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: ORA111850
Title: A 35-day, multi-centre, randomised, parallel-group, double-blind, placebo-controlled proof of concept study to investigate the effects of GSK1521498 on body weight and composition, eating behaviour and related brain function, in obese subjects with over-eating behaviours.
Rationale: The primary outcome of this study was the therapeutic efficacy of GSK1521498 on weight reduction in obese subjects with over-eating behaviour. In addition, the study was designed to enrich the mechanistic understanding of how GSK1521498 acts on brain function and behaviour to achieve its expected effects on fat mass and body weight. The study was also designed to provide preliminary data on how individual differences in eating behaviour and other markers might be used to predict treatment response. In addition, possible adverse effects of GSK1521498 on other aspects of hedonically driven behaviour, such as processing of sexual or financially rewarding stimuli, as well as by standard affective and cognitive changes were carefully measured.
Phase: Phase IIa.
Study Period: 06-Sep-2010 to 27-May-2011.
Study Design: A repeat dose, multi-centre, randomised, parallel-group, double-blind, placebo-controlled study.
Centres: Three centres in the United Kingdom.
Indication: Obesity.
Treatment: The total treatment duration was 35 days. The first 7 days were a single-blind placebo run-in period, after which subjects were randomised in a 1:1:1 ratio to one of three treatment groups for a 28-day double-blind treatment period, as follows: oral GSK1521498 5 mg daily; oral GSK1521498 2 mg daily; oral placebo daily. Subjects were instructed to take the investigational product every morning for 35 days, mainly as an outpatient. After 7 days of treatment (placebo run-in), compliant subjects were admitted for the first of three major in-unit assessment sessions scheduled for Days -2/-1/1/2 (involving a 3-night stay) and Days 13/14 and 27/28 (both involving a 1- or 2-night stay). Efficacy, pharmacodynamic, safety and pharmacokinetic assessments were conducted.
Objectives: The primary objective was to test the hypothesis that GSK1521498 caused clinically and statistically significant (at least -2.1 kg) placebo-controlled change from baseline body weight after 28 days of repeat dosing with 2 mg or 5 mg in obese subjects with moderate-to-high binge eating behaviours.
Statistical Methods: Sample size calculations were based on the primary endpoint of body weight change from baseline, for which prior data are available from a study showing the effects of sibutramine. Assuming GSK1521498 (2 mg and/or 5 mg) achieved the same difference from placebo as sibutramine and the same between-subject standard deviation was seen (SD_b=1.6 kg), the sample size of 20 subjects per group would provide 96% power to detect this difference with a 2.5%, 2-sided type-I error rate for each comparison (i.e., overall 5% type-I error). Efficacy analyses: The efficacy analyses were performed using the intent-to-treat (ITT) population. *Primary efficacy analyses:* weight data from the three treatment arms (GSK1521498 2 mg, GSK1521498 5 mg and placebo) were fitted into the model described below. Changes from baseline in total body weight after 14 and 28 days of treatment were analysed using a repeated measures analysis of covariance (ANCOVA) model using SAS PROC MIXED procedure with Restricted Maximum Likelihood estimation method. Model effects accounted for stratification variable and included baseline weight, gender, treatment, visit and treatment-by-visit interactions. An appropriate variance-covariance matrix was chosen to account for repeated measures within the same subject across visits based on Akaike's Information Criterion. Two pair-wise comparisons were conducted to test the main effects of GSK1521498 5 mg vs. placebo and GSK1521498 2 mg vs. placebo. The Hochberg step-up procedure was used to control the overall type-I error at 5% for primary analysis on Day 28. Adjusted means, two-sided p-values and 95% confidence limits for the treatment differences after 28 days were presented. *Secondary efficacy analyses:* Treatment comparisons of change from baseline in fat mass after 14 and 28 days' treatment were analysed using the same model described in the primary analysis. Percentage change from baseline in body weight and fat mass after 14 and 28 days' treatment were analysed using a repeated measures ANCOVA as described in the primary efficacy analysis. The analysis was based on log-transformed data and the reverse transformation was used to express results in terms of relative effects (i.e., percentages). Model effects accounted for stratification variable and included log (baseline weight), gender, treatment and visit and treatment-by-visit interactions. Relationships between weight loss and fat mass loss, changes in eating behaviour, reward-related brain function, hedonic and motivational processing were explored. Therapeutic effects of GSK1521498 on body weight and other efficacy endpoints in obese patients were correlated with over-eating behaviour at baseline.

Safety analyses: The safety data analysis was performed using the safety population. Safety data were presented in tabular and/or graphical format and summarized descriptively. Vital signs (including blood pressures and heart rate), cognitive tests and neuropsychiatric symptom scales (Beck Depression Inventory [BDI],Beck Anxiety Inventory [BAI] etc) were analysed in a similar way to the primary endpoint to report placebo-controlled change from baseline scores on each of the vital signs, cognitive and psychiatric safety endpoints.

