

Safety and efficacy of dual therapy with GSK233705 and salmeterol versus monotherapy with salmeterol, tiotropium, or placebo in a crossover pilot study in partially reversible COPD patients

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Background: GSK233705 is an inhaled, long-acting muscarinic antagonist in development for the treatment of chronic obstructive pulmonary disease (COPD). This study was performed to see if the addition of GSK233705 to salmeterol would provide greater bronchodilation than salmeterol or tiotropium alone in COPD.

Methods: In an incomplete-block, three-period, crossover design, dually responsive patients received three of the following five treatments: GSK233705 20 µg plus salmeterol 50 µg twice-daily; GSK233705 50 µg plus salmeterol 50 µg twice-daily; salmeterol 50 µg or placebo, each twice-daily; and tiotropium 18 µg or placebo once-daily for 7 days. Each treatment period was separated by a 14-day washout. The primary efficacy endpoint was morning (trough) forced expiratory volume in 1 second (FEV₁) on Day 8, following 7 days of treatment. Secondary endpoints included pulmonary function, plethysmography, pharmacokinetics of GSK233705 and salmeterol, adverse events (AEs), electrocardiograms (ECGs), vital signs, and laboratory parameters.

Results: A total of 47 patients were randomized. The mean % predicted normal postbronchodilator FEV₁ was 55% at screening. Compared with placebo (n = 24), the adjusted mean change from baseline in trough FEV₁ on Day 8 was 215 mL higher with GSK233705 20 µg + salmeterol (n = 23) and 203 mL higher with GSK233705 50 µg + salmeterol (n = 27), whereas with salmeterol (n = 27) and tiotropium (n = 28) the changes were 101 mL and 118 mL higher, respectively. The primary efficacy results were supported by the results from the other secondary lung function assessments. AEs were reported by similar proportions of patients across the treatment groups, with headache the most frequently reported treatment-related AE reported by one subject receiving each of GSK233705 20 µg + salmeterol, tiotropium, and placebo. No significant differences were seen in vital signs, ECGs, or laboratory parameters between the groups.

Conclusion: The addition of GSK233705 to salmeterol in partially reversible COPD patients resulted in greater bronchodilation than salmeterol or tiotropium alone and was well tolerated.

Keywords: COPD, bronchodilation, dual therapy, LAMA, LABA

Background

Bronchodilators are the cornerstone of the symptomatic management of COPD and current Global initiative for chronic Obstructive Lung Disease guidelines recommend

the use of long-acting inhaled bronchodilators in moderate to very severe COPD.^{1,2} The benefits of bronchodilators include not only the control of symptoms but also improvements in lung function, hyperinflation, exercise performance, exacerbation rate, and health status.

Long-acting inhaled bronchodilators include both long-acting β -agonists (LABA), such as formoterol or salmeterol, and long-acting muscarinic antagonists (LAMA), such as tiotropium bromide. For patients who are not sufficiently controlled on maintenance monotherapy, combining bronchodilators of different classes, in particular a LAMA and a LABA, has been advocated.³ LABA/LAMA combinations appear to play an important role in maximizing bronchodilation and are well tolerated by the majority of patients.⁴⁻⁸

The scientific rationale for combining a LABA and muscarinic antagonist in COPD has been reviewed by several authors.^{9,10} Complementary bronchodilation may be obtained either by directly relaxing the smooth muscle through stimulation of β_2 adrenoceptors or by inhibiting the action of acetylcholine at muscarinic receptors with muscarinic antagonists, indirectly leading to smooth muscle relaxation. Most studies published to date have reported the use of a combination of a twice-daily LABA with tiotropium^{4-8,11,12} or twice-daily LABA with short-acting muscarinic antagonists.^{13,14}

There are a number of LAMAs in clinical development as monotherapies and in fixed combinations with LABAs.^{9,10} GlaxoSmithKline (GSK) are also developing novel LAMAs and one such compound is twice-daily GSK233705, also known as darotropium, a high-affinity pan-active muscarinic receptor antagonist (data on file). Phase I and II studies have assessed the efficacy, safety, tolerability, pharmacodynamics, and pharmacokinetics of single and repeat doses of GSK233705 and shown it to be generally well tolerated and an effective bronchodilator.

This pilot study in COPD patients responsive to both β -agonists and antimuscarinics was performed to see if the addition of GSK233705 to salmeterol would provide greater bronchodilation than salmeterol or tiotropium alone.

Methods

Patients and methods

Patients were recruited between October 2006 and May 2007 at nine centers in Finland, Germany, the Netherlands, and the UK. All patients gave written informed consent and the protocol was approved by the appropriate institutional

review boards and conducted in accordance with good clinical practice guidelines and the most recent version of the Declaration of Helsinki. Patients aged 40–75 years with a clinical history of COPD according to the American Thoracic Society/European Respiratory Society (ATS/ERS) definition,² a smoking history of ≥ 10 pack years, a postbronchodilator forced expiratory volume in 1 second (FEV_1) of $\geq 40\%$ to $\leq 75\%$ of predicted normal, and a postbronchodilator FEV_1 /forced vital capacity (FVC) ratio of $\leq 70\%$ were recruited. In order to recruit the optimum patient population for the study, patients also had to demonstrate responsiveness/reversibility to both 80 mcg ipratropium bromide and 400 mcg salbutamol. Responsiveness/Reversibility was defined as an increase in FEV_1 of $\geq 12\%$ and ≥ 150 mL following inhalation of each bronchodilator administered on different occasions. Subjects with very large improvements in $FEV_1 > 500$ mL at testing were excluded as this suggested the possibility of an alternative diagnosis.

