UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 8-K

Current Report Pursuant
to Section 13 or 15(d) of the
Securities Exchange Act of 1934

Date of Report (Date of earliest event Reported): **September 25, 2011**

THERAVANCE, INC.

(Exact Name of Registrant as Specified in its Charter)

Delaware	**000-30319**	**94-3265960**
(State or Other Jurisdiction of Incorporation)	(Commission File Number)	(I.R.S. Employer Identification Number)

901 Gateway Boulevard
South San Francisco, California 94080
(650) 808-6000
(Addresses, including zip code, and telephone numbers, including area code, of principal executive offices)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 8.01 Other Events.

On September 25, 2011, at the European Respiratory Society Annual Congress in Amsterdam, Netherlands, GlaxoSmithKline (GSK) presented three posters on the Phase 2 and 2b studies of GSK573719 (‘719), a long-acting muscarinic antagonist (LAMA), in patients with chronic obstructive pulmonary disease (COPD). ‘719 is the LAMA component in LAMA/LABA (‘719/Vilanterol), an investigational product being developed under the LABA collaboration between GSK and Theravance, Inc. for the treatment of COPD.

GSK also presented a poster on the Phase 2a study of GSK961081 (‘081), an investigational compound within the inhaled bifunctional muscarinic antagonist-beta$_2$ agonist (MABA) program that was licensed to GSK from Theravance in 2005 under the companies’ Strategic Alliance Agreement.

The four posters are attached hereto as Exhibits 99.1 to 99.4 and are incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit	**Description**
Exhibit 99.1	Dose-related efficacy of GSK573719, a new long-acting muscarinic receptor antagonist (LAMA) offering sustained 24-hour bronchodilation in COPD
Exhibit 99.2	Phase II study of once-daily GSK573719 Inhalation Powder, a new long-acting muscarinic antagonist, in patients with chronic

	obstructive pulmonary disease (COPD)
Exhibit 99.3	Safety, pharmacokinetics (PK) and pharmacodynamics (PD) of single doses of GSK573719 Inhalation Powder, a new long-acting muscarinic antagonist (LAMA), in patients with COPD
Exhibit 99.4	The pharmacodynamics of GSK961081 in patients with COPD

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

THERAVANCE, INC.

Date: September 26, 2011

By: /s/ **Michael W. Aguiar**
Michael W. Aguiar
Chief Financial Officer

EXHIBIT INDEX

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Poster No. P878

Dose-related efficacy of GSK573719, a new long-acting muscarinic receptor antagonist (LAMA) offering sustained 24-hour bronchodilation in COPD

M Decramer(1), F Maltais(2), G Feldman(3), J Brooks(4), S Harris(5), G Crater(5)

(1)Pneumology Section, Katholiedi Universiteit Leuven, Leuven Belgium; (2)Institut Universitaire de cardiologie et de pneumologie de Québec, Université Laval, Québec, Canada; (3)Research, South Carolina Pharmaceutical Research, Spartanburg, South Carolina, United States; (4)Respiratory Medicines Development Center, GlaxoSmithKline, Uxbridge, United Kingdom; (5)Respiratory Medicines Development Center, GlaxoSmithKline, RTP, United States

AIMS

- Bronchodilators form the foundation of pharmacological treatment of COPD.(1)
- Long-acting inhaled bronchodilators, comprising the anticholinergic class of long-acting muscarinic antagonists (LAMAs) and long-acting $beta_2$-agonists (LABAs) are recommended for symptomatic management of moderate-to-very severe COPD, providing a more efficacious and convenient alternative to short-acting bronchodilators.(1)
- GSK573719 is an inhaled LAMA with sustained 24-hour activity under development as a once-daily therapy for COPD.
- GSK573719 is being developed in combination with the LABA, vilanterol.
- Previous clinical pharmacology studies have demonstrated that single and repeat dose administration of GSK573719 is safe and well tolerated in healthy volunteers and patients with COPD over the range of doses tested (10 to 1000mcg).(2),(3)
- The primary objectives of this study were to evaluate the efficacy and safety of three doses of GSK573719 (125, 250, and 500mcg once daily) compared with placebo in patients with COPD, in order to inform the selection of an optimal effective and safe dose for future clinical development.

METHODS

Patients

- Men and women with COPD, aged 40 to 80 years with a smoking history of $\geq$10 pack-years and post-bronchodilator FEV_1 $\leq$70% and $\geq$35% predicted and FEV_1 /FVC $\leq$0.70.

Study Design

- Randomised, double-blind, parallel-group 28-day treatment period.
- On-treatment clinic visits were scheduled on Day 1, Day 2, Day 7, Day 14, Day 28, and Day 29.
- Serial assessments were obtained over 0-6h post-dose on Day 1 and Day 28 for spirometry, ECG, and vital signs. Pre-dose assessments were obtained at all clinic visits.
- Following a 1-week run-in period, eligible patients were randomised to treatment with one of three doses of GSK573719 (125mcg, 250mcg, or 500mcg) or placebo. All treatments were taken once daily via a novel single-step activation dry powder inhaler.
- Salbutamol was available for rescue use.
- Patients receiving inhaled corticosteroids (ICS) alone or in a fixed combination with a bronchodilator at screening were allowed to continue the ICS at an equivalent dose and regimen throughout the study. Other COPD medications were discontinued prior to the start of study participation.

Assessments and variables

- Primary endpoint: change from baseline in trough FEV_1 at Day 29 (mean FEV_1 values obtained 23 and 24h after dosing on treatment Day 28).
- Secondary endpoints: weighted mean FEV_1 0 to 6h and serial FEV_1 at 1, 3, 6, 23, and 24h after dosing on Day 1 and Day 28.
- Safety, PK, and other efficacy data were collected, including use of rescue salbutamol.

RESULTS

Study Population

- A total of 288 patients were randomised, of whom 3 did not receive treatment, so the ITT population consisted of 285 patients. The treatment groups were well matched for patient demographics (except for gender) and disease characteristics at baseline (Table 1).

Spirometry

- The primary efficacy endpoint of change from baseline in trough FEV_1 at Day 29 demonstrated statistically significant differences in favour of GSK573719 for all doses compared with placebo (Table 2).

· On Days 1 and 28, greater increases from baseline were observed in 0–6h weighted mean FEV_1 values for all doses of GSK573719 compared with placebo (Table 3).

· All doses of GSK573719 demonstrated statistically significant improvements over placebo ($p \leq 0.038$) in serial FEV_1 at each measured time point over 24h at Day 1 and Day 28 (Figure 1).

· Differences from placebo in change from baseline in trough FVC were statistically significant for all doses of GSK573719 at all time points with the exception of the 125mcg dose at Day 29 (Figure 2).

Use of rescue salbutamol

· During the treatment period, all GSK573719 treatment groups experienced a greater percentage of rescue-free days compared with placebo at each week and across weeks 1 through to 4 (Table 4).

Safety

· The incidence of adverse events with the 125mcg and 250mcg doses was similar to placebo. A higher incidence of cough and headache was observed with the 250mcg and 500mcg doses (Table 5).

· Serious adverse events were reported for one patient in each of the active treatment groups (retinal detachment, gastroenteritis viral, COPD exacerbation in 125, 250, and 500mcg, respectively). None were considered to be related to study treatment and none were fatal.

· There were no apparent treatment related changes in vital signs or ECG assessments.