Pharmacodynamic/biomarker analyses: The pharmacodynamic/biomarker analyses were performed using the pharmacodynamic population. Statistical analyses were carried out for the following pharmacodynamic endpoints: change from baseline on scores from eating questionnaires and experiments, hedonic and cognitive functions, fasting hormone levels, fasting glucose and lipid panel, brain function parameters.

Pharmacokinetic and pharmacokinetic/pharmacodynamic analyses: Plasma GSK1521498 concentration-time data were analysed by non-compartmental methods with WinNonlin version 5.2 or later. Calculations were based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters were determined on Days 1 and 28, as data permitted: maximum observed plasma concentration (Cmax), time to Cmax (tmax), observed time prior to first quantifiable plasma concentration (tlag, Day 1 only) area under the plasma concentration-time curve [AUC(0-24)].

Trough concentration (Ctau) samples collected on Days 7, 14 and 21 were used to assess attainment of steady state of GSK1521498.

To assess accumulation (Ro) of plasma GSK1521498, a mixed effect ANOVA model with a fixed effect term for day and random effect for subject was performed on $\log_e$-transformed AUC(0-24) and Cmax separately. Accumulation for each dose level was estimated by exponentiating the difference in least squares means (Day 28 - Day 1) and associated 90% confidence interval (CI).

Pharmacokinetic/pharmacodynamic relationships between GSK1521498 exposure and various pharmacodynamic endpoints including fat mass, body weight, eating behaviour and brain function were explored. In the event that significant pharmacokinetic/ pharmacodynamic relationships were identified, parameters relating GSK1521498 exposures to the various pharmacodynamic endpoints (including estimation of possible dose-response relationships) were to be determined and reported as appropriate.

Study Population: Obese but essentially healthy male and female subjects aged 18-60 years, inclusive, with body mass index ≥30 kg/m^2 and a Binge Eating Scale (BES) score ≥19.

Number of Subjects:	**Run-in only**	**Placebo**	**498 2 mg**	**498 5 mg**	**Total**
Planned N	0	20	20	20	60
Dosed N	4	21	21	21	67
Completed n (%)	0	21 (100)	18 (86)	21 (100)	60 (90)
Total Number Subjects Withdrawn n (%)	4 (100)	0	3 (14)	0	7 (10)
Withdrawn due to Adverse Event n (%)	1 (25)	0	2 (10)[a]	0	3 (4)[a]
Withdrawn at Investigator discretion n (%)	2 (50)	0	1 (5)	0	3 (4)
Subject Withdrew Consent n (%)	1 (25)	0	0	0	1 (1)
Demographics	**Run-in only**	**Placebo**	**498 2 mg**	**498 5 mg**	**Total**
N (All subjects)	4	21	21	21	67
Mean Age in Years (sd)	44.8 (9.50)	41.3 (9.22)	44.9 (10.08)	37.8 (10.06)	41.5 (10.00)
Females: Males	2: 2	11: 10	12: 9	12: 9	37: 30
Mean Weight in kg (sd)	109.7 (21.68)	109.2 (18.17)	110.9 (23.63)	104.0 (9.82)	108.1 (18.11)
Mean Body Mass Index in kg/m^2 (sd)	36.2 (4.15)	37.8 (4.87)	37.1 (5.37)	37.1 (4.38)	37.3 (4.76)
White/Caucasian/European Heritage n (%)	4 (100)	17 (81)	19 (90)	17 (81)	57 (85)
African American/African Heritage n (%)	0	3 (14)	2 (10)	3 (14)	8 (12)
White - Arabic/North African Heritage n (%)	0	1 (5)	0	1 (5)	2 (3)

a. Includes one subject withdrawn from the study due to a serious adverse event.

Efficacy: Treatment differences vs. placebo for change from baseline body weight (kg) are summarised below.

Visit	**Treatment**	**N (n)**	**LS Mean Difference**	**95% CI**	**p-value**	**Adjusted p-value[a]**
Day 14	498 2 mg	21 (21)	-0.18	(-0.74, 0.38)	0.5186	ND
	498 5 mg	21 (21)	-0.04	(-0.61, 0.54)	0.9019	ND
Day 28	498 2 mg	21 (20)	-0.53	(-1.56, 0.50)	0.3057	0.6029
	498 5 mg	21 (21)	-0.27	(-1.31, 0.77)	0.6029	0.6029

Based on repeated measures analysis of covariance. ND = not done.

a. Hochberg's adjustment for multiple comparisons was conducted on primary comparisons of change from baseline body weight

at Day 28 only.

Treatment differences vs. placebo for percentage change from baseline in body weight are summarised below.

