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Study No: SCO104962
Title : A randomized, double-blind, double dummy, 3 way cross-over study evaluating the effects of SERETIDE™ 50/500mcg twice daily plus tiotropium bromide 18mcg once daily compared with the individual treatments (tiotropium bromide 18mcg alone and SERETIDE™ 50/500mcg alone) in the treatment of subjects with COPD.
Rationale: Both SERETIDE (salmeterol/fluticasone propionate combination [SFC]) and tiotropium (TIO) are approved treatments for chronic obstructive pulmonary disease (COPD), and are frequently co-prescribed with limited data to support. Recent studies have provided some preliminary data on triple combination therapy using an inhaled corticosteroid/long-acting b2-agonist together with a long-acting muscarinic antagonist in COPD. The purpose of this study was to evaluate the effects on lung function of a combination of SFC 50/500mcg twice daily plus TIO 18mcg once daily compared with the individual treatments (TIO 18mcg once daily alone and SFC 50/500mcg twice daily alone) in subjects with COPD. The study utilised a range of lung function measures involving spirometry, plethysmography and impulse oscillometry (IOS) in order to fully assess the benefits of triple therapy.
Phase: IV
Study Period: 21 December 2005 – 18 August 2006
Study Design: Randomised, double blind, double dummy, 3-way crossover
Centres: Five centres in two countries participated in this study: one in Belgium and four in the UK.
Indication: COPD
Treatment: Subjects were randomised, following a 2-week run-in phase, to one of six sequence groups, according to a Williams square design. Subjects initially received either SFC 50/500mcg twice daily, TIO 18mcg once daily or SFC 50/500mcg twice daily plus TIO 18mcg once daily for two weeks. Following this, subjects had a 2-week wash-out and then received one of the other two regimens for two weeks. Following another 2-week wash-out, subjects received the final of the 3 regimens. Each subject received all three treatment options in a randomised double-blinded fashion.
Objectives: The primary objective of the study was to compare the effects of SFC 50/500mcg twice daily plus TIO 18mcg once daily with the individual treatments (TIO 18mcg once daily alone and SFC 50/500mcg twice daily alone) on lung function based on airways conductance using plethysmography in subjects with COPD during a 2-week treatment period.
Primary Outcome/Efficacy Variable: Area under the curve (AUC) _(0-4hr) for Specific Airway Conductance, (sGaw; 1/kPa*s) after the morning dose of study medication on Day 14
Secondary Outcome/Efficacy Variables: AUC _(0-4hr) sGaw (1/kPa*s) after the morning dose of study medication on Day 1 AUC _(0-4hr) specific airway resistance (sRaw) (kPa.s) after the morning dose of each study medication on each of Days 1 and 14 AUC _(0-4hr) airway resistance (Raw) (kPa/(L/s)) after the morning dose of study medication on each of Days 1 and 14 Post-dose sGaw, sRaw and Raw at 30, 75, 120 and 240 minutes after the morning dose of treatment on Days 1 and 14 Trough forced expiratory volume in one second (FEV ₁), forced vital capacity (FVC), FEV ₁ /FVC ratio, inspiratory capacity (IC), residual volume (RV), total lung capacity (TLC), thoracic gas volume at functional residual capacity (TGV _{FRC}), sRaw, sGaw and Raw measured at the Day 14 clinic visit prior to the morning dose of study medication and before the use of rescue medication Post-dose FEV ₁ , FVC, FEV ₁ /FVC ratio, IC, RV, TLC, TGV _{FRC} (measured at 120 and 240 minutes after the morning dose of study medication) on Days 1 and 14 Trough IOS respiratory resistance at 5Hz and 20Hz (R5 and R20 respectively), difference between R5 and R20 (R5-R20), resonant frequency (RF), reactance at 5Hz (X5), reactance area (AX) measured at the Day 14 clinic visit prior to the morning dose of study medication and before the use of rescue medication Post-dose IOS R5, R20, R5-R20, RF, X5, AX (measured at 120 and 240 minutes after the morning dose of study medication) on Days 1 and 14 Transition Dyspnoea Index (TDI) score after each study medication on Day 14 Morning peak expiratory flow rate (PEFR) as recorded in the diary record card (DRC) Use of rescue medication (number of occasions per 24-hour period) as recorded in the DRC Symptom scores: cough, breathlessness, sputum colour, sputum production and sleep quality as recorded in the DRC Subject and investigator global assessment after each study medication on Day 14
Statistical Methods: The primary population for the analysis of efficacy was the Modified ITT (MITT) Population and this was used for the

analysis of all efficacy endpoints. The MITT Population comprised all subjects who were randomised and who, during each of at least two treatment periods, received at least one dose of study treatment and completed the Baseline and at least one post-treatment efficacy assessment. The protocol stated at least one post-treatment sGaw assessment but this was modified to allow the inclusion of any subject who had a relevant post-treatment efficacy assessment on a parameter other than sGaw. The Per Protocol (PP) Population comprised all subjects in the MITT Population except those who were considered to have violated the protocol in a way which might affect efficacy and was used for a confirmatory analysis of the primary efficacy parameter only. The treatment comparisons, which were considered of equal importance, were as follows: i. SFC+TIO vs. TIO and ii. SFC+TIO vs. SFC. Primary treatment comparisons were performed using the MITT Population, on the primary endpoint of sGaw AUC_(0-4hr). 97.5% Confidence Intervals (CI) were calculated to account for the two treatment comparisons and all significance tests used a 2.5% level of significance rather than the usual 5%. Safety results were reported for the Safety Population, comprising all subjects who received at least one dose of study medication.

Study Population:

Eligible subjects had moderate to severe stable COPD (Stage II/III) as defined by the Global Initiative for Chronic Obstructive Lung Disease. Subjects aged 40-80 years inclusive with an established history of COPD and who were current or ex-smokers with a smoking history of ≥ 10 pack-years with a post-bronchodilator FEV₁ of $>30\%$ to $\leq 75\%$ of predicted normal, a post-bronchodilator FEV₁ / FVC ratio $\leq 70\%$ and a score of ≥ 2 on the Modified Medical Research Council (MRC) Dyspnoea Scale at Visit 1 were eligible for inclusion in this study.

A subject was not eligible for inclusion in this study if any of the following criteria applied: had a COPD exacerbation within the 4 weeks prior to Visit 1; had any changes in COPD medication in the 4 weeks prior to Visit 1, had a current medical diagnosis of asthma and/or allergic rhinitis; had a medical diagnosis of narrow-angle glaucoma, prostatic hyperplasia or bladder neck obstruction that in the opinion of the investigator prevented them from entering the study; had known respiratory disorders other than COPD (e.g. lung cancer, sarcoidosis, tuberculosis or lung fibrosis)

