Respiratory Medicine (2012) 106, 91–101

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD

Nicola A. Hanania [a], Glenn D. Crater [b,*], Andrea N. Morris [b], Amanda H. Emmett [b], Dianne M. O'Dell [b], Dennis E. Niewoehner [c]

[a] *Section of Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston, TX, USA*
[b] *GlaxoSmithKline, Respiratory Medicines Discovery and Development, Research Triangle Park, 5 Moore Drive, NC 27709, USA*
[c] *Pulmonary Section, Minneapolis VA Health Care System, Minneapolis, MN, USA*

Received 20 June 2011; accepted 8 September 2011
Available online 29 October 2011

KEYWORDS
COPD;
Long-acting beta$_2$-agonist;
Inhaled corticosteroid;
Bronchodilator;
Triple therapy

Summary
Background: Combining maintenance medications with different mechanisms of action may improve outcomes in COPD. In this study we evaluated the efficacy and safety of fluticasone/salmeterol (FSC) (250/50 mcg twice daily) when added to tiotropium (18 mcg once daily) (TIO) in subjects with symptomatic moderate to severe COPD.
Methods: This was a 24-week, randomized, double-blind, parallel group, multi-center study. Subjects 40 years or older with cigarette smoking history $\geq$10 pack-years and with the diagnosis of COPD and post-bronchodilator FEV_1 $\geq$40 to $\leq$ 80% of predicted normal and FEV_1/FVC of $\leq$0.70 were enrolled. Following a 4-week treatment with open-label TIO 18 mcg once daily, subjects were randomized in a double-blind fashion to either the addition of FSC 250/50 DISKUS twice daily or matching placebo. The primary efficacy endpoint was AM pre-dose FEV_1 and secondary endpoints included other measures of lung function, rescue albuterol use, health status and exacerbations.
Results: The addition of FSC to TIO significantly improved lung function indices including AM pre-dose FEV_1, 2 h post-dose FEV_1, AM pre-dose FVC, 2 h post-dose FVC and AM pre-dose IC compared with TIO alone. Furthermore, this combination was superior to TIO alone in reducing rescue albuterol use. However, there were no significant differences between the treatment groups in health status or COPD exacerbations. The incidence of adverse events was similar in both groups.
Conclusions: The addition of FSC to subjects with COPD treated with TIO significantly improves lung function without increasing the risk of adverse events. NCT00784550.

* Corresponding author. Tel.: +1 919 483 8225; fax: +1 919 483 4300.
E-mail address: glenn.d.crater@gsk.com (G.D. Crater).

0954-6111/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2011.09.002

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the leading causes of morbidity and mortality worldwide.[1,2] The most distinguishing feature of COPD is dyspnea which can be related to airflow obstruction and hyperinflation as documented by spirometric evaluation. Current treatment guidelines for COPD emphasize the need for treating symptomatic patients with this disease. Treatments include pharmacological and non-pharmacological interventions which are used in a stepwise fashion according to severity. Inhaled pharmacotherapy, consisting of a long-acting $beta_2$-agonist, a long-acting muscarinic antagonist, an inhaled corticosteroid (not indicated for the treatment of COPD as monotherapy), or some combination of the preceding, is the foundation for managing stable COPD. As monotherapy, each of these three classes of drugs improves lung function, and health status, and reduces the risk of exacerbations; all to a similarly modest extent.[3] However, important questions remain as to the clinical benefit, cost, safety, and appropriate target population when these classes of drugs are used in combination in patients with symptomatic COPD.

The rationale for prescribing a long-acting $beta_2$ agonist along with inhaled corticosteroids in COPD patients is well established, and these two classes of drugs are available as combined formulations of fluticasone/salmeterol, budesonide/formoterol, and mometasone/formoterol (currently only approved for asthma).[4–7] The combined fluticasone/salmeterol formulation and the once daily inhaled anticholinergic, tiotropium, are currently the two most widely prescribed COPD medications and they appear to confer similar clinical benefits without clear superiority of one over the other.[8] Fluticasone/salmeterol and tiotropium are frequently used together as so-called "triple therapy", but this clinical practice is based on inadequate evidence. Two small, short-term trials yielded conflicting results as to whether the combination of fluticasone/salmeterol and tiotropium improved lung function over that obtained with either fluticasone/salmeterol or tiotropium alone.[9,10] In a larger one-year trial, fluticasone/salmeterol added to tiotropium did not reduce COPD exacerbations to a greater extent than tiotropium alone, the primary outcome, but did improve selected secondary outcomes, including lung function and respiratory health status.[11] In this study we evaluated the efficacy and safety of fluticasone/salmeterol (FSC) (250/50 mcg twice daily) when added to tiotropium (TIO) (18 mcg once daily), compared to TIO alone in symptomatic subjects with moderate to severe COPD.

Methods

Study design

This was a 24-week, randomized, double-blind, parallel group study conducted at 33 centers in the US (study code ADC111114, NCT 00784550). After initial evaluation, eligible subjects completed a 4-week run-in period in which open-label TIO only was administered. Following run-in, subjects who had a modified Medical Research Council dyspnea scale score of $\geq$2 were eligible for randomization.[12] Subjects who experienced a COPD exacerbation or respiratory tract infection that required treatment with antibiotics, systemic corticosteroids, or hospitalization during the run-in period were excluded. Subjects were randomized in a 1:1 double-blind fashion to open-label TIO 18 mcg once daily via HandiHaler plus FSC 250/50 mcg via DISKUS® (FSC; Advair, Seretide, GlaxoSmithKline, Research Triangle Park, NC, USA) twice daily or open-label TIO 18 mcg once daily plus Placebo DISKUS twice daily. Treatment groups were stratified by albuterol reversibility to ensure the proportion of subjects with albuterol reversibility was similar across groups. The use of concurrent inhaled long-acting bronchodilators ($beta_2$-agonist and anticholinergic), ipratropium/albuterol combination products, oral $beta_2$-agonists, inhaled and oral corticosteroids, and theophylline preparations were not allowed during the treatment period. Albuterol was supplied as rescue medication during run-in and throughout the rest of the study. A follow-up phone call was performed approximately 2 weeks following the end of study treatment period or early withdrawal visit. The study was approved by the institutional review board or ethics committee of each site, and all participants provided written informed consent prior to conduct of study procedures.

