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.

GSK Medicine: Orlistat
Study No: EMI111963
Title: A longitudinal Magnetic Resonance Imaging (MRI) Study of Changes in Regional Body Composition During Orlistat (60mg) - Assisted Dieting.
Rationale: Magnetic Resonance Imaging (MRI) measurements of abdominal visceral fat volume are more precise and have greater relevance to a range of health risks and clinical conditions than more commonly used measures such as total body fat, body weight, and body mass index (BMI). It previously has been shown that combining a reduced calorie, low fat diet with the lipase inhibitor orlistat 60mg, results in significantly greater overall weight loss than placebo plus diet. However, it is unknown whether this weight loss treatment (i.e., orlistat-60mg assisted diet) is accompanied by a reduction in visceral fat tissue, or changes in other tissue or fluid compartments. This study consists of two parts. Part I is a simple enabling study to confirm the similarity of the body fat MRI methodology established at the GlaxoSmithKline Clinical Imaging Centre to that in use at Hammersmith Hospital, and to establish the test-retest reliability of our implementation. Part II is a study to examine the change-from-baseline in body composition at 3 months with orlistat 60mg plus a reduced calorie, low fat diet (i.e., approx 30% of calories from fat).
Phase: IV
Study Period: 03 Feb 2009 to 28 Aug 2009
Study Design: An open label, non-randomized study conducted in two parts.
Centre: GlaxoSmithKline Clinical Imaging Centre, Hammersmith Hospital, London, UK
Indication: Obesity
Treatment: In Part II only, the subjects were instructed to take the Orlistat 60mg capsule orally, 3 times daily with each main meal and to take a multivitamin daily at least 2 hours before or after taking the medication.
Objectives: The primary objective in part 1 was to estimate the variation between Magnetic Resonance Imaging/Magnetic Resonance Spectroscopy data obtained from the same subjects studied at the Hammersmith Hospital and at the GlaxoSmithKline Clinical Imaging Centre. The primary objective in part 2 was to test for a change from baseline in visceral adipose tissue as measured by MRI following 3 months of orlistat 60mg plus a reduced calorie, low fat diet in overweight/obese subjects.
Statistical Methods: Part I; the statistical analyses were performed to study the variation between MRI/MRS measurements obtained from Hammersmith and the Clinical Imaging Centre. The test-retest reliability of these measurements at the Clinical Imaging Centre was also investigated. Final analyses included: - Bland-Altman plots of the mean against the difference of paired MRI/MRS (magnetic

Resonance Spectroscopy) values from each site to assess the variability of differences between measurements (same method used for test-retest reliability),
- the coefficient of variation for differences between paired values,
- the intra-class correlation coefficient was calculated to assess the agreement between the sites or between replicated measurements,
- scatter plots to visualise agreement between paired values (comparing sites or assessing test-re-test reliability).

Part II; changes in MRI/MRS and anthropometric endpoints were analysed with the following statistical methods:
- Analysis of covariance for changes from baseline (or ratios to baseline for log transformed endpoints) in MRI/MRS measurements,
- repeated measures analyses of anthropometric endpoints (weight, waist measurements, Body Mass Index),
- plots of mean changes from baseline with 95% confidence intervals

Study Population:

Healthy male or female between 18 and 60 years of age (inclusive) with normal eating habits (Part II).
Body Mass Index within the range of:
• 20 - 32 kg/m2 inclusive (Part I).
• 25 - 34.90 kg/m2 inclusive (Part II)
Approximately 1/3 of subjects BMI between 25.0-27.9 kg/m2
Approximately 2/3 of subjects BMI between 28.0-34.9 kg/m2
Waist circumference (Part II): Females: > 35 inches, Males: > 40 inches

Number of Subjects:	Part I	Part II
Planned N	10	26
Enrolled N	8	27
Number of subjects included in All Subjects (Safety) population, n:	8	26
Number of subjects completed as planned, n (%):	8	24 (88%)
Number of subjects withdrawn (any reason), n (%):		3 (11%
Number of subjects withdrawn for Adverse Event, n (%):		2 (7%)
Reasons for subject withdrawal, n (%)		
Adverse Event (AE)		2 (7%)
Investigator Discretion		1 (4%)
Demographics, All Subjects population,	N=8	N=26
Age in Years, Mean (Range)	34.5 (21-50)	39.8 (22-56)
Sex, n (%)		
Female:	3 (38%)	7 (27%)
Male:	5 (63%)	19 (73%)
BMI (kg/m^2), Mean (Range)	26.2 (20.9-31.1)	31.2 (27.3-35.6)
Height (M), Mean (Range)	1.76 (1.64-1.83)	1.74 (1.56-1.92)
Waist circumference (cm) (Range)	89.7 (72-102)	106.2 (90-121)
Weight, Mean (Range)	81.0 (56.1-96.4)	95.2 (73.3-122.5)

