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# Effect of Pharmacotherapy on Rate of Decline of Lung Function in COPD: Results from the TORCH Study

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## AT A GLANCE COMMENTARY

### Scientific Knowledge on the Subject

The decline in forced expiratory volume in one second ($FEV_1$) has been accepted as a key marker for progression of COPD. To date, smoking cessation is the only intervention that has conclusively been shown to alter the rate of decline in $FEV_1$.

### What This Study Adds to the Field

This is first study to show that pharmacotherapy with combined salmeterol 50μg plus fluticasone propionate 500μg, or either component alone can reduce the rate of decline of $FEV_1$ in patients with moderate-to-severe COPD, thus slowing disease progression.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

## Abstract

***Rationale*: Chronic obstructive pulmonary disease (COPD) is characterized by an accelerated decline in lung function. No drug has been shown conclusively to reduce this decline.**

***Objective*: In a post-hoc analysis of the TOwards a Revolution in COPD Health (TORCH) study we investigated the effects of combined salmeterol 50µg plus fluticasone propionate 500µg, either component alone or placebo, on the rate of post-bronchodilator forced expiratory volume in one second ($FEV_1$) decline in patients with moderate-to-severe COPD.**

***Methods*: Randomized, double-blind, placebo-controlled study conducted from September 2000 to November 2005 in 42 countries. Of 6112 patients from the efficacy population, 5343 were included in this analysis.**

***Measurements and main results*: Spirometry was measured every 24 weeks for 3years. There were 26,539 on-treatment observations. The adjusted rate of decline in $FEV_1$ was 55mL/year for placebo, 42mL for salmeterol, 42mL for fluticasone propionate and 39mL/year for salmeterol plus fluticasone propionate. Salmeterol plus fluticasone propionate reduced the rate of $FEV_1$ decline by 16mL/year compared with placebo (95% CI, 7 to 25; *P*<0.001). The difference was smaller for fluticasone propionate and salmeterol compared with placebo (13mL/year, 95% CI,**

**5 to 22; *P*=0.003). Rates of decline were similar among the active treatment arms. $FEV_1$ declined faster in current smokers and patients with a lower body mass index, and varied between world regions. Patients who exacerbated more frequently had a faster $FEV_1$ decline.**

***Conclusions*: Pharmacotherapy with salmeterol plus fluticasone propionate, or the components, reduces the rate of decline of $FEV_1$ in patients with moderate-to-severe COPD, thus slowing disease progression.**

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***This study (GSK Study Code SCO30003) has been registered at Clinicaltrials.gov, number NCT00268216.***

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a major cause of morbidity worldwide (1), is characterized by airflow obstruction, as determined by the ratio of the forced expiratory volume in one second ($FEV_1$) and forced vital capacity (FVC). Disease progression has been assessed using the rate of $FEV_1$ decline, which is greater than normal in COPD (2, 3). To date, smoking cessation is the only intervention that has conclusively been shown to alter the rate of decline in $FEV_1$ (4).

While the pathogenesis of COPD is complex, studies suggest that airway inflammation plays an important role in disease progression (3, 5, 6). The intensity of inflammation relates to the degree of airflow obstruction (5), and may result from oxidant-induced damage. However, neither the antioxidant drug N-acetyl cysteine nor the non-specific anti-inflammatory effects of inhaled corticosteroids have been shown to modify the rate of decline in $FEV_1$ (7–11). Meta-analyses of the inhaled corticosteroid (ICS) studies have yielded conflicting results (12–14). Salmeterol and other long-acting beta-agonists are highly selective bronchodilators that have been shown to improve lung function, dyspnea, and health status in relatively short-term studies (15, 16). However, their possible long-term effect on rate of decline in $FEV_1$ has never been evaluated. It has recently been shown that the administration of an ICS combined with a long-acting beta-agonist modifies the expression of inflammation in mucosal biopsies and sputum of patients with COPD (6), raising the possibility that this pharmacological combination could have an effect on the rate of decline of lung function.

The TOwards a Revolution in COPD Health (TORCH) study investigated the effect of salmeterol/fluticasone propionate (SFC) and either component alone compared with

placebo on mortality, as well as the impact on the rate of exacerbations, health-related quality of life, and post-bronchodilator $FEV_1$. The primary efficacy analysis has already been published (17). The original report concentrated on the effect of therapy on mortality as the primary outcome, and presented the mean effect on lung function over 3 years as a supportive analysis, without addressing the change in the rate of $FEV_1$ decline, a variable that has been accepted as a reasonable surrogate marker for disease progression.

Before treatment unblinding, we decided to test the hypothesis that pharmacotherapy would modify the rate of decline of post-bronchodilator $FEV_1$, compared with placebo. We also conducted an exploratory analysis of the factors that could affect $FEV_1$ rate of decline, since an association has been reported between frequency of exacerbation and an increased rate of decline of $FEV_1$ (18, 19). Some of these results have been previously reported in the form of an abstract (20).

## METHODS

### Design Overview

Details of the TORCH study design have been published elsewhere (17, 21). TORCH was a multi-center, randomized, double-blind, parallel-group, placebo-controlled study. All corticosteroids and inhaled long-acting bronchodilators were stopped before the run-in period, but other COPD medications were allowed. After a 2-week run-in period, eligible patients were stratified by smoking status and randomized to receive either SFC 50/500 µg, salmeterol (SAL) 50 µg, fluticasone propionate (FP) 500 µg or placebo

twice daily for 3 years via a Diskus®/Accuhaler™ inhaler (GlaxoSmithKline, UK) (see Online Data Supplement).

The primary efficacy endpoint of TORCH was all-cause mortality at 3 years. Other efficacy endpoints included rate of exacerbations (see Online Data Supplement**)**, health status, and post-bronchodilator spirometry every 24 weeks.

**Setting and Participants**

Details of the study settings and patient inclusion and exclusion criteria have been published previously (17). All patients gave informed consent and the study was approved by ethical review boards and conducted in accordance with the Declaration of Helsinki. For this analysis we included all patients with a baseline and at least one on-treatment $FEV_1$.

**Randomization and Interventions**

Full details of the randomization procedure have been reported previously (17, 21).

