

Impact of Salmeterol/Fluticasone Propionate versus Salmeterol on Exacerbations in Severe Chronic Obstructive Pulmonary Disease

Peter Kardos, Marion Wencker, Thomas Glaab, and Claus Vogelmeier

Respiratory Medicine, Maingau Hospital, Frankfurt am Main; Therapeutic Area Respiratory, GlaxoSmithKline, Munich; and Department of Respiratory Medicine, Philipps University, Marburg, Germany

Rationale: Exacerbations of chronic obstructive pulmonary disease (COPD) greatly contribute to declining health status and the progression of the disease, thereby incurring significant direct and indirect health care costs. The prevention of exacerbations, therefore, is an important treatment goal.

Objectives: To assess the impact of combination therapy with salmeterol/fluticasone propionate compared with salmeterol alone on moderate and severe exacerbations in patients with severe COPD and a history of repeated exacerbations.

Methods: Randomized, double-blind, parallel-group study. After a 4-wk run-in period, 994 clinically stable patients were randomized to one of two treatment groups: 507 patients received the salmeterol/fluticasone combination 50/500 μ g twice daily and 487 received salmeterol 50 μ g twice daily for 44 wk.

Main Results: The total number of exacerbations was 334 in the combination therapy and 464 in the salmeterol group ($p < 0.0001$). The annualized rate of moderate and severe exacerbations per patient was 0.92 in the combination therapy and 1.4 in the salmeterol group, corresponding to a 35% decrease. In addition, the mean time to first exacerbation in the combination therapy group was significantly longer compared with that of the salmeterol group (128 vs. 93 d, $p < 0.0001$). Other endpoints, including health-related quality of life, peak expiratory flow, and use of rescue medication, were significantly improved in the combination therapy group. Both treatments were well tolerated.

Conclusions: This study demonstrates that combination therapy with salmeterol/fluticasone compared with salmeterol monotherapy significantly reduces the frequency of moderate/severe exacerbations in patients with severe COPD.

Keywords: inhaled corticosteroids; long-acting β_2 -agonists; combination treatment; chronic obstructive pulmonary disease; exacerbation

The number of individuals affected by chronic obstructive pulmonary disease (COPD) has been increasing in the last decades. As a consequence, COPD is expected to become the third most frequent cause of death worldwide by 2020 (1). Exacerbations of COPD are a major cause of morbidity (2). In particular, they greatly contribute to decline of health-related quality of life (3), increase in symptoms and breathlessness (4, 5), progression of the disease (6, 7), and increased risk of mortality (8). In addition, exacerbations induce enormous economic costs (9). They can occur at any stage of the disease but become more frequent as lung function impairment worsens (6, 10, 11).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Little evidence is available on the additional effect of inhaled corticosteroids in reducing exacerbations if prescribed in patients with severe COPD receiving long-acting bronchodilators.

What This Study Adds to the Field

This study shows a statistically significant, and clinically relevant, 35% reduction in COPD exacerbations as an effect of addition of inhaled corticosteroid to long-acting bronchodilator therapy.

Reducing exacerbations may therefore have a positive impact on patients' symptoms, progression of the disease, and health care expenditure. Several drug therapies have been shown to reduce exacerbations: inhaled long-acting bronchodilators such as salmeterol (SAL) or tiotropium are known to decrease exacerbation rates (12, 13); fixed combinations of inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABAs) have also been shown to be effective (14, 15).

The American Thoracic Society/European Respiratory Society guidelines recommend adding ICS to bronchodilator therapy for patients with an FEV₁ less than 50% predicted who have repeated exacerbations (16). To date, however, there is conflicting evidence for an additive effect of ICS treatment over long-acting bronchodilators alone with regard to exacerbations. SAL and fluticasone propionate (FP) in combination (SFC) showed, in one trial, a trend for a reduction in exacerbation rates compared with SAL alone (14). In a meta-analysis, a significant effect on exacerbations was shown in favor of ICS/LABA combination therapy over LABAs alone (17). However, this meta-analysis included two trials with a budesonide/formoterol combination (15, 18) that failed to show a reduction of exacerbations with formoterol versus placebo.

With this background, we designed a study assessing the efficacy of SFC versus standard treatment with SAL alone in patients with severe COPD and frequent exacerbations. Some of the results of the present study have been previously reported in abstract form (19, 20).

