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: B2C106093
Title: Multi-centre, randomized, double-blind, placebo-controlled, four-way incomplete block crossover study, to examine efficacy, safety, tolerability, pharmacodynamics and pharmacokinetics of single and repeat administration of three inhaled doses of GW642444H (25, 100, and 400 mcg once daily).
Rationale: GW642444H, a novel, potent and selective long-acting inhaled beta2-adrenoceptor agonist, is being developed for once daily treatment of asthma and chronic obstructive pulmonary disease. Systemic side effects related to beta2-agonist treatment such as tachycardia, tremor, hyperglycaemia and hypokalaemia are generally mild and are limited by local administration, and also tend to show tachyphylaxis. As systemic exposure is limited through rapid breakdown, GW642444H has the potential to be administered at higher doses, as significant accumulation is not expected (GW642444H has an apparent half-life of ~2 h). In order to explore a wider therapeutic window with GW642444H than previously examined in subjects with asthma and to understand any potential tachyphylaxis, the present study comprised GW642444H doses of 25, 100 and 400 mcg/day. Effects of GW642444H were also compared with salmeterol (50 mcg twice daily).
Phase: IIa
Study Period: 23 May 2006–11 January 2007
Study Design: Multi-centre, randomised, double-blind, placebo-controlled, four-way incomplete block crossover.
Centres: Two centres in Germany and one centre each in Russia, Sweden, New Zealand and the UK.
Indication: None.
Treatment: At each dosing occasion, subjects received either a single dose of GW642444 (25, 100 or 400 mcg; as the alpha-phenylcinnamate salt [GW642444H]) in the morning and placebo in the evening, a single dose of salmeterol (50 mcg) in the morning and evening, or placebo in the morning and evening by oral inhalation in accordance with the randomisation schedule. All treatments were administered via a DISKUS™ inhaler. Subjects were dosed for 14 days in each period.
Objectives: To determine the trough (mean of 23 and 24 h) forced expiratory volume in 1 second (FEV1) after 14 day repeat dose inhaled GW642444H (25, 100 and 400 mcg) administered once daily in subjects with persistent asthma.
Statistical Methods: The study was powered (94%) to detect a 200 mL difference between any dose of GW642444H and placebo in change from baseline in trough FEV1 derived from the mean of the 23 and 24 h post-dose assessments on Day 14. Additionally, the study was powered (98%) to detect a 200 mL difference in trough FEV1 between salmeterol and placebo. The primary endpoint was change from baseline in trough FEV1 using the mean of the 23 and 24 h post-dose FEV1 assessments after dosing on Day 14. The primary analysis was performed using mixed effects analysis of covariance with baseline trough FEV1, centre, sex, age, treatment, period and the mean of the subjects' baseline values as fixed effects and subject as a random coefficient. The three primary treatment comparisons of interest for the assessment of trough FEV1 derived from the mean of the 23 and 24 h post dose assessments on Day 14 were: GW642444H 25 mcg versus placebo, GW642444H 100 mcg versus placebo, and GW642444H 400 mcg versus placebo. The treatment effects relating to these comparisons were estimated together with 95% confidence intervals. The following pharmacodynamic endpoints were measured on Days 1, 7 and 14: change from baseline in weighted mean (0–4 h) and maximum increase from baseline (0–4 h) for blood glucose; and maximum decrease from baseline value (0–4 h) and weighted mean change from baseline (0–4 h) for blood potassium. These endpoints were analysed using mixed effects analysis of covariance with baseline value, centre, sex, age, treatment, period and the mean of the subjects' baseline values as fixed effects and subject as a random coefficient. Statistical analysis of maximum observed concentration (Cmax) and area under the concentration-time curve from zero (pre-dose) to time of last quantifiable concentration (AUC(0–t)) was performed after a log transformation of the data from Days 1, 7 and 14 to evaluate the accumulation ratio using a mixed effects model provided that drug was detected in at least 75% of subjects on an active treatment on Days 7 and 14, and in at least 70% of subjects on an active treatment on Day 1. The Full Analysis Set included all subjects who were randomised to treatment and had taken at least one dose of study medication. A total of 55 of 56 (98%) subjects were included in the Full Analysis Set. The Per Protocol Population included subjects from the Full Analysis Set who had no major protocol deviations. A total of 54 of 56 (96%) subjects were included in this population. The Pharmacokinetic Concentration Population included subjects from the Full Analysis Set for whom a

pharmacokinetic sample was obtained and analysed. A total of 54 of 56 (96%) subjects were included in this population.
The Pharmacokinetic Parameters Population included all subjects in the Pharmacokinetic Concentration Population who provided any pharmacokinetic parameter information. A total of 53 of 56 (95%) subjects were included in this population.