**Outcomes and Follow-up**

In this report, the primary outcome was the rate of post-bronchodilator $FEV_1$ decline. At visit 1 (start of the 2-week run-in period), the highest of three acceptable measurements of $FEV_1$ was recorded before, and 30 minutes after, inhalation of 400 µg albuterol as recommended by the ATS (22). Reversibility was calculated as a percentage of the predicted normal $FEV_1$ (23). Patients refrained from using short-acting bronchodilators for at least 6 hours, and long-acting $beta_2$ agonists (LABA) for at least 12 hours, prior to visit 1. At visit 2 (baseline) and every 24 weeks thereafter, post-bronchodilator

measurements of $FEV_1$ were obtained (prior to which subjects were not required to withhold their COPD medication).

Spirometers were regularly calibrated according to manufacturer recommendations and a calibration log was kept. Lung function data were reviewed centrally during the study and queried if values differed significantly in consecutive visits (criteria used for the query are published in the Online Data Supplement). After completion of the study, the variability of the spirometric values was assessed by analyzing the variance of individual regression slopes and comparing them to those obtained in the ISOLDE trial (11), in which spirometric measurements were the primary endpoint and were closely monitored.

**Statistical Analysis**

The study was powered on the primary endpoint of all-cause mortality, as described previously (17, 21), and was not formally powered for the analysis of rate of decline in $FEV_1$.

The effect of treatment on rate of decline of absolute $FEV_1$, percentage change in a year and as percentage of predicted $FEV_1$ was analyzed using a random coefficients model including terms for treatment, time on treatment in years, treatment by time interaction, and covariates of smoking status, gender, age, baseline $FEV_1$, region (see Table 2 footnote for countries included in each region), and body mass index (BMI). This methodology was the same as that used in other landmark studies, which assessed rate of decline in lung function in COPD (9–11). To derive the percentage change in a year, the logarithm of $FEV_1$ was analyzed. In order to eliminate immediate improvements, the decline was evaluated from 24 weeks onward (the time at which the first on-treatment

measurement was made). The effects of covariates on the rate of $FEV_1$ decline were investigated using this model as exploratory analyses, including the covariate by time interaction individually for smoking status, gender, age, baseline percentage predicted $FEV_1$, region, ethnic origin, BMI, previous exacerbation history, and baseline St George's Respiratory Questionnaire (SGRQ). We also tested whether the treatment effect on the rate of decline was consistent for subgroups by including a treatment-by-covariate-by-time interaction individually in this model.

A further analysis was performed by calculating individual patient slopes from the regression analysis of each subject's $FEV_1$ values and applying ANCOVA to these slopes. At least two on-treatment $FEV_1$ measurements were required for this analysis.

Additionally, we report exploratory summary statistics of individual patient slopes categorized by number of exacerbations reported during the study, and by whether subjects survived or died during the 3 years of the study. All analyses were performed on an intention-to-treat basis using SAS software version 8.2 (SAS Institute, Inc, Cary, North Carolina) on a unix platform. For the principal analyses, a threshold for statistical significance was set at 0.05. For the effect of covariates on the slopes, which were exploratory analyses, the threshold was set at 0.10.

**Role of the Funding Source**

Funding was provided by GlaxoSmithKline. The Steering Committee, comprising six academics and three representatives of the sponsor, developed the design and concept, approved the statistical plan, had full access to and interpreted the data, wrote the manuscript, and was responsible for decisions with regard to publication.

## RESULTS

### Patients

A total of 6112 patients comprised the efficacy population of TORCH. Of these, 5343 (87%) had at least one on-treatment $FEV_1$ and were included in the decline analysis (Figure 1). The characteristics of these patients at baseline are shown in Table 1. The number of patients was smaller in the placebo compared with the active treatment arms because more patients withdrew within the first 24 weeks from the placebo arm (17% in placebo compared with 12% in the SAL and FP arms, and 9% in the combination arm). During the study, 187 (3%) patients took tiotropium while on study medication (44 [3%] placebo, 62 [4%] SAL, 40 [3%] FP, and 41 [3%] SFC).

### Rate of Decline of $FEV_1$

A total of 26 539 on-treatment observations were available for the analysis. The maximum number of on-treatment measurements a patient could contribute to the estimation of the rate of $FEV_1$ decline was 6, and 64% of patients contributed this number. The average number of measurements was 5, with only 19% of patients having 3 or fewer, primarily due to early withdrawal or death. In the placebo arm, patients withdrawing before the end of the study had a faster rate of decline (76 mL/year) compared with those completing the trial (54 mL/year).

The rate of absolute decline of $FEV_1$ for each arm is summarized in Table 2 and that of % predicted $FEV_1$ is shown in Table 3. Figure 2 shows the adjusted means and standard errors at each visit and fitted lines from the random coefficients model of $FEV_1$. The rate of decline of $FEV_1$ was slowest in patients on SFC and fastest in those

randomized to the placebo arm. From week 24 onwards, the adjusted rate of decline in $FEV_1$ was 39 mL/year for SFC, 42 mL/year for both SAL and FP and 55 mL/year for placebo, a reduction of 16 mL/year with SFC compared with placebo ($P < 0.001$), and 13 mL versus placebo for both FP and SAL ($P = 0.003$) (Figure 2). These treatment differences remained when the values were expressed as % predicted $FEV_1$ (Table 3) or as % of the baseline value (where the rate of decline was 3%/year for SFC, 4%/year for SAL and FP and 5%/year for placebo). In addition, the analysis of individual regression slopes produced similar findings. The standard deviations of individual regression slopes were similar in all treatment groups ranging from 160 to 180 mL/year. These values are similar to those observed in the ISOLDE trial (166 mL/year for FP and 187 mL/year for placebo).

**Effect of Covariates on $FEV_1$ Slopes of Rate of Decline**

A slower rate of decline in absolute ml/year was observed in former smokers, females, patients 65 years and older, and those with $FEV_1 < 30\%$ predicted. Patients with a BMI $\geq 25$ showed a slower decline in lung function (Table 4).The rate of decline in patients from the Asia Pacific and Eastern Europe regions was slower than that of patients from the other regional groups. These relationships were preserved when the rate of $FEV_1$ decline was expressed as a percentage change in a year for all of these covariates except gender, where there was no difference, and in patients with $FEV_1 < 30\%$ predicted (see Online Table 1). In this group of patients, the $FEV_1$ declined by 28 mL/year, compared to 47mL/year for the other patients (Table 4), but when this change was expressed as a percentage of baseline (4%/year) it was within the range of

the other groups (4.4%/year and 3.3%/year for 30–49% and ≥ 50% predicted $FEV_1$ respectively, Online Table 1).