Study population

Inclusion criteria to be enrolled in this study were: age 40 years and older, diagnosis of COPD according to ATS-ERS criteria, cigarette smoking history $\geq$10 pack-years, post-albuterol FEV_1 $\geq$40 to $\leq$ 80% of predicted normal and a post-albuterol FEV_1/FVC of $\leq$0.70 according to NHANES III reference values.[13,14] Principal exclusion criteria were: clinical diagnosis of respiratory disorder other than COPD, long-term oxygen, BMI $\geq$40 kg/m^2, clinically significant and uncontrolled medical disorder, lung resection surgery within the past year, and inability to give informed consent.

Efficacy assessments

The primary efficacy measure was AM pre-dose FEV_1 at endpoint (the last scheduled measure of pre-dose FEV_1 during the 24-week treatment period). Secondary efficacy measures included 2 h post-dose FEV_1, AM pre-dose FVC, 2 h post-dose FVC, AM pre-dose IC, and domain scores on the Chronic Respiratory Disease Questionnaire-Self-Administered Standardized (CRQ-SAS), all at endpoint.[15] Other efficacy measures included rescue albuterol use and health care utilization for COPD exacerbations. Exploratory endpoints included scores on the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) scale and scores on the Hospital Anxiety and Depression Scale (HADS).[16,17] The CRQ-SAS, QIDS-SR, and HADS were self-administered by the study subjects. Use of the CRQ-SAS, authored by Drs. Gordon Guyatt and Holger Schunemann, was granted under license from McMaster University, Hamilton, Canada.

Pulmonary function testing was conducted at screening (for albuterol reversibility testing) and at randomization and weeks 4, 8, 16, 24. Centralized spirometry services were provided by nSpire Health, Inc. of Longmont, CO, US. The CRQ-SAS, QIDS-SR, and HADS were all assessed at randomization and at weeks 8 and 24 and the early withdrawal visit. Subjects completed diary cards daily to record

use of rescue albuterol, blinded study drug (DISKUS), and open-label TIO. Treatment compliance with the study HandiHaler and DISKUS was determined by dividing total number of inhalations recorded in the subject diary card by the total number of inhalations prescribed $\times$ 100.

Safety assessments

Safety was assessed by standard adverse event monitoring procedures, including the incidence and type of pneumonia.

Statistical analysis

Statistical analyses were performed using SAS version 9.1 software in a UNIX reporting environment. Using a two-sample two-sided *t*-test with a standard deviation estimate of 250 mL for pre-dose FEV_1 change from baseline, 133 subjects per treatment group were needed to detect a significant difference of 100 mL between treatment groups at the 0.05 significance level with 90% power. The analysis population was the Intent-to-treat population which included all subjects randomized to study drug. The target enrollment of approximately 350 randomized subjects allowed for early discontinuations from the study.

The primary efficacy measure was change from baseline in pre-dose FEV_1 at endpoint where endpoint was defined as the last scheduled measure of pre-dose FEV_1 during the 24-week treatment period. The primary efficacy measure and secondary efficacy measures of pre-dose FVC and IC, 2-h post-dose FEV_1 and FVC, and CRQ-SAS scores were compared between treatment groups using analysis of covariance (ANCOVA) with terms for treatment group, investigator, reversibility stratum and baseline value. The analysis of COPD exacerbations compared the rate of exacerbations per subject per the 24-week treatment period between treatment groups using a Poisson regression model, including terms for treatment group, pooled investigator, reversibility stratum and baseline severity (baseline FEV_1 percent predicted), with log (time of treatment) as an offset variable. Rescue albuterol use and QIDS-SR and HADS scores were compared between treatment groups with an ANCOVA model.

A hierarchical testing procedure to control type I error for multiplicity was used for the treatment comparisons of efficacy endpoints. The Hochberg method was also used to control the overall type I error rate across the secondary efficacy measures. Exploratory analyses were not adjusted for multiplicity.

Results

Study subjects

A total of 633 subjects were screened, 342 were randomized, and 264 (77%) completed the study (Fig. 1).