METHODS

Patients

Outpatients with severe COPD, defined according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages III and IV (post-bronchodilator FEV₁ < 50% predicted), were recruited who

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Correspondence and requests for reprints should be addressed to Peter Kardos, M.D., Group Practice and Center for Respiratory and Sleep Medicine, Allergy, Maingau Hospital, Scheffelstrasse 2, 60318 Frankfurt am Main, Germany. E-mail: pkardos@aol.com

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fulfilled the following additional inclusion criteria: FEV₁/FVC of 70% predicted or less, age of 40 yr or more, smoking history of 10 pack-years or more, and a documented history of two or more moderate to severe exacerbations in the last year before the study. Patients with COPD exacerbations, hospital admissions, or change in COPD therapy during the 4 wk before Visit 1 or during the 4-wk run-in period were excluded. Patients with asthma, significant lung diseases other than COPD, and need for long-term oxygen therapy or chronic systemic steroid use were also excluded.

Exacerbations were defined according to Rodriguez-Roisin (21): moderate (grade II) exacerbations, such as a worsening of COPD symptoms that required both a change of respiratory medication (increased dose of prescribed or addition of new drugs, i.e., antibiotics, mucolytics, systemic steroids, theophylline) and medical assistance; severe (grade III) exacerbations, such as deterioration in COPD resulting in hospitalization or emergency room treatment. In case of worsening symptoms, patients were instructed to contact the investigator and attend the clinic for an unscheduled visit. Details of the episode were recorded in each patient's case report form. Family doctor and emergency room visits or hospital treatment were also recorded at each scheduled visit. Moreover, patients were instructed to record any changes in COPD medication on a diary card.

In addition, we performed a *post hoc* analysis using an alternative definition for a moderate exacerbation used in previous studies (14, 15, 18). Moderate exacerbations were classified as requiring the use of antibiotics and/or systemic steroids.

Approval from local ethics committees was obtained at all participating sites, and all patients gave written, informed consent. This study conformed to the Declaration of Helsinki and Good Clinical Practice recommendations.

Study Design

This was a randomized, double-blind, parallel-group multicenter study conducted at 95 respiratory centers in Germany. Recruited patients participated in a 4-wk run-in period in which patients were required to remain on stable medication without exacerbations. This was followed by a 44-wk treatment period. During this study, individuals were evaluated eight times: on Weeks -4 (run-in, Visit 1), 0 (baseline, Visit 2), 4 (Visit 3), 12 (Visit 4), 20 (Visit 5), 28 (Visit 6), 36 (Visit 7), and 44 (Visit 8). Patients were randomized to receive either 50 µg SAL plus 500 µg FP combination (SFC; Seretide, Advair; GlaxoSmithKline, Munich, Germany) or 50 µg SAL (Serevent; GlaxoSmithKline) twice daily via Diskus (Glaxo Wellcome GmbH & Co, Bad Oldesloe, Germany) for 44 wk. At Visit 2, consecutive numbers were assigned to patients that determined the blinded treatment based on a centrally generated list with blocks of six. Drug-dispensing and drug-accountability records were kept. During the run-in and treatment periods, inhaled salbutamol was used as reliever medication, and regular treatment with short-acting bronchodilators, antioxidants/mucolytics, short-acting oral β_2 -agonists, and theophylline was permitted. All non-COPD medications, including preexisting selective β -blocker therapy, could be continued if the dose remained constant. Acute moderate and severe exacerbations were treated with systemic corticosteroids and/or antibiotics. Long-acting bronchodilators, including tiotropium and systemic steroids (except as treatment for exacerbations), were not permitted throughout the study.

Measurements

The primary endpoint was the number of moderate and severe exacerbations in each treatment group. Secondary endpoints included time to first exacerbation, prebronchodilator peak flow (PEF), post-bronchodilator FEV₁, and disease-specific quality of life as evaluated by the St. George's Respiratory Questionnaire (SGRQ), which investigated three different domains consisting of activity, symptom, and impact scores. Post-bronchodilator spirometry was performed 30 min after 400 µg salbutamol (or after 200 µg salbutamol when the patient had taken bronchodilators within the last 6 h) at Visits 1, 2, 5, and 8. Predicted values were calculated according to the European Community for Steel and Coal statement (22). Bronchodilator reversibility was assessed at the first and second visits only, and at least 6 h after the last use of short-acting bronchodilators or 12 h after the use of LABAs (tiotropium was not yet available). Daily morning pretreatment PEF, symptoms,

breathlessness (Medical Research Council [MRC] dyspnea score), reliever medication use, and COPD medications were recorded on diary cards.

