Relationship between eosinophil count and pneumonia risk in patients with COPD: a meta-analysis

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Target journal: *The Lancet*

Journal restrictions:

	Journal limit	**Current word count**
Abstract	300 words	300 words
Manuscript text only	3000 words	2807 words
References	30	30
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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta–analysis, or both.	Yes, page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Yes, page 4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Yes, page 8/9
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Yes, pages 8/9
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No, this was a post-hoc analysis
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow–up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Yes, pages 10,11, 23
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Yes, GSK clinical trial registry, page 10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	We did not use an electronic search strategy- we know from GSK study records all GSK studies that met the required criteria.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta–analysis).	Yes, page 10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	We used individual patient data as these were GSK studies
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Yes, pages 11 and 12
Risk of bias in individual	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	All studies selected are randomised double blind parallel group studies and so risk of

studies			bias is minimal
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Yes, pages 11 and 12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta–analysis.	Yes, page10, combined as “All analyses were performed using a Cox proportional hazards model, stratifying by trial “. Consistency tested as “A test of heterogeneity across trials was performed for each of the analyses by fitting an additional model, which included a term for eosinophil subgroup by trial interaction.”

Summary

Background Inhaled corticosteroids (ICS) are important for chronic obstructive pulmonary disease (COPD) management, although there is an associated low risk of increased pneumonia in patients with moderate-to-severe COPD. Patients with circulating eosinophils ≥2% are more responsive to ICS than those with <2% eosinophils. We have investigated whether this blood eosinophil threshold identifies patients who differ in their risk of pneumonia in a post-hoc meta-analysis.

Methods Data from ten clinical trials that evaluated patients with COPD over a period of ≥24 weeks: NCT01053988, NCT01054885, NCT01009463, NCT01017952, NCT00361959, SCO30002, SFCA3006, SFCA3007, SCO100470, and SFCB3024 were analysed. Pneumonia adverse events (AEs) were identified using specified terms from the Medical Dictionary for Regulatory Activities. Patients were stratified according to baseline blood eosinophil levels and whether or not they had received ICS treatment.

Findings In this analysis, 4043 patients had <2% blood eosinophils and 6818 patients had ≥2% blood eosinophils at baseline. Pneumonia AEs occurred in more patients with <2% blood eosinophils than those with ≥2% (3·7% and 3·2%, respectively, hazard ratio [HR] 1·31; 95% confidence interval [CI] 1·06– 1·62). Pneumonia incidence for patients with <2% versus ≥2% blood eosinophils, respectively, was 3·8% versus 2·4% (HR 1·53; 95% CI 1·01–2·31) without ICS treatment and 4·5% versus 3·9% (HR 1·25; 95% CI 0·98–1·60) with ICS treatment. Limitations included differences in trial duration, population, comparators, pneumonia definition, and the lack of pneumonia-defined endpoints.

Interpretation Patients with COPD and blood eosinophils <2% experienced more pneumonia AEs than those with ≥2%. The magnitude of this increased risk was small and should be further explored in large, prospective studies. These data should be considered when making treatment decisions, alongside the knowledge that patients with COPD and baseline blood eosinophil counts <2% respond less well to ICS, compared with patients whose blood eosinophil counts are ≥2%.

Funding GSK-sponsored analysis.

Research in context panel

Evidence before this study

Patients with chronic obstructive pulmonary disease (COPD) are at increased risk of pneumonia. Blood eosinophil count has recently been identified as a potential biomarker of the ability of ICS to prevent exacerbations of COPD. However, it has not been established whether blood eosinophil count has any predictive value for pneumonia risk in patients with COPD. Such a relationship is possible as eosinopenia has been associated with sepsis and may therefore be a marker of airway infection. This meta-analysis was performed using data from clinical trials in the GSK trial registry using fluticasone propionate (FP) or fluticasone furoate (FF) that had followed patients with COPD. The criteria for trial inclusion were pre-determined, reducing potential bias in trial selection. Criteria were as follows: randomised double-blind COPD trials of at least 24 weeks in duration that included an ICS arm and a non-ICS arm, where blood eosinophil levels were measured and individual patient data were available for analysis. A common approach to identifying pneumonia adverse events (AEs) was applied across all the trials. Modelling was used to analyse the time to development of the first pneumonia AE and to compare the risk of pneumonia between eosinophil subgroups <2% and ≥2%.

Added value of this study

This meta-analysis investigated the incidence of pneumonia AEs to determine whether blood eosinophil level was related to the risk of pneumonia in patients with COPD. From a total of 10 861 evaluable patients, of whom 4043 had a blood eosinophil count <2% and 6818 had a blood eosinophil count ≥2%, a higher proportion of patients from the former group experienced pneumonia AEs, compared with the latter (3·7% and 3·2% of patients, respectively, hazard ratio, 1·31; 95% confidence interval 1·06–1·62).

Implications of all the available evidence

The preliminary finding that patients with COPD and a baseline blood eosinophil count <2% had a trend towards increased incidence of pneumonia, compared with those with a blood eosinophil count ≥2%, should be considered alongside the knowledge that patients with <2% blood eosinophils may gain a smaller magnitude of exacerbation reduction with the addition of ICS to long-acting beta$_2$ agonist treatment.

Introduction

Patients with chronic obstructive pulmonary disease (COPD) are at increased risk of pneumonia,[1] while among patients with pneumonia, COPD is the most frequently identified co-morbid respiratory condition.[2] Pneumonia in patients with COPD has been associated with worse outcomes than in otherwise healthy individuals, including more frequent requirements for mechanical ventilation and higher intensive care unit mortality.[3] Recognised risk factors include older age (>55 years), reduced forced expiratory volume in 1 second (FEV_1; particularly <50% of predicted), a history of COPD exacerbations, a low body mass index, and worsening dyspnoea.[4]

Inhaled corticosteroids (ICS) are beneficial for the management of COPD, improving symptoms and reducing the frequency and severity of exacerbations.[5] For example, the ICS/long-acting $beta_2$ agonist (LABA) combination therapy of fluticasone furoate (FF)/vilanterol (VI) significantly reduced the annual rate of moderate and severe exacerbations by an approximate ratio of 0·7–0·8, compared with VI alone, in patients with moderate-to-severe COPD.[6]

ICS use has been associated with an increased risk of pneumonia in patients with COPD; this was first identified in the TOwards a Revolution in COPD Health (TORCH) study,[7] although no association with increased mortality was found in that study. The association between ICS and pneumonia in patients with COPD has been subsequently confirmed by randomised, controlled trials, meta-analysis of randomised controlled trials, and database studies.[8–10] These findings affirm the importance of identifying COPD patients who are most at risk of pneumonia.

Blood eosinophil count has recently been identified as a potentially useful biomarker of the ability of ICS to reduce COPD exacerbations.[11–13] An eosinophil count of ≥2% of blood leukocytes has been shown to be a sensitive indicator of airway eosinophilia.[14] Following long-term treatment with FF/VI, patients with COPD and ≥2% blood eosinophils had a 29% reduction in the rate of moderate/severe exacerbations, compared with VI, whereas those with <2% blood eosinophils had a 10% reduction.[11] Patients with <2% blood eosinophils may be more likely to have infection-related corticosteroid resistant neutrophilic airway inflammation (as sepsis has been associated with eosinopenia),[15] and a previous meta-analysis has shown that this population responds equally well to oral antibiotics alone as to the combination of oral antibiotics and prednisolone at the time of an

exacerbation.[16] If this is the case, then patients with COPD and <2% blood eosinophils might be at particular risk of ICS-related pneumonia.

We tested the hypothesis that patients with a blood eosinophil count <2% are at increased risk of pneumonia (compared with patients with ≥2% blood eosinophils) in a post-hoc meta-analysis of data collected from ten clinical trials that evaluated patients with COPD over a period of ≥24 weeks, where information on pre-randomisation blood eosinophil count was available.

Methods

Clinical trials

Data were compiled from ten clinical trials that had followed patients with COPD for at least 24 weeks and had blood eosinophil measurements available (table 1). The following criteria were used for trial selection: randomised, parallel-group, double-blind clinical trials in patients with COPD that included fluticasone propionate (FP)/salmeterol (SAL) or FF/VI arms; inclusion of a non-ICS containing treatment arm; and pre-randomisation blood samples for measurement of eosinophil levels. The trials were identified from the GSK clinical trial registry. Patients were eligible for inclusion in this post-hoc analysis of pneumonia incidence if a full blood count (with differential count) or a blood eosinophil count, taken prior to randomised treatment, was available.

Four phase 3 trials assessed FF and VI in combination and as monotherapies (NCT01053988, NCT01054885, NCT01009463, and NCT01017952). Five phase 3 trials investigated FP and SAL as a combination or monotherapy (SCO30002, SFCA3006, SFCA3007, SCO100470, and SFCB3024). The phase 4 trial NCT00361959 compared the FP/SAL combination therapy with tiotropium (TIO).

All trials enrolled patients aged ≥40 years, with a smoking history of ≥10 pack-years and an established history of COPD as defined by the American Thoracic Society/European Respiratory Society.[17] Full trial design information, patient inclusion and exclusion criteria, and outcomes are available in the primary publications (SFCA3006;[18,19] NCT00361959;[10] NCT01053988;[20] NCT01054885;[21] NCT01009463 and NCT01017952),[6] and in the GSK clinical trial register (SCO30002, SFCA3007, SCO100470, and SFCB3024).

All ten trials complied with the principles of Good Clinical Practice[22] and the declaration of Helsinki,[23] with the approval of appropriate ethics committees or institutional review boards. All patients provided written, informed consent prior to participation.

Pneumonia analysis

The analysis used a broad set of terms to identify pneumonia adverse events (AEs). AEs reported by the investigator were coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 18). An extensive set of MedDRA preferred AE terms was used to ensure cases of pneumonia were not missed (table 2). This list was previously used to identify pneumonia for FF/VI and was retrospectively applied to all trials in this analysis.