Number of Subjects:	SFC+TIO (N=31)	TIO (N=37)	SFC (N=31)
Planned N	48	48	48
Dosed N	31	37	31
Completed n (%)	27 (87%)	29 (78%)	27 (87%)
Prematurely withdrawn n (%)	1 (3%)	3 (8%)	1 (3%)
Completed but did not start next period n (%)	3 (10%)	5 (14%)	3 (10%)
Withdrawn due to Adverse Events n (%)	4 (13%)	4 (11%)	4 (13%)
Withdrawn due to Lack of Efficacy n (%)	0	0	0
Withdrawn for Other Reasons n (%)	0	4 (11%)	0
Demographics	Safety Population (N=41)		MITT Population (N=30)
Females: Males	10:31		7:23
Mean Age in Years (SD)	63.4 (8.67)		62.7 (8.55)
Mean Weight in Kg (SD)	76.38 (17.620)		79.38 (17.099)
White	40 (98%)		29 (97%)
African American / African heritage	1 (2%)		1 (3%)
Efficacy results:			
Primary efficacy results:			
AUC _(0-4hr) sGaw (1/kPa*s) at Day 14 (MITT)			
Day 14	SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
n	27	30	27
Baseline raw geometric mean (SD logs)	0.443 (0.6037)	0.429 (0.4212)	0.420 (0.4263)
Endpoint raw geometric mean (SD logs)	0.739 (0.4080)	0.593 (0.4682)	0.589 (0.4832)
Endpoint adjusted geometric mean	0.732	0.600	0.575
Ratio of SFC+TIO to individual treatments		1.221	1.273
97.5% CI		(1.101, 1.354)	(1.144, 1.416)
p-value		<0.001	<0.001
Secondary efficacy results:			
AUC _(0-4hr) sGaw (1/kPa*s) at Day 1 (MITT)			
	SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)

n		28	30	27
Baseline raw geometric mean (SD logs)		0.451 (0.5991)	0.429 (0.4212)	0.420 (0.4263)
Endpoint raw geometric mean (SD logs)		0.666 (0.4718)	0.603 (0.4148)	0.577 (0.4285)
Endpoint adjusted geometric mean		0.645	0.608	0.586
Ratio of SFC+TIO to individual treatments 97.5% CI			1.060 (0.967,1.163)	1.101 (0.999,1.212)
Specific Airway Resistance AUC _(0-4hr) sRaw (kPa.s) on Days 1 and 14 (MITT)				
		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
Day 1, n		28	30	27
Baseline raw geometric mean (SD logs)		2.219 (0.5991)	2.331 (0.4212)	2.380 (0.4263)
Endpoint raw geometric mean (SD logs)		1.501 (0.4718)	1.658 (0.4148)	1.733 (0.4285)
Endpoint adjusted geometric mean		1.551	1.644	1.707
Ratio of SFC+TIO to individual treatments 97.5% CI			0.943 (0.860,1.035)	0.909 (0.825,1.001)
Day 14, n		27	30	27
Baseline raw geometric mean (SD logs)		2.257 (0.6037)	2.331 (0.4212)	2.380 (0.4263)
Endpoint raw geometric mean (SD logs)		1.352 (0.4080)	1.686 (0.4682)	1.697 (0.4832)
Endpoint adjusted geometric mean		1.366	1.668	1.739
Ratio of SFC+TIO to individual treatments 97.5% CI			0.819 (0.739,0.908)	0.786 (0.706,0.874)
Airway Resistance AUC _(0-4hr) Raw (kPa/(L/s)) on Days 1 and 14 (MITT)				
		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
Day 1, n		28	30	27
Baseline raw geometric mean (SD logs)		0.435 (0.3556)	0.436 (0.3042)	0.445 (0.3112)
Endpoint raw geometric mean (SD logs)		0.304 (0.3605)	0.331 (0.3027)	0.341 (0.3186)
Endpoint adjusted geometric mean		0.308	0.332	0.337
Ratio of SFC+TIO to individual treatments 97.5% CI			0.928 (0.857,1.005)	0.916 (0.843,0.994)
Day 14, n		27	30	27
Baseline raw geometric mean (SD logs)		0.444 (0.3451)	0.436 (0.3042)	0.445 (0.3112)
Endpoint raw geometric mean (SD logs)		0.283 (0.2918)	0.331 (0.3304)	0.342 (0.3701)
Endpoint adjusted geometric mean		0.285	0.329	0.347
Ratio of SFC+TIO to individual treatments 97.5% CI			0.867 (0.785,0.957)	0.820 (0.742,0.907)
Post-Treatment Specific Conductance (sGaw; 1/kPa*s) on Days 1 and 14 (MITT)				
Visit		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
Day 1				
30Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	0.451 (0.6105)	0.429 (0.4212)	0.420 (0.4263)
	Endpoint raw geometric mean (SD logs)	0.626 (0.4749)	0.575 (0.3733)	0.558 (0.4049)
	Endpoint adjusted geometric mean	0.605	0.583	0.562
	Ratio of SFC+TIO to individual treatments 97.5% CI		1.037 (0.952,1.130)	1.076 (0.984,1.176)
75Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	0.451 (0.5991)	0.429 (0.4212)	0.420 (0.4263)
	Endpoint raw geometric mean (SD logs)	0.674 (0.4517)	0.608 (0.4291)	0.565 (0.4546)
	Endpoint adjusted geometric mean	0.652	0.616	0.570
	Ratio of SFC+TIO to individual treatments 97.5% CI		1.059 (0.927,1.210)	1.144 (0.997,1.314)
120Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	0.451 (0.5991)	0.429 (0.4212)	0.420 (0.4263)
	Endpoint raw geometric mean (SD logs)	0.705 (0.4781)	0.624 (0.4346)	0.607 (0.4420)

	Endpoint adjusted geometric mean	0.681	0.633	0.612
	Ratio of SFC+TIO to individual treatments 97.5% CI		1.077 (0.952,1.217)	1.112 (0.979,1.263)
240Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	0.451 (0.5991)	0.429 (0.4212)	0.420 (0.4263)
	Endpoint raw geometric mean (SD logs)	0.707 (0.4845)	0.643 (0.4371)	0.613 (0.4796)
	Endpoint adjusted geometric mean	0.683	0.652	0.619
	Ratio of SFC+TIO to individual treatments 97.5% CI		1.047 (0.923,1.186)	1.103 (0.969,1.256)
Visit Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
30Min	n	26	30	27
	Baseline raw geometric mean (SD logs)	0.440 (0.6148)	0.429 (0.4212)	0.420 (0.4263)
	Endpoint raw geometric mean (SD logs)	0.731 (0.4403)	0.587 (0.4670)	0.573 (0.4902)
	Endpoint adjusted geometric mean	0.720	0.594	0.560
	Ratio of SFC+TIO to individual treatments 97.5% CI		1.212 (1.081,1.358)	1.286 (1.143,1.447)
75Min	n	27	29	27
	Baseline raw geometric mean (SD logs)	0.443 (0.6037)	0.430 (0.4286)	0.420 (0.4263)
	Endpoint raw geometric mean (SD logs)	0.752 (0.3996)	0.613 (0.4793)	0.601 (0.4649)
	Endpoint adjusted geometric mean	0.744	0.618	0.587
	Ratio of SFC+TIO to individual treatments 97.5% CI		1.203 (1.074,1.348)	1.268 (1.128,1.426)
120Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	0.443 (0.6037)	0.429 (0.4212)	0.420 (0.4263)
	Endpoint raw geometric mean (SD logs)	0.763 (0.4044)	0.611 (0.4681)	0.605 (0.5036)
	Endpoint adjusted geometric mean	0.755	0.618	0.591
	Ratio of SFC+TIO to individual treatments 97.5% CI		1.221 (1.089,1.370)	1.278 (1.135,1.439)
240Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	0.443 (0.6037)	0.429 (0.4212)	0.420 (0.4263)
	Endpoint raw geometric mean (SD logs)	0.746 (0.4419)	0.587 (0.5176)	0.593 (0.4933)
	Endpoint adjusted geometric mean	0.737	0.594	0.580
	Ratio of SFC+TIO to individual treatments 97.5% CI		1.241 (1.088,1.415)	1.272 (1.110,1.456)
Analysis of Post-Treatment Specific Resistance (sRaw; kPa.s on Days 1 and 14 (MITT))				
Visit Day 1		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
30Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	2.218 (0.6105)	2.331 (0.4212)	2.380 (0.4263)
	Endpoint raw geometric mean (SD logs)	1.599 (0.4749)	1.738 (0.3733)	1.794 (0.4049)
	Endpoint adjusted geometric mean	1.654	1.716	1.779
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.964 (0.885,1.050)	0.930 (0.850,1.017)
75Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	2.219 (0.5991)	2.331 (0.4212)	2.380 (0.4263)
	Endpoint raw geometric mean (SD logs)	1.483 (0.4517)	1.645 (0.4291)	1.769 (0.4546)
	Endpoint adjusted geometric mean	1.533	1.624	1.755
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.944 (0.826,1.079)	0.874 (0.761,1.003)
120Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	2.219 (0.5991)	2.331 (0.4212)	2.380 (0.4263)
	Endpoint raw geometric mean (SD logs)	1.419 (0.4781)	1.602 (0.4346)	1.648 (0.4420)

