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# Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results

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ABSTRACT**:** Inhaled corticosteroids (ICS) are important in reducing exacerbation frequency associated with chronic obstructive pulmonary disease (COPD). However, little is known about the risk of associated infections.

In a post-hoc analysis of the TOwards a Revolution in COPD Health (TORCH) study, we analysed and identified potential risk factors for adverse event reports of pneumonia in this randomised, double-blind trial comparing twice-daily inhaled salmeterol 50mcg (SAL), fluticasone propionate 500mcg (FP), and the combination (SFC) with placebo in 6,184 patients with moderate-severe COPD over 3 years.

Despite a higher withdrawal rate in the placebo arm, after adjusting for time on treatment, a greater rate of pneumonia was reported in the FP and SFC treatment arms (84 and 88 per 1,000 treatment years, respectively) compared with SAL and placebo (52 and 52 per 1,000 treatment years, respectively). Risk factors for pneumonia were age ≥55 years, $FEV_1$ <50% predicted, COPD exacerbations in the year prior to the study, worse MRC dyspnoea scores and

BMI <25kg/$m^2$. No increase in pneumonia deaths with SFC was observed; this could not be concluded for FP.

Despite the benefits of ICS-containing regimens in COPD management, health-care providers should remain vigilant regarding the possible development of pneumonia as a complication in COPD patients receiving such therapies.

**Running title:** Pneumonia risk with inhaled steroids in COPD

**KEYWORDS:** Chronic obstructive pulmonary disease; fluticasone propionate; inhaled corticosteroid; pneumonia; safety

Chronic obstructive pulmonary disease (COPD) is associated with significant mortality and morbidity and patients with COPD are at increased risk of contracting pneumonia [1–3]. Conversely, COPD is the most common co-morbid disease in patients hospitalised for community-acquired pneumonia (CAP) [1, 2, 4]. Furthermore, patients with COPD who are hospitalised for pneumonia have been reported to exhibit higher mortality than patients without COPD [4–6].

Mechanisms to explain the increased risk for pneumonia in this population are not fully elucidated, but may in part be related to altered innate host mechanisms that result in increased carriage of potentially pathogenic microorganisms and altered function of immune effector cells [7–13]. Moreover, the carriage of such pathogenic organisms is related to disease severity, *i.e.* increased in patients with worse airflow obstruction, *i.e.* forced expiratory volume in 1 second ($FEV_1$) <50% [9–14]. In addition, cross-sectional studies have shown increased microbiological colonisation of the lower respiratory tract during exacerbations of COPD compared with the stable state [15, 16].

Chronic colonisation with potentially pathogenic organisms can complicate ascertaining the etiologic microbe. Moreover, patients with more severe disease are often treated with inhaled and/or systemic corticosteroids in an attempt to either decrease the rate of exacerbations or provide symptomatic benefit. Although it is recognised that systemic corticosteroids may mask some of the clinical manifestations of pneumonia, such as fever, it is unclear to what extent inhaled steroids would also affect the clinical presentation.

The TOwards a Revolution in COPD Health (TORCH) study assessed the impact of the inhaled corticosteroid fluticasone propionate (FP) in combination with the long-acting beta agonist, salmeterol (SAL), in reducing all-cause mortality [17]. It was observed in TORCH that despite a reduction in moderate and severe COPD exacerbations with FP either alone or as combination therapy (SFC), there was an increase in the probability of having a pneumonia reported as an adverse event (AE) compared with patients randomised to placebo or SAL. Similar findings were seen in a recent 2-year study comparing SFC with tiotropium [18] and in a 1-year prospective trial of SFC 250 mcg/50 mcg *versus* SAL 50 mcg twice daily [19]. This analysis explores in more detail the increased pneumonia signal observed in the ICS-containing treatment arms in TORCH.

## METHODS

### *Study design*

The design of the TORCH trial has been previously described in detail in recent publications [17, 20]. In brief, patients were randomised using a double-blind parallel group design to receive twice daily administration of either FP 500 mcg, SAL 50 mcg, SFC (in a single device) 50 mcg/500 mcg, or placebo. Patients were followed for 3 years with the primary outcome being all-cause mortality. Secondary efficacy parameters included moderate (treatment with antibiotics and/or systemic corticosteroids) and/or severe (requiring hospitalisation) exacerbations and quality of life as measured by the St George's Respiratory Questionnaire (SGRQ).