Assessments (statistical methods)

Patients were stratified based on their last pre-randomisation blood eosinophil count, primarily using the 2% cut-off identified in a previous analysis of two phase 3 trials (NCT10119463 and NCT01017952).[11]

As treatments varied across the trials, therapy was classified as ICS containing (ie, FP, FF, or these ICS in combination with LABA drugs) and not ICS containing (ie, SAL, VI, TIO, or placebo).

Three comparisons were performed: (i) <2% versus ≥2% eosinophil subgroups with treatment as a covariate; (ii) <2% versus ≥2% eosinophil subgroups in non-ICS-treated groups; and (iii) <2% versus ≥2% eosinophil subgroups in ICS-treated groups. Additional analyses were performed, repeating the comparisons above using cut-offs of 100, 200, 300, and 400 cells/mm^3. All analyses were performed using a Cox proportional hazards model, stratifying by trial with a term for baseline blood eosinophil count. A test of heterogeneity across trials was performed for each of the analyses by fitting an additional model, which included a term for eosinophil subgroup by trial interaction. For comparison (i) described above, in each trial, and across all trials, an assessment of treatment by eosinophil interaction was conducted. A Kaplan–Meier plot of time to first pneumonia was produced according to eosinophil count and treatment (ICS containing *vs* non-ICS containing).

Results

The demographic characteristics of 10 861 evaluable patients are provided in table 3, by treatment. The majority of patients included in this analysis were male. Patients were stratified by baseline blood eosinophil count: overall, 4043 patients had <2% blood eosinophils and had a mean age of 63·1 years while 6818 patients had ≥2% blood eosinophils and a mean age of 63·6 years (table 3; individual trial data are given in supplementary table 1). The blood eosinophil counts at screening for all trials are summarised in figure 1; more patients had blood eosinophils at or above the 2% threshold than below it.

Baseline lung function varied across the treatments, with mean predicted pre-bronchodilator (BD; trough) FEV_1 values of 36·8–54·9% (<2% blood eosinophil subgroup) and 36·8–55·9% (≥2% blood eosinophil subgroup) (supplementary table 2). Within a treatment group, the mean FEV_1 values were similar for the two eosinophil subgroups; reflecting that different treatments were included in trials of differing COPD severities. Post-BD reversibility was generally comparable between the <2% and ≥2% blood eosinophil subgroups, across all therapies (mean values ranged from 7·9% to 20·2%, reflecting the different entry criteria regarding FEV_1 reversibility and severity in the different trials).

Pneumonia analysis

The incidence of investigator-reported pneumonia AEs was low across all trials. It should be noted that, as not all diagnoses of pneumonia were confirmed (eg, by X-ray), other respiratory infective states may also have been included here.

Pneumonia AE incidences are detailed in table 4 according to trial, treatment group, and blood eosinophil count. In the four trials with a higher incidence of pneumonia overall (SFCB3024, NCT01009463, NCT01017952, and NCT00361959), there was a trend towards numerically higher pneumonia incidence for patients with <2% blood eosinophils, compared with a count ≥2% (table 4). These four trials with the highest incidence of pneumonia were also the trials contributing the highest number of patients, were generally of longer duration than other trials in the analysis, and also included only patients with a history of COPD exacerbations. For these reasons, it was not unexpected that a higher incidence in pneumonia would be observed in these trials. However, the test of eosinophils by trial interaction (heterogeneity) was not significant (p=0·937), so there is no evidence of an inconsistent effect of eosinophil levels on pneumonia incidence across trials. The eosinophil by treatment with ICS as a covariate p value was not significantly different for each trial, considered separately (p=0·087–

0·897), or for all trials combined (p=0·596) (figure 2); so there was no evidence of an inconsistent effect of eosinophils on pneumonia incidence between the ICS- and non-ICS-treated groups. When all trials were considered together, there was a slightly increased incidence of pneumonia in patients with <2% blood eosinophils (3·7%, 149 cases), compared with ≥2% blood eosinophils (3·2%, 215 cases), with a lower confidence interval (CI) for the hazard ratio (HR) above unity (HR 1·31; 95% CI 1·06–1·62) (figure 2).

Alternative patient stratifications according to eosinophil thresholds of 100, 200, 300, and 400 cells/mm^3 are detailed in supplementary table 3. When a cut-off of 100 cells/mm^3 was used, a comparable pneumonia incidence rate was observed (of 3·6% *vs* 3·3%, below and above the cut-off, respectively), compared with the 2% blood eosinophil cut-off, whereas the trend for slightly higher incidence with lower eosinophil counts disappeared at cut-offs of 200, 300, and 400 cells/mm^3 (supplementary figure 1).

A higher proportion of patients with <2% blood eosinophils experienced serious pneumonia AEs than those with ≥2% blood eosinophils (87/4043 [2·15%] and 108/6818 [1·58%], respectively, of patients in all trials) (table 4). Fatal pneumonia AEs were rare in patients with both <2% or ≥2% blood eosinophils, and all on-treatment fatalities occurred in trials of at least 52 weeks in duration (5/4043 [0·12%] and 7/6818 [0·10%], respectively, of patients in all trials), except for one placebo patient in trial SFCA3006 (table 4).

The trend for increased incidence of pneumonia in patients with <2% blood eosinophils was similar when patients were stratified according to ICS treatment (figure 3). Patients with <2% and ≥2% eosinophils, respectively, had pneumonia incidences of 3·8% versus 2·4% in the non-ICS-treated groups (HR 1·53; 95% CI 1·01–2·31), and 4·5% versus 3·9% in the ICS-treated groups (HR 1·25; 95% CI 0·98–1·60). The tests of trial by eosinophil interaction were not significant in either case (p=0·616 and p=0·883, respectively). In each of the ICS treated and non-ICS treated groups, those with eosinophils <2% had a small increased probability of pneumonia compared to those with eosinophils ≥2%, consistent with the Cox regression analysis presented.

Baseline eosinophil counts did not appear to be associated with a difference in the time of first pneumonia AE incidence (supplementary figure 2). ICS treatment, however, was associated with an increased probability of a pneumonia event for both those with eosinophils <2% and those with eosinophils ≥2%, with approximately

double the proportion of ICS-treated patients having experienced ≥1 pneumonia AE by 52 weeks, compared with non ICS-treated patients.

Discussion

Using a large database of clinical trials, we identified that patients with COPD and blood eosinophil counts of <2% having a small increased risk of pneumonia. Overall, patients with COPD had comparable trough and post-BD lung function regardless of their baseline eosinophil count.

Notably in our analysis, the increased pneumonia risk in patients with COPD and eosinophil count <2% was not apparent in trials where there was a lower overall incidence of reported pneumonia. These tended to be trials of shorter duration in patients with less severe COPD (SFCA3006, SFCA3007, SCO100470, NCT01053988, NCT01054885, and SCO30002). Some of the trials analysed here were conducted before the TORCH study, which reported an increased risk of pneumonia in patients treated with FP.[4,7] Trials conducted prior to TORCH may have placed less emphasis on differentiation of pneumonia from other AEs. Future analyses will be able to evaluate the association between blood eosinophil counts <2% and pneumonia in more depth, using data from recent and ongoing trials, where these parameters have been specified from the outset.

The association of circulating eosinophil levels with airway inflammation in COPD does not have a clearly defined mechanism. Eosinophil reference ranges vary between laboratories, although 0–6% of blood leukocytes may be considered a typical normal range.[24] Eosinophils are a component of T helper 2-mediated immunity and have an arsenal of antimicrobial defences.[25] These include granule proteins and the capacity to release extracellular DNA traps that have microbicidal activity.[26] The presence of eosinophil counts ≥2% may thus reflect an improved capacity to clear lung infections before they progress to pneumonia. Conversely, circulating eosinophil counts <2% may indicate increased susceptibility to pneumonia or may be acquired, for example, as a consequence of a recent infection (such as sepsis).[15]

A ≥2% blood eosinophil count has been shown to be a sensitive marker of airway eosinophilia.[27] Patients with COPD and ≥2% blood eosinophil counts have been reported to experience a greater magnitude of benefit from ICS treatment with regard to exacerbation reduction;[11–13] however, this interpretation has been queried in the

absence of confirmation by prospective studies.[28] Conversely, in patients with COPD, blood eosinophil counts below this 2% threshold have been identified as an indicator of lower response to ICS treatment.[14]

In common with other findings, there was a relationship between ICS treatment and a shorter time to the first pneumonia AE. ICS have a known association with pneumonia risk,[8] but this risk must be weighed against the benefit of treatment. As ICS have been shown to reduce the exacerbation rate by a greater magnitude in patients with COPD and blood eosinophil counts ≥2%, compared with <2%,[11–13] the risk-benefit of ICS treatment may be different for patients with blood eosinophil counts above and below 2%.

Alternative eosinophil thresholds may also be informative. For example, eosinophil counts <50 cells/mm^3 have previously been correlated with adverse outcomes in a combinatorial score including Dyspnoea, Eosinopenia, Consolidation, Acidaemia and Atrial Fibrillation (DECAF).[29] Therefore, our post-hoc analyses also compared circulating eosinophil counts above and below a range of thresholds (for which there were sufficient patients to make comparisons): 100, 200, 300, and 400 cells/mm^3. The proportion of patients with pneumonia did not change substantially when a threshold level of 100 cells/mm^3 was used to define higher or lower circulating eosinophil counts, compared with the 2% cut-off.

A key strength of our analysis was the data source of a large number of clinical trials: more than 10 000 well-characterised patients had available baseline eosinophil counts, enabling an insight into their risk of pneumonia. Further strengths were that a uniform definition of pneumonia[4] was used in all trials in this analysis, and that the analysis was not only based on AE reports of pneumonia, but used a pre-defined comprehensive list of AE terms from MedDRA that could identify pneumonia. Our finding is potentially clinically important as blood eosinophils are a readily available and often routinely measured biomarker.