Race, n (%)		
African American/African Heritage	1 (13%)	2 (8%)
Asian - Central/South Asian Heritage	1 (13%)	1 (4%)
Asian - East Asian Heritage		1 (4%)
Asian – South East Asian Heritage		3 (12%)
White – White/Caucasian/European Heritage	6 (75%)	17 (65%)
Mixed Race		2 (8%)

Pharmacodynamic (PD) Endpoints:

Part I

MRI measures with the highest reproducibility were Visceral Adipose Tissue, Subcutaneous Adipose tissue, and total abdominal fat (i.e. visceral adipose tissue and Subcutaneous Adipose tissue combined) Inter-Muscular Adipose Tissue and Intra Hepatic Lipids were relatively less reproducible with higher Coefficient of Variation and lower Intra-Class Correlation.

The within-subject variability between Clinical Imaging Centre and Hammersmith Hospital was generally greater than the variability between repeat measurements done on the same individual at the Clinical Imaging Centre.

Part II

Change in MRI/MRS and other efficacy endpoints at Three Months

The results showed a significant reduction from baseline in most MRI measurements of adipose tissue.

There was a significant reduction from baseline in Visceral Adipose Tissue (-11%, p=0.0225), Subcutaneous Adipose tissue (-12%, p<0.0001), total abdominal fat (-12%, p=0.0001), and pericardial fat (-10%, p=0.0342). Inter-Muscular Adipose Tissue did not show any significant reduction.

A significant reduction in Intra Hepatic Lipids (-43%, p=0.0003) was observed, however there was no significant change in Intra-MyoCellular Lipids.

A significant reduction was observed from baseline in Body Mass Index (-6%), waist circumference (-5%), and weight (-6%) after (all ps<0.0001).

Significant reductions from baseline were also found for Low Density Lipoprotein and High Density Lipoprotein cholesterol, as well as heart rate and blood pressure. There was a significant reduction in High Density Lipoprotein levels and no significant change in triglyceride levels, over the 3 month treatment

Correlations between changes in endpoints at 3 months

Correlations between changes in MRI/MRS and clinical endpoints were also calculated.

Changes in Visceral Adipose Tissue were significantly correlated with changes in weight (r=0.68, p=0.0009). Changes in Subcutaneous Adipose tissue was significantly correlated with changes in weight (r=0.92, p<0.0001) and with changes in waist circumference (r=0.59, p=0.0094). Changes in Intra Hepatic Lipids was also significantly correlated with changes in weight (r=0.68, p=0.0005).

Changes in Visceral Adipose Tissue and Intra Hepatic Lipids were not significantly correlated with changes in waist circumference, although it is possible that this may be due to the relatively small sample size which only allows us to detect rather large levels of correlation.

Changes in MRI endpoints were highly correlated together, and some correlations could also be seen with safety endpoints.

Results are reported in full in the following published paper: [Thomas et al, Pragmatic

study of orlistat 60 mg on obesity. Eur J Clin Nutr 65(2011) 1256-62]		
Safety results: AEs and serious adverse event (SAE) data was collected throughout the duration of Part I and from study visit 1 (baseline) until follow-up during Part II		
AE: There were no Adverse events to report from Part I. A summary of Adverse events reported in Part II are listed below:	Event	Occurrence (percentage) (N=26)
Gastrointestinal Disorders		
	Diarrhoea	7 (27)
	Flatulence	1 (4)
	Haematochezia	1 (4)
	Proctalgia	1 (4)
Immune System Disorders	Seasonal Allergy	5 (19)
Infections and Infestations	Lower Respiratory Tract Infection	1 (4)
	Sinusitis	1 (4)
Nervous System Disorders	Headache	2 (8)
Injury, poisoning and procedural complications	Joint injury	1 (4)
Musculoskeletal and connective tissue disorders	Back pain	1 (4)
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	1 (4)
Serious Adverse Events: There were no SAEs recorded on this study.		