Health status was evaluated using the validated German version of SGRQ (23, 24) at Visits 1, 2, 5, and 8. A change of greater or equal to 4 units was considered clinically meaningful, with negative values indicating an improvement in quality of life (25). Visits 3, 6, and 7 included distribution and collection of study medications plus diary cards.

Statistical Analysis

Data were analyzed for patients who received at least one dose of study drug. Data are expressed as mean and 95% confidence intervals (95% CIs) unless otherwise stated. All hypothesis testing was two-sided. *p* values of less than 5% were considered statistically significant, with a predetermined β of 0.20. The number of moderate and severe exacerbations was analyzed using a maximum likelihood Poisson regression model: treatment, sex, smoking status, age, and baseline FEV₁ (% predicted) were used as factors, and time in study as an offset variable. From the Poisson regression model, annualized exacerbation rates were calculated. The time to first moderate/severe exacerbation was visualized with Kaplan-Meier plots and analyzed using the log-rank test and a Cox's proportional hazards model for the analysis of instantaneous risk. Changes in lung function parameters were analyzed using analysis of covariance (ANCOVA), with the baseline value as the only covariate. Daily diary card PEF values were aggregated per patient separately for the screening period and the total treatment period before the ANCOVA was performed. Similar ANCOVA analyses were performed for MRC scores, rescue medication, and SGRQ scores. We estimated that 467 patients per group would be needed to detect a 0.4 difference in mean annual exacerbation counts at the 5% significance level with 80% power, assuming an SD of 2.

RESULTS

Patients

In total, 1,109 patients were recruited between March 2002 and December 2003; 111 patients were not randomized because of failure to meet the inclusion criteria. After the run-in period, 998 patients were randomized to study treatment: 507 to SFC and 487 patients to SAL, respectively. Four individuals were excluded from the analysis due to missing randomization code. Figure 1 illustrates the study design. Demographic data, baseline characteristics, and withdrawal rates did not differ between groups as shown in Table 1. In the study population, there were 99 withdrawals in the SFC group and 103 in the SAL group, both mainly due to adverse events that were primarily linked to COPD deterioration. There was no difference in the probability of remaining in the study at any particular time point.

Exacerbations

In the SFC treatment group, the observed number of all moderate plus severe exacerbations was significantly reduced: SFC, 334 exacerbations in 210 patients; SAL, 464 exacerbations in 241 patients; $p < 0.0001$. The annualized rates of moderate/severe exacerbations were 0.92 per patient in the SFC and 1.4 per patient in the SAL treatment groups ($p < 0.0001$), corresponding to an estimated treatment effect ratio of 0.65 (95% CI, 0.57–0.76). This translates into a 35% reduction of the mean exacerbation rate (estimated from the Poisson regression model).

A *post hoc* analysis of exacerbations requiring antibiotics and/or systemic steroids found 318 versus 444 exacerbations in the SFC and SAL groups, respectively ($p < 0.0001$). Details of exacerbations are shown in Table 2.

Figure 2 illustrates the cumulative risk of the occurrence of moderate/severe exacerbations over time.

The mean time to first exacerbation was 128 versus 93 d in the SFC and SAL groups, respectively. The hazard ratio was 1.47

