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: B2C101762

Title: A multi-centre, randomised, double-blind, placebo-controlled, dose ascending, four way crossover study to examine efficacy (FEV1), safety, tolerability, pharmacodynamics and pharmacokinetics of single and repeat doses of GW642444.

Rationale: GW642444 is a new potent and selective beta-2-receptor agonist under development as a potential once-daily inhaled bronchodilator therapy for patients with asthma and chronic obstructive pulmonary disease (COPD). This study was designed to provide information on the safety and efficacy and pharmacokinetics of inhaled dry powder GW642444 under single and repeat dose conditions in mild to moderate asthmatic subjects.

Phase: IIa

Study Period: 01 January 2005 – 07 June 2005.

Study Design: A multicentre, randomised, double-blind, placebo-controlled, dose ascending, four-way crossover study.

Centres: Two centres in Germany and one centre in Sweden.

Indication: Asthma.

Treatment: Screening took place within 4 weeks prior to the first dose. In each of four periods, subjects received a single inhaled GW642444 dose on Day 1 and six further doses on days 2–7. Repeat dosing was conditional on tolerability on Day 1. Randomisation was structured as follows: 12 subjects received GW642444 50 μg, 100 μg and 200 μg for a total of 7 days in sequential escalating fashion, with randomly assigned placebo; and 16 subjects received two dose strengths of GW642444 (either 50 μg and 100 μg, or 100 μg and 200 μg for a total of 7 days) in sequential escalating fashion, with salmeterol 50 μg (dosed only on Day 1 and switched to placebo for repeat dosing) and placebo. There was a washout of 6 to 28 days between doses. Each subject was in the study for approximately 56 days, with a maximum of 122 days.

Objectives: To determine the 24-h forced expiratory volume in 1 second (FEV1) after a single dose of GW642444 in mild to moderate asthmatic subjects.

Statistical Methods: The study was powered to detect a 0.25-L difference in FEV1 at 24 h post-dose, using a two-sided 95% confidence interval (CI). The primary endpoint was FEV1 at 24 h after a single dose. Change from baseline and log-transformed serial FEV1, and change from baseline maximum and weighted mean FEV1 were analysed using mixed effects models. Mean peak expiratory flow rate (PEFR) parameters, derived (maximum/minimum and weighted mean) Day 1 and Day 7 heart rate, QT interval corrected according to Bazett's (QTcB) or Fridericia (QTcF) formula, blood pressure, blood potassium and blood glucose parameters were analysed using a mixed effects model. Treatment differences (or ratios) for each GW642444 dose level versus placebo and salmeterol versus placebo were presented with 95% CI. Time to maximum/minimum endpoints were analysed using non-parametric methods. To evaluate the accumulation ratio, log-transformed data for pharmacokinetic parameters was analysed using a mixed effects model. The ratio of GW642444 to salmeterol maximal plasma concentration (Cmax) was also analysed for Day 1. Treatment ratios and 90% CI were calculated.

Study Population: Male or female (not of child-bearing potential) non-smoking subjects with mild to moderate asthma, clinically stable asthma in the 4 weeks preceding screening, and pre-bronchodilator FEV1 >60% predicted. Subjects had reversible airway disease (FEV1 increase of ≥12% over baseline and absolute change ≥300 mL 30 minutes after salbutamol 400 μg). Subjects with mean QTcB >430 msec (male) or >450 msec (female) were excluded.

Number of Subjects:	**Total**
Planned N	28
Dosed N	28
Completed n (%)	27 (96)
Total Number Subjects Withdrawn N (%)	1 (4)
Withdrawn due to Adverse Events n (%)	1 (4)

Demographics	Total
N (All Subjects)	28
Females : Males	1 : 27
Mean Age in Years (SD)	38 (12.4)
Mean Weight in kg (SD)	83.8 (9.17)
Race n (%)	
White	25 (89)
African American/African Heritage	1 (4)
Asian – South East Asian Heritage	1 (4)
Mixed Race	1 (4)

Efficacy Endpoints: A summary of mean (standard deviation) FEV1 data (L) at selected time points is presented below.