TABLE 1. DEMOGRAPHICS & BASELINE POPULATION

		GSK573719		
Demographics	**Placebo N=71**	**125 mcg N=71**	**250 mcg N=72**	**500 mcg N=71**
Mean age, years (SD)	62.3 (6.80)	60.1 (8.75)	60.3 (8.45)	62.6 (9.30)
Male (n, %)	47 (66)	36 (51)	42 (58)	37 (52)
Race (n, %)				
White	70 (99)	67 (94)	69 (96)	69 (97)
African American/African Heritage	1 (1)	4 (6)	3 (4)	1 (1)
African American/African Heritage & White	0	0	0	1 (1)
BMI (kg/m^2), Mean (SD)	25.60 (4.130)	26.91 (4.398)	27.25 (4.723)	26.42 (4.606)
Baseline Characteristics				
Current/former smoker, %	61/39	59/41	61/39	63/37
Smoking history, pack-years, Mean (SD)	37.6 (15.34)	46.2 (22.06)	39.7 (22.13)	46.4 (22.42)
Post-bronchodilator(a) FEV_1, L, Mean (SD)	1.569 (0.4279)	1.626 (0.4933)	1.631 (0.4752)	1.482 (0.3875)
Post-bronchodilator(a) FEV_1, % predicted, Mean (SD)	51.4 (8.95)	53.9 (8.94)	53.8 (9.97)	51.7 (9.21)
Reversibility to bronchodilator(a), %, Mean (SD)	15.5 (12.87)	12.0 (14.46)	11.2 (12.05)	13.8 (11.56)
Baseline salbutamol use (puffs/day), Mean (SD)	4.01 (2.863)	2.83 (2.633)	3.09 (2.562)	3.62 (3.573)
Baseline trough pre-dose FEV_1, L, Mean (SD)	1.349 (0.4438)	1.466 (0.4737)	1.480 (0.5772)	1.320 (0.4242)

(a)salbutamol

TABLE 2. CHANGE FROM BASELINE IN TROUGH FEV_1 ON DAY 29

		GSK573719		
Trough FEV_1 (L)	**Placebo N=71**	**125 mcg N=71**	**250 mcg N=72**	**500 mcg N=71**
Day 29				
n	67	64	68	64
LS Mean (SE)	1.417 (0.025)	1.576 (0.025)	1.586 (0.025)	1.567 (0.025)
LS Mean Change (SE)	0.013 (0.025)	0.171 (0.025)	0.181 (0.025)	0.163 (0.025)
Difference vs. Placebo		**0.159**	**0.168**	**0.150**
95% CI		**0.088, 0.229**	**0.099, 0.238**	**0.080,0.220**
p-value		**<0.001**	**<0.001**	**<0.001**

Note: Repeated Measures analysis adjusted for baseline, country, sex, age, treatment, smoking status, day, day by baseline interaction and day by treatment interaction

TABLE 3. REPEATED MEASURES 0–6H WM FEV_1 (L)

		GSK573719		
Trough FEV_1 (L)	**Placebo N=71**	**125 mcg N=71**	**250 mcg N=72**	**500 mcg N=71**
Day 1				
n	70	70	71	70
LS Mean (SE)	1.408 (0.015)	1.614 (0.015)	1.627 (0.014)	1.576 (0.015)
LS Mean Change (SE)	0.005 (0.015)	0.211 (0.015)	0.224 (0.014)	0.173 (0.015)

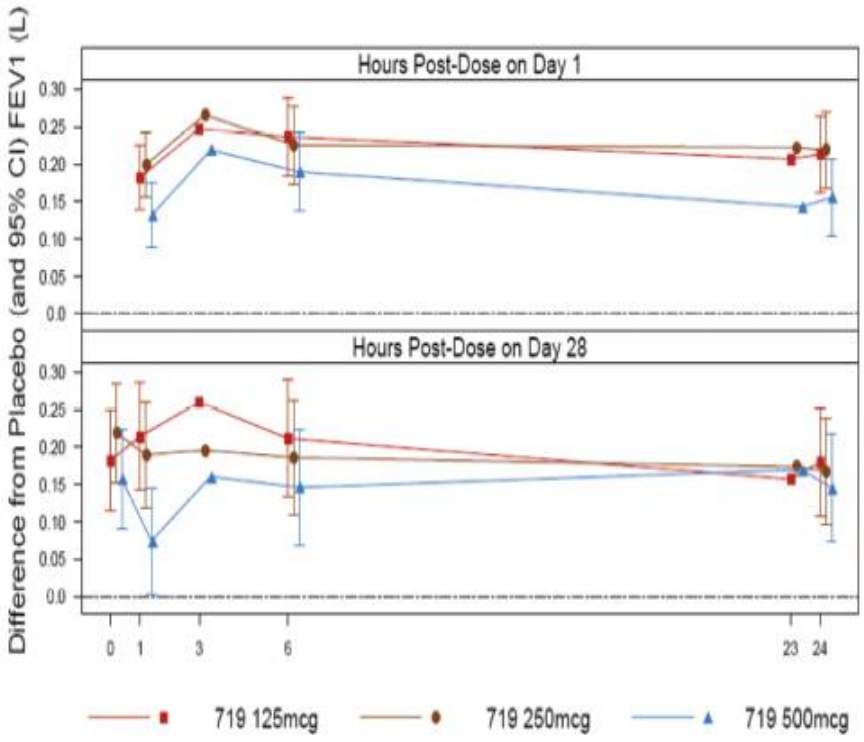
Difference vs. Placebo		0.206	0.219	0.168
95% CI		(0.165, 0.247)	(0.179, 0.260)	(0.128, 0.208)
p-value		<0.001	<0.001	<0.001
Day 28				
n	65	64	68	64
LS Mean (SE)	1.412 (0.024)	1.623 (0.024)	1.608 (0.023)	1.526 (0.024)
LS Mean Change (SE)	0.009 (0.024)	0.220 (0.024)	0.204 (0.023)	0.122 (0.024)
Difference vs. Placebo		0.211	0.196	0.113
95% CI		(0.145, 0.277)	(0.130, 0.261)	(0.047, 0.179)
p-value		<0.001	<0.001	<0.001

Note: Repeated measures analysis adjusted for baseline, country, sex, age, treatment, smoking status, day, day by baseline interaction and day by treatment interaction.

TABLE 4. USE OF RESCUE SALBUTAMOL WEEKS 1–4

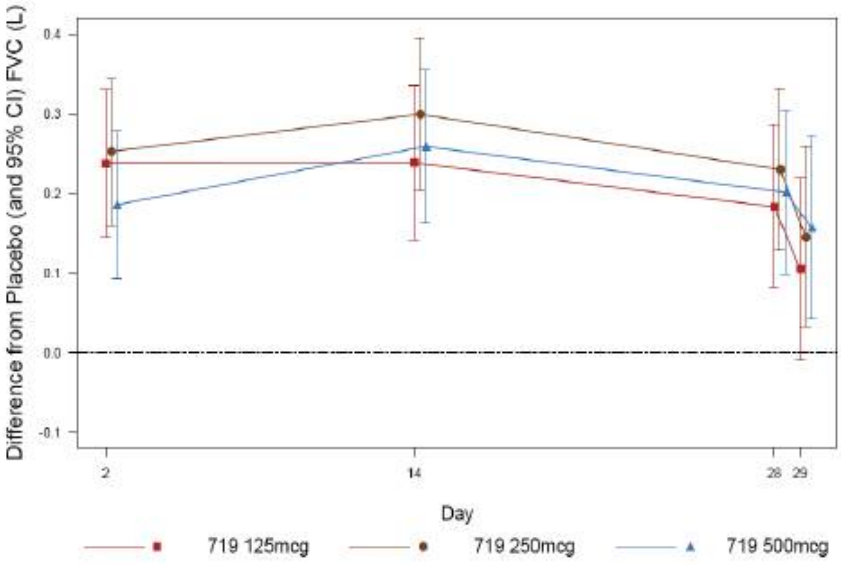
		GSK573719		
Weeks 1–4	**Placebo N=71**	**125 mcg N=71**	**250 mcg N=72**	**500 mcg N=71**
n	59	67	65	64
Change from baseline (puffs/day) LS Mean (SE)	–0.764 (0.202)	–1.355 (0.189)	–1.654 (0.191)	–1.042 (0.193)
Difference vs. Placebo		–0.591	–0.890	–0.277
95% CI		(–1.143, –0.038)	(–1.441, –0.340)	(–0.828, 0.273)
Change from baseline in % of days with no salbutamol use Raw Mean (SD)	10.87 (32.147)	26.92 (42.785)	22.35 (34.267)	15.36 (29.621)

FIGURE 1. ADJUSTED MEAN DIFFERENCE FROM PLACEBO (95% CI) IN CHANGE FROM BASELINE IN FEV_1 OVER TIME AT DAY 1 AND DAY 28



Note: Repeated Measures analysis adjusted for baseline, country, sex, age, treatment, smoking status, time, time by baseline interaction and time by treatment interaction.

FIGURE 2. ADJUSTED MEAN DIFFERENCES FROM PLACEBO IN CHANGE FROM BASELINE IN TROUGH FVC (L) OVER TIME



Note: Repeated Measures analysis adjusted for baseline, country, sex, age, treatment, smoking status, day, day by baseline interaction and day by treatment interaction.