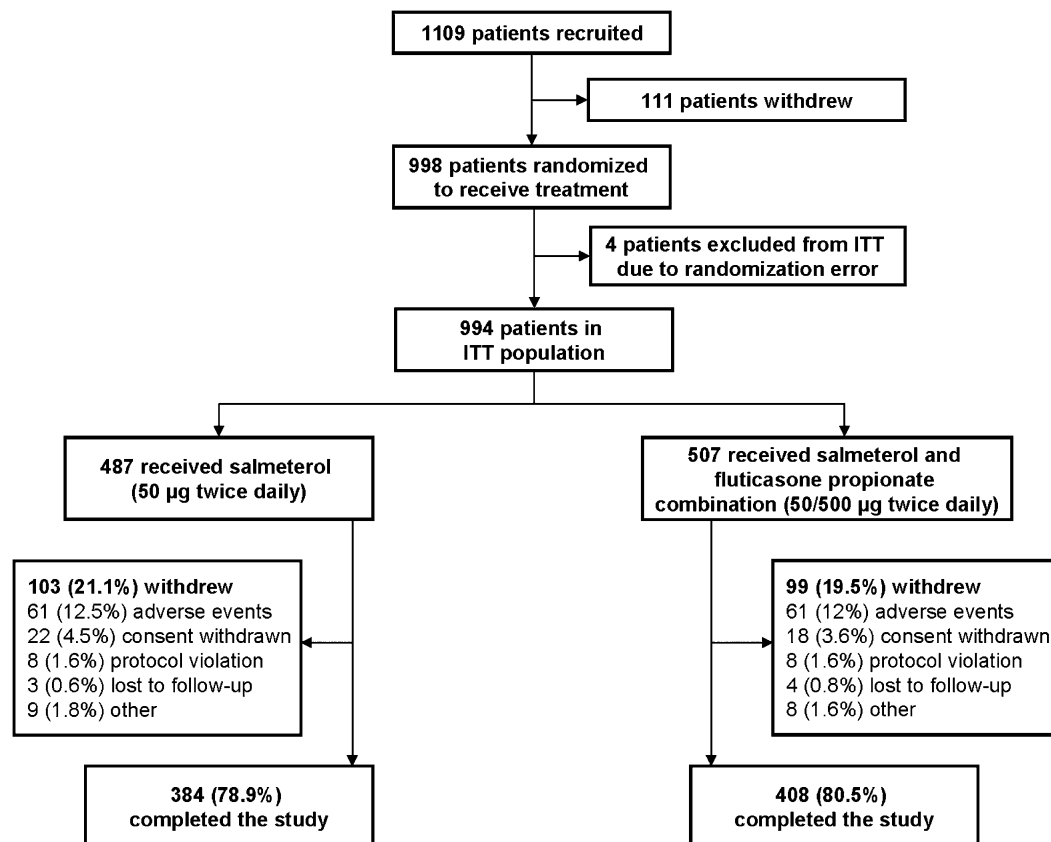


Figure 1. Trial profile illustrating the number of patients recruited, randomized, assigned to an intention-to-treat (ITT) population, and completing the study.

(95% CI, 1.21–1.79). Thus, patients in the SAL group had a 47% time-independent increased risk to suffer the first exacerbation. The number of patients needed-to-treat with SFC versus SAL to prevent one moderate/severe exacerbation per year was 2.08.

Lung Function

Both treatments showed a small increase in post-bronchodilator FEV₁ during the 44-wk period over baseline (SFC: 0.07 L; 95% CI, 0.037–0.103 L; SAL: 0.05 L; 95% CI, 0.016–0.084 L). The difference between the two treatment groups was not significantly different ($p = 0.63$). There was also a slight improvement in FVC over baseline with both therapies (SFC: 0.11 L; 95%

CI, 0.05–0.17 L; SAL: 0.10 L; 95% CI, 0.05–0.16; $p = 0.59$). Mean morning prebronchodilator PEF was improved from baseline in the two treatment groups. SFC significantly increased morning PEF by 18.0 L/min compared with 4.4 L/min (95% CI, 0.01–8.77 L/min) by SAL alone after 44 wk of treatment ($p < 0.0001$).

Health-related Quality of Life and Relief Medication

Baseline mean SGRQ total scores were 51.9 in the SFC group and 51.8 in the SAL group, respectively. Compared with baseline, the SGRQ total score was significantly improved in the SFC but not in the SAL group at Week 44 (–2.9 vs. –0.7, $p = 0.0126$, respectively). Thus, the mean differences between

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS

	SFC	SAL
Mean age, yr	63.8 (8.3)	64 (8.2)
Male, %	74	77.6
Current smokers, %	40.6	44.4
Mean pack-years	36.8	37
Mean number of moderate/severe exacerbations in previous year	2.91	2.87
Previous ICS use,* %	49.7	49.9
Previous LABA use,* %	53.6	55.4
Prebronchodilator FEV ₁ , L	1.13 (0.38)	1.12 (0.41)
Post-bronchodilator FEV ₁ , L	1.17 (0.32)	1.18 (0.31)
Post-bronchodilator FEV ₁ , % predicted	40.4 (8.9)	40.3 (8.5)
Reversibility, % predicted FEV ₁	6.5	7.4
FEV ₁ /FVC, %	57.6 (14)	57.8 (14.7)

Definition of abbreviations: ICS = inhaled corticosteroids; LABA = long-acting β_2 -agonist; SAL = salmeterol; SFC = salmeterol/fluticasone propionate.