Visit	Treatment	N (n)	LS Mean Difference	95% CI	p-value
Day 14	498 2 mg	21 (21)	-0.220	(-0.778, 0.341)	0.4336
	498 5 mg	21 (21)	-0.045	(-0.622, 0.535)	0.8769
Day 28	498 2 mg	21 (20)	-0.636	(-1.627, 0.365)	0.2077
	498 5 mg	21 (21)	-0.277	(-1.292, 0.749)	0.5895

Fat mass: No significant treatment differences were observed for change from baseline fat mass or percentage change from baseline on Day 28 for the GSK1521498 2 mg and 5 mg groups compared with placebo (see table below).

Parameter	Visit	Treatment	N (n)	LS Mean Difference	95% CI	p-value
Change in fat mass (kg)	Day 28	498 2 mg	21 (18)	-0.30	(-1.41, 0.80)	0.5836
		498 5 mg	21 (21)	0.16	(-0.92, 1.24)	0.7671
Change in fat mass (%)	Day 28	498 2 mg	21 (18)	-0.601	(-2.698, 1.540)	0.5730
		498 5 mg	21 (21)	0.966	(-1.163, 3.140)	0.3700

No significant effects of baseline body weight, baseline BES and gender on body weight changes were found.
Positive correlations were observed in weight changes vs. changes in other parameters including fat mass (Pearson's coefficient 0.744, p<0.0001), total BES (Pearson's coefficient 0.402, p = 0.0018), Y-BOCS-BE compulsive score (Pearson's coefficient 0.338, p = 0.0084) and Y-BOCS-BE obsessive score (Pearson's coefficient 0.388, p = 0.0022).
Negative correlation was seen in weight changes vs. lean mass changes (Pearson's coefficient -0.358, p = 0.0053).
Body mass index: There was no notable reduction in observed mean body mass index on Day 28 compared with baseline in the placebo, GSK1521498 2 mg and 5 mg groups.
Hip-waist circumference ratio: There was no notable reduction in observed mean hip-waist circumference ratio on Day 28 compared with baseline in the placebo, GSK1521498 2 mg and 5 mg groups.

Safety results: Adverse event and serious adverse event (SAE) data were collected from administration of study medication (including the placebo run-in period) until follow-up. In addition, any SAEs assessed as related to study participation (e.g., investigational product, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication were to be recorded from the time a subject consented to participate in the study up to and including any follow-up contact. The most frequently reported on-therapy AEs are summarised below.

Most Frequent Adverse Events	Placebo	GSK1521498 2 mg	GSK1521498 5 mg
N (Safety)	21	21	21
No. subjects with AEs n (%)	16 (76)	18 (86)	17 (81)
Most frequent on-therapy AEs (two or more subjects in any group)			
Headache	8 (38)	10 (48)	10 (48)
Nasopharyngitis	5 (24)	4 (19)	2 (10)
Nausea	3 (14)	3 (14)	4 (19)
Fatigue	2 (10)	3 (14)	4 (19)
Cough	3 (14)	3 (14)	2 (10)
Dizziness	2 (10)	3 (14)	2 (10)
Back pain	2 (10)	1 (5)	3 (14)
Diarrhoea	0	4 (19)	1 (5)
Dyspepsia	3 (14)	1 (5)	1 (5)
Arthralgia	0	3 (14)	1 (5)
Dysmenorrhoea	1 (5)	1 (5)	2 (10)
Nasal obstruction	2 (10)	1 (5)	1 (5)
Abdominal discomfort	0	1 (5)	2 (10)
Feeling hot	2 (10)	1 (5)	0
Infusion site swelling	1 (5)	0	2 (10)
Constipation	0	0	2 (10)
Generalised pain	2 (10)	0	0
Tremor	0	2 (10)	0

Serious Adverse Events: There was an SAE of persecutory delusion with onset on Day 26 of GSK1521498 2 mg; the subject was withdrawn from the study. The treatment blind was broken to allow full clinical assessment of this subject. The SAE was considered unrelated to study medication by the Investigator, as on careful questioning of both subject and collateral history from parents there was evidence that some of these thoughts had been present before study start. This SAE is now resolved.

Other Safety Results: There was no evidence of a treatment difference between GSK1521498 and placebo in the analysis of change from baseline to steady state Days 7-28 mean vital signs values.

Differences vs. placebo for change from baseline in Visual Analogue Mood Scale (VAMS) and Hospital Anxiety and Depression Scale (HADS) scores on Day 28 are summarised below.