TABLE 5. MOST FREQUENT ADVERSE EVENTS(a)

Most Frequent AEs(b) n (%)	Placebo N=71	GSK573719 125 mcg N=71	GSK573719 250 mcg N=72	GSK573719 500 mcg N=71
Any AEs	16 (23)	18 (25)	17 (24)	24 (34)
Cough	2 (3)	0	6 (8)	8 (11)
Headache	3 (4)	3 (4)	4 (6)	6 (8)
Nasopharyngitis	3 (4)	2 (3)	1 (1)	2 (3)
Dysgeusia	1 (1)	1 (1)	1 (1)	1 (1)
Abdominal pain upper	1 (1)	1 (1)	0	1 (1)
Back pain	0	2 (3)	1 (1)	0
Gastroenteritis viral	0	1 (1)	1 (1)	1 (1)
Hypertension	2 (3)	1 (1)	0	0
Sinus congestion	1 (1)	1 (1)	0	1 (1)
Cystitis	1 (1)	1 (1)	0	0
Dry mouth	0	0	1 (1)	1 (1)
Nasal congestion	1 (1)	0	1 (1)	0
Product taste abnormal	0	1 (1)	0	1 (1)
Sputum increased	0	0	2 (3)	0

(a) Adverse events reported on-treatment
(b) Most frequent adverse events are defined as events occurring in more than one subject across the treatment groups

CONCLUSIONS

- Treatment with GSK573719 125mcg, 250mcg, and 500mcg once-daily for 28 days resulted in statistically significant improvements in pulmonary function compared with placebo in patients with COPD.
- Overall, the lung function findings from this study support a once-daily dosing interval for GSK573719.
- The results of this study show that GSK573719 is efficacious and well-tolerated over 28 days when used in the treatment of patients with COPD.

REFERENCES

(1) GOLD. Global Initiative for Chronic Obstructive Lung Disease (Updated 2010). http://www.gold.org.

(2) Kelleher D, et al. ERS Annual Congress 2011. Poster number P834.

(3) Mehta R, et al. ERS Annual Congress 2011. Poster number P822 and Poster number P3972.

ACKNOWLEDGEMENTS

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- The study was sponsored by GlaxoSmithKline (ClinicalTrials.gov: NCT01030965; AC4113589).

Presented at the European Respiratory Society Annual Congress, 24-28 September 2011, Amsterdam, Netherlands

Poster No. P834

Phase II study of once-daily GSK573719 Inhalation Powder, a new long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD)

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INTRODUCTION

· Bronchodilators are an important treatment option for chronic obstructive pulmonary disease (COPD).(1)

· GSK573719 is a new, long-acting muscarinic antagonist (LAMA) in development for once-daily treatment of COPD.

OBJECTIVES

· To assess the safety/tolerability (primary) and pharmacokinetics (secondary) of repeat once-daily doses of inhaled GSK573719, administered to COPD patients for 7 days.

METHODS

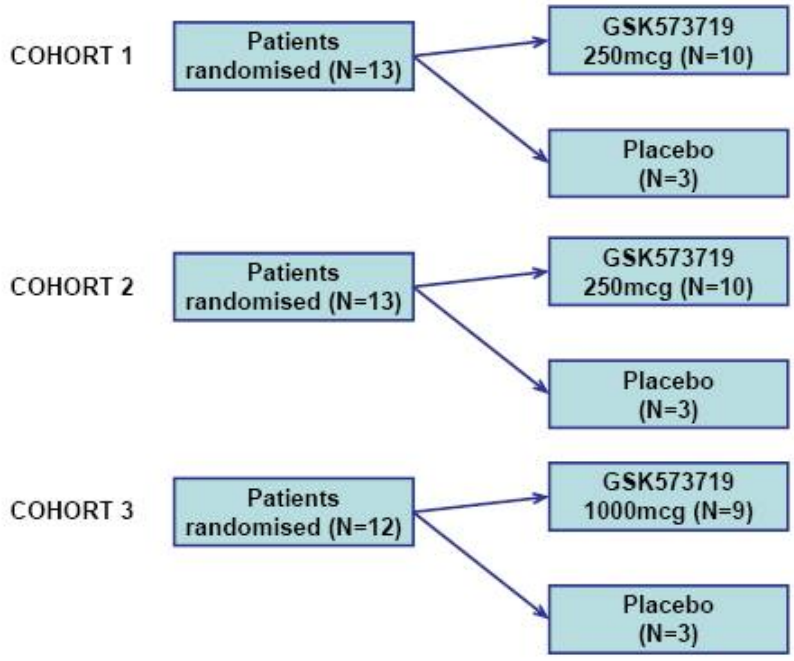
· This was a phase IIa, randomised, double-blind, placebo-controlled, repeat-dose, parallel-group study.

· All patients had COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and characterised by post-bronchodilator FEV_1 $\geq$35% and $\leq$80% of predicted normal. There were no bronchodilator reversibility requirements for entry into the study.

· Exclusion criteria included: past or present disease likely to affect the safety of the patient or influence study outcomes; positive pre-study drug/alcohol screen; positive pregnancy test; positive test for HIV or hepatitis B or C; and, for cohorts 1 and 2, patients with a CYP2D6 poor metabolisers genotype.

· Patients were randomised to receive once-daily GSK573719 (0.4% magnesium stearate formulation) or placebo. Initially, two cohorts were planned: one with GSK573719 250mcg as the active treatment and one with a dose of 1000mcg. However, due to a dosing error, three patient cohorts were created: two with the 250mcg dose and one with 1000mcg (Figure 1).

FIGURE 1. STUDY DESIGN



· Study treatment was administered once daily over the 7-day study period by a novel, single-step activation dry powder inhaler (novel DPI).

· Inhaled salbutamol was permitted as relief (rescue) medication. Inhaled corticosteroids ($\leq$1000mcg/day of fluticasone propionate or equivalent) were also permitted, provided the dose remained constant throughout the study and the preceding 6 weeks. Long-acting $beta_2$ agonists (LABAs) and tiotropium were not permitted.

· Primary endpoints were: adverse events (AEs), blood pressure, heart rate (HR), electrocardiogram (ECG), 24h Holter monitoring, lung function (for safety only), use of rescue medication (salbutamol) and laboratory safety tests.

· Secondary endpoints were: plasma and urine concentrations of GSK573719, and other pharmacokinetic (PK) parameters derived from these data.

· No statistical techniques were used to calculate the sample size, which was based on feasibility alone.

· Safety/tolerability analyses were based on the ‘all subjects’ population, defined as all patients receiving at least one dose of study medication. The PK population comprised members of the ‘all subjects’ population from whom a PK sample was obtained and analysed.

RESULTS

Patients

· Thirty-eight patients were randomised to receive GSK573719 (250mcg: N=20; 1000mcg: N=9) or placebo (N=9). All 38 received study medication and were included in the ‘all subjects’ group. 26/29 (90%) recipients of GSK573719 were included in the PK population.

· Patients’ baseline characteristics are summarised in Table 1; there were no major differences between the study groups.

Safety and tolerability

· In total, 43 AEs were reported by 21/38 (55%) randomised patients.

· Treatment-related AEs were reported by 1/9 (11%) placebo recipients, 4/20 (20%) patients receiving GSK573719 250mcg and 5/9 (56%) receiving 1000mcg (Table 2).

· No deaths or serious AEs were reported.

· Three patients (two receiving GSK573719 250mcg and one receiving 1000mcg) were withdrawn from the study because of AEs: chest pain, respiratory tract infection and dyspnoea. In only one of these cases (dyspnoea; GSK573719 1000mcg group) was the AE considered to be related to study medication.