The retrospective nature of analysis by eosinophil level in the individual trials was a weakness of our meta-analysis, which means it was not possible to discern the mechanisms that may have explained any increased risk of pneumonia in patients with blood eosinophil counts <2% and COPD, nor the stability of blood eosinophil counts in relation to the timing of a pneumonia AEs; these questions may be investigated in future trials. Subsequent trials could, for example, be designed to collect data related to interventions that are known to reduce the pneumonia risk, such as influenza and pneumococcal vaccination,[30] in addition to blood eosinophil

counts over time. Additional limitations of our analysis included differences in trial duration, under-powering, population and treatment comparators, and that the trials did not include patients with mild COPD. The utility of baseline blood eosinophil count as a biomarker in patients with mild COPD remains to be determined. Finally, as mentioned above, the lack of a unified requirement for confirmed pneumonia diagnosis across all trials as they were conducted may have limited the ability of our meta-analysis to critically appraise pneumonia risk according to baseline eosinophil count, however within an individual trial the definition was the same. It remains to be seen whether prospective trials that include pneumonia as a pre-defined endpoint (such as the ongoing trial NCT02164513) will validate our observation of pneumonia risk in patients with COPD and a blood eosinophil count <2%.

We identified a smaller magnitude of increased risk of pneumonia than that of certain previously identified risk factors, such as having increased age and severe airflow limitation or ICS treatment itself.[4] Nevertheless, these data do suggest that when assessing pneumonia risk in COPD, patients with an eosinophil count <2% and a high baseline risk of pneumonia should be considered most at risk while deriving less benefit from ICS treatment.[11]

Conclusions

An eosinophil count <2% in patients with COPD appears to indicate a slightly increased risk of experiencing pneumonia. Given the small magnitude of this increased risk, the clinical relevance of this finding is unclear. Further investigations are warranted to confirm this observation.

Funding

Funding for this meta-analysis was provided by GSK. The individual studies reported in this analysis were also funded by GSK.

Trial	Reference
SFCA3006	Mahler et al, 2001 and 2002
SCO30002*	http://www.gsk-clinicalstudyregister.com/files2/gsk-sco30002-clinical-study-report-redact-v02.pdf
SFCA3007*	http://www.gsk-clinicalstudyregister.com/files2/sfca3007-clinical-study-report-redact-v02.pdf
SCO100470*	http://www.gsk-clinicalstudyregister.com/files2/gsk-sco100470-clinical-study-report-redact-v02.pdf
SFCB3024*	http://www.gsk-clinicalstudyregister.com/files2/sfcb3024-clinical-study-report-redact-v02.pdf
NCT00361959	Wedzicha et al, 2008
NCT01053988	Kerwin et al, 2013
NCT01054885	Martinez et al, 2013
NCT01009463 and NCT01017952	Dransfield et al, 2013

*Trials predating the requirement for trial registration have no assigned NCT number.

Contributors

All authors contributed to the conception and design of these analyses and were involved in the interpretation of the data. The data analysis was conducted by IDP, SL and NB.

Declaration of interests

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Anzueto A	University of Texas Health, San Antonio	Recipient of consulting fees, lecture fees, and travel support from AstraZeneca, Bayer-Schering Pharma, Boehringer Ingelheim, Dey Pharma, GlaxoSmithKline, and Pfizer.
Barnes N	GSK	GSK employee and holds shares in GSK

Acknowledgments

These analyses were funded by GSK. Dawn Midwinter, GSK, assisted with statistical analysis and Sandra Williams, Veramed Ltd, assisted with programming.

Editorial support in the form of development of the draft outline and manuscript first draft in consultation with the authors, editorial suggestions to draft versions of this paper, assembling tables and figures, collating author comments, copyediting, fact checking, referencing, and graphic services was provided by Jennifer Lawton, PhD and Katherine St. John, PhD at Gardiner-Caldwell Communications (Macclesfield, UK), and was funded by GSK.

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Tables

Table 1: Overview of all clinical trials included in this analysis

Trial number	Phase	Number of patients, as randomised and dosed (ITT)	Treatment arms	Trial duration	Primary endpoint	Additional endpoints
SCO30002 (GSK SCO30002 clinical study report)	3	387	SAL/FP 50/500; FP 500; PBO	52 weeks	Time from the beginning of treatment to first moderate or severe COPD exacerbation	Number and severity of moderate or severe exacerbations; pre- and post-bronchodilator FEV_1, FVC, and FEV_1/FVC; PEFR; quality of life
SFCA3006[18,19]	3	674	SAL/FP 50/500; SAL 50; FP 500; PBO	24 weeks	Mean change from baseline in morning pre-dose and 2-hour post-dose FEV_1	Serial FEV_1 over 12 hours on Day 1; COPD exacerbations; PEFR; CBSQ; Baseline/Transition Dyspnoea Index; CRDQ score at each visit
SFCA3007 (GSK SFCA3007 clinical study report)	3	723	SAL/FP 50/500; SAL 50; FP 250; PBO	24 weeks	Mean change from baseline in morning pre-dose and 2-hour post-dose FEV_1	CBSQ; Baseline/Transition Dyspnoea Index; COPD exacerbations; PEFR; CRDQ score at each visit
HZC112206 (NCT0105398)[20]	3	1030	FF/VI 100/25; FF/VI 50/25; FF 100; VI 25; PBO	24 weeks	Change from baseline in weighted mean FEV_1 0–4 hours post-dose on Day 168; change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV_1 at Day 169	CRQ-SAS dyspnoea score on Day 168; change from baseline in peak post-dose FEV_1 0–4 hours on Day 1; time to onset (increase of 100 mL above baseline in FEV_1) on Day 1
SCO100470 (GSK SCO100470 clinical study report)	3	1050	SAL/FP 50/250; SAL 50	24 weeks	Change from baseline in mean trough FEV_1 and mean Transition Dyspnoea Index focal score at endpoint	Change from baseline in pre- and post-bronchodilator FEV_1, trough FVC, FEV_1/FVC, and SGRQ at different time points; PEFR
HZC112207 (NCT0105488)[21]	3	1224	FF/VI 200/25; FF/VI 100/25; FF 200; FF 100; VI 25; PBO	24 weeks	0–4 h weighted mean FEV_1 on Day 168; change from baseline in trough (23–24 hours post-dose) FEV_1 on Day 169	CRQ-SAS dyspnoea score on Day 168; change from baseline in peak post-dose FEV_1 0–4 hours on Day 1; time to onset (increase of 100 mL above baseline in FEV_1) on Day 1
SCO40036 (NCT0036195)[10]	4	1323	SAL/FP 50/500; TIO	104 weeks	Rate of healthcare utilisation, based on COPD exacerbations	Exacerbation rate based on symptoms, oral corticosteroid, or antibiotic treatment; time to next exacerbation; duration and difference between healthcare utilisation
SFCB3024 (GSK SFCB3024 clinical study report)	3	1465	SAL/FP 50/500; SAL 50; FP 500; PBO	52 weeks	Pre-bronchodilator FEV_1	Number of moderate or severe COPD exacerbations; quality of life SGRQ score
HZC102871 (NCT0100946)[6]	3	1622	FF/VI 200/25; FF/VI 100/25; FF/VI 50/25; VI 25	52 weeks	Annual rate of moderate and severe COPD exacerbations	Time to first occurrence of moderate or severe COPD exacerbation; annual rate of exacerbations requiring systemic/oral corticosteroid; change from baseline in trough FEV_1 at week 52
HZC102970 (NCT0101795)[6]	3	1633	FF/VI 200/25; FF/VI 100/25; FF/VI 50/25; VI 25	52 weeks	Annual rate of moderate and severe COPD exacerbations	Time to first occurrence of moderate or severe COPD exacerbation; annual rate of exacerbations requiring systemic/oral corticosteroid; change from baseline in trough FEV_1 at week 52

CBSQ=Chronic Bronchitis Symptoms Questionnaire. COPD=chronic obstructive pulmonary disease. CRDQ=Chronic Respiratory Disease Questionnaire. CRQ-SAS=self-administered standardised CRDQ. FEV_1=forced expiratory volume in 1 second. FF=fluticasone furoate. FP=fluticasone propionate. FVC=forced vital capacity. ITT=intent to treat population. PBO=placebo. PEFR=peak expiratory flow rate. SAL=salmeterol. SGRQ=St George's Respiratory Questionnaire. TIO=tiotropium. VI=vilanterol.

Table 2: **Preferred Terms for pneumonia adverse events**

MedDRA Preferred Term		
Acute pulmonary histoplasmosis	Nocardiosis	Pneumonia measles
Atypical mycobacterial pneumonia	Organising pneumonia	Pneumonia moraxella
Atypical pneumonia	Pneumocystis jiroveci pneumonia	Pneumonia mycoplasmal
Blastomycosis	Pneumonia	Pneumonia necrotising
Bronchopneumonia	Pneumonia adenoviral	Pneumonia parainfluenzae viral
Bronchopneumopathy	Pneumonia anthrax	Pneumonia pneumococcal
Candida pneumonia	Pneumonia aspiration	Pneumonia primary atypical
Coccidioidomycosis	Pneumonia bacterial	Pneumonia respiratory syncytial viral
Cryptococcosis	Pneumonia blastomyces	Pneumonia salmonella
Empyema	Pneumonia bordetella	Pneumonia staphylococcal
Enterobacter pneumonia	Pneumonia chlamydial	Pneumonia streptococcal
Histoplasmosis	Pneumonia cryptococcal	Pneumonia toxoplasmal
Infectious pleural effusion	Pneumonia cytomegaloviral	Pneumonia tularaemia
Legionella test positive	Pneumonia escherichia	Pneumonia viral
Lobar pneumonia	Pneumonia fungal	Pneumonic plague
Lung consolidation	Pneumonia haemophilus	Pneumonitis
Lung infection	Pneumonia helminthic	Pulmonary tuberculosis
Lung infection pseudomonal	Pneumonia herpes viral	Pyopneumothorax
Miliary pneumonia	Pneumonia influenzal	Q fever
Mycobacterium test positive	Pneumonia klebsiella	Tuberculosis
	Pneumonia legionella	

Table 3: **Overview of demographic characteristics, according to blood eosinophil count and treatment received**

