, Janssens E, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. *Eur Respir J* 2005;26:214-22.

Copyright © 2012 Massachusetts Medical Society.