TABLE 1. PATIENTS’ BASELINE CHARACTERISTICS

		GSK573719			
Characteristic	Placebo (N=9)	Cohort 1 250mcg (N=10)	Cohort 2 250mcg (N=10)	Cohort 3 1000mcg (N=9)	All patients (N=38)
Mean age, years (SD)	66.2 (4.47)	63.3 (8.21)	64.7 (6.31)	64.2 (7.97)	64.6 (6.72)
Male, n (%)	5 (56)	6 (60)	8 (80)	5 (56)	24 (63)
White/Caucasian/European (n, %)	9 (100)	10 (100)	10 (100)	9 (100)	38 (100)
Mean weight, kg (SD)	68.73 (11.47)	71.42 (17.33)	75.12 (11.51)	68.90 (11.23)	71.16 (12.96)
Mean body mass index, kg/m^2 (SD)	24.73 (4.13)	25.63 (3.70)	26.10 (3.20)	25.00 (3.04)	25.39 (3.44)

TABLE 2. DRUG-RELATED AEs

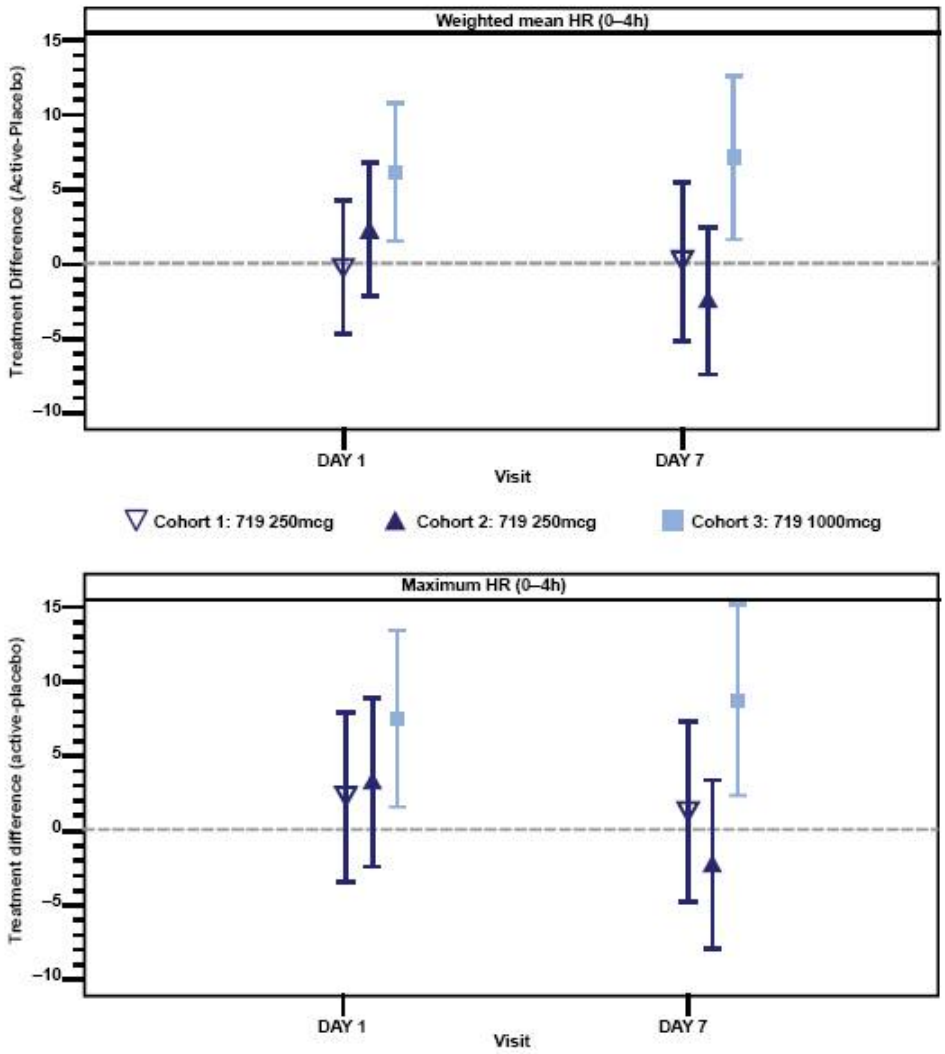
		Cohort 1	Cohort 2	Cohort 3
			GSK573719	
Preferred Term	Placebo (N=9)	250mcg (N=10)	250mcg (N=10)	1000mcg (N=9)
Subjects with any drug-related AE, n (%)	1 (11)	0	4 (40)	5 (56)
Headache	1 (11)	0	0	1 (11)
Dysgeusia	0	0	1 (10)	0
Hypoaesthesia	1 (11)	0	0	0
Bronchospasm	0	0	1 (10)	0
Dyspnoea	0	0	0	1 (11)
Oropharyngeal pain	0	0	0	1 (11)
Arrhythmia	0	0	1 (10)	0
Tachycardia	0	0	1 (10)	0
Flushing	1 (11)	0	0	0
Hypertension	0	0	1 (10)	0
Dry mouth	0	0	0	1 (11)
Feeling abnormal	0	0	0	1 (11)
Thirst	0	0	0	1 (11)
Blood pressure increased	0	0	0	1 (11)
Pruritus	1 (11)	0	0	0

· There was no evidence of a difference between the GSK573719 250mcg group and the placebo group on Days 1 or 7, with respect to weighted mean HR (0–4h) and maximum HR (0–4h) (Figure 2).

· Change from baseline HR was in the same range for all study groups.

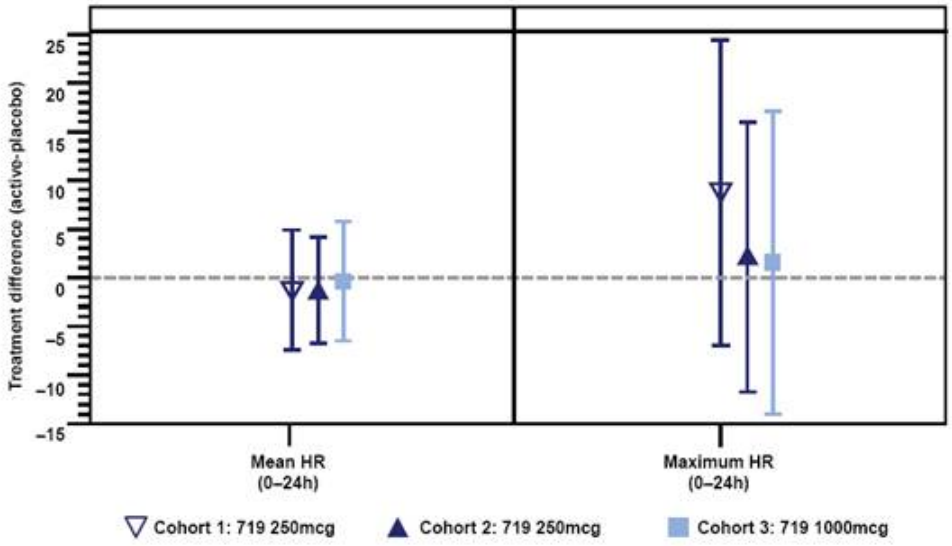
· Differences between the GSK573719 1000mcg and placebo groups were apparent in relation to weighted mean HR (0–4h) and maximum HR (0–4h). However, sensitivity analysis using a GLIMMIX model indicated that these findings may have been attributable to a single outlying patient.

FIGURE 2. WEIGHTED MEAN AND MAXIMUM HR (0–4h): TREATMENT DIFFERENCES VERSUS PLACEBO (DAYS 1 AND 7)



· Holter parameters for maximum HR (0–24h) and mean HR (0–24h) showed no evidence of any differences between the study groups on Day 7 (Figure 3).

FIGURE 3. MEAN AND MAXIMUM HR (0–24h) FROM HOLTER MONITORING: TREATMENT DIFFERENCES VERSUS PLACEBO (DAY 7)



· No correlation was observed between C_{max} and HR or any other pharmcodynamic parameters.

Pharmacokinetics

· GSK573719 was absorbed rapidly, with T_{max} values of 5–15min (Table 3). Plasma concentrations subsequently declined rapidly, meaning overall systemic exposure was low.

· 1–2% of the total dose of GSK573719 was excreted unchanged in the urine.

