Synopsis

Identifier: HM2008/00600/00 **Study Number:** DAN106587

Title:

A placebo controlled, single blind, randomised study investigating the safety, tolerability and pharmacokinetics of escalating single and escalating repeated oral doses (up to 28 days) of GSK598809 in healthy male and female volunteers.

Investigator:

[redacted] MA MD FRCP FFPM.

Study centre:

[redacted] United Kingdom.

Publication(s):

None at the time of this report.

Study period:

Initiation Date: 01 March 2007

Completion Date: 22 August 2008

Phase of development:

Phase I.

Objectives:

Primary objectives:

- To assess the safety and tolerability of single and repeated oral doses of GSK598809 in healthy male and female volunteers.
- To assess the pharmacokinetics of GSK598809 after single and repeated oral doses in healthy male and female volunteers.
- To characterise the effect of repeat doses of GSK598809 on the pharmacokinetics of oral doses of cytochrome P450 1A2 (CYP1A2) enzyme substrate (caffeine) in healthy male volunteers.

Secondary objectives:

- To assess the pharmacodynamics of single and repeated doses of GSK598809, as measured by its effect on the following: tests of cognition/impulsivity; mood; extrapyramidal movements; serum prolactin, growth hormone (GH) and thyroid stimulating hormone (TSH), total and free testosterone, luteinising hormone (LH) and follicle stimulating hormone (FSH) if possible.
- To investigate, if any, the relationship between plasma concentrations of GSK598809 and pharmacodynamic variables.
- To characterise exposure to GSK685249 after single and repeat GSK598809 administration.

Methodology:

The study protocol comprised four parts, as detailed below. All of the parts were single-blind, randomised and placebo-controlled. Study administration information is detailed in Attachment 1, study schematic diagrams for each part can be found in Attachment 2, and time and events tables for each part in Attachment 3.

Part 1: ascending single and repeat dose in males (Cohorts 1 to 4): Subjects in each cohort were randomised to receive GSK598809 or placebo in a 3:1 ratio (parallel-group study). Subjects received a single dose of GSK598809 or placebo, followed by a washout period of 1 week. After the washout, subjects received repeat dose GSK598809 or placebo once daily for 28 days (Days 8–35, inclusive). GSK598809 doses were as follows: 10 mg in Cohort 1; 25 mg in Cohorts 2 and 3; 40 mg in Cohort 4.

Part 2: ascending single dose in males (Cohort 5): Subjects were randomised to receive one of the following sequences: ADEF, DAEF, DEAF, or DEFA in a 1:1:1:1 ratio, where A = Placebo, D = GSK598809 75 mg, E = GSK598809 130 mg, F = GSK598809 175 mg. In this crossover study, each subject took part in four dosing periods, with a washout of at least 6 days between doses.

Part 3: caffeine interaction in males (Cohort 6): Subjects were randomised to receive GSK598809 100 mg or placebo in a 3:1 ratio (parallel-group study). Each subject took a single dose of caffeine on Day -1 and single dose GSK598809/placebo on Day 1. Then, after a 1-week washout, subjects received 28 daily doses of GSK598809/ placebo (Days 8–35, inclusive). On Day 35, caffeine and GSK598809 were co-administered.

Part 4: single and repeat dose in females (Cohort 7): Subjects were randomised to receive GSK598809 100 mg or placebo in a 3:1 ratio (parallel-group study). Each subject received single dose GSK598809/placebo on Day 1, and after a 1-week washout, 28 daily doses of GSK598809/ placebo on Days 8–35, inclusive.

All study parts: All subjects were screened within 28 days before the study. Subjects were institutionalised from the day prior to dosing until completion of each session. On Days -1, 1, 14, 21, 34 (Day 34 for Cohort 6 only) and Day 35, subjects fasted from midnight until 4 h after dosing and were required to remain in bed for 6 h after dosing.

Subjects were not allowed any water for 1 h before and after dosing. On Days 1, 14, 21, 34 (Day 34 for Cohort 6 only) and Day 35, subjects received the same standard lunch.

For defined periods, restrictions were placed on consumption of grapefruit, poppy seeds, caffeine, alcohol, and xanthine. Restrictions were also placed on tobacco use, physical activity, activities with the potential to change the circadian rhythm, and sun bed use. Stopping criteria for the study were based on tolerability, safety (adverse events [AEs], vital signs, electrocardiogram (ECG), liver chemistry, prolactin) and pharmacokinetics.

A follow-up visit took place 7–14 days following the final dose of study medication.

Number of subjects:

In Parts 1, 3 and 4, 16 subjects in each cohort were randomised to receive GSK598809 or placebo and in Part 2 eight subjects were randomised. In total 104 subjects were dosed, as planned (88 males and 16 females).

Subject disposition and demographics:

Subject disposition and demographic details are presented in Table 1.

Table 1 Subject Disposition and Demographics

Number of Subjects	Single and repeat dose cohorts		Single dose Cohort 5 [3]
	Males [1]	Females [2]	
Planned, N	80	16	8
Randomised, N	80	16	8
Safety Population, n (%)	80 (100)	16 (100)	8 (100)
PK Concentration Population, n (%)	59 (74)	12 (75)	8 (100)
Completed, n (%)	74 (93)	15 (94)	8 (100)
Total Withdrawn (any reason), n (%)	6 (8)	1 (6)	0
Withdrawn due to Serious Adverse Event, n (%)	1 (1)	0	0
Withdrawn due to Adverse Events, n (%)	3 (4) [4]	0	0
Subject decided to withdraw, n (%)	3 (4)	1 (6)	0
Demographics			
Age in Years, Mean (Range)	28.2 (18–48)	27.6 (21–39)	30.8 (24–47)
Sex, n (%)			
Female:	0	16 (100)	0
Male:	80 (100)	0	8 (100)

Source Data: Table 9.1 to Table 9.9

1. Placebo/GSK598809 10 mg, 25 mg, 40 mg, 100 mg single dose and repeat dose for 28 days; 20 subjects on placebo and 60 subjects on GSK598809.
2. Placebo/GSK598809 100 mg single dose and repeat dose for 28 days; four subjects on placebo and 12 on GSK598809.
3. Placebo/GSK598809 75 mg, 130 mg, 175 mg single dose; eight subjects on placebo and GSK598809.
4. One of these AEs was classed as an SAE and is also included in the row above.
5. Rounded from source data.

Continued

Table 1 Subject Disposition and Demographics (continued)

Demographics (continued)	Single and repeat dose cohorts		Single dose Cohort 5 [3]
	Males [1]	Females [2]	
Body Mass Index in kg/m^2, Mean (Range) [5]	24.27 (18.7–29.8)	23.15 (19.7–26.6)	23.64 (19.6–27.6)
Height in cm, Mean (Range)	179.0 (160–197)	165.1 (154–176)	179.0 (171–185)
Weight in kg, Mean (Range)	77.75 (58.1–99.2)	63.07 (50.0–73.2)	75.93 (58.5–94.5)
Ethnicity, n (%)			
Hispanic or Latino:	7 (9)	4 (25)	1 (13)
Not Hispanic or Latino:	73 (91)	12 (75)	7 (88)
Race, n (%)			
White – White/Caucasian/European Heritage	76 (95)	14 (88)	7 (88)
African American/African Heritage	2 (3)	1 (6)	1 (13)
American Indian or Alaskan Native	1 (1)	0	0
Asian – South East Asian Heritage	1 (1)	0	0
Mixed Race	0	1 (6)	0

Source Data: Table 9.1 to Table 9.9

1. Placebo/GSK598809 10 mg, 25 mg, 40 mg, 100 mg single dose and repeat dose for 28 days; 20 subjects on placebo and 60 subjects on GSK598809.
2. Placebo/GSK598809 100 mg single dose and repeat dose for 28 days; four subjects on placebo and 12 on GSK598809.
3. Placebo/GSK598809 75 mg, 130 mg, 175 mg single dose; eight subjects on placebo and GSK598809.