### *Adverse event and serious adverse events*

To aid in the detection of AEs, at each study visit, after the patient was allowed to spontaneously mention any problems, the investigator asked the following standard questions: 1) "Have you had any (other) medical problems since your last visit/assessment?" and 2) "Have you taken any new medicines, other than those given to you within this study since your last visit/assessment?" In TORCH, an AE was defined as any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of the blinded study product, whether or not it was considered to be related to that product.

A serious adverse event (SAE) was any AE that resulted in any of the following outcomes: 1) death, 2) if in the view of the investigator it placed the patient in immediate risk of death, 3) resulted in a hospitalisation or prolonged an existing hospitalisation, or 4) any other important medical event, which based upon the medical judgment of the investigator, jeopardised the patient and may have required medical or surgical intervention to prevent one of the aforementioned outcomes. Once aware of an SAE, the investigator was required to complete a separate case report form to provide all known information regarding the event. The form was updated when additional information was received. From these reports, narratives of the serious events were compiled by GlaxoSmithKline's Global Clinical Safety and Pharmacovigilance department for subsequent review.

Patients who prematurely withdrew from the study were to have a follow-up visit 2 weeks after cessation of study drug where any AEs were recorded. Thus, the time period during which AEs and SAEs were collected and recorded started at the time the patient consented to participate in the study and ended at the end of the 2-week follow-up period. Patients were provided with a medication diary card in order to facilitate capture of this information.

***Collection of pneumonia events***

There were no protocol-defined criteria for pneumonia nor were chest x-rays, sputum cultures or laboratory evaluations required to confirm the clinical diagnosis. In addition, no specific queries were made to the investigators with

respect to pneumonia. Investigators recorded all AEs, including pneumonia reports, in the case report form. These events were subsequently coded using the Medical Dictionary for Regulatory Affairs (MedDRA, Version 8.1). Events of physician-reported pneumonias were coded by MedDRA to the following terms and summarised to allow a more complete assessment of all physician-reported pneumonias: Pneumonia, bronchopneumonia, lobar pneumonia, lung infection, pneumonia bacterial, pneumonia chlamydial, pneumonia necrotising, pneumonia staphylococcal, pneumonia streptococcal, superinfection lung, pneumonitis, pneumonia primary atypical, bronchopneumopathy, lung infection pseudomonal, and *Pneumocystis jiroveci* pneumonia.

***SAE events of pneumonia and data extraction***

The narrative reports of pneumonia as a SAE were initially reviewed with particular attention to supportive, confirmatory information; specifically, attainment of a chest x-ray, unilateral *versus* bilateral infiltrates, measurement of the white blood cell count, mention of a febrile state, and microbiological assessment of sputum, blood or pleural fluid, if present. The narratives were subsequently reviewed by one of the authors (Courtney Crim) to determine whether any of the above diagnostic procedures may have been conducted, although not explicitly described. For example, if the narrative indicated that the patient was treated for pneumonia in the anterior right upper lobe segment, it was assumed that a chest x-ray had been obtained, although not explicitly described. Other notations were made as to the presence of concomitant disorders that may

have accounted for the x-ray appearance (*e.g.* congestive heart failure or lung cancer). Hence, as all the AEs of pneumonia were not definitively adjudicated and/or distinguished from other potential concomitant pulmonary parenchymal disorders, they are described here as “reported pneumonia.”

In a separate analysis, an independent clinical endpoints committee (CEC), which remained blind to treatment allocation of the patients, adjudicated all deaths using all available including information from medical records, autopsy reports, and death certificates [21]. For the CEC to ascribe a death as being related to pneumonia, radiographic evidence of an infiltrate had to be present. From the review of these data sources, deaths due to pneumonia were identified.

***Statistical analysis***

Patients were included in the analysis if they took at least one dose of study medication. They were analysed according to the treatment they took for the majority of the treatment period, which, apart from one exception, was the treatment to which they were randomised.

The number and proportion of patients who were reported as having any of the above grouped pneumonia terms as an AE or SAE which started between treatment start and stop date inclusive was summarised by treatment group. Due to differential treatment exposure between the treatment groups, the rate of pneumonia events per 1,000 treatment years was calculated by dividing the

number of AEs by the number of years patients were exposed to study treatment, then multiplying by 1,000.