Parameter	Treatment	N (n)	LS Mean Difference	95% CI	p-value
VAMS					
Alertness	498 2 mg	21 (20)	2.33	(-8.324, 12.990)	0.6629
	498 5 mg	21 (21)	-7.10	(-17.659, 3.462)	0.1836
Calmness	498 2 mg	21 (20)	0.04	(-9.509, 9.580)	0.9941
	498 5 mg	21 (21)	-3.64	(-13.135, 5.846)	0.4451
Contented-ness	498 2 mg	21 (20)	-0.23	(-8.959, 8.495)	0.9578
	498 5 mg	21 (21)	-5.54	(-14.204, 3.119)	0.2053
HADS					
Anxiety	498 2 mg	21 (20)	-0.92	(-1.922, 0.084)	0.0718
	498 5 mg	21 (21)	-0.33	(-1.327, 0.667)	0.5096
Depression	498 2 mg	21 (20)	-0.09	(-0.949, 0.766)	0.8318
	498 5 mg	21 (21)	-0.45	(-1.293, 0.393)	0.2896

Differences vs. placebo for change from baseline in cognitive scores on Day 28 are summarised below. An asterisk signifies a p-value <0.05. No substantial sedation signal was detected during 4 weeks of dosing.

Parameter	Treatment	N (n)	LS Mean Difference	95% CI	p-value
POA score (msec)	498 2 mg	21 (18)	21.15	(-32.480, 74.787)	0.4333
	498 5 mg	21 (21)	2.86	(-48.795, 54.523)	0.9120
DVRT (msec)	498 2 mg	21 (18)	6.23	(-11.047, 23.506)	0.4735
	498 5 mg	21 (21)	-4.40	(-20.693, 12.160)	0.5967
DVA (msec)	498 2 mg	21 (18)	0.37	(-2.437, 3.177)	0.7929
	498 5 mg	21 (21)	-3.30	(-5.976, -0.630)	0.0164*
CRT (msec)	498 2 mg	21 (18)	8.70	(-23.872, 41.269)	0.5951
	498 5 mg	21 (21)	4.27	(-26.798, 35.336)	0.7842
SRT (msec)	498 2 mg	21 (18)	6.25	(-14.002, 26.495)	0.5385
	498 5 mg	21 (21)	6.33	(-13.443, 26.110)	0.5232
RVIP reaction time (msec)	498 2 mg	21 (18)	-10.2	(-45.787, 25.473)	0.5703
	498 5 mg	21 (20)	9.92	(-24.727, 44.570)	0.5683
RVIP accuracy (%)	498 2 mg	21 (18)	3.83	(-3.001, 10.652)	0.2666
	498 5 mg	21 (20)	1.69	(-5.248, 8.619)	0.6282
Immediate word recall	498 2 mg	21 (18)	0.29	(-0.72, 1.30)	0.5650
	498 5 mg	21 (21)	0.45	(-0.51, 1.42)	0.3505
Delayed word recall	498 2 mg	21 (18)	-0.24	(-1.13, 0.66)	0.5985
	498 5 mg	21 (21)	-0.05	(-0.90, 0.81)	0.9151
N-back reaction time (msec)					
0-Back	498 2 mg	21 (17)	-20.674	(-52.466, 11.119)	0.1978
	498 5 mg	21 (20)	-2.308	(-31.865, 27.248)	0.8761
1-Back	498 2 mg	21 (17)	26.737	(-52.448, 105.923)	0.5012
	498 5 mg	21 (20)	5.100	(-71.783, 81.984)	0.8947
2-Back	498 2 mg	21 (17)	-0.805	(-80.375, 78.765)	0.9839
	498 5 mg	21 (20)	31.706	(-43.635, 107.048)	0.4024
N-back accuracy (%)					
0-Back	498 2 mg	21 (17)	-2.480	(-5.697, 0.738)	0.1281
	498 5 mg	21 (20)	-0.440	(-3.463, 2.583)	0.7714
1-Back	498 2 mg	21 (17)	1.754	(-6.537, 10.046)	0.6730
	498 5 mg	21 (20)	2.654	(-5.231, 10.540)	0.5025
2-Back	498 2 mg	21 (17)	5.751	(-1.155, 12.657)	0.1008
	498 5 mg	21 (20)	2.206	(-4.339, 8.752)	0.5020
Interference scores from Food and Normal Stroop task (msec)					
Normal stroop	498 2 mg	21 (18)	-104.59	(-191.3, -17.84)	0.0191*
	498 5 mg	21 (20)	-52.33	(-136.6, 31.96)	0.2186

Non-palatable food	498 2 mg	21 (18)	32.13	(-29.53, 93.80)	0.3008
	498 5 mg	21 (20)	44.88	(-15.76, 105.52)	0.1437
Palatable food stroop	498 2 mg	21 (18)	20.75	(-37.43, 78.93)	0.4776
	498 5 mg	21 (20)	12.09	(-43.78, 67.96)	0.6661

POA = Power of Attention; DVRT = Digit Vigilance Reaction Time; DVA = Digit Vigilance Accuracy; CRT = Choice Reaction Time; SRT = Simple Reaction Time; RVIP = Rapid Visual Information Processing; N-back = N-back working memory.