All values are presented as absolute numbers or as mean $\pm$ SD.

* Includes combinations of ICS/LABA.

TABLE 2. NUMBER OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS AND TREATMENT

	SFC	SAL
Number of moderate and severe exacerbations*	334	464
Number of moderate exacerbations	297	413
Medication use to treat moderate exacerbations, no. of prescriptions		
Antibiotics and OCS	135	181
Antibiotics	88	73
OCS	58	139
Other	16	20
Number of severe exacerbations	37	51

Definition of abbreviations: OCS = oral corticosteroids; SAL = salmeterol; SFC = salmeterol/fluticasone propionate.

* Moderate exacerbations: worsening of chronic obstructive pulmonary disease (COPD) symptoms that required both a change of respiratory medication (increased dose of prescribed drug or addition of new drugs, i.e., antibiotics, mucolytics, systemic steroids, theophylline) and medical assistance. Severe exacerbations: deterioration in COPD resulting in hospitalization or emergency room treatment.

treatment groups at Week 44 were -2.3 for the SGRQ total score ($p = 0.0126$). The number of patients with a clinically meaningful improvement of SGRQ total score greater than -4 points was significantly higher in the SFC group (41.7 vs. 30%, $p = 0.0019$).

Further breakdown of the SGRQ into the individual domains showed the following differences in favor of SFC: symptoms score, -3.7 ($p = 0.0015$); impact score, -1.6 ($p = 0.139$); and activity score, -2.1 ($p = 0.0449$) (Figure 3).

It is likely that these results were driven by exacerbation rates, because patients that did not develop an exacerbation showed an improvement of the total SGRQ score in both treatment arms (mean change in total score, -3.5). In contrast, patients with exacerbations in both groups demonstrated a worsening of the total score (mean change in total score, $+1.0$). The mean difference in SGRQ scores between patients with versus patients without exacerbations was -4.5 (95% CI, -6.1 to -2.9 ; $p < 0.0001$).

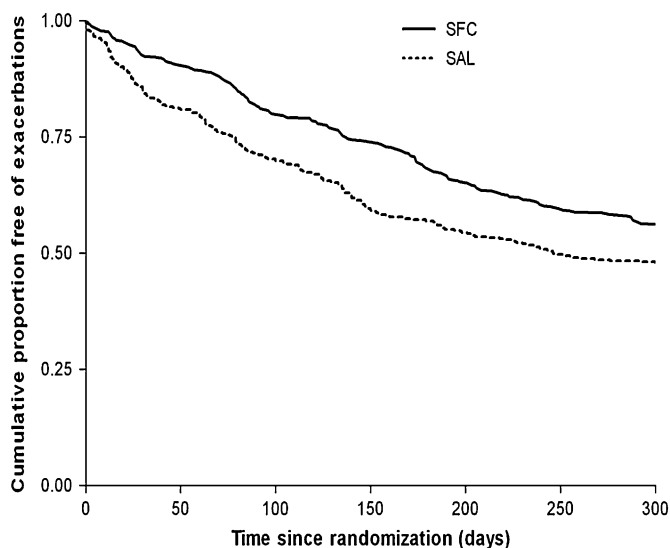


Figure 2. Kaplan-Meier plot of time to first moderate or severe chronic obstructive pulmonary disease exacerbation by treatment group.

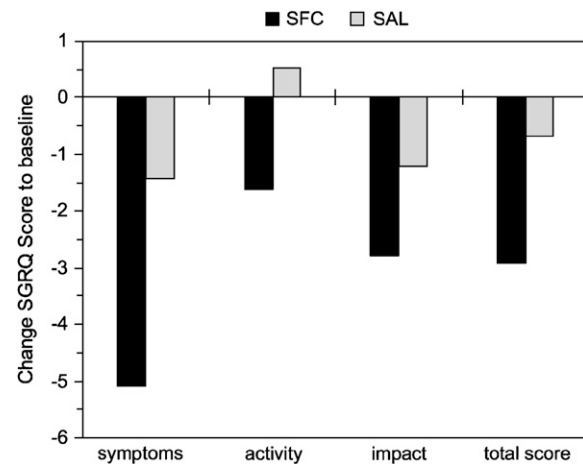


Figure 3. Changes in single St. George's Respiratory Questionnaire (SGRQ) quality-of-life domains and SGRQ total score from baseline over the study period. Baselines values were as follows: salmeterol (SAL; shaded columns): symptoms, 62.8; activity, 65.1; impact, 40.7; and total score: 51.8. Combination of SAL and fluticasone propionate (SFC; solid columns): symptoms, 63.6; activity, 64.8; impact, 40.8; and total score, 51.9. Improvements are indicated by a minus sign. $p < 0.05$ versus SAL.