The time to first pneumonia was compared between treatment groups using Kaplan-Meier estimates and the log-rank test, stratified by smoking status. Kaplan-Meier cumulative incidence curves were also produced.

To identify risk factors for pneumonia, a Cox's proportional hazards model for time to first pneumonia was fitted, using covariates of smoking status, age, % predicted $FEV_1$ (in GOLD stages), gender, exacerbations in the year prior to the study, body mass index (BMI), MRC dyspnoea score and treatment. Interactions of these factors with treatment were fitted in this model, one at a time, with all covariates present in the model. P-values were considered statistically significant at <0.05.

## RESULTS

### *Patients*

Of the 8,554 patients recruited into the study, 6,184 were randomised into one of the four treatment arms. One patient was randomised to placebo but took FP for the majority of the treatment period and was therefore analysed with the FP group. The demographic and baseline characteristics of this 'safety' population are shown in table 1. The mean age was 65 years, 76% were male, mean smoking history was 48 pack-years, and baseline post-bronchodilator $FEV_1$ was 44% of predicted.

The mean extent of exposure to study medication was higher in all active treatment groups compared with placebo, and was greatest in the group that took SFC (table 2). There was an 8% increase in exposure over placebo in both the FP and SAL groups, and a 13% increase in exposure in the patients randomised to SFC.

### *Pneumonia reported as AEs*

By definition, pneumonia events were also classified as exacerbations; however, these pneumonia-related exacerbations only constituted 7% of total exacerbations and approximately 20% of the severe exacerbations. During the course of the study, there were more patients who had an AE report of pneumonia on FP or SFC compared with those in the SAL and placebo groups (14% and 16% *versus* 11% and 9%, respectively; table 2). When adjusted for

time on treatment, the rate of these events remained higher in the FP and SFC groups (84 and 88 per 1,000 treatment years, respectively) compared with the SAL and placebo groups (52 and 52 per 1000 treatment years, respectively). In addition, the proportion of patients with more than one pneumonia event reported in the placebo, SAL, FP, and SFC groups were 1.6%, 1.1%, 3.2% and 3.5%, respectively.

Kaplan-Meier probability estimates revealed that the time to first pneumonia was significantly shorter in both arms containing the ICS (fig. 1). The hazard ratio for SFC *versus* placebo was 1.64 (95% CI 1.33–2.02) representing a 64% increase in the risk of pneumonia at any time within 3 years (table 3), with a similar effect for FP. Using an analysis of rates, it is estimated there would be one extra case of pneumonia for every 31 patients receiving treatment with SFC over 1 year.

***Pneumonia reported as SAEs***

A similar trend as above was also observed for pneumonias reported as SAEs; more patients receiving an ICS-containing regimen reported a SAE-designated pneumonia compared with either SAL or placebo (table 2). Moreover, pneumonia rate remained higher in both the FP and SFC groups when adjusted for time on treatment. To observe one extra SAE of pneumonia following treatment with SFC over 1 year, the “number-needed-to-harm” (NNH) would be 47.

Presumptive or definitive evidence of performed chest radiography was identified in 72% of the SAE-designated pneumonia narratives from the SAEs

and were similar across the treatment groups (75%, 66%, 70% and 76% for placebo, SAL, FP and SFC, respectively). Parenchymal infiltrates were described in 81% of these cases; other concomitant disorders included lung neoplasia, congestive heart failure, pleural effusions, bronchiectasis, and pneumothorax. In the cases where there was no evidence that chest radiology was performed, concomitant disorders included subsequently confirmed lung neoplasia, sepsis, and myocardial infarction – with and without cardiogenic shock. Moreover, these associated disorders did not occur predominantly in any specific treatment group.

Presence of fever and/or leukocytosis was reported in low numbers in both the ICS-containing (11 FP and 3 SFC) and non-ICS-containing (2 placebo and 5 SAL) regimens. Although attempts at microbiologic identification were infrequently noted (12%), the most common reported pathogens from either blood, sputum or via fiberoptic bronchoscopy were *S. pneumoniae, H. influenzae, K. pneumonia,* and *P. aeruginosa*. No opportunistic pathogens were reported as a SAE in any individual from any treatment group and patients with culture-unconfirmed, non-fatal pneumonia clinically responded to conventional antibiotics, further suggestive that these patients were not infected with an opportunistic pathogen. However, there was one non-SAE of *Pneumocystis jiroveci* pneumonia reported from a patient randomised to placebo who was serologically positive for the HIV virus.