	Endpoint adjusted geometric mean	1.468	1.581	1.633
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.929 (0.822,1.050)	0.899 (0.792,1.021)
240Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	2.219 (0.5991)	2.331 (0.4212)	2.380 (0.4263)
	Endpoint raw geometric mean (SD logs)	1.414 (0.4845)	1.554 (0.4371)	1.632 (0.4796)
	Endpoint adjusted geometric mean	1.465	1.534	1.617
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.955 (0.843,1.083)	0.906 (0.796,1.032)
Visit Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
30Min	n	26	30	27
	Baseline raw geometric mean (SD logs)	2.271 (0.6148)	2.331 (0.4212)	2.380 (0.4263)
	Endpoint raw geometric mean (SD logs)	1.368 (0.4403)	1.702 (0.4670)	1.744 (0.4902)
	Endpoint adjusted geometric mean	1.389	1.683	1.786
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.825 (0.736,0.925)	0.778 (0.691,0.875)
75Min	n	27	29	27
	Baseline raw geometric mean (SD logs)	2.257 (0.6037)	2.327 (0.4286)	2.380 (0.4263)
	Endpoint raw geometric mean (SD logs)	1.331 (0.3996)	1.631 (0.4793)	1.663 (0.4649)
	Endpoint adjusted geometric mean	1.344	1.618	1.704
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.831 (0.742,0.931)	0.789 (0.701,0.887)
120Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	2.257 (0.6037)	2.331 (0.4212)	2.380 (0.4263)
	Endpoint raw geometric mean (SD logs)	1.310 (0.4044)	1.637 (0.4681)	1.654 (0.5036)
	Endpoint adjusted geometric mean	1.325	1.618	1.693
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.819 (0.730,0.918)	0.782 (0.695,0.881)
240Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	2.257 (0.6037)	2.331 (0.4212)	2.380 (0.4263)
	Endpoint raw geometric mean (SD logs)	1.340 (0.4419)	1.703 (0.5176)	1.685 (0.4933)
	Endpoint adjusted geometric mean	1.356	1.683	1.725
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.806 (0.706,0.919)	0.786 (0.687,0.901)
Analysis of Post-Treatment Airway Resistance (Raw; kPa/(L/s)) on Days 1 and 14 (MITT)				
Visit Day 1		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
30 Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	0.436 (0.3620)	0.436 (0.3042)	0.445 (0.3112)
	Endpoint raw geometric mean (SD logs)	0.321 (0.3390)	0.345 (0.2880)	0.354 (0.2891)
	Endpoint adjusted geometric mean	0.326	0.345	0.351
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.945 (0.872,1.023)	0.928 (0.855,1.007)
75 Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	0.435 (0.3556)	0.436 (0.3042)	0.445 (0.3112)
	Endpoint raw geometric mean (SD logs)	0.300 (0.3524)	0.329 (0.3161)	0.343 (0.3050)
	Endpoint adjusted geometric mean	0.305	0.329	0.340
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.928 (0.839,1.026)	0.898 (0.809,0.996)
120 Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	0.435 (0.3556)	0.436 (0.3042)	0.445 (0.3112)
	Endpoint raw geometric mean (SD logs)	0.289 (0.3818)	0.326 (0.3115)	0.328 (0.3426)
	Endpoint adjusted geometric mean	0.295	0.326	0.326

	Ratio of SFC+TIO to individual treatments 97.5% CI		0.905 (0.815,1.004)	0.905 (0.813,1.008)
240 Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	0.435 (0.3556)	0.436 (0.3042)	0.445 (0.3112)
	Endpoint raw geometric mean (SD logs)	0.289 (0.3863)	0.310 (0.3269)	0.325 (0.3903)
	Endpoint adjusted geometric mean	0.295	0.310	0.322
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.950 (0.855,1.054)	0.915 (0.822,1.019)
Visit Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
30 Min	n	26	30	27
	Baseline raw geometric mean (SD logs)	0.450 (0.3453)	0.436 (0.3042)	0.445 (0.3112)
	Endpoint raw geometric mean (SD logs)	0.287 (0.3068)	0.334 (0.3436)	0.350 (0.3829)
	Endpoint adjusted geometric mean	0.288	0.332	0.356
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.867 (0.778,0.966)	0.810 (0.725,0.904)
75 Min	n	27	29	27
	Baseline raw geometric mean (SD logs)	0.444 (0.3451)	0.438 (0.3083)	0.445 (0.3112)
	Endpoint raw geometric mean (SD logs)	0.280 (0.2888)	0.316 (0.3668)	0.338 (0.3478)
	Endpoint adjusted geometric mean	0.282	0.312	0.344
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.903 (0.797,1.024)	0.820 (0.722,0.932)
120 Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	0.444 (0.3451)	0.436 (0.3042)	0.445 (0.3112)
	Endpoint raw geometric mean (SD logs)	0.277 (0.3000)	0.324 (0.3413)	0.336 (0.3927)
	Endpoint adjusted geometric mean	0.279	0.323	0.341
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.863 (0.778,0.958)	0.816 (0.734,0.908)
240 Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	0.444 (0.3451)	0.436 (0.3042)	0.445 (0.3112)
	Endpoint raw geometric mean (SD logs)	0.282 (0.3389)	0.336 (0.3815)	0.339 (0.3976)
	Endpoint adjusted geometric mean	0.284	0.334	0.345
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.849 (0.749,0.962)	0.824 (0.725,0.936)
Trough Raw and sGaw on Day 14 (MITT)				
Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
n		27	30	27
Trough Raw (kPa/(L/s))				
	Baseline raw geometric mean (SD logs)	0.444 (0.3451)	0.436 (0.3042)	0.445 (0.3112)
	Endpoint raw geometric mean (SD logs)	0.335 (0.2386)	0.382 (0.2445)	0.389 (0.3345)
	Endpoint adjusted geometric mean	0.336	0.381	0.392
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.882 (0.803,0.968)	0.857 (0.779,0.943)
Trough sGaw (1/kPa*s)				
	Baseline raw geometric mean (SD logs)	0.443 (0.6037)	0.429 (0.4212)	0.420 (0.4263)
	Endpoint raw geometric mean (SD logs)	0.598 (0.3932)	0.502 (0.3917)	0.509 (0.4871)
	Endpoint adjusted geometric mean	0.590	0.506	0.502
	Ratio of SFC+TIO to individual treatments 97.5% CI		1.165 (1.043,1.302)	1.175 (1.048,1.318)
Trough Spirometry Measures (MITT)				
Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
n		27	30	27
Trough FEV₁ (L)				