Patients were excluded from the study if they had suffered a COPD exacerbation, had changes in COPD medication, or taken antibiotics within 4 weeks prior to screening or during the run-in period. Patients were also excluded if they had: a current diagnosis of asthma, a history of asthma, known respiratory disorders (apart from COPD), previous lung surgery, or required long-term oxygen therapy or pulmonary rehabilitation at screening. Patients were excluded if they had significant unstable cardiovascular disease.

Study design

This was a multicenter, randomized, partially blinded (active versus placebo treatment), placebo-controlled, three-way crossover study. Each subject was randomized to receive three of a possible five treatments (incomplete block design). The five treatments were: GSK233705 20 μ g plus salmeterol 50 μ g twice-daily; GSK233705 50 μ g plus salmeterol 50 μ g twice-daily; salmeterol 50 μ g twice-daily; tiotropium bromide 18 μ g once daily; and placebo (GSK study number AC2106956; clinical trials.gov NCT00422604).¹⁵ After a 2-week run-in period to establish a stable baseline, subjects were randomized to treatment sequences which comprised three 7-day treatment periods, each separated by a 14-day wash-out period. Two types of inhaler were used for the study (Diskus/Accuhaler™ [GlaxoSmithKline, London, UK] for GSK233705, salmeterol, and placebo and HandiHaler™ [Boehringer Ingelheim, Ingelheim am Rhein, Germany] for tiotropium bromide and placebo).

Concomitant medication

Inhaled salbutamol was provided as a relief medication. Other permitted medications included inhaled corticosteroids at a dose of up to 1000 µg/day of fluticasone propionate or equivalent (provided the dose had remained constant for 6 weeks prior to screening and would remain constant throughout the study). Patients who were taking LABA/ICS combination treatments had the LABA component stopped and replaced by the equivalent dose of inhaled corticosteroid (ICS) as monotherapy.

Outcome measurements

Lung function was determined by measuring the spirometry parameters FEV₁ and FVC, and the plethysmography parameters airway conductance (sGaw), airways resistance (Raw), inspiratory capacity (IC), and residual volume (RV). Both trough (measured before the morning dose on Day 2 and Day 8) and postdose (measured on Day 1 and Day 7) spirometry and plethysmography values were recorded with plethysmography assessments conducted after spirometry. Serial spirometry was performed on Day 1 and Day 7 of each treatment period predose and at 1, 2, 4, 9, 12, and 24 hours following the morning dose of study medication. Plethysmography was performed predose and at 3, 11, and 25 hours postdose on Day 1 and Day 7. Subjects also recorded morning peak expiratory flow (PEF) prior to the morning dose of study medication and relief salbutamol rescue use on daily record cards during the run-in, wash-out, and treatment periods.

The primary efficacy endpoint was morning predose (trough) FEV₁ on Day 8, following 7 days of treatment. Secondary lung function endpoints included trough FEV₁ on Day 2; postdose FEV₁, FVC, and plethysmography measurements on Day 1 and Day 7; trough FVC and trough plethysmography measurements on Day 2 and Day 8; and morning predose PEF and rescue medication recorded on the daily record card.

Safety endpoints included the incidence of adverse events (AEs), incidence of COPD exacerbations, vital signs (systolic and diastolic blood pressure and heart rate), and clinical laboratory tests (hematology, chemistry, and urinalysis). In addition, 12-lead electrocardiograms (ECGs) and 24-hour Holter monitoring were conducted during the study. Vital signs and 12-lead ECGs were measured at 15 and 45 minutes, 2, 4, 8, and 24 hours postdose on Day 1 and 7 of each treatment period. Lead II ECG monitoring was performed for 6 hours postdose at each treatment visit.

Pharmacokinetic assessments

Blood samples were collected to determine plasma concentrations of GSK233705 and salmeterol predose, 5, 15, and 30 minutes, and 1 hour and 2 hours postdose on Day 1. On Day 7, samples were collected as for Day 1 plus additional samples at 4 and 12 hours. Plasma samples were analyzed for GSK233705 and salmeterol using a validated analytical method based on protein precipitation, followed by high-performance liquid chromatography with mass spectrometry. The lower limit of quantification was 0.01 ng/mL for GSK233705 and 0.025 ng/mL for salmeterol. Urine samples were also analyzed for GSK233705 using a validated analytical method based on dilution followed by high-performance liquid chromatography with mass spectrometry analysis.

Statistical analysis

The sample size was based on estimates of precision of the anticipated treatment differences in FEV₁, rather than formal powering, since this was a preliminary hypothesis-generating study. Three analysis populations were used. The modified per protocol (MPP) population, which comprised all subjects who completed at least one posttreatment lung-function assessment in at least two treatment periods and in which major deviations from the protocol did not occur, was used to analyze efficacy. The safety population included all subjects who were randomized and had received at least one dose of study medication and was used for all safety summaries and analyses, background, and demography summaries. Analyses of vital signs and 12-lead ECG data included all subjects in the safety population who recorded a posttreatment value for the relevant parameter in at least two treatment periods. The pharmacokinetic (PK) concentration population comprised all subjects in the safety population for whom a PK sample was obtained and analyzed.

The primary comparison for which treatment differences were estimated was of each dose of GSK233705 plus salmeterol versus placebo. Secondary comparisons for which treatment differences were estimated were for each dose of GSK233705 plus salmeterol versus salmeterol alone or tiotropium. Trough FEV₁ values on Day 2 and Day 8 were analyzed using a mixed effects analysis of covariance with period, baseline FEV₁ by day, treatment by day, and mean baseline FEV₁ by day fitted as fixed effects and subject as a random coefficient; adjusted means and treatment differences were calculated along with corresponding 95% confidence intervals (CIs). Trough FEV₁ on Day 2 and trough

FVC endpoints were analyzed similarly. Prior to analysis, plethysmography parameters (sGaw, Raw, IC, and RV) were log_e-transformed; the transformed parameters were analyzed in the same way as the primary efficacy parameter and back transformed prior to reporting. No formal statistical analysis was performed on safety data except for the maximum, minimum, and weighted mean parameters for 12-lead ECG QTc Fridericia's formula (F) and QTc Bazett's formula (B) and supine vital signs data, which were analyzed in the same way as the primary efficacy parameter.

The PK parameters were calculated by standard non-compartmental analysis using WinNonlin® Pro (Pharsight, St Louis, MO). Plasma concentration data were listed and summarized (in tabular form as well as mean, median, and individual subject plots on the semilogarithmic and linear scales).

Results

Study population

A total of 47 dually responsive subjects were randomized, received treatment, and comprised the safety population. Four subjects (8.5%) were excluded from the MPP population due to failing to complete a baseline and posttreatment assessment for at least one efficacy parameter in at least two periods.

In the MPP population, 23 subjects received GSK233705 20 µg + salmeterol, 27 received GSK233705 50 µg + salmeterol, 27 received salmeterol alone, 28 received tiotropium alone, and 24 received placebo. The mean % predicted postbronchodilator FEV₁ was 55% at screening and the mean percent reversibilities to ipratropium and salbutamol were 26% and 23%, respectively. The demographic and baseline characteristics of the safety and MPP study populations are shown in Table 1.

Efficacy

Primary endpoint

Trough FEV₁ on Day 8

Raw mean trough FEV₁ on Day 8 was higher for all active treatments than for placebo (Figure 1). All active treatments increased trough FEV₁ on Day 8 by more than 120 mL compared with baseline, whereas the increase after placebo treatment was only 20 mL (adjusted mean differences).

Compared with placebo, the increase in trough FEV₁ was 215 mL higher with GSK233705 20 µg + salmeterol and 203 mL higher with GSK233705 50 µg + salmeterol,

Table 1 Baseline demographics and characteristics of the safety and modified per protocol (MPP) populations

	Safety population (N = 47)	MPP population (N = 43)
Age (years)		
Mean (SD)	62.6 (6.9)	62.3 (7.1)
Range	47–75	47–75
Gender, n (%)		
Female	18 (38%)	18 (42%)
Male	29 (62%)	25 (58%)
Ethnicity, n (%)		
White	47 (100%)	43 (100%)
Body mass index (kg/m ²)		
Mean (SD)	25.3 (2.9)	25.3 (3.0)
Range	20.2–30.9	20.2–30.9
Smoking history		
Current/former n (%)	23 (49%)/24 (51%)	21 (49%)/22 (51%)
Years smoked		
Mean (SD)	38.8 (8.9)	38.6 (9.0)
Range	20–60	20–60
Number of cigarettes/day		
Mean (SD)	20.5 (7.8)	20.7 (7.8)
Range	5–40	5–40
Smoking pack years		
Mean (SD)	40.0 (19.2)	40.3 (19.4)
Range	11.5–90.0	11.5–90.0
Postbronchodilator		
FEV ₁ at screening		
% predicted normal FEV ₁		
Mean (SD)	55.3 (10.5)	54.8 (9.5)
Range	39.8–84.9	39.8–72.1
% reversibility in baseline		
FEV ₁ ipratropium		
Mean (SD)	26.3 (11.3)	25.7 (10.7)
Range	9.3–52.4	9.3–52.4
Salbutamol		
Mean (SD)	24.6 (11.5)	23.3 (9.4)
Range	10.6–66.7	10.6–52.7
COPD medication during treatment		
N (%)	37 (79%)	34 (79%)
Inhaled corticosteroids during treatment		
N (%)	25 (53%)	23 (53%)

Abbreviations: FEV₁, forced expiratory volume in 1 second; SD, standard deviation.

whereas with salmeterol and tiotropium alone the increases were 101 mL and 118 mL higher, respectively. Larger increases from baseline in trough FEV₁ on Day 8 were also seen with the combination treatments compared with the individual treatments (Table 2). For all treatment comparisons performed, the lower 95% CI for the treatment difference was >0, giving strong statistical evidence of a benefit of the combination treatments over placebo, salmeterol, and tiotropium, and of salmeterol and tiotropium over placebo (Table 2).

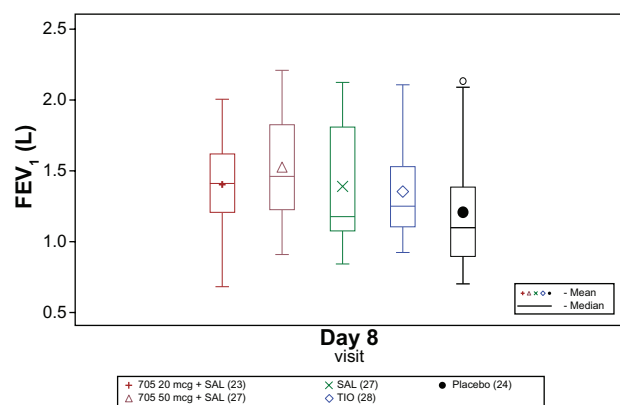


Figure 1 Box plot of raw mean trough (morning, predose) forced expiratory volume in 1 second (FEV_1) on Day 8 (modified per protocol population).

Abbreviations: SAL, salmeterol; TIO, tiotropium.

Secondary endpoints

Trough FEV_1 on Day 2

Raw mean trough FEV_1 on Day 2 was higher for all active treatments than for placebo (Figure 2), and all treatments increased trough FEV_1 on Day 2 compared with baseline. Compared with placebo, the increase from baseline in trough FEV_1 was 306 mL higher with GSK233705 20 μ g + salmeterol and 251 mL higher with GSK233705 50 μ g + salmeterol, whereas with salmeterol and tiotropium the increases were 105 mL and 136 mL higher, respectively. Larger increases from baseline in trough FEV_1 on Day 2 were also seen with the combination treatments compared with the individual treatments: 201 mL versus salmeterol and 170 mL versus tiotropium for GSK233705 20 μ g + salmeterol and 145 mL versus salmeterol and 115 mL versus tiotropium for GSK233705 50 μ g + salmeterol.

For all treatment comparisons performed, the lower 95% CI for the treatment difference was >0 , giving strong statistical evidence of a benefit of the combination treatments

over placebo, salmeterol, and tiotropium, and of salmeterol and tiotropium over placebo (Table 3).

Trough FVC and postdose FVC

Trough FVC and postdose FVC values followed a similar pattern to that observed for the FEV_1 endpoints. Compared with placebo, the change from baseline in trough FVC on Day 8 was 411 mL higher with GSK233705 20 μ g + salmeterol and 355 mL higher with GSK233705 50 μ g + salmeterol, whereas with salmeterol and tiotropium the changes were 144 mL and 257 mL higher, respectively. Trough FVC values and treatment differences on Day 2 were generally higher than those recorded on Day 8. For all comparisons of combination treatments and tiotropium with placebo, the lower 95% CI for the treatment difference was >0 , giving strong statistical evidence of a benefit. The evidence was less strong for the benefit of salmeterol over placebo. Correspondingly there was statistical evidence (lower 95% CI >0) of a benefit of combination treatment over salmeterol, but no consistent statistical evidence of a benefit over tiotropium.

All active treatments increased postdose serial FEV_1 , and postdose FVC relative to placebo at all time points on both days, with the combination treatments again showing an improvement compared with salmeterol alone and tiotropium alone (Figure 3). For all comparisons of combination treatments with placebo, the lower 95% CI for the ratio between treatments was >0 , giving strong statistical evidence of a benefit.

Plethysmography

All active treatments increased trough sGaw on Day 8 by more than 22% compared with baseline, whereas placebo treatment showed a 3% decrease from baseline. The ratio to baseline compared with placebo was 49.8% higher with GSK233705 20 μ g + salmeterol and 65.9% higher with

Table 2 Analysis of trough (morning, predose) forced expiratory volume in 1 second (L) on Day 8 (modified per protocol population)

	GSK233705 20 μ g + salmeterol	GSK233705 50 μ g + salmeterol	Salmeterol	Tiotropium	Placebo
n	22	26	27	28	24
Baseline raw mean (SD)	1.16 (0.31)	1.29 (0.43)	1.29 (0.42)	1.20 (0.34)	1.19 (0.36)
Endpoint adjusted mean (SE)	1.46 (0.03)	1.45 (0.03)	1.35 (0.03)	1.37 (0.03)	1.25 (0.03)
Adjusted mean change from baseline (SE)	0.24 (0.03)	0.22 (0.03)	0.12 (0.03)	0.14 (0.03)	0.02 (0.03)
Difference from placebo (SE)	0.21 (0.04)	0.20 (0.03)	0.10 (0.03)	0.12 (0.03)	
95% CI	(0.14, 0.29)	(0.13, 0.27)	(0.03, 0.17)	(0.05, 0.18)	
Difference from salmeterol (SE)	0.11 (0.03)	0.10 (0.03)			
95% CI	(0.04, 0.18)	(0.04, 0.17)			
Difference from tiotropium (SE)	0.10 (0.03)	0.08 (0.03)			
95% CI	(0.03, 0.17)	(0.02, 0.15)			

Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error of the mean.

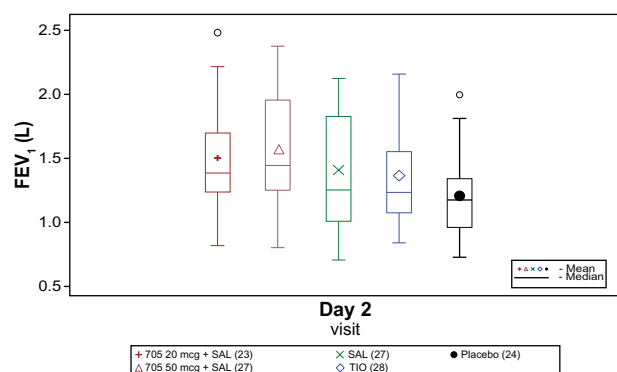


Figure 2 Box plot of raw mean trough (morning, predose) forced expiratory volume in 1 second (FEV₁) on Day 2 (modified per protocol population).

Abbreviations: SAL, salmeterol; TIO, tiotropium.

GSK233705 50 µg + salmeterol, whereas with salmeterol and tiotropium bromide the ratios were 26.6% and 29.8% higher, respectively.

Postdose sGaw, trough Raw, and postdose Raw also reflected the spirometric results (as did IC and RV to a lesser extent) (Table 4).

Morning PEF

The combination treatments both increased PEF by approximately 35 L/min compared with placebo whereas salmeterol and tiotropium increased PEF by 20 L/min and 15 L/min, respectively. For all treatment comparisons performed, the lower 95% CI for the treatment difference was >0, indicating strong statistical evidence of a benefit of the combination treatments over placebo, salmeterol and tiotropium, and of salmeterol and tiotropium over placebo.

Rescue use

For subjects receiving GSK233705 20 µg + salmeterol and GSK233705 50 µg + salmeterol, 52.4%, and 46.2% never

needed to use their salbutamol rescue medication during the treatment period, compared with 44.4% of subjects receiving salmeterol, 32.1% of subjects receiving tiotropium, and 16.7% of subjects receiving placebo.

Safety

AEs

The safety profiles were similar across all treatments. The most common AEs with onset while on-treatment were headache and ventricular extrasystoles (Table 5). Headache was the most frequently reported treatment-related AE and was reported by one subject on each of GSK233705 20 µg + salmeterol, tiotropium, and placebo. No serious AEs were reported in treated subjects. Four subjects were withdrawn; three due to an exacerbation (two following treatment with placebo and one after salmeterol) and one subject on salmeterol treatment had an AE of nonsustained ventricular tachycardia (<30 beats), which led to withdrawal from the study.

Vital signs

The changes in heart rate from baseline on Day 1 and Day 7 were similar for all treatments including placebo. There was some evidence of a small increase in heart rate on salmeterol compared with placebo on Day 1, with lower CIs above zero for the comparisons of both weighted mean and maximum heart rate over 0–24 hours. Similar evidence was seen for a decrease in heart rate on the combination treatments compared with salmeterol, with upper CIs < 0 for the comparison of each combination treatment with salmeterol for weighted mean and minimum heart rate, and for the comparison of GSK233705 50 µg + salmeterol with salmeterol for maximum heart rate. These differences were small, with maximum and minimum 95% CIs less than ±6.4 bpm. However, similar evidence was not seen on Day 7.

Table 3 Analysis of trough (morning, predose) forced expiratory volume in 1 second (L) on Day 2 (modified per protocol population)

	GSK233705 20 µg + salmeterol	GSK233705 50 µg + salmeterol	Salmeterol	Tiotropium	Placebo
n	23	27	27	28	24
Baseline raw mean (SD)	1.18 (0.32)	1.29 (0.42)	1.29 (0.42)	1.20 (0.34)	1.19 (0.36)
Endpoint adjusted mean (SE)	1.55 (0.03)	1.49 (0.03)	1.34 (0.03)	1.37 (0.03)	1.24 (0.03)
Adjusted mean change from baseline (SE)	0.32 (0.03)	0.23 (0.028)	0.12 (0.03)	0.15 (0.03)	0.01 (0.03)
Difference from placebo (SE)	0.31 (0.04)	0.25 (0.04)	0.10 (0.04)	0.14 (0.037)	
95% CI	(0.23, 0.38)	(0.17, 0.33)	(0.03, 0.18)	(0.06, 0.21)	
Difference from salmeterol (SE)	0.20 (0.04)	0.14 (0.04)			
95% CI	(0.12, 0.28)	(0.07, 0.22)			
Difference from tiotropium (SE)	0.17 (0.04)	0.11 (0.04)			
95% CI	(0.09, 0.25)	(0.04, 0.19)			

Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error of the mean.

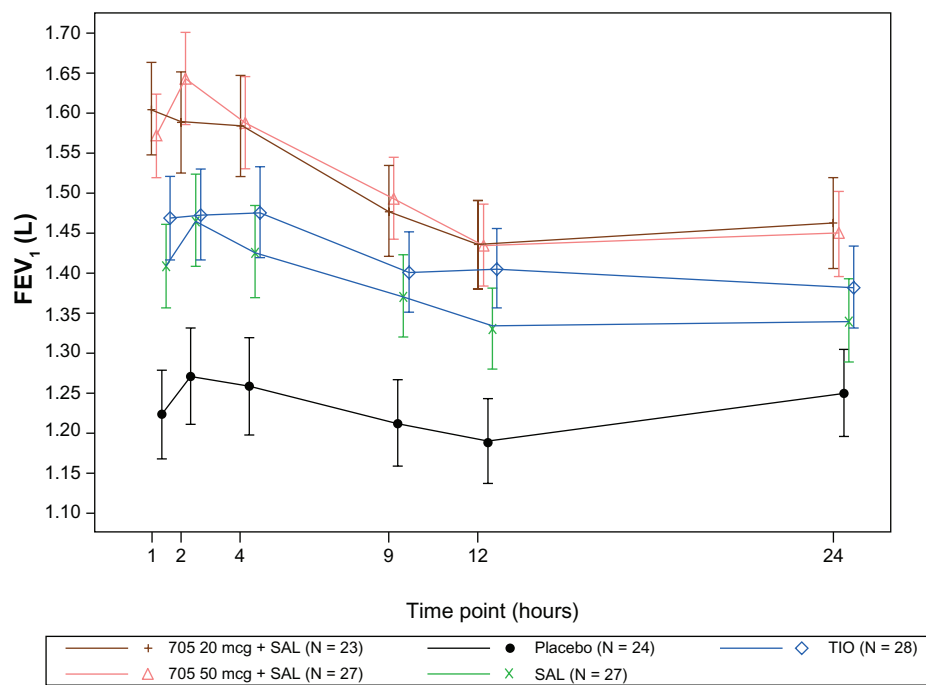


Figure 3 Adjusted mean (95% confidence interval) forced expiratory volume in 1 second (FEV₁) over time on Day 7 (modified per protocol population).
Abbreviations: SAL, salmeterol; TIO, tiotropium.

Table 4 Trough sGaw, Raw, IC, and RV on Day 2 and Day 8 (modified per protocol population)

	GSK233705 20 µg + salmeterol	GSK233705 50 µg + salmeterol	Salmeterol	Tiotropium	Placebo
Day 2					
n	23	27	27	27	24
Trough sGaw					
Endpoint adjusted geometric mean	0.79	0.84	0.56	0.59	0.47
Ratio of individual treatments to placebo (95% CI)	1.68 (1.48, 1.91)	1.77 (1.57, 2.00)	1.19 (1.05, 1.35)	1.26 (1.11, 1.42)	
Trough Raw					
Endpoint adjusted geometric mean	0.26	0.25	0.36	0.33	0.42
Ratio of individual treatments to placebo (95% CI)	0.62 (0.54, 0.70)	0.60 (0.53, 0.67)	0.86 (0.76, 0.97)	0.80 (0.71, 0.90)	
Trough IC					
Endpoint adjusted geometric mean	2.25	2.17	2.01	2.09	1.98
Ratio of individual treatments to placebo (95% CI)	1.13 (1.06, 1.21)	1.09 (1.03, 1.16)	1.02 (0.96, 1.08)	1.06 (0.99, 1.12)	
Trough RV					
Endpoint adjusted geometric mean	3.02	3.06	3.31	3.32	3.57
Ratio of individual treatments to placebo (95% CI)	0.85 (0.78, 0.92)	0.857 (0.79, 0.93)	0.93 (0.85, 1.01)	0.932 (0.86, 1.01)	
Day 8					
n	21	26	27	28	24
Trough sGaw					
Endpoint adjusted geometric mean	0.66	0.73	0.56	0.57	0.44
Ratio of individual treatments to placebo (95% CI)	1.50 (1.31, 1.70)	1.66 (1.47, 1.87)	1.27 (1.12, 1.43)	1.30 (1.15, 1.47)	
Trough Raw					
Endpoint adjusted geometric mean	0.31	0.29	0.36	0.35	0.44
Ratio of individual treatments to placebo (95% CI)	0.71 (0.62, 0.81)	0.65 (0.58, 0.74)	0.81 (0.72, 0.92)	0.80 (0.71, 0.91)	
Trough IC					
Endpoint adjusted geometric mean	2.16	2.17	2.03	2.07	1.93
Ratio of individual treatments to placebo (95% CI)	1.12 (1.04, 1.20)	1.12 (1.05, 1.20)	1.05 (0.98, 1.12)	1.07 (1.00, 1.14)	
Trough RV					
Endpoint adjusted geometric mean	3.03	3.03	3.33	3.31	3.59
Ratio of individual treatments to placebo (95% CI)	0.84 (0.79, 0.90)	0.84 (0.79, 0.90)	0.93 (0.87, 0.98)	0.92 (0.87, 0.98)	

Abbreviations: CI, confidence interval; IC, inspiratory capacity; Raw, airways resistance; RV, residual volume; sGaw, plethysmography parameters airway conductance.

Table 5 Adverse events (AEs) with onset on-treatment experienced by more than one subject on any treatment (safety population)

AE n (%)	GSK233705 20 µg + salmeterol (N = 23)	GSK233705 50 µg + salmeterol (N = 27)	Salmeterol (N = 29)	Tiotropium (N = 28)	Placebo (N = 26)
Subjects with any AE	14 (61%)	11 (41%)	16 (55%)	16 (57%)	12 (46%)
Nasopharyngitis	1 (4%)	0	1 (3%)	1 (4%)	2 (8%)
Urinary tract infection	1 (4%)	0	1 (3%)	1 (4%)	2 (8%)
Influenza	2 (9%)	0	0	2 (7%)	0
Headache	4 (17%)	2 (7%)	2 (7%)	5 (18%)	3 (11%)
Dizziness	1 (4%)	2 (7%)	0	1 (4%)	0
Ventricular extrasystoles	1 (4%)	1 (4%)	3 (10%)	1 (4%)	0
Ventricular tachycardia	1 (4%)	0	2 (7%)	1 (4%)	0
Supraventricular tachycardia	1 (4%)	0	0	2 (7%)	0
Supraventricular extrasystoles	0	0	2 (7%)	0	0
Back pain	0	0	2 (7%)	0	3 (11%)
Leukocyturia	0	2 (7%)	0	1 (4%)	0
Fatigue	0	0	0	1 (4%)	2 (8%)

The changes in systolic and diastolic blood pressure from baseline on Day 1 and Day 7 were similar between all treatments including placebo. Treatment differences for weighted mean, maximum and minimum systolic and diastolic blood pressure over 0–4 hours and 0–24 hours were small, and in all cases except one the CIs for all treatment comparisons contained zero.

ECGs

No clinically significant changes in ECG traces during any visit postbaseline were reported for any treatment. Summary statistics for Holter ECG parameters (maximum, mean and minimum heart rate, maximum and mean uncorrected QT, maximum RR, mean QTc(B) and QTc(F), number of RR intervals >2 msec, and number of ventricular couplets, triplets and nonsustained ventricular tachycardias, and supraventricular tachycardias) were similar for all treatments at screening and on Day 1 and Day 7.

Pharmacokinetics

The bioanalytical method (LLQ of 0.01 ng/mL) for GSK233705 was not sensitive enough to fully characterize the PK profile of subjects due to the low level of GSK233705 detected in plasma. Overall, 52% of data were nonquantifiable. Following single and repeat inhaled dose administration, GSK233705 was rapidly absorbed. The median t_{max} was 5 minutes, irrespective of dose levels (20 µg and 50 µg) and sampling days (Day 1 and Day 7). Plasma concentrations declined rapidly following the occurrence of C_{max} . Plasma concentrations following repeat inhaled administration were on average higher than those after single dosing for both dose levels suggestive of accumulation. Moderate to high between-subject variability in C_{max} was observed with values

of the coefficient of variation ranging from 42% to 60% on Day 1, and from 42% to 52% on Day 7 across dose levels. Moderate to high between-subject variability in $AUC_{(0-t)}$ was also observed with values of the coefficient of variation ranging from 29% to 67% on Day 1, and from 98% to 130% on Day 7 across dose levels (Table 6).

The bioanalytical method (LLQ of 0.025 ng/mL) for salmeterol was not sensitive enough to fully characterize the PK profile of subjects due to the low level of salmeterol detected in plasma. For salmeterol, overall 55% (604/1092) of data was nonquantifiable. The median t_{max} was 30 minutes or less irrespective of sampling day or whether salmeterol was administered alone or in combination with GSK233705. Moderate between-subject variability in C_{max} was observed with values of the coefficient of variation ranging from 29% to 38% on Day 1, and from 41% to 53% on Day 7 across treatment regimens. Moderate to high between-subject variability in $AUC_{(0-t)}$ was also observed with values of the coefficient of variation ranging from 35% to 54% on Day 1, and from 68% to 124% on Day 7 across treatment regimens.

Discussion

The objectives of this pilot study were to investigate the bronchodilatory efficacy, safety, and tolerability of twice-daily therapy with two different long-acting bronchodilators in a COPD population optimized to demonstrate a response. These were administered concurrently (GSK233705 + salmeterol) and compared primarily with placebo but also compared with twice-daily salmeterol monotherapy or once-daily tiotropium monotherapy in subjects with moderate to severe COPD. The primary lung function measurements were made using spirometry, and this was supported by plethysmography, which provides a further sensitive assessment of lung

Table 6 Summary pharmacokinetic statistics on Day 1 and Day 7

Parameter	Treatment	Analyte: GSK233705						Analyte: Salmeterol					
		Day 1			Day 7			Day 1			Day 7		
		N/n	Geometric mean 95% CI/CV (%)	N/n	Geometric mean 95% CI/CV (%)	N/n	Geometric mean 95% CI/CV (%)	N/n	Geometric mean 95% CI/CV (%)	N/n	Geometric mean 95% CI/CV (%)	N/n	Geometric mean 95% CI/CV (%)
AUC ₍₀₋₄₎ (h ³ ·ng/mL)	705 20 µg + SAL	23/4	0.020 (0.013, 0.032)/29	23/12	0.022 (0.013, 0.037)/98	23/10	0.055 (0.039, 0.077)/49	23/16	0.116 (0.084, 0.162)/68				
	705 50 µg + SAL	27/14	0.018 (0.013, 0.026)/67	27/26	0.088 (0.059, 0.131)/130	27/11	0.059 (0.042, 0.083)/54	27/20	0.071 (0.045, 0.112)/124				
	SAL	N/A	N/A	N/A	N/A	29/14	0.059 (0.049, 0.072)/35	29/24	0.091 (0.064, 0.129)/99				
C _{max-high} (ng/mL)	705 20 µg + SAL	23/23	0.013 (0.011, 0.015)/42	23/22	0.019 (0.016, 0.023)/42	23/23	0.036 (0.032, 0.041)/28	23/22	0.052 (0.042, 0.064)/50				
	705 50 µg + SAL	27/27	0.023 (0.019, 0.029)/60	27/27	0.048 (0.040, 0.058)/52	27/27	0.036 (0.031, 0.041)/38	27/27	0.052 (0.042, 0.064)/53				
	SAL	N/A	N/A	N/A	N/A	29/29	0.037 (0.032, 0.042)	29/29	0.049 (0.042, 0.056)/41				
t _{max} (h) ^a	705 20 µg + SAL	23/10	0.080 (0.05, 0.27)	23/20	0.080 (0.08, 0.50)	23/20	0.520 (0.05, 2.08)	23/20	0.425 (0.08, 1.98)				
	705 50 µg + SAL	27/25	0.080 (0.03, 2.08)	27/27	0.080 (0.05, 0.52)	27/19	0.400 (0.08, 1.07)	27/24	0.500 (0.05, 11.92)				
	SAL	N/A	N/A	N/A	N/A	29/23	0.480 (0.05, 2.00)	29/26	0.250 (0.08, 4.00)				
t _{last} (h) ^a	705 20 µg + SAL	23/10	0.230 (0.08, 2.10)	23/20	0.495 (0.08, 4.17)	23/20	1.000 (0.05, 2.10)	23/20	2.010 (0.08, 11.85)				
	705 50 µg + SAL	27/25	0.500 (0.03, 2.08)	27/27	4.020 (0.25, 11.95)	27/19	1.000 (0.08, 2.10)	27/24	2.000 (0.50, 11.93)				
	SAL	N/A	N/A	N/A	N/A	29/23	1.900 (0.12, 2.25)	29/16	2.050 (0.32, 12.00)				

Note: ^aPresented as median and range.

Abbreviations: AUC₍₀₋₄₎, area under concentration–time curve from time 0 to time of last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; N/A, not applicable; SAL, salmeterol; t_{max}, time of maximum observed plasma concentration; t_{last}, last time point where the concentration is above the limit of quantification.

function¹⁶ and also takes into account effects on both the large and small airways.

A crossover design was chosen because the within-patient variability in FEV₁ was expected to be less than between-patient variability, with each patient acting as their own control. An incomplete-block, rather than a complete-block, crossover design was adopted (with three periods) to reduce the study duration and overall burden on patients. To fully blind the study, each subject would have needed to use both inhalers on a double-dummy basis and to take multiple inhalations morning and evening. In order to reduce the number of inhalers subjects needed to take daily, the study was blinded for active versus placebo treatments but not with respect to inhaler type. The duration of 2 weeks for washout was also sufficient to minimize the possibility of carry-over effects of both salmeterol and tiotropium. It is recognized however that a limitation of the study was that there was no GSK233705 monotherapy arm.

Concurrent use of GSK233705 at doses of 20 µg or 50 µg twice-daily plus salmeterol 50 µg twice-daily for 7 days resulted in clinically important 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 improvement versus placebo in bronchodilation with both doses of GSK233705 plus salmeterol was not only higher than the 100 mL criterion described by Donohue¹⁷ as a difference that COPD patients can perceive but also was well above the range (100–140 mL) proposed as a minimal clinically important difference.¹⁸

The clinical improvements seen in lung function were also supported by the results of daily diary card assessments, morning PEF measurements, and rescue medication use, all of which suggested that dual bronchodilator treatment has the potential to produce a clinically important additional benefit on symptoms compared with a single agent. It has previously been shown that these two classes of bronchodilator added together result in a significant reduction in salbutamol use as rescue therapy and symptoms of dyspnoea.^{5,19} This study provides further support for these observations. Although this study did not include symptom assessments, the need for rescue medication is a useful surrogate of symptomatic benefit and reductions in the use of rescue medication were seen with the combination treatments compared with each of the individual treatments.

The positive primary efficacy results were supported by the results from all of the remaining lung function assessments.

Although this was a small study, and the endpoints not formally powered, the results were consistent across

virtually every endpoint studied and the sizes of the treatment differences were compelling. No obvious dose response was observed between the two doses of GSK233705 in combination with salmeterol for any of the endpoints, but the study was not designed to differentiate between doses.

The safety findings from this study demonstrated that the safety profiles were similar across all treatments. No clinically significant effects on heart rate were observed with concurrent administration of GSK233705 and salmeterol and, importantly, analysis of 24-hour Holter ECG measurements did not identify any change in the incidence of the minor rhythm abnormalities frequently observed in COPD patients.

The pharmacokinetic information obtained in this study was limited due to a large amount of nonquantifiable data. However, the results showed that, following single and repeat inhaled doses, there was rapid absorption of both GSK233705 and salmeterol with a median time to C_{max} (t_{max}) of 5 minutes for GSK233705 and 30 minutes for salmeterol. The PK parameters for salmeterol were similar in the presence and absence of GSK233705, demonstrating an absence of any PK interaction between the two drugs.

Results from this study support previous findings which have demonstrated that a long-acting β-agonist added to a long-acting anticholinergic (tiotropium bromide) produce incremental effects on lung function. Data from both short-term^{4-6,16} and long-term studies provide additional evidence that combining LAMAs and LABAs helps to maximize bronchodilation and improve symptoms and quality of life in patients with moderate to severe disease.^{7-8,20} Importantly, in this study no increase in the risk of side effects was observed with the combinations compared with monotherapies.

Most subjects recruited for this study had moderate disease and were documented to demonstrate significant bronchodilator responses to both anticholinergics and β₂-agonists. This further supports the use of LABA/LAMA combination therapy in moderate COPD if maintenance treatment with a single long-acting bronchodilator does not suffice.¹⁻³ Published evidence to date also supports the use of a combination therapy with tiotropium plus a LABA even in those COPD patients with more severe symptoms.^{8,21,22} However, limited analyses have been performed to date to assess the differential effects of LAMA therapy by severity of COPD. Clinical studies have included patients with disease severity ranging from moderate to very severe disease. Tashkin et al⁶ found that while improvements in lung function were greater in more severe COPD, dyspnea scores improved irrespective of severity.

It has been hypothesized that activity of the sympathetic system is more prominent during the day, whereas increased parasympathetic system activity is found during the night.^{21–25} It therefore seems appropriate to target bronchoconstriction through two distinct mechanisms (anticholinergic and sympathomimetic) to maximize the bronchodilator response over 24 hours and help to overcome inter- and intra-patient variability in bronchomotor tone associated with COPD.²⁶

A range of once and twice daily LAMAs are currently in clinical development as monotherapies in COPD.^{9,10} A number of novel once-daily fixed-dose combination bronchodilators are also in phase III development, including QVA149 (a combination of indacaterol and NVA237)²⁷ and vilanterol plus GSK573719.²⁸

Conclusion

This study helps to demonstrate that combinations of these two classes of medications can achieve significant bronchodilation compared to monotherapy. The addition of GSK233705 to salmeterol resulted in greater bronchodilation than salmeterol or tiotropium alone and was well tolerated. This particular bronchodilator combination is at present not being progressed further because once-daily alternatives are favored and being developed.

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Authors' contributions

Amanda Deans, Jean Brooks, Claire Maden, Suus Baggen, Rashmi Mehta, and Anthony Cahn (as employees of the study sponsor, GSK) contributed to the design, analysis, and interpretation of the study, and oversaw its conduct. All authors contributed equally to the development of the manuscript, and approved the final version for submission.

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