There was one protocol violation. [redacted]
The violation was not considered to have a notable impact on the pharmacodynamic outcomes and so the subject was included in all pharmacodynamic analyses.

Diagnosis and main criteria for inclusion:

Healthy adult male or female subjects aged 18–50 years, inclusive, with body weight ≥50 kg and body mass index within the range 18.5–29.9 kg/m^2 (inclusive) were recruited.

Treatment administration:

Subjects were assigned to study treatment in accordance with the randomisation schedule prepared before the start of the study (see Methodology Section above). Investigational products were supplied as follows:

- GSK598809 5 mg oral capsules (bulk/packed batch numbers: 061116749/061118454; 071137375/ 071138388).
- GSK598809 25 mg oral capsules (bulk/packed batch numbers: 061116809/061118455; 071137376/071138389; 071137376/071141637; 071149318/081150634).

- Matching placebo oral capsules (bulk/packed batch numbers: 061116735/061118457; 061130161/071140776; 061130161/081150636).

Criteria for evaluation:

Primary safety and tolerability endpoints were as follows: AEs, laboratory values, blood pressure, heart rate, ECG variables, temperature, and respiratory rate.

Primary pharmacokinetic endpoints for single dose GSK598809 were: GSK598809 area under the plasma concentration-time curve to last measurable concentration (AUC(0-t)), AUC extrapolated to infinity (AUC(0-∞)), AUC from time zero to 24 h (AUC(0-24)), maximum observed plasma concentration (Cmax), time to Cmax (tmax), apparent elimination half-life (t½), and percentage of AUC extrapolated (AUC%ex). Primary endpoints for repeat dose GSK598809 were AUC over the dosing interval (AUC(0-τ)), AUC(0-t), Cmax, tmax, pre-dose (trough) plasma concentration at steady state (Cτ), t½, accumulation ratio (Ro) and time invariance of pharmacokinetics. Primary pharmacokinetic endpoints also included plasma AUC(0-∞) of caffeine and paraxanthine/caffeine plasma ratio at 8 h after dosing with and without GSK598809.

Secondary endpoints were as follows: for pharmacodynamics, Barnes akathisia rating scale (BARS), abnormal involuntary movement scale (AIMS), Simpson Angus scale (SAS), serum prolactin, GH and TSH, total and free testosterone, LH and FSH concentrations; profile of mood state (POMS) questionnaire, choice reaction time (CRT) test, motor impulsivity task (stop-signal task, SST), digit symbol substitution test (DSST), verbal learning memory test (VLMT); for pharmacokinetics, GSK685249 parameters AUC(0-t), AUC(0-τ), AUC(0-∞) (on Day 35 only), Cmax, tmax, and t½.

Plasma samples were analysed for GSK598809 and GSK685249 using a validated analytical method based on protein precipitation, followed by high performance liquid chromatography-tandem mass spectrometry (HPLC/MS/MS). The lower limit of quantification (LLQ) for GSK598809 and GSK685249 was 0.5 ng/mL, using a 50 μL aliquot of plasma with a higher limit of quantification of 500 ng/mL for both GSK598809 and GSK685249, respectively. The computer systems that were used to acquire and quantify data included Analyst Version 1.4.1, 1.4.2 and SMS2000 version 2.0 and 2.1.

Statistical methods:

Sample size: Sample size was primarily based on feasibility. However, for repeat dose sessions, according to preliminary results of the GSK598809 first time in human (FTIH) study, a within-subject coefficient of variation (CV) of about 11.7% was estimated from AUC exposure data. It was estimated that, with such variability, and 12 subjects in each active treatment group, the lower and upper bounds of the 90% confidence interval of the main pharmacokinetic parameters (Ro and time invariance) would have been obtained by dividing/multiplying the point estimates by a factor of 1.09. Hence, if the estimate of ratio was equal to 1, the 90% confidence interval would have been 0.92 to 1.09.

Single dose: It was estimated that with eight subjects treated over the planned dose range of GSK598809 75, 120 and 175 mg, the semi-width of the 90% confidence interval of the slope in the dose proportionality assessment would have been 0.12.

Interim analyses: There were no formal interim analyses. Safety and pharmacokinetic data were reviewed by the study team in study Sections 1 and 2 to assist in dose escalation decisions. All analyses from male data (Sections 1 to 3) were reported separately, following a partial database freeze. This was presented under 'interim' reporting effort in the Harmonisation of Reporting and Analysis Program (HARP).

Final analyses: Final analyses were performed separately for males and females. Summary statistics were produced for plasma concentrations and derived pharmacokinetic parameters of GSK598809, GSK685249 and caffeine. Mean and median plasma concentration-time data were plotted for GSK598809 and GSK685249.

Repeat dose: Accumulation ratio of GSK598809 was estimated on Day 14 and Day 35 using a mixed effects model after $\log_e$ transformation of AUC(0-24). GSK598809 time invariance was estimated using a mixed effects model after $\log_e$ transformation of AUC (AUC(0-∞) on Day 1 and AUC(0-τ) after repeated doses). GSK598809 steady-state was assessed using Cτ levels, after $\log_e$ transformation of the data. A mixed effects model was fitted for each treatment regimen separately.

The effect of GSK598809 on caffeine pharmacokinetics was assessed. A mixed effects analysis of variance model was fitted to $\log_e$-transformed pharmacokinetic parameters.

Statistical analysis of AUC(0-24) and Cmax was carried out for GSK598809 to assess dose proportionality using the power model. Each parameter was $\log_e$-transformed prior to analysis of variance.

Statistical analyses of AUC(0-∞) and Cmax on Day 1 and AUC(0-24) and Cmax on Day 35 (Day 34 for Section 3) were carried out for GSK598809 100 mg to assess the effect of gender. A mixed effects model was fitted with gender as a fixed effect.

Statistical analysis of reaction times for cognitive tests (VLMT, DSST, SST and CRT) was performed using a mixed effects model. Least squares (LS) means were produced for treatment by time and plotted with 95% confidence intervals.

Single dose: Statistical analysis of AUC(0-24) and Cmax was carried out for GSK598809 to assess dose proportionality using the power model. Each parameter was $\log_e$-transformed prior to analysis of variance.

Statistical analysis of reaction times for the cognitive tests (VLMT, SST, CRT,VLMT and DSST) was performed using a mixed effects model. Plots of mean (± standard deviation) values were produced for hormones (prolactin, GH, TSH), AIMS, SAS, and POMS total score. Data for BARS were listed. Safety data were listed and summarised.

Summary:

Safety:

All adverse events: The proportion of subjects experiencing any AE was similar for single and repeat dose GSK598809 regimens and placebo. None of the AEs appeared to notably increase in frequency with increasing GSK598809 dose. All AEs in the study

were of mild or moderate intensity except for an SAE of appendicitis, which was categorised as severe in intensity (details are presented below in the SAE Section).

Headache was the most frequently reported AE irrespective of causality in the single and repeat dose cohorts (Cohorts 1 to 4, Cohort 6 and Cohort 7). There was no apparent difference in the incidence of headache between those subjects who received placebo versus those who received GSK598809, nor between males and females. Five females reported somnolence at the GSK598809 100 mg dose and none of the males reported somnolence after GSK598809 dosing (Table 2).

