The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: AC2106956

Title: A multicentre, randomised, partially blinded, placebo-controlled, three-way crossover, incomplete block design study to investigate the safety, tolerability, pharmacodynamics/ efficacy and pharmacokinetics of dual bronchodilator therapy with salmeterol 50 μg twice-daily plus two different doses of GSK233705B (20 and 50 μg twice-daily), compared with placebo, salmeterol 50 μg twice-daily alone, and Tiotropium 18 μg once-daily alone, in subjects with chronic obstructive pulmonary disease.

Rationale: The purpose of this study was to provide data on safety, tolerability and bronchodilatory effect of the long-acting muscarinic antagonist GSK233705B when administered concurrently with the long-acting beta2-agonist salmeterol, compared with salmeterol alone, tiotropium bromide 18 μg alone and placebo in subjects with chronic obstructive pulmonary disease (COPD).

Phase: IIA.

Study Period: Initiation 24 Oct 2006, Completion 31 May 2007.

Study Design: This was a multicentre, randomised, partially blinded, placebo-controlled, three-way crossover, incomplete block design study. Following a two-week run-in period, subjects entered the treatment phase of the study which comprised three seven-day treatment periods, each separated by a 14-day wash-out period. At the end of the treatment phase of the study, there was a two-week safety follow-up period. Each subject received three of the possible five treatments in a randomised partially blinded fashion: GSK233507B 20 μg twice-daily plus salmeterol 50 μg twice-daily, GSK233507B 50 μg twice-daily plus salmeterol 50 μg twice-daily, salmeterol 50 μg twice-daily alone, tiotropium bromide 18 μg once-daily alone, and placebo either once- or twice-daily. On Day 1 and Day 7 of each treatment period serial lung function, safety monitoring and pharmacokinetic sampling were conducted.

Centres: This was a multicentre study conducted at nine centres in Finland, Germany, The Netherlands and the United Kingdom.

Indication: COPD.

Treatment: All study medications were delivered via the DISKUS/ACCUHALER inhaler, except tiotropium bromide and matching placebo, which were delivered via Handihaler. Both salmeterol and placebo were formulated with lactose. Salmeterol 50 μg and GSK233705 were both administered twice-daily, Tiotropium bromide 18 μg was administered once daily, and matching placebos were administered either twice daily or once daily.

Objectives: The primary objective was to estimate the bronchodilatory effect of GSK233507B when administered concurrently with salmeterol 50 μg twice-daily for seven days in subjects with COPD, compared with placebo. The secondary objectives were to:

- Estimate the bronchodilatory effect of salmeterol 50 μg twice-daily alone and once-daily Tiotropium bromide 18 μg alone, compared with that of placebo and of concurrent treatment with GSK2323507B plus salmeterol 50 μg, when administered for 7 days in subjects with COPD.
- Assess the safety and tolerability of concurrent treatment with GSK233507B plus salmeterol 50 μg, as well as salmeterol 50 μg twice-daily alone and once-daily tiotropium bromide 18 μg alone, when administered for seven days in subjects with COPD.
- Assess the pharmacokinetics of GSK233507B when administered concurrently with salmeterol 50 μg, and of salmeterol 50 μg twice-daily administered concurrently with GSK233507B or alone, in COPD subjects dosed for seven days.

Primary Outcome/Efficacy Variable: Morning pre-dose (trough) forced expiratory volume in one second (FEV_1) on Day 8 following 7 days of treatment.

Secondary Outcome/Efficacy Variable(s): Morning pre-dose (trough) FEV_1 on Day 2 of treatment; post-dose FEV_1 on Day 1 and 7; morning pre-dose (trough) forced vital capacity (FVC) on Day 2 and 8; post-dose serial FVC on Day 1 and 7 of treatment; morning pre-dose (trough) specific airway conductance (sGaw), airways resistance (Raw), inspiratory capacity (IC) and residual volume (RV) on Day 2 and Day 8; post-dose sGaw, Raw, IC and RV on Day 1

and Day 7; and morning pre-dose peak expiratory flow rate (PEF) and rescue medication use recorded on daily record cards.

Statistical Methods: In this study no formal hypotheses were utilised or tested as the main aim of this study was to estimate the bronchodilatory effects of GSK233507B in combination with salmeterol compared with other treatment regimens. Sixty subjects were considered to be required to ensure that approximately 45 evaluable subjects were achieved to provide an acceptable precision of ≤0.107 L around estimates of treatment differences in FEV_1. Five populations were used for analysis: the All Subjects Enrolled Population, the Modified Per Protocol Population (MPP) for efficacy analysis, the Safety Population, the Pharmacokinetics (PK) Concentration Population and the PK Parameter Population. Endpoints, including the primary efficacy endpoint trough FEV_1, were analysed using mixed effects models fitted in SAS using PROC MIXED; adjusted means and treatment differences were calculated along with corresponding 95% confidence intervals. Prior to analysis, plethysmography parameters (sGaw, Raw, IC and RV) were log e-transformed. No formal statistical analysis was performed on safety data except for the maximum, minimum and weighted mean parameters for 12-lead electrocardiogram (ECG) $QTc_{(F)}$ and $QTc_{(B)}$ and supine vital signs parameters, which were analysed in the same way as the primary efficacy parameter. Statistical analyses were not adjusted for study centre because treatment comparisons were within-subject comparisons. Treatment by period interaction and carry-over effects were not investigated. Exposure from time 0 to last measurable concentration ($AUC_{(0-t)}$), C_{max}, t_{last} and t_{max} were determined from individual plasma concentration-time profiles. Exploratory plots of plasma GSK233507B and salmeterol C_{max} versus derived PD parameters were produced to assess any PK/PD relationships. Pharmacogenetic blood samples were not analysed.