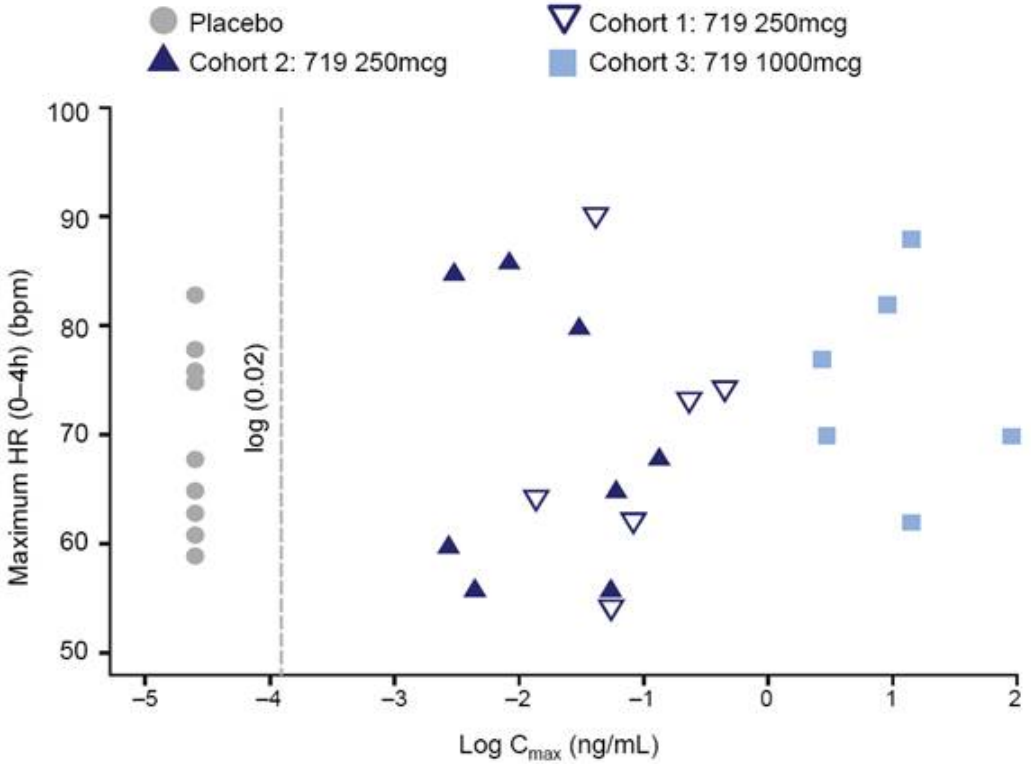
· There was no apparent relationship between C_{max} and maximum HR (0–4h) on Day 1 or Day 7 (Figure 4).

· Considering both doses of GSK573719, plasma data indicated 1.5–1.9-fold drug accumulation on Day 7 versus Day 1, while urine data indicated 1.8–2.4-fold accumulation of unchanged drug.

TABLE 3. PHARMACOKINETIC PARAMETERS

Parameter	Cohort	DAY 1 N/n	DAY 1 Geometric mean 95% CI/CV (%)	DAY 7 N/n	DAY 7 Geometric mean 95% CI/CV (%)
$AUC_{(0-t)}$ (h*ng/mL)	1 (250mcg)	8/8	0.2607 (0.1902, 0.3573)/39.1	8/6	0.5551 (0.2140, 1.4400)/113.2
	2 (250mcg)	9/9	0.0361 (0.0057, 0.2256)/1707.8	9/8	0.3053 (0.1306, 0.7133)/134.3
	3 (1000mcg)	9/9	0.9330 (0.1042, 8.3488)/5820.5	9/6	4.8620 (3.1620, 7.4759)/42.8
C_{max} (ng/mL)	1 (250mcg)	8/8	0.2165 (0.1668, 0.2810)/32.0	8/6	0.3321 (0.1882, 0.5859)/58.3
	2 (250mcg)	9/9	0.0792 (0.0346, 0.1809)/147.6	9/8	0.1645 (0.0945, 0.2860)/74.2
	3 (1000mcg)	9/9	1.5284 (1.0388, 2.2486)/53.6	9/6	2.7586 (1.5350, 4.9576)/60.5
T_{max} (h)	1 (250mcg)	8/8	0.080 (0.08, 0.50)	8/6	0.080 (0.02, 0.25)
	2 (250mcg)	9/8	0.250 (0.08, 0.28)	9/8	0.165 (0.08, 0.32)
	3 (1000mcg)	9/9	0.250 (0.08, 0.28)	9/6	0.240 (0.07, 0.25)
T_{last}	1 (250mcg)	8/8	4.000 (2.00, 8.12)	8/6	6.000 (2.00, 27.05)
	2 (250mcg)	9/8	2.000 (0.08, 4.00)	9/8	6.015 (2.00, 24.00)
	3 (1000mcg)	9/9	8.000 (0.08, 8.00)	9/6	24.010 (24.00, 24.48)

FIGURE 4. SEMI-LOG PLOTS OF INDIVIDUAL CHANGE FROM BASELINE MAXIMUM HR (0–4h) VERSUS C_{MAX} FOLLOWING REPEAT DOSE (DAY 7)



CONCLUSIONS

· Repeat doses of once-daily GSK573719 were well tolerated by patients with COPD.

· Increases in weighted mean and maximum HR (0–4h) versus placebo were seen with GSK573719 1000mcg compared with 250mcg. However 24h Holter monitoring showed no significant HR differences over 24h. There was no correlation between HR and C_{max} and change from baseline HR with GSK573719 was in the same range as seen for placebo.

· GSK573719 was absorbed rapidly and accumulation was low (1.5- to 1.9-fold).

· The favourable safety and tolerability of once-daily GSK573719 administered by a novel DPI supports the development of this once-daily LAMA for COPD.

REFERENCE

(1) Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Available at: http://www.goldcopd.com/Guidelines/guidelines-resources.html. Accessed 19 July 2011.

ACKNOWLEDGEMENTS

· This trial was sponsored by GlaxoSmithKline (ClinicalTrials.gov: NCT00732472; AC4105211).

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Poster No. P822

Safety, pharmacokinetics (PK) and pharmacodynamics (PD) of single doses of GSK573719 Inhalation Powder, a new long-acting muscarinic antagonist (LAMA), in patients with COPD

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INTRODUCTION

- Bronchodilators are important for the management of symptoms in chronic obstructive pulmonary disease (COPD).(1)
- GSK573719 is a new, long-acting muscarinic antagonist (LAMA) offering sustained 24h bronchodilation.

OBJECTIVES

- To assess the safety/tolerability (primary), pharmacokinetics and pharmacodynamics (secondary) of single-dose inhaled GSK573719 in ipratropium-responsive COPD patients.

METHODS

- This was a phase II, randomised, double-blind, placebo-controlled, double dummy, four-way crossover study with incomplete block design.
- Patients aged 40–75 years were eligible for inclusion in the study, provided they had a history of COPD (American Thoracic Society/European Respiratory Society criteria), post-bronchodilator FEV_1/FVC <0.7, FEV_1 between 40% and 80% of predicted normal, and showed a minimum 25% increase in specific airways conductance (sG_{aw}) 2h after inhaling 80mcg ipratropium bromide. Female patients had to be without childbearing potential.
- The following were considered as exclusion criteria: any past or present medical condition likely to affect the study outcome; positive pre-study drug or alcohol screen; positive test for HIV or hepatitis B or C; any medication known to be a CYP 2D6 inhibitor or substrate; and a CYP 2D6 poor metaboliser genotype.
- Four treatments were evaluated and compared with placebo: GSK573719 (250, 500 or 1000mcg), tiotropium (18mcg). Patients were randomised to receive one of twelve different sequences of study medication (Table 1). Each sequence included one dose of placebo and three of the four treatments. A 14-day washout period was scheduled between each dose.

TABLE 1. TREATMENT SEQUENCES

Sequence	Period 1	Period 2	Period 3	Period 4
1	250mcg	500mcg	Tiotropium	Placebo
2(a)	250mcg	500mcg	1000mcg	Placebo
3(a)	250mcg	Placebo	500mcg	1000mcg
4(a)	250mcg	500mcg	Placebo	1000mcg
5(a)	Placebo	250mcg	500mcg	1000mcg
6	250mcg	Placebo	Tiotropium	500mcg
7	Placebo	Tiotropium	250mcg	500mcg
8	Tiotropium	Placebo	250mcg	500mcg
9	Tiotropium	250mcg	500mcg	Placebo
10	Tiotropium	250mcg	Placebo	500mcg
11	Placebo	250mcg	Tiotropium	500mcg
12	250mcg	Placebo	500mcg	Tiotropium

(a)Three subjects were randomised to each of these sequences. One subject was randomised to each of the other sequences

- GSK573719 was administered via DISKUS™ (GlaxoSmithKline plc) and tiotropium was administered via HandiHaler™ (Boehringer Ingelheim Inc.).
- Inhaled salbutamol was permitted as relief (rescue) medication. Inhaled corticosteroids (£1000mcg/day of fluticasone propionate or equivalent) were also permitted, provided the dose remained constant during the study and the preceding 4 weeks. Inhaled long acting bronchodilators were not permitted.
- Primary endpoints were: adverse events (AEs), blood pressure, heart rate (HR), electrocardiogram (ECG), 24h Holter and 4h lead II ECG monitoring, lung function and laboratory safety tests.
- Secondary endpoints were: serial post-dose measurements of sG_{aw}, airways conductance and FEV_1; plasma and urine concentrations of GSK573719; and pharmacokinetic parameters derived from the plasma and urine concentrations.
- Sample size was calculated from change in sG_{aw}: assuming a within-subject standard deviation of 0.205 and between-subject standard deviation of 0.280, 24 subjects would be needed for 98% power to detect a 30% increase in sG_{aw} between placebo and GSK573719 at the 5% significance level.