Table 2 Summary of Adverse Events Reported in Two or More Subjects on any Regimen – Single and Repeat Dose Cohorts

Most Frequent Adverse Events	Placebo Males	GSK598809 Males				Placebo Females	GSK598809 Females
		10 mg	25 mg	40 mg	100 mg		100 mg
	N = 20	N = 12	N = 24	N = 12	N = 12	N = 4	N = 12
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	15 (75)	11 (92)	15 (63)	11 (92)	7 (58)	3 (75)	11 (92)
Any AE related to investigational product	12 (60)	5 (42)	11 (46)	5 (42)	5 (42)	3 (75)	10 (83)
Most Frequent AEs (≥2 subjects on any regimen)							
Headache	8 (40)	5 (42)	11 (46)	4 (33)	5 (42)	3 (75)	7 (58)
Dizziness	3 (15)	2 (17)	1 (4)	3 (25)	2 (17)	0	5 (42)
Cough	2 (10)	1 (8)	1 (4)	0	0	0	0
Abnormal dreams	1 (5)	0	3 (13)	0	0	0	1 (8)
Myalgia	1 (5)	0	0	1 (8)	1 (8)	0	2 (17)
Pharyngolaryngeal pain	1 (5)	3 (25)	1 (4)	2 (17)	0	0	0
Rhinitis	1 (5)	2 (17)	2 (8)	1 (8)	1 (8)	0	0
Somnolence	1 (5)	0	0	0	0	0	5 (42)
Affect lability	0	0	0	0	0	0	2 (17)
Arthralgia	0	2 (17)	0	0	0	0	0
Constipation	0	0	0	2 (17)	0	1 (25)	0
Dysmenorrhoea	0	0	0	0	0	2 (50)	4 (33)
Dyspepsia	0	1 (8)	2 (8)	0	0	1 (25)	0
Herpes virus infection	0	2 (17)	0	0	0	0	0
Nausea	0	1 (8)	0	0	1 (8)	0	2 (17)
Upper respiratory tract infection	0	4 (33)	0	0	0	0	0

Source Data: Table 10.1, Table 10.3, Table 10.4 and Table 10.6
AE = adverse event.

Headache was the only AE that occurred in more than one subject on any single dose regimen in Cohort 5 (Table 3). With the exception of one male subject at one time point who reported a single episode of twitching of his leg during the GSK598809 175 mg dosing period that could not be objectively verified, no abnormalities of movement were noted.

Table 3 Summary of Adverse Events Reported in Two or More Subjects on any Regimen – Single Dose Cohort 5 (Males)

Most Frequent Adverse Events	Placebo	GSK598809		
		75 mg	130 mg	175 mg
	N = 8	N = 8	N = 8	N = 8
	n (%)	n (%)	n (%)	n (%)
Any AE	2 (25)	3 (38)	4 (50)	4 (50)
Any AE related to investigational product	1 (13)	3 (38)	2 (25)	3 (38)
Most Frequent AEs (≥2 subjects on any regimen)				
Headache	2 (25)	1 (13)	2 (25)	1 (13)

Source Data: Table 10.2 and Table 10.5
AE = adverse event.

Serious adverse events:

[redacted] This SAE led to withdrawal from the study. The event was not considered related to study medication by the Investigator and was classed as resolved by the end of the study (Table 10.31). Further details of the SAE are presented below in the Case Narratives Section.

Adverse events leading to withdrawal:

[redacted] This subject showed other out-of-range laboratory values including alanine aminotransferase (ALT) and aspartate aminotransferase (AST). However, ALT, AST and CPK all returned to normal at follow-up. These values were most likely exercise-induced. All bilirubin values during the study were within the normal range. [redacted]

- [redacted] (CPK was not recorded at screening so there are no baseline values).
- [redacted]

- [redacted]

Other safety parameters:

Average clinical chemistry and haematology values over time generally showed similar patterns following all single and repeat dose treatments including placebo, in both male and female subjects (Table 10.19 to Table 10.24). There was one exception, serum prolactin, which increased following both single and repeat dose GSK598809 (see below, Pharmacodynamics Section).

Individual clinical chemistry values of potential clinical importance were reported in 15 subjects (14%), all of whom were male (Table 10.33). These subjects were randomised to placebo (three subjects), GSK598809 10 mg (two), 25 mg (five), 40 mg (two), 75 mg (one; prior to first dose), 100 mg (one), and 175 mg (one). [redacted] None of the other clinical chemistry values were reported as AEs.

Individual haematology values of potential clinical importance were reported in eight subjects (8%), seven male and one female (Table 10.34 and Table 10.35). These subjects were randomised to placebo (four subjects), GSK598809 10 mg (one), 75 mg (one), and 100 mg (two). None of these haematology values were reported as AEs.

No safety concerns were raised on urinalysis dipstick results (Table 10.25 to Table 10.27). In females, several urinalyses were noted to be abnormal for red blood cells and white blood cells above the laboratory normal. In one woman, asymptomatic cystitis was present, which resolved spontaneously within 24 h. In some women, subsequent reminders about procedures for mid-stream urines resulted in normal values. No urine abnormalities were noted in males. There were no urinary casts in either males or females. None of the above abnormalities were considered clinically significant.

No notable changes in average vital signs values (systolic and diastolic blood pressure, heart rate and respiration rate) were observed following any of the GSK598809 treatments or placebo (Table 10.28 to Table 10.30).

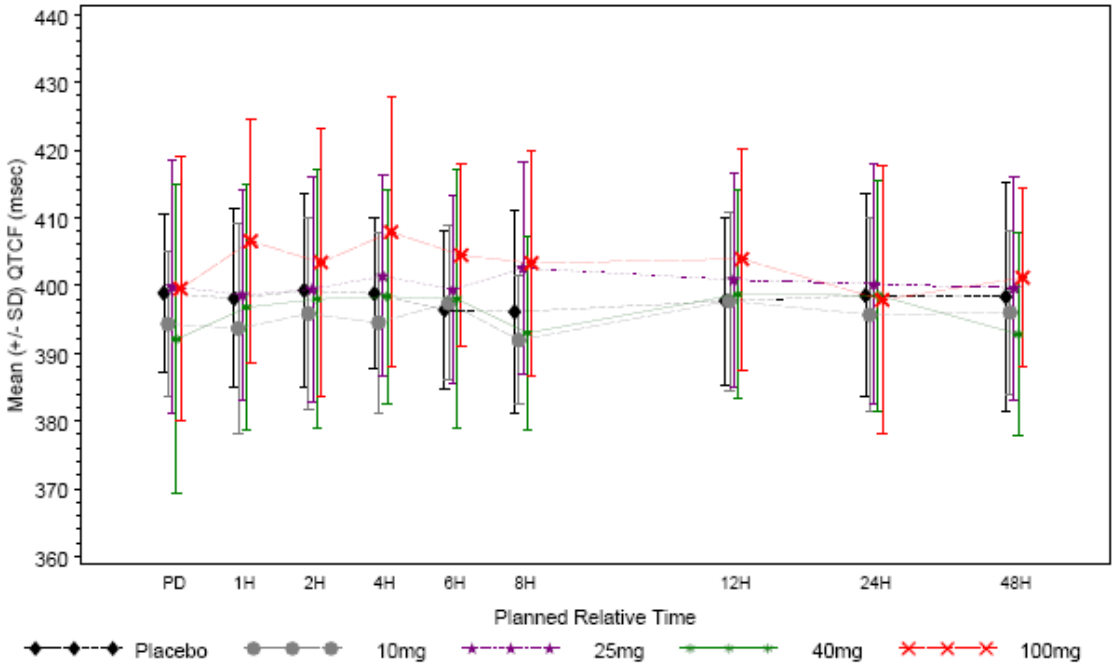
No safety concerns were raised on individual ECG. No subject met stopping criteria, therefore no subject had QTcF >60 msec above baseline or >500 msec. Average ECG interval values (PR, QRS, QTc) are presented by treatment and time point in Table 10.13 to Table 10.18.

Post-hoc exploratory plots of mean (SD) QTcF were produced by treatment and time point for the male single dose cohort (Figure 10.1) and by treatment, time point and

gender for the repeat dose cohorts. Figure 1 and Figure 2 show the mean QTcF (msec) at the indicated time points after 28 days of repeat dosing in males and females. Plots of mean (SD) QTcF by treatment and time point are presented for Days 1, 8 and 14 in the repeat dose cohorts in Figure 10.3 (males) and Figure 10.4 (females).