Study Population: Male and female (of non-childbearing potential) subjects, aged 40-75 years inclusive, with a diagnosis of COPD. Subjects had to have a post-bronchodilator FEV_1 of ≥40% to ≤75% of predicted normal and an FEV_1/FVC ratio of ≤70% and to demonstrate a bronchodilator response to both ipratropium bromide and salbutamol. Subjects had to be current smokers or ex-smokers with a smoking history of ≥10 pack-years. Key exclusion criteria included a diagnosis of asthma, COPD exacerbations or changes in COPD medication in the last four weeks prior to Screening, and respiratory disorders other than COPD.

Study Population	***Total***				
Planned, N	60				
Randomised, N	47				
Completed, n	43				
	Placebo	**GSK233507B 20μg+SAL**	**GSK233507B 50μg+SAL**	**SAL**	**TIO**
Treated	26	23	27	29	28
Completed, n (%)	24 (92.3)	23 (100)	27 (100)	27 (93.1)	28 (100)
Total Number Subjects Withdrawn (any reason), n (%)	2 (7.7)	0	0	2 (6.9)	0
Withdrawn due to Adverse Events, n (%)	0	0	0	1 (3.4)	0
Withdrawn due to Exacerbation, n (%)	2 (7.7)	0	0	1 (3.4)	0

Demographics	***Total***
N (MPP Population)	43
Females n (%) : Males n (%)	18 (41.9) / 25 (58.1)
Mean Age, years (SD)	62.3 (7.11)
White/Caucasian/European heritage, n (%)	43 (100)

Primary Efficacy Results:

Primary outcome variable: Morning, pre-dose (trough) FEV_1 (L) on Day 8.

	Placebo (N=24)	**GSK233507B 20μg+SAL (N=23)**	**GSK233507B 50μg+SAL (N=27)**	**SAL (N=27)**	**TIO (N=28)**
n	24	22	26	27	28

Mean Baseline (SD)	1.187 (0.3624)	1.159 (0.3057)	1.292 (0.4285)	1.286 (0.4249)	1.198 (0.3382)
Endpoint adjusted mean (SE)	1.249 (0.0275)	1.464 (0.0289)	1.452 (0.0266)	1.350 (0.0262)	1.367 (0.0258)
Adjusted mean change from baseline (SE)	0.020 (0.0275)	0.236 (0.0289)	0.223 (0.0266)	0.121 (0.0262)	0.139 (0.0258)
Difference from Placebo (SE) 95% CI		0.215 (0.0364) 0.143, 0.288	0.203 (0.0345) 0.134, 0.271	0.101 (0.0343) 0.033, 0.169	0.118 (0.0338) 0.051, 0.185
Difference from SAL (SE) 95% CI		0.114 (0.0355) 0.044, 0.185	0.102 (0.0333) 0.036, 0.168		
Difference from TIO (SE) 95% CI		0.097 (0.0350) 0.028, 0.166	0.084 (0.0331) 0.019, 0.150		

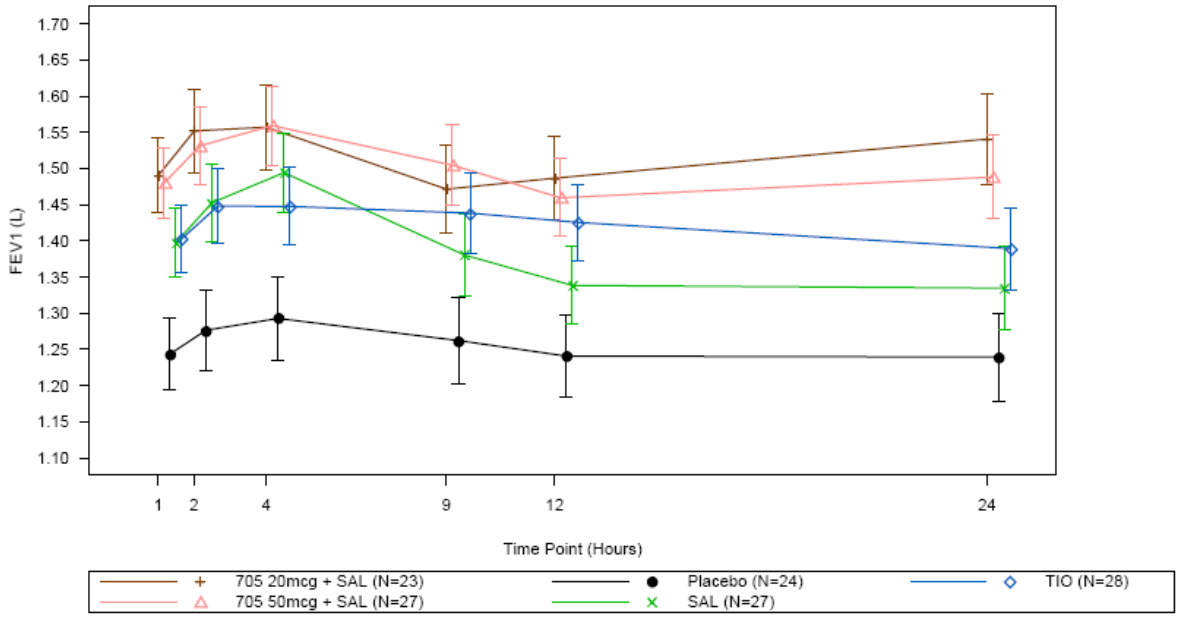
Secondary Outcome Variable(s):

Morning, pre-dose (trough) FEV_1 (L) on Day 2.