Time point	Placebo	GW642444			Salmeterol
		50 μg	100 μg	200 μg	50 μg
	N = 28	N = 21	N = 27	N = 18	N = 16
Day 1 pre-dose	3.36 (0.797)	3.33 (0.695)	3.28 (0.782)	3.25 (0.831)	3.36 (0.901)
1 h	3.41 (0.783)	3.76 (0.833)	3.69 (0.785)	3.79 (0.758)	3.82 (0.872)
24 h	3.24 (0.842)	3.61 (0.769)	3.51 (0.823)	3.47 (0.878)	3.63 (1.026)
Day 7 pre-dose	3.20 (0.898)	3.58 (0.727)	3.53 (0.790)	3.47 (0.874)	3.39 (0.931)
1 h	3.26 (0.905)	3.74 (0.750)	3.65 (0.765)	3.69 (0.800)	3.47 (0.944)
24 h	3.23 (0.885)	3.55 (0.677)	3.51 (0.826)	3.43 (0.903)	3.45 (0.946)

Results of statistical analysis of baseline-corrected serial Day 1 and Day 7 FEV1 at 24 h are presented below.

Time point	FEV1 difference (95% CI) vs. placebo (L)			
	GW642444 50 μg	GW642444 100 μg	GW642444 200 μg	Salmeterol 50 μg
Day 1 24 h	0.42 (0.28, 0.56)	0.37 (0.24, 0.50)	0.34 (0.19, 0.50)	0.34 (0.19, 0.50)
Day 7 24 h	0.36 (0.21, 0.50)	0.37 (0.24, 0.50)	0.30 (0.14, 0.45)	0.16 (0.01, 0.32)

Statistical analysis of baseline-corrected serial Day 1 and Day 7 log-transformed FEV1 (L) at 24 h was as follows.

Time point	FEV1 ratio (95% CI) vs. placebo			
	GW642444 50 μg	GW642444 100 μg	GW642444 200 μg	Salmeterol 50 μg
Day 1 24 h	1.14 (1.09, 1.19)	1.12 (1.08, 1.17)	1.11 (1.06, 1.17)	1.10 (1.05, 1.16)
Day 7 24 h	1.13 (1.08, 1.18)	1.13 (1.08, 1.18)	1.10 (1.05, 1.16)	1.06 (1.01, 1.11)

Results of statistical analysis of morning PEFR (L/minute) on selected days are presented below.

Comparison (test – reference)	Day	Adjusted mean PEFR		Difference	95% CI
		Test	Reference		
GW642444 50 μg – placebo	2	545.1	499.4	45.7	(24.6, 66.8)
	7	558.0	490.0	68.0	(46.7, 89.3)
GW642444 100 μg – placebo	2	529.0	499.4	29.5	(10.1, 49.0)
	7	546.8	490.0	56.7	(37.1, 76.3)
GW642444 200 μg – placebo	2	534.9	499.4	35.4	(13.2, 57.6)
	7	534.6	490.0	44.5	(22.2, 66.9)
Salmeterol 50 μg – placebo	2	527.3	499.4	27.8	(5.2, 50.5)
	7	509.1	490.0	19.1	(–3.7, 41.9)

Pharmacodynamic Endpoints: Results of statistical analysis of derived supine vital signs parameters are presented below.

Parameter	Day	Heart rate difference (95% CI) vs. placebo (bpm)			
		GW642444 50 μg	GW642444 100 μg	GW642444 200 μg	Salmeterol 50 μg
Maximum 0–8 h	1	0.34 (–3.12, 3.80)	–0.37(–3.42, 2.69)	3.81 (0.10, 7.53)	2.49 (–1.11, 6.09)
	7	–0.37 (–3.86, 3.12)	–2.02 (–5.09, 1.06)	0.65 (–3.08, 4.37)	0.22 (–3.39, 3.84)
Weighted mean 0–8 h	1	1.11 (–1.29, 3.51)	0.21 (–1.91, 2.34)	2.70 (0.12, 5.28)	1.76 (–0.74, 4.26)
	7	–1.09 (–3.51, 1.33)	–0.71 (–2.85, 1.43)	1.42 (–1.16, 4.00)	–1.06 (–3.57, 1.46)
Maximum 0–4 h	1	2.46 (–0.79, 5.72)	0.57 (–2.32, 3.46)	4.72 (1.24, 8.20)	1.63 (–1.76, 5.03)
	7	–3.55 (–6.83, –0.27)	–2.69 (–5.61, 0.22)	1.69 (–1.80, 5.19)	–1.06 (–4.48, 2.35)
Weighted mean 0–4 h	1	2.41 (0.05, 4.77)	0.77 (–1.33, 2.86)	3.62 (1.09, 6.15)	1.96 (–0.51, 4.43)
	7	–2.58 (–4.96, –0.20)	–0.90 (–3.01, 1.22)	1.92 (–0.62, 4.46)	–1.11 (–3.59, 1.37)
		Blood pressure difference (95% CI) vs. placebo (mmHg)			