Dyspnea as assessed by the MRC dyspnea score worsened slightly during the study period in SAL-treated patients, whereas it improved in individuals receiving SFC. The difference in MRC scores between treatment groups was statistically significant ($+0.14$ [SAL] vs. -0.02 [SFC], $p < 0.0001$). In parallel, the mean use of reliever medication decreased by 0.2 puffs per day in patients receiving SFC compared with baseline, whereas it increased slightly by 0.06 puffs in the SAL group ($p = 0.001$).

Safety

The number of adverse events (AEs) was similar in both treatment groups (SFC: 314 and 320 for SAL). Drug-related AEs were noted in 49 (9.7%) cases in the SFC group and 40 (8.2%) cases in the SAL group. Oropharyngeal candidiasis was the most frequent drug-related AE in the SFC group ($n = 8$). Withdrawals due to COPD exacerbations were lower in the SFC group (31 vs. 46 patients). Twenty-three cases of suspected pneumonia were observed in the SFC group and seven in the SAL group.

The rate of discontinuations due to other AEs was comparable between both treatment groups and the AE profile was similar in both groups. No treatment-associated patterns were detectable regarding the incidence or cause of death (SFC, $n = 7$ [1.4%], vs. SAL, $n = 9$ [1.9%]) or serious AEs (SFC, $n = 76$ [15%], vs. SAL, $n = 88$ [18.1%]).

DISCUSSION

Our study found a 35% reduction in moderate and severe exacerbations in the SFC treatment arm as compared with the SAL arm. A *post hoc* analysis of moderate plus severe exacerbations, as defined in several other studies by use of antibiotics and/or systemic steroids (14, 15, 18), showed no significant impact on these results (14, 15). SAL alone has previously been shown to effectively reduce the rate of exacerbations (12, 26). The additional reduction achieved with SFC in this study is therefore likely to be of clinical importance for patients with severe COPD.

Several large clinical trials have already demonstrated the efficacy of both LABAs and ICS treatment on exacerbations

(14, 15, 18). Thus, we designed the study without a placebo and FP monotherapy arm, but with sufficient statistical power to assess the clinically important and still unanswered question whether addition of FP to the therapy with SAL might elicit an additional benefit on frequency of exacerbations in a homogeneous cohort of patients with severe, frequently exacerbating COPD. The parallel group design with two therapeutic regimes is very similar to usual-care conditions and, if applied to study patients, it ensures a high external validity of the results. This study shows that there is an additive effect of FP on the rate of exacerbations over SAL alone, confirming a trend seen in the Trial of Inhaled Steroids and long-acting β_2 -Agonists (TRISTAN) study (14).

Recently, concerns have been raised about the appropriate statistical evaluation of exacerbation rates (27). In short, the statistical analysis has to account not only for the raw number of exacerbations but also for the treatment exposure of each patient, and for between-patient variation of exacerbation rates. Our study accounted *a priori* for differential dropout using Poisson regression with time in study as an offset variable. Even though we did not observe differential dropout in this study, the statistical methodology would have appropriately taken this into account.

Several mechanisms have been proposed to explain the ability of SAL monotherapy to reduce exacerbations, including sustained bronchodilatation (12) and improved mucociliary clearance (28), but these hypotheses remain to be proven.

It is now evident that COPD is a systemic and local inflammatory disease (29), and a multitude of inflammatory cells, including macrophages, CD8 and CD4 T lymphocytes, eosinophils, and neutrophils, are present in COPD from the very early stages and increase in numbers with disease severity (30). It has been shown that, in addition to eosinophils, FP also reduces the CD8:CD4 ratio in bronchial epithelium (31, 32), neutrophils in sputum (33), and systemic markers of inflammation (34). These results were just recently established for SFC as well, and a reduction of inflammatory markers may also be related to a reduction in exacerbations (35).

The number needed-to-treat with SFC versus SAL to prevent one moderate/severe exacerbation per year was 2.08. In comparison, 18 patients needed to be treated for 5 yr with antihypertensive drugs to prevent one cardiovascular event (36) and 52 patients for 6 yr with pravastatin to prevent one myocardial infarction (37).