The effect of treatment on $FEV_1$ decline was similar irrespective of smoking status, gender, age, baseline $FEV_1$, region of the world, ethnicity, BMI, previous exacerbations, and baseline SGRQ. The differences between placebo and the treatment arms were unaffected by whether the patients had taken ICS or LABA in the 12 months prior to the study (see Online Tables 2 and 3).

We observed no association between previous exacerbation history based on patient recall and $FEV_1$ decline (Table 4). However, there appeared to be an association between number of exacerbations documented during the duration of the study and the rate of decline of $FEV_1$ (see Table 5), with higher rates of decline being evident in patients experiencing more exacerbations.

## DISCUSSION

COPD is characterized by airflow obstruction, which is usually progressive (2, 3), and hence, the measured decline in $FEV_1$ has been accepted as a key marker for disease progression and a target for therapeutic trials. The longitudinal analysis of lung function from the TORCH data set presented here is the first to identify significant reductions in $FEV_1$ decline in those patients receiving active treatment.

The normal rate of $FEV_1$ decline in healthy subjects is approximately 30 mL/year (24, 25). The modeled rate of decline in post-bronchodilator $FEV_1$ in patients receiving placebo in TORCH was 55 mL per year; similar to that seen in the Lung Health Study 1 (–52 mL) (26), Lung Health Study 2 (–47 mL) (10), BRONCUS (–54 mL) (7), and

ISOLDE studies (–59 mL) (11), and slightly lower than in EUROSCOP (–69 mL) (9), where the baseline $FEV_1$ was higher and all randomized subjects were current smokers. We identified a significantly lower rate of decline in $FEV_1$ (by 13–16 mL per year) in those patients receiving active therapy. Rate of decline was similar among the three active treatment arms of the study. Although treatment did not abolish the accelerated decline in lung function, it did ameliorate it substantially, decreasing the excess $FEV_1$ decline attributable to historically obtained values in patients with COPD (27).

All three treatments showed improvements in post-bronchodilator $FEV_1$ relative to placebo at each visit, but the mechanism responsible for the effect on rate of decline is not clear, as all treatments have potentially significant non-bronchodilator effects (6, 28, 29). Whether the maintenance of airway patency and reduction in hyperinflation, improvements in mucociliary clearance, or decreases in airway inflammation contribute singly or together to produce the observed functional change cannot be determined in TORCH, and further mechanistic studies are needed. The results of the forthcoming UPLIFT trial, where a long-acting bronchodilator drug tiotropium is compared to placebo with lung function decline as its primary outcome, may help clarify mechanisms, since tiotropium is a bronchodilator without primary anti-inflammatory action (30, 31).

In the TORCH trial, there were significant reductions in exacerbations in all treatment arms, with the greatest reductions observed with the SFC combination (17). This is consistent with our data, in which treatment decreased the rate of decline in $FEV_1$ and this effect was greatest in patients receiving SFC. There was an association between exacerbation frequency documented during the study and $FEV_1$ decline, supporting previous observations (18, 19) (Table 5). However, in patients who had no exacerbations during the study, the rate of decline was significantly faster in the placebo

group compared with active treatments (56 mL/year vs. 27–31 mL/year), which suggests that the effect of treatment on exacerbations was not the sole mechanism responsible for the reduced rate of decline with active treatment.

Our results confirm those of previous studies, which have shown that smoking status, age and baseline percent predicted $FEV_1$ affect the rate of lung function decline (32). However, our data extend these observations in the Lung Health Study population to patients with more severe COPD. Additionally, we have identified two novel factors associated with $FEV_1$ decline, specifically BMI and region of origin, although these could also be due to differences in height. Together with already known variables such as baseline lung function, smoking status, and exacerbation frequency they may help explain between-subject differences in $FEV_1$ decline. Lung function declined least (35 mL/year) in patients with a BMI of 29 or higher, was higher in patients with BMI between 25 and 29 (42 mL/year) but greatest in patients with a baseline BMI below 25 (51 mL/year). This suggests an important association between systemic consequences of the disease and disease progression in the lungs (33, 34), but does not necessarily indicate causality. Interestingly, patients from the Asia Pacific and Eastern Europe regions, as well as patients of Asian and American Hispanic ethnic origins had a slower rate of decline compared with Western Europeans and North Americans even when expressed as percentage change in $FEV_1$. This may be related to the fact that patients in Asia Pacific and Eastern Europe had lower mean $FEV_1$ absolute and % predicted at baseline (Online Table 4), thus providing less capacity for $FEV_1$ to decline over time. Alternatively, other factors yet unexplored such as genetic, socio-economic, or environmental differences may be important.

Female patients lost $FEV_1$ at a slower rate than men, a similar result to that reported in the long-term follow-up of the Lung Health Study (4). Women who quit smoking in that study lost an average of 22 mL/year compared with men who lost an average of 30 mL/year. In the smokers, the values were 54 and 66 mL/year, respectively. In this TORCH dataset, women lost 39 mL/year, whereas men lost 47 mL/year irrespective of smoking status. This difference disappeared when the rate of decline was expressed as a percentage change in a year, with women losing 4.2% versus 3.9% per year for men. These results suggest that the gender difference was related to airway size rather than intrinsic biologic differences in the progression of COPD.

There were some limitations to our study. As in other long-term COPD trials (35, 36), many patients failed to complete the study, with significantly more withdrawing from the placebo limb. Moreover, those withdrawing showed more rapid deterioration in lung function, a finding noted by others (37). This preferential dropout in the placebo arm of those patients whose function worsens more rapidly (evidenced by the greater decline in patients who withdrew early compared with those who completed) actually minimizes the differences observed in rate of $FEV_1$ decline. In addition, the random coefficients model (11) gives most weight to patients who complete the trial, and hence, the differences in lung function decline we report may be conservative estimates of the true treatment effect. We are confident that our principal findings are reliable, since they were consistent whether expressed in mL/year or as percentage change per year. It has been suggested that changing the usual therapy of the COPD patient can influence the results of interventional studies (38). This was not the case in TORCH where prior therapy with

ICS or LABA was unrelated to the beneficial effect of therapy on the rate of $FEV_1$ decline.

Another limitation of the study was that the $FEV_1$ was not a primary outcome in this mortality trial. However, post-bronchodilator lung function was extensively measured and the more than 26 000 spirometric assessments obtained over the 3 years of the study provided a unique opportunity to evaluate how lung function evolved in patients randomized to different treatments.