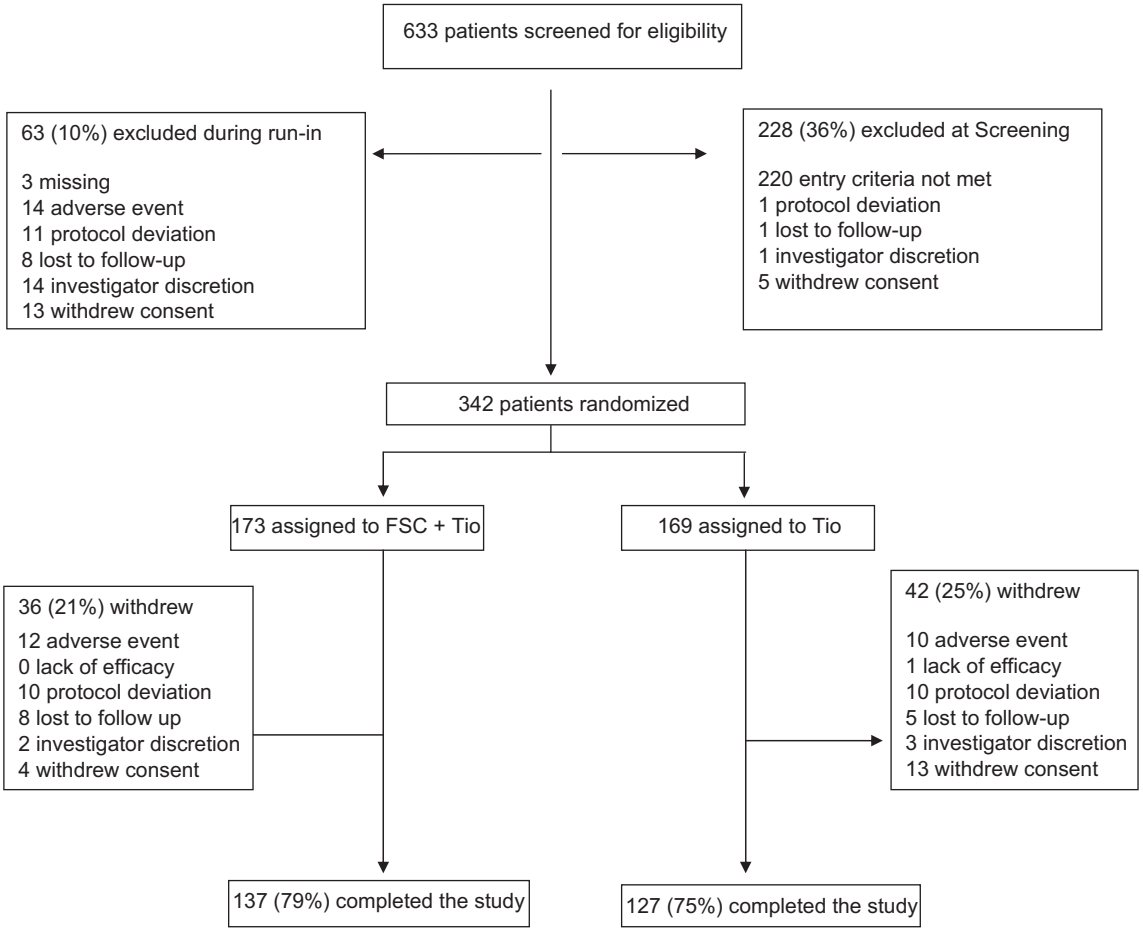

Figure 1 Consort Diagram.

In the FSC + TIO group, 137 (79%) subjects completed the study compared with 127 (75%) subjects in the TIO group. A total of 78 subjects (36 in the FSC + TIO group and 42 in the TIO group) prematurely withdrew from the study. The most common reason for premature withdrawal was adverse event. Demographic and baseline characteristics are summarized in Table 1. Overall, demographics were similar between the two groups, but slightly more males were enrolled in the FSC + TIO group (50%) compared with the TIO group (43%).

Lung function

During the run-in, treatment with open-label TIO significantly increased mean pre-dose FEV_1 from screening levels (increases of 100 ± 20 mL; $p < 0.001$) for within group change from screening. Mean change from baseline at endpoint (last scheduled measure of pre-dose FEV_1 during the 24-week treatment period) was 101 ± 21.8 mL in the FSC + TIO group and −16 ± 20.4 mL in the TIO group (least squares (LS) mean difference of 115 mL, $p < 0.001$). Significant improvements for this endpoint were seen with the FSC + TIO group compared with the TIO group at Weeks 4, 8, 16, and 24, (Fig. 2a.).The mean change from baseline at endpoint in post-dose FEV_1 was 233 ± 23.1 mL in the FSC + TIO group and 77 ± 20.6 mL in the TIO group (LS mean difference of 154 mL, $p < 0.001$). The differences in improvement of this endpoint were also significant for subjects treated with FSC + TIO compared with TIO at Weeks 4, 8, 16, and 24 (Fig. 2b). During run-in, treatment with open-label TIO statistically significantly increased mean AM pre-dose FVC from screening levels (increases of 130 ± 30 mL and 140 ± 30 mL in subjects subsequently randomized to FSC + TIO and TIO, respectively, $p < 0.001$ for within group change from screening). Mean change from baseline at endpoint in AM pre-dose FVC was 95 ± 32.7 mL in the FSC + TIO group and −28 ± 30.6 mL in the TIO group (LS mean difference of 122 mL, $p = 0.006$). The differences in improvement of this endpoint were also significant in the FSC + TIO group compared with the TIO group at Weeks 4, 8, 16, and 24 (Fig. 3a). Mean change from baseline at endpoint in post-dose FVC was 265 ± 35.9 mL in the FSC + TIO group and 87 ± 31.2 mL in the TIO group (LS mean difference of 175 mL, $p < 0.001$). These improvements were also significant with the FSC + TIO group compared with the TIO group at Weeks 4, 8, 16, and 24 (Fig. 3b). Mean change from baseline at endpoint in AM pre-dose IC was 107 ± 28.4 mL in the FSC + TIO group and −8 ± 28.1 mL in the TIO group (LS mean difference of 141 mL, $p < 0.001$). These improvements were also significant with the FSC + TIO group compared with the TIO group at Weeks 4, 8, 16, and 24 (Fig. 3c). Lung function endpoints for subjects with ≤50% and >50% predicted pre-bronchodilator FEV_1 at baseline are summarized in Table 2. In summary, the FSC + TIO group exhibited a statistically significant improvement from baseline at endpoint compared with the TIO group for all lung function measures examined. In subjects with moderate COPD (FEV1>50% predicted), the FSC + TIO group exhibited a statistically significant improvement from baseline at endpoint compared with the TIO group for 2 h post-dose FEV_1. However, for all other lung function endpoints, the differences between the FSC + TIO and TIO groups were not statistically significant.

Table 1 Demographic and Baseline Characteristics.

