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Rapid review

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity

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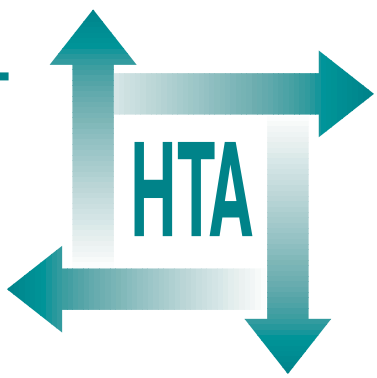
Health Technology Assessment
NHS R&D HTA Programme



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A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity

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Competing interests: Dr Susan Jebb, a member of the expert panel for this report, has been a member of the Roche Medical Advisory Board in the past and has undertaken industrial consultancy and educational projects on behalf of Roche. Professor Peter Kopelman, a member of the expert panel, has undertaken clinical trials in obese participants for Roche.

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Contents

List of abbreviations

ANCOVA	analysis of covariance*
ANOVA	analysis of variance*
BMI	body mass index
BP	blood pressure
CI	confidence interval
DBP	diastolic blood pressure
DEC	Development and Evaluation Committee
df	degrees of freedom
ECG	electrocardiogram
EMEA	European Medicines Evaluation Agency
GI	gastrointestinal*
HDL-C	high-density lipoprotein cholesterol
ITT	intention-to-treat
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
LSM	least squares mean
NA	not applicable*
NNT	number needed to treat*
NS	not stated*
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of the mean*
tds	three times per day*
VLDL-C	very-low-density lipoprotein cholesterol
WMD	weighted mean difference

* Used only in appendices

Executive summary

Background

The prevalence of obesity in developed societies is increasing. Obesity is associated with an increased risk of co-morbidity, including cardiovascular disease and diabetes. Following the withdrawal of fenfluramine and dexfenfluramine, interest has focused on a novel anti-obesity drug orlistat.

Objective

To systematically assess the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.

Methods

Search strategy

Nineteen electronic databases were searched from inception to June 2000. Additionally, Internet searches were carried out, bibliographies of retrieved articles were examined and submissions were received from the manufacturer of orlistat.

Inclusion and exclusion criteria

Randomised controlled trials (RCTs) evaluating the effectiveness of orlistat used for weight loss or maintenance of weight loss in overweight or obese patients were eligible for inclusion. Primary outcome measures were changes in body weight, fat content or fat distribution. Secondary outcomes were changes in obesity-related risk-factor profiles, such as lipid levels, indicators of glycaemic control and blood pressure. Studies recruiting people with eating disorders such as anorexia nervosa and bulimia nervosa were excluded.

Process of study selection

Assessment of titles and abstracts was performed independently by two reviewers. If either reviewer considered a reference to be relevant, the full paper was retrieved. Full papers were assessed against the review selection criteria by two independent reviewers, and disagreements were resolved through discussion.

Data extraction

Data were extracted by one reviewer into structured summary tables and checked by a second reviewer. Any disagreements about data were resolved by discussion.

Quality assessment

Each included trial was assessed against a comprehensive checklist for methodological quality. Quality assessment was performed independently by two reviewers with disagreements resolved by discussion.

Methods of analysis/synthesis

This report is a narrative summary, with results grouped according to study endpoint. Statistical pooling was undertaken in groups of trials that were considered to be sufficiently similar.

Estimation of quality of life, costs and cost-effectiveness and/or cost per quality-adjusted life-year

Relevant economic evaluations were identified from the search strategy described above. Assessment of methodological quality was undertaken using principles outlined in published guidelines.

Company submissions

Data from company submissions were subject to the same selection and appraisal processes as other studies considered for inclusion in the review, except that only RCTs with a duration of at least 1 year were selected.

Results

Results of the search strategy

Fourteen RCTs (including three company submissions) and two economic evaluations (including one company submission) were included in the review.

Results of the quality assessment

Methodological quality of trials was moderate to good. The main problems were lack of detail on methods used to produce true randomisation, small sample sizes in some cases and failure to use intention-to-treat analysis. It is likely that

maintenance of blinding was difficult due to adverse effects associated with the study medication.

