Online Supplement

Table S1 Demographics and baseline characteristics for 24-week studies of FP/SAL in patients with COPD by baseline blood eosinophil level

Treatment	**FP/SAL**		**FP**		**SAL**		**Placebo**	
Eosinophil level	**<2%**	**≥2%**	**<2%**	**≥2%**	**<2%**	**≥2%**	**<2%**	**≥2%**
SFCA3006								
N	87	76	80	87	76	84	86	94
Age, mean years (SD)	61.7 (9.52)	62.0 (9.10)	64.6 (9.50)	64.3 (9.19)	62.6 (8.74)	64.3 (10.03)	63.6 (8.10)	64.3 (8.56)
Male (%)	56	68	56	66	57	71	77	73
Current smokers (%)	52	39	54	39	58	36	57	50
Pack years, median (range)	55.0 (15–150)	54.5 (20–132)	52.5 (23–120)	54.0 (20–200)	53.5 (20–193)	50.0 (20–150)	64.5 (20–165)	60.0 (20–150)
FEV_1 % predicted, mean (SD)	47.1 (12.48)	50.8 (15.28)	47.7 (11.95)	49.9 (15.13)	48.9 (12.67)	47.6 (13.65)	49.2 (12.85)	48.8 (14.09)
FEV_1 % reversibility, mean (SD)	18.2 (14.56)	23.1 (18.44)	18.5 (14.33)	19.9 (13.67)	20.3 (14.02)	22.0 (18.26)	20.9 (14.65)	17.8 (13.69)
SFCA3007								
N	83	93	88	94	88	89	98	83
Age, mean years (SD)	61.2 (10.22)	65.5 (10.64)	62.6 (9.65)	63.9 (9.09)	63.2 (9.17)	65.2 (10.38)	64.6 (9.05)	64.9 (8.35)
Male (%)	47	72	66	67	48	67	64	72
Current smokers (%)	48	39	59	38	60	42	53	41
Pack years, median (range)	60.0 (20–135)	50.0 (20–220)	60.0 (20–120)	60.0 (20–162)	58.0 (20–180)	57.0 (20–224)	60.0 (22–140)	50.0 (20–165)
FEV_1 % predicted, mean (SD)	51.3 (13.33)	47.5 (12.49)	49.4 (12.68)	50.0 (13.60)	50.6 (12.68)*	49.3 (12.82)	50.3 (13.98)	50.4 (14.69)
FEV_1 % reversibility, mean (SD)	19.8 (14.61)	20.7 (14.64)	19.0 (13.97)	20.2 (14.16)	21.5 (16.62)*	21.1 (14.20)	18.6 (14.80)	22.0 (16.96)
SCO100470								

N	175	332	-	-	184	329	-	-
Age, mean years (SD)	62.7 (9.25)	64.0 (9.35)	-	-	62.9 (9.51)	64.0 (8.76)	-	-
Male (%)	75	80	-	-	74	80	-	-
Current smokers (%)	44	41‡	-	-	47	41‖	-	-
Pack years, median (range)	38.0 (6–125)	35.0 (6–158)‡	-	-	36.0 (4–150)	36.0 (10–135)‖	-	-
s	63.5 (8.80)†	63.3 (9.03)§	-	-	63.3 (8.40)¶	63.0 (9.15)**	-	-
FEV_1 % reversibility, mean (SD)	2.9 (3.98)†	2.9 (3.83)§	-	-	2.9 (4.07)¶	3.4 (4.24)**	-	-
Moderate/severe exacerbations in prior 12 months, n (%)								
0	104 (59)	191 (58)			114 (62)	181 (55)		
1	33 (19)	84 (25)			41 (22)	82 (25)		
2	22 (13)	30 (9)			20 (11)	42 (13)		
>2	16 (9)	27 (8)			9 (5)	24 (7)		

*n=87.

†n=174.

‡n=332.

§n=328.

¶n=182.

‖n=329.

**n=327.

COPD, chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; FP = fluticasone propionate; SAL = salmeterol; SD = standard deviation.

Table S2 Summary of screening baseline blood eosinophil and white blood count data

Treatment	FP/SAL	FP	SAL	Tiotropium	Placebo
TRISTAN (SFCB3024)					
N	341	360	355	-	347
Eosinophils, % (SD)	3.62 (2.413)	3.42 (2.239)	3.75 (2.544)	-	3.72 (2.353)
Eosinophils, mm^3 (SD)	254.60 (200.803)	247.78 (182.597)	270.39 (206.370)	-	265.68 (179.001)
White blood cells, mm^3 (SD)	7198.5 (1944.36)*	7487.3 (2222.92)†	7208.1 (1938.39)‡	-	7321.8 (1902.26)§
INSPIRE (SCO40036)					
N	634	-	-	635	-
Eosinophils, % (SD)	2.76 (2.281)	-	-	2.71 (2.219)	-
Eosinophils, mm^3 (SD)	212.35 (178.598)	-	-	208.14 (175.812)	-
White blood cells, mm^3 (SD)	8043.4 (2411.25)	-	-	8057.3 (2362.58)	-
SFCA3006					
N	163	167	160	-	180
Eosinophils, % (SD)	2.55 (2.433)	2.44 (1.788)	2.49 (1.811)	-	2.53 (1.808)
Eosinophils, mm^3 (SD)	189.38 (233.670)	170.82 (139.242)	175.03 (130.927)	-	181.87 (139.170)
White blood cells, mm^3 (SD)	7401.0 (1995.95)	6954.7 (1825.09)	7278.4 (1898.01)	-	7304.6 (2150.20)
SFCA3007					
N	176	182	177	-	181
Eosinophils, % (SD)	2.46 (1.657)	2.43 (1.735)	2.50 (1.950)	-	2.30 (1.685)
Eosinophils, mm^3 (SD)	172.37 (121.182)	178.75 (130.499)	187.31 (161.910)	-	167.17 (124.027)
White blood cells, mm^3 (SD)	7277.6 (1806.43)	7537.1 (2079.11)	7560.6 (1967.03)	-	7415.2 (1901.96)
SCO100470					
N	507	-	513	-	-
Eosinophils, % (SD)	3.18 (2.851)	-	3.37 (3.154)	-	-
Eosinophils, mm^3 (SD)	238.78 (249.783)	-	250.22 (305.034)¶	-	-
White blood cells, mm^3 (SD)	7541.8 (1910.65)	-	7563.7 (2317.14)‖	-	-

*n=344.

†n=361.

‡n=356.

§n=348.
¶n=511.
‖n=512.
FP, fluticasone propionate; SAL, salmeterol; SD, standard deviation.

Table S3 Adjusted mean number of exacerbations/year according to study treatment and baseline blood eosinophil subgroup

Treatment	**FP/SAL**		**FP**		**SAL**		**Tiotropium**		**Placebo**	
Eosinophil level	**<2%**	**≥2%**	**<2%**	**≥2%**	**<2%**	**≥2%**	**<2%**	**≥2%**	**<2%**	**≥2%**
TRISTAN (SFCB3024)										
n	92	247	94	266	86	269	-	-	81	266
Adjusted mean	1.43	1.14	1.18	1.32	1.23	1.28	-	-	1.44	1.82
INSPIRE (SCO40036)										
Excluding history of exacerbations										
n	263	371	-	-	-	-	287	348	-	-
Adjusted mean	1.57	1.60	-	-	-	-	1.32	2.14	-	-
Including history of exacerbations										
n	263	371	-	-	-	-	287	348	-	-
Adjusted mean	1.34	1.47	-	-	-	-	1.25	1.79	-	-
SCO30002										
Excluding history of exacerbations										
n	45	84	50	74	-	-	-	-	50	70
Adjusted mean	1.77	0.89	1.16	0.87	-	-	-	-	0.94	1.08
Including history of exacerbations										
n	45	83	50	74	-	-	-	-	50	70
Adjusted mean	1.68	0.84	1.06	0.81	-	-	-	-	0.88	1.02

FP, fluticasone propionate; SAL, salmeterol.