Parameter	Day	GW642444 50 μg	GW642444 100 μg	GW642444 200 μg	Salmeterol 50 μg
Minimum DBP 0–8 h	1	–1.19 (–3.79, 1.41)	–1.10 (–3.37, 1.16)	–2.46 (–5.20, 0.28)	0.07 (–2.60, 2.73)
	7	–2.42 (–5.04, 0.20)	–1.84 (–4.12, 0.44)	–1.54 (–4.29, 1.21)	–1.66 (–4.34, 1.01)
Weighted mean DBP 0–8 h	1	–1.25 (–3.33, 0.83)	–0.99 (–2.79, 0.81)	–1.33 (–3.52, 0.85)	0.47 (–1.65, 2.59)
	7	–1.53 (–3.62, 0.57)	–2.01 (–3.82, –0.20)	–0.55 (–2.75, 1.64)	–0.58 (–2.71, 1.55)
Maximum SBP 0–8 h	1	–0.78 (–4.09, 2.53)	–0.38 (–3.31, 2.54)	0.61 (–2.97, 4.18)	–0.11 (–3.57, 3.34)
	7	–0.58 (–3.91, 2.76)	–0.55 (–3.50, 2.39)	–0.70 (–4.28, 2.88)	0.58 (–2.89, 4.04)
Weighted mean SBP 0–8 h	1	–1.12 (–3.70, 1.45)	–1.66 (–3.92, 0.60)	–0.42 (–3.21, 2.38)	–0.87 (–3.54, 1.81)
	7	–0.34 (–2.93, 2.26)	0.17 (–2.11, 2.44)	0.63 (–2.17, 3.42)	0.39 (–2.29, 3.07)
Results of statistical analysis of baseline-corrected derived 12-lead ECG endpoints are presented below.					
		QTc parameter difference (95% CI) vs. placebo (msec)			
Parameter	Day	GW642444 50 μg	GW642444 100 μg	GW642444 200 μg	Salmeterol 50 μg
Maximum QTcB 0–8 h	1	8.11 (1.31, 14.92)	5.29 (–0.75, 11.33)	10.61 (3.34, 17.87)	8.21 (1.07, 15.36)
	7	1.12 (–5.75, 7.99)	1.60 (–4.49, 7.69)	6.03 (–1.26, 13.32)	–0.78 (–7.96, 6.40)
Weighted mean QTcB 0–8 h	1	6.06 (1.97, 10.16)	4.12 (0.51, 7.73)	5.34 (0.95, 9.72)	7.13 (2.83, 11.43)
	7	3.30 (–0.83, 7.43)	3.44 (–0.20, 7.07)	4.77 (0.37, 9.17)	0.42 (–3.89, 4.73)
Maximum QTcF 0–8 h	1	4.75 (–0.69, 10.18)	3.29 (–1.55, 8.14)	4.68 (–1.09, 10.45)	2.46 (–3.25, 8.17)
	7	0.16 (–5.33, 5.64)	0.88 (–4.00, 5.77)	2.69 (–3.10, 8.48)	–0.37 (–6.11, 5.37)
Weighted mean QTcF 0–8 h	1	4.05 (0.73, 7.36)	3.24 (0.28, 6.19)	2.62 (–0.90, 6.15)	4.05 (0.57, 7.54)
	7	3.26 (–0.09, 6.60)	2.80 (–0.18, 5.78)	2.48 (–1.05, 6.02)	1.42 (–2.08, 4.92)
Results of statistical analysis of baseline-corrected weighted mean, maximum and minimum potassium and glucose are presented below.					
		Blood parameter difference (95% CI) vs. placebo (mmol/L)			
Parameter	Day	GW642444 50 μg	GW642444 100 μg	GW642444 200 μg	Salmeterol 50 μg
WM glucose 0–4 h	1	0.08 (–0.04, 0.19)	0.07 (–0.03, 0.17)	0.11 (–0.01, 0.24)	0.16 (0.04, 0.27)
	7	–0.06 (–0.17, 0.06)	0.01 (–0.09, 0.11)	0.03 (–0.09, 0.16)	–0.02 (–0.14, 0.10)
Max glucose 0–4 h	1	0.12 (–0.06, 0.30)	0.09 (–0.07, 0.25)	0.20 (0.01, 0.39)	0.29 (0.10, 0.48)
	7	-0.15 (–0.33, 0.03)	-0.02 (–0.18, 0.14)	0.05 (–0.14, 0.24)	-0.05 (–0.24, 0.14)
WM potassium 0–4 h	1	–0.04 (–0.16, 0.07)	–0.03 (–0.14, 0.07)	–0.06 (–0.18, 0.07)	0.02 (–0.10, 0.15)
	7	–0.08 (–0.20, 0.04)	–0.12 (–0.23, –0.02)	–0.09 (–0.22, 0.04)	–0.03 (–0.15, 0.10)
Min potassium 0–4 h	1	-0.04 (–0.14, 0.06)	-0.02 (–0.11, 0.07)	-0.07 (–0.18, 0.04)	-0.09 (–0.20, 0.01)
	7	-0.02 (–0.13, 0.08)	-0.09 (–0.18, 0.00)	-0.07 (–0.18, 0.03)	-0.05 (–0.16, 0.06)