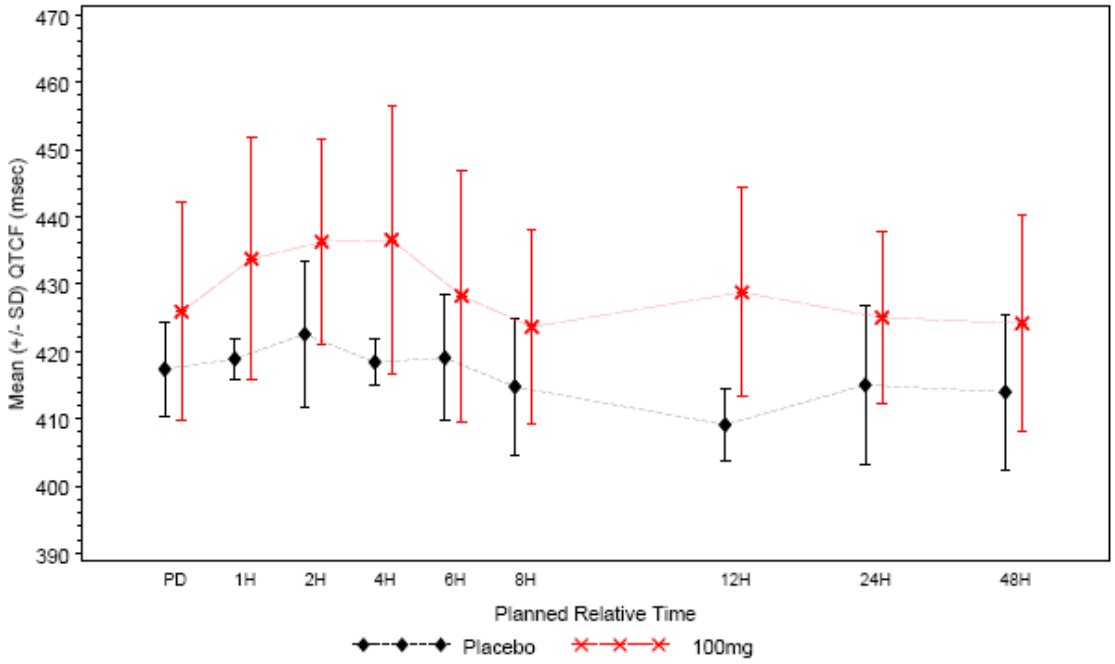
Across all days and time points mean change from baseline in QTcF did not exceed 14 msec for females on GSK598809 100 mg and did not exceed 17 msec for females on placebo (Table 10.18). Mean change from baseline in QTcF did not exceed 13 msec for males on GSK598809 100 mg and did not exceed 12 msec on placebo (Table 10.16). Higher mean changes from baseline were observed on the GSK598809 100 mg regimen compared with the other dose levels in males. In the statistical analysis of maximum change from baseline on Day 35 (Figure 10.2), no difference was found between GSK598809 10 mg, 25 mg and 40 mg compared with the placebo cohort. However, the comparison between 100 mg and placebo suggested an average increase of 7 msec in the maximum change from baseline on Day 35.

Figure 1 Plot of Mean (Standard Deviation) of QTcF by GSK598809 Treatment and Time – Male Repeat Dose Day 35 (Post SAC)



Source: Figure 10.3

Figure 2 Plot of Mean (Standard Deviation) of QTcF by GSK598809 Treatment and Time – Female Repeat Dose Day 35 (Post SAC)



Source: Figure 10.4

Pharmacokinetics:

GSK598809 Pharmacokinetic Parameters

Repeated ascending dose:

In all subjects, whatever the dose, geometric mean GSK598809 Cmax and AUCs on Days 14, 21 and 35 (after 28 days of repeat dosing) were higher than on Day 1, with an average accumulation ratio of 2–3. Overall, Cmax and AUC values showed no marked gender effect. Selected pharmacokinetic parameters for GSK598809 10 mg to 40 mg doses are summarised in Table 4 and for GSK598809 100 mg dose in Table 5.

Table 4 Summary of Selected Plasma GSK598809 Pharmacokinetic Parameters – 10 to 40 mg Doses

Dose	GSK598809 Parameters	N	Day 1	N	Day 14	N	Day 21	N	Day 35
10 mg Male	Cmax (ng/mL)[1]	12	73.8 (23)	11	94.7 (32)	11	95.3 (19)	11	99.0 (25)
	AUC(0-∞) (ng.h/mL)[1]	12	409 (23)	-	-	-	-	-	-
	AUC(0-t) (ng.h/mL)[1]	12	386 (23)	11	603 (27)	11	643 (21)	11	1126 (39)
	AUC(0-24) (ng.h/mL)[1]	12	293 (16)	9	605 (28)	4	604 (14)	11	693 (24)
	tmax (h)[2]	12	1.0 (1.0–2.0)	11	1.0 (1.0–2.0)	11	1.5 (1.0–2.0)	11	1.0 (1.0–2.0)
	t½ (h)[1]	12	18.9 (24)	-	-	-	-	11	21.4 (23)
	Ro[1]	-	-	9	2.06 (21)	4	2.14 (9)	11	2.34 (15)
	Cτ (ng/mL)[1]	-	-	11	12.6 (42)	-	-	11	15.1 (37)
25 mg Male	Cmax (ng/mL)[1]	24	167 (28)	23	228 (27)	23	247 (27)	22	273 (25)
	AUC(0-∞) (ng.h/mL)[1]	24	921 (24)	-	-	-	-	-	-
	AUC(0-t) (ng.h/mL)[1]	24	898 (24)	23	1657 (27)	23	1722 (27)	22	3084 (36)
	AUC(0-24) (ng.h/mL)[1]	24	682 (21)	16	1570 (28)	15	1588 (27)	22	19370 (24)
	tmax (h)[2]	24	1.5 (0.5–2.8)	23	1.5 (0.5–4.0)	23	1.5 (0.5–3.0)	22	1.5 (1.0–4.0)
	t½ (h)[1]	24	15.0 (20)	-	-	-	-	22	18.8 (19)
	Ro[1]	-	-	16	2.37 (15)	15	2.47 (18)	22	2.81 (17)
	Cτ (ng/mL)[1]	-	-	23	37.0 (44)	-	-	22	45.4 (45)
40 mg Male	Cmax (ng/mL)[1]	12	287 (26)	12	379 (23)	12	414 (22)	11	439 (14)
	AUC(0-∞) (ng.h/mL)[1]	12	1712 (19)	-	-	-	-	-	-
	AUC(0-t) (ng.h/mL)[1]	12	1689 (19)	12	2901 (18)	12	3149 (18)	11	5688 (29)
	AUC(0-24) (ng.h/mL)[1]	12	1325 (16)	7	3031 (15)	7	3027 (16)	11	3544 (20)
	tmax (h)[2]	12	1.5 (1.0–3.0)	12	2.0 (1.0–3.0)	12	1.5 (1.0–2.0)	11	1.0 (1.0–2.0)
	t½ (h)[1]	12	13.8 (23)	-	-	-	-	11	19.0 (27)
	Ro[1]	-	-	7	2.19 (12)	7	2.24 (15)	11	2.64 (19)
	Cτ (ng/mL)[1]	-	-	12	65.4 (35)	-	-	11	77.2 (29)

Source Data: Table 11.4 and Table 11.7

1. Geometric mean (CV%).
2. Median (range).

Cmax = maximal observed plasma concentration; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC(0-t) = AUC to last measurable concentration; AUC(0-24) = AUC from zero to 24 h post dose; tmax = time to maximal observed plasma concentration; t½ = apparent elimination half-life; Ro = accumulation ratio; Cτ = pre-dose (trough) plasma concentration at steady state.