Study Population: Subjects with clinically stable persistent asthma within the 4 weeks preceding screening and a screening pre-bronchodilator FEV1 between 60 and 90%. Subjects had to demonstrate reversibility to salbutamol ≥12.0% and an absolute change of ≥300 mL within 30 minutes following a single 400 mcg salbutamol dose. Subjects were required to be using inhaled corticosteroids (ICS) at a total daily dose of 200–500 mcg of fluticasone propionate or equivalent ICS. Female subjects were required to be of non-childbearing potential.

Number of Subjects:	
Planned N	60
Randomised N[1]	56
Completed n (%)	51 (93)
Total Number Subjects Withdrawn N (%)	4 (7)
Withdrawn due to Adverse Events n (%)	3 (5)
Withdrawn for Other Reasons n (%)	1 (2)
Demographics	
N	55
Females: Males	15:40
Mean Age in years (SD)	43.8 (15.0)
White n (%)	50 (91)
Asian n (%)	2 (4)
Asian and White n (%)	2 (4)
Native Hawaiian or Other Pacific Islander n (%)	1 (2)

1. One subject was randomised in error and did not receive any study medication.

Efficacy Endpoints: Change from baseline and treatment differences in trough clinic FEV1 (Full Analysis Set; L) are presented below.

	Placebo N=52	**GW642444H 25 mcg N=34**	**GW642444H 100 mcg N=37**	**GW642444H 400 mcg N=34**	**Salmeterol 50 mcg BID N=53**
Day 1					
Trough FEV_1 (n)	52	34	37	34	53
LS Mean (SE)		2.98 (0.05)	3.07 (0.04)	3.20 (0.05)	3.08 (0.04)
LS Mean Change (SE)	0.030 (0.04)	0.235 (0.05)	0.315 (0.04)	0.448 (0.05)	0.326 (0.04)
Difference from placebo					
LS Mean Difference		0.205	0.286	0.418	0.296
95% CI		0.129, 0.282	0.211, 0.360	0.343, 0.493	0.230, 0.363
p-value		<0.001	<0.001	<0.001	<0.001
Day 7					
Trough FEV_1 (n)	52	34	37	34	53
LS Mean (SE)		2.83 (0.05)	2.88 (0.04)	2.99 (0.05)	2.88 (0.04)
LS Mean Change (SE)	-0.033 (0.04)	0.082 (0.05)	0.134 (0.04)	0.243 (0.05)	0.126 (0.04)
Difference from placebo					
LS Mean Difference		0.115	0.166	0.276	0.159
95% CI		0.025, 0.204	0.080, 0.253	0.188, 0.363	0.081, 0.237
p-value		0.012	<0.001	<0.001	<0.001
Day 14					
Trough FEV_1 (n)	52	34	37	34	53
LS Mean (SE)		2.97 (0.05)	2.99 (0.05)	3.04 (0.05)	2.89 (0.04)
LS Mean Change (SE)	-0.020 (0.04)	0.218 (0.05)	0.235 (0.05)	0.294 (0.05)	0.137 (0.04)
Difference from placebo					
LS Mean Difference		0.238	0.255	0.314	0.158
95% CI		0.154, 0.322	0.174, 0.337	0.232, 0.396	0.085, 0.231
p-value		<0.001	<0.001	<0.001	<0.001

BID=twice daily; CI=confidence interval; LS=least squares; SE=standard error.

Pharmacokinetic Endpoints: A summary of selected plasma GW642444 and salmeterol pharmacokinetic parameters is presented below.