A theoretical limitation was the less rigorous monitoring of spirometry compared with other trials primarily evaluating lung function decline. However, the standard deviation of our $FEV_1$ measurements was comparable to that in previous studies, where spirometry was performed more frequently and using more rigorous quality control (10, 11). These data suggest that measuring post-bronchodilator spirometry in a larger number of patients, as in TORCH, compensated for any inherent between-tests variability in $FEV_1$

In summary, we have shown for the first time that pharmacologic therapy slows the decline in lung function in COPD patients. Given the progressive nature of COPD, halving of the excess decline in $FEV_1$ is likely to be clinically important in patients such as those who participated in TORCH.

## Contributors

The Steering Committee, comprising six academics and three representatives of the sponsor, developed the design and concept, approved the statistical plan, had full access to and interpreted the data, wrote the manuscript, and was responsible for decisions with regard to publication. B. Celli led the writing of this paper. N.E. Thomas and J.A. Anderson performed statistical analyses. The academic authors vouch for the veracity and completeness of the data and the data analyses. The study sponsor did not place any restrictions with regard to statements made in the final paper.


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## REFERENCES


1. Chapman KR, Mannino DM, Soriano JB, Vermeire PA, Buist AS, Thun MJ, Connell C, Jemal A, Lee TA, Miravitlles M, Aldington S and Beasley R. Epidemiology and costs of chronic obstructive pulmonary disease. *Eur Respir J* 2006;27:188–207.
2. 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;23:932–946.
3. GOLD 2007. Global Initiative for Chronic Obstructive Lung Disease. Updated 2007. Available from: www.goldcopd.com. Last accessed 28 March 2008.
4. Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. *Am J Respir Crit Care Med* 2002;166:675–679.
5. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, Cherniack RM, Rogers RM, Sciurba FC, Coxson HO, Paré PD. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:2645–2653.
6. Barnes NC, Qiu YS, Pavord ID, Parker D, Davis PA, Zhu J, Johnson M, Thomson NC, Jeffery PK on behalf of the SCO30005 Study Group. Anti-inflammatory effects of salmeterol/fluticasone propionate in chronic obstructive lung disease. *Am J Respir Crit Care Med* 2006;173:736–743.
7. Decramer M, Rutten-van Molken M, Dekhuijzen PN, Troosters T, van Herwaarden C, Pellegrino R, van Schayck C, Olivieri D, Del Donno M, De backer W. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet* 2005;365:1552–1560.

8. Vestbo J, Sørensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999;353:1819–1823.
9. Pauwels RA, Löfdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, Ohlsson SV, for The European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. *N Engl J Med* 1999;340:1948–1953.
10. Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000;343:1902–1909.
11. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000;320:1297–1303.
12. Sutherland ER, Allmers H, Ayas NT, Venn AJ, Martin RJ. Inhaled corticosteroids reduce the progression of airflow limitation in chronic obstructive pulmonary disease: a meta-analysis. *Thorax* 2003;58:937–941.
13. Soriano JB, Sin DD, Zhang X, Camp PG, Anderson JA, Anthonisen NR, Buist AS, Burge PS, Calverley PM, Connett JE, Petersson S, Postma DS, Szafranski W, Vestbo J. A pooled analysis of FEV1 decline in COPD patients randomised to inhaled corticosteroids or placebo. *Chest* 2007;131:682–689.

14. Highland KB, Strange C, Heffner JE. Long-term effects of inhaled corticosteroids on FEV1 in patients with chronic obstructive pulmonary disease. A meta-analysis. *Ann Intern Med* 2003;138:969–973.
15. Stockley RA, Chopra N, Rice L. Addition of salmeterol to existing treatment in patients with COPD: a 12 month study. *Thorax* 2006;61:122–128.
16. Stockley RA, Whitehead PJ, Williams MK. Improved outcomes in patients with chronic obstructive pulmonary disease treated with salmeterol compared with placebo/usual therapy: results of a meta-analysis. *Respir Res* [serial online] 2006; vol 7. Available from: http://respiratory-research.com/content/7/1/147.
17. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J, for the TORCH investigators. Efficacy of salmeterol and fluticasone propionate on mortality in chronic obstructive pulmonary disease: the TORCH survival trial. *N Engl J Med* 2007;356:775–789.
18. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;57:847–852.
19. Kanner RE, Anthonisen NR, Connett JE. Lower respiratory illnesses promote FEV1 decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease: results from the Lung Health Study. *Am J Respir Crit Care Med* 2001;164:358–364.
20. Celli B, Ferguson GT, Anderson JA, Jenkins CR, Jones PW, Vestbo J, Yates JC, Calverley PMA. Salmeterol/fluticasone propionate (SFC) improves lung function and reduces the rate of decline over three years in the TORCH survival study. *Am J Respir Crit Care Med* 2007;175 (abstracts issue):A763.

21. Vestbo J, TORCH Study Group. The TORCH (TOwards a Revolution in COPD Health) survival study protocol. *Eur Respir J* 2004;24:206–210.
22. American Thoracic Society. Standardization of spirometry – 1994 update. *Am J Respir Crit Care Med* 1995;152:1107–1136.
23. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:5–40.
24. James AL, Palmer LJ, Kicic E, Maxwell PS, Lagan SE, Ryan GF, Musk AW. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. *Am J Respir Crit Care Med* 2005;171:109–114.
25. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998 22;339:1194–1200.
26. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA Jr, Enright PL, Kanner RE, O'Hara P, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA* 1994;272:1497–1505.
27. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977;1:1645–1648.
28. Johnson M, Rennard S. Alternative mechanisms for long-acting beta(2)-adrenergic agonists in COPD. *Chest* 2001;120:258–270.
29. Calverley P. Are inhaled corticosteroids systemic therapy for chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 2004;170:721–722.

30. Decramer M, Celli B, Tashkin DP, Pauwels RA, Burkhart D, Cassino C, Kesten S. Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: the Uplift Trial. *COPD* 2004;1:303–312.
31. Powrie DJ, Wilkinson TMA, Donaldson GC, Jones P, Scrine K, Viel K, Kesten S, Wedzicha JA. Effect of tiotropium on sputum and serum inflammatory markers and exacerbations in COPD. *Eur Respir J* 2007;30:472–478.
32. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. *Am J Respir Crit Care Med* 2000;161:381–390.
33. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005–1012.
34. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1791–1797.
35. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, Anderson J, Maden C, TRial of Inhaled STeroids ANd long-acting beta2 agonists study group. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;361:449–456.
36. Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, Peterson S, Olsson H. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003;21:74–81.