Baseline raw mean (SD)	1.218 (0.3928)	1.267 (0.4408)	1.196 (0.4169)
Endpoint raw mean (SD)	1.510 (0.3932)	1.337 (0.4734)	1.379 (0.4418)
Endpoint adjusted mean (SE)	1.515 (0.0337)	1.303 (0.0317)	1.405 (0.0337)
Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.212 (0.0445) (0.109,0.315)	0.110 (0.0450) (0.007,0.214)
Trough FVC (L)			
Baseline raw mean (SD)	2.895 (0.6314)	2.885 (0.7091)	2.806 (0.7375)
Endpoint raw mean (SD)	3.284 (0.6568)	3.058 (0.6341)	3.097 (0.7482)
Endpoint adjusted mean (SE)	3.251 (0.0556)	3.053 (0.0527)	3.126 (0.0555)
Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.198 (0.0646) (0.048,0.347)	0.125 (0.0657) (-0.026,0.277)
Trough FEV₁/FVC ratio			
Baseline raw mean (SD)	0.418 (0.1143)	0.434 (0.1107)	0.424 (0.1123)
Endpoint raw mean (SD)	0.456 (0.1174)	0.429 (0.1212)	0.451 (0.1208)
Endpoint adjusted mean (SE)	0.450 (0.0089)	0.432 (0.0083)	0.454 (0.0086)
Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.018 (0.0113) (-0.008,0.044)	-0.003 (0.0111) (-0.029,0.022)
Trough IC (L)			
Baseline raw geometric mean (SD logs)	1.986 (0.2661)	1.987 (0.2947)	1.899 (0.3129)
Endpoint raw geometric mean (SD logs)	2.243 (0.2789)	2.041 (0.2878)	2.123 (0.2583)
Endpoint adjusted geometric mean	2.214	2.046	2.119
Ratio of SFC+TIO to individual treatments 97.5% CI		1.082 (1.019,1.150)	1.045 (0.982,1.112)
Trough RV (L)			
Baseline raw geometric mean (SD logs)	3.638 (0.3486)	3.743 (0.3414)	3.766 (0.3811)
Endpoint raw geometric mean (SD logs)	3.269 (0.3769)	3.611 (0.3517)	3.436 (0.3962)
Endpoint adjusted geometric mean	3.336	3.583	3.405
Ratio of SFC+TIO to individual treatments 97.5% CI		0.931 (0.875,0.991)	0.980 (0.919,1.044)
Trough TLC (L)			
Baseline raw geometric mean (SD logs)	6.808 (0.2311)	6.933 (0.2320)	6.921 (0.2478)
Endpoint raw geometric mean (SD logs)	6.827 (0.2401)	6.888 (0.2351)	6.874 (0.2416)
Endpoint adjusted geometric mean	6.878	6.858	6.853
Ratio of SFC+TIO to individual treatments 97.5% CI		1.003 (0.980,1.026)	1.004 (0.981,1.027)
Trough TGV_{FRC} (L)			
Baseline raw geometric mean (SD logs)	4.738 (0.3316)	4.813 (0.3332)	4.901 (0.3515)
Endpoint raw geometric mean (SD logs)	4.478 (0.3541)	4.756 (0.3219)	4.646 (0.3543)
Endpoint adjusted geometric mean	4.541	4.726	4.620
Ratio of SFC+TIO to individual treatments 97.5% CI		0.961 (0.926, 0.997)	0.983 (0.946, 1.021)
Analysis of Trough Respiratory Resistance (MITT)			
Day 14	SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
n	27	28	21
Trough R5 (kPa/(L/s))			
Baseline raw mean (SD)	0.630 (0.1847)	0.645 (0.1720)	0.638 (0.1962)
Endpoint raw mean (SD)	0.539 (0.1322)	0.591 (0.1387)	0.602 (0.1607)
Endpoint adjusted mean (SE)	0.544 (0.0208)	0.583 (0.0206)	0.604 (0.0232)

Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.039 (0.0243) (-0.095, 0.017)	-0.061 (0.0262) (-0.121, -0.000)
Trough R20 (kPa/(L/s))			
Baseline raw mean (SD)		0.347 (0.0940)	0.361 (0.1009)
Endpoint raw mean (SD)		0.336 (0.0817)	0.353 (0.0933)
Endpoint adjusted mean		0.338 (0.0078)	0.352 (0.0077)
Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.014 (0.0111) (-0.039, 0.012)	-0.025 (0.0118) (-0.052, 0.002)
Trough R5-R20 (kPa/(L/s))			
Baseline raw mean (SD)		0.283 (0.1344)	0.284 (0.1169)
Endpoint raw mean (SD)		0.204 (0.1044)	0.238 (0.0923)
Endpoint adjusted mean		0.203 (0.0179)	0.233 (0.0178)
Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.029 (0.0156) (-0.065, 0.007)	-0.039 (0.0169) (-0.078, 0.001)
Trough RF (Hz)			
Baseline raw mean (SD)		25.241 (5.9153)	25.936 (5.3170)
Endpoint raw mean (SD)		21.403 (4.8343)	25.074 (5.1559)
Endpoint adjusted mean		21.825 (0.6467)	24.733 (0.6378)
Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-2.907 (0.8242) (-4.817, -0.998)	-1.769 (0.8865) (-3.822, 0.283)
Trough X5 (kPa/(L/s))			
Baseline raw mean (SD)		-0.400 (0.2106)	-0.362 (0.1600)
Endpoint raw mean (SD)		-0.254 (0.1364)	-0.326 (0.1688)
Endpoint adjusted mean		-0.258 (0.0223)	-0.327 (0.0224)
Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.068 (0.0237) (0.013, 0.123)	0.079 (0.0243) (0.023, 0.135)
Trough AX (kPa/L)			
Baseline raw mean (SD)		3.358 (2.2098)	3.251 (1.9018)
Endpoint raw mean (SD)		1.940 (1.2429)	2.764 (1.5576)
Endpoint adjusted mean		1.971 (0.2347)	2.710 (0.2333)
Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.739 (0.2380) (-1.290, -0.188)	-0.678 (0.2532) (-1.265, -0.091)
Post-dose Spirometry Measures			
FEV₁ (L)			
Day 1		SFC+TIO (N=29)	TIO (N=30)
120 Min	n	28	30
	Baseline raw mean (SD)	1.246 (0.4135)	1.267 (0.4408)
	Endpoint raw mean (SD)	1.504 (0.4625)	1.418 (0.4922)
	Endpoint adjusted mean (SE)	1.471 (0.0293)	1.419 (0.0287)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.052 (0.0305) (-0.018, 0.122)
240 Min	n	28	30
	Baseline raw mean (SD)	1.246 (0.4135)	1.267 (0.4408)
	Endpoint raw mean (SD)	1.530 (0.4838)	1.435 (0.5014)
	Endpoint adjusted mean (SE)	1.497 (0.0293)	1.436 (0.0287)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.062 (0.0305) (-0.008, 0.131)
			0.040 (0.0303) (-0.029, 0.110)

Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	27	30	27
	Baseline raw mean (SD)	1.218 (0.3298)	1.267 (0.4408)	1.196 (0.4169)
	Endpoint raw mean (SD)	1.623 (0.4597)	1.412 (0.4939)	1.493 (0.4868)
	Endpoint adjusted mean (SE)	1.605 (0.0337)	1.408 (0.0319)	1.513 (0.0328)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.198 (0.0430) (0.099,0.296)	0.093 (0.0415) (-0.003,0.188)
240 Min	n	26	30	27
	Baseline raw mean (SD)	1.224 (0.3993)	1.267 (0.4408)	1.196 (0.4169)
	Endpoint raw mean (SD)	1.640 (0.4895)	1.368 (0.5207)	1.498 (0.4569)
	Endpoint adjusted mean (SE)	1.615 (0.0338)	1.364 (0.0319)	1.518 (0.0328)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.251 (0.0431) (0.152,0.350)	0.097 (0.0416) (0.002,0.193)