	Placebo (N=24)	**GSK233507B 20µg+SAL (N=23)**	**GSK233507B 50µg+SAL (N=27)**	**SAL (N=27)**	**TIO (N=28)**
n	24	23	27	28	24
Mean Baseline (SD)	1.187 (0.3624)	1.181 (0.3164)	1.289 (0.4205)	1.286 (0.4249)	1.198 (0.3382)
Endpoint adjusted mean (SE)	1.240 (0.0300)	1.546 (0.0309)	1.490 (0.0285)	1.345 (0.0286)	1.375 (0.0280)
Adjusted mean change from baseline (SE)	0.011 (0.0300)	0.317 (0.0309)	0.262 (0.0285)	0.117 (0.0286)	0.147 (0.0280)
Difference from Placebo(SE) 95% CI		0.306 (0.0398) 0.227, 0.385	0.251 (0.0379) 0.175, 0.326	0.105 (0.0381) 0.030, 0.181	0.136 (0.0375) 0.061, 0.210
Difference from SAL (SE) 95% CI		0.201 (0.0388) 0.124, 0.278	0.145 (0.0367) 0.072, 0.218		
Difference from TIO (SE) 95% CI		0.170 (0.0383) 0.094, 0.246	0.115 (0.0364) 0.043, 0.187		

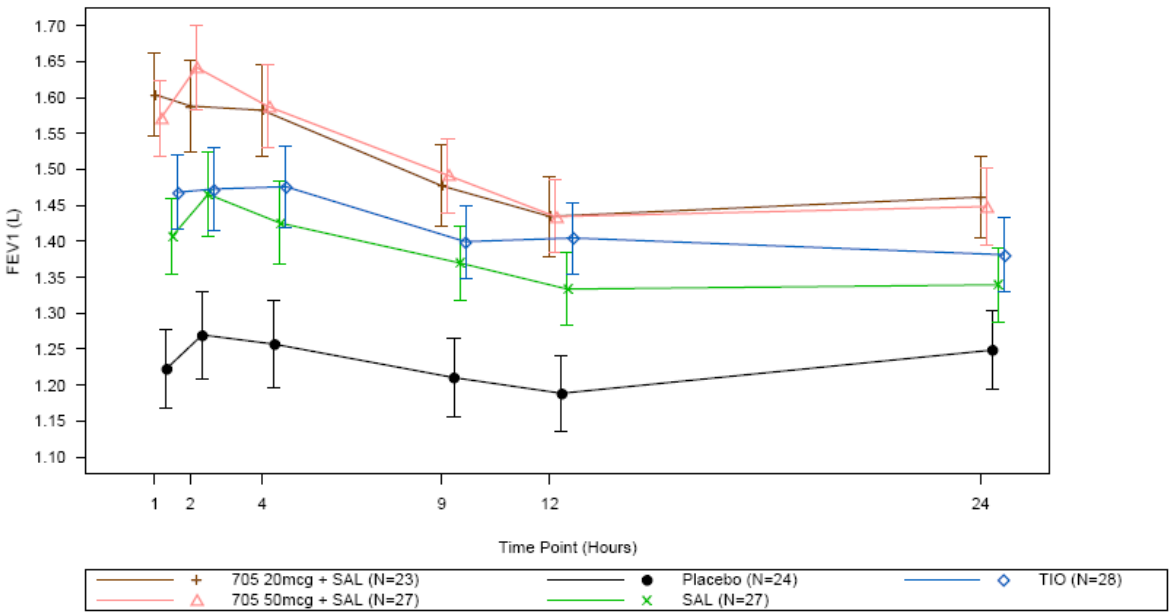
Post-dose serial FEV_1 (L) on Day 1 and Day 7.

Day 1



TIO and matching placebo were dosed once-daily (morning dose only) whilst the other treatments (including matching placebo) were dosed twice daily.

Day 7



TIO and matching placebo were dosed once-daily (morning dose only) whilst the other treatments (including matching placebo) were dosed twice daily.

Morning, pre-dose (trough) FVC (L) on Day 2 and Day 8

Day 2

	Placebo (N=24)	**GSK233507B 20µg+SAL (N=23)**	**GSK233507B 50µg+SAL (N=27)**	**SAL (N=27)**	**TIO (N=28)**
n	24	23	27	27	28
Mean Baseline (SD)	2.814 (0.7429)	3.057 (0.7954)	3.042 (0.6913)	3.023 (0.7657)	2.926 (0.8030)
Endpoint adjusted mean (SE)	2.987 (0.0569)	3.412 (0.0582)	3.349 (0.0538)	3.136 (0.0539)	3.173 (0.0529
Adjusted mean change from baseline (SE)	0.019 (0.0569)	0.444 (0.0582)	0.382 (0.0538)	0.169 (0.0539)	0.205 (0.0529)
Difference from Placebo (SE) 95% CI		0.425 (0.0743) 0.277,0.572	0.362 (0.0697) 0.224,0.501	0.149 (0.0708) 0.009,0.290	0.186 (0.0695) 0.048,0.324
Difference from SAL (SE) 95% CI		0.275 (0.0713) 0.134,0.417	0.213 (0.0674) 0.079,0.347		
Difference from TIO (SE) 95% CI		0.239 (0.0702) 0.100,0.378	0.177 (0.0670) 0.044,0.310		