Analysis performed using a negative binomial regression model with covariates of either: treatment, gender, history of exacerbations, baseline % predicted FEV_1, percentage eosinophil group and treatment by percentage eosinophils interaction; or treatment, gender, baseline % predicted FEV_1, percentage eosinophil group and treatment by percentage eosinophils interaction.

Table S4 Analysis of moderate and severe exacerbations negative binomial model by treatment and percentage eosinophils using a 3% cut-off in INSPIRE and TRISTAN

	Eosinophil level <3%		**Eosinophil level ≥3%**	
Treatment comparison	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**
INSPIRE (SCO40036) (n=1,269)				
FP/SAL versus tiotropium (excluding history of exacerbations covariate)	0.94 (0.77, 1.15)	0.542	0.83 (0.63, 1.09)	0.177
FP/SAL versus tiotropium (including history of exacerbations covariate)	0.91 (0.75, 1.10)	0.330	0.93 (0.71, 1.22)	0.614
TRISTAN (SFCB3024) (n=1,403)				
FP/SAL versus placebo	0.91 (0.68, 1.22)	0.517	0.56 (0.43, 0.75)	**<0.001**
FP/SAL versus SAL	1.09 (0.82, 1.45)	0.554	0.85 (0.64, 1.12)	0.241
FP/SAL versus FP	0.97 (0.74, 1.29)	0.854	0.92 (0.69, 1.21)	0.550
FP versus placebo	0.93 (0.70, 1.24)	0.629	0.61 (0.47, 0.80)	**<0.001**
SAL versus placebo	0.83 (0.62, 1.11)	0.217	0.67 (0.51, 0.87)	**0.003**

FP, fluticasone propionate; SAL, salmeterol.

Analysis performed using a negative binomial regression model with covariates of either: treatment, gender, history of exacerbations, baseline % predicted FEV_1, percentage eosinophil group and treatment by percentage eosinophils interaction; or treatment, gender, baseline % predicted FEV_1, percentage eosinophil group and treatment by percentage eosinophils interaction.

Table S5 An analysis of the rate of exacerbations requiring antibiotics

	Eosinophil level <2%		Eosinophil level ≥2%	
Treatment comparison	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**
INSPIRE (SCO40036) (n=1,269)				
FP/SAL versus tiotropium (excluding history of exacerbations covariate)	1.46 (1.13, 1.89)	**0.004**	0.95 (0.76, 1.19)	0.652
FP/SAL versus tiotropium (including history of exacerbations covariate)	1.32 (1.03, 1.70)	**0.030**	1.05 (0.84, 1.30)	0.670
TRISTAN (SFCB3024) (n=1,403)				
FP/SAL versus placebo	1.43 (0.92, 2.24)	0.115	0.93 (0.72, 1.22)	0.615
FP/SAL versus SAL	1.63 (1.05, 2.53)	**0.028**	1.14 (0.88, 1.48)	0.324
FP/SAL versus FP	1.44 (0.95, 2.19)	0.086	0.93 (0.72, 1.19)	0.567
FP versus placebo	0.99 (0.63, 1.56)	0.979	1.01 (0.78, 1.30)	0.964
SAL versus placebo	0.88 (0.55, 1.40)	0.586	0.82 (0.63, 1.07)	0.143

Analysis performed using a negative binomial regression model with covariates of either: treatment, gender, history of exacerbations, baseline % predicted FEV_1, percentage eosinophil group and treatment by percentage eosinophils interaction; or treatment, gender, baseline % predicted FEV_1, percentage eosinophil group and treatment by percentage eosinophils interaction.

FP, fluticasone propionate; SAL, salmeterol.

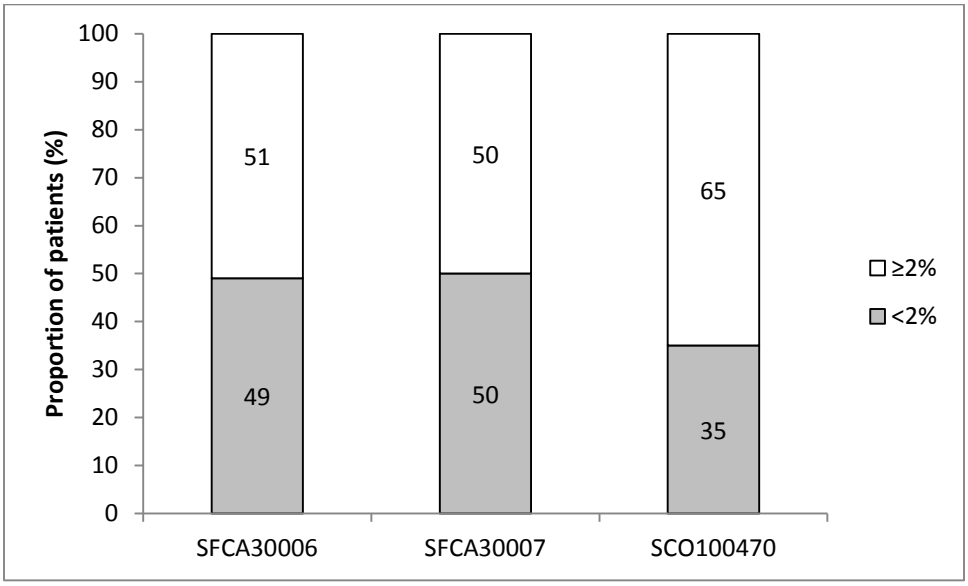
Table S6 An analysis of the rate of exacerbations requiring oral corticosteroids

	Eosinophil level <2%		Eosinophil level ≥2%	
Treatment comparison	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**
INSPIRE (SCO40036) (n=1,269)				
FP/SAL versus tiotropium (excluding history of exacerbations covariate)	1.08 (0.79, 1.51)	0.633	0.53 (0.40, 0.70)	**<0.001**
FP/SAL versus tiotropium (including history of exacerbations covariate)	0.99 (0.72, 1.38)	0.974	0.58 (0.44, 0.76)	**<0.001**
TRISTAN (SFCB3024) (n=1,403)				
FP/SAL versus placebo	0.74 (0.43, 1.27)	0.274	0.50 (0.36, 0.69)	**<0.001**
FP/SAL versus SAL	1.02 (0.60, 1.74)	0.932	0.82 (0.59, 1.13)	0.219
FP/SAL versus FP	1.08 (0.64, 1.83)	0.775	0.93 (0.67, 1.28)	0.658
FP versus placebo	0.69 (0.41, 1.15)	0.154	0.54 (0.39. 0.73)	**<0.001**
SAL versus placebo	0.72 (0.43, 1.22)	0.224	0.61 (0.45, 0.82)	**0.001**

Analysis performed using a negative binomial regression model with covariates of either: treatment, gender, history of exacerbations, baseline % predicted FEV_1, percentage eosinophil group and treatment by percentage eosinophils interaction; or treatment, gender, baseline % predicted FEV_1, percentage eosinophil group and treatment by percentage eosinophils interaction.

FP, fluticasone propionate; SAL, salmeterol.

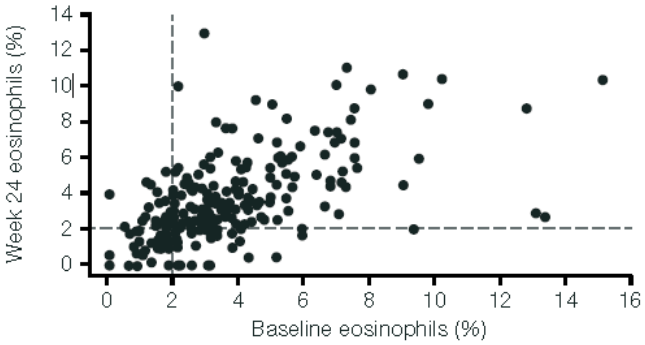
Figure S1 Proportion of all patients with baseline blood eosinophil level <2% and ≥2% in 24-week studies of FP/SAL in patients with COPD.