	FSC + TIO (n = 173)	TIO (n = 169)
Age, mean (years)	61.3	61.0
Gender, % male	50%	43%
Race, %White/%African American	95/4	96/4
Duration COPD, mean (years)	6.9	6.4
Current Smoker, %	59%	57%
Pack-Years, mean	55.4	54.7
Reversible, n (%)[a]	64 (37)	61 (36)
BMI, mean (kg/m**2)	27.0	27.6
Post-Bronchodilator FEV_1 L, (% predicted)	1.67, (56)	1.70, (57.4)
GOLD Stage II (n, %)	109 (63)	122 (72)
GOLD Stage III (n, %)	64 (37)	47 (28)
Exacerbations in past 12 mos requiring hospitalization, n (%)		
0	165 (95)	162 (96)
1	8 (5)	6 (4)
≥2	0	1 (<1)
Exacerbations in past 12 mos requiring oral corticosteroids/ antibiotic, n (%)		
0	117 (68)	125 (74)
1	45 (26)	35 (21)
2	7 (4)	6 (4)
≥3	4 (2)	3 (2)
Mean mMRC Dyspnea Score	2.4	2.5

[a] defined as a post-albuterol increase in FEV_1 of ≥200 mL and ≥12% from the pre-albuterol baseline.

Rescue albuterol use

Mean baseline values for albuterol use were 2.3 puffs/day in both the FSC + TIO and TIO groups. At endpoint, albuterol use was reduced to 1.8 puffs/day in the FSC + TIO group and increased to 2.4 puffs/day in the TIO group with an LS mean difference (SE) of −0.6 (0.24), $p = 0.010$. Albuterol use was statistically significantly reduced in the FSC + TIO group compared with the TIO group when evaluated over 1−24 weeks and over 4 week periods throughout the study except at Weeks 17−20 when the difference between groups was not statistically significant (Fig. 4).

Health status

A summary of CRQ-SAS domain scores (mastery, fatigue, emotional function, and dyspnea) at baseline and endpoint is provided in Table 3. There were no statistically significant changes from baseline to endpoint on any domain score between the two groups.

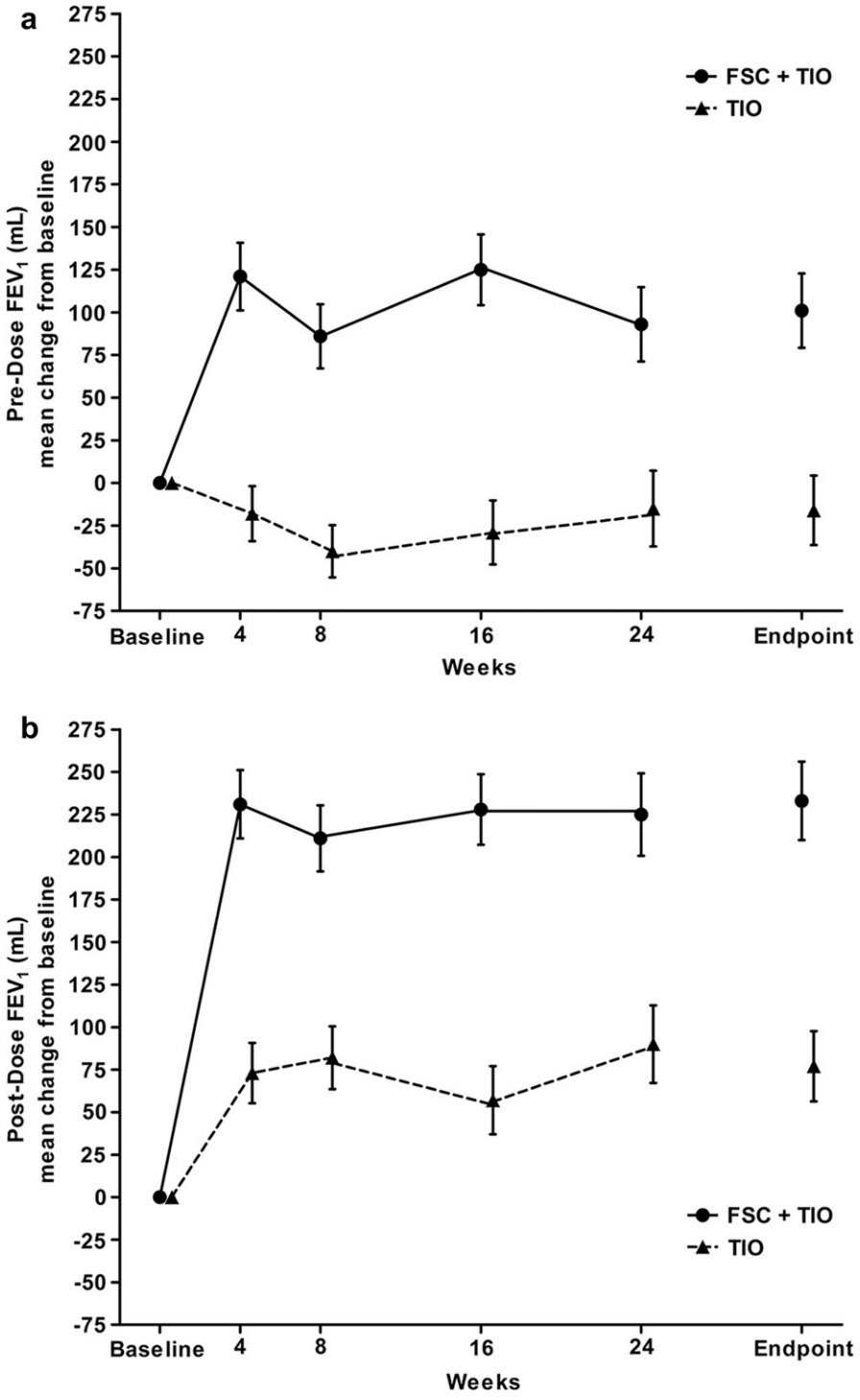

Figure 2 a&b Change in FEV_1.