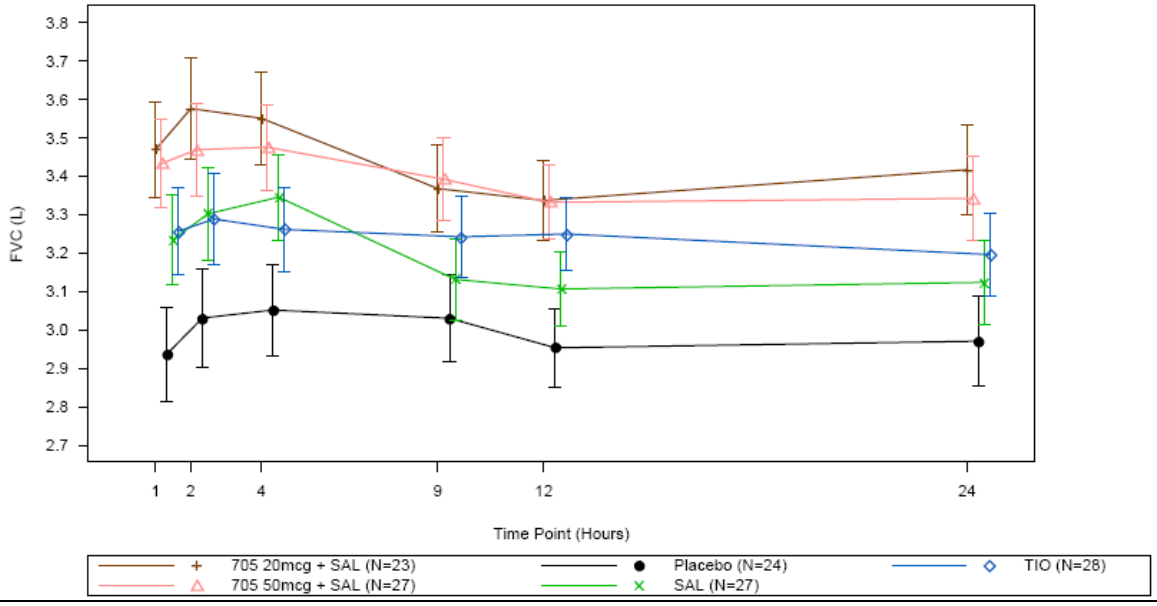
Day 8

	Placebo (N=24)	**GSK233507B 20µg+SAL (N=23)**	**GSK233507B 50µg+SAL (N=27)**	**SAL (N=27)**	**TIO (N=28)**
n	24	22	26	27	28
Mean Baseline (SD)	2.814 (0.7429)	2.984 (0.7313)	3.056 (0.7013)	3.023 (0.7657)	2.926 (0.8030)
Endpoint adjusted mean (SE)	2.956 (0.0557)	3.367 (0.0579)	3.311 (0.0533)	3.100 (0.0527)	3.213 (0.0518)
Adjusted mean change from baseline (SE)	-0.012 (0.0557)	0.399 (0.0579)	0.343 (0.0533)	0.132 (0.0527)	0.245 (0.0518)
Difference from Placebo (SE) 95% CI		0.411 (0.0731) 0.266,0.556	0.355 (0.0684) 0.219,0.491	0.144 (0.0690) 0.007,0.281	0.257 (0.0677) 0.123,0.392

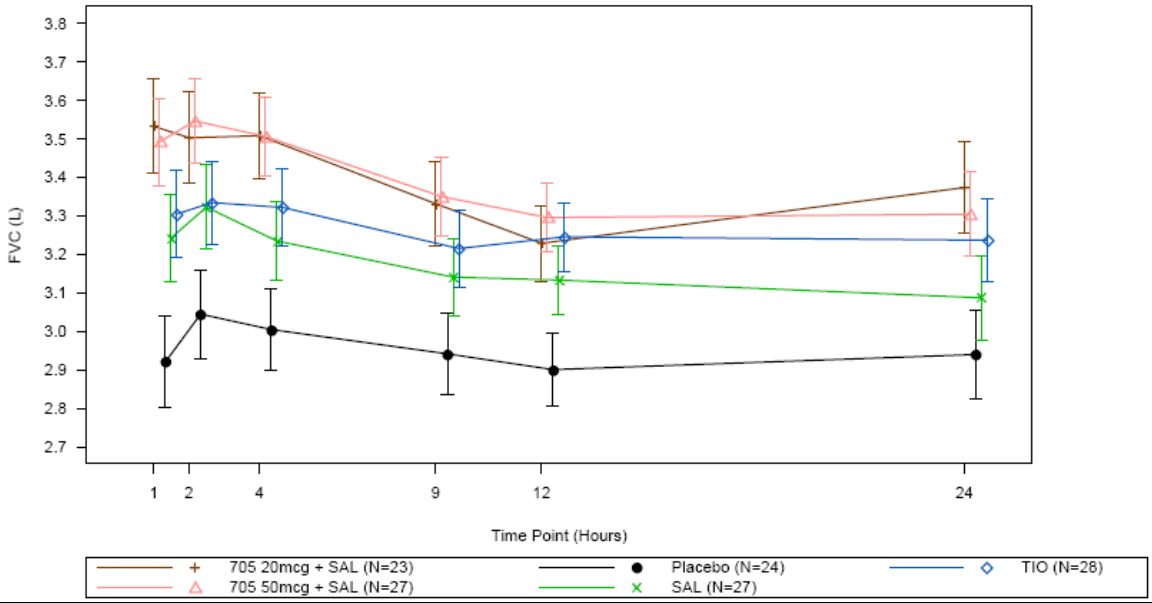
Difference from SAL (SE) 95% CI		0.267 (0.0702) 0.128,0.407	0.211 (0.0660) 0.080,0.342		
Difference from TIO (SE) 95% CI		0.154 (0.0692) 0.016,0.292	0.098 (0.0657) -0.033,0.228		

Post-dose serial FVC (L) on Day 1 and Day 7.

Day 1



Day 7



*Morning, pre-dose (trough) sGaw (1/kPa*s), Raw (kPa.s), IC (L) and RV (L) on Day 2 and Day 8.*

Day 2	**Placbo (N=24)**	**GSK233507B 20µg+SAL (N=23)**	**GSK233507B 50µg+SAL (N=27)**	**SAL (N=27)**	**TIO (N=28)**
n	24	23	27	27	27