Evidence of clinical effectiveness and cost-effectiveness

Most of the trials showed greater weight loss and better weight maintenance with orlistat compared to placebo at all endpoints (statistically significant differences for both outcomes). Orlistat 120 mg three times daily was the optimum regimen in terms of weight loss. Most trials showed significant improvement in at least some lipid concentration parameters, and, in three RCTs, orlistat produced statistically significant reductions in blood pressure relative to placebo. In obese patients with type 2 diabetes, orlistat resulted in a significantly greater weight loss at 1 year compared with placebo, and some parameters of glycaemic control and lipid concentration also showed significantly greater improvements compared with placebo. The incidence of gastrointestinal adverse events was consistently higher in orlistat groups compared with placebo, and orlistat use was associated with lower serum levels of fat-soluble vitamins.

The cost per quality-adjusted life-year for orlistat was £45,881.

Conclusions

Implications for clinical practice

Although many trials have demonstrated statistically significant differences between groups in terms of weight loss in favour of orlistat versus placebo, the differences may not always be of clinical significance. The clinical significance of between-group differences for secondary outcomes may also be debatable. Possible adverse effects should be taken into account when prescribing orlistat, particularly gastrointestinal effects.

Implications for future research

Future trials should ensure good methodological quality. Further research is required to determine the effects of orlistat in different patient groups according to gender, age, ethnicity and social class. Clinical trials should be designed to match protocols observed in clinical practice with regard to patient selection and treatment.

Chapter 1
Background

The prevalence of obesity

Epidemiological surveys in England indicate that the prevalence of obesity, defined as a body mass index (BMI) of greater than 30 kg/m^2,[1] is increasing.[2–4] In 1994, it was estimated that, for those aged over 16 years, 44% of men were classified as overweight (BMI > 25–30 kg/m^2) and 13% classified as obese (BMI > 30 kg/m^2). For women, the figures were 31 and 16%, respectively. In 1998, the respective figures had risen to 46 and 17% in men, and 32 and 21% in women.[4] Projected figures for 2000 for prevalence of overweight individuals and obesity in both sexes were 50 and 20%, respectively.[5]

Those at risk of becoming obese

It is deemed that large sections of the population in developed societies are at risk of developing obesity.[6] Those considered to be particularly at risk include Asian people,[7] children from families where one or both parents are overweight or obese[8–10] and those giving up smoking.[11] High birth weight may also be associated with an increased risk of obesity later in life.[10]

The risk of obesity is also associated with social class (defined as social class of head of household) and household income. In 1998, it was estimated that 14% of women in social class I were obese, compared with 18% in social class III (non-manual) and 28% in social class V. However, the pattern of association was less clear for overweight women and for obese and overweight men. In terms of household income, the prevalence of obesity in both sexes decreases as income increases. However, the relationship between income and being overweight in both sexes is less clear. These data are age-standardised.[4] Findings from a systematic review of childhood predictors of adult obesity showed that there is a link between low socio-economic status in early life and obesity in adulthood.[10]

The risk of becoming obese increases with age, up to a certain point, in both sexes. In 1998, it was estimated that 16% of men aged 25–34 years were obese (BMI > 30 kg/m^2), compared with 23% aged 55–64 years. For women, the respective figures were 16 and 29%. It should be noted, however, that the BMI tends to decrease in older people. This decline begins between 65 and 74 years in men, and from 75 years onwards in women.[4] It is also thought that men and women are at greater risk of becoming obese at certain points in the life cycle, with an increased risk for men during the late 30s. Women may be more vulnerable when entering marriage, during pregnancy, during the menopause and at retirement.[1]

Health risks of obesity

Health risks of obesity include increased risk of coronary heart disease, hyperlipidaemia, hypertension, diabetes, cholelithiasis, degenerative joint disease, social and psychological problems[12] and obstructive sleep apnoea.[13–16] More specifically, there is a link between android or abdominal obesity and coronary heart disease, hypercholesterolaemia, hypertension and diabetes.[17–19]

It has been suggested that even modest reductions in weight may be associated with health benefits, with reductions in blood pressure (BP), cholesterol and triglycerides achievable with just a 5–10% reduction in initial body weight.[20] In order to obtain long-term health benefits, however, weight loss must be maintained. Concern has been expressed over weight cycling (or 'yo-yo dieting') whereby some individuals alternate between periods of weight loss and weight regain. However, the association between weight cycling and morbidity remains unclear.[21–25]