FVC (L)				
Day 1		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	28	30	27
	Baseline raw mean (SD)	2.952 (0.6890)	2.885 (0.7091)	2.806 (0.7375)
	Endpoint raw mean (SD)	3.485 (0.7494)	3.226 (0.7745)	3.289 (0.8974)
	Endpoint adjusted mean (SE)	3.434 (0.0644)	3.232 (0.0627)	3.346 (0.0654)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.202 (0.0671) (0.048,0.355)	0.088 (0.0690) (-0.070,0.246)
240 Min	n	28	30	27
	Baseline raw mean (SD)	2.952 (0.6890)	2.885 (0.7091)	2.806 (0.7375)
	Endpoint raw mean (SD)	3.506 (0.7111)	3.236 (0.7121)	3.214 (0.7949)
	Endpoint adjusted mean (SE)	3.462 (0.0644)	3.242 (0.0627)	3.2863 (0.0654)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.220 (0.0671) (0.066,0.373)	0.200 (0.0690) (0.042,0.357)
Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	27	30	27
	Baseline raw mean (SD)	2.895 (0.6314)	2.885 (0.7091)	2.806 (0.7375)
	Endpoint raw mean (SD)	3.561 (0.7423)	3.253 (0.7009)	3.292 (0.7636)
	Endpoint adjusted mean (SE)	3.540 (0.0675)	3.238 (0.0640)	3.330 (0.0674)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.301 (0.0784) (0.122,0.481)	0.210 (0.0799) (0.027,0.393)
240 Min	n	26	30	27
	Baseline raw mean (SD)	2.878 (0.6374)	2.885 (0.7091)	2.806 (0.7375)
	Endpoint raw mean (SD)	3.510 (0.7821)	3.073 (0.6930)	3.244 (0.7640)
	Endpoint adjusted mean (SE)	3.503 (0.0680)	3.058 (0.0640)	3.281 (0.0674)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.445 (0.0788) (0.265,0.626)	0.222 (0.0804) (0.038,0.406)
FEV ₁ /FVC ratio				
Day 1		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	28	30	27
	Baseline raw mean (SD)	0.419 (0.1123)	0.434 (0.1107)	0.424 (0.1123)

	Endpoint raw mean (SD)	0.438 (0.1303)	0.441 (0.1239)	0.445 (0.1304)
	Endpoint adjusted mean (SE)	0.437 (0.0067)	0.439 (0.0065)	0.447 (0.0067)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.002 (0.0076) (-0.019,0.015)	-0.010 (0.0076) (-0.028,0.007)
240 Min	n	28	30	27
	Baseline raw mean (SD)	0.419 (0.1123)	0.434 (0.1107)	0.424 (0.1123)
	Endpoint raw mean (SD)	0.439 (0.1292)	0.443 (0.1258)	0.445 (0.1297)
	Endpoint adjusted mean (SE)	0.438 (0.0067)	0.441 (0.0065)	0.446 (0.0067)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.003 (0.0076) (-0.020,0.014)	-0.008 (0.0076) (-0.025,0.009)
Day 14	SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)	Day 14
120 Min	n	27	30	27
	Baseline raw mean (SD)	0.418 (0.1143)	0.434 (0.1107)	0.424 (0.1123)
	Endpoint raw mean (SD)	0.460 (0.1191)	0.432 (0.1219)	0.457 (0.1286)
	Endpoint adjusted mean (SE)	0.452 (0.0075)	0.437 (0.0071)	0.458 (0.0073)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.015 (0.0088) (-0.005,0.035)	-0.005 (0.0087) (-0.025,0.014)
240 Min	n	26	30	27
	Baseline raw mean (SD)	0.422 (0.1148)	0.434 (0.1107)	0.424 (0.1123)
	Endpoint raw mean (SD)	0.472 (0.1282)	0.440 (0.1282)	0.464 (0.1155)
	Endpoint adjusted mean (SE)	0.460 (0.0076)	0.444 (0.0071)	0.465 (0.0073)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.016 (0.0088) (-0.005,0.036)	-0.005 (0.0088) (-0.025,0.015)
IC (L)				
Day 1		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	2.024 (0.2796)	1.987 (0.2947)	1.899 (0.3129)
	Endpoint raw geometric mean (SD logs)	2.329 (0.2533)	2.226 (0.2679)	2.165 (0.2963)
	Endpoint adjusted geometric mean	2.281	2.226	2.194
	Ratio of SFC+TIO to individual treatments 97.5% CI		1.025 (0.966,1.088)	1.040 (0.978,1.107)
240 Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	2.024 (0.2796)	1.987 (0.2947)	1.899 (0.3129)
	Endpoint raw geometric mean (SD)	2.327 (0.2691)	2.238 (0.2395)	2.140 (0.2966)
	Endpoint adjusted geometric mean	2.280	2.238	2.167
	Ratio of SFC+TIO to individual treatments 97.5% CI		1.019 (0.960,1.082)	1.052 (0.989,1.119)
Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	1.986 (0.2661)	1.987 (0.2947)	1.899 (0.3129)
	Endpoint raw geometric mean (SD logs)	2.389 (0.2573)	2.146 (0.2686)	2.180 (0.2906)
	Endpoint adjusted geometric mean	2.368	2.150	2.184
	Ratio of SFC+TIO to individual treatments 97.5% CI		1.102 (1.037,1.171)	1.084 (1.019,1.154)
240 Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	1.986 (0.2661)	1.987 (0.2947)	1.899 (0.3129)
	Endpoint raw geometric mean (SD)	2.414 (0.2367)	2.086 (0.2548)	2.174 (0.2784)
	Endpoint adjusted geometric mean	2.395	2.091	2.175

	Ratio of SFC+TIO to individual treatments 97.5% CI		1.146 (1.078,1.217)	1.101 (1.035,1.172)
RV (L)				
Day 1		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	3.648 (0.3424)	3.743 (0.3414)	3.766 (0.3811)
	Endpoint raw geometric mean (SD logs)	3.161 (0.3537)	3.286 (0.3443)	3.278 (0.3870)
	Endpoint adjusted geometric mean	3.218	3.266	3.254
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.985 (0.939,1.033)	0.989 (0.941,1.039)
240 Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	3.648 (0.3424)	3.743 (0.3414)	3.766 (0.3811)
	Endpoint raw geometric mean (SD logs)	3.018 (0.3307)	3.354 (0.3588)	3.259 (0.3692)
	Endpoint adjusted geometric mean	3.070	3.335	3.236
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.921 (0.878,0.966)	0.949 (0.903,0.997)
Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	3.638 (0.3486)	3.743 (0.3414)	3.766 (0.3811)
	Endpoint raw geometric mean (SD logs)	2.977 (0.3595)	3.388 (0.3665)	3.246 (0.3676)
	Endpoint adjusted geometric mean	3.032	3.364	3.216
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.901 (0.852, 0.953)	0.943 (0.890,0.999)
240 Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	3.638 (0.3486)	3.743 (0.3414)	3.766 (0.3811)
	Endpoint raw geometric mean (SD logs)	3.034 (0.3512)	3.432 (0.3492)	3.254 (0.3663)
	Endpoint adjusted geometric mean	3.088	3.409	3.224
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.906 (0.856,0.959)	0.958 (0.904,1.015)
TLC (L)				
Day 1		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	6.865 (0.2310)	6.933 (0.2320)	6.921 (0.2478)
	Endpoint raw geometric mean (SD logs)	6.853 (0.2306)	6.781 (0.2337)	6.823 (0.2383)
	Endpoint adjusted geometric mean	6.869	6.764	6.830
	Ratio of SFC+TIO to individual treatments 97.5% CI		1.016 (0.996,1.035)	1.006 (0.986,1.025)
240 Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	6.865 (0.2310)	6.933 (0.2320)	6.921 (0.2478)
	Endpoint raw geometric mean (SD logs)	6.764 (0.2359)	6.840 (0.2354)	6.783 (0.2377)
	Endpoint adjusted geometric mean	6.780	6.823	6.790
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.994 (0.975,1.013)	0.999 (0.979,1.018)
Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	6.808 (0.2311)	6.933 (0.2320)	6.921 (0.2478)
	Endpoint raw geometric mean (SD logs)	6.768 (0.2340)	6.858 (0.2350)	6.787 (0.2401)
	Endpoint adjusted geometric mean	6.810	6.832	6.770
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.997 (0.978,1.016)	1.006 (0.986,1.026)
240 Min	n	27	30	27