COPD exacerbations and health care utilization

There were 25 (14%) and 26 (15%) subjects in the FSC + TIO and TIO groups who experienced 26 and 30 exacerbations, respectively. The mean exacerbation rate was not statistically significantly different between the groups (0.14 and 0.17 in the FSC + TIO and TIO groups, respectively, $p = 0.531$). The rate of exacerbations by HCU (i.e., use of systemic corticosteroids and/or antibiotics, unscheduled or urgent care physician/clinic office visits, hospitalizations and/or emergency room visits) could not be calculated due to the low number of events in each group. Most of the exacerbations (92% in the FSC + TIO group and 73% in the TIO group) did not result in an urgent care, ER visit, or hospital stay. The majority of exacerbations resulted in one office visit (20 [77%] and 18 [60%]) in the FSC + TIO and TIO

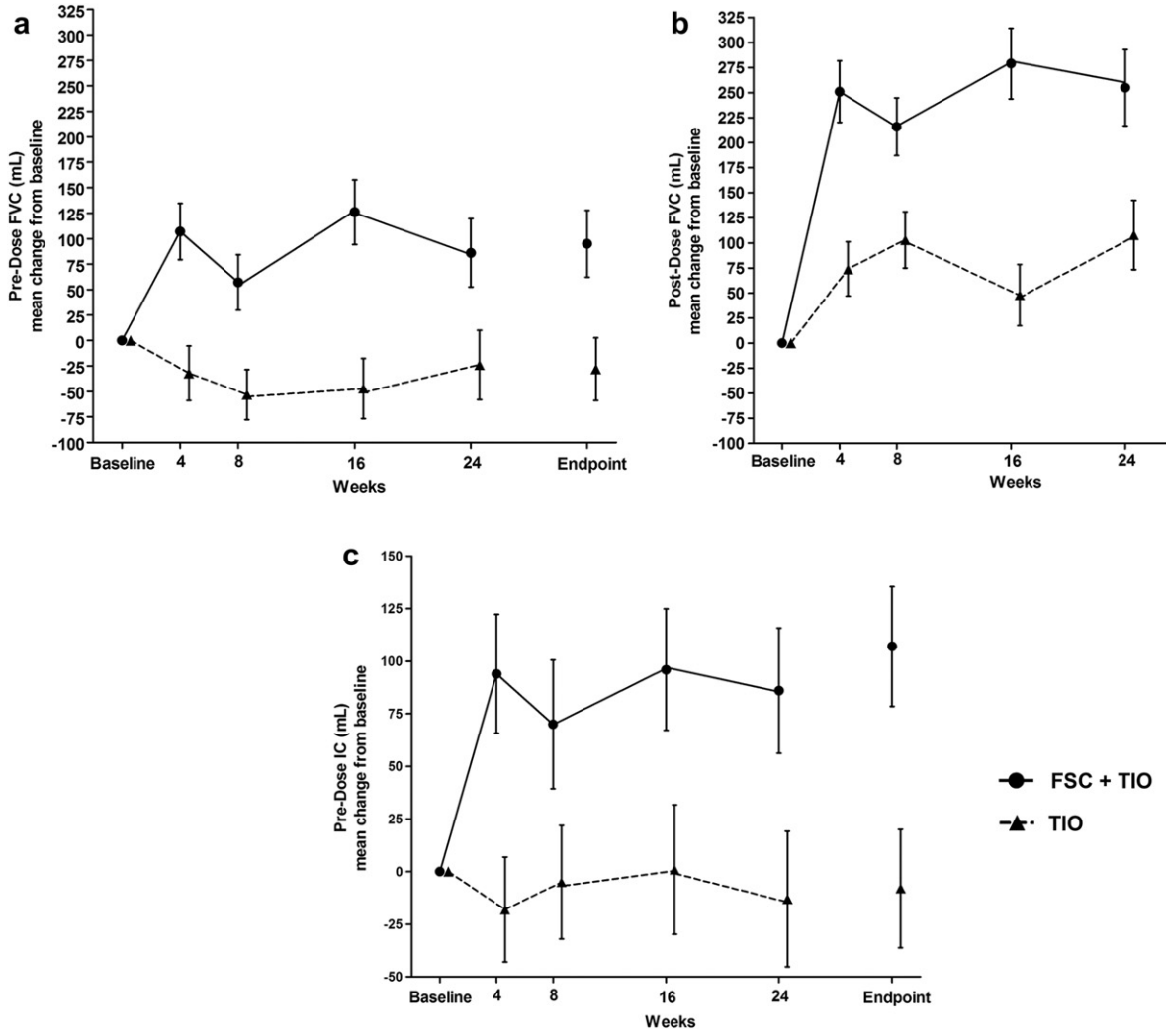

Figure 3 a,b &c Changes in FVC and IC.

Table 2 Differences in Lung Function Endpoints for Subjects with ≤50% and >50% predicted pre-bronchodilator FEV_1 at Baseline.

	≤50%		>50%	
	FSC + TIO $n = 66$	TIO $n = 61$	FSC + TIO $n = 104$	TIO $n = 107$
AM Pre-Dose FEV_1 at Endpoint (mL)				
LS Mean Difference, (SE)	202 (46.1)		50 (36.8)	
p value	<0.001		0.178	
2 H Post-Dose FEV_1 at Endpoint (mL)				
LS Mean Difference, (SE)	258 (49.3)		82 (36.6)	
p value	<0.001		0.026	
AM Pre-Dose FVC at Endpoint (mL)				
LS Mean Difference, (SE)	203 (74.5)		40 (50.8)	
p value	0.007		0.431	
2 H Post-Dose FVC at Endpoint (mL)				
LS Mean Difference, (SE)	268 (85.6)		84 (47.8)	
p value	0.002		0.081	
AM Pre-Dose IC at Endpoint (mL)				
LS Mean Difference, (SE)	218 (64.5)		53 (49.4)	
p value	0.001		0.286	