***Pneumonia deaths***

Deaths due to pneumonia as reported by the investigator occurred in <1% of all patients (table 2). Based on these small numbers no evidence was seen for a difference in any active treatment compared with placebo in the time to first fatal pneumonia event. As also shown in table 2, there was no increase in CEC-adjudicated deaths within the SFC arm compared with placebo and SAL, although there were six more deaths in the FP arm.

***Risk factors for pneumonia***

Irrespective of randomised treatment, the risk factors for pneumonia in this study population are summarised in figure 2. This shows the hazard ratios and associated 95% confidence intervals for the factors from a Cox's proportional model for time to first pneumonia. These treatment-independent risk factors for pneumonia were older age (especially >65 years), lower % predicted $FEV_1$ (especially <30% predicted), any COPD exacerbations in the year prior to the study, worse MRC dyspnoea score (especially categories 4 and 5), and lower BMI. For example, patients with a $FEV_1$ <30% predicted had a 72% increase in the risk of pneumonia compared with patients whose $FEV_1$ was ≥50%.

After adjusting for other risk factors, there was no evidence that current smokers were at greater risk than former smokers, or that gender was a risk factor. There was no interaction between age and ICS on the probability of pneumonia.

There was no evidence that these risk factors interacted with treatment, except for BMI (p=0.032). Table 4 shows the Kaplan-Meier estimates of the probabilities of pneumonia for the four subgroups of BMI and their hazard ratios. It can be seen that the probabilities of pneumonia for ICS-containing arms *versus* non ICS-containing arms were 17% *versus* 11% and 13% *versus* 13%, for BMI 25 to <29 and ≥29 respectively. However, the corresponding probabilities were 25% *versus* 20% and 22% *versus* 12% for BMI <20 and 20 to <25. Thus, it appears that patients with lower BMI were not only more at risk of pneumonia, but also that in this population the association of ICS usage and pneumonia appeared stronger.

## DISCUSSION

Current guidelines for the management of COPD recommend adding inhaled corticosteroids to long-acting bronchodilators for patients with severe disease and/or frequent exacerbations. This recommendation is substantiated by recent publications demonstrating that ICS/long-acting beta-agonist combinations result in a decreased rate of COPD exacerbations, including this study [17–19, 22, 23]. However, this present analysis suggests that ICS-containing regimens are associated with increased reports of pneumonia. This observation is of concern in light of publications suggesting increased morbidity and mortality when pneumonia develops in patients with COPD [4–6, 24].

Patients receiving placebo withdrew at a significantly higher rate than those receiving active treatment, and the withdrawal rate was lowest for those in the SFC group [17]. To adjust for this differential drop-out, we also reported the pneumonia incidence rate as events per 1,000 treatment years; the observation of higher pneumonia events still persisted in the ICS-containing regimens. In addition, the time to the first pneumonia event was considerably shorter in the ICS-containing-treatment arms and was clearly discernible at 6 months.

The increase in reports of pneumonia as an AE in the ICS-containing treatment arms occurred despite a decrease in overall COPD exacerbations, of which pneumonia was a subset. Signs and symptoms of COPD exacerbations and pneumonia often overlap [25] and it is possible that both over- and under-

diagnosis of pneumonia occurred, particularly as chest radiographs were not required to confirm the diagnosis. It is also noteworthy that the reports of pneumonia SAEs (*i.e.* death, hospitalisation, or prolonged hospitalisation) as a percentage of the total pneumonias were no more frequent in the FP or SFC groups compared with placebo (~60%). This observation suggests that any episodes of pneumonia that occur with concomitant ICS treatment are unlikely to result in a more complex or complicated clinical course. In further support of this observation, no opportunistic pathogens were reported in any pneumonia episode; however, extensive microbiological investigations were not required or routinely undertaken in every case. On the other hand, patients with COPD are chronically colonised with potential pathogens, which complicates ascertaining a specific etiologic agent using non-invasive techniques [9, 26, 27] and also may not permit differentiation between exacerbation and pneumonia microbiologically.