Trough sGaw					
Endpoint adjusted geometric mean	0.472	0.793	0.837	0.561	0.593
Adjusted geometric mean ratio to baseline	1.034	1.739	1.834	1.231	1.300
Ratio to placebo (95% CI)		1.682(1.478,1.913)	1.774(1.570,2.004)	1.191(1.053,1.346)	1.257(1.112,1.421)
Ratio to SAL (95% CI)		1.412(1.245,1.603)	1.490(1.325,1.676)		
Ratio to TIO (95% CI)		1.337(1.179,1.517)	1.411(1.253,1.588)		
Trough Raw					
Endpoint adjusted geometric mean	0.418	0.259	0.249	0.358	0.335
Adjusted geometric mean ratio to baseline	0.986	0.610	0.588	0.845	0.790
Ratio to placebo (95% CI)		0.619(0.545,0.703)	0.596(0.528,0.672)	0.857(0.759,0.967)	0.801(0.710,0.904)
Ratio to SAL (95% CI)		0.723(0.638,0.818)	0.696(0.620,0.781)		
Ratio to TIO (95% CI)		0.773(0.684,0.873)	0.744(0.661,0.836)		
Trough IC					
Endpoint adjusted geometric mean	1.982	2.248	2.170	2.014	2.094
Adjusted geometric mean ratio to baseline	1.028	1.166	1.126	1.045	1.086
Ratio to placebo (95% CI)		1.134(1.065,1.208)	1.095(1.032,1.162)	1.016(0.956,1.080)	1.057(0.995,1.122)
Ratio to SAL (95% CI)		1.116(1.049,1.187)	1.078(1.017,1.142)		
Ratio to TIO (95% CI)		1.073(1.010,1.141)	1.036(0.978,1.098)		
Trough RV					
Endpoint adjusted geometric mean	3.566	3.022	3.057	3.307	3.323
Adjusted geometric mean ratio to baseline	0.971	0.823	0.833	0.901	0.905
Ratio to placebo (95% CI)		0.847(0.778,0.923)	0.857(0.790,0.930)	0.927(0.854,1.007)	0.932(0.857,1.014)
Ratio to SAL (95% CI)		0.914(0.841,0.992)	0.925(0.855,1.000)		
Ratio to TIO (95% CI)		0.909(0.837,0.988)	0.920(0.850,0.996)		
Day 8	**Placbo (N=24)**	**GSK233507B 20µg+SAL (N=23)**	**GSK233507B 50µg+SAL (N=27)**	**SAL (N=27)**	**TIO (N=28)**
n	24	21	26	27	28
Trough sGaw					
Endpoint adjusted geometric mean	0.441	0.660	0.731	0.558	0.572
Adjusted geometric mean ratio to baseline	0.966	1.448	1.603	1.224	1.254
Ratio to placebo (95% CI)		1.498(1.315,1.707)	1.659(1.469,1.874)	1.266(1.121,1.430)	1.298(1.150,1.464)
Ratio to SAL (95% CI)		1.183(1.042,1.344)	1.310(1.165,1.473)		
Ratio to TIO (95% CI)		1.154(1.017,1.310)	1.278(1.137,1.437)		
Trough Raw					
Endpoint adjusted geometric mean	0.437	0.310	0.286	0.356	0.350
Adjusted geometric mean ratio to baseline	1.032	0.732	0.676	0.840	0.825
Ratio to placebo (95% CI)		0.710(0.620,0.812)	0.655(0.577,0.743)	0.814(0.718,0.923)	0.800(0.706,0.906)
Ratio to SAL (95% CI)		0.872(0.765,0.993)	0.804(0.713,0.907)		
Ratio to TIO (95% CI)		0.887(0.780,1.009)	0.819(0.725,0.925)		

Trough IC					
Endpoint adjusted geometric mean	1.935	2.159	2.168	2.029	2.074
Adjusted geometric mean ratio to baseline	1.004	1.120	1.125	1.052	1.076
Ratio to placebo (95% CI)		1.116(1.039,1.198)	1.120(1.048,1.197)	1.048(0.980,1.121)	1.072(1.004,1.145)
Ratio to SAL (95% CI)		1.064(0.992,1.141)	1.069(1.002,1.140)		
Ratio to TIO (95% CI)		1.041(0.972,1.114)	1.045(0.981,1.114)		
Trough RV					
Endpoint adjusted geometric mean	3.587	3.032	3.030	3.326	3.313
Adjusted geometric mean ratio to baseline	0.977	0.826	0.825	0.906	0.903
Ratio to placebo (95% CI)		0.845(0.791,0.903)	0.845(0.795,0.898)	0.927(0.872,0.985)	0.924(0.869,0.982)
Ratio to SAL (95% CI)		0.912(0.856,0.971)	0.911(0.860,0.965)		
Ratio to TIO (95% CI)		0.915(0.859,0.974)	0.915(0.863,0.970)		

*Post-dose serial sGaw (1/kPa*s), Raw (kPa.s), IC (L) and RV (L) on Day 1 and Day 7.*

Day 1	**Placebo (N=24)**	**GSK233507B 20μg+SAL (N=23)**	**GSK233507B 50μg+SAL (N=27)**	**SAL (N=27)**	**TIO (N=28)**
Post-dose sGaw					
Endpoint adjusted geometric mean (SD logs): 3h/ 11h/ 25h	0.485 / 0.450 / 0.472	0. 852 / 0.719 / 0.790	0.893 / 0.801 / 0.836	0.775 / 0.580 / 0.560	0.708 / 0.675 / 0.599
Ratio of individual treatments to placebo (95% CI):					
3h		1.756 (1.539, 2.003)	1.839 (1.623, 2.085)	1.596 (1.408, 1.810)	1.458 (1.287,1.652)
11h		1.599 (1.410, 1.812)	1.781 (1.581, 2.006)	1.289 (1.144, 1.453)	1.500 (1.333,1.689)
25h		1.673 (1.475, 1.897)	1.770 (1.571, 1.995)	1.186 (1.052, 1.337)	1.269 (1.126,1.430)
Post-dose Raw					
Endpoint adjusted geometric mean (SD logs): 3h/ 11h/ 25h	0.408 / 0.426 / 0.416	0.251 / 0.294 / 0.260	0.239 / 0.265 / 0.250	0.268 / 0.350 / 0.359	0.286 / 0.293 / 0.331
Ratio of individual treatments to placebo (95% CI):					
3 h		0.616 (0.542,0.700)	0.585 (0.518,0.661)	0.657 (0.582,0.743)	0.700 (0.620,0.790)
11 h		0.690 (0.615,0.774)	0.621 (0.557,0.693)	0.823 (0.738,0.919)	0.687 (0.616,0.766)
25 h		0.624 (0.551,0.707)	0.601 (0.534,0.677)	0.863 (0.766,0.973)	0.795 (0.706,0.895)
Post-dose IC					
Endpoint adjusted geometric mean (SD logs): 3h/ 11h/ 25h	2.007 / 1.860 / 1.991	2.303 / 2.242 / 2.240	2.208 / 2.238 / 2.168	2.141 / 2.097 / 2.011	2.164 / 2.146 / 2.106
Ratio of individual treatments to placebo (95% CI):					
3 h		1.147 (1.070,1.231)	1.100 (1.029,1.176)	1.067 (0.996,1.142)	1.078 (1.009,1.152)
11 h		1.206 (1.118,1.300)	1.203 (1.120,1.293)	1.128 (1.048,1.213)	1.154 (1.075,1.239)
25 h		1.125 (1.056,1.198)	1.089 (1.026,1.156)	1.010 (0.950,1.073)	1.058 (0.996,1.123)
Post-dose RV					
Endpoint adjusted geometric mean (SD logs): 3h/ 11h/ 25h	3.486 / 3.605 / 3.588	2.940 / 3.119 / 3.009	3.012 / 3.279 / 3.056	3.149 / 3.418 / 3.294	3.187 / 3.252 / 3.323
Ratio of individual treatments to placebo (95% CI):					
3 h		0.843 (0.771,0.923)	0.864 (0.793,0.941)	0.903 (0.829,0.984)	0.914 (0.838,0.998)
11 h		0.865 (0.803,0.931)	0.910 (0.847,0.976)	0.948 (0.883,1.018)	0.902 (0.839,0.969)
25 h		0.839 (0.767,0.917)	0.852 (0.782,0.927)	0.918 (0.842,1.000)	0.926 (0.848,1.011)