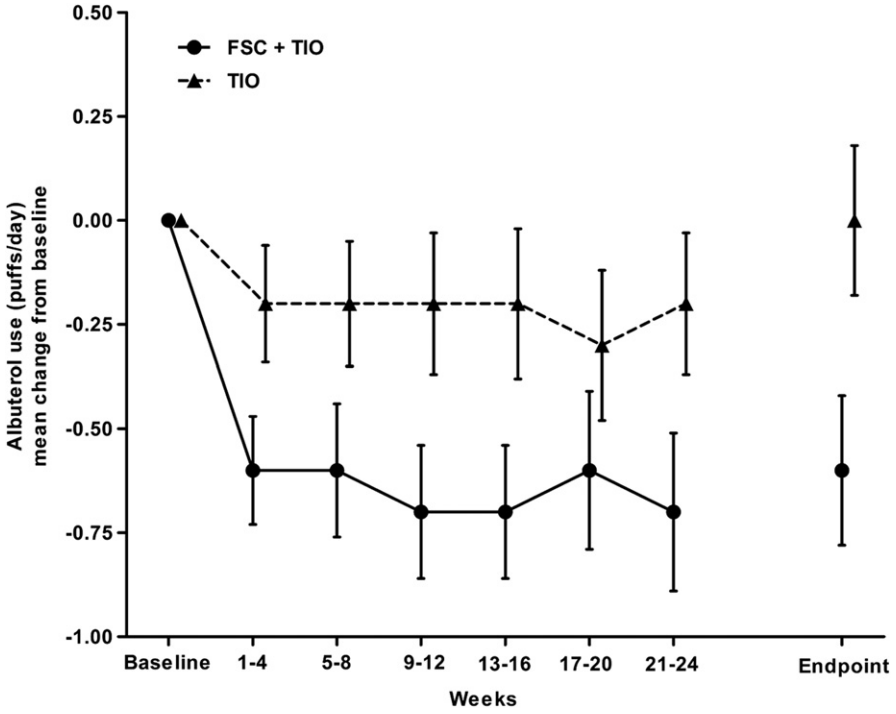

Figure 4 Rescue Albuterol Use.

groups, respectively. A total of 17 (65%) and 26 (87%) exacerbations in the FSC + TIO and TIO groups, respectively, were treated with a course of oral corticosteroids while 23 (88%) and 17 (57%) exacerbations in the FSC + TIO and TIO groups, respectively, were treated with antibiotics.

Exploratory endpoints

At endpoint, the mean QID-SR scores were 6.2 and 6.8 for the FSC + TIO and TIO groups, respectively. The difference between groups at endpoint was not statistically significantly different (LS mean difference of 0.0 and SE of 0.37, $p = 0.947$). A total of 70 and 71 subjects in the FSC + TIO and TIO groups, respectively, met the criteria of having at least mild depression (score of $\geq$6 at baseline). When the analysis was performed with subjects who met the criteria of at least mild depression at baseline, there was also no statistically significant difference between groups (Table 4).

There were no statistically significant differences between groups on the HADS at endpoint (LS mean difference of −0.1 and SE of 0.28, $p = 0.789$). A total of 35 and

Table 3 Other Secondary Endpoints.

	FSC + TIO ($n = 173$)	TIO ($n = 169$)	LS Mean difference	p-value
CRQ-SAS				
Mastery				
BL, mean	4.98	5.05	0.2	0.069
Endpoint, mean	5.23	5.09		
Fatigue				
BL, mean	3.91	3.82	0.09	0.470
Endpoint, mean	4.10	3.97		
Emotional Function				
BL, mean	4.59	4.56	0.08	0.394
Endpoint, mean	4.81	4.71		
Dyspnea				
BL, mean	4.72	4.66	0.02	0.879
Endpoint, mean	4.88	4.85		
COPD Exacerbations				
Subjects w/an exacerbation, n (%)	25 (14)	26 (15)		
Number of COPD exacerbation	26	30		
Mean exacerbation rate	0.14	0.17		0.531

BL = Baseline.

Table 4 Scores on the QIDS-SR and Depression and Anxiety Scores on the HADS.

	FSC + TIO $n = 173$	TIO $n = 169$
QIDS-SR		
n	163	155
BL Mean Score (SE)	5.9 (0.31)	6.6 (0.38)
Endpoint		
n	152	157
Mean Score (SE)	6.2 (0.35)	6.8 (0.37)
Change from BL		
n	144	145
Mean Score (SE)	0.3 (0.28)	0.1 (0.28)
LS Mean Difference, (SE)	0.0 (0.37)	
p value	0.947	
HADS		
Depression Scale		
n	168	163
BL Mean Score (SE)	4.6 (0.29)	4.8 (0.30)
Endpoint		
n	157	163
Mean Score (SE)	4.6 (0.31)	4.8 (0.31)
Change from BL		
n	154	158
Mean Score (SE)	−0.1(0.22)	−0.1(0.19)
LS Mean Difference, (SE)	−0.1(0.28)	
p value	0.789	
Anxiety Scale		
n	169	164
BL Mean Score (SE)	4.9 (0.31)	5.5 (0.33)
Endpoint		
n	155	161
Mean Score (SE)	5.1 (0.34)	5.1 (0.35)
Change from BL		
n	153	158
Mean Score (SE)	−0.0 (0.26)	−0.4 (0.23)
LS Mean Difference, (SE)	0.3 (0.32)	
p value	0.438	

BL = Baseline.

40 subjects in the FSC + TIO and TIO groups, respectively, met the criteria of having at least mild depression on the HADS (score of ≥8 at baseline). When the analysis was performed with subjects who met the criteria of at least mild depression at baseline, there was also no statistically significant difference between groups. A total of 42 and 49 subjects in the FSC + TIO and TIO groups, respectively, met the criteria of having at least mild anxiety on the HADS (score of ≥8 at baseline). When the analysis was performed with subjects who met the criteria of at least mild anxiety at baseline, there was also no statistically significant difference between groups (Table 4).

Safety

Adverse events were reported for a slightly higher percentage of subjects in the FSC + TIO (56%) group compared with the TIO (50%) group (Table 5). A total of 7 (4%) and 13 (8%) subjects in the FSC + TIO and TIO groups, respectively experienced an SAE. The most frequent SAE was COPD occurring in 5 (3%) subjects in the TIO group. All other SAEs occurred in <1% of subjects in each group. Two subjects in the FSC + TIO group experienced pneumonia during treatment.