Recently, Ernst and colleagues reported the results of a nested case-control study within a cohort of nearly 176,000 patients with COPD that examined ICS use and the risk of hospitalisation for pneumonia [24]. Compared with non-ICS users within the past year, patients receiving at least 1,000 mcg/day of FP equivalent had a rate ratio for pneumonia hospitalisation of 2.25 (95% CI 2.07–2.44). In addition, the length of pneumonia hospitalisation was similar whether or not patients were current users of ICS (mean 11.7 days *versus* 11.8 days), as was all-cause mortality within 30 days of being hospitalised for pneumonia for patients dispensed ICS in the prior 2 months (8.2% of 18,005 patients) compared

with those who were not dispensed ICS (7.4% of 5,937 patients) [24]. In TORCH, the mortality rate due to pneumonia in the SFC group was similar to both the placebo and SAL groups as reported by both the investigators and the CEC. Moreover, whereas the investigators may not have had confirmatory chest radiographs during their assessment, the CEC did have access to medical records and x-rays and required radiographic evidence of an infiltrate in order to adjudicate a death as due to pneumonia [21]. The number of on-treatment deaths attributable to pneumonia (as adjudicated by the CEC) was not different between the placebo and SFC groups. Although a mortality study, TORCH was not designed to evaluate pneumonia as a specific fatal event and as such, was not adequately powered to detect differences in fatal pneumonias between treatment groups. However, these data, although limited by few events, suggest that any increase in pneumonia events with an ICS-containing COPD regimen does not lead to increased pneumonia mortality.

The mechanism/pathogenesis of increased pneumonia with ICS is unclear. It is generally recognised that exacerbations of COPD are frequently associated with infection. Thus, there is an apparent paradox whereby an ICS-containing regimen reduces the incidence of one infective complication of COPD (*i.e.* exacerbation) yet potentially increases another (*i.e.* pneumonia). It is possible that ICS can alter local immune mechanisms in the airways, as this class of compounds is quite effective in the management of the inflammatory aspects of asthma [28]. On the other hand, there are no reports of excess pneumonia AEs

with ICS use in randomised clinical trials in asthmatics. Although corticosteroids are felt to be less effective in modulating neutrophil function compared with other effector cells, such as eosinophils or mast cells [28], several reports suggest that ICS-containing regimens may reduce sputum neutrophilia in patients with COPD [29, 30], perhaps by decreasing neutrophil chemotaxis [31]. On the other hand, there is some evidence that salmeterol may alter neutrophil function either through decreased adhesion to airway epithelium [32] or capillary endothelium [33] or by inhibiting respiratory burst activity [34]; yet an increase in the pneumonia signal was not observed with SAL therapy in this trial. The observation of a pneumonia signal was unexpected and TORCH was not designed to address the mechanism. However, by multivariate analysis, risk factors for pneumonia regardless of treatment were advancing age (≥55 years), poor lung function ($FEV_1$ <50% predicted), BMI <25, and a history of exacerbations in the year prior to study entry. We were unable to identify factors that further increased the risk for pneumonia in patients receiving a steroid-containing regimen. Although we have also provided a NNH to indicate the increased risk for pneumonia, it is important to note that NNH, in contrast with the hazard ratio, depends on the underlying percentage of patients who have the event of concern and treatment duration. For example and as discussed, the reported pneumonia rates differed between individuals age 55 years and above with those younger; also, rates differed between those with an $FEV_1$ less than 50% predicted and patients with less severe airflow obstruction. Thus, the NNH would differ between these different age groups (or groups based on lung

function), simply due to the difference in the underlying rate; on the other hand, the actual increased risk due to SFC in each of these different groups was observed to be similar to the overall increase of 64%.

Use of an ICS regimen does decrease the rate of exacerbations. Since the clinical presentation of COPD exacerbations and pneumonia often overlap, it remains critical for the health-care professional to remain vigilant for the possible development of pneumonia and implement early and appropriate therapy.

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## FIGURE LEGENDS

**Figure 1** Kaplan-Meier estimate of time to first pneumonia for patients taking placebo, salmeterol (SAL), fluticasone propionate (FP), and fluticasone propionate-salmeterol combination (SFC), Values in the table below the figure are the numbers of patients at risk at randomisation and following 48, 96, and 156 weeks of treatment. Vertical bars represent standard errors.