Day 7	**Placebo (N=24)**	**GSK233507B 20μg+SAL (N=23)**	**GSK233507B 50μg+SAL (N=27)**	**SAL (N=27)**	**TIO (N=28)**
Post-dose sGaw					
Endpoint adjusted geometric mean (SD logs): 3h/ 11h/ 25h	0.461 / 0.407 / 0.441	0.876 / 0.686 / 0.659	0.898 / 0.687 / 0.730	0.705 / 0.543 / 0.556	0.717 / 0.618 / 0.575
Ratio of individual treatments to placebo (95% CI):					
3h		1.899 (1.652,2.183)	1.947 (1.709,2.217)	1.528 (1.341,1.742)	1.554 (1.365,1.769)
11h		1.684 (1.470,1.928)	1.686 (1.486,1.913)	1.334 (1.176,1.515)	1.518 (1.339,1.721)
25h		1.494 (1.309,1.705)	1.655 (1.462,1.873)	1.261 (1.115,1.427)	1.303 (1.153,1.473)
Post-dose Raw					
Endpoint adjusted geometric mean (SD logs): 3h/ 11h/ 25h	0.456 / 0.485 / 0.436	0.243 / 0.311 / 0.312	0.237 / 0.297 / 0.288	0.296 / 0.366 / 0.357	0.290 / 0.318 / 0.348
Ratio of individual treatments to placebo (95% CI):					
3 h		0.532 (0.462,0.613)	0.520 (0.455,0.593)	0.648 (0.568,0.740)	0.636 (0.558,0.725)
11 h		0.642 (0.561,0.735)	0.613 (0.540,0.695)	0.755 (0.666,0.857)	0.656 (0.579,0.743)
25 h		0.716 (0.628,0.818)	0.661 (0.584,0.748)	0.821 (0.725,0.929)	0.798 (0.706,0.902)
Post-dose IC					
Endpoint adjusted geometric mean (SD logs): 3h/ 11h/ 25h	1.984 / 1.969 / 1.944	2.348 / 2.171 / 2.151	2.225 / 2.156 / 2.171	2.091 / 1.977 / 2.026	2.162 / 2.038 / 2.088
Ratio of individual treatments to placebo (95% CI):					
3 h		1.183 (1.106,1.265)	1.121 (1.054,1.193)	1.054 (0.989,1.123)	1.090 (1.024,1.159)
11 h		1.102 (1.034,1.175)	1.095 (1.032,1.162)	1.004 (0.945,1.066)	1.035 (0.976,1.098)
25 h		1.106 (1.029,1.189)	1.117 (1.044,1.195)	1.042 (0.973,1.116)	1.074 (1.005,1.148)
Post-dose RV					
Endpoint adjusted geometric mean (SD logs): 3h/ 11h/ 25h	3.220 / 3.630 / 3.612	2.891 / 2.944 / 3.003	2.989 / 3.232 / 3.036	3.129 / 3.376 / 3.313	2.962 / 3.314 / 3.318
Ratio of individual treatments to placebo (95% CI):					
3 h		0.898 (0.824,0.979)	0.928 (0.858,1.005)	0.972 (0.897,1.052)	0.920 (0.848,0.997)
11 h		0.811 (0.753,0.873)	0.890 (0.832,0.952)	0.930 (0.869,0.995)	0.913 (0.852,0.978)
25 h		0.831 (0.781,0.885)	0.841 (0.794,0.890)	0.917 (0.866,0.971)	0.919 (0.867,0.974)

	Placebo (N=24)	**GSK233507B 20μg+SAL (N=23)**	**GSK233507B 50μg+SAL (N=27)**	**SAL (N=27)**	**TIO (N=28)**
		21	27		26
		278.54 (72.684)	305.77 (96.237)		258.18 (73.711)
Endpoint adjusted mean (SE)		289.70 (14.078)	288.57 (13.898)		269.57 (13.922)
		35.45 (6.016) 23.47,47.43	34.32 (5.472) 23.42,45.22		15.32 (5.562) 4.24,26.40
		15.36 (5.811) 3.78,26.93	14.23 (5.208) 3.85,24.60		
		20.13 (5.707) 8.76,31.50	19.00 (5.325) 8.39,29.61		
	Placebo (N=24)	**GSK233507B 20μg+SAL (N=23)**	**GSK233507B 50μg+SAL (N=27)**	**SAL (N=27)**	**TIO (N=28)**
	24	21	26	27	28
	1.78 (1.452)	0.52 (0.844)	0.71 (0.964)	0.92 (1.404)	1.13 (1.399)