	Baseline raw geometric mean (SD logs)	6.808 (0.2311)	6.933 (0.2320)	6.921 (0.2478)
	Endpoint raw geometric mean (SD logs)	6.784 (0.2385)	6.776 (0.2324)	6.790 (0.2406)
	Endpoint adjusted geometric mean	6.826	6.750	6.773
	Ratio of SFC+TIO to individual treatments 97.5% CI		1.011 (0.992,1.031)	1.008 (0.988,1.028)
TGV_{FRC} (L)				
Day 1		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	4.755 (0.3259)	4.813 (0.3332)	4.901 (0.3515)
	Endpoint raw geometric mean (SD logs)	4.400 (0.3397)	4.466 (0.3383)	4.539 (0.3354)
	Endpoint adjusted geometric mean	4.439	4.451	4.525
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.997 (0.966,1.030)	0.981 (0.949,1.014)
240 Min	n	28	30	27
	Baseline raw geometric mean (SD logs)	4.755 (0.3259)	4.813 (0.3332)	4.901 (0.3515)
	Endpoint raw geometric mean (SD logs)	4.327 (0.3393)	4.485 (0.3467)	4.515 (0.3367)
	Endpoint adjusted geometric mean	4.366	4.470	4.500
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.977 (0.946,1.008)	0.970 (0.938,1.003)
Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	4.738 (0.3316)	4.813 (0.3332)	4.901 (0.3515)
	Endpoint raw geometric mean (SD logs)	4.281 (0.3387)	4.558 (0.3379)	4.486 (0.3542)
	Endpoint adjusted geometric mean	4.326	4.529	4.471
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.955 (0.925,0.986)	0.968 (0.936,1.001)
240 Min	n	27	30	27
	Baseline raw geometric mean (SD logs)	4.738 (0.3316)	4.813 (0.3332)	4.901 (0.3515)
	Endpoint raw geometric mean (SD logs)	4.272 (0.3462)	4.579 (0.3257)	4.498 (0.3526)
	Endpoint adjusted geometric mean	4.317	4.550	4.484
	Ratio of SFC+TIO to individual treatments 97.5% CI		0.949 (0.919,0.980)	0.963 (0.931,0.996)
Analysis of Post-Treatment IOS Parameters on Days 1 and 14 (MITT)				
Respiratory Resistance at 5Hz (R5; kPa/(L/s))				
Day 1		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	28	29	24
	Baseline raw mean (SD)	0.634 (0.1822)	0.640 (0.1714)	0.633 (0.1874)
	Endpoint raw mean (SD)	0.511 (0.1721)	0.516 (0.1391)	0.529 (0.1445)
	Endpoint adjusted mean (SE)	0.511 (0.0160)	0.515 (0.0157)	0.526 (0.0172)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.003 (0.0206) (-0.050,0.043)	-0.015 (0.0215) (-0.064,0.034)
240 Min	n	27	29	23
	Baseline raw mean (SD)	0.627 (0.1827)	0.640 (0.1714)	0.631 (0.1915)
	Endpoint raw mean (SD)	0.483 (0.1195)	0.503 (0.1034)	0.503 (0.1375)
	Endpoint adjusted mean (SE)	0.484 (0.0162)	0.502 (0.0157)	0.498 (0.0175)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.018 (0.0207) (-0.065,0.030)	-0.014 (0.0220) (-0.064,0.036)
Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	27	27	23

	Baseline raw mean (SD)	0.630 (0.1847)	0.639 (0.1714)	0.658 (0.2060)
	Endpoint raw mean (SD)	0.494 (0.1359)	0.543 (0.1394)	0.594 (0.2016)
	Endpoint adjusted mean (SE)	0.491 (0.0217)	0.550 (0.0218)	0.579 (0.0231)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.059 (0.0261) (-0.119,0.001)	-0.087 (0.0268) (-0.149,-0.026)
240 Min	n	26	27	22
	Baseline raw mean (SD)	0.635 (0.1865)	0.639 (0.1714)	0.644 (0.1912)
	Endpoint raw mean (SD)	0.469 (0.1073)	0.535 (0.1367)	0.544 (0.1237)
	Endpoint adjusted mean (SE)	0.465 (0.0219)	0.542 (0.0218)	0.551 (0.0233)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.078 (0.0263) (-0.138,-0.017)	-0.086 (0.0272) (-0.148,-0.023)
Respiratory Resistance at 20Hz (R20; kPa/(L/s))				
Day 1		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	28	29	24
	Baseline raw mean (SD)	0.350 (0.0932)	0.358 (0.1005)	0.345 (0.0932)
	Endpoint raw mean (SD)	0.309 (0.0728)	0.328 (0.0786)	0.333 (0.0895)
	Endpoint adjusted mean (SE)	0.308 (0.0079)	0.327 (0.0078)	0.335 (0.0085)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.019 (0.0107) (-0.043,0.006)	-0.027 (0.0111) (-0.052,-0.001)
240 Min	n	27	29	23
	Baseline raw mean (SD)	0.348 (0.0947)	0.358 (0.1005)	0.345 (0.0953)
	Endpoint raw mean (SD)	0.311 (0.0735)	0.340 (0.0888)	0.325 (0.0942)
	Endpoint adjusted mean (SE)	0.312 (0.0080)	0.338 (0.0078)	0.327 (0.0087)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.026 (0.0108) (-0.051,-0.002)	-0.016 (0.0113) (-0.042,0.010)
Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	27	27	23
	Baseline raw mean (SD)	0.347 (0.0940)	0.357 (0.1000)	0.357 (0.1005)
	Endpoint raw mean (SD)	0.324 (0.0802)	0.336 (0.0861)	0.366 (0.1103)
	Endpoint adjusted mean (SE)	0.326 (0.0083)	0.338 (0.0083)	0.361 (0.0089)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.012 (0.0117) (-0.039,0.015)	-0.035 (0.0121) (-0.062,-0.007)
240 Min	n	26	27	22
	Baseline raw mean (SD)	0.349 (0.0953)	0.357 (0.1000)	0.355 (0.0914)
	Endpoint raw mean (SD)	0.315 (0.0812)	0.318 (0.0715)	0.339 (0.0809)
	Endpoint adjusted mean (SE)	0.315 (0.0084)	0.321 (0.0083)	0.337 (0.0091)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.006 (0.0118) (-0.033,0.021)	-0.022 (0.0122) (-0.050,0.007)
R5-R20 (kPa/(L/s))				
Day 1		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	28	29	24
	Baseline raw mean (SD)	0.284 (0.1320)	0.282 (0.1154)	0.288 (0.1216)
	Endpoint raw mean (SD)	0.203 (0.1324)	0.188 (0.0888)	0.196 (0.1015)
	Endpoint adjusted mean (SE)	0.202 (0.0132)	0.189 (0.0130)	0.191 (0.0141)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.013 (0.0156) (-0.022,0.049)	0.011 (0.0164) (-0.026,0.048)