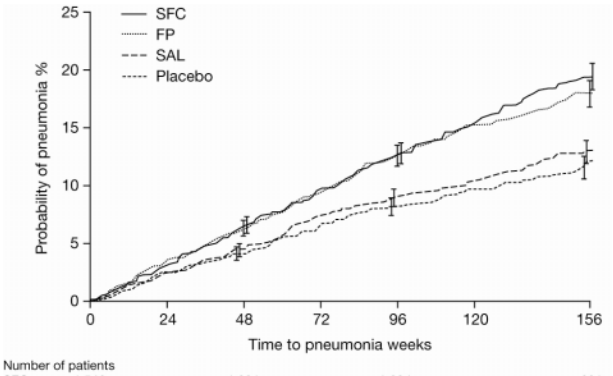


**Figure 2** Risk factors for pneumonia: hazard ratios (HR) with 95% confidence intervals (CI) from Cox proportional hazards model using covariates of smoking status, age, % predicted $FEV_1$ (in GOLD stages), gender, exacerbations in the year prior to the study, body mass index (BMI), MRC dyspnoea score and treatment.

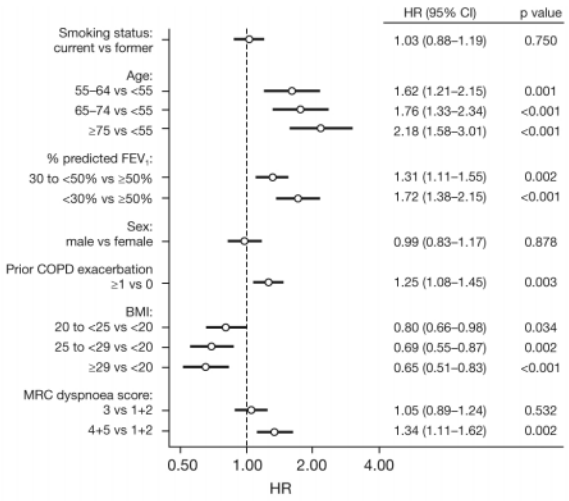
HR (95% CI)
p value
Smoking status:
current vs former
1.03 (0.88–1.19)
0.750
Age:
55–64 vs <55
1.62 (1.21–2.15)
0.001
65–74 vs <55
1.76 (1.33–2.34)
<0.001
≥75 vs <55
2.18 (1.58–3.01)
<0.001
% predicted FEV1:
30 to <50% vs ≥50%
1.31 (1.11–1.55)
0.002
<30% vs ≥50%
1.72 (1.38–2.15)
<0.001
Sex:
male vs female
0.99 (0.83–1.17)
0.878
Prior COPD exacerbation
≥1 vs 0
1.25 (1.08–1.45)
0.003
BMI:
20 to <25 vs <20
0.80 (0.66–0.98)
0.034
25 to <29 vs <20
0.69 (0.55–0.87)
0.002
≥29 vs <20
0.65 (0.51–0.83)
<0.001
MRC dyspnoea score:
3 vs 1+2
1.05 (0.89–1.24)
0.532
4+5 vs 1+2
1.34 (1.11–1.62)
0.002
0.50
1.00
2.00
4.00
HR

**TABLE 1** Baseline characteristics (safety population)

| | **Placebo (n=1,544)** | **SAL 50 (n=1,542)** | **FP 500 (n=1,552)** | **SFC 50/500 (n=1,546)** | **Total (n=6,184)** |
|---|---|---|---|---|---|
| Age (years) | | | | | |
| Mean (SD) | 65 (8) | 65 (8) | 65 (8) | 65 (8) | 65 (8) |
| Gender (n, %) | | | | | |
| Male | 1175 (76%) | 1176 (76%) | 1169 (75%) | 1164 (75%) | 4684 (76%) |
| Female | 369 (24%) | 366 (24%) | 383 (25%) | 382 (25%) | 1500 (24%) |
| Smoking status (n, %) | | | | | |
| Former | 880 (57%) | 885 (57%) | 886 (57%) | 879 (57%) | 3530 (57%) |
| Current | 664 (43%) | 657 (43%) | 666 (43%) | 667 (43%) | 2654 (43%) |
| Total pack years | | | | | |
| Mean (SD) | 49 (27) | 49 (29) | 49 (27) | 47 (27) | 49 (28) |
| Baseline | | | | | |
| $FEV_1$ (% predicted post-bronchodilator) | 44 (13) | 44 (13) | 45 (13) | 45 (14) | 44 (13) |
| % Reversibility | | | | | |
| Mean (SD) | 10 (11) | 10 (11) | 10 (11) | 10 (11) | 10 (11) |