37. Calverley PM, Spencer S, Willits L, Burge PS, Jones PW. Withdrawal from treatment as an outcome in the ISOLDE study of COPD. *Chest* 2003;124:1350–1356.
38. Suissa S, Ernst P, Vandemheen KL, Aaron SD. Methodological issues in therapeutic trials of chronic obstructive pulmonary disease. *Eur Respir J* 2008;[Epub ahead of print].

## FIGURE LEGENDS

***Figure 1.*** Modified patient disposition diagram and analyses populations, based on full CONSORT diagram published in Calverley et al NEJM 2007 (17).

FP = fluticasone propionate; SAL = salmeterol; SFC = salmeterol/fluticasone propionate combination.

***Figure 2.*** Adjusted means at each visit and rate of decline (mL/year) in post-bronchodilator $FEV_1$ by treatment (random coefficients model).

The slope over time was calculated from week 24 to week 156, as indicated by the arrows, and was significantly steeper in the patients receiving placebo versus those receiving active therapies. FP = fluticasone propionate; SAL = salmeterol; SFC = salmeterol/fluticasone propionate combination.

*$p \leq 0.003$ compared with placebo. Note: Vertical bars represent standard errors of the adjusted means at each visit. The number of patients at each clinic visit with $FEV_1$ measurements is shown below the graph.

**TABLE 1. BASELINE* CHARACTERISTICS OF SUBJECTS WITH AT LEAST ONE ON-TREATMENT $FEV_1$, INCLUDED IN THE ANALYSIS OF $FEV_1$ DECLINE.**

| Characteristic | Placebo (*n* = 1261) | SAL (*n* = 1334) | FP (*n* = 1356) | SFC (*n* = 1392) |
|---|---|---|---|---|
| Mean age (SD), years | 64.8 (8.2) | 64.9 (8.2) | 64.9 (8.4) | 64.9 (8.3) |
| Male, n (%) | 976 (77) | 1029 (77) | 1026 (76) | 1049 (75) |
| Mean body mass index (SD), $kg/m^2$ | 25.5 (5.2) | 25.4 (5.2) | 25.3 (5.0) | 25.4 (5.3) |
| Current smoker, n (%) | 563 (45) | 600 (45) | 596 (44) | 601 (43) |
| Baseline post-bronchodilator $FEV_1$ (SD), mL | 1257 (444) | 1231 (431) | 1233 (437) | 1236 (455) |
| % predicted post-bronchodilator FEV, (SD) mL | 45.0 (13.0) | 44.3 (13.3) | 44.8 (13.3) | 44.7 (13.4) |
| Region, n (%) | | | | |
| USA | 271 (21) | 290 (22) | 299 (22) | 312 (22) |
| Asia Pacific | 170 (13) | 175 (13) | 177 (13) | 175 (13) |
| Eastern Europe | 257 (20) | 270 (20) | 270 (20) | 273 (20) |
| Western Europe | 387 (31) | 410 (31) | 412 (30) | 433 (31) |
| Other | 176 (14) | 189 (14) | 198 (15) | 199 (14) |

*Baseline was at randomization visit.

*Definition of abbreviations*: *CI* = confidence interval; $FEV_1$ = forced expiratory volume in 1 second; FP = fluticasone propionate; SAL = salmeterol; SD = standard deviation; SFC = salmeterol/fluticasone propionate combination.

**TABLE 2. ADJUSTED* YEARLY RATE OF DECLINE IN $FEV_1$ BY TREATMENT GROUP**

| | **Placebo (*n* = 1261)** | **SAL (*n* = 1334)** | **FP (*n* = 1356)** | **SFC (*n* = 1392)** |
|---|---|---|---|---|
| Adjusted rate of decline (SE), mL/year | –55.3 (3.2) | –42.3 (3.1) | –42.3 (3.1) | –39.0 (3.0) |
| Active treatment minus placebo (SE), mL/year | – | 13.0 (4.4) | 13.0 (4.4) | 16.3 (4.4) |
| 95% CI | – | 4.3, 21.7 | 4.3, 21.7 | 7.7, 24.9 |
| *P* value | – | 0.003 | 0.003 | < 0.001 |
| SFC minus components (SE), mL/year | – | 3.3 (4.3) | 3.3 (4.3) | – |
| 95% CI | – | –5.1, 11.7 | –5.1, 11.6 | – |
| *P* value | – | 0.441 | 0.445 | – |

*Random coefficients model including smoking status, gender, age, baseline $FEV_1$, region, body mass index (BMI), treatment, time and treatment by time.

*Definition of abbreviations*: CI = confidence interval; $FEV_1$ = forced expiratory volume in 1 second; FP = fluticasone propionate; SAL = salmeterol; SE = standard error; SFC = salmeterol/fluticasone propionate combination.

**TABLE 3. ADJUSTED* YEARLY RATE OF DECLINE IN %PREDICTED $FEV_1$ BY TREATMENT GROUP**

| | **Placebo (*n* = 1261)** | **SAL (*n* = 1334)** | **FP (*n* = 1356)** | **SFC (*n* = 1392)** |
|---|---|---|---|---|
| Adjusted rate of decline (SE), %/year | –1.5 (0.1) | –1.0 (0.1) | –1.1 (0.1) | –0.9 (0.1) |
| Active treatment minus placebo (SE), %/year | – | 0.5 (0.2) | 0.4 (0.2) | 0.6 (0.2) |
| 95% CI | – | 0.2, 0.8 | 0.1, 0.8 | 0.3, 0.9 |
| *P* value | – | 0.002 | 0.006 | < 0.001 |
| SFC minus components (SE),%/year | – | 0.1 (0.2) | 0.1 (0.2) | – |
| 95% CI | – | –0.2, 0.4 | –0.2, 0.4 | – |
| *P* value | – | 0.627 | 0.401 | – |

*Random coefficients model including smoking status, gender, age, baseline %predicted $FEV_1$, region, body mass index (BMI), treatment, time and treatment by time.

*Definition of abbreviations*: CI = confidence interval; $FEV_1$ = forced expiratory volume in 1 second; FP = fluticasone propionate; SAL = salmeterol; SE = standard error; SFC = salmeterol/fluticasone propionate combination.