Differences vs. placebo for change from baseline in Profile of Mood States - Brief (POMS-B), Beck Depression Inventory (BDI-II) and Beck Anxiety Inventory (BAI) scores on Day 28 are summarised below. There was no evidence of any effects on mood following treatment with GSK1521498.

Parameter	Treatment	N (n)	LS Mean Difference	95% CI	p-value
POMS-B total	498 2 mg	21 (20)	-1.34	(-5.818, 3.144)	0.5529
	498 5 mg	21 (21)	-0.47	(-4.885, 3.952)	0.8334
BDI-II	498 2 mg	21 (20)	0.02	(-1.560, 1.601)	0.9797
	498 5 mg	21 (21)	0.22	(-1.354, 1.787)	0.7832
BAI	498 2 mg	21 (20)	-0.11	(-1.415, 1.203)	0.8717
	498 5 mg	21 (21)	-0.41	(-1.696, 0.886)	0.5319

Pharmacokinetics: A summary of plasma pharmacokinetics of GSK1521498 is presented in the table below.

Parameter	Treatment	Day	N	n	Estimate[1]	95% CI
AUC(0-24) (ng.h/mL)	2 mg	1	21	21	124 (28.9)	(109, 141)
		28	21	18	416 (24.0)	(370, 468)
	5 mg	1	21	20	388 (23.1)	(349, 431)
		28	21	18	1070 (36.1)	(897, 1270)
Cmax (ng/mL)	2 mg	1	21	21	11.3 (37.1)	(9.58, 13.3)
		28	21	18	29.0 (27.0)	(25.4, 33.1)
	5 mg	1	21	21	37.6 (24.6)	(33.7, 42.0)
		28	21	21	76.8 (28.6)	(67.6, 87.3)
tmax (h)	2 mg	1	21	21	3.00 (2.00, 14.1)	NA
		28	21	18	2.44 (2.00, 6.03)	NA
	5 mg	1	21	21	3.00 (1.00, 6.00)	NA
		28	21	21	2.00 (1.17, 6.28)	NA
tlag (h)	2 mg	1	21	21	0.00 (0.00, 2.00)	NA
	5 mg	1	21	21	0.00 (0.00, 2.00)	NA

NA: Not Applicable.
[1] Presented as geometric mean (between-subject CV%) with the exception of tmax and tlag which are presented as median (min, max).

Dose Proportionality: A slightly greater than dose-proportional increase in systemic exposure, based on assessment of AUC(0-24) and Cmax, was observed following a single dose of GSK1521498. However, dose-proportionality was observed after 28 days of repeat oral dosing.
Accumulation Ratio: Accumulation, based on AUC(0-24) and Cmax, following 28 days of repeat oral dosing of GSK1521498 ranged from approximately 2.0 to 3.3-fold.

Pharmacodynamics (PD): Eating behaviour questionnaires: Total BES scores numerically reduced over time across all treatment arms including placebo. No statistically significant treatment differences were observed for change from baseline for total BES for GSK1521498 2 mg and 5 mg compared with placebo (see table below).

Visit	Treatment	N (n)	LS Mean Difference	95% Confidence Interval	p-value
Day 13	498 2 mg	21 (20)	1.287	(-1.481, 4.054)	0.3558
	498 5 mg	21 (20)	0.330	(-2.456, 3.115)	0.8133
Day 27	498 2 mg	21 (18)	0.840	(-2.757, 4.437)	0.6417
	498 5 mg	21 (20)	2.426	(-1.139, 5.990)	0.1782

No statistically significant treatment differences were observed for change from baseline for Yale-Brown Obsessive Compulsive Scales modified for binge eating (Y-BOCS-BE), total Hunger, Craving and Fullness Questionnaire scores or Three Factor Eating Questionnaire scores for GSK1521498 2 mg and 5 mg compared with placebo. No notable changes in Appetite Visual Analogue Scales were observed.

Experimental eating behaviour measures: For hedonic response to sweetened dairy products, statistically significant treatment effects were detected in the GSK1521498 5 mg group for the foods containing 9–19.1% fat levels and 8–16% sucrose levels, with GSK1521498 suppressing hedonic preference compared with placebo on Day 14 and/or Day 28. For the mean difference (Day 28–Day 14) of change from baseline hedonic response, statistically significant treatment differences between GSK1521498 5 mg and placebo were observed for the 9% fat, 19.1% fat and 8% sucrose samples, suggesting a greater treatment effect at Day 28. No statistically significant treatment effects on hedonic response were observed for the GSK1521498 2 mg treatment group compared with placebo.