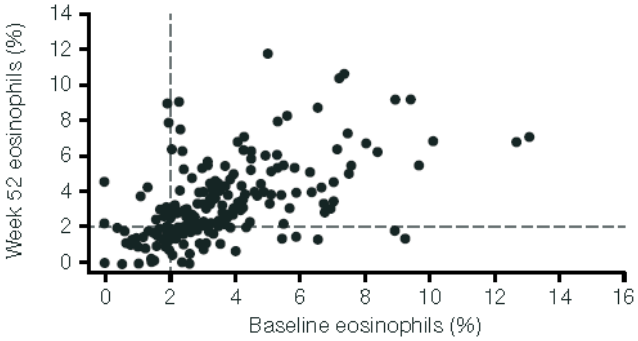
COPD, chronic obstructive pulmonary disease; FP, fluticasone propionate; SAL, salmeterol.

Figure S2 Scatter plot of (A) 24-week post-baseline blood eosinophils versus baseline blood eosinophils, (B) 52-week post-baseline blood eosinophils versus baseline blood eosinophils, and (C) 24-week post-baseline blood eosinophils versus 52-week post-baseline blood eosinophils, in the placebo group of TRISTAN (SFCB3024).

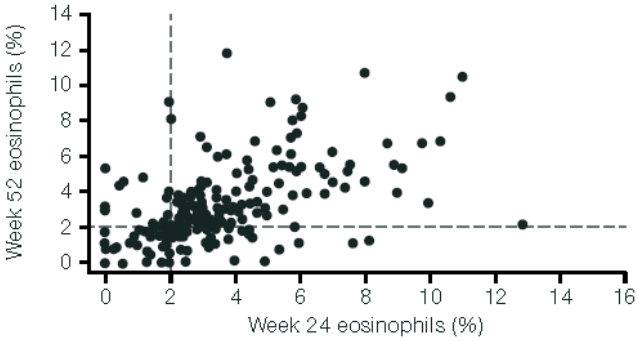
A



B

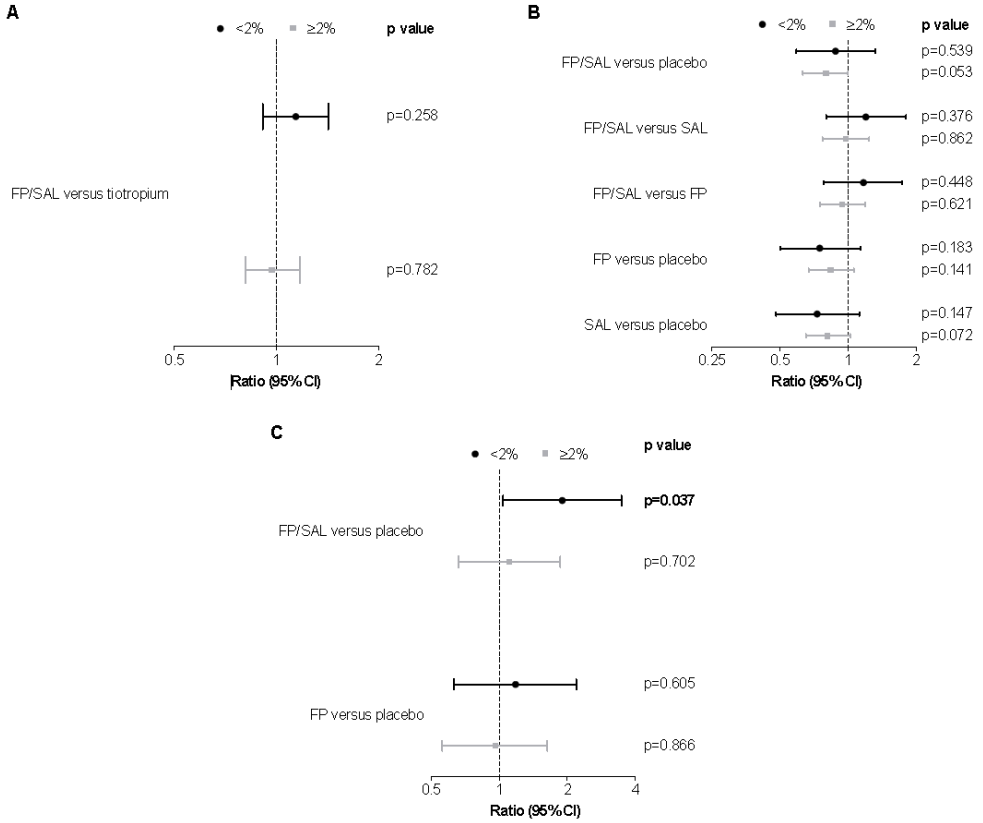


C



Dashed line represents 2% eosinophils.

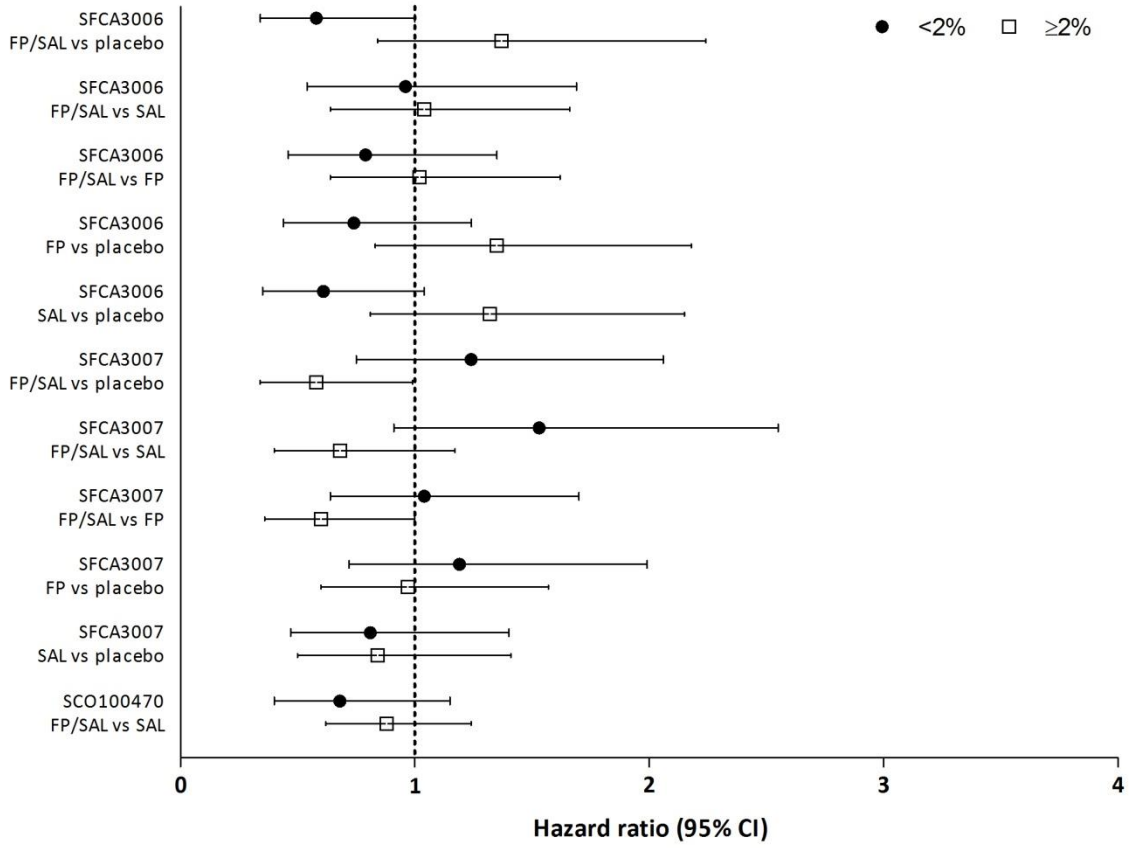
Figure S3 Analysis of time to first moderate/severe exacerbation with FP/SAL and monocomponents for treatment comparisons of interest in ≥1-year studies by baseline blood eosinophil level in (A) INSPIRE (B) TRISTAN and (C) SCO30002