240 Min	n	27	29	23
	Baseline raw mean (SD)	0.279 (0.1321)	0.282 (0.1154)	0.286 (0.1241)
	Endpoint raw mean (SD)	0.171 (0.0778)	0.163 (0.0585)	0.178 (0.0793)
	Endpoint adjusted mean (SE)	0.172 (0.0133)	0.163 (0.0130)	0.172 (0.0143)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.009 (0.0157) (-0.027,0.044)	-0.000 (0.0168) (-0.038,0.038)
Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	27	27	23
	Baseline raw mean (SD)	0.283 (0.1344)	0.281 (0.1183)	0.301 (0.1307)
	Endpoint raw mean (SD)	0.171 (0.0891)	0.207 (0.1025)	0.228 (0.1360)
	Endpoint adjusted mean (SE)	0.163 (0.0184)	0.213 (0.0185)	0.217 (0.0193)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.049 (0.0191) (-0.093,-0.005)	-0.054 (0.0197) (-0.099,-0.009)
240 Min	n	26	27	22
	Baseline raw mean (SD)	0.286 (0.1360)	0.281 (0.1183)	0.289 (0.1262)
	Endpoint raw mean (SD)	0.155 (0.0654)	0.217 (0.1044)	0.205 (0.0989)
	Endpoint adjusted mean (SE)	0.148 (0.0186)	0.223 (0.0185)	0.212 (0.0195)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.075 (0.0193) (-0.120,-0.031)	-0.064 (0.0200) (-0.110,-0.018)
Resonant Frequency (RF; Hz)				
Day 1		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	28	29	24
	Baseline raw mean (SD)	25.423 (5.8839)	25.984 (5.2277)	26.584 (5.5697)
	Endpoint raw mean (SD)	20.704 (5.6605)	21.479 (5.0241)	22.185 (4.9954)
	Endpoint adjusted mean (SE)	21.148 (0.6324)	21.404 (0.6229)	21.688 (0.6772)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.257 (0.7533) (-1.974,1.460)	-0.541 (0.7944) (-2.349,1.267)
240 Min	n	27	29	23
	Baseline raw mean (SD)	25.340 (5.9790)	25.984 (5.2277)	26.843 (5.5453)
	Endpoint raw mean (SD)	20.502 (5.1666)	22.476 (5.1994)	22.008 (4.8554)
	Endpoint adjusted mean (SE)	20.926 (0.6397)	22.400 (0.6226)	21.298 (0.6893)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-1.474 (0.7592) (-3.204,0.256)	-0.371 (0.8121) (-2.221,1.478)
Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	27	27	23
	Baseline raw mean (SD)	25.241 (5.9153)	25.990 (5.4103)	26.416 (5.5027)
	Endpoint raw mean (SD)	20.296 (4.5002)	23.028 (5.1606)	23.419 (4.7896)
	Endpoint adjusted mean (SE)	20.593 (0.7611)	22.841 (0.7650)	23.400 (0.8136)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-2.247 (0.9643) (-4.465,-0.030)	-2.806 (0.9921) (-5.085,-0.527)
240 Min	n	26	27	22
	Baseline raw mean (SD)	25.288 (6.0273)	25.990 (5.4103)	26.894 (5.6507)
	Endpoint raw mean (SD)	19.634 (4.4881)	23.405 (5.7866)	23.270 (5.3645)
	Endpoint adjusted mean (SE)	19.994 (0.7663)	23.216 (0.7650)	22.971 (0.8189)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-3.222 (0.9699) (-5.454,-0.991)	-2.977 (1.0013) (-5.280,-0.674)

Respiratory System Reactance (X5; kPa/(L/s))				
Day 1		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	28	29	24
	Baseline raw mean (SD)	-0.395 (0.2084)	-0.357 (0.1599)	-0.412 (0.1632)
	Endpoint raw mean (SD)	-0.245 (0.1648)	-0.254 (0.1345)	-0.275 (0.1463)
	Endpoint adjusted mean (SE)	-0.242 (0.0148)	-0.269 (0.0147)	-0.257 (0.0158)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.027 (0.0190) (-0.017,0.070)	0.015 (0.0193) (-0.030,0.059)
240 Min	n	27	29	23
	Baseline raw mean (SD)	-0.393 (0.2122)	-0.357 (0.1599)	-0.419 (0.1627)
	Endpoint raw mean (SD)	-0.244 (0.1520)	-0.254 (0.1416)	-0.265 (0.1483)
	Endpoint adjusted mean (SE)	-0.242 (0.0149)	-0.266 (0.0147)	-0.242 (0.0160)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.025 (0.0190) (-0.019,0.068)	0.001 (0.0195) (-0.044,0.045)
Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120 Min	n	27	27	23
	Baseline raw mean (SD)	-0.400 (0.2106)	-0.361 (0.1630)	-0.437 (0.1646)
	Endpoint raw mean (SD)	-0.234 (0.1601)	-0.268 (0.1645)	-0.323 (0.2008)
	Endpoint adjusted mean (SE)	-0.232 (0.0228)	-0.286 (0.0230)	-0.298 (0.0241)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.054 (0.0294) (-0.014,0.121)	0.066 (0.0293) (-0.001,0.133)
240 Min	n	26	27	22
	Baseline raw mean (SD)	-0.402 (0.2145)	-0.361 (0.1630)	-0.416 (0.1666)
	Endpoint raw mean (SD)	-0.203 (0.1160)	-0.311 (0.1876)	-0.299 (0.1605)
	Endpoint adjusted mean (SE)	-0.207 (0.0229)	-0.320 (0.0230)	-0.303 (0.0242)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		0.113 (0.0296) (0.045,0.181)	0.096 (0.0296) (0.028,0.163)
Low Frequency Reactance Area (AX; kPa/L)				
Day 1		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120min	n	28	29	24
	Baseline raw mean (SD)	3.362 (2.1686)	3.219 (1.8755)	3.475 (1.8790)
	Endpoint raw mean (SD)	1.921 (1.7812)	1.912 (1.2961)	2.045 (1.4282)
	Endpoint adjusted mean (SE)	1.909 (0.1586)	1.977 (0.1565)	1.918 (0.1677)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.068 (0.1737) (-0.466,0.329)	-0.009 (0.1817) (-0.424,0.406)
240min	n	27	29	23
	Baseline raw mean (SD)	3.341 (2.2070)	3.219 (1.8755)	3.527 (1.9038)
	Endpoint raw mean (SD)	1.776 (1.5502)	1.833 (1.1148)	1.921 (1.3169)
	Endpoint adjusted mean (SE)	1.771 (0.1597)	1.878 (0.1564)	1.740 (0.1692)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.107 (0.1747) (-0.506,0.293)	0.032 (0.1842) (-0.390,0.453)
Day 14		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
120min	n	27	27	22
	Baseline raw mean (SD)	3.358 (2.2098)	3.228 (1.9340)	3.564 (1.9294)
	Endpoint raw mean (SD)	1.676 (1.4701)	2.189 (1.7553)	2.360 (1.5883)
	Endpoint adjusted mean (SE)	1.655 (0.2395)	2.187 (0.2415)	2.228 (0.2538)

	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-0.532 (0.2550) (-1.118,0.054)	-0.573 (0.2616) (-1.175,0.028)
240min	n	26	27	22
	Baseline raw mean (SD)	3.400 (2.2428)	3.228 (1.9340)	3.551 (1.9310)
	Endpoint raw mean (SD)	1.387 (0.8685)	2.472 (1.9739)	2.282 (1.4223)
	Endpoint adjusted mean (SE)	1.392 (0.2408)	2.446 (0.2415)	2.177 (0.2538)
	Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-1.053 (0.2566) (-1.643,-0.464)	-0.785 (0.2632) (-1.389,-0.180)
Summary of TDI Scores at Day 14, Number (%) of subjects with improvement/no change/deterioration (MITT)				
	SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)	
N	29	30	26	
TDI Total Score				
Improvement: TDI ≥1	21 (72%)	8 (27%)	14 (54%)	
No change: TDI =0	6 (21%)	15 (50%)	9 (35%)	
Deterioration TDI ≤-1	2 (7%)	7 (23%)	3 (12%)	
TDI Functional Impairment Score				
Improvement: TDI ≥1	12 (41%)	4 (13%)	10 (38%)	
No change: TDI =0	16 (55%)	22 (73%)	16 (62%)	
Deterioration TDI ≤-1	1 (3%)	4 (13%)	0 (0%)	
TDI Magnitude of Task Score				
Improvement: TDI ≥1	20 (69%)	6 (20%)	13 (50%)	
No change: TDI =0	7 (24%)	18 (60%)	10 (38%)	
Deterioration TDI ≤-1	2 (7%)	6 (20%)	3 (12%)	
TDI Magnitude of Effort Score				
Improvement: TDI ≥1	17 (59%)	7 (23%)	10 (38%)	
No change: TDI =0	10 (34%)	20 (67%)	13 (50%)	
Deterioration TDI ≤-1	2 (7%)	3 (10%)	3 (12%)	
TDI Total Score				
n	29	30	26	
Endpoint raw mean (SD)	2.3 (2.55)	0.2 (3.09)	1.7 (2.76)	
Endpoint adjusted mean (SE)	2.3 (0.53)	0.2 (0.52)	1.6 (0.55)	
Difference between SFC+TIO and individual treatments (SE) 97.5% CI		2.2 (0.59) (0.8,3.5)	0.7 (0.61) (-0.7,2.1)	
	SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)	
Morning PEFR (L/min)				
n	28	30	25	
Endpoint raw mean (SD)	265.8 (99.16)	244.2 (101.19)	249.1 (90.96)	
Endpoint adjusted mean (SE)	259.6 (17.99)	244.7 (17.91)	248.6 (18.13)	
Difference between SFC+TIO and individual treatments (SE) 97.5% CI		14.9 (6.64) (-0.4,30.3)	11.0 (6.96) (-5.1,27.1)	
Ventolin use as Rescue Medication in a 24 hour period				
n	28	30	25	
Endpoint raw mean (SD)	1.6 (1.60)	2.6 (2.50)	2.0 (2.23)	
Endpoint adjusted mean (SE)	1.6 (0.39)	2.6 (0.39)	2.1 (0.40)	
Difference between SFC+TIO and individual treatments (SE) 97.5% CI		-1.0 (0.21) (-1.5,-0.6)	-0.6 (0.22) (-1.1,-0.1)	
Mean Cough Score ¹				
n	28	30	25	