Improvements in mean morning prebronchodilator PEF versus baseline are in line with other COPD studies in patients with so-called irreversible COPD (14, 15, 18), showing an increase of 18 L/min and 4.4 L/min in the SFC and SAL group, respectively. In contrast, FEV₁ and FVC showed only very small changes versus baseline because, as suggested by GOLD, we measured spirometry after bronchodilatation.

From the patients' perspective, health status is an outcome measure that may reflect potential benefits across a range of endpoints. Similar to other studies (14, 15, 18), in this trial SGQR total score improved significantly in the SFC group by -2.9 , and in the SAL group by -0.7 units compared with baseline. Neither the improvement, nor the difference between treatments, albeit statistically significant, reached the 4-unit difference of clinical relevance, although significantly more patients achieved a 4-unit difference in the SFC group. In analyzing patients according to their exacerbation status regardless of treatment allocation, individuals without exacerbations showed a significant and clinically meaningful improvement in total SGRQ score of -4 units, whereas patients with exacerbations worsened. Thus, health status changes are largely driven by exacerbations, supporting re-

sults of Donaldson and colleagues (38) and Spencer and Jones (39).

Both SFC and SAL therapies were equally well tolerated and the number of all reported adverse events was similar, including the number of serious adverse events. However, disparity was reported regarding seven cases of suspected pneumonia in the SAL group, whereas 23 cases with suspected pneumonia were observed in the SFC group. In this study, it was not mandatory to confirm a suspected pneumonia by chest X-ray. Thus, there remains a relevant uncertainty regarding the accuracy of the diagnosis. Only half of the events (14 and 4 in the SFC and SAL groups, respectively) were deemed as serious by the investigators, and none were considered to be related to study medication. Two cases of pneumonia (one in each group) were noted as a secondary cause of death. It is unclear if this increase in suspected pneumonia despite decreasing overall exacerbations is due to an increase in pneumonic infiltrates or merely a different clinical presentation of exacerbations under ICS treatment. It is worth mentioning that, in the SFC group, a higher proportion of antibiotics per exacerbation was deemed necessary by the investigators (67.7 vs. 54.7%). Clearly, more research is needed to investigate these issues.

Another clinical implication is as clear as it is simple: in contrast to recommendations in current German guidelines (40), only half of the recruited patients were either receiving LABAs and/or ICS before inclusion in the study. This might partially explain the reduction in the historic prestudy exacerbation rate from 2.8 to 1.4 under SAL treatment. A further potential explanation may be the beneficial effect of the inclusion of patients in controlled trials, as observed in many other studies. Nonetheless, many patients with severe COPD and repeated exacerbations are currently undertreated in Germany.

In conclusion, this study shows that the combination SFC has an additional effect on exacerbations that exceeds that of SAL. SFC can greatly reduce exacerbation frequency in a high-risk population of patients with severe COPD.

Conflict of Interest Statement: P.K. has been reimbursed by Altana, AstraZeneca, GlaxoSmithKline (GSK), Novartis, and Viatrix for attending several conferences. He has participated as a speaker in scientific meetings or courses organized and financed by various pharmaceutical companies [Altana, AstraZeneca (AZ), Berlin-Chemie, Boehringer-Ingelheim, Cefalon, GSK, Novartis, Pfizer] and served on advisory boards for the following companies: AZ, Boehringer-Ingelheim, GSK, Novartis, Pfizer. He has received aggregated honoraria of \$12,000 in 2005 from GSK and \$11,000 from Novartis. His group has received \$14,000, \$18,000, and \$15,000 in 2003, 2004, and 2005, respectively, from Altana, AZ, GSK, and Novartis as research grants for participating in several multicenter clinical trials. M.W. is an employee of GSK. T.G. is an employee of GSK. C.V. has given presentations in the last 3 years at industry symposia sponsored by Altana, AZ, Bayer, Boehringer-Ingelheim, GSK, Merck Darmstadt, Novartis, Pfizer, Sanofi-Aventis, and Talecris. He also served on advisory boards for Altana, AZ, Bayer, Boehringer-Ingelheim, GSK, Pfizer, and Sanofi-Aventis. In addition, his institution took part in clinical studies sponsored by Astra Zeneca, GSK, and Intermune. In 2005, aggregated honoraria and industry-sponsored grants comprised \$22,000 from Altana, \$50,000 from AZ, and \$30,000 from GSK.

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