Pharmacokinetic Endpoints: Day 1 and Day 7 geometric mean (CV%) plasma GW642444 parameters were as follows.

Treatment	Day	n	Cmax (pg/mL)	AUClast (pg•h/mL)	Tmax (h)[1]
GW642444 50 μg	1	4	34.2 (3.4)	Not available	0.27 [0.12–2.03]
	7	8	43.1 (24.4)	Not available	0.15 [0.10–0.68]
GW642444 100 μg	1	19	52.2 (34.0)	48.5 (50.2) (n=10)	0.32 [0.08–1.02]
	7	26	61.0 (39.4)	54.0 (41.3) (n=18)	0.35 [0.07–1.08]
GW642444 200 μg	1	18	100.3 (35.3)	146.1 (85.5) (n=16)	0.56 [0.08–1.07]
	7	18	114.9 (44.7)	196.0 (74.7) (n=17)	0.15 [0.10–1.05]

1. Values presented are median [range].

Analysis of the observed accumulation in GW642444 pharmacokinetic parameters is presented below as ratio (Day 7/Day 1) and 90% CI.

Treatment	Cmax (pg/mL)	AUClast (pg•h/mL)	AUC(0–40 mins)
GW642444 50 μg	1.25 (0.90, 1.75)	Not available	Not available
GW642444 100 μg	1.21 (1.03, 1.42)	1.10 (0.78, 1.57)	1.04 (0.83, 1.31)
GW642444 200 μg	1.14 (0.96, 1.36)	1.37 (1.02, 1.85)	1.11 (0.92, 1.33)

Safety results:

Adverse Events:	Placebo	GW642444 50 μg	GW642444 100 μg	GW642444 200 μg	Salmeterol 50 μg
N (All Subjects)	28	21	27	18	16
No. subjects with AEs n (%)	10 (36)	9 (43)	13 (48)	9 (50)	6 (38)
Most Frequent AEs (more than one subject with any treatment)					
Headache	5 (18)	4 (19)	8 (30)	4 (22)	2 (13)

Nasopharyngitis	3 (11)	1 (5)	2 (7)	2 (11)	2 (13)
Chest discomfort	0	2 (10)	0	0	1 (6)
Serious Adverse Events, n (%): None					
Publications: None at the time of this report.					