Dose	Day	N (n)[5]	AUC(0–t) (pg.h/mL)[1]	Cmax (pg/mL)[1]	Cmax (pg/mL)[1,3]	Cmax (pg/mL)[1,4]	tmax (h)[2]
GW642444H 25 mcg	1	32 (4)	177 (-) (n=1)	40.8 (27.1)	0.212 (765)	31.2 (13.3)	0.38 (0.07-0.52)
	7	34 (3)	173 (-) (n=1)	43.7 (58.5)	0.171 (456)	31.0 (17.3)	0.50 (0.50-1.02)
	14	33 (4)	87.2 (148) (n=2)	60.3 (54.6)	0.217 (956)	32.6 (28.5)	0.19 (0.08-0.25)
GW642444H 100 mcg	1	36 (27)	72.5 (54.4) (n=20)	70.3 (53.9)	13.7 (6930)	56.8 (62.5)	0.30 (0.08-1.03)
	7	36 (25)	137 (55.0) (n=14)	65.0 (37.7)	8.98 (10200)	51.3 (49.8)	0.55 (0.50-1.02)
	14	36 (30)	91.8 (92.8) (n=27)	91.3 (58.9)	29.3 (3130)	75.9 (72.7)	0.25 (0.07-1.03)
GW642444H 400 mcg	1	34 (34)	470 (100) (n=33)	264 (77.8)	264 (77.8)	264 (77.8)	0.49 (0.07-0.57)
	7	32 (32)	574 (70.7) (n=32)	266 (59.8)	266 (59.8)	266 (59.8)	0.53 (0.50-1.07)
	14	33 (33)	740 (61.8) (n=31)	347 (77.1)	347 (77.1)	347 (77.1)	0.28 (0.07-1.00)
Salmeterol 50 mcg	1	53 (30)	44.0 (60.2) (n=16)	39.2 (39.2)	NA	NA	0.51 (0.07-2.02)
	7	53 (34)	109 (43.4) (n=23)	38.9 (31.7)	NA	NA	0.75 (0.47-4.03)
	14	53 (43)	71.7 (87.5) (n=32)	46.8 (42.3)	NA	NA	0.13 (0.07-2.00)

NA=not applicable

1. Geometric mean (CV%)
2. Median (range)
3. Lower limit of quantification (LLQ) imputed with 0.1 pg/mL
4. LLQ imputed with 30 pg/mL
5. N represents the number of subjects who had pharmacokinetic samples analysed, n represents the number of subjects who had ≥1 concentration above LLQ

Pharmacokinetic Parameter	Treatment	Ratio of Geometric Least Squares Means (90% Confidence Interval)	
		Day 7: Day 1	Day 14: Day 1
AUC(0–t)	GW642444H 400 mcg	1.24 (1.08, 1.42)	1.51 (1.31, 1.73)
Cmax	GW642444H 100 mcg	ND	1.35 (1.15, 1.58)
	GW642444H 400 mcg	0.99 (0.86, 1.14)	1.33 (1.15, 1.53)

ND=not evaluated as GW642444H was not detected in at least 75% of subjects at this dose.

Pharmacodynamic Endpoints:

Weighted mean change from baseline (0–4 h) and treatment differences in blood glucose (mmol/L) are presented below.