Table 5 Summary of Selected Plasma GSK598809 Pharmacokinetic Parameters – 100 mg Dose

Dose	GSK598809 Parameters	N	Day 1	N	Day 14	N	Day 21	N	Day 34
100 mg Male	Cmax (ng/mL)[1]	11	866 (21)	11	1046 (20)	11	1011 (30)	11	1056 (23)
	AUC(0-∞) (ng.h/mL)[1]	11	5506 (24)	-	-	-	-	-	-
	AUC(0-t) (ng.h/mL)[1]	11	5442 (24)	11	8475 (22)	11	8389 (18)	11	19188 (26)
	AUC(0-24) (ng.h/mL)[1]	11	4039 (22)	5	8975 (20)	6	7726 (17)	11	8865 (22)
	tmax (h)[2]	11	1.0 (1.0–2.0)	11	1.5 (0.5–2.0)	11	1.5 (1.0–3.0)	11	1.5 (1.0–3.0)
	t½ (h)[1]	11	14.8 (18)	-	-	-	-	11	18.4 (32)
	Ro[1]	-	-	5	1.93 (8)	6	2.06 (21)	11	2.20 (13)
	Cτ (ng/mL)[1]	-	-	11	189 (33)	-	-	11	230 (33)
100 mg Female	Cmax (ng/mL)[1]	12	856 (21)	12	1209 (33)	12	1163 (24)	11	1229 (31)
	AUC(0-∞) (ng.h/mL)[1]	12	6445 (20)	-	-	-	-	-	-
	AUC(0-t) (ng.h/mL)[1]	12	6187 (18)	12	8778 (22)	12	8525 (25)	11	16715 (33)
	AUC(0-24) (ng.h/mL)[1]	12	4068 (15)	6	7808 (14)	7	8032 (22)	11	9005 (20)
	tmax (h)[2]	12	1.5 (1.0–3.0)	12	1.1 (0.5–2.0)	12	1.5 (1.0–2.0)	11	1.5 (1.0–4.0)
	t½ (h)[1]	12	21.3 (21)	-	-	-	-	11	27.0 (27)
	Ro[1]	-	-	6	1.98 (14)	7	1.93 (28)	11	2.19 (20)
	Cτ (ng/mL)[1]	-	-	12	214 (30)	-	-	11	247 (37)

Source Data: Table 11.4, Table 11.6, Table 11.7 and Table 11.9

1. Geometric mean (CV%).
2. Median (range).

Cmax = maximal observed plasma concentration; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC(0-t) = AUC to last measurable concentration; AUC(0-24) = AUC from zero to 24 h post dose; tmax = time to maximal observed plasma concentration; t½ = apparent elimination half-life; Ro = accumulation ratio; Cτ = pre-dose (trough) plasma concentration at steady state.

Single ascending dose:

Following single oral administration of GSK598809 75, 130 and 175 mg, GSK598809 t½ values ranged from approximately 13 to 27 h in individual subjects.

Selected pharmacokinetic parameters for Cohort 5 are summarised in Table 6.

Table 6 Summary of Selected Plasma GSK598809 Pharmacokinetic Parameters – Cohort 5

GSK598809 Parameters	GSK598809 Dose					
	N	75 mg	N	130 mg	N	175 mg
Cmax (ng/mL)[1]	8	584 (23)	8	969 (25)	8	1609 (10)
AUC(0-∞) (ng.h/mL)[1]	8	3734 (11)	7	8135 (15)	8	13638 (14)
AUC(0-t) (ng.h/mL)[1]	8	3624 (12)	8	7243 (22)	8	13215 (11)
AUC(0-24) (ng.h/mL)[1]	8	2766 (10)	8	5427 (18)	8	8910 (6)
tmax (h)[2]	8	1.0 (0.5–1.5)	8	1.0 (1.0–2.0)	8	1.0 (1.0–2.0)
t½ (h)[1]	8	17.2 (26)	7	18.4 (19)	8	18.5 (28)

Source Data: Table 11.5 and Table 11.8

1. Geometric mean (CV%).
2. Median (range).

Cmax = maximal observed plasma concentration; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC(0-t) = AUC to last measurable concentration; AUC(0-24) = AUC from zero to 24 h post dose; tmax = time to maximal observed plasma concentration; t½ = apparent elimination half-life.

GSK685249 Pharmacokinetic Parameters

Repeated ascending dose:

In male and female subjects, whatever the dose, geometric mean GSK685249 Cmax on Days 14, 21 and 35 (after 28 days of repeat dosing) was slightly lower than on Day 1. In contrast, geometric mean AUC on Days 14, 21 and 35 was higher than on Day 1. The average accumulation ratio was 2 (1.1–2.4) in males and 1.5 (1.4–1.6) in females. Overall, GSK685249 Cmax and AUC parameters showed no marked difference between males and females. GSK685249 t½ was roughly estimated and could not be delineated in all subjects; thus, results should be viewed with caution.

Selected GSK685249 pharmacokinetic parameters are summarised in Table 7.

Table 7 Summary of Selected Plasma GSK685249 Pharmacokinetic Parameters – Repeat Dose Cohorts

GSK598809 Dose	GSK685249 Parameters	N	Day 1		Day 35 (34 in 100 mg)
25 mg Male	Cmax (ng/mL)[1]	12	4.53 (32)	10	4.11 (19)
	AUC(0-∞) (ng.h/mL)[1]	9	11.6 (31)	-	-
	AUC(0-t) (ng.h/mL)[1]	12	8.09 (34)	10	38.9 (47)
	AUC(0-24) (ng.h/mL)[1]	9	11.8 (37)	8	28.3 (9)
	tmax (h) [2]	12	1.2 (0.5–2.0)	10	1.0 (1.0–4.0)
	t½ (h)[1]	9	2.39 (58)	5	56.10 (63)
	Ro[1]	-	-	8	2.42 (31)
	Cτ (ng/mL)[1]	-	-	10	0.722 (22)
40 mg Male	Cmax (ng/mL)[1]	12	9.72 (28)	11	5.79 (19)
	AUC(0-∞) (ng.h/mL)[1]	11	32.9 (30)	-	-
	AUC(0-t) (ng.h/mL)[1]	12	26.2 (29)	11	83.5 (28)
	AUC(0-24) (ng.h/mL)[1]	12	30.2 (21)	11	43.0 (17)
	tmax (h) [2]	12	1.0 (1.0–2.0)	11	1.0 (1.0–2.0)
	t½ (h)[1]	12	7.16 (64)	8	59.10 (90)
	Ro[1]	-	-	11	1.43 (22)
	Cτ (ng/mL)[1]	-	-	10	1.07 (27)
100 mg Male	Cmax (ng/mL)[1]	11	15.5 (15)	11	15.8 (156)
	AUC(0-∞) (ng.h/mL) [1]	11	69.9 (25)	-	-
	AUC(0-t) (ng.h/mL) [1]	11	55.9 (26)	11	247 (22)
	AUC(0-24) (ng.h/mL) [1]	11	52.4 (17)	11	98.8 (39)
	tmax (h) [2]	11	1.0 (0.5–1.5)	11	1.0 (0.0–2.0)
	t½ (h) [1]	11	15.0 (37)	11	58.29 (57)
	Ro[1]	-	-	11	1.89 (35)
	Cτ (ng/mL) [1]	-	-	11	4.17 (303)
100 mg Female	Cmax (ng/mL)[1]	12	17.1 (34)	11	15.5 (31)
	AUC(0-∞) (ng.h/mL) [1]	8	89.5 (33)	-	-
	AUC(0-t) (ng.h/mL)[1]	12	63.2 (38)	11	212 (21)
	AUC(0-24) (ng.h/mL)[1]	12	57.4 (25)	11	96.5 (18)
	tmax (h) [2]	12	1.0 (0.5–2.0)	11	1.0 (1.0–2.0)
	t½ (h)[1]	9	21.8 (41)	10	52.8 (26)
	Ro[1]	-	-	11	1.63 (16)
	Cτ (ng/mL)[1]	-	-	11	2.64 (18)

Source Data: Table 11.13, Table 11.15, Table 11.16 and Table 11.18

1. Geometric mean (CV%).
2. Median (range).

Cmax = maximal observed plasma concentration; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC(0-t) = AUC to last measurable concentration; AUC(0-24) = AUC from zero to 24 h post dose; tmax = time to maximal observed plasma concentration; t½ = apparent elimination half-life; Ro = accumulation ratio; Cτ = pre-dose (trough) plasma concentration at steady state.