	Placebo	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	VI 25	FF 100	FF 200	SAL/FP 50/250	SAL/FP 50/500	SAL 50	FP 250	FP 500	TIO 18	Total
N	1268	1026	1216	1016	1226	410	203	696	1316	1245	183	678	665	11 148
n with available eosinophil count	1240	998	1196	993	1205	405	201	683	1267	1205	182	651	635	10 861
Blood eosinophil count: <2%														
n	474	335	428	373	444	139	71	258	488	434	88	224	287	4043
Mean age, years [SD]	63·0 [8·62]	63·9 [9·46]	62·6 [9·48]	62·3 [9·42]	62·9 [9·47]	62·2 [8·71]	63·1 [8·43]	62·2 [9·58]	63·5 [8·92]	63·2 [9·08]	62·6 [9·65]	63·7 [9·12]	64·8 [8·05]	63·1 [9·13]
Gender, male, n (%)	338 (71)	191 (57)	256 (60)	212 (57)	257 (58)	88 (63)	52 (73)	170 (66)	368 (75)	270 (62)	58 (66)	144 (64)	232 (81)	2636 (65)
Mean BMI, kg/m^2	26·49	26·56	26·60[†]	26·43[‡]	26·52	25·30	26·59	26·49[§]	25·81	26·22[‖]	26·78	25·76	25·16	26·23[¶]
Exacerbations requiring antibiotics and/or OCS, within prior year,[*] total n	209	335	428	373	444	139	71	175	308	184	nm	49	287	3002
n (%): 0	149 (71)	81 (24)	147 (34)	90 (24)	134 (30)	101 (73)	48 (68)	116 (66)	111 (36)	123 (67)	nm	22 (45)	120 (42)	1242 (41)
1	31 (15)	170 (51)	201 (47)	198 (53)	205 (46)	34 (24)	18 (25)	25 (14)	81 (26)	40 (22)	nm	8 (16)	90 (31)	1101 (37)
2	18 (9)	63 (19)	52 (12)	64 (17)	80 (18)	2 (1)	1 (1)	20 (11)	55 (18)	15 (8)	nm	11 (22)	41 (14)	422 (14)
>2	11 (5)	21 (6)	28 (7)	21 (6)	25 (6)	2 (1)	4 (6)	14 (8)	61 (20)	6 (3)	nm	8 (16)	36(13)	237 (8)
Exacerbations requiring hospitalisation, within prior year,[*] total n	209	335	428	373	444	139	71	175	308	184	nm	50	287	3003
n (%): 0	190 (91)	272 (81)	353 (82)	309 (83)	384 (86)	125 (90)	63 (89)	157 (90)	232 (75)	165 (90)	nm	38 (76)	207 (72)	2495 (83)
1	17 (8)	49 (15)	61 (14)	57 (15)	49 (11)	11 (8)	8 (11)	17 (10)	61 (20)	17 (9)	nm	11 (22)	63 (22)	421 (14)
2	1 (<1)	10 (3)	11 (3)	6 (2)	6 (1)	3 (2)	0	1 (<1)	10 (3)	1 (<1)	nm	0	14 (5)	63 (2)
>2	1 (<1)	4 (1)	3 (<1)	1 (<1)	5 (1)	0	0	0	5 (2)	1 (<1)	nm	1 (2)	3 (1)	24 (<1)
Blood eosinophil count: ≥2%														
n	766	663	768	620	761	266	130	425	779	771	94	427	348	6818
Mean age, years [SD]	63·7 [8·62]	63·4 [9·21]	63·5 [8·78]	63·6 [8·74]	63·2 [9·25]	62·4 [9·01]	61·2 [9·33]	64·3[**] [9·65]	63·5 [8·71]	63·8[††] [9·02]	63·9 [9·09]	64·1 [8·62]	64·4 [8·46]	63·6[‡‡] [8·94]
Gender, male, n (%)	567 (74)	401 (60)	466 (61)	377 (61)	490 (64)	190 (71)	97 (75)	333 (78)	615 (79)	582 (75)	63 (67)	309 (72)	298 (86)	4788 (70)
Mean BMI, kg/m^2	26·40[§§]	26·93	27·06	26·56	26·47[‖‖]	26·96	26·84	26·96[¶¶]	26·04	26·81[†††]	26·83	26·19	25·69	26·58[***]
Exacerbations requiring antibiotics and/or OCS, within prior year,[*] total n	322	663	768	620	761	266	130	332	454	329	nm	74	348	5067
n (%): 0	231 (72)	128 (19)	223 (29)	126 (20)	226 (30)	208 (78)	90 (69)	208 (63)	171 (38)	199 (60)	nm	30 (41)	108 (31)	1948 (38)
1	51 (16)	347 (52)	379 (49)	351 (57)	342 (45)	48 (18)	33 (25)	73 (22)	126 (28)	72 (22)	nm	16 (22)	107 (31)	1945 (38)
2	27 (8)	133 (20)	104 (14)	97 (16)	119 (16)	9 (3)	5 (4)	30 (9)	86 (19)	38 (12)	nm	15 (20)	84 (24)	747 (15)
>2	13 (4)	55 (8)	62 (8)	46 (7)	74 (10)	1 (<1)	2 (2)	21 (6)	71 (16)	20 (6)	nm	13 (18)	49 (14)	427 (8)
Exacerbations requiring hospitalisation, within prior year,[*] total n	323	663	768	620	761	266	130	332	454	329	nm	74	348	5068
n (%): 0	297 (92)	546 (82)	642 (84)	497 (80)	645 (85)	243 (91)	115 (88)	296 (89)	351 (77)	300 (91)	nm	62 (84)	264 (76)	4258 (84)
1	24 (7)	92 (14)	110 (14)	113 (18)	98 (13)	22 (8)	13 (10)	32 (10)	80 (18)	25 (8)	nm	9 (12)	60 (17)	678 (13)
2	2 (<1)	21 (3)	10 (1)	6 (<1)	13 (2)	1 (<1)	2 (2)	2 (<1)	17 (4)	3 (<1)	nm	1 (1)	17 (5)	95 (2)
>2	0	4 (<1)	6 (<1)	4 (<1)	5 (<1)	0	0	2 (<1)	6 (1)	1 (<1)	nm	2 (3)	7 (2)	37 (<1)

BMI=body mass index. FF=fluticasone furoate. FP=fluticasone propionate. ICS=inhaled corticosteroids. nm=not measured. OCS=oral corticosteroids. PBO=placebo. SAL=salmeterol. TIO=tiotropium. VI=vilanterol.

[*]Trials: HZC112206, HZC112207, HZC102871, HZC102970, SCO30002, SCO100470, and SCO40036; [†]n=427; [‡]n=372; [§]n=257; [‖]n=432; [¶]n=4038; [**]n=423; [††]n=770; [‡‡]n=6815; [§§]n=765; [‖‖]n=759; [¶¶]n=422; [***]n=6811.

Table 4: **Summary of pneumonia adverse events for (A) FF/VI and (B) SAL/FP trials by blood eosinophil count**

A

Trials (duration)	**NCT01053988^{-Exac} (24 weeks in duration)**					**NCT01054885^{-Exac} (24 weeks in duration)**						**NCT01009463^{+Exac} (52 weeks in duration)**				**NCT01017952^{+Exac} (52 weeks in duration)**			
n (%)*	FF/VI 100/25	FF/VI 50/25	FF 100	VI 25	PBO	FF/VI 200/25	FF/VI 100/25	FF 200	FF 100	VI 25	PBO	FF/VI 200/25	FF/VI 100/25	FF/VI 50/25	VI 25	FF/VI 200/25	FF/VI 100/25	FF/VI 50/25	VI 25
Blood eosinophil count: <2%																			
n	78	77	62	75	66	88	90	71	77	85	93	146	119	115	148	139	141	143	136
Pneumonia	2 (2·6)	3 (3·9)	1 (1·6)	2 (2·7)	2 (3·0)	2 (2·3)	0	1 (1·4)	1 (1·3)	0	0	10 (6·8)	9 (7·6)	9 (7·8)	8 (5·4)	9 (6·5)	10 (7·1)	8 (5·6)	6 (4·4)
Serious pneumonia	0	1 (1·3)	1 (1·6)	1 (1·3)	1 (1·5)	2 (2·3)	0	0	0	0	0	3 (2·1)	5 (4·2)	4 (3·5)	1 (0·7)	6 (4·3)	5 (3·5)	4 (2·8)	3 (2·2)
Fatal pneumonia	0	0	0	0	0	0	0	0	0	0	0	2 (1·4)	0	0	0	0	0	0	1 (0·7)
Blood eosinophil count: ≥2%																			
n	127	127	141	128	141	114	113	130	125	112	112	247	278	277	255	259	250	259	266
Pneumonia	3 (2·4)	0	3 (2·1)	3 (2·3)	1 (0·7)	2 (1·8)	1 (0·9)	2 (1·5)	1 (0·8)	2 (1·8)	0	20 (8·1)	16 (5·8)	20 (7·2)	8 (3·1)	14 (5·4)	15 (6·0)	10 (3·9)	5 (1·9)
Serious pneumonia	1 (0·8)	0	2 (1·4)	2 (1·6)	0	1 (0·9)	0	2 (1·5)	0	2 (1·8)	0	10 (4·0)	6 (2·2)	10 (3·6)	1 (0·4)	3 (1·2)	8 (3·2)	5 (1·9)	3 (1·1)
Fatal pneumonia	0	0	0	0	0	0	0	0	0	0	0	4 (1·6)	0	0	0	0	1 (0·4)	0	0