Table 5 Most Common (>2%) Adverse Events During Treatment.

	FSC + TIO $n = 173$	TIO $n = 169$
Any event *n*, %	97 (56)	85 (50)
Chronic obstructive pulmonary disease	24 (14)	24 (14)
Headache	11 (6)	9 (5)
Back pain	5 (3)	9 (5)
Nasopharyngitis	5 (3)	6 (4)
Oropharyngeal pain	6 (3)	4 (2)
Bronchitis	6 (3)	3 (2)
Oral candidiasis	5 (3)	1 (<1)
Dyspnea	0	5 (3)

Discussion

Management of COPD aims to control symptoms, improve pulmonary function and reduce exacerbations. Maintenance medications which include long-acting bronchodilators as stand alone or in combination with inhaled corticosteroids are recommended by evidence-based guidelines for all patients with symptomatic COPD.[18] Recent COPD guidelines have recommended that combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects.[18] In this study, we evaluated the efficacy and safety of administering "triple therapy" with tiotropium, and FSC combination in subjects with moderate to severe COPD compared to the use of tiotropium alone. The results of our 24-week study demonstrate a clear superiority for this approach of combination therapy when added to tiotropium in improving all indices of lung function and reducing rescue medication use without any increase incidence of adverse events compared to when tiotropium was used alone. These effects are more pronounced in patients with severe disease (pre-bronchodilator FEV_1 ≤50% predicted).

Tiotropium and FSC are the two most prescribed medications for the treatment of COPD, and are frequently co-prescribed in clinical practice. Tiotropium has been shown to be effective in improving trough FEV_1, dyspnea, health status, and exacerbations compared to placebo.[19–21] Randomized trials have demonstrated that treatment with FSC at strengths of 250/50 mcg and 500/50 mcg BID results in greater improvement in lung function and dyspnea compared with the individual components in patients with COPD.[22–24] In the United States (US), only the 250/50 strength of FSC is indicated for the twice daily maintenance

treatment of airflow obstruction in patients with COPD associated with chronic bronchitis or emphysema and for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) who have a history of exacerbations.

While intuitively, the combination of FSC with tiotropium confers additional benefit in COPD compared to single bronchodilator (i.e., tiotropium) alone, there are only a few studies to support this. Furthermore there are also limited data on the use of such combination in patients with moderate disease. A 3-month pilot study of treatment of FSC 500/50 plus placebo, tiotropium plus placebo, or FSC 500/50 plus tiotropium showed that all groups had significant improvements in trough FEV_1 at the end of the study compared to baseline. However, the greatest difference occurred in the FSC 500/50 plus tiotropium group.[9] Another study[11] compared the effect of FSC 250/25 plus tiotropium, tiotropium plus salmeterol, and tiotropium plus placebo over one year. The study was not adequately powered to show a statistically significant difference among groups on the primary endpoint of exacerbations. However, the FSC plus tiotropium group improved lung function, hospitalizations for exacerbations and St. George's Respiratory Questionnaire (SGRQ) scores compared to tiotropium plus placebo. Of note, the tiotropium plus salmeterol group did not improve these endpoints compared to tiotropium plus placebo which suggests that dual bronchodilator therapy was no better than a single bronchodilator in this study. However, other studies have indeed shown beneficial effects when two long-acting bronchodilators are used in combination compared to monotherapy.[25–27] A recent study evaluated the anti-inflammatory effects of FSC, fluticasone propionate + tiotropium or tiotropium alone and demonstrated that anti-inflammatory effects of fluticasone propionate in FSC probably contribute to the clinical benefits seen with this combination.[28] Another study[10] examined the effect of FSC 500/50 plus tiotropium compared with either treatment alone. This study showed that the triple therapy was superior to either agent alone in AUC_{0-4hr} sGAW and sRAW at 14 days and other lung function measurements as well as improvement in symptomatic endpoints such as the Transition Dyspnea Index (TDI) and the use of rescue medication. In another recent study[29] which enrolled patients with severe disease and past history of COPD exacerbation, the use of another combination (budesonide/formoterol combination) conferred significant improvement in lung function, health status and reduced severe exacerbations when added to tiotropium when compared to tiotropium alone. Of note, the triple combination studies mentioned above all showed statistically significant differences with triple combination therapy on a variety of lung function and symptomatic endpoints in COPD. In addition, the patient populations in these studies ranged from moderate (FEV_1 $\leq$75% predicted normal) to severe (FEV_1 <50% predicted normal) indicating that a wide range of COPD severities do benefit from triple combination therapy compared to dual or single bronchodilator therapy alone. However, many of these studies included a small number of subjects, focused on a subgroup of severe COPD and/or examined the higher dose of FSC, 500/50.

While treatment guidelines recommend the addition of ICS as a pharmacotherapy for COPD to patients with severe disease, the use of "triple therapy" is often used in clinical practice in the U.S in the general COPD population. We therefore elected to evaluate the effects of such combination in a real life scenario and thus included a wider range of COPD patients using the FSC dose formulation currently approved in the U.S. The trial was designed to include a larger proportion of subjects with GOLD Stage 2 disease than have been enrolled in most previous trials evaluating inhaled pharmacotherapy in COPD.[10] We also did not restrict this combination therapy to subjects with previous history of exacerbations as has been done in previous studies. We demonstrated a significant statistical and clinically meaningful improvement in lung function measures in the study population although this improvement was more pronounced in subjects with more severe disease. Furthermore, a significant effect on the reduction in the use of rescue medication supports the positive effects on lung function observed.

In addition to evaluating the effects of this combination on lung function, we evaluated the effects on health status utilizing the CRQ-SAS questionnaire. No statistically significant differences were found between the FSC + TIO and TIO groups on this endpoint. This may be explained by the fact that subjects in both groups had mild to no impairment on the domains of the CRQ-SAS at baseline. Therefore, a treatment effect could not be observed. Further, we did not demonstrate any superiority of the "triple combination" in this study to tiotropium alone on exacerbations of COPD and health care utilization. However, the incidences of these in both groups were relatively small and the study was neither powered nor long enough to capture such events. In addition, we did not enrich the study population with subjects at risk of exacerbations as we attempted to evaluate this in subjects with a broad range of COPD severity.