**TABLE 4. EFFECT OF BASELINE COVARIATES ON $FEV_1$ SLOPES (ML/YEAR)***

| | Number of subjects in analysis | Baseline mean $FEV_1$ (SD), mL | Adjusted rate of $FEV_1$ decline (SE), mL/year | Effect of covariates on slopes |
|---|---|---|---|---|
| Smoking status | | | | $P < 0.001$ |
| Current (n = 2630) | 2360 | 1300 (457) | –55.0 (2.3) | |
| Former (n = 3482) | 2983 | 1191 (424) | –36.6 (2.1) | |
| Gender | | | | $P = 0.027$ |
| Female (n = 1481) | 1263 | 1019 (339) | –38.5 (3.2) | |
| Male (n = 4631) | 4080 | 1307 (448) | –46.6 (1.8) | |
| Age | | | | $P < 0.001$ |
| < 55 (n = 701) | 633 | 1473 (542) | –51.7 (4.3) | |
| 55–64 (n = 1972) | 1746 | 1284 (455) | –51.3 (2.6) | |
| 65–74 (n = 2670) | 2323 | 1172 (391) | –39.5 (2.4) | |
| ≥ 75 (n = 769) | 641 | 1125 (360) | –36.7 (4.7) | |
| % predicted $FEV_1$ | | | | $P < 0.001$ |
| < 30 (n = 937) | 778 | 711 (160) | –28.4 (4.3) | |
| 30–49 (n = 3019) | 2630 | 1114 (264) | –47.2 (2.2) | |
| ≥ 50 (n = 2156) | 1935 | 1620 (395) | –47.0 (2.5) | |
| Region | | | | $P < 0.001$ |
| USA (n = 1388) | 1172 | 1205 (451) | –49.4 (3.4) | |

| | | | | |
|---|---|---|---|---|
| Asia Pacific (n = 758) | 697 | 1045 (400) | –30.7 (4.2) | |
| Eastern Europe (n = 1154) | 1070 | 1341 (435) | –38.2 (3.3) | |
| Western Europe (n = 1908) | 1642 | 1307 (423) | –50.9 (2.8) | |
| Other (n = 904) | 762 | 1178 (441) | –48.4 (4.2) | |
| Ethnic Origin | | | | $P < 0.001$ |
| White (n = 5006) | 4338 | 1278 (439) | –48.1 (1.7) | |
| Black (n = 95) | 83 | 1139 (429) | –43.4 (13.1) | |
| Asian (n = 769) | 705 | 1046 (400) | –30.6 (4.2) | |
| American Hispanic (n = 193) | 173 | 1107 (468) | –22.4 (8.4) | |
| Other (n = 49) | 44 | 1121 (333) | –46.8 (17.4) | |
| BMI | | | | $P < 0.001$ |
| < 20 (n = 824) | 719 | 1024 (393) | –51.1 (4.4) | |
| 20 to < 25 (n = 2301) | 2003 | 1195 (427) | –50.5 (2.5) | |
| 25 to < 29 (n = 1642) | 1424 | 1316 (440) | –42.1 (2.9) | |
| ≥ 29 (n = 1345) | 1197 | 1351 (358) | –35.1 (3.2) | |
| Exacerbations in the year prior to study | | | | $P = 0.800$ |
| 0 (n = 2626) | 2314 | 1282 (439) | –45.8 (2.3) | |
| 1 (n = 1513) | 1340 | 1244 (447) | –44.5 (3.1) | |
| ≥ 2 (n = 1973) | 1689 | 1176 (435) | –43.4 (2.8) | |
| Baseline SGRQ Total Score | | | | $P = 0.122$ |

| | | | |
|---|---|---|---|
| < 38 (n = 1427) | 1140 | 1381 (431) | –43.0 (3.3) |
| 38 to < 50 (n = 1276) | 992 | 1251 (418) | –42.0 (3.6) |
| 50 to < 62 (n = 1135) | 964 | 1180 (430) | –53.0 (3.7) |
| ≥ 62 (n = 1120) | 966 | 1144 (426) | –47.5 (3.9) |

*Random coefficients model including smoking status, gender, age, baseline $FEV_1$, region, body mass index (BMI), prior exacerbations, treatment, time and treatment by time, and covariate by time (the term for covariate by time was added one at a time to the multivariate model including all the covariates).

*Definition of abbreviations*: $FEV_1$ = forced expiratory volume in 1 second; SD = standard deviation; SE = standard error.

**TABLE 5. SUMMARY OF INDIVIDUAL $FEV_1$ REGRESSION SLOPES BY EXACERBATION RATE**

| | Placebo (*n* = 1137) | | | SAL (*n* = 1232) | | | FP 500 (*n* = 1242) | | | SFC (*n* = 1292) | | | Total (*n* = 4903) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean Slope | SD | n | Mean slope | SD | n | Mean Slope | SD | n | Mean Slope | SD | n | Mean Slope | SD |
| **Moderate/severe exacerbation (rate per annum)** | | | | | | | | | | | | | | | |
| 0 | 294 | –55.6 | 184.7 | 341 | –29.3 | 192.9 | 309 | –30.7 | 208.2 | 362 | –26.9 | 225.4 | 1306 | –34.9 | 204.4 |
| > 0 to 1.0 | 421 | –59.1 | 144.9 | 475 | –43.2 | 128.5 | 467 | –47.8 | 122.7 | 499 | –42.2 | 135.4 | 1862 | –47.7 | 132.9 |
| > 1.0 | 422 | –64.2 | 213.8 | 416 | –55.3 | 164.7 | 466 | –52.6 | 155.4 | 431 | –58.8 | 170.2 | 1735 | –57.6 | 176.8 |