	Placebo N=52	25 mcg 444H N=34	100 mcg 444H N=37	400 mcg 444H N=34	50 mcg BID Salm N=53
Day 1					
0–4 h (n)	50	34	36	33	53
LS Mean Change (SE)	-0.04 (0.06)	-0.01 (0.06)	0.02 (0.06)	0.30 (0.06)	0.17 (0.06)
Difference from Placebo					
LS Mean Difference		0.03	0.06	0.34	0.21
95% CI		-0.07, 0.13	-0.04, 0.16	0.23, 0.44	0.12, 0.29
p-value		0.568	0.209	<0.001	<0.001
Day 7					
0–4 h (n)	49	34	36	34	52
LS Mean Change (SE)	-0.05 (0.06)	-0.04 (0.07)	-0.02 (0.07)	0.10 (0.07)	0.09 (0.06)
Difference from Placebo					
LS Mean Difference		0.01	0.03	0.15	0.14
95% CI		-0.11, 0.13	-0.08, 0.14	0.04, 0.27	0.04, 0.24
p-value		0.861	0.612	0.010	0.006
Day 14					
0–4 h (n)	49	32	35	33	52
LS Mean Change (SE)	0.02 (0.05)	-0.01 (0.06)	0.10 (0.06)	0.23 (0.06)	0.17 (0.05)
Difference from Placebo					
LS Mean Difference		-0.03	0.08	0.21	0.15
95% CI		-0.12, 0.07	-0.02, 0.17	0.12, 0.31	0.06, 0.23
p-value		0.578	0.105	<0.001	<0.001
BID=twice daily; CI=confidence interval; LS=least squares; SE=standard error.					
Maximum increase from baseline (0–4 h) and treatment differences in blood glucose (mmol/L) are presented below.					
	Placebo **N=52**	**25 mcg** **444H** **N=34**	**100 mcg** **444H** **N=37**	**400 mcg** **444H** **N=34**	**50 mcg BID** **Salm** **N=53**
Day 1					
0–4 h (n)	51	34	37	34	53
LS Mean Change (SE)	0.25 (0.07)	0.29 (0.08)	0.35 (0.08)	0.72 (0.08)	0.49 (0.07)
Difference from Placebo					
LS Mean Difference		0.03	0.09	0.47	0.24
95% CI		-0.11, 0.18	-0.05, 0.23	0.33, 0.61	0.11, 0.36
p-value		0.650	0.187	<0.001	<0.001
Day 7					
0–4 h (n)	50	34	37	34	53
LS Mean Change (SE)	0.26 (0.07)	0.29 (0.08)	0.26 (0.08)	0.47 (0.08)	0.39 (0.07)
Difference from Placebo					
LS Mean Difference		0.03	0.00	0.20	0.12
95% CI		-0.12, 0.18	-0.14, 0.14	0.06, 0.35	-0.01, 0.25
p-value		0.682	0.978	0.007	0.060
Day 14					
0–4 h (n)	49	33	36	34	52
LS Mean Change (SE)	0.30 (0.07)	0.19 (0.08)	0.35 (0.07)	0.60 (0.08)	0.49 (0.07)
Difference from Placebo					
LS Mean Difference		-0.11	0.05	0.30	0.19
95% CI		-0.25, 0.03	-0.08, 0.18	0.17, 0.44	0.07, 0.31
p-value		0.109	0.472	<0.001	0.002
BID=twice daily; CI=confidence interval; LS=least squares; SE=standard error.					
Weighted mean change from baseline (0–4 h) and treatment differences in blood potassium (mmol/L) are presented below.					

	Placebo N=52	25 mcg 444H N=34	100 mcg 444H N=37	400 mcg 444H N=34	50 mcg BID Salm N=53
Day 1					
0–4 h (n)	50	34	37	34	53
LS Mean Change (SE)	0.10 (0.03)	0.03 (0.04)	0.05 (0.04)	-0.10 (0.04)	0.04 (0.03)
Difference from Placebo					
LS Mean Difference		-0.07	-0.05	-0.20	-0.06
95% CI		-0.14, 0.01	-0.12, 0.02	-0.28, -0.13	-0.13, 0.00
p-value		0.070	0.195	<0.001	0.049
Day 7					
0–4 h (n)	49	34	36	34	52
LS Mean Change (SE)	0.08 (0.05)	0.04 (0.05)	0.04 (0.05)	0.03 (0.05)	0.03 (0.05)
Difference from Placebo					
LS Mean Difference		-0.04	-0.04	-0.05	-0.05
95% CI		-0.15, 0.06	-0.15, 0.06	-0.15, 0.06	-0.14, 0.04
p-value		0.423	0.390	0.366	0.272
Day 14					
0–4 h (n)	49	33	35	33	51
LS Mean Change (SE)	0.13 (0.03)	0.09 (0.04)	0.09 (0.04)	-0.04 (0.04)	0.03 (0.03)
Difference from Placebo					
LS Mean Difference		-0.04	-0.03	-0.17	-0.09
95% CI		-0.11, 0.04	-0.11, 0.04	-0.25, -0.09	-0.16, -0.03
p-value		0.342	0.368	<0.001	0.005
BID=twice daily; CI=confidence interval; LS=least squares; SE=standard error.					
Maximum decrease from baseline (0–4 h) and treatment differences in blood potassium (mmol/L) are presented below.					
	Placebo **N=52**	**25mcg** **444H** **N=34**	**100mcg** **444H** **N=37**	**400mcg** **444H** **N=34**	**50mcg BID Salm** **N=53**
Day 1					
0-4 h (n)	51	34	37	34	53
LS Mean Change (SE)	-0.10 (0.03)	-0.15 (0.04)	-0.16 (0.04)	-0.27 (0.04)	-0.16 (0.03)
Difference from Placebo					
LS Mean Difference		-0.05	-0.06	-0.17	-0.06
95% CI		-0.13 , 0.03	-0.14, 0.02	-0.25, -0.09	-0.13, 0.01
p-value		0.210	0.115	<0.001	0.094
Day 7					
0–4 h (n)	50	34	37	34	53
LS Mean Change (SE)	-0.19 (0.04)	-0.27 (0.05)	-0.25 (0.05)	-0.22 (0.05)	-0.23 (0.04)
Difference from Placebo					
LS Mean Difference		-0.08	-0.06	-0.03	-0.04
95% CI		-0.17, 0.02	-0.15, 0.03	-0.13, 0.06	-0.12, 0.04
p-value		0.110	0.179	0.465	0.363
Day 14					
0-4 h (n)	49	33	36	34	52
LS Mean Change (SE)	-0.06 (0.03)	-0.14 (0.04)	-0.11 (0.04)	-0.23 (0.04)	-0.11 (0.03)
Difference from Placebo					
LS Mean Difference		-0.07	-0.05	-0.17	-0.05
95% CI		-0.15, 0.00	-0.12, 0.03	-0.24, -0.09	-0.11, 0.02
p-value		0.055	0.211	<0.001	0.151
BID=twice daily; CI=confidence interval; LS=least squares; SE=standard error.					