Analysis performed using a Cox's proportional hazards model with covariates of: treatment, gender, history of exacerbations (INSPIRE and SCO30002 only), baseline % predicted FEV_1, percentage eosinophil group and treatment by percentage eosinophils interaction

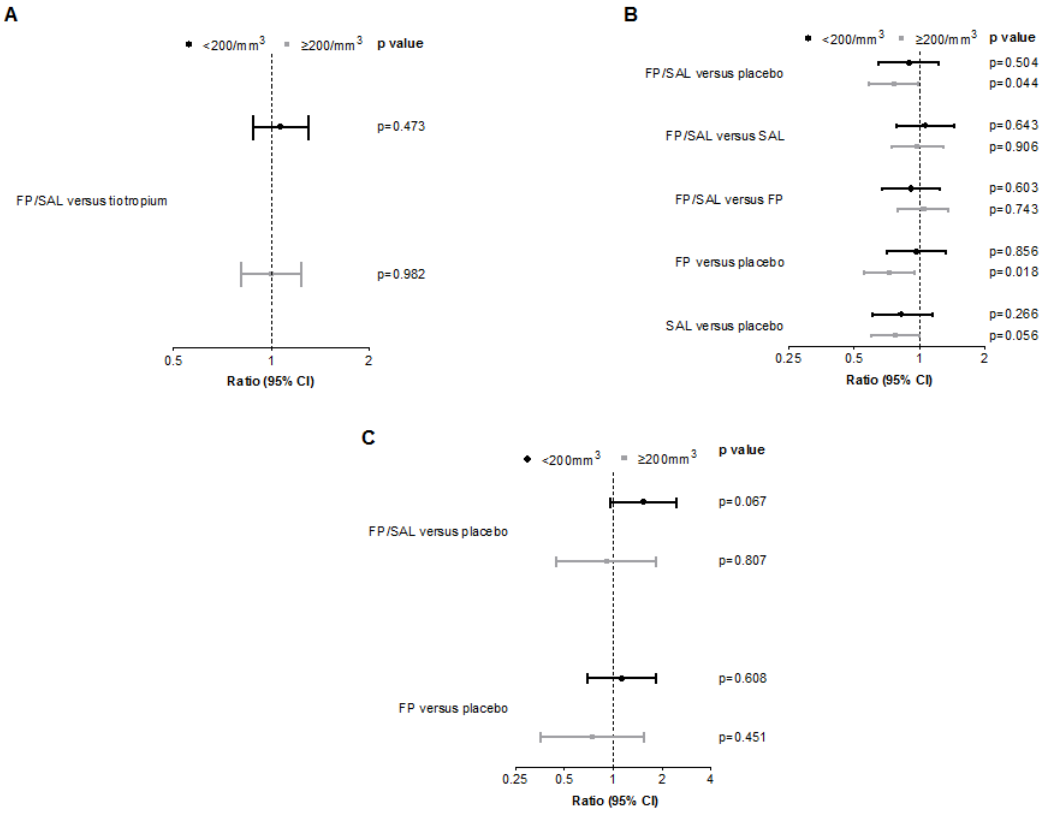
<1 favours first-named treatment; >1 favours second-named treatment or placebo. CI, confidence interval; FP, fluticasone propionate; SAL, salmeterol. *Note:* Statistically significant comparisons (p<0.05) shown in bold font.

Figure S4 Time to first moderate/severe exacerbation by treatment comparison and baseline blood eosinophil subgroup in 24-week studies of FP/SAL in patients with COPD, for selected treatment comparisons.



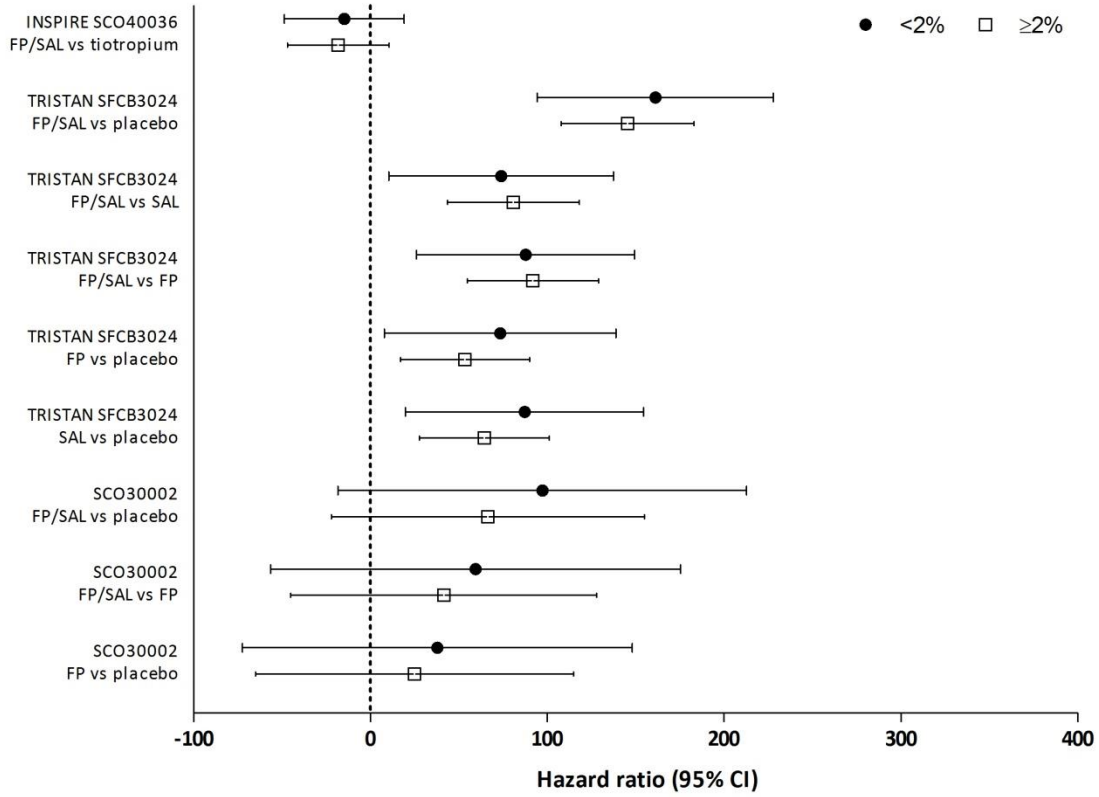
<1 favours first-named treatment; >1 favours second-named treatment or placebo. CI, confidence interval; COPD, chronic obstructive pulmonary disease; FP, fluticasone propionate; SAL, salmeterol.

Figure S5 Time to first moderate/severe exacerbation with FP/SAL versus tiotropium, FP, SAL, or placebo by baseline blood eosinophil absolute count in (A) INSPIRE (B) TRISTAN and (C) SCO30002