## *FIGURES*

### *Figure 1.*

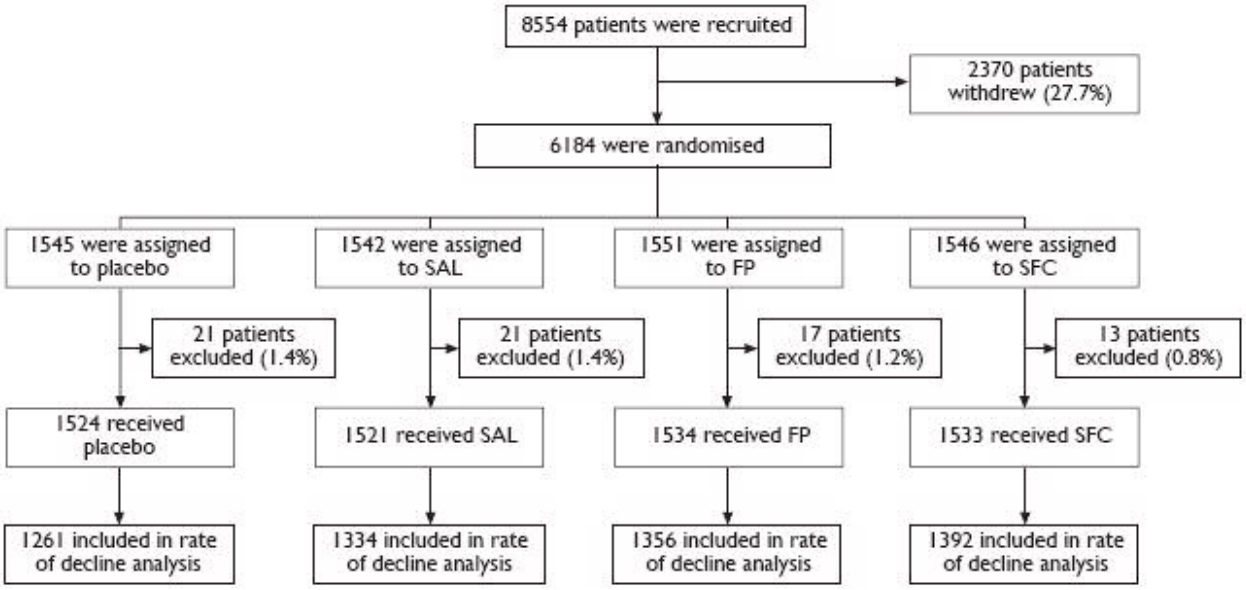
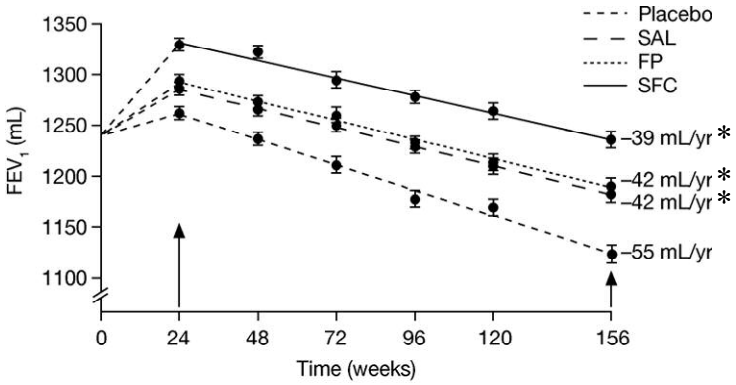


***Figure 2.***




No. of patients

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 1261 | 1248 | 1128 | 1049 | 979 | 906 | 819 |
| SAL | 1334 | 1317 | 1218 | 1127 | 1054 | 1012 | 934 |
| FP | 1356 | 1346 | 1230 | 1157 | 1078 | 1006 | 908 |
| SFC | 1392 | 1375 | 1281 | 1180 | 1139 | 1073 | 975 |

# Effect of Pharmacotherapy on Rate of Decline of Lung Function in COPD: Results from the TORCH Study

**Bartolome R. Celli, Nicola E. Thomas, Julie A. Anderson, Gary T. Ferguson, Christine Jenkins, Paul W. Jones, Jørgen Vestbo, Katharine Knobil, Julie C Yates, Peter M.A. Calverley**

**ONLINE DATA SUPPLEMENT**

## ONLINE DATA SUPPLEMENT

### Randomization Procedures

After a 2-week run-in period, eligible patients were randomly assigned, in permuted blocks with stratification according to country and smoking status generated by the sponsor, assigned by central telephone system administered by Clinphone, to treatment with salmeterol 50 µg, fluticasone propionate 500 µg, salmeterol/fluticasone propionate 50/500 µg or placebo all twice daily.

### Exacerbation Definition and Measurement

An exacerbation was defined as an episode requiring the administration of antibiotics and/or corticosteroids and/or hospitalization. Patients were asked about such episodes in the year before study entry (referred to as exacerbation history) and were contacted every 3 months while they remained in the study to record new events.

### Methods of Quality Control for Spirometry

During the study, data quality was monitored continually. Subjects whose $FEV_1$ profiles met one or more of the following criteria were flagged, reviewed and followed-up with the sites to see if data entry errors had been made. These criteria were introduced and implemented before unblinding of treatment allocation

- Within subject standard deviation (SD) > 800 mL for post bronchodilator $FEV_1$ values including visits prior to treatment start
- Within subject SD > 500 mL for on-treatment post bronchodilator $FEV_1$ values
- Individual rate of decline > 750 mL/year in either direction

- Change from baseline > 1 L at any visit
- Percentage increase/decrease between consecutive visits greater than expected (60% change if previous FEV value < 1 L; 40% change if previous FEV value ≥ 1 L to < 1.5 L; 40% change if previous FEV value ≥ 1.5 L to < 2 L; 0% change if previous FEV value > 2 L).

These criteria were not used to eliminate data, but to identify data that required checking.

**ONLINE TABLE 1. EFFECT OF BASELINE COVARIATES ON $FEV_1$ SLOPES, EXPRESSED AS PERCENTAGE RATE OF DECLINE PER YEAR***

| | Number of subjects in analysis | Baseline mean $FEV_1$ (SD), mL | Adjusted % rate of $FEV_1$ decline, %/year | Effect of covariates on slopes |
|---|---|---|---|---|
| Smoking status | | | | $P < 0.001$ |
| Current (n = 2630) | 2360 | 1300 (457) | –4.6 | |
| Former (n = 3482) | 2983 | 1191 (424) | –3.5 | |
| Gender | | | | $P = 0.275$ |
| Female (n = 1481) | 1263 | 1019 (339) | –4.2 | |
| Male (n = 4631) | 4080 | 1307 (448) | –3.9 | |
| Age | | | | $P = 0.013$ |
| < 55 (n = 701) | 633 | 1473 (542) | –4.3 | |
| 55–64 (n = 1972) | 1746 | 1284 (455) | –4.3 | |
| 65–74 (n = 2670) | 2323 | 1172 (391) | –3.6 | |
| ≥ 75 (n = 769) | 641 | 1125 (360) | –3.6 | |
| Percentage predicted $FEV_1$ | | | | $P < 0.001$ |
| < 30 (n = 937) | 778 | 711 (160) | –4.0 | |
| 30–49 (n = 3019) | 2630 | 1114 (264) | –4.4 | |
| ≥ 50 (n = 2156) | 1935 | 1620 (395) | –3.3 | |
| Region | | | | $P < 0.001$ |