FP: fluticasone propionate; SAL: salmeterol; SD: standard deviation; SFC: salmeterol plus fluticasone propionate combination

**TABLE 2** Pneumonia in the safety population

| | **Placebo (n=1,544)** | **SAL 50 (n=1,542)** | **FP 500 (n=1,552)** | **SFC 50/500 (n=1,546)** |
|---|---|---|---|---|
| Total treatment exposure (years) | 3278 | 3531 | 3555 | 3700 |
| Patients with AEs, n | 139 | 162 | 224 | 248 |
| No. of events | 170 | 182 | 300 | 324 |
| Rate/1000 treatment yrs | 52 | 52 | 84 | 88 |
| Patients with SAEs, n | 86 | 99 | 150 | 157 |
| No. of events | 97 | 105 | 184 | 204 |
| Rate/1000 treatment yrs | 30 | 30 | 52 | 55 |
| Patients with fatal SAEs, n | 10 | 11 | 15 | 12 |
| Rate/1,000 treatment yrs | 3.1 | 3.1 | 4.2 | 3.2 |
| CEC adjudicated primary cause of death up to 3 years | | | | |
| On treatment, n (%) | 7 (0.5) | 9 (0.6) | 13 (0.8) | 8 (0.5) |

AE: adverse event; CEC: clinical endpoint committee; FP: fluticasone propionate; SAE: serious adverse event; SAL: salmeterol; SFC: salmeterol plus fluticasone propionate combination

**TABLE 3** Time to first pneumonia

| | **Placebo (n=1,544)** | **SAL 50 (n=1,542)** | **FP 500 (n=1,552)** | **SFC 50/500 (n=1,546)** |
|---|---|---|---|---|
| No. of patients with pneumonia | 139 | 162 | 224 | 248 |
| Probability* of pneumonia by 3 years (%) | 12.3 | 13.3 | 18.3 | 19.6 |
| | | **Hazard ratio** | **95% CI** | **p** |
| SFC *versus* placebo | | 1.64 | 1.33–2.02 | <0.001 |
| FP *versus* placebo | | 1.53 | 1.24–1.89 | <0.001 |
| SAL *versus* placebo | | 1.09 | 0.87–1.37 | 0.465 |
| ICS *versus* non-ICS | | 1.52 | 1.32-1.76 | <0.001 |

*Kaplan-Meier estimate of probability

CI: confidence interval; FP: fluticasone propionate; SAL: salmeterol; SFC: salmeterol plus fluticasone propionate combination; ICS: FP+SFC; non-ICS: Placebo+SAL

**TABLE 4** Kaplan-Meier estimate of the impact of BMI on time to first pneumonia, comparing ICS (FP or SFC) to non-ICS regimens (SAL or placebo)

| | BMI | | | |
|---|---|---|---|---|
| | <20 | 20 to <25 | 25 to <29 | ≥29 |
| **ICS** | | | | |
| Number of patients | 423 | 1,161 | 838 | 676 |
| Probability* of event, % (95% CI) | 25 (21–30) | 22 (19–24) | 17 (14–20) | 13 (10–16) |
| **Non-ICS** | | | | |
| Number of patients | 407 | 1,158 | 832 | 689 |
| Probability* of event, % (95% CI) | 20 (15–25) | 12 (10–14) | 11 (9–14) | 13 (10–16) |
| Hazard Ratio (95% CI) | 1.30 (1.02-1.64) | 1.98 (1.67-2.34 | 1.60 (1.30-1.98) | 1.00 (0.79-1.26) |

*Kaplan-Meier estimate of probability of pneumonia at 3 years

BMI: body mass index; CI: confidence interval; FP: fluticasone propionate; ICS: inhaled corticosteroid; SAL: salmeterol; SFC: salmeterol plus fluticasone propionate combination