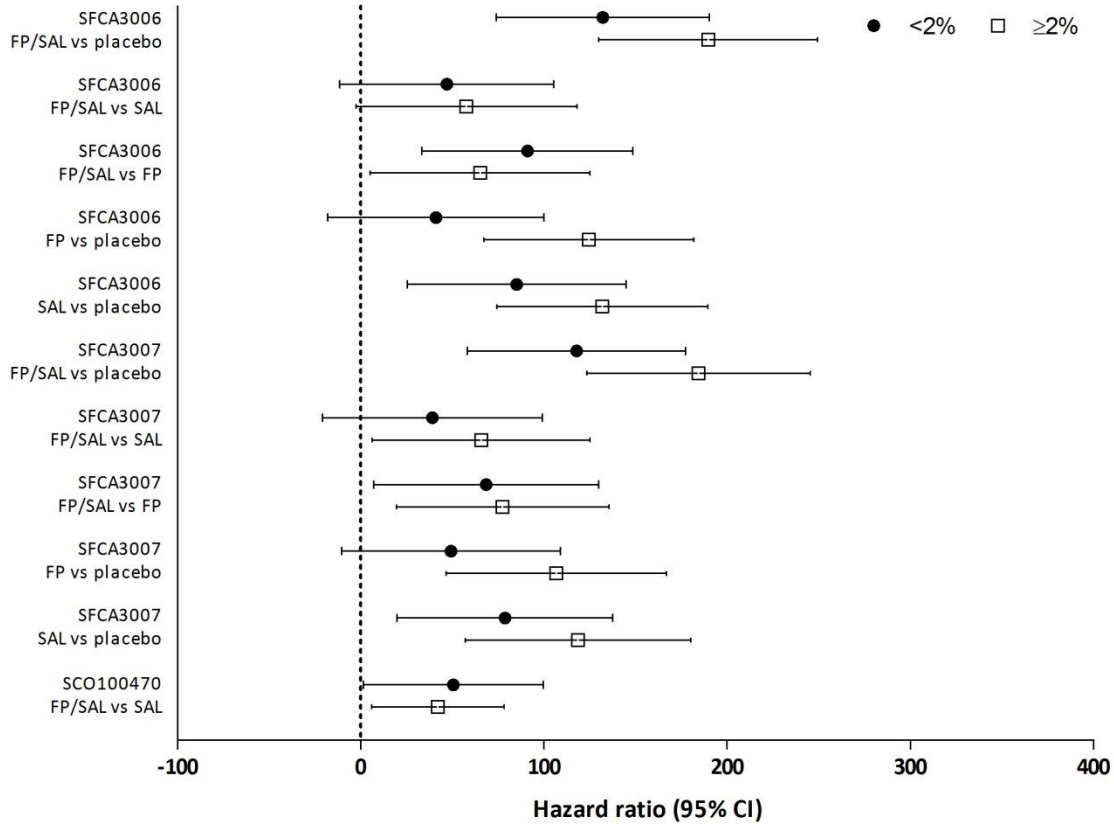
Analysis performed using a Cox's proportional hazards model with covariates of either: treatment, gender, history of exacerbations, baseline % predicted FEV_1, percentage eosinophil group and treatment by percentage eosinophils interaction; or treatment, gender, baseline % predicted FEV_1, percentage eosinophil group and treatment by percentage eosinophils interaction.

Figure S6 Weighted mean (95% CI) FEV_1 by treatment comparison and baseline blood eosinophil subgroup in ≥1-year studies of FP/SAL in patients with COPD (selected treatment comparisons).



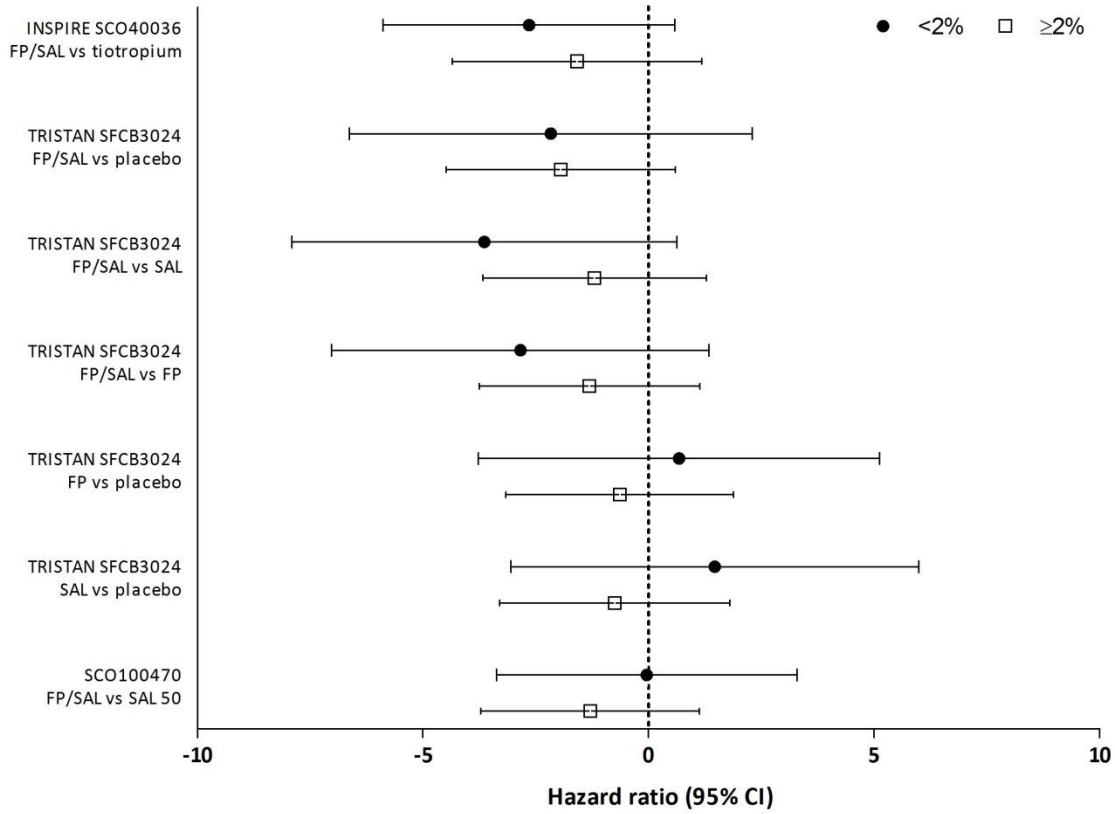
>0 favours first-named treatment; <0 favours second-named treatment or placebo. CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FP, fluticasone propionate; SAL, salmeterol. *Note:* Weighted means were measured as follows: SCO40036, week 2–104 trough FEV_1; SFCB3024, week 2–52 pre-bronchodilator FEV_1; SCO30002, visit 4–9 pre-bronchodilator FEV_1 (24–>52 weeks).

Figure S7 Weighted mean (95% CI) FEV_1 by treatment comparison and baseline blood eosinophil subgroup in 24-week studies of FP/SAL in patients with COPD, for selected treatment comparisons.



>0 favours first-named treatment; <0 favours second-named treatment or placebo. CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FP, fluticasone propionate; SAL, salmeterol. *Note:* Weighted means were measured as follows: SFCA3006, Week 1–24 pre-dose FEV_1; SFCA3007, Week 1–24 pre-dose FEV_1; SCO100470, Week 4–24 trough FEV_1.

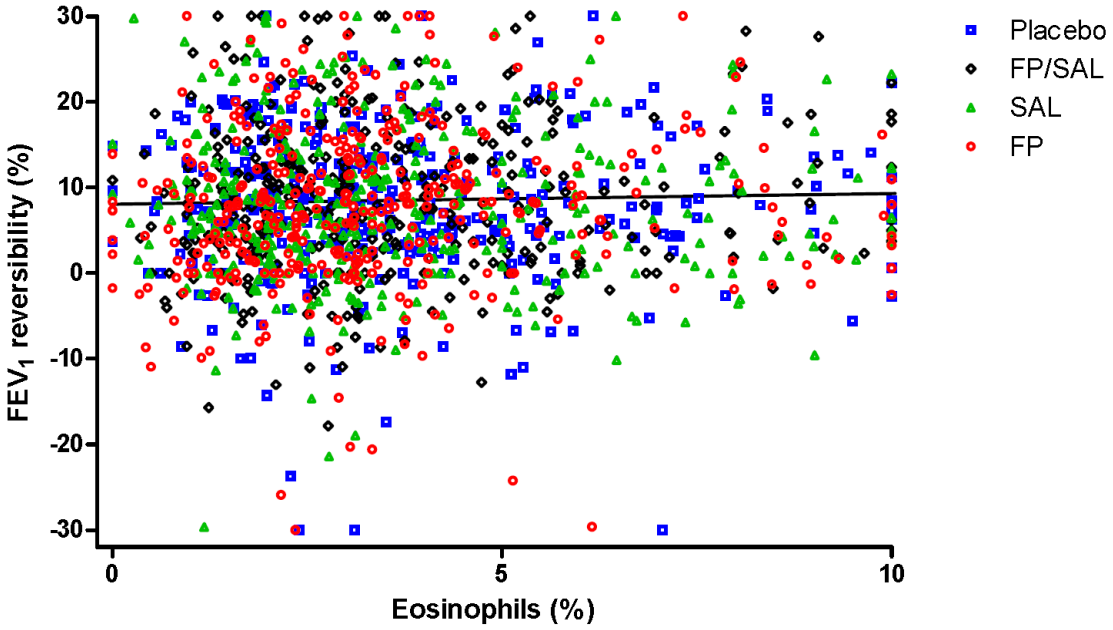
Figure S8 Response to treatment on SGRQ score at study end by treatment comparison and baseline blood eosinophil subgroup in studies of FP/SAL in patients with COPD in which this endpoint was recorded (selected treatment comparisons).