RESULTS

Patients

- Twenty-four patients entered the study, four of whom withdrew prematurely because of AEs. Treatments received prior to withdrawal were GSK573719 250mcg; tiotropium; placebo; and GSK573719 250mcg followed by GSK573719 500mcg.
- Except for the four withdrawals, all patients received all of their allocated doses of study medication.
- As a result, 21 patients received placebo, 22 received GSK573719 250mcg, 21 received GSK573719 500mcg, 13 received GSK573719 1000mcg and 8 received tiotropium 18mcg.
- Table 2 provides a summary of patient demographics.

TABLE 2. PATIENTS' BASELINE CHARACTERISTICS

Characteristic	Value for the study population (N=24)
Mean age, years (range)	56.0 (48–67)
Male (n, %)	19 (79)
White/Caucasian/European (n, %)	24 (100)
Mean height, cm (range)	174.9 (157–187)
Mean weight, kg (range)	80.76 (57.7–102.0)
Mean body mass index, kg/m^2 (range)	26.37 (21.1–31.5)

Safety and tolerability

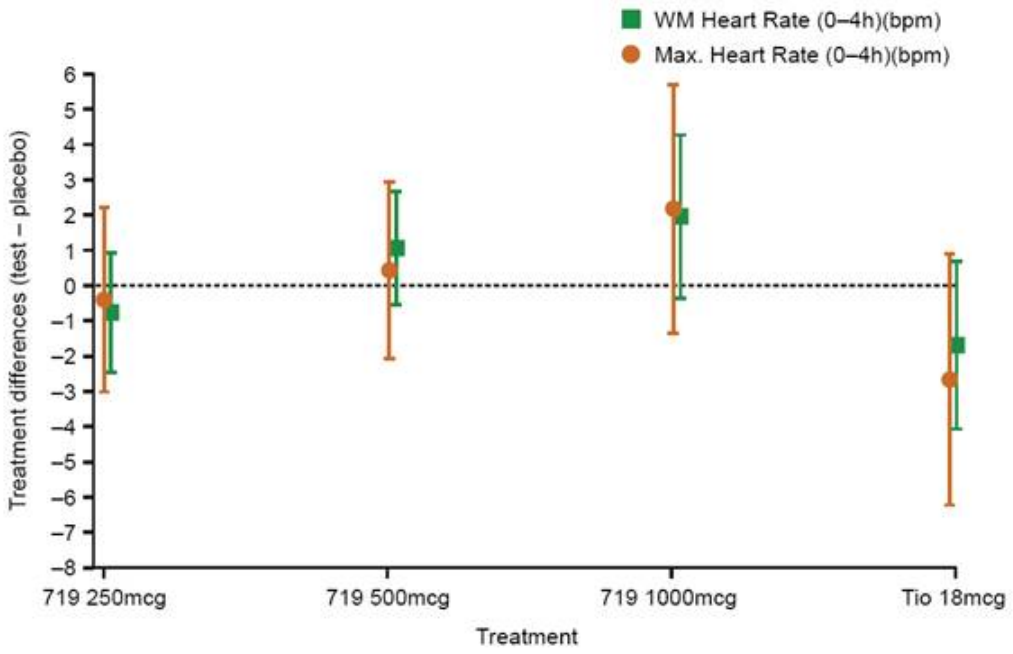
- The proportion of patients reporting any AEs after GSK573719 ranged between 31% and 41% (Table 3). In comparison, 38% of patients reported AEs following tiotropium and 29% reported AEs after receiving placebo.
- Treatment-related AEs were reported by 5–23% of patients after receiving GSK573719, compared with 10% after receiving placebo (Table 3). No treatment-related AEs were reported following inhalation of tiotropium.

TABLE 3. SUMMARY OF AEs

		GSK573719			
n (%)	Placebo (N=21)	250mcg (N=22)	500mcg (N=21)	1000mcg (N=13)	Tiotropium 18mcg (%) (N=8)
Patients with any AE	6 (29)	9 (41)	8 (38)	4 (31)	3 (38)
Patients with any treatment - related AE	2 (10)	1 (5)	4 (19)	3 (23)	0
Headache	2 (10)	1 (5)	2 (10)	1 (8)	0
Atrial fibrillation	0	0	0	1 (8)	0
Dizziness	0	0	2 (10)	1 (8)	0
Pharyngolaryngeal pain	0	0	0	2 (15)	0
Ventricular tachycardia	0	0	1 (5)	0	0

- The most common treatment-related AEs with GSK573719 were headache, dizziness and pharyngolaryngeal pain.
- None of the AEs associated with premature withdrawal from the study (exacerbation of COPD [n=1], respiratory distress [n=2] and intermittent atrial fibrillation [n=1]) were considered as related to study medication.
- There were no deaths or serious AEs during the study.
- There was no clear evidence of a difference between any of the active treatments and placebo, with respect to either weighted mean HR (0–4h) or maximum HR (0–4h) (Figure 1). There were trends towards increased values with increasing doses of GSK573719 and decreased values with tiotropium, but all 95% confidence intervals (CIs) for difference versus placebo spanned zero.

FIGURE 1. WEIGHTED MEAN AND MAXIMUM HR (0–4h): TREATMENT DIFFERENCES RELATIVE TO PLACEBO



- For the maximum and weighted mean (0–4h) systolic blood pressure, the GSK573719 250mcg and 500mcg dose groups showed decreases in both these measures, while the GSK573719 1000mcg and tiotropium 18mcg groups both showed increases. Maximum and weighted mean (0–4h) diastolic blood pressure, in general, showed decreases relative to placebo, except for GSK573719 1000mcg, where increases were seen.

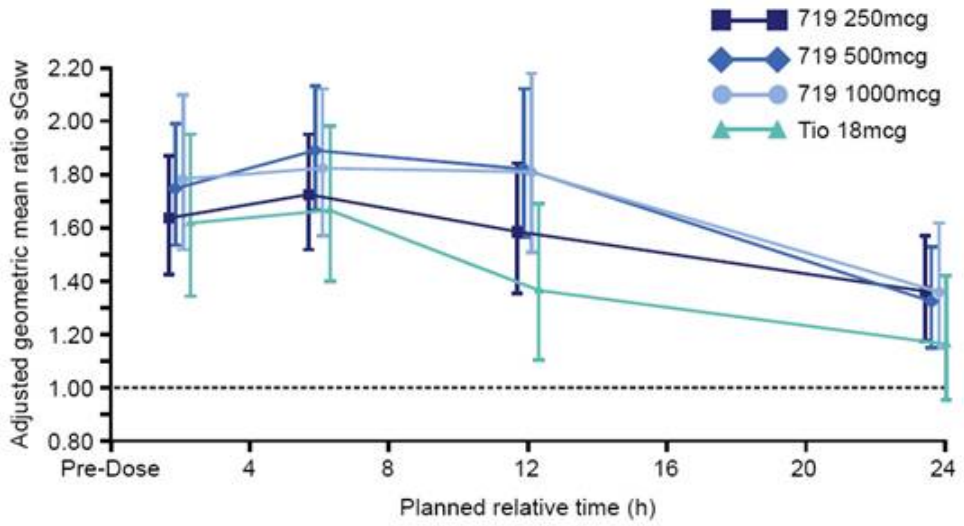
- Holter parameters for maximum HR (0–24h) and mean HR (0–24h) showed a trend towards a decrease versus placebo with all active treatments. Most 95% CIs spanned zero, with the exception of those for maximum HR following GSK573719 500mcg and 1000mcg. The 1000mcg dose produced a mean decrease of 7.7bpm versus placebo (95% CI: 1.8–13.5bpm).

- There were no notable changes in mean haematology parameters, mean clinical chemistry parameters or urinalysis.