Endpoint adjusted mean (SE)	1.52 (0.221)	0.55 (0.231)	0.75 (0.216)	1.04 (0.214)	1.20 (0.211)
		-0.97 (0.235) -1.43,-0.50	-0.77 (0.215) -1.20,-0.34	-0.48 (0.215) -0.91,-0.05	-0.31 (0.213) -0.74,0.11
		-0.49 (0.228) -0.94,-0.03	-0.29 (0.208) -0.70,0.13		
		-0.65 (0.219) -1.09,-0.22	-0.45 (0.208) -0.87,-0.04		

An adverse event (AE) was defined as any untoward medical occurrence experienced by a study subject during the course of the study, whether or not considered related to the medicinal product. In total, four subjects were withdrawn from the study; one due to an AE of non-sustained ventricular tachycardia (after receiving salmeterol) and three due to COPD exacerbations (one after receiving salmeterol and two whilst receiving or after receiving placebo).

AEs with onset on-treatment experienced by more than 1 subject on any treatment **System Organ Class, n (%)**	**Placebo (N=26)**	**GSK233507B 20μg+SAL (N=23)**	**GSK233507B 50μg+SAL (N=27)**	**SAL (N=29)**	**TIO (N=28)**
Subjects with any AE, n(%)	12 (46.2)	14 (60.9)	11 (40.7)	16 (55.2)	16 (57.1)
Infections and infestations					
Nasopharyngitis	2 (7.7)	1 (4.3)	0	1 (3.4)	1 (3.6)
Urinary tract infection	2 (7.7)	1 (4.3)	0	1 (3.4)	1 (3.6)
Influenza	0	2 (8.7)	0	0	2 (7.1)
Nervous system disorders					
Headache	3 (11.5)	4 (17.4)	2 (7.4)	2 (6.9)	5 (17.9)
Dizziness	0	1 (4.3)	2 (7.4)	0	1 (3.6)
Cardiac disorders					
Ventricular extrasystoles	0	1 (4.3)	1 (3.7)	3 (10.3)	1 (3.6)
Ventricular tachycardia	0	1 (4.3)	0	2 (6.9)[a]	1 (3.6)
Supraventricular tachycardia	0	1 (4.3)	0	0	2 (7.1)
Supraventricular extrasystoles	0	0	0	2 (6.9)	0
Musculoskeletal and connective tissue disorders					
Back pain	3 (11.5)	0	0	2 (6.9)	0
Renal and urinary disorders					
Leukocyturia	0	0	2 (7.4)	0	1 (3.6)
General disorders and administration site conditions					
Fatigue	2 (7.7)	0	0	0	1 (3.6)

a. One subject was withdrawn due to non-sustained ventricular tachycardia upon completion of the salmeterol treatment period.

Treatment-related AEs

Treatment-related AE System Organ Class, n (%)	Placebo (N=26)	GSK233507B 20μg+SAL (N=23)	GSK233507B 50μg+SAL (N=27)	SAL (N=29)	TIO (N=28)
Any AE	2 (7.7)	3 (13.0)	1 (3.7)	3 (10.3)	1 (3.6)
Nervous system disorders				0	
Headache	1 (3.8)	1 (4.3)	0	0	1 (3.6)
Dizziness	0	1 (4.3)	0	0	0
Investigations					
Blood glucose increased	0	0	0	1 (3.4)	0
Electrocardiogram PR prolongation	0	0	0	1 (3.4)	0
Respiratory, thoracic and mediastinal disorders					
Cough	1 (3.8)	1 (4.3)	0	0	0
Throat irritation	0	0	1 (3.7)	0	0
Cardiac disorders					
Ventricular tachycardia	0	0	0	1 (3.4)	0
Gastrointestinal disorders					
Dry mouth	0	1 (4.3)	0	0	0

Serious Adverse Events: A serious adverse event (SAE) was defined as any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation (complications that occurred during hospitalisation were AEs; complications that prolonged hospitalisation or fulfilled any other serious criteria, were an SAE), resulted in disability/incapacity to conduct normal life functions, or was a congenital anomaly/birth defect. From the time a subject consented to participate in and completed the study (including any follow-up period), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GlaxoSmithKline concomitant medication, were reported promptly to GlaxoSmithKline. No deaths or non-fatal SAEs were reported during treatment.

Additional safety assessments: safety profiles (AEs, vital signs, blood biochemistry and haematology, and extensive ECG monitoring) were similar across all treatments, with no clinically significant changes in all cardiovascular indices for concurrent administration of GSK233705B with salmeterol.

Pharmacokinetics: The bioanalytical method, using a lower limit of quantification of 0.01 ng/mL for GSK233705B and 0.025 ng/mL for salmeterol, was not sensitive enough to fully characterise the pharmacokinetic profile of subjects due to the low level of these compounds detected in plasma following administration of GSK233705B 20 µg + salmeterol, GSK233705B 50 µg + salmeterol, or salmeterol only. Overall, 52% of GSK233705B plasma data and 55% of salmeterol plasma data were non-quantifiable.

Summary Statistics of Day 1 GSK233705B AUC(0-t), Cmax, tmax, and tlast

Parameter	Dose	N	n	Geometric Mean	95% CI	CV_b(%)
$AUC_{(0-t)}$ (h*ng/mL)	705 20 µg + SAL	23	4	0.020	(0.013, 0.032)	29.49
	705 50 µg + SAL	27	14	0.018	(0.013, 0.026)	66.67
C_{max_high} (ng/mL)	705 20 µg + SAL	23	23	0.013	(0.011, 0.015)	41.90
	705 50 µg + SAL	27	27	0.023	(0.019, 0.029)	59.66
t_{max} (h)[a]	705 20 µg + SAL	23	10	0.080	(0.05, 0.27)	NA
	705 50 µg + SAL	27	25	0.080	(0.03, 2.08)	NA
t_{last} (h)[a]	705 20 µg + SAL	23	10	0.230	(0.08, 2.10)	NA
	705 50 µg + SAL	27	25	0.500	(0.03, 2.08)	NA

a. Presented as Median and range.