B

Trials (duration)	**SCO30002$^{-Exac/+Exac}$ (52 weeks in duration)**			**SFCA3006^{-Exac} (24 weeks in duration)**				**SFCA3007^{-Exac} (24 weeks in duration)**				**SCO100470^{-Exac} (24 weeks in duration)**		**NCT00361959$^{-Exac/+Exac}$ (104 weeks in duration)**		**SFCB3024^{+Exac} (52 weeks in duration)**			
n (%)*	SAL/FP 50/500	FP 500	PBO	SAL/FP 50/500	SAL 50	FP 500	PBO	SAL/FP 50/250	SAL 50	FP 250	PBO	SAL/FP 50/250	SAL 50	SAL/FP 50/500	TIO	SAL/FP 50/500	SAL 50	FP 500	PBO
Blood eosinophil count: <2%																			
n	45	50	50	87	76	80	86	83	88	88	98	175	184	263	287	93	86	94	81
Pneumonia	1 (2·2)	0	0	1 (1·1)	0	1 (1·3)	1 (1·2)	0	1 (1·1)	1 (1·1)	0	1 (0·6)	1 (0·5)	27 (10·3)	10 (3·5)	5 (5·4)	6 (7·0)	3 (3·2)	5 (6·2)
Serious pneumonia	0	0	0	1 (1·1)	0	0	0	0	1 (1·1)	1 (1·1)	0	1 (0·6)	1 (0·5)	25 (9·5)	8 (2·8)	4 (4·3)	4 (4·7)	2 (2·1)	2 (2·5)
Fatal pneumonia	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (0·8)	0	0	0	0	0
Blood eosinophil count: ≥2%																			
n	84	74	70	76	84	87	94	93	89	94	83	332	329	371	348	248	269	266	266
Pneumonia	2 (2·4)	0	1 (1·4)	1 (1·3)	0	2 (2·3)	0	0	0	1 (1·1)	0	2 (0·6)	3 (0·9)	22 (5·9)	13 (3·7)	11 (4·4)	12 (4·5)	15 (5·6)	3 (1·1)
Serious pneumonia	0	0	1 (1·4)	1 (1·3)	0	2 (2·3)	0	0	0	0	0	1 (0·3)	3 (0·9)	16 (4·3)	11 (3·2)	3 (1·2)	6 (2·2)	7 (2·6)	1 (0·4)
Fatal pneumonia	0	0	0	0	0	0	1 (1·1)	0	0	0	0	0	0	1 (0·3)	0	0	0	0	0

$^{+Exac}$Conducted in patients with a history of COPD exacerbations; $^{-Exac}$Conducted in patients without a history of COPD exacerbation.

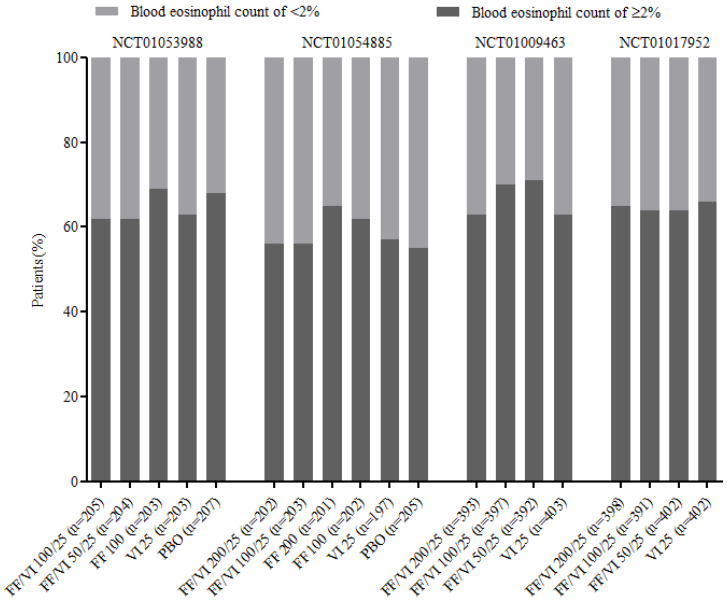
FF=fluticasone furoate. FP=fluticasone propionate. PBO=placebo. SAL=salmeterol. TIO=tiotropium. VI=vilanterol.

*The number of patients with a pneumonia event is presented, as some patients experienced ≥1 event.

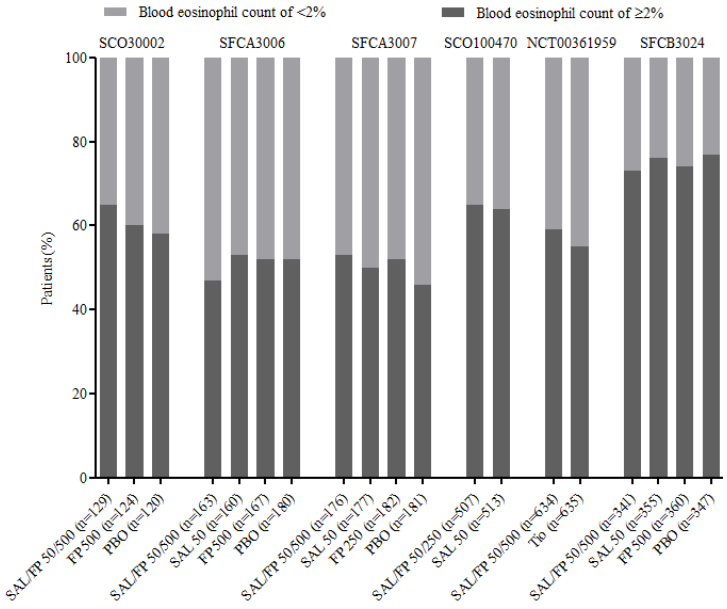
Figures

Figure 1: **Summary of eosinophil blood count at screening in (A) FF/VI and (B) SAL/FP trials**

A

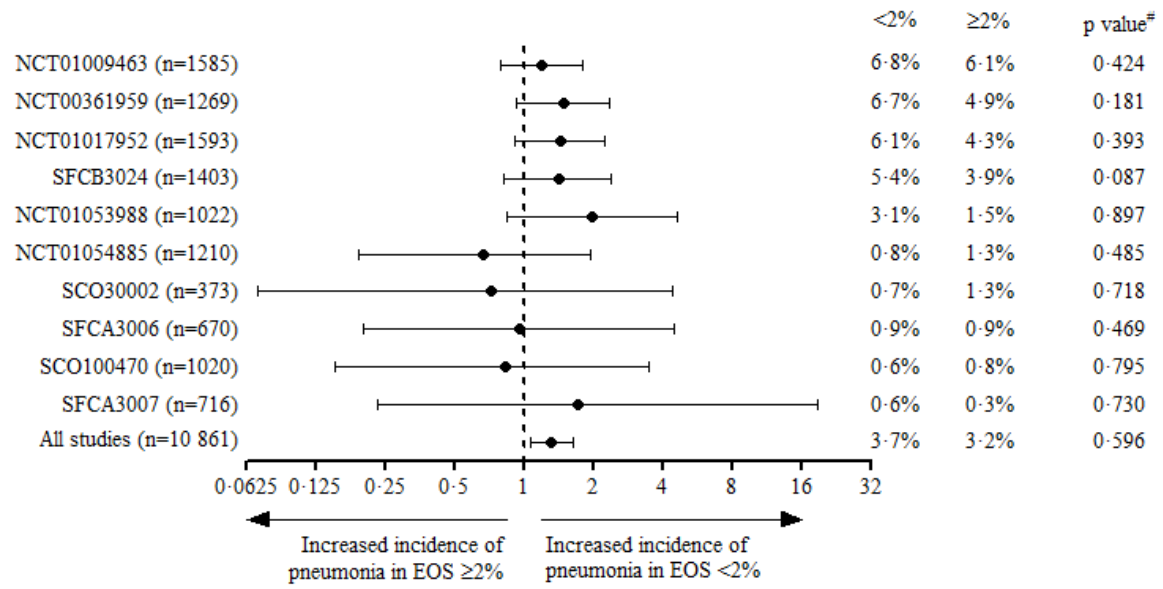


B



FP=fluticasone propionate. PBO=placebo. SAL=salmeterol. TIO=tiotropium.

Figure 2: **Forest plot showing the effect of eosinophil subgroup (<2% *vs* ≥2%) on pneumonia for each trial**

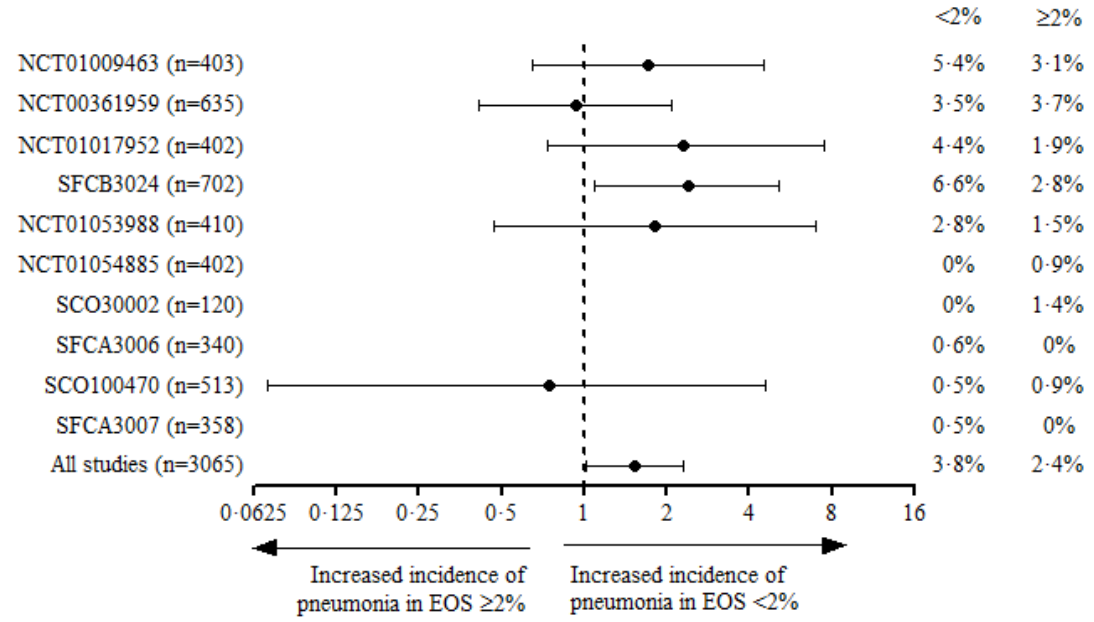


The time to pneumonia between patients with blood eosinophils above and below 2% was analysed using a Cox proportional hazards model stratified by trial (all trials, analysis only) and including terms for treatment and eosinophil subgroup. CI=confidence interval. EOS=eosinophil.