Single ascending dose:

Following single oral administration of GSK598809 75, 130 and 175 mg, GSK685249 t½ could not be delineated in all subjects. Consequently, these results should be viewed with caution. Selected GSK685249 pharmacokinetic parameters are summarised in Table 8.

Table 8 Summary of Selected Plasma GSK685249 Pharmacokinetic Parameters – Cohort 5

GSK685249 Parameters	GSK598809 Dose					
	N	75 mg	N	130 mg	N	175 mg
Cmax (ng/mL)[1]	8	16.2 (24)	8	15.8 (35)	8	22.3 (24)
AUC(0-∞) (ng.h/mL)[1]	6	62.8 (31)	3	111.4 (18)	7	175.6 (15)
AUC(0-t) (ng.h/mL)[1]	8	47.9 (28)	8	77.7 (28)	8	142.0 (19)
AUC(0-24) (ng.h/mL)[1]	7	52.8 (16)	8	59.4 (25)	8	87.6 (18)
tmax (h)[2]	8	1.0 (0.5–1.5)	8	1.0 (0.5–1.5)	8	1.0 (0.5–2.0)
t½ (h)[1]	6	9.1 (69)	3	26.1 (22)	8	35.3 (58)

Source Data: Table 11.14 and Table 11.17

1. Geometric mean (CV%).
2. Median (range).

Cmax = maximal observed plasma concentration; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC(0-t) = AUC to last measurable concentration; AUC(0-24) = AUC from zero to 24 h post dose; tmax = time to maximal observed plasma concentration; t½ = apparent elimination half-life.

Caffeine pharmacokinetic parameters

Plasma caffeine tmax, Cmax and AUCs were similar on Day -1 (caffeine alone) and on Day 35 (28 days of GSK598809 dosing + single dose caffeine on the final day) (Table 9).

Table 9 Summary of Selected Plasma Caffeine Pharmacokinetic Parameters

Caffeine Parameters	N	Day -1	N	Day 35
Cmax (ng/mL)[1]	11	1960 (18)	11	1687 (18)
AUC(0-∞) (ng.h/mL)[1]	11	12135 (30)	11	12490 (31)
AUC(0-t) (ng.h/mL)[1]	11	11259 (31)	11	11563(33)
tmax (h)[2]	11	2.0 (0.5–2.0)	11	2.0 (0.5–2.2)
t½ (h)[1]	11	4.19 (31)	11	4.17 (31)
RC8[2]	11	1.0 (0.7–1.6)	11	0.9 (0.5–1.5)

Source Data: Table 11.20 and Table 11.21

1. Geometric mean (CV%).
2. Median (range).

Cmax = maximal observed plasma concentration; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC(0-t) = AUC to last measurable concentration; tmax = time to maximal observed plasma concentration; t½ = apparent elimination half-life; RC8 = paraxanthine/caffeine plasma ratio at 8 h.

Statistical Analyses of GSK598809 Pharmacokinetic Parameters

Accumulation ratio:

The average increase in GSK598809 exposure (AUC(0-24)) was slightly larger at Day 35, i.e., after 28 days of repeat dosing, than at Day 14 (after 7 days of repeat dosing), and was generally large overall (Table 10). GSK598809 25 mg dose displayed the highest accumulation, with exposure increased by 137% after 1 week of dosing, further increased to +182% after 4 weeks of repeat dosing. Accumulation was lower for the highest dose of GSK598809 100 mg for males (+100% and +119% after 1 week and 4 weeks, respectively). Accumulation for females at GSK598809 100 mg was similar to males.

Table 10 Summary of Results of Statistical Analysis of Plasma GSK598809 to Estimate Accumulation Ratio

Comparison Test vs. Reference	Regimen	Geometric LS Mean Test	Geometric LS Mean Reference	Ratio	90% Confidence Interval
AUC(0-24) on Day 14 vs. AUC(0-24) on Day 1	10 mg (males)	598.64	293.30	2.04	(1.86, 2.25)
	25 mg (males)	1618.88	682.31	2.37	(2.24, 2.52)
	40 mg (males)	2917.06	1324.94	2.20	(2.00, 2.42)
	100 mg (males)	8058.82	4039.03	2.00	(1.84, 2.17)
	100 mg (females)	7968.12	4068.25	1.96	(1.75, 2.19)
AUC(0-24) on Day 35 vs. AUC(0-24) on Day 1	10 mg (males)	688.47	293.30	2.35	(2.15, 2.56)
	25 mg (males)	1921.38	682.31	2.82	(2.67,2.97)
	40 mg (males)	3505.37	1324.94	2.65	(2.44, 2.87)
	100 mg (males)	8865.20	4039.03	2.19	(2.07, 2.33)
	100 mg (females)	8953.71	4068.25	2.20	(2.01, 2.41)

Source Data: Table 11.22 and Table 11.23
LS = least squares; AUC(0-24) = area under the plasma concentration-time curve from time zero to 24 h post dose.

Time invariance:

Kinetics of GSK598809 were altered after repeat dosing of 10 mg, 100 mg (males) and 100 mg (females): at Days 14 and 35, time invariance ratio ranged from 1.279 to 1.661 (Table 11). After 1 week of repeat dose GSK598809 25 mg and 40 mg the time invariance ratio was higher, and it further increased after 4 weeks. These results should be evaluated in conjunction with the evaluation of steady-state and non dose-linear pharmacokinetics.

Table 11 Summary of Results of Statistical Analysis of Plasma GSK598809 to Estimate Time Invariance

GSK598809 Regimen	Comparison Test vs. AUC(0-∞) Day 1	Geometric LS Mean Test	Geometric LS Mean Reference	Ratio	90% Confidence Interval
10 mg (males)	AUC(0-24) Day 14	589.69	409.40	1.440	(1.332, 1.558)
	AUC(0-24) Day 35	680.12	409.40	1.661	(1.545, 1.787)
25 mg (males)	AUC(0-24) Day 14	1636.94	921.15	1.777	(1.678, 1.882)
	AUC(0-24) Day 35	1929.52	921.15	2.095	(1.991, 2.203)
40 mg (males)	AUC(0-24) Day 14	2914.23	1712.62	1.702	(1.551, 1.867)
	AUC(0-24) Day 35	3492.31	1712.62	2.039	(1.887, 2.204)
100 mg (males)	AUC(0-24) Day 14	8146.77	5506.18	1.480	(1.395, 1.569)
	AUC(0-24) Day 35	8865.20	5506.18	1.610	(1.543, 1.680)
100 mg (females)	AUC(0-24) Day 14	8241.60	6444.71	1.279	(1.172, 1.396)
	AUC(0-24) Day 35	9043.80	6444.71	1.403	(1.310, 1.504)

Source Data: Table 11.24 and Table 11.25

AUC(0-24) = area under the plasma concentration-time curve from time zero to 24 h post dose; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; LS = least squares.

Steady state of GSK598809:

Steady state was statistically confirmed by Day 35 for GSK598809 10 mg, 25 mg and 40 mg, with both the point estimate and 90% confidence interval being within 0.91–1.10 (Table 12). For GSK598809 100 mg (males), this criterion was already met by Day 14 (after 7 days' repeat dosing). For GSK598809 100 mg (females), this criterion was met at Day 14; however, at Day 35 results just exceeded the criterion, so steady-state could be defined as putative (point estimate was within 0.91–1.10 while the upper confidence limits were outside that range).