>0 favours first-named treatment; <0 favours second-named treatment or placebo. CI, confidence interval; COPD, chronic obstructive pulmonary disease; FP, fluticasone propionate; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire.

Figure S9 Scatter plot of % bronchodilator reversibility and % eosinophil level for (A) TRISTAN and (B) INSPIRE

A



B

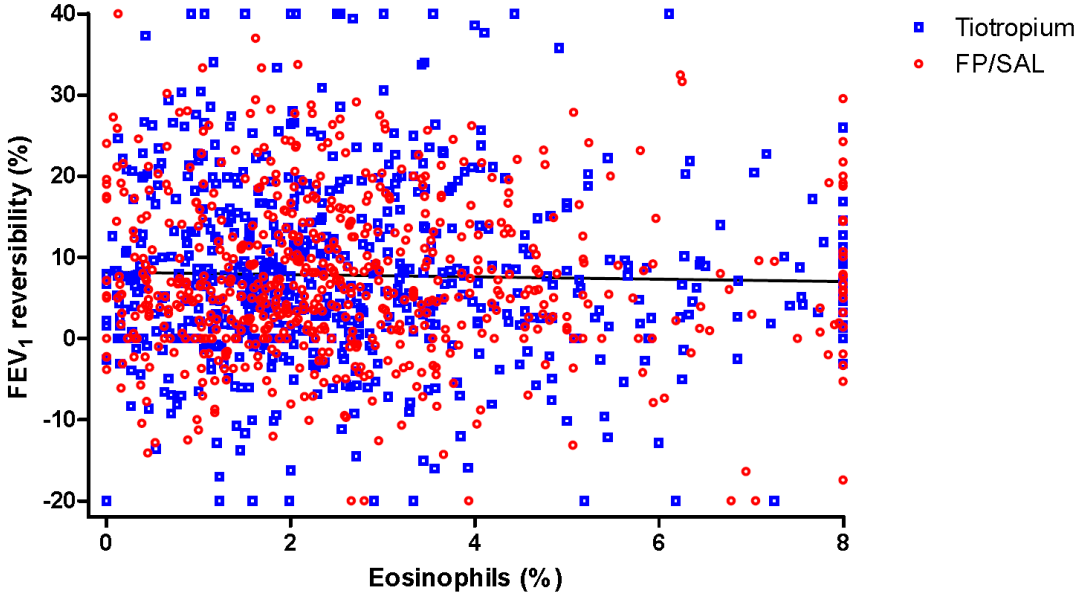
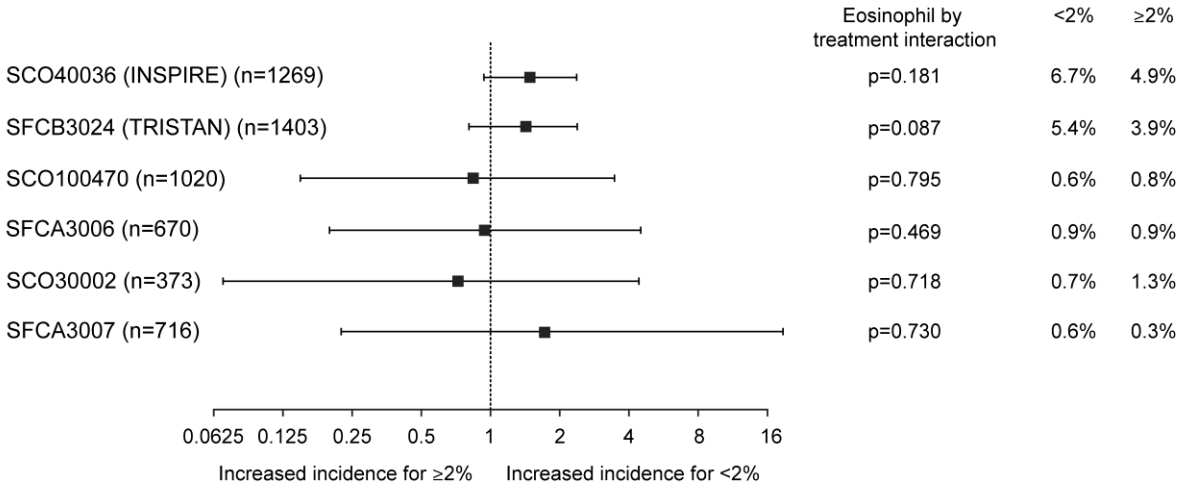


Figure S10 Association between baseline blood eosinophil subgroup and pneumonia by study.



Note: in this analysis treatments were defined as inhaled corticosteroid containing or non-corticosteroid containing.

Statistical Analysis Plan (Online Supplement)

Division: Worldwide Development
Retention Category: GRS019
Information Type: Summary Document Analysis Plan

Title:	Summary Document Analysis Plan for analysis of exacerbations, FEV_1 and SGRQ in Fluticasone Propionate (CI18781) and Salmeterol/Fluticasone Propionate Combination Studies (CCI18781+GR33343) in COPD subjects

Compound Number: CCI18781+GR33343

Effective Date:

Description: The document describes details of analyses of exacerbations and FEV1 event reports in GSK studies conducted with Fluticasone Propionate (FP) or Salmeterol/Fluticasone Propionate (SFC) for COPD. Analyses will be conducted for each identified study separately.

Subject: salmeterol, fluticasone propionate

Author: Lettis, Sally

Sally Lettis
Director Clinical Statistics

Date 21-NOV-2012

Approved by**:** E-mail approval obtained

Neil Barnes Global Franchise Medical Head, Respiratory •	**Date** 08 –November 2013
David Stempel Global Medical Lead, Respiratory	**Date**

TABLE OF CONTENTS

PAGE

ABBREVIATIONS

BD	Twice daily
COPD	Chronic obstructive pulmonary disease
FF	Fluticasone Furoate
FP	Fluticasone Propionate
GSK	GlaxoSmithKline
ICS	Inhaled Corticosteroid
OD	Once daily
Salm	Salmeterol
SFC	Salmeterol/Fluticasone Propionate Combination
VI	Vilanterol

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
Seretide
Advair

Trademarks not owned by the GlaxoSmithKline group of companies

INTRODUCTION

Exploratory analyses performed for the rate of moderate and severe exacerbations from the two fluticasone furoate/vilanterol exacerbation studies HZC102871 and HZC102970 suggest that subjects with increased blood eosinophils at baseline (>2%) experience a higher annual rate of moderate and severe exacerbations than those without (≤2%). Furthermore, larger reductions in the rate of exacerbations were observed for fluticasone furoate/vilanterol compared with vilanterol alone in the group with blood eosinophils >2% at baseline than in the overall population.

This finding is further supported by published literature. For example, in a large longitudinal cohort study in the general adult population, Jansen et al showed that cigarette smoking and hyperresponsiveness are associated with an increased risk of developing respiratory symptoms, and especially so when eosinophilia is present (Jansen et al). Petsky et al also demonstrated that asthma patients with sputum eosinophilia were at increased risk of exacerbations (Petsky et al).

The purpose of the analyses described in this analysis plan is to test these hypotheses using data from SFC and FP COPD studies.

The results of the exploratory analyses examining the relationship between blood eosinophilia and the rate of exacerbations in FF/VI studies HZC102871 and HZC102970 will be included in the clinical report of the analyses described in this analysis plan.