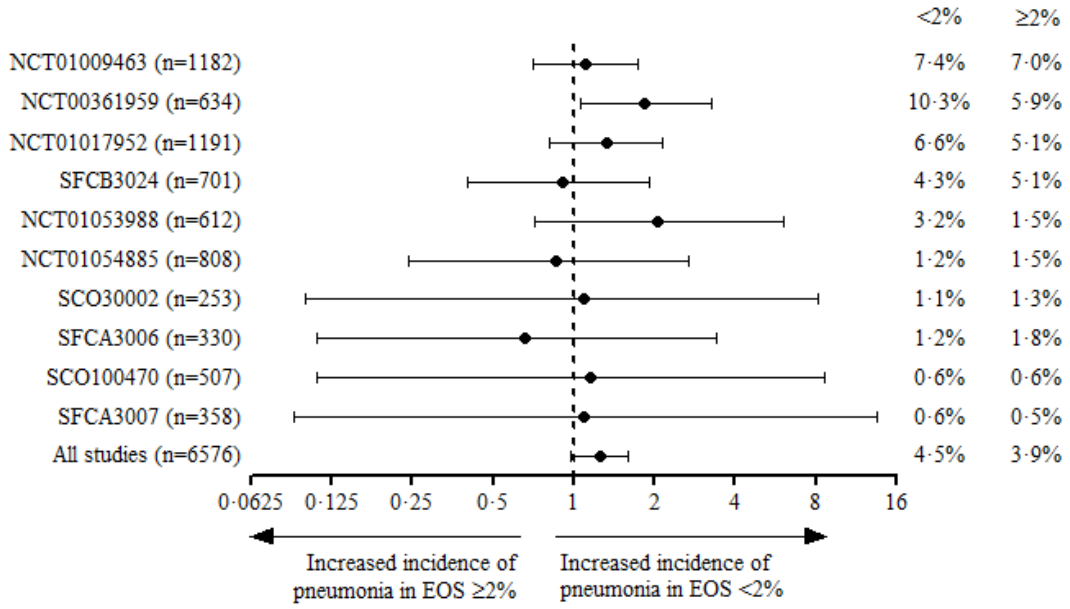
*The p value is for test of treatment by eosinophil interaction from a Cox proportional hazards model with an additional term for treatment by eosinophil interaction.

Figure 3: **Forest plot showing the effect of eosinophil subgroup (<2% *vs* ≥2%) on pneumonia for each trial, for (A) non-ICS treated and (B) ICS treated groups**

A



B



The time to pneumonia between patients with blood eosinophils above and below 2% in ICS treated or non-ICS treated groups was analysed using a Cox proportional hazards model stratified by trial (all trials, analysis only) and including terms for treatment and eosinophil subgroup. Treatment is defined as ICS containing and non-ICS containing. The n for all trials only includes those trials where the incidence of pneumonia in eosinophil subgroup was >0%. No hazard ratio or 95% CI is displayed for trials where the incidence of pneumonia in the <2% or ≥2% eosinophil subgroups was zero in the non ICS-treated groups (HZC112207, SCO30002, SFCA3006, and SFCA3007). CI=confidence interval. EOS=eosinophil. ICS=inhaled corticosteroids.

Supplementary data

Supplementary Table 1: **Overview of demographic characteristics for (A) FF/VI and (B) SAL/FP trials by blood eosinophil count**

A

Trials (duration)	NCT01053988-Exac (24 weeks in duration)					NCT01054885-Exac (24 weeks in duration)						NCT01009463+Exac (52 weeks in duration)				NCT01017952+Exac (52 weeks in duration)			
	FF/VI 100/25	FF/VI 50/25	FF 100	VI 25	PBO	FF/VI 200/25	FF/VI 100/25	FF 200	FF 100	VI 25	PBO	FF/VI 200/25	FF/VI 100/25	FF/VI 50/25	VI 25	FF/VI 200/25	FF/VI 100/25	FF/VI 50/25	VI 25
Blood eosinophil count: <2%																			
n	78	77	62	75	66	88	90	71	77	85	93	146	119	115	148	139	141	143	136
Mean age, years [SD]	62·2 [8·86]	64·4 [9·02]	62·4 [10·32]	63·1 [9·57]	61·9 [7·98]	60·1 [8·57]	61·2 [8·61]	63·1 [8·43]	62·0 [7·23]	62·2 [8·67]	61·7 [8·17]	63·0 [10·11]	63·0 [10·20]	63·7 [8·98]	62·9 [9·72]	63·0 [9·02]	63·4 [9·69]	63·7 [10·11]	63·2 [9·70]
Gender, male, n (%)	51 (65)	57 (74)	36 (58)	46 (61)	50 (76)	57 (65)	65 (72)	52 (73)	52 (68)	63 (74)	67 (72)	85 (58)	66 (55)	63 (55)	80 (54)	70 (50)	74 (52)	71 (50)	68 (50)
Mean BMI, kg/m^2	25·97	25·39	25·33	25·19	25·45	25·06	25·67	26·59	25·29	26·05	26·93	27·20	26·81†	27·01	26·46	26·51‡	27·37	26·83	27·60
Exacerbations requiring antibiotics/OCS,* total n	78	77	62	75	66	88	90	71	77	85	93	146	119	115	148	139	141	143	136
n (%): 0	62 (79)	60 (78)	43 (69)	60 (80)	55 (83)	62 (70)	65 (72)	48 (68)	58 (75)	59 (69)	73 (78)	13 (9)	10 (8)	7 (6)	11 (7)	15 (11)	10 (7)	14 (10)	4 (3)
1	14 (18)	14 (18)	17 (27)	11 (15)	9 (14)	20 (23)	22 (24)	18 (25)	17 (22)	24 (28)	16 (17)	95 (65)	80 (67)	73 (63)	95 (64)	83 (60)	85 (60)	83 (58)	75 (55)
2	2 (3)	3 (4)	1 (2)	3 (4)	1 (2)	4 (5)	3 (3)	1 (1)	1 (1)	1 (1)	4 (4)	28 (19)	19 (16)	25 (22)	33 (22)	32 (23)	28 (20)	35 (24)	43 (32)
>2	0	0	1 (2)	1 (1)	1 (2)	2 (2)	0	4 (6)	1 (1)	1 (1)	0	10 (7)	10 (8)	10 (9)	9 (6)	9 (6)	18 (13)	11 (8)	14 (10)
Exacerbations requiring hospitalisation,* total n	78	77	62	75	66	88	90	71	77	85	93	146	119	115	148	139	141	143	136
n (%): 0	74 (95)	72 (94)	57 (92)	68 (91)	62 (94)	82 (93)	78 (87)	63 (89)	68 (88)	78 (92)	85 (91)	116	93 (78)	90 (78)	124 (84)	111 (80)	108 (77)	110 (77)	114 (84)
1	4 (5)	4 (5)	5 (8)	6 (8)	3 (5)	6 (7)	12 (13)	8 (11)	6 (8)	6 (7)	7 (8)	(79)25	19 (16)	21 (18)	19 (13)	26 (19)	26 (18)	24 (17)	18 (13)
2	0	1 (1)	0	1 (1)	0	0	0	0	3 (4)	1 (1)	1 (1)	(17)	5 (4)	3 (3)	3 (2)	2 (1)	6 (4)	6 (4)	1 (<1)
>2	0	0	0	0	1 (2)	0	0	0	0	0	0	4 (3)	2 (2)	1 (<1)	2 (1)	0	1 (<1)	3 (2)	3 (2)
												1 (<1)							
Blood eosinophil count: ≥2%																			
n	127	127	141	128	141	114	113	130	125	112	112	247	278	277	255	259	250	259	266
Mean age, years [SD]	62·5 [8·29]	61·8 [9·14]	63·1 [9·10]	63·6 [9·69]	62·2 [9·18]	62·0 [8·68]	62·5 [8·96]	61·2 [9·33]	61·7 [8·90]	60·3 [8·66]	62·1 [8·14]	64·1 [8·77]	63·8 [8·59]	63·8 [9·15]	63·9 [9·26]	63·9 [8·70]	64·3 [9·10]	63·7 [9·27]	63·7 [9·08]
Gender, male, n (%)	86 (68)	76 (60)	94 (67)	92 (72)	91 (65)	78 (68)	78 (69)	97 (75)	96 (77)	83 (74)	85 (76)	157 (64)	161 (58)	172 (62)	153 (60)	142 (55)	141 (56)	153 (59)	162 (61)
Mean BMI, kg/m^2	27·52	26·46	25·84	25·79	26·32§	26·54	26·70	26·84	28·22	26·57	26·90	26·20	27·25	26·78	26·04‖	26·91	26·77	27·32	27·15
Exacerbations requiring antibiotics/OCS,* total n	127	127	141	128	141	114	113	130	125	112	112	247	278	277	255	259	250	259	266
n (%): 0	97 (76)	94 (74)	111 (79)	91 (71)	108 (77)	88 (77)	88 (78)	90 (69)	97 (78)	88 (79)	93 (83)	22 (9)	21 (8)	13 (5)	21 (8)	16 (6)	17 (7)	21 (8)	26 (10)
1	28 (22)	24 (19)	25 (18)	32 (25)	26 (18)	22 (19)	21 (19)	33 (25)	23 (18)	21 (19)	12 (11)	168 (68)	175 (63)	180 (65)	139 (55)	161 (62)	155 (62)	143 (55)	150 (56)
2	2 (2)	8 (6)	5 (4)	1 (<1)	5 (4)	2 (2)	1 (<1)	5 (4)	4 (3)	1 (<1)	4 (4)	35 (14)	52 (19)	59 (21)	59 (23)	60 (23)	49 (20)	66 (25)	58 (22)
>2	0	1 (<1)	0	4 (3)	2 (1)	2 (2)	3 (3)	2 (2)	1 (<1)	2 (2)	3 (3)	22 (9)	30 (11)	25 (9)	36 (14)	22 (8)	29 (12)	29 (11)	32 (12)
Exacerbations requiring hospitalisation,* total n	127	127	141	128	141	114	113	130	125	112	112	247	278	277	255	259	250	259	266
n (%): 0	117 (92)	121 (95)	127 (90)	119 (93)	134 (95)	100 (88)	101 (89)	115 (88)	116 (93)	104 (93)	100 (89)	186 (75)	227 (82)	226 (82)	211 (83)	211 (81)	197 (79)	199 (77)	211 (79)
1	10 (8)	6 (5)	13 (9)	9 (7)	7 (5)	14 (12)	12 (11)	13 (10)	9 (7)	7 (6)	11 (10)	56 (23)	42 (15)	40 (14)	39 (15)	43 (17)	46 (18)	46 (18)	43 (16)
2	0	0	1 (<1)	0	0	0	0	2 (2)	0	1 (<1)	1 (<1)	4 (2)	5 (2)	9 (3)	5 (2)	2 (<1)	5 (2)	12 (5)	7 (3)
>2	0	0	0	0	0	0	0	0	0	0	0	1 (<1)	4 (1)	2 (<1)	0	3 (1)	2 (<1)	2 (<1)	5 (2)