Table 12 Summary of Results of Statistical Analysis of GSK598809 to Assess Steady State

GSK598809 Regimen	Day	Slope	90% Confidence Interval
10 mg (males)	14	1.11	(1.08, 1.15)
	35	0.99	(0.94, 1.04)
25 mg (males)	14	1.10	(1.08, 1.12)
	35	1.01	(0.99, 1.03)
40 mg (males)	14	1.10	(1.07, 1.13)
	35	1.00	(0.96, 1.05)
100 mg (males)	14	1.04	(1.02, 1.07)
	34	1.00	(0.97, 1.04)
100 mg (females)	14	1.03	(1.00, 1.06)
	35	1.05	(0.99, 1.11)

Source Data: Table 11.26 and Table 11.27

Effect of GSK598809 on caffeine and caffeine metabolic ratio:

Caffeine AUC(0-∞) showed only a small increase of 3% when taken after GSK598809 100 mg repeat dose, compared with caffeine alone. The confidence interval for the ratio did not show a significant effect of GSK598809 on caffeine AUC(0-∞).

The ratio of geometric means for metabolic Ro, paraxanthine/caffeine plasma ratio at 8 h after dosing showed a small decrease of 7% when taken after 100 mg repeat doses of GSK598809, compared with caffeine alone. Together with the confidence interval for the ratio, this indicated there was no significant effect of GSK598809 on CYP1A2 enzyme activity (Table 13).

Table 13 Summary of Results of Effect of Single and Repeated Doses of GSK598809 on Plasma Caffeine Pharmacokinetics (in Males)

Comparison	Response Variable	LS Geometric Mean Test	LS Geometric Mean Ref.	Ratio	90% CI for Ratio
Day 35 vs. Day -1	AUC(0-∞) (ng.h/mL)	12490.32	12135.29	1.03	(0.96, 1.11)
	Metabolic Ro (8 h)	0.98	1.06	0.93	(0.82, 1.05)

Source Data: Table 11.28

LS = least squares; Ref. = reference; CI = confidence interval; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; metabolic Ro = paraxanthine/caffeine plasma ratio.

Dose proportionality (single dose):

Both the adjusted mean slopes were above the value of 1, suggesting a more than proportional increase of AUC(0-∞) and Cmax values with increasing doses. The 90% confidence intervals for GSK598809 AUC(0-∞) and Cmax were not contained within the range 0.74 to 1.26; thus, dose proportionality across GSK598809 doses 75 mg to 175 mg was not statistically confirmed (Table 14).

Table 14 Summary of Results of Statistical Analysis of Plasma GSK598809 to Estimate Single Dose Proportionality (Males)

Parameter	Adjusted Mean Slope	Standard Error	90% CI for slope	CV Within %
AUC(0-∞) (ng.h/mL)	1.516	0.063	(1.404, 1.627)	10.9
Cmax (ng/mL)	1.161	0.113	(0.963, 1.358)	19.6

Source Data: Table 11.29

CI = confidence interval; CV within = within-subject coefficient of variation; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; Cmax = maximal observed plasma concentration.

Dose proportionality (repeat dose):

Both the adjusted mean slopes were above the value of 1, suggesting a more than proportional increase of AUC(0-∞) and Cmax values with increasing doses. The 90% confidence interval for GSK598809 AUC(0-24) was not contained within the range (0.90 to 1.10) and results showed a more than proportional increase; thus, dose proportionality was not statistically confirmed. However, the 90% confidence interval for Cmax was

contained within range and therefore dose proportionality was confirmed for Cmax over the dose range 10–100 mg (Table 15).

Table 15 Summary of Results of Statistical Analysis of Plasma GSK598809 to Estimate Repeat Dose Proportionality (Males)

Parameter	Adjusted Mean Slope	Standard Error	90% CI for slope	CV Within %
AUC(0-24) (ng.h/mL)	1.115	0.041	(1.046, 1.183)	23.0
Cmax (ng/mL)	1.024	0.040	(0.957, 1.092)	22.6

Source Data: Table 11.30
CI = confidence interval; CV within = within-subject coefficient of variation; AUC(0-24) = area under the plasma concentration-time curve from time zero to 24 h post dose; Cmax = maximal observed plasma concentration.

Assessment of the effect of gender with GSK598809 100 mg:

Day 1 AUC(0-∞) was slightly higher for females than for males following GSK598809 100 mg administration. The confidence interval for the ratio (1.00, 1.37) suggested that the overall exposure after single dosing was likely to be higher for females than for males. Day 1 Cmax was similar for males and females, as was AUC(0-24) on Day 35. Day 35 Cmax was slightly higher for females than for males with GSK598809 100 mg (Table 16).

Table 16 Summary of Results of Effect of Gender (Females: Males) on Plasma GSK598809 Pharmacokinetics at 100 mg

Day	Parameter	LS Geometric Mean Test (Females)	LS Geometric Mean Ref. (Males)	Ratio	90% CI for Ratio
Day 1	AUC(0-∞) (ng.h/mL)	6444.71	5506.18	1.17	(1.00, 1.37)
	Cmax (ng/mL)	856.27	865.99	0.99	(0.85, 1.15)
Day 35	AUC(0-24) (ng.h/mL)	9004.64	8865.20	1.02	(0.87, 1.18)
	Cmax (ng/mL)	1229.16	1055.83	1.16	(0.96, 1.42)

Source Data: Table 11.31
LS = least squares; Ref. = reference; CI = confidence interval; AUC(0-∞) = area under the plasma concentration-time curve from time zero extrapolated to infinity; Cmax = maximal observed plasma concentration; AUC(0-24) = area under the plasma concentration-time curve from time zero to 24 h post dose.

Pharmacodynamics:

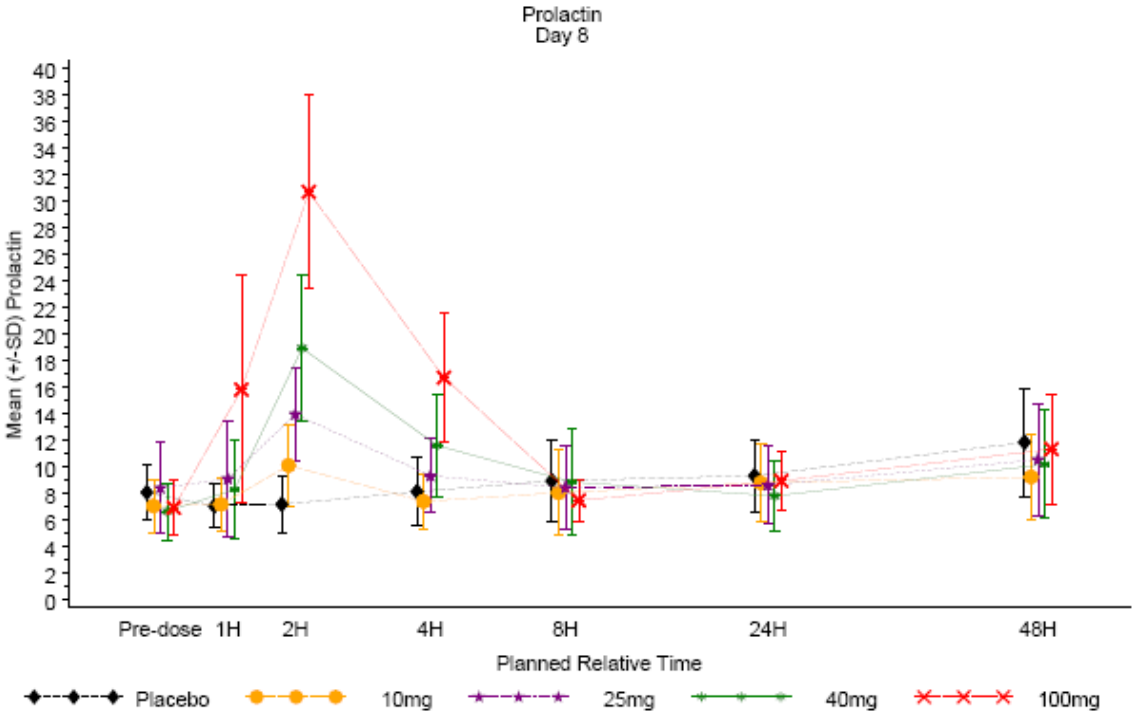
Hormones

Prolactin:

On Day 8 of repeat dosing in males, there was an apparent dose-dependent increase in serum prolactin at around 2 h and resolving by 8 h post dose (Figure 3). The mean increase was less than 2 x the ULN and was not considered clinically significant. There were no clinical findings that could be attributed to these transient increases in prolactin. The increases in prolactin did not consistently occur in all males on all dosing days, and they occurred more frequently in the early dosing periods. With continued dosing in the

repeat dose period, the magnitude of the increase was smaller than after single doses. A similar, but larger, elevation of serum prolactin was observed also in women; however it occurred even in a subject on placebo, occurred most frequently in the early periods and as for the male, resolved by the end of each dosing day and had no clinical sequelae.

Figure 3 Mean (Standard Deviation) Prolactin (Repeat Dose Day 8) in Males



Source: Figure 12.1

A similar trend of increased prolactin was seen in female subjects receiving repeated 100 mg doses of GSK598809 (Cohort 7) (Figure 12.4).

In single dose Cohort 5, similar results were found, with notably higher levels of prolactin in subjects on all active treatments, particularly GSK598809 130 mg and 175 mg, peaking at 2 h after dosing (Figure 12.2).

Growth hormone:

There was no distinct trend in GH levels between the regimens in repeat dose cohorts (Figure 12.1 and Figure 12.3). In the single dose cohort, subjects receiving GSK598809 175 mg showed higher levels of GH than with other treatments at 1 h, 2 h and 4 h, although there was great variability at these time points (Figure 12.2).

Thyroid stimulating hormone:

When considering pre-dose levels, there were no notable differences between the treatment regimens for post dose levels of TSH (Figure 12.1 to Figure 12.3).

Additional hormones (females):

For total and free testosterone in female subjects, no clear trend was observed when comparing GSK598809 100 mg with placebo (Figure 12.3).

In female subjects, no changes in LH and FSH were considered clinically significant or associated with any changes in prolactin. No clear trend was observed when comparing GSK598809 100 mg with placebo.

Barnes Akathisia, Abnormal Involuntary Movement, and Simpson Angus Scales

There were no notable trends observed for AIMS and SAS (Figure 12.5 to Figure 12.10).

[redacted]

Profile of Mood States (males)

A slight increase in the POMS total score for subjects receiving GSK598809 175 mg single dose was observed mainly at 2 h after dosing. This increase seemed to be principally related to changes in fatigue-inertia, confusion bewilderment and vigour-activity domains (Figure 12.12).

In repeat dose cohorts, male subjects receiving placebo had noticeably lower POMS mood disturbance total score than those receiving active doses, although this was also the case at the pre-dose time point on all days. A slight decrease in the score for vigour-activity domain for subjects receiving GSK598809 100 mg RD, occurring up to 4–6 h of treatment could be noticed up to Day 28, after 21 days of repeat dosing, but was not evident at Day 35.

This pattern was not present in female subjects receiving GSK598809 100 mg RD.

Overall, although the POMS showed some slight changes, these variations had no obvious dose relationship and were not considered clinically significant.

Cognitive Tests

Choice reaction time:

Reaction times were slightly longer for subjects on all three dose levels of GSK598809 compared with placebo for CRT after single dosing (Figure 12.15). Slightly longer reaction times were also observed following GSK598809 100 mg repeat dose compared with placebo for female subjects (Figure 12.16).

Motor impulsivity (stop-signal task):

Stop reaction times were slightly higher after GSK598809 130 mg and 175 mg single dose (Figure 12.18). This trend was not observed for repeat dose stop reaction time, with

subjects on placebo having slightly longer reaction times. No difference was observed between GSK598809 100 mg and placebo for female repeat dose SST reaction times.

Digit Symbol Substitution Test (DSST):

For the single dose cohort, DSST total score at 24 h post dose was slightly higher for subjects receiving GSK598809 130 mg and 175 mg than placebo. There was no notable difference between the treatments at 3 h post dose (Figure 12.21).

No specific patterns were seen with repeat dose treatments (Figure 12.22).

Verbal Learning and Memory Test (VLMT):

For the single dose cohort subjects on GSK598809 175 mg had slightly slower recognition reaction times compared with subjects on the other regimens. Recognition reaction times for male subjects on GSK598809 25 mg, 40 mg and 100 mg were consistently quicker than repeat dose placebo (at Days 14, 28 and 35), but no difference was observed between treatments for the female repeat dose cohort.

No changes from placebo were evidenced for the number of items recalled correctly for delayed and immediate recall (Figure 12.23) either after single or repeat doses.

Conclusions:

Safety

- GSK598809 was generally well tolerated at all doses tested (single doses up to 175 mg and repeat doses up to 100 mg for 28 days) in both males and females.
- There was one SAE, a case of appendicitis in a subject receiving GSK598809 10 mg repeat dose, which was considered unrelated to study medication. Two subjects were withdrawn due to AEs, one following GSK598809 25 mg repeat dose and one with GSK598809 40 mg repeat dose.
- One of the withdrawals was due to a non-drug-related AE of increased muscle enzyme (CPK) on repeat dose GSK598809 25 mg, which resolved spontaneously.
- Average clinical chemistry (except prolactin, see below) and haematology values showed similar patterns following all treatments including placebo, in both male and female subjects.
- No safety concerns were raised on urinalysis dipstick results.
- No notable changes in average vital signs (systolic and diastolic blood pressure, heart rate and respiration rate) were observed following GSK598809 or placebo.
- No safety concerns were raised on individual ECG. No subject met stopping criteria. Higher mean increases in QTcF over baseline were observed after repeat dosing on the highest dose level (GSK598809 100 mg) compared to repeat dosing with placebo. No notable differences were observed for the other dose levels when compared to placebo.

Pharmacokinetics

- Repeated administration of GSK598809 was associated with a dose-independent accumulation (2 to 3 in the dose range 10 to 100 mg).
- AUC after repeat dose was slightly higher than predicted after single dose. This might be partially due to non-linear PK of the drug.
- Deviation from dose proportionality was confirmed in the dose range 75 to 175 mg for both AUC, and Cmax after single dose with greater than dose-proportional increases in these parameters.
- Steady state was statistically confirmed for GSK598809 by Day 35 (after 28 days of repeat dosing) for all dose regimens.
- There was no significant effect of GSK598809 on CYP1A2 activity assessed using a caffeine probe.
- No marked gender effect was seen on AUC and Cmax of GSK598809 and GSK685249.

Pharmacodynamics

- Prolactin levels transiently increased following GSK598809 in a dose-related manner. However, with continued dosing in the repeat dose period, the magnitude of the increase was smaller than after single doses.
- For the cognitive tests mixed trends were observed for reaction times, DSST and VLMT by treatment. In general, no marked differences between placebo and any dose of GSK598809 were observed after single and repeat doses.
- Although the POMS showed some slight changes (mainly in fatigue-inertia, confusion bewilderment and vigour-activity domains for males) their variability was quite high, had no obvious dose or time relationship and were not considered clinically significant. No difference between treatments was observed for females.
- There were no notable effects of GSK598809 on BARS, AIMS or SAS scales.

Date of Report:

June 2009