OBJECTIVE(S)

The objectives are:

- To evaluate if blood eosinophilia is associated with increased rate of moderate and severe exacerbations (use of antibiotics, OCS or hospitalization for COPD), increased risk of time to first moderate or severe exacerbation, increased rate of FEV_1 decline, decreased HRQoL as measured by SGRQ and decreased lung function as measured by trough FEV_1
- To evaluate if treatment with an ICS (FP) reduces the rate of moderate and severe exacerbations, reduces the risk of time to first moderate or severe exacerbation, reduces the rate of FEV_1 decline, improves HRQoL (as measured by SGRQ) and/or increases trough FEV_1 to a greater extent in those with blood eosinophilia than those without.

STUDIES TO BE INCLUDED

Criteria for Study Selection

The following criteria will be used to select studies:

- Clinical trials that include any FP or SFC for COPD worldwide as a randomized study drug not in combination with another study drug

Randomised, parallel-group, double-blind

- At least 24 weeks duration
- Constant study dose of SFC
- In addition to SFC or FP, inclusion of a non-steroid containing treatment arm
- Blood samples for eosinophils at baseline or screening

Only data collected during the double-blind treatment period will be used.

1.1. Studies Selected

FP and SFC COPD studies of at least 24 weeks duration and which included a non-steroid containing arm were reviewed for inclusion in this analysis; these are listed in Table 1. The reason for excluding any of these studies from the analysis is also documented in this table. A list of FP and SFC COPD studies reviewed but excluded for any of the other reasons listed in Section 3.1 is provided in Appendix 1.

Table 1 SFC and FP COPD Studies of at least 24 weeks duration and which included a non-steroid containing arm

Study	SFC Dose Or FP Dose	Comparators	Duration	Reason for Exclusion
SCO30003 (TORCH)	50/500	Placebo, Salmeterol, FP	156 weeks	No eosinophil data
SCO40036 (INSPIRE)	50/500	Tiotropium	104 weeks	
SFCB3024 (TRISTAN)	50/500	Placebo, Salmeterol, FP	52 weeks	
SCO40002 (COSMIC)	50/500	Salmeterol	52 weeks	No eosinophil data
SCO30002	50/500 (MDI)	Placebo, FP	52 weeks	
SCO30006 (VIVACE)	50/500	Salmeterol	44 weeks	No eosinophil data
SFCA3006	50/500	Placebo, Salmeterol, FP	24 weeks	
SCO100540	50/500	Placebo	24 weeks	
SFCA3007	50/250	Placebo, Salmeterol, FP	24 weeks	
SCO100470	50/250	Salmeterol	24 weeks	
SCO100250	50/250	Salmeterol	52 weeks	No eosinophil data
SCO40041	50/250	Salmeterol	104 weeks	No eosinophil data
SCO40043	50/250	Salmeterol	52 weeks	No eosinophil data
ADC113874	50/250	Salmeterol	29 weeks	No eosinophil data
FLIT78 (ISOLDE)	500	Placebo	3 years	
FLTA3025	250, 500	Placebo	24 weeks	
FLIT97	500	Placebo	24 weeks	

PLANNED ANALYSES

Meta-analyses

This summary document analysis plan describes analyses for each study separately.

No formal meta-analysis will be conducted.

ANALYSIS POPULATIONS

The analysis population for this analysis will comprise the primary analysis population used within each individual study report.

TREATMENT COMPARISONS

Primary Comparisons of Interest: Eosinophil Levels

Blood eosinophil categories are defined in Section 8.1.1. For each definition, one category will be defined as the reference group and comparisons made between each other category and the reference category.

Primary Comparisons of Interest: Treatment Differences

The treatment comparisons of interest will be of ICS vs non-steroid containing arms within each individual study, as appropriate. Specifically:

- SFC vs SAL alone
- SFC vs Tiotropium
- SFC vs placebo
- FP vs placebo

1.2. Data Display Treatment Descriptors

All table headers and treatment formats will use the convention described in Table 2.

Table 2 Table Headers and Treatment Formats

Table Header	Treatment description
Placebo	Placebo
SFC 50/250	SFC 50/250 BD
SFC 50/500	SFC 50/500 BD

Table Header	Treatment description
SAL 50	Salmeterol 50 BD
FP 250	FP 250 BD
FP 500	FP 500 BD
Tio	Tiotropium

2. GENERAL CONSIDERATIONS FOR DATA ANALYSES

All programming will be performed in a HARP environment using SAS Version 9.1.3 or a later release.

Multicentre Studies

Neither centre nor geographical region will be included in the analysis models.

Multiple Comparisons and Multiplicity

This is a post-hoc analysis and no adjustments will be made for multiple testing.

DATA HANDLING CONVENTIONS

Subgroup and covariate definitions

Blood eosinophils

Two definitions will be applied:

- Percentage (2 categories): <2%, ≥2%
- Absolute (4 categories): <100/mm^3, 100/mm^3-<200/mm^3, 200/mm^3-<300/mm^3, >=300/mm^3 (depending on subgroup size some categories may be amalgamated for analysis). If the majority of subjects fall into one of these categories then an alternative categorization with intermediate cut points may be considered.

In addition, exploratory analyses will be performed with absolute eosinophils on a continuous scale.

Other covariates

The analyses described in Section 9 will use the following covariates:

- FEV_1 analyses: age, sex, baseline FEV_1
- SGRQ total score analyses: age, sex and baseline SGRQ total score
- Exacerbation analyses: sex, baseline %predicted FEV_1 and frequency of prior exacerbations (0, 1, 2+ where captured)

EFFICACY ANALYSES

Each study will be analysed separately.

Time to First Moderate or Severe Exacerbation

The following analysis will be performed for each study where exacerbations were included as an efficacy measure or where moderate and severe exacerbations were both recorded as a safety endpoint. In many studies only exacerbations meeting the definition of serious were captured as an Adverse Event unless exacerbations were explicitely defined as an efficacy endpoint. These studies will not be included due to the low numbers of only severe exacerbations.

It should be noted that selecting COPD exacerbations based on Adverse Event recording may be incomplete. This is because the verbatim text recorded by the investigator may code to an alternative preferred term (e.g. bronchitis, dyspnoea, upper respiratory tract infection, lower respiratory tract infection, cough, infective exacerbation of chronic obstructive airways disease) rather than the preferred term of "Chronic obstructive pulmonary disease " Analyses of exacerbation data reported as adverse events rather than as a specific efficacy endpoint should therefore be considered in the light of these limitations.

Separate analyses will be performed for each of the two eosinophil subgroups defined in Section 8.

The proportion of subjects experiencing an on-treatment moderate or severe exacerbation will be tabulated by treatment group and eosinophil subgroup level.

The analysis of time to first moderate or severe exacerbation will be performed using a Cox's proportional hazards model. The model will include covariates for treatment group, sex, %predicted FEV_1 at baseline, frequency of prior exacerbations (where recorded) and eosinophil subgroup. Hazard ratios for the comparisons defined in Section 6.1 will be presented together with associated p-values and 95% CIs. Forest plots will be produced to present results from each individual study on one display.

In addition, Kaplan-Meier survivor functions will be obtained for each level of the eosinophil sub-group using PROC LIFETEST with a TIME statement.

The analysis will be repeated including a term for eosinophil subgroup by treatment interaction. Hazard ratios for the treatment comparisons defined in Section 6.2 will be presented for each level of the eosinophil subgroup together with associated p-values and 95% CIs. Forest plots will be produced to present results from each individual study on one display.

Kaplan-Meier functions will be obtained for each treatment and each level of the eosinophil subgroup.

Rate of Moderate and Severe Exacerbations

The following analysis will be performed for each study where rate of moderate or severe exacerbations was included as an efficacy endpoint.

Separate analyses will be performed for each of the two eosinophil subgroups defined in Section 8.