B

Trials (duration)	SCO30002[-Exac/+Exac] (52 weeks in duration)			SFCA3006[-Exac] (24 weeks in duration)				SFCA3007[-Exac] (24 weeks in duration)				SCO100470[-Exac] (24 weeks in duration)		NCT00361959[-Exac/+Exac] (104 weeks in duration)		SFCB3024[+Exac] (52 weeks in duration)			
	SAL/FP 50/500	FP 500	PBO	SAL/FP 50/500	SAL 50	FP 500	PBO	SAL/FP 50/250	SAL 50	FP 250	PBO	SAL/FP 50/250	SAL 50	SAL/FP 50/500	TIO	SAL/FP 50/500	SAL 50	FP 500	PBO
Blood eosinophil count: <2%																			
n	45	50	50	87	76	80	86	83	88	88	98	175	184	263	287	93	86	94	81
Mean age, years [SD]	64·4 [9·08]	63·0 [9·44]	66·9 [9·02]	61·7 [9·52]	62·6 [8·74]	64·6 [9·50]	63·6 [8·10]	61·2 [10·22]	63·2 [9·17]	62·6 [9·65]	64·6 [9·05]	62·7 [9·25]	62·9 [9·51]	64·1 [8·79]	64·8 [8·05]	63·1 [8·49]	64·4 [8·38]	63·3 [8·64]	60·3 [8·23]
Gender, male, n (%)	39 (87)	42 (84)	37 (74)	49 (56)	43 (57)	45 (56)	66 (77)	39 (47)	42 (48)	58 (66)	63 (64)	131 (75)	137 (74)	208 (79)	232 (81)	72 (77)	48 (56)	57 (61)	55 (68)
Mean BMI, kg/m^2	26·86	26·28	26·81	27·31	26·69	25·82	27·64	26·27	26·63	26·78	26·42	26·60[¶]	26·40	25·41	25·16	25·04	25·00	25·44	25·48
Exacerbations requiring antibiotics/OCS,[*] total n	45	49	50	nm	nm	nm	nm	nm	nm	nm	nm	175	184	263	287	nm	nm	nm	nm
n (%): 0	18 (40)	22 (45)	21 (42)									116 (66)	123 (67)	93 (35)	120 (42)				
1	10 (22)	8 (16)	6 (12)									25 (14)	40 (22)	71 (27)	90 (31)				
2	8 (18)	11 (22)	13 (26)									20 (11)	15 (8)	47 (18)	41 (14)				
>2	9 (20)	8 (16)	10 (20)									14 (8)	6 (3)	52 (20)	36 (13)				
Exacerbations requiring hospitalisation,[*] total n	45	50	50	nm	nm	nm	nm	nm	nm	nm	nm	175	184	263	287	nm	nm	nm	nm
n (%): 0	36 (80)	38 (76)	43 (86)									157 (90)	165 (90)	196 (75)	207 (72)				
1	9 (20)	11 (22)	7 (14)									17 (10)	17 (9)	52 (20)	63 (22)				
2	0	0	0									1 (<1)	1 (<1)	10 (4)	14 (5)				
>2	0	1 (2)	0									0	1 (<1)	5 (2)	3 (1)				
Blood eosinophil count: ≥2%																			
n	84	74	70	76	84	87	94	93	89	94	83	330	329	371	348	248	269	266	266
Mean age, years [SD]	63·7 [10·50]	65·1 [8·13]	64·7 [8·62]	62·0 [9·10]	64·3 [10·03]	64·3 [9·19]	64·3 [8·56]	65·5 [10·64]	65·2 [10·38]	63·9 [9·09]	64·9 [8·35]	64·0 [9·35]	64·0[††] [8·76]	64·3 [8·06]	64·4 [8·46]	62·8 [8·80]	62·8 [8·47]	63·7 [8·57]	64·3 [8·50]
Gender, male, n (%)	69 (82)	60 (81)	59 (84)	52 (68)	60 (71)	57 (66)	69 (73)	67 (72)	60 (67)	63 (67)	60 (72)	266 (80)	263 (80)	305 (82)	298 (86)	189 (76)	199 (74)	192 (72)	203 (76)
Mean BMI, kg/m^2	27·10	27·17	26·95	27·17	27·93	26·69	27·40	26·52	26·25	26·83	26·90	27·08[**]	26·91[††]	25·73	25·69	25·81	26·54	25·76	25·59
Exacerbations requiring antibiotics/OCS, [*] total n	83	74	69	nm	nm	nm	nm	nm	nm	nm	nm	332	329	371	348	nm	nm	nm	nm
n (%): 0	27 (33)	30 (41)	30 (43)									208 (63)	199 (60)	144 (39)	108 (31)				
1	22 (27)	16 (22)	13 (19)									73 (22)	72 (22)	104 (28)	107 (31)				
2	21 (25)	15 (20)	18 (26)									30 (9)	38 (12)	65 (18)	84 (24)				
>2	13 (16)	13 (18)	8 (12)									21 (6)	20 (6)	58 (16)	49 (14)				
Exacerbations requiring hospitalisation,[*] total n	83	74	70	nm	nm	nm	nm	nm	nm	nm	nm	332	329	371	348	nm	nm	nm	nm
n (%): 0	65 (78)	62 (84)	63 (90)									296 (89)	300 (91)	286 (77)	264 (76)				
1	14 (17)	9 (12)	6 (9)									32 (10)	25 (8)	66 (18)	60 (17)				
2	3 (4)	1 (1)	1 (1)									2 (<1)	3 (<1)	14 (4)	17 (5)				
>2	1 (1)	2 (3)	0									2 (<1)	1 (<1)	5 (1)	7 (2)				

[+Exac]Conducted in patients with a history of COPD exacerbations; [-Exac]Conducted in patients without a history of COPD exacerbations.

BMI=body mass index. FF=fluticasone furoate. FP=fluticasone propionate. ICS=inhaled corticosteroids. nm=not measured. OCS=oral corticosteroids. PBO=placebo. SAL=salmeterol. TIO=tiotropium. VI=vilanterol. WBC=white blood cell.

[*]Within 12 months prior to screening, trials: HZC112206, HZC112207, HZC102871, HZC102970, SCO30002, SCO100470, and SCO40036; [†]n=118; [‡]n=138; [§]n=140; [‖]n=253; [¶]n=174; [**]n=329; [††]n=328.

Supplementary Table 2: **Summary of lung function at screening for FF/VI and SAL/FP trials by blood eosinophil count**

	Placebo	**FF/VI 50/25**	**FF/VI 100/25**	**FF/VI 200/25**	**VI 25**	**FF 100**	**FF 200**	**SAL/FP 50/250**	**SAL/FP 50/500**	**SAL 50**	**FP 250**	**FP 500**	**TIO 18**
N	1268	1026	1216	1016	1226	410	203	696	1316	1245	183	678	665
Blood eosinophil count: <2%													
Pre-BD FEV_1 % predicted													
mean	43·9	41·7	41·9	41·4	42·5	43·5	41·3	54·9	40·9	50·4	41·7	46·6	36·8
(SD)	(12·78)	(13·36)	(13·62)	(13·29)	(13·83)	(13·30)	(11·86)	(12·76)	(11·91)	(14·03)	(10·74)	(13·07)	(9·01)
n	473	333	425	367	443	137	70	257	488	432	88	224	285
Post-BD FEV_1 % predicted													
mean	49·5	46·7	46·4	45·8	46·9	46·9	45·7	59·5	44·4	55·4	49·4	50·8	39·3
(SD)	(13·28)	(13·54)	(13·50)	(12·69)	(13·49)	(12·82)	(12·04)	(11·91)	(12·47)	(13·22)	(12·68)	(13·04)	(9·20)
n	471	332	423	371	440	137	71	257	488	431	88	224	287
FEV_1 % reversibility													
mean	14·5	13·7	12·8	12·6	12·5	10·6	11·6	9·8	9·4	11·9	19·0	10·4	7·9
(SD)	(13·71)	(14·05)	(14·50)	(14·30)	(14·89)	(16·67)	(12·29)	(12·21)	(11·10)	(13·50)	(13·97)	(12·21)	(12·03)
n	471	331	422	366	439	136	70	258	488	433	88	224	285
Blood eosinophil count: ≥2%													
Pre-BD FEV_1 % predicted													
mean	45·4	40·3	41·4	40·6	41·0	42·5	43·5	55·9	42·6	50·9	41·9	47·7	36·8
(SD)	(13·29)	(13·40)	(13·11)	(13·67)	(12·56)	(13·04)	(13·23)	(12·98)	(13·07)	(14·06)	(11·74)	(13·93)	(8·95)
n	766	657	763	614	750	264	129	421	779	769	94	426	348
Post-BD FEV_1 % predicted													
mean	50·6	45·4	46·8	45·4	46·3	47·9	47·9	59·8	46·0	55·3	50·0	52·4	39·5
(SD)	(13·50)	(13·37)	(12·98)	(13·72)	(12·63)	(12·34)	(12·00)	(11·87)	(13·75)	(13·65)	(13·60)	(14·61)	(8·67)
n	764	659	763	612	757	265	129	421	779	769	94	426	348
FEV_1 % reversibility													
mean	13·2	15·5	15·3	14·3	15·2	15·5	12·8	8·7	9·1	10·2	20·2	11·0	8·6
(SD)	(13·80)	(16·60)	(16·35)	(19·62)	(17·01)	(17·53)	(15·25)	(11·07)	(12·11)	(12·65)	(14·16)	(13·46)	(13·20)
n	764	655	760	608	751	264	129	425	779	771	94	426	348