| | | | | |
|---|---|---|---|---|
| USA (n = 1388) | 1172 | 1205 (451) | –4.6 | |
| Asia Pacific (n = 758) | 697 | 1045 (400) | –3.4 | |
| Eastern Europe (n = 1154) | 1070 | 1341 (435) | –3.2 | |
| Western Europe (n = 1908) | 1642 | 1307 (423) | –4.1 | |
| Other (n = 904) | 762 | 1178 (441) | –4.4 | |
| Ethnic Origin | | | | $P = 0.015$ |
| White (n = 5006) | 4338 | 1278 (439) | –4.1 | |
| Black (n = 95) | 83 | 1139 (429) | –4.7 | |
| Asian (n = 769) | 705 | 1046 (400) | –3.4 | |
| American Hispanic (n = 193) | 173 | 1107 (468) | –2.2 | |
| Other (n = 49) | 44 | 1121 (333) | –5.0 | |
| BMI | | | | $P < 0.001$ |
| < 20 (n = 824) | 719 | 1024 (393) | –5.1 | |
| 20 – < 25 (n = 2301) | 2003 | 1195 (427) | –4.6 | |
| 25 – < 29 (n = 1642) | 1424 | 1316 (440) | –3.5 | |
| ≥ 29 (n = 1345) | 1197 | 1351 (358) | –2.8 | |
| Exacerbations in the year prior to study | | | | $P = 0.793$ |
| 0 (n = 2626) | 2314 | 1282 (439) | –3.9 | |
| 1 (n = 1513) | 1340 | 1244 (447) | –3.8 | |
| ≥ 2 (n = 1973) | 1689 | 1176 (435) | –4.1 | |

| | | | |
|---|---|---|---|
| Baseline SGRQ Total Score | | | $P = 0.004$ |
| < 38 (n = 1427) | 1140 | 1381 (431) | –3.5 |
| 38 – < 50 (n = 1276) | 992 | 1251 (418) | –3.8 |
| 50 – < 62 (n = 1135) | 964 | 1180 (430) | –4.5 |
| ≥ 62 (n = 1120) | 966 | 1144 (426) | –4.4 |

*Random coefficients model including smoking status, gender, age, baseline $FEV_1$, region, body mass index (BMI), treatment, time and treatment by time, and covariate by time.

*Definition of abbreviations*: $FEV_1$ = forced expiratory volume in 1 second; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire

**ONLINE TABLE 2. ADJUSTED* YEARLY RATE OF DECLINE IN $FEV_1$ BY TREATMENT GROUP AND PREVIOUS ICS USE IN THE YEAR PRIOR TO THE STUDY**

| | Placebo | SAL | FP | SFC |
|---|---|---|---|---|
| ICS use in the year prior to study | | | | |
| Number of subjects | 623 | 591 | 640 | 674 |
| Adjusted rate of decline (SE), mL/year | –58 (4) | –46 (4) | –46 (4) | –39 (4) |
| No ICS use in the year prior to study | | | | |
| Number of subjects | 605 | 705 | 687 | 689 |
| Adjusted rate of decline (SE), mL/year | –52 | –39 | –39 | –38 |

*Random coefficients model including smoking status, gender, age, baseline $FEV_1$, region, body mass index (BMI), treatment, time and treatment by time.

*Definition of abbreviations*: ICS = inhaled corticosteroids; $FEV_1$ = forced expiratory volume in 1 second; FP = fluticasone propionate; SAL = salmeterol; SE = standard error; SFC = salmeterol/fluticasone propionate combination.

**ONLINE TABLE 3. ADJUSTED* YEARLY RATE OF DECLINE IN $FEV_1$ BY TREATMENT GROUP AND PREVIOUS LABA USE IN THE YEAR PRIOR TO THE STUDY**

| | Placebo | SAL | FP | SFC |
|---|---|---|---|---|
| LABA Use in the year prior to study | | | | |
| Number of subjects | 445 | 470 | 484 | 526 |
| Adjusted rate of decline (SE), mL/year | –58 (5) | –44 (5) | –43 (5) | –38 (5) |
| No LABA Use in the year prior to study | | | | |
| Number of subjects | 777 | 824 | 827 | 828 |
| Adjusted rate of decline (SE), mL/year | –52 | –39 | –39 | –38 |

*Random coefficients model including smoking status, gender, age, baseline $FEV_1$, region, body mass index (BMI), treatment, time and treatment by time.

*Definition of abbreviations*: LABA = long-acting beta agonists; $FEV_1$ = forced expiratory volume in 1 second; FP = fluticasone propionate; SAL = salmeterol; SE = standard error; SFC = salmeterol/fluticasone propionate combination.

**ONLINE TABLE 4. BASELINE LUNG FUNCTION FOR POPULATION WITH AT LEAST ONE ON-TREATMENT $FEV_1$ MEASUREMENT BY REGION***

| | USA (*N* = 1388) *n* = 1172 | Asia Pacific (*N* = 758) *n* = 697 | Eastern Europe (*N* = 1154) *n* = 1070 | Western Europe (*N* = 1908) *n* = 1642 | Other (*N* = 904) *n* = 762 | Total Population (*N* = 6112) *n* = 5343 |
|---|---|---|---|---|---|---|
| **Baseline lung function, mean (SD)** | | | | | | |
| Post-bronchodilator $FEV_1$, mL | 1205 (451) | 1045 (400) | 1341 (435) | 1307 (423) | 1178 (441) | 1239 (442) |
| % predicted post-bronchodilator $FEV_1$ | 44.1 (14.1) | 40.8 (13.9) | 45.7 (12.4) | 46.7 (12.8) | 43.4 (13.4) | 44.7 13.4) |
| % predicted post-bronchodilator $FEV_1$, n (%) | | | | | | |
| < 30 | 201 (17) | 173 (25) | 107 (10) | 167 (10) | 130 (17) | 778 (15) |
| 30 to 49 | 569 (49) | 330 (47) | 539 (50) | 793 (48) | 399 (52) | 2630 (49) |
| ≥ 50 | 402 (34) | 194 (28) | 424 (40) | 682 (42) | 233 (31) | 1935 (36) |

*Countries included in each region are as follows. **USA**: USA; **Asia Pacific**: China, Hong Kong, Malaysia, Philippines, Singapore, Taiwan, Thailand; **Eastern Europe**: Bulgaria, Croatia, Czech Republic, Hungary, Estonia, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, Ukraine; **Western Europe**: Austria, Belgium, Denmark, Finland, France, Germany,

Greece, Iceland, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom; **Other**: Australia, New Zealand, South Africa, Canada, Argentina, Brazil, Chile, Mexico.

*Definition of abbreviations*: $FEV_1$ = forced expiratory volume in 1 second; SD = standard deviation.