In *post-hoc* analyses, significant decreases in change from baseline hedonic response were observed for high sucrose samples (categorised as 8, 16 and 32%) for GSK1521498 5 mg vs. placebo for Day 14 ($p = 0.002$), Day 28 ($p = 0.002$) and the difference (Day 28–Day 14) ($p = 0.010$). Significant decreases were seen for high fat samples (categorised as 9, 19.1 and 38.9%) for GSK1521498 5 mg vs. placebo on Day 14 ($p = 0.046$) and Day 28 ($p = 0.016$). In an analysis averaged across all fat and sucrose levels, significant decreases were seen for GSK1521498 5 mg vs. placebo for Day 14 ($p = 0.022$), Day 28 ($p = 0.012$) and the difference (Day 28–Day 14) ($p = 0.044$).

For sensory stimuli responses to sweetened dairy products, creaminess intensity ratings were significantly increased for GSK1521498 2 mg compared with placebo in the 3.5% fat samples on Days 14 and 28. Ratings for perceived fat content were significantly increased for GSK1521498 2 mg and 5 mg compared with placebo in the 3.5% fat samples on Day 14. Sweetness intensity ratings were significantly increased for GSK1521498 2 mg compared with placebo in the 4% sucrose sample on Day 14 and in the 2% and 4% sucrose samples on Day 28. Sweetness intensity ratings were significantly increased for GSK1521498 5 mg compared with placebo in the 38.9% fat and 4% sucrose samples on Day 14 and in the 16% sucrose sample on Day 28.

A statistically significant reduction in energy intake from *ad-lib* snacking was detected in the low fat/high sugar category for the GSK1521498 5 mg group on Day 14, with a food intake reduction of 61 kcal compared with placebo ($p = 0.03$). No statistically significant treatment effects were detected for change from baseline in energy intake based on macronutrient content. The greatest energy difference was observed for carbohydrates in the GSK1521498 5 mg group on Day 14, with an 81 kcal reduction in food intake compared with placebo ($p = 0.06$). No statistically significant treatment effects were detected for change from baseline in hedonic responses to *ad-lib* snacking in any food category for GSK1521498 vs. placebo.

Except for a statistically significant increase in change from baseline requested dessert portion observed for GSK1521498 5 mg compared with placebo in the 60% fat category, with an increase of 0.46 portions ($p = 0.02$), no statistically significant treatment effects were detected for change from baseline in both food ranking and food portion from main course and desserts in buffet meals in any food category for GSK1521498 vs. placebo in all three fat categories (20%, 40% and 60%).

For the buffet meal, a significant reduction of 184 kcal in Day 28 dessert calorie intake for the 60% fat category was observed for GSK1521498 5 mg compared with placebo. No significant treatment effects were seen for main course, dessert or combined main course and dessert, in the 20% and 40% fat categories. In a *post-hoc* analysis averaged across fat categories, significant decreases in change from baseline food intake for combined main course and dessert were seen for GSK1521498 5 mg vs. placebo on Day 14 (419 kcal, $p = 0.041$) and Day 28 (467 kcal, $p = 0.009$).

For the restaurant menu meal, a significant decrease of 306 kcal in change from baseline vs. placebo was observed for Day 27 combined main course and dessert calorie intake at the 60% fat category in the GSK1521498 2 mg group. No significant reductions in calorie intake were observed for the 20% and 40% fat categories. However, a significant increase of 219 kcal in change from baseline vs. placebo was observed for Day 13 main course calorie intake at the 20% fat category in the GSK1521498 5 mg group. In a *post-hoc* analysis, there was no effect on total calorie intake (averaged across fat categories) in the restaurant meal.

No statistically significant treatment differences were observed for change from baseline in total 24-h energy intake on Day 14 or Day 28 for the GSK1521498 2 mg and 5 mg groups compared with placebo. A non-significant reduction in adjusted mean 24-h energy intake not-by-fat category was detected in the GSK1521498 5 mg group, with a 415 kcal reduction compared with placebo ($p = 0.06$) on Day 28. In the analysis by fat category, a non-significant 254 kcal reduction was seen in the high fat category for GSK1521498 5 mg vs. placebo on Day 28 ($p = 0.191$).

Hedonic function questionnaires: No significant treatment differences were observed for GSK1521498 vs. placebo for change from baseline in Temporal Experience of Pleasure Scale or Changes in Sexual Functioning Questionnaire-14.

Food-related cognitive function measures: Compared with placebo, GSK1521498 5 mg attenuated temporal discounting of delayed rewards of £30 and 80 chocolate bars: a statistically significant increase in change from baseline total AUC vs. placebo was observed for the £30 and 80 chocolate bars rewards in the GSK1521498 5 mg group. This suggests that GSK1521498 5 mg increased the tendency for subjects to opt for delayed rewards (in the case of small monetary rewards, £30, and large chocolate rewards, 80 chocolate bars), thereby reducing impulsive choosing with regard to these rewards. No significant treatment differences were observed between GSK1521498 2 mg and placebo.