Safety results: Adverse event (AE) and serious AE (SAE) data were collected and recorded from the start of study treatment until the follow-up contact. A summary of AEs reported by more than one subject in any group is presented below.

Adverse Event, n (%)	Placebo N=52	GW642444H 25 mcg N=34	GW642444H 100 mcg N=37	GW642444H 400 mcg N=34	Salmeterol 50 mcg BID N=52
n (%) of subjects with any AE	29 (56)	16 (47)	14 (38)	18 (53)	28 (54)
Headache	10 (19)	5 (15)	4 (11)	9 (26)	11 (21)
Nasopharyngitis	6 (12)	6 (18)	2 (5)	3 (9)	8 (15)
Hyperglycemia	2 (4)	0	0	3 (9)	2 (4)
Cough	0	0	1 (3)	1 (3)	4 (8)
Pharyngolaryngeal pain	1 (2)	1 (3)	0	1 (3)	3 (6)
Nausea	0	1 (3)	1 (3)	1 (3)	1 (2)
Back pain	0	1 (3)	1 (3)	1 (3)	0
Blood creatine phosphokinase increased	1 (2)	0	0	0	2 (4)
Chest discomfort	3 (6)	0	0	0	0
Dizziness	1 (2)	0	0	1 (3)	1 (2)
Hyperkalemia	1 (2)	0	1 (3)	0	1 (2)
Hypertension	1 (2)	0	0	0	2 (4)
Productive cough	1 (2)	0	0	1 (3)	1 (2)
Abdominal pain upper	1 (2)	0	0	1 (3)	0
Asthenia	0	1 (3)	0	1 (3)	0
Bradycardia	2 (4)	0	0	0	0
Conjunctivitis	0	1 (3)	1 (3)	0	0
Cystitis	1 (2)	0	0	0	1 (2)
Diarrhea	1 (2)	0	0	0	1 (2)
Hyperhidrosis	0	0	1 (3)	0	1 (2)
Insomnia	0	1 (3)	1 (3)	0	0
Migraine	0	0	0	1 (3)	1 (2)
Muscle spasm	0	0	1 (3)	1 (3)	0
Nasal congestion	0	0	0	1 (3)	1 (2)
Pruritus	2 (4)	0	0	0	0

BID=twice daily.

Three subjects experienced AEs that led to withdrawal: an AE of bradycardia after placebo; an AE of common cold after GW642444H 25 mcg; and an AE of second degree heart block type 1 after salmeterol. The bradycardia and heart block were considered by the Investigator to be related to study medication.

Serious Adverse Events, n (%) [n considered by the Investigator to be related, possibly related or probably related to study medication]: 0.