Endpoint raw mean (SD)		1.4 (0.59)	1.5 (0.75)	1.2 (0.72)
Endpoint adjusted mean (SE)		1.4 (0.13)	1.5 (0.13)	1.3 (0.14)
Difference between SFC+TIO and individual treatments (SE)			-0.1 (0.12)	0.1 (0.12)
97.5% CI			(-0.4,0.2)	(-0.1,0.4)
1. 0 = no cough, 1 = mild cough, 2 = moderate coughing, 3 = severe cough				
Mean Breathlessness Score ²				
n		28	30	25
Endpoint raw mean (SD)		1.5 (0.56)	1.7 (0.78)	1.5 (0.72)
Endpoint adjusted mean (SE)		1.5 (0.13)	1.7 (0.13)	1.6 (0.13)
Difference between SFC+TIO and individual treatments (SE)			-0.2 (0.11)	-0.1 (0.11)
97.5% CI			(-0.5,0.0)	(-0.3,0.2)
2. 0 = not breathless, 1 = on moderate exertion, 2 = on mild exertion, 3 = on minimal exertion				
Interval		SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
Mean Sputum Production Score ³				
Treatment	n	28	30	25
	Mean	1.3	1.2	1.1
	SD	0.75	0.91	0.85
	Median	1.5	1.1	1.0
	Min	0	0	0
	Max	2	3	2
3. 0 = none, 1 = mild, 2 = moderate, 3 = severe				
Mean Sputum Colour Score ⁴				
Treatment	n	28	30	25
	Mean	1.4	1.4	1.2
	SD	0.85	0.99	0.92
	Median	1.9	1.5	1.4
	Min	0	0	0
	Max	3	3	3
4. 0 = none, 1 = colourless, 2 = white/grey, 3 = light yellow/green, 4 = dark yellow/green				
Mean Sleep Quality Score ⁵				
	n	28	30	25
	Mean	2.1	2.0	2.1
	SD	0.45	0.55	0.49
	Median	2.0	1.9	2.0
	Min	1	1	1
	Max	3	3	3
5. 0 = very poor night's sleep, 1 = poor night's sleep, 2 = good night's sleep, 3 = very good night's sleep				
Summary of Overall Evaluation of Response to Therapy (MITT)				
Assessor	Grade	SFC+TIO (N=29)	TIO (N=30)	SFC (N=27)
Subject	Significantly improved	7 (24%)	1 (3%)	4 (15%)
	Moderately improved	10 (34%)	3 (10%)	8 (30%)
	Mildly improved	5 (17%)	4 (13%)	2 (7%)
	No change	3 (10%)	11 (37%)	8 (30%)
	Mildly worse	4 (14%)	5 (17%)	5 (19%)
	Moderately worse	0 (0%)	3 (10%)	0 (0%)
	Significantly worse	0 (0%)	3 (10%)	0 (0%)
Clinician	Significantly improved	9 (31%)	1 (3%)	3 (11%)
	Moderately improved	7 (24%)	3 (10%)	3 (11%)
	Mildly improved	6 (21%)	4 (13%)	6 (22%)
	No change	4 (14%)	12 (40%)	10 (37%)
	Mildly worse	3 (10%)	5 (17%)	5 (19%)

	Moderately worse	0 (0%)	4 (13%)	0 (0%)
	Significantly worse	0 (0%)	1 (3%)	0 (0%)

Safety results:

An on therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. An on therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication but not later than one day after the last date of study medication.

On-therapy Adverse Events reported by the highest number of subjects (Safety Population)

Adverse Event n (%) subjects reporting	SFC+TIO (N=31)	TIO (N=37)	SFC (N=31)
Any Adverse Event	23 (74)	23 (62)	22 (71)
Dyspnoea exacerbated	6 (19)	5 (14)	3 (10)
Headache	4 (13)	4 (11)	4 (13)
Nasopharyngitis	3 (10)	2 (5)	2 (6)
Cough	2 (6)	5 (14)	3 (10)
Diarrhoea	2 (6)	2 (5)	3 (10)
Productive cough	2 (6)	1 (3)	3 (10)
Lower respiratory tract infection	2 (6)	1 (3)	2 (6)
Pharyngolaryngeal pain	2 (6)	1 (3)	1 (3)
Wheezing	2 (6)	1 (3)	1 (3)
Dyspnoea	2 (6)	0	0
Non-cardiac chest pain	2 (6)	0	0
Back Pain	1 (3)	5 (14)	1 (3)
Arthralgia	1 (3)	2 (5)	0
Constipation	1 (3)	1 (3)	0
Dry mouth	1 (3)	1 (3)	0
COPD	0	1 (3)	2 (6)
Nasal congestion	0	1 (3)	2 (6)
Abdominal pain upper	0	2 (5)	0
Abdominal distension	0	1 (3)	1 (3)
Nausea	0	0	2 (6)
Angina pectoris	0	1 (3)	0
Dyspnoea exertional	0	1 (3)	0
Eyelid infection	0	1 (3)	0
Feeling hot	0	1 (3)	0
Gout	0	1 (3)	0
Herpes simplex	0	1 (3)	0
Hyponatraemia	0	1 (3)	0
Infective exacerbation of COPD	0	1 (3)	0
Intermittent claudication	0	1 (3)	0
Muscle spasms	0	1 (3)	0
Myalgia	0	1 (3)	0
Pain	0	1 (3)	0
Skin hyperpigmentation	0	1 (3)	0

Serious Adverse Events, including both fatal and non-fatal events [n considered by the investigator to be related, possibly related, or probably related to study medication]:

Serious Adverse Events n (%) subjects reporting	SFC+TIO (N=31)	TIO (N=37)	SFC (N=31)
	n (%) [related]	n (%) [related]	n (%) [related]
Any Adverse Event	2 (6%)	1 (3%)	1 (3%)
Lung squamous cell carcinoma stage unspecified	1 (3) [0]	0	0
Rectal cancer	0	0	1 (3) [0]
Non-cardiac chest pain	1 (3) [0]	0	0
Lower respiratory tract infection	0	1 (3) [1]	0

Hyponatraemia	0	1 (3) [0]	0
Lung disorder	0	0	1 (3) [0]
Subjects with fatal SAEs, n (%)	0	0	0
Conclusions: See publication below			
Publications: Superiority of the 'triple' therapy of salmeterol/fluticasone propionate (SFC) and tiotropium (TIO) vs. individual components in COPD. Singh D, Brooks J, Hagan G, O'Connor BJ. Eur Respir J 2007; 30 (suppl 51):210s, Abstract 1298			

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