NA : not applicable. $AUC_{(0-t)}$= area under concentration-time curve from time 0 to time of last quantifiable concentration. C_{max} = maximum observed plasma concentration. t_{max} = time of maximum observed plasma concentration. t_{last} = last time point where the concentration is above the limit of quantification.

Summary Statistics of Day 7 GSK233705B AUC(0-t), Cmax, and tmax

Parameter	Dose	N	n	Geometric Mean	95% CI	CV_b(%)
$AUC_{(0-t)}$ (h*ng/mL)	705 20 µg + SAL	23	12	0.022	(0.013, 0.037)	98.08
	705 50 µg + SAL	27	26	0.088	(0.059, 0.131)	129.61
C_{max_high} (ng/mL)	705 20 µg + SAL	23	22	0.019	(0.016, 0.023)	41.77
	705 50 µg + SAL	27	27	0.048	(0.040, 0.058)	51.82
t_{max} (h)[a]	705 20 µg + SAL	23	20	0.080	(0.08, 0.50)	NA
	705 50 µg + SAL	27	27	0.080	(0.05, 0.52)	NA
t_{last} (h) [a]	705 20 µg + SAL	23	20	0.495	(0.08, 4.17)	NA
	705 50 µg + SAL	27	27	4.020	(0.25, 11.95)	NA

a. Presented as Median and range.
NA : not applicable. $AUC_{(0-t)}$= area under concentration-time curve from time 0 to time of last quantifiable concentration.
C_{max} = maximum observed plasma concentration. t_{max} = time of maximum observed plasma concentration. CI = confidence interval.

Summary Statistics of Day 1 Salmeterol AUC(0-t), Cmax, tmax, and tlast

Parameter	**Dose**	**N**	**n**	**Geometric Mean**	**95% CI**	**CV_b(%)**
$AUC_{(0-t)}$ (h*ng/mL)	705 20 µg + SAL	23	10	0.055	(0.039, 0.077)	49.42
	705 50 µg + SAL	27	11	0.059	(0.042, 0.083)	53.62
	SAL	29	14	0.059	(0.049, 0.072)	34.64
C_{max}_high (ng/mL)	705 20 µg + SAL	23	23	0.036	(0.032, 0.041)	28.50
	705 50 µg + SAL	27	27	0.036	(0.031, 0.041)	37.51
	SAL	29	29	0.037	(0.032, 0.042)	35.91
t_{max} (h)[a]	705 20 µg + SAL	23	20	0.520	(0.05, 2.08)	NA
	705 50 µg + SAL	27	19	0.500	(0.08, 1.07)	NA
	SAL	29	23	0.480	(0.05, 2.00)	NA
t_{last} (h) [a]	705 20 µg + SAL	23	20	1.000	(0.05, 2.10)	NA
	705 50 µg + SAL	27	19	1.000	(0.08, 2.10)	NA
	SAL	29	23	1.900	(0.12, 2.25)	NA

a. presented as Median and range.
NA : not applicable. $AUC_{(0-t)}$ = area under concentration-time curve from time 0 to time of last quantifiable concentration. C_{max} = maximum observed plasma concentration. t_{max} = time of maximum observed plasma concentration. t_{last}= last time point where the concentration is above the limit of quantification.

Summary Statistics of Day 7 Salmeterol AUC(0-t), Cmax, and tmax

Parameter	**Dose**	**N**	**n**	**Geometric Mean**	**95% CI**	**CV_b(%)**
$AUC_{(0-t)}$ (h*ng/mL)	705 20 µg + SAL	23	16	0.116	(0.084, 0.162)	68.35
	705 50 µg + SAL	27	20	0.071	(0.045, 0.112)	123.66
	SAL	29	24	0.091	(0.064, 0.129)	98.56
C_{max_high} (ng/mL)	705 20 µg + SAL	23	22	0.052	(0.042, 0.064)	50.43
	705 50 µg + SAL	27	27	0.052	(0.042, 0.063)	52.93
	SAL	29	29	0.049	(0.042, 0.056)	40.88
t_{max} (h) [a]	705 20 µg + SAL	23	20	0.425	(0.08, 1.98)	NA
	705 50 µg + SAL	27	24	0.500	(0.05, 11.92)	NA
	SAL	29	26	0.250	(0.08, 4.00)	NA
t_{last} (h) [a]	705 20 µg + SAL	23	20	2.010	(0.08, 11.85)	NA
	705 50 µg + SAL	27	24	2.000	(0.50, 11.93)	NA
	SAL	29	26	2.050	(0.32, 12.00)	NA

a. presented as Median and range.
NA: not applicable. $AUC_{(0-t)}$ = area under concentration-time curve from time 0 to time of last quantifiable concentration. C_{max} = maximum observed plasma concentration. t_{max} = time of maximum observed plasma concentration. CI = confidence interval.

Conclusion:

- Concurrent use of GSK233705B at doses of 20 µg or 50 µg twice-daily plus salmeterol 50 µg

twice-daily for 7 days resulted in improvements in lung function which were greater than those seen with placebo, salmeterol 50 μg twice-daily alone or tiotropium 18 μg once-daily alone.

- The improvements in lung function were supported by daily diary card assessments of morning PEF and rescue medication use.
- No dose response was observed across the GSK233705B 20 μg + salmeterol and GSK233705B 50 μg + salmeterol combination treatments for any of the endpoints.
- The safety results (AEs, vital signs, blood biochemistry and haematology, and extensive ECG monitoring) indicated that the safety profiles were similar across all treatments.
- No clinically significant changes in all cardiovascular indices were observed with concurrent administration of GSK233705B with salmeterol.

No publications at the time of posting.