The annual rate of moderate and severe exacerbations will be analysed using a generalized linear model, assuming the negative binomial distribution. The response variable will be the number of recorded, on-treatment, moderate and severe exacerbations experienced per subject. The explanatory variables will be treatment group, sex, %predicted FEV_1 at baseline, frequency of prior exacerbations (where recorded) and eosinophil subgroup. The model will also include the logarithm of time on treatment per subject (derived from exposure start and stop) as an offset variable. From this model, point estimates and 95% CIs for the difference in exacerbation rates for the comparisons in Section 6.1 will be obtained.

Forest plots will be produced to present results from each individual study on one display.

The analysis will be repeated including a term for treatment by eosinophil subgroup interaction. From this model, point estimates and 95% CIs for treatment differences for each level of the subgroup will be obtained. Forest plots will be produced to present results from each individual study on one display.

FEV_1

The following analysis will be performed for each study. The analysis will use trough FEV_1 if recorded or alternatively post-bronchodilator FEV_1 or alternatively post-dose FEV_1.

Separate analyses will be performed for each of the two eosinophil subgroups defined in Section 8.

Analysis will be performed using mixed models repeated measures (MMRM) and will include covariates of age, sex, baseline FEV_1, treatment group, eosinophil subgroup, Day, Day by baseline interaction, Day by eosinophil subgroup interaction and Day by treatment interaction, where Day is nominal (and is therefore equivalent to fitting Visit). Missing data are not directly imputed in this analysis. From this model, point estimates and 95% CIs for the difference in trough FEV_1 for the comparisons in Section 6.1 will be obtained for each Day. Forest plots will be produced to present results from each individual study on one display.

Plots of LSmeans over time by each level of the subgroup will be produced.

The analysis will be repeated including a term for day by treatment group by eosinophil subgroup interaction. From this model, point estimates and 95% CIs for treatment differences for each level of the subgroup on each day will be obtained. Forest plots will be produced to present results from each individual study on one display.

Plots of LSmeans over time by treatment group for each level of the subgroup will be produced.

Rate of Decline in FEV_1 - Random Coefficients Model

This analysis will only be conducted for studies of at least two years duration and will be performed for each study separately.

Separate analyses will be performed for each of the two eosinophil subgroups defined in Section 8.

In this analysis, time will be treated as a continuous variable, and is defined as the number of days which have elapsed since the start of treatment.

The rate of decline in FEV_1 over time will be investigated using a random coefficients model. FEV_1 will be fitted as the response variable. Fixed effects will include age, sex, baseline FEV_1, treatment group, eosinophil subgroup and time. Subject effects will be assumed to be random. The eosinophil by time interaction will permit point estimates and 95% CIs for slope differences between each level of the subgroup to be obtained. Forest plots will be produced to present results from each individual study on one display. The random coefficients model allows random variation between slopes of individual subjects, as well as intercepts of individual subjects.

Further models will be used to investigate the rate of decline for each level of the eosinophil subgroup by fitting separate random coefficients models for each level. FEV_1 will be fitted as the response variable. Fixed effects will include age, sex, baseline FEV_1, treatment group and time. Subject effects will be assumed to be random. The treatment group by time interaction will permit point estimates and 95% CIs for slope differences between treatments for each level of the subgroup to be obtained. Forest plots will be produced to present results from each individual study on one display.

Rate of Decline in FEV_1 - Individual Regression Slopes

This analysis will only be conducted for studies of at least two years duration and will be performed for each study separately.

Separate analyses will be performed for each of the two eosinophil subgroups defined in Section 8.

A supportive analysis for rate of decline in FEV_1 will also be performed, where a slope of decline in FEV_1 is calculated for each individual subject by fitting a regression line for FEV_1 over visits recorded.

These values will then be analysed using analysis of covariance, with terms for age, sex, baseline FEV_1 analysis, treatment group and eosinophil subgroup. From this model, point estimates and 95% CIs for the difference in rate of decline for the comparisons defined in Section 6.1 will be obtained. Forest plots will be produced to present results from each individual study on one display.

This analysis will be repeated including a treatment by eosinophil subgroup interaction. From this model, point estimates and 95% CIs for treatment differences for each level of the

subgroup will be obtained. Forest plots will be produced to present results from each individual study on one display.

SGRQ

Analysis of SGRQ will only be performed if consistent trends are seen for the exacerbation and FEV_1 analyses.

The analysis will be performed for each study where SGRQ was included as an endpoint.

Separate analyses will be performed for each of the two eosinophil subgroups defined in Section 8.

The analysis will use the same methodology as described for FEV_1 in Section 9.3.

REFERENCES

GlaxoSmithKline Document Number RM2009/00009/01 Protocol: HZC102970, a 52-week efficacy and safety study to compare the effect of three dosage strengths of fluticasone furoate/GW642444 inhalation powder with GW642444M on the annual rate of exacerbations in subjects with chronic obstructive pulmonary disease. 2010

GlaxoSmithKline Document Number RM2009/00237/01 Protocol: HZC102871, a 52-week efficacy and safety study to compare the effect of three dosage strengths of fluticasone furoate/GW642444 inhalation powder with GW642444M on the annual rate of exacerbations in subjects with chronic obstructive pulmonary disease. 2010

Jansen DF, Schouten JP, Vonk JM, Rijcken B, Timens W, Kraan J, Weiss ST, Postma DS. Smoking and airway hyperresponsiveness especially in the presence of blood eosinophilia increase the risk to develop respiratory symptoms: a 25-year follow-up study in the general adult population. Am J Respir Crit Care Med 1999;160: 259–264.

Petsky HL, Cates CJ, Lasserson TJ, Li AM, Turner C, Kynaston JA, Chang AB. A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils) Thorax 2012; 67: 199-208.

3. APPENDIX

Appendix 1: Seretide COPD studies not included in analysis

Study	SFC Dose	Comparators	Duration	Reason for exclusion
SCO30008	50/500	Tiotropium	3 weeks	Duration < 24 weeks
SCO40030	50/250	Placebo, Salmeterol	8 weeks	Duration < 24 weeks
SCO40011	50/250	Ipratropium/Albuterol	8 weeks	Duration < 24 weeks
SCO40012	50/250	Ipratropium/Albuterol	8 weeks	Duration < 24 weeks
SCO100646	50/250	Salmeterol	16 weeks	Switch study design so subjects not on SFC for whole treatment period
SCO100648	50/500	Open label	52 weeks	Open label
SCO101717	50/500	Open label	12 weeks	Open label
SCO40055	50/250	FP	52 weeks	Only contains steroid treatment arms
SCO30005	50/500	Placebo	13 weeks	Duration < 24 weeks
SCO40034	50/500	Tiotropium	12 weeks	Duration < 24 weeks
SCO104925	50/500	Placebo, Salmeterol, FP	12 weeks	Duration < 24 weeks
ADC112355	50/250	Placebo	16 weeks	Duration < 24 weeks
ASQ112989	50/250	Placebo, Salmeterol	6 weeks	Duration < 24 weeks

Eosinophil Analysis Plan: Deviations from Plan

SCOPE

The analysis plan covered studies of FP as monotherapy as well as studies of FP in combination with salmeterol. The analyses described in this paper refer only to those studies with FP in combination with salmeterol.

CLARIFICATIONS TO/DEviations FROM PLAN

Absolute eosinophil subgroup

Prior to performing any analysis and based on the distribution of absolute eosinophil levels in these studies, the decision was made to analyse as 2 categories <200/mm3 and ≥200/mm3 rather than 4 categories as detailed in the RAP. The exploratory analyses of absolute eosinophils as a continuous variable were not performed.

SCO100540

The decision was made to exclude study SCO100540 from the analyses as eosinophils were only collected in a subset of subjects.

Annual Rate of Moderate and Severe Exacerbations

The annual rate of moderate and severe exacerbations analyses have only been performed for the three studies of at least 1 year duration (SFCB3024, SCO40036, SCO30002).

Two of these studies recorded prior history of exacerbation and two did not. Hence, in addition to what was specified in the analysis plan, analyses of this endpoint for SCO40036 and SCO30002 were repeated excluding prior history of exacerbation as a covariate for consistency with the one-year studies where this was not recorded.