Compared with placebo, GSK1521498 5 mg reduced attentional bias to food cues (for the longer presentation [2000 msec] of the cues) in the Visual Probe Task: a statistically significant treatment difference vs. placebo was observed on Day 28 in the GSK1521498 5 mg group, showing a reduction of 12 msec in change from baseline attentional bias toward the food cue under a stimulus duration of 2000 msec (p = 0.04). No significant treatment differences were observed for attentional bias (500 msec) or overall mean attentional bias in the Visual Probe Task. No significant treatment differences were observed in Stimulus Response Compatibility task approach bias on Day 28.
For the Grip-Force Task wanting component, no significant treatment differences were observed for GSK1521498 vs. placebo for change from baseline in Day 28 normalised area under grip-force curve. No significant treatment differences were observed for GSK1521498 vs. placebo for change from baseline in Grip-Force Task liking VAS score. Upon further analysis of the data, by comparing the difference between reward categories (high fat and low fat) across visits, a subtle but significant dose by time by reward category interaction was found between the placebo and 5 mg drug conditions for the area under grip-force curve. This suggests GSK1521498 5 mg decreased the motivational salience of high calorie food.

Fasted blood biomarkers: Treatment differences for GSK1521498 vs. placebo for change from baseline in fasted hormone levels on Day 28 (excluding outliers) are summarised below. The observed changes for insulin and cortisol levels were not considered to be of clinical significance.

Parameter	Treatment	N (n)	LS Mean Difference	95% CI	p-value
Adrenocorticotropic hormone (ng/L)	498 2 mg	21 (18)	0.02	(-9.44, 9.49)	0.9959
	498 5 mg	21 (18)	8.34	(-1.08, 17.77)	0.0815
Adiponectin (ug/mL)	498 2 mg	21 (19)	0.29	(-0.32, 0.90)	0.3408
	498 5 mg	21 (19)	-0.05	(-0.66, 0.55)	0.8565
Total cortisol (nmol/L)	498 2 mg	21 (17)	31.5	(-48.7, 111.6)	0.4342
	498 5 mg	21 (19)	86.4	(8.3, 164.5)	0.0308*
Ghrelin (pg/mL)	498 2 mg	21 (19)	59.335	(-13.386, 132.057)	0.1077
	498 5 mg	21 (19)	33.040	(-40.369, 106.449)	0.3708
Insulin (pmol/L)	498 2 mg	21 (19)	-24.4	(-48.2, -0.6)	0.0444*
	498 5 mg	21 (20)	-22.5	(-45.8, 0.8)	0.0582
Leptin (ug/L)	498 2 mg	21 (18)	-6.90	(-12.94, -0.87)	0.0258*
	498 5 mg	21 (17)	-4.47	(-10.57, 1.63)	0.1472

Treatment differences for GSK1521498 vs. placebo for change from baseline in fasted metabolic tests on Day 28 are summarised below. No significant treatment difference was observed for GSK1521498 vs. placebo for haemoglobin A1c on Day 28.

Parameter	Treatment	N (n)	LS Mean Difference	95% CI	p-value
Cholesterol (mmol/L)	498 2 mg	21 (16)	-0.08	(-0.33, 0.18)	0.5568
	498 5 mg	21 (19)	0.03	(-0.22, 0.28)	0.8173
C-peptide (ug/L)	498 2 mg	21 (19)	-0.091	(-0.401, 0.220)	0.5599
	498 5 mg	21 (20)	-0.157	(-0.465, 0.151)	0.3100
Free fatty acids (umol/L)	498 2 mg	21 (18)	2.5	(-158.4, 163.4)	0.9748
	498 5 mg	21 (18)	8.1	(-152.8, 169.1)	0.9193
Glucose (mmol/L)	498 2 mg	21 (18)	0.05	(-0.20, 0.31)	0.6666
	498 5 mg	21 (19)	0.05	(-0.21, 0.30)	0.7199
HDL cholesterol (mmol/L)	498 2 mg	21 (16)	0.028	(-0.084, 0.141)	0.6134
	498 5 mg	21 (19)	0.040	(-0.068, 0.149)	0.4599
LDL cholesterol (mmol/L)	498 2 mg	21 (16)	0.002	(-0.227, 0.230)	0.9885
	498 5 mg	21 (19)	0.081	(-0.136, 0.298)	0.4580
Plasma triglycerides (mmol/L)	498 2 mg	21 (16)	-0.28	(-0.56, 0.01)	0.0590
	498 5 mg	21 (19)	-0.21	(-0.49, 0.06)	0.1269

HDL = high density lipoprotein; LDL = low density lipoprotein.