Measurements of obesity

Definitions of the terms 'overweight' and 'obesity' vary between studies. The BMI (body weight in kg divided by the height in m^2) is frequently used as a method of classification in research, clinical practice and public health settings (*Table 1*).[26] However, the BMI does not take into account factors such as size of body frame, proportion of lean mass, gender and age. Measures of central obesity, such as waist circumference, are

TABLE I *Classification of weight according to BMI level*[26]

World Health Organisation classification	BMI (kg/m^2)	Risk of comorbidities
Underweight	< 18.5	Low (but risk of other clinical problems increased)
Normal range	18.5–24.9	Average
Overweight	25.0–29.9	Mildly increased
Obese	≥ 30.0	
Class I	30.0–34.9	Moderate
Class II	35.0–39.9	Severe
Class III	≥ 40.0	Very severe

considered to be better predictors of cardiovascular risk.[17] Other measurements include body weight, percentage over ideal body weight, skinfold thickness and other more detailed measures of body composition, such as densitometry.

Options for the management of obesity

A range of interventions is available for the management of overweight and obesity. These include work/school/community programmes (for primary prevention), dietary modification, exercise programmes, behaviour modification programmes, pharmacological agents, commercial programmes (e.g. Weight Watchers) and alternative therapies. Surgery is usually reserved for those suffering from very severe obesity (BMI > 40 kg/m^2), for whom less invasive methods of weight loss have failed. The various weight management strategies may be used alone or in combination. A number of literature reviews have covered the broad range of interventions available,[27–30] and recent reports have offered guidelines for the management of obesity.[28,31]

Pharmacological agents used to treat obesity

In 1997, dexfenfluramine and fenfluramine were withdrawn by the manufacturer due to reported cases of valvular heart disease. Following this event, interest in a novel anti-obesity agent, orlistat, was intensified.

Orlistat

Orlistat (Xenical®) is produced by Roche Products Limited, Welwyn Garden City, UK. The parent company is Hoffmann-La Roche. It has been licensed in the UK since September 1998 as an anti-obesity drug, and was approved by the Food and Drug Administration in April 1999. Orlistat is an inhibitor of gastric and pancreatic lipases, and inhibits the hydrolysis of dietary triglycerides, consequently limiting the absorption of monoglycerides and free fatty acids. Orlistat is indicated for patients with a BMI of ≥ 30 kg/m^2, or a BMI of ≥ 28 kg/m^2 in the presence of other risk factors, such as hypertension, diabetes or hyperlipidaemia.[32]

Orlistat is contraindicated in patients with chronic malabsorption syndrome or cholestasis, in pregnancy or while breastfeeding and in patients with known hypersensitivity to orlistat or to any component of this product. Adverse effects include liquid oily stools, faecal urgency, flatulence and, less frequently, abdominal and rectal pain, headache, menstrual irregularities, anxiety and fatigue.[32]

Orlistat is licensed for use with a mildly hypocaloric diet.[32] Prescribing guidelines indicate that treatment with orlistat should only be initiated in patients who have achieved a weight loss of at least 2.5 kg in 4 weeks using a dietary programme alone.[32,33] It is also recommended that orlistat treatment should be discontinued after 12 weeks in patients who lose less than 5% of their initial body weight.[33] European prescribing guidelines reflect these recommendations and state that the duration of treatment with orlistat should not be longer than 2 years.[34]

Other drugs

Sibutramine (Meridia®) is produced by Knoll Pharmaceutical Company (BASF Pharma is the parent company). It is not yet licensed for any use in the UK, but was approved by the Food and Drug Administration in the USA in November 1997 for the treatment of obesity. It is a dopamine, norepinephrine and serotonin reuptake inhibitor, and also stimulates thermogenesis, thus increasing energy expenditure. Sibutramine is indicated

in the management of patients with a BMI of ≥ 30 kg/m^2, or in those with a BMI of ≥ 27 kg/m^2 in the presence of other risk factors (i.e. hypertension, diabetes or hyperlipidaemia).

Sibutramine increases BP in some patients and, therefore regular monitoring is required. It is contraindicated in those receiving monoamine oxidase inhibitors, patients with hypersensitivity to sibutramine or any of the inactive ingredients of sibutramine, sufferers of anorexia nervosa and those taking other centrally acting appetite suppressants.

More frequent