Because the course of COPD is often complicated by anxiety and depression, we included the exploratory endpoints of depression and anxiety in this study. We were unable to demonstrate any effects of either intervention on these outcomes in this study. This may be explained by the fact that the incidence of anxiety and depression at baseline was modest and the duration of treatment may have been too short to demonstrate differences. This needs further exploration in longer term studies that include patients with more severe disease where the rates of depression and anxiety are higher.

Our safety surveillance during the study revealed a reassuring safety profile of the "triple combination" with no increased incidence of adverse events or serious adverse events compared to TIO alone therapy.

Our study has several limitations. A longer study duration may have helped to fully examine the effect of triple therapy on the incidence of exacerbations. In addition, quality of life and other endpoints affecting quality of life (depression and anxiety) were not improved with a triple therapy regimen, but these subjects had little to mild impairment on the CRQ-SAS, QIDS, and HADS upon study entry which precluded observing a treatment effect.

In summary, the results of this study support the use of "triple therapy" in COPD patients to augment the benefits of tiotropium alone in symptomatic patients with COPD.

Funding

This study (ADC111114, NCT01013948) was funded by GlaxoSmithKline, Research Triangle Park, NC. The authors did not receive any money for writing the manuscript. These data have been presented in part at the 2010 Annual meeting of the American College of Chest Physicians in Vancouver, BC.

Conflict of interest

Nicola A. Hanania, MD has received research grant support and honoraria for serving as a consultant and on the speaker bureau of GlaxoSmithKline.

Dennis Niewoehner has received advisory or consulting fees from Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, Forest Research, Novartis, Merck, Nycomed, Sanofi Aventis, Sepracor, and Bayer Schering within the past 3 years.

Acknowledgments

DN, GC, AM, AE, DO and NAH were involved with the initial concept of the paper, were extensively involved with the writing, and retained full editorial control throughout the development of the manuscript. Final approval was solely endorsed by the authors. All authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors.

Glenn Crater, Andrea Morris, Amanda Emmett, and Dianne O'Dell are GSK employees and own stock in the company.

References

1. Urbano FL, Pascual RM. Contemporary issues in the care of patients with chronic obstructive pulmonary disease. *J Manag Care Pharm* 2005;**11**(5 Suppl A):S14—6. S2-13; quiz.
2. Mannino DM, Braman S. The epidemiology and economics of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2007;**4**(7):502—6.
3. Wilt TJ, Niewoehner D, MacDonald R, Kane RL. Management of stable chronic obstructive pulmonary disease: a systematic review for a clinical practice guideline. *Ann Intern Med* 2007; **147**(9):639—53.
4. Ferguson GT, Anzueto A, Fei R, Emmett A, Knobil K, Kalberg C. Effect of fluticasone propionate/salmeterol (250/50 microg) or salmeterol (50 microg) on COPD exacerbations. *Respir Med* 2008;**102**(8):1099—108.
5. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;**356**(8):775—89.
6. 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**(6):912—9.
7. Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003;**21**(1):74—81.
8. Welsh EJ, Cates CJ, Poole P. Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2010;**5**:CD007891.
9. Cazzola M, Andò F, Santus P, Ruggeri P, Di Marco F, Sanduzzi A, et al. 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**(5):556—61.
10. 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**(7):592—8.
11. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, 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**(8):545—55.
12. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; **54**(7):581—6.
13. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;**23**(6):932—46.
14. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;**159**(1):179—87.
15. Schünemann HJ, Puhan M, Goldstein R, Jaeschke R, Guyatt GH. Measurement properties and interpretability of the Chronic respiratory disease questionnaire (CRQ). *COPD* 2005;**2**(1): 81—9.
16. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med* 1996;**26**(3):477—86.
17. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**(6):361—70.
18. GOLD. *GOLD - the global initiative for chronic obstructive lung disease*. Global Strategy for Diagnosis, Management, and Prevention of COPD [Internet]. Available from: http://www.goldcopd.org/; 2009 [cited 2010 Jul 12].
19. Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;**19**(2):217—24.
20. Tashkin DP, Pearle J, Iezzoni D, Varghese ST. Formoterol and tiotropium compared with tiotropium alone for treatment of COPD. *COPD* 2009;**6**(1):17—25.
21. Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JAD, Korducki L, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005;**143**(5):317—26.
22. Mahler DA, Wire P, Horstman D, Chang C, Yates J, Fischer T, et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;**166**(8):1084—91.
23. Hanania NA, Darken P, Horstman D, Reisner C, Lee B, Davis S, et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. *Chest* 2003;**124**(3): 834—43.

24. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;**361**(9356):449—56.
25. van Noord JA, Aumann JL, Janssens E, Smeets JJ, Verhaert J, Disse B, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. *Eur Respir J* 2005;**26**(2):214—22.
26. van Noord JA, Aumann JL, Janssens E, Smeets JJ, Zaagsma J, Mueller A, et al. Combining tiotropium and salmeterol in COPD: effects on airflow obstruction and symptoms. *Respir Med* 2010; **104**(7):995—1004.
27. Rabe KF, Timmer W, Sagkriotis A, Viel K. Comparison of a combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD. *Chest* 2008;**134**(2): 255—62.
28. Perng D, Tao C, Su K, Tsai C, Liu L, Lee Y. Anti-inflammatory effects of salmeterol/fluticasone, tiotropium/fluticasone or tiotropium in COPD. *Eur Respir J* 2009;**33**(4):778—84.
29. Welte T, Miravitlles M, Hernandez P, Eriksson G, Peterson S, Polanowski T, et al. Efficacy and tolerability of budesonide/-formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;**180**:741—50.