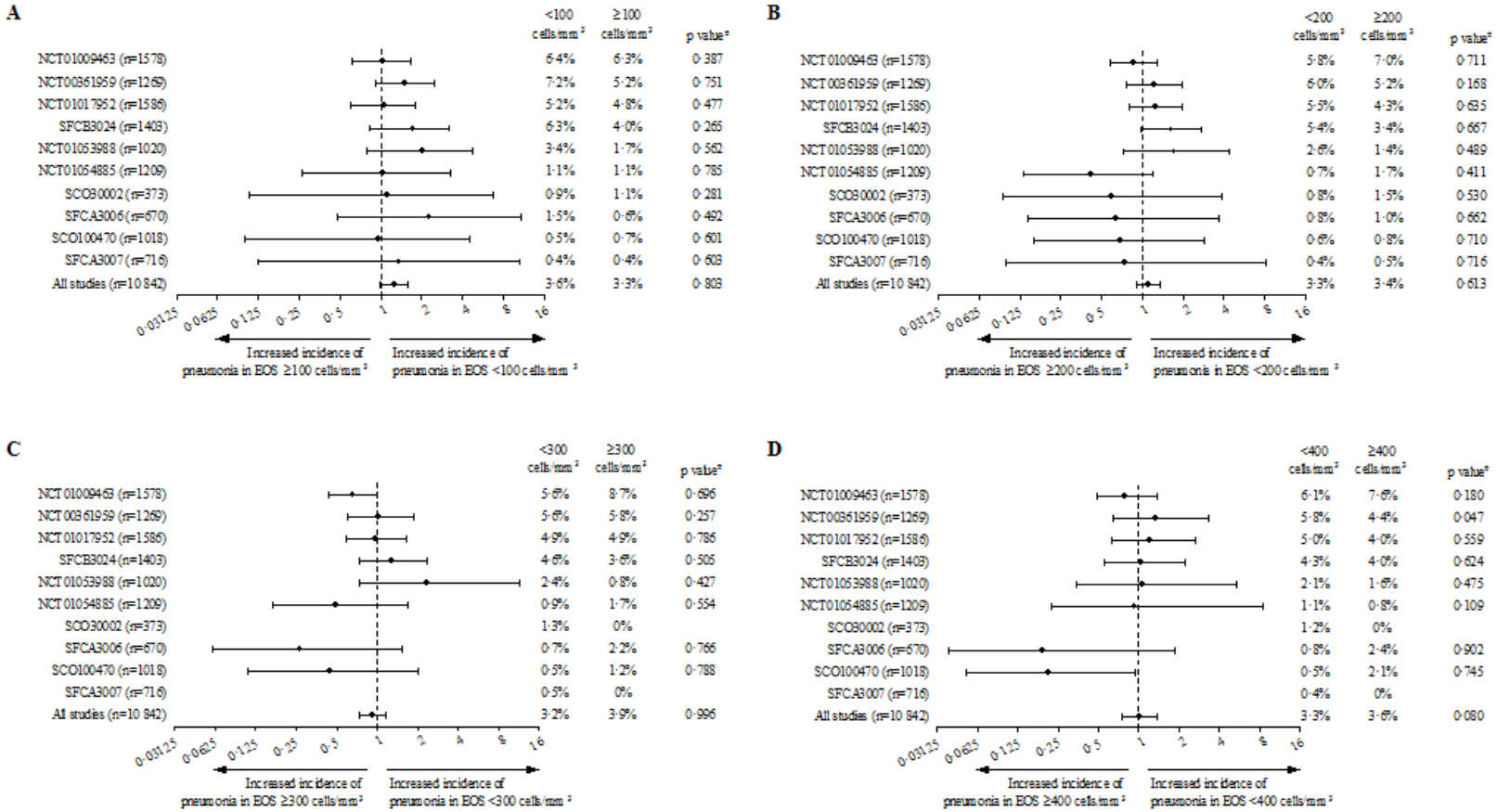
BD=bronchodilator. FEV_1=forced expiratory volume in 1 second. FF=fluticasone furoate. FP=fluticasone propionate. PBO=placebo. SAL=salmeterol. SD=standard deviation. TIO=tiotropium. VI=vilanterol.

Supplementary Table 3: **Classification of patients according to baseline eosinophil counts above and below the following cut-offs: 100/mm^3, 200/mm^3, 300/mm^3, and 400/mm^3**

Trial	Treatment group	Baseline eosinophil counts (/mm^3)							
		<100	≥100	<200	≥200	<300	≥300	<400	≥400
NCT01009463	ICS	215	964	611	568	875	304	1009	170
	No ICS	84	315	240	159	311	88	346	53
NCT01017952	ICS	229	958	638	549	898	289	1033	154
	No ICS	76	323	196	203	298	101	354	45
NCT01053988	ICS	124	488	328	284	472	140	535	77
	No ICS	80	328	205	203	309	99	358	50
NCT01054885	ICS	194	614	485	323	653	155	728	80
	No ICS	85	316	243	158	323	78	360	41
SCO100470	ICS	100	407	271	236	386	121	440	67
	No ICS	99	412	262	249	372	139	438	73
SCO30002	ICS	71	182	160	93	211	42	229	24
	No ICS	38	82	78	42	102	18	113	7
NCT00361959	ICS	147	487	359	275	501	133	566	68
	No ICS	159	476	369	266	511	124	568	67
SFCA3006	ICS	99	231	243	87	284	46	313	17
	No ICS	101	239	236	104	294	46	315	25
SFCA3007	ICS	106	252	246	112	313	45	336	22
	No ICS	120	238	251	107	308	50	334	24
SFCB3024	ICS	81	620	315	386	513	188	604	97
	No ICS	77	625	297	405	475	227	575	127

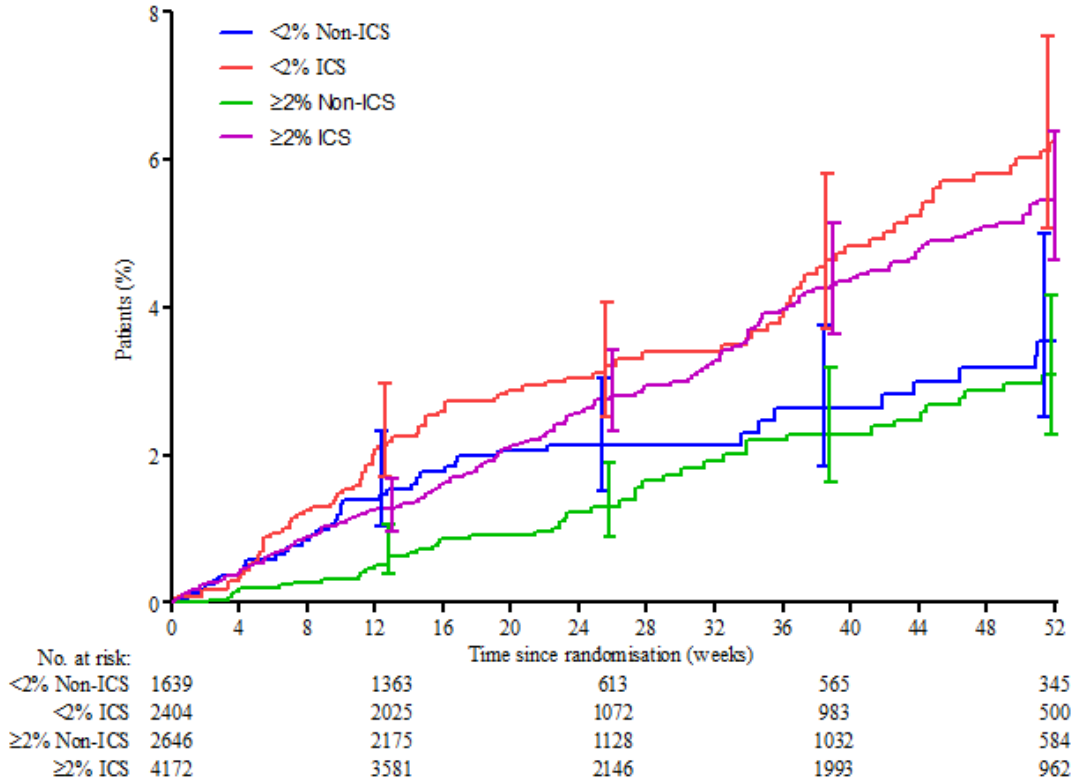
ICS=inhaled corticosteroids.

Supplementary Figure 1: **Forest plot showing the effect of eosinophil levels on pneumonia for each trial, for eosinophil subgroups (A) < and ≥ 100 cells/mm^3, (B) < and ≥ 200 cells/mm^3, (C) < and ≥ 300 cells/mm^3, and (D) < and ≥ 400 cells/mm^3**



The time to first pneumonia between patients with blood eosinophils above and below each of the cut-offs was analysed using a Cox proportional hazards model, stratified by trial (all trials, analysis only) and including terms for treatment and eosinophil subgroup. Treatment was defined as ICS containing and non-ICS containing.
CI=confidence interval. EOS=eosinophil.
*The p value is for test of treatment by eosinophil interaction from a Cox proportional hazards model with an additional term for treatment by eosinophil interaction.

Supplementary Figure 2: **Kaplan–Meier estimate of the time to first on-treatment pneumonia adverse event, by baseline blood eosinophil percentage and ICS use**



Confidence intervals are presented at weeks 13, 26, 39, and 52 only. ICS=inhaled corticosteroid.