Functional magnetic resonance imaging (fMRI) data: In the food processing task, a statistically significant reduction in mean reaction time was observed in the high reward non-food trial for GSK1521498 2 mg compared with placebo, with a 390 msec reduction in change from baseline mean reaction time (p = 0.03). A statistically significant increase was observed for GSK1521498 2 mg compared with placebo in the interaction between contrasts 1 and 2 in the hypothalamus, with an increase of 30.62 AU compared with placebo (p = 0.002). Statistically significant decreases were observed for GSK1521498 2 mg for high reward non-food vs. low reward non-food in the hypothalamus and midbrain, with decreases of 17.1 AU and 15.7 AU, respectively, compared with placebo (p = 0.03 and 0.04, respectively).

In the reward processing task, statistically significant treatment effects were detected in the GSK1521498 5 mg group in both the proportion of high-probability stimulus in the money-neutral trial (9.6% reduction, p = 0.04) and in the price of chocolate won (p = 0.05) compared with placebo. No significant treatment effects were detected in the fMRI data.
In both the emotional processing task and erotic stimuli task, no statistically significant treatment effects were detected in either mean reaction time or fMRI data.
The fMRI analyses are ongoing at the time of writing. A very conservative approach was taken to analyse these data using the extraction of signal from specified ROI's to extract Beta values, but more robust methods are currently being explored using whole-brain analysis.

Pharmacokinetic/Pharmacodynamic Endpoints:

Change from baseline in body weight and fat mass: No clear trends relating GSK1521498 exposure to change from baseline in body weight or fat mass on Day 28 were apparent.

Change in total binge eating score on Day 27: No clear trend relating GSK1521498 AUC(0–24) to changes in total BES were apparent. However, between-subject variability in BES appeared to be reduced in subjects on active treatment relative to placebo with no clear difference between subjects receiving GSK1521498 2 mg or 5 mg.

Change in mean total energy intake: A potential trend for decreasing mean total energy intake (Days 14 and 28 combined) was apparent. A similar trend was noted for mean total energy intake for Day 28 alone. Total energy intake appeared to increase modestly relative to placebo in the 2 mg dose group [AUC(0–24) ranging from approximately 230 to 630 ng.h/mL)] with modest decreases relative to placebo in the 5 mg dose group [AUC(0–24) ranging from approximately 460 to 2250 ng.h/mL].

Change in mean Day 14 and 28 hedonic response: A clear trend for decreased hedonic response to dairy products was noted. Decreases in hedonic response were most apparent for subjects in the 5 mg dosing group [AUC(0–24) ranging from approximately 460 to 2250 ng.h/mL].

Change in mean *ad-lib* snacking: No clear trends relating GSK1521498 AUC(0–24) to *ad-lib* snacking energy intake for high fat/high sugar, low fat/high sugar or low fat/low sugar foods was noted for Days 14 and 28 combined. Consistent with this observation, no trends were apparent when comparing AUC(0–24) to energy intake on Day 28 alone. A trend relating GSK1521498 AUC(0–24) to decreased energy intake for the high fat/low sugar food category was noted for Days 14 and 28 combined. A similar trend was noted when comparing AUC(0–24) with energy for high fat/low sugar food caloric intake on Day 28 alone. Despite statistical significance on Day 14, no clear relationship between GSK1521498 AUC(0–24) and caloric intake for the low fat/high sugar category on Day 14 was apparent.

Change in Y-BOCS-BE on Day 27: No clear trends relating GSK1521498 exposure to Y-BOCS-BE compulsive, obsessive or total scores were apparent.

Caloric intake of high-fat (60% fat) dessert: A trend for decreased caloric intake of the high-fat dessert with increasing GSK1521498 exposure on Day 28 was noted.

Attentional bias score (2000 ms on Day 28): An apparent trend for decreased attentional bias score (2000 ms) with increasing GSK1521498 exposure was noted. Responses associated with the 2 mg dose group (AUC(0–24) range 230 to 630 ng.h/mL) were similar to placebo with a trend for the greatest decreases associated with the 5 mg dose group (AUC(0–24 range 460 to 2250 ng.h/mL).

Caloric intake for buffet meal (high fat) on Day 28: No apparent trend relating AUC(0–24) with caloric intake in for the buffet meal (high fat category) was noted.

Genetics: Exploratory genetic analyses by *OPRM1* rs1799971 G carriage was performed on the following endpoints: relative change in body weight at Day 28 compared with baseline, relative change in 24-h energy intake (kcal) at Day 28 compared with baseline, relative change in energy intake *ad-lib* snack at Day 28 compared with baseline and relative change in hedonic response at Day 28 compared with baseline. No statistically significant associations were revealed. Additional exploratory analyses are on-going at the time of writing.