Pharmacodynamics

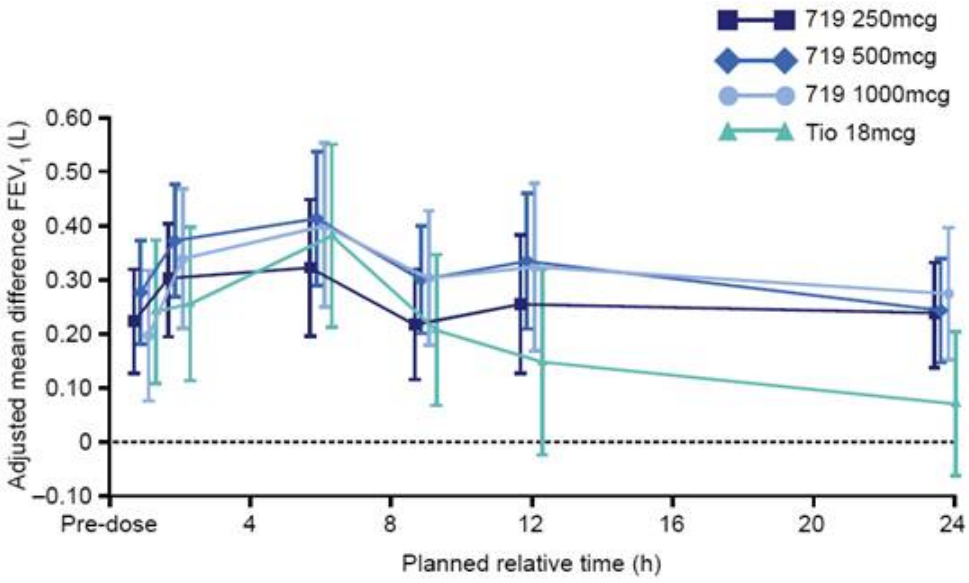
- sG_{aw} values were higher for all active treatment groups compared with placebo over the 24h assessment period, with differences versus placebo peaking at 6h post-dose with all treatments (Figure 2). Differences versus placebo were greatest following GSK573719 500mcg and 1000mcg, and least following tiotropium.

FIGURE 2. GEOMETRIC MEAN SPECIFIC AIRWAYS CONDUCTANCE (sG_{aw}): POST-TREATMENT DIFFERENCES RELATIVE TO PLACEBO



- Broadly similar results were seen with FEV_1, with increases versus placebo in all active groups peaking at 6h post-treatment (Figure 3).

FIGURE 3. MEAN FEV_1: POST-TREATMENT DIFFERENCES RELATIVE TO PLACEBO



Pharmacokinetics

- Pharmacokinetic data were non-quantifiable in 40–61% of plasma samples.
- Available plasma data indicated that GSK573719 was rapidly absorbed, with t_{max} values of 5–15min (Table 4); plasma half-life was 1–2h.
- The half-life of GSK573719 in urine was 11–12h. Renal clearance values were estimated to be 5.32, 6.40, and 6.83L/h for the 250mcg, 500mcg and 1000mcg doses, respectively.
- 1–1.3% of administered GSK573719 was excreted unchanged in the urine.

TABLE 4. PLASMA PHARMACOKINETIC PARAMETERS

Parameter	Dose	N/n	Geometric mean	95% CI	CV (%)
AUC(0-t) (h*ng/mL)	250mcg	22/22	0.10271	(0.07763, 0.13589)	70.0
	500mcg	21/21	0.35491	(0.27070, 0.46531)	65.2
	1000mcg	13/13	0.96100	(0.81529, 1.13276)	27.7
C_{max} (ng/mL)	250mcg	22/22	0.12615	(0.10494, 0.15164)	43.4
	500mcg	21/21	0.30389	(0.25430, 0.36314)	40.7
	1000mcg	13/13	0.83228	(0.72619, 0.95386)	22.9
T_{max} (h)(a)	250mcg	22/22	0.090	(0.08, 0.50)	NA
	500mcg	21/21	0.100	(0.07, 0.27)	NA
	1000mcg	13/13	0.250	(0.08, 0.28)	NA

(a)Presented as median and range

CONCLUSIONS

- Single doses of GSK573719 were well tolerated and produced clinically significant improvements in lung function among COPD patients.
- GSK573719 was rapidly absorbed.
- Mean sG_{aw} and FEV_1 responses were significantly higher for all active treatments versus placebo.
- No correlation was observed between heart rate and C_{max}, and heart rate following GSK573719 was in the same range as that following placebo.

REFERENCE

(1) Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline: Global Strategy for the diagnosis, management, and prevention of Chronic Obstructive Pulmonary Disease (updated 2010). http://www.goldcopd.com/. Accessed 14th July 2011.

ACKNOWLEDGEMENTS

- This trial was sponsored by GlaxoSmithKline (ClinicalTrials.gov: NCT00515502; AC4108123).
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The pharmacodynamics of GSK961081 in patients with COPD

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Poster No. P823

INTRODUCTION

- Inhaled muscarinic antagonists (MA) and beta2-adrenoceptor agonists (BA) are the mainstay of treatment of COPD. Clinical trials in COPD patients have shown that combining agents from these two classes leads to greater efficacy and therefore long-acting bronchodilators with different mechanisms are frequently co-prescribed in patients with COPD.
- GSK961081 (formerly TD5959) is a dual pharmacophore that has both long-acting muscarinic antagonist activity and long-acting beta2-adrenoceptor agonist activity in a single molecule (MABA).(1),(2)
- This study was conducted to determine the safety, tolerability, pharmacokinetics and pharmacodynamics, both pulmonary and systemic, of inhaled GSK961081 in patients with COPD.

OBJECTIVES

Primary

- To evaluate the pulmonary pharmacodynamic profile of GSK961081 following 14 days' dosing in patients with COPD.

Secondary

- To evaluate the safety and tolerability of GSK961081 given for 14 days in patients with COPD.
- To evaluate the systemic pharmacodynamic effects of GSK961081 given for 14 days in patients with COPD .
- To evaluate the systemic pharmacokinetics of GSK961081 given for 14 days in patients with COPD.

METHODS

- This was a randomised, double-blind, double-dummy, placebo and active comparator controlled, incomplete block crossover study.
- Male and female (of non-child bearing potential) COPD patients with FEV_1 $\leq$80 % predicted and FEV_1/FVC $\leq$0.7 post-bronchodilator and reversibility to salbutamol and ipratropium were enrolled.
- Long-acting inhaled bronchodilators were prohibited from 72h before screening until after completion of all treatment periods. Salbutamol was permitted as rescue medication during the study but was required to be withheld for 6h before any lung function assessment. Inhaled corticosteroids (ICS) of <1000mcg fluticasone propionate (or equivalent) were permitted provided the dose was stable for 6 weeks before screening .
- Each patient received 3 out of the following 4 treatments for 14 days, with a washout period of at least 14 days between treatments
  - 400mcg GSK961081 DPI (via DISKUS®) plus placebo (matched for tiotropium) in the morning and placebo (via DISKUS) in the evening
  - 1200mcg GSK961081 DPI (via DISKUS) plus placebo (matched for tiotropium) in the morning plus placebo (via DISKUS) in the evening
  - placebo (via DISKUS) plus placebo (matched for tiotropium) in the morning and placebo (via DISKUS) in the evening
  - 50mcg salmeterol (via DISKUS) plus 18mcg tiotropium in the morning and 50 mcg salmeterol (via DISKUS) in the evening.
- FEV_1, heart rate, 12-lead ECG (QTcF), blood potassium and glucose and plasma GSK961081 were measured before and frequently after dosing. Adverse events were monitored and laboratory safety tests were done.

RESULTS

Demographics

- Fifty (16 female, 34 male) patients were randomised with 43, 29, 32 and 41 receiving placebo, 400mcg GSK961081, 1200mcg GSK961081 and tiotropium plus salmeterol, respectively.
- Patients were aged 58.3 years (range 41–74); 18 were former smokers and 32 were current smokers; 11 patients took ICS.

Safety and tolerability

- Three patients discontinued prematurely from the study
  - one patient was withdrawn due to an exacerbation of COPD requiring steroid treatment whilst taking tiotropium plus salmeterol

- two withdrew for personal reasons unrelated to the study.

- There were no serious adverse events; adverse events were similar across all groups with the exception of tremor (n=2, 1200mcg dose), dysguesia (n=2, 1200mcg dose; n=2, 400mcg dose) and dry mouth (n=1, 1200mcg dose) seen after GSK961081 only.

- There were no clinically significant abnormal 12-lead ECG findings or laboratory safety test findings.

Pulmonary pharmacodynamics

- After 14 days' dosing there were significant improvements in trough FEV_1 for all active treatments (Figure 1)

  - for 400mcg GSK961081, 1200mcg GSK961081 and tiotropium plus salmeterol adjusted mean (95% confidence interval [CI]) differences vs placebo were 0.115L (0.024, 0.205), 0.168L (0.080, 0.255) and 0.103L (0.026, 0.180), respectively (all $p<0.05$).

- Onset of bronchodilatation was faster for both doses of GSK961081 than for tiotropium plus salmeterol

  - fifteen minutes after treatment on Day 1 adjusted mean (95% CI) difference vs placebo were 0.209L (0.156, 0.262) and 0.222L (0.170, 0.274) for 400mcg and 1200mcg GSK961081 respectively and 0.117L (0.072, 0.162) for tiotropium plus salmeterol (Figure 2).

FIGURE 1. FEV_1 (L) DIFFERENCE TO PLACEBO ON DAY 14

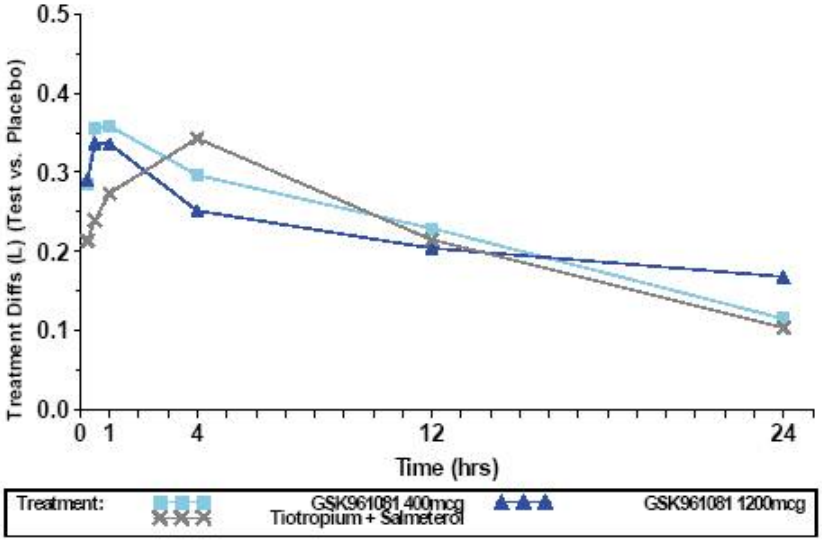
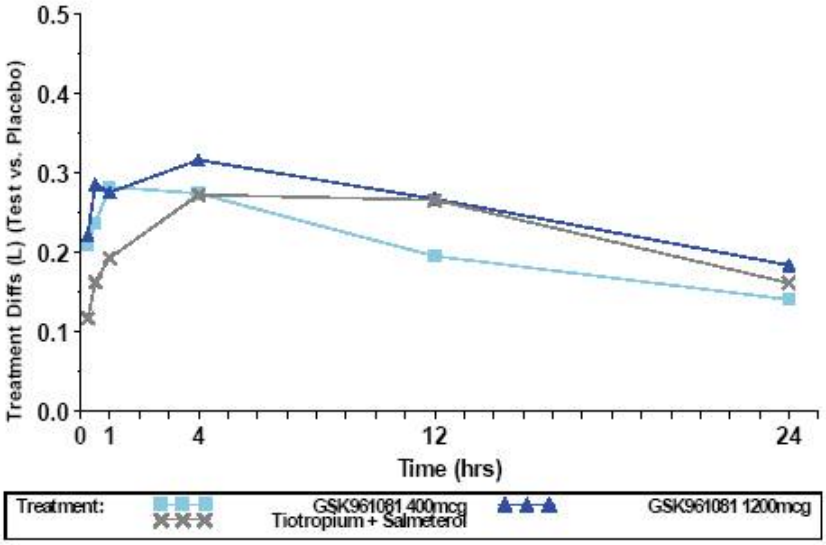


FIGURE 2. FEV_1 (L) DIFFERENCE TO PLACEBO ON DAY 1



Systemic pharmacodynamics

- There was no significant difference in maximum change from baseline heart rate, glucose or QTcF 0–4h after the final dose of any active treatment vs placebo (Table 1).

- There was a small, non-clinically significant decrease in potassium 0–4h after the final dose of all active treatments (Table 1).

TABLE 1. SUMMARY OF SYSTEMIC PD FOLLOWING 14 DAYS' DOSING

Parameter (units)	Comparison	Diff in Adj Mean	95% CI
Max change from baseline heart rate 0–4h (bpm)	400mcg vs placebo	1.58	–1.15, 4.31
	1200mcg vs placebo	2.60	–0.02, 5.23
	Tio+Sal vs placebo	1.82	–0.69, 4.33
Max change from baseline QTcF 0–4h (msec)	400mcg vs placebo	0.44	–3.95, 4.84
	1200mcg vs placebo	1.60	–2.63, 5.82
	Tio+Sal vs placebo	–0.71	–4.60, 3.19
Min change from baseline potassium 0–4h (mmol/L)	400mcg vs placebo	–0.11	–0.22, –0.01
	1200mcg vs placebo	–0.19	–0.29, –0.09
	Tio+Sal vs placebo	–0.10	–0.19, –0.01
Max change from baseline glucose 0–4h (mmol/L)	400mcg vs placebo	0.11	–0.11, 0.34
	1200mcg vs placebo	0.14	–0.07, 0.36
	Tio+Sal vs placebo	0.18	–0.02, 0.38

Systemic pharmacokinetics

TABLE 2. SUMMARY OF GSK961081 PK: GEOMETRIC MEAN (95% CI)

Parameter (units)	Day	400mcg N=29	1200mcg N=32
C_{max} (pg/mL)	1	101 (80.4, 126) [n=29]	243 (182, 323) [n=32]
	7	102 (87.0, 121) [n=28]	256 (203, 322) [n=32]
	14	119 (101, 140) [n=28]	280 (220, 356) [n=32]
t_{max} (h)(a)	1	0.48 (0.5, 1.1) [n=28]	0.50 (0.5, 8.0) [n=31]
	7	0.50 (0.5, 0.8) [n=28]	0.50 (0.5, 1.0) [n=31]
	14	0.50 (0.5, 1.0) [n=28]	0.50 (0.4, 1.0) [n=31]
t_{last} (h)(a)	1	1.05 (0.5, 4.0) [n=28]	4.00 (1.00, 8.00) [n=31]
	7	2.00 (0.5, 6.0) [n=28]	6.00 (2.0, 6.1) [n=31]
	14	2.00 (1.0, 24.1) [n=28]	11.80 (2.0, 24.4) [n=31]
AUC(0–t) (pg.h/mL)	1	75.1 (53.6, 105) [n=29]	264 (170, 409) [n=32]
	7	99.8 (69.9, 143) [n=28]	459 (324, 652) [n=32]
	14	134 (98.1, 183) [n=28]	705 (506, 983) [n=32]
AUC(0–2) (pg.h/mL)	1	160 (125, 204) [n=10]	311 (266, 364) [n=28]
	7	144 (127, 164) [n=18]	341 (296, 393) [n=31]
	14	157 (130, 189) [n=19]	374 (328, 427) [n=31]

(a)Median (range)
N = number of patients
n = number of patients with non-missing observation
AUC = area under the curve. CI = Confidence interval

- Systemic exposure to GSK961081 increased from Day 1 to Day 14 (Table 2). Maximum plasma concentration (C_{max}) and AUC from 0–2h post-dose (AUC[0–2]) had an accumulation ratio of approximately 1.2-fold (Day 14/Day 1).

- AUC to the last quantifiable concentration (AUC[0–t]) had an accumulation ratio of approximately 2.2-fold (Day 14/Day 1), which is likely a reflection of the increase in t_{last} over the dosing period.

CONCLUSIONS

- After 14 days' dosing with GSK961081 there were significant improvements in trough FEV_1.

- There was no significant difference in maximum change from baseline, heart rate, glucose or QTcF 0–4h after the final dose of any active treatment vs placebo. There was a small decrease in potassium 0–4h after the final dose of all active treatments.

- Adverse events were similar across all groups with the exception of tremor (n=2, 1200mcg dose), dysguesia (n=2, 1200mcg dose; n=2, 400mcg dose) and dry mouth (n=1, 1200mcg dose) seen after GSK961081 only.

- GSK961081 was well tolerated and showed significant bronchodilatation meriting further evaluation as a potential therapy for COPD.

References

(1) Aiyar J, et al. In vitro characterization of TD-5959: a novel bifunctional molecule with muscarinic antagonist and beta$_2$-adrenergic agonist activity. Am J Respir Crit Care Med 179;2009:A4552.

(2) Pulido-Rios MT, et al. TD-5959: a novel bifunctional muscarinic antagonist beta$_2$-adrenergic agonist with potent and sustained in vivo bronchodilator activity in guinea pigs. Am J Respir Crit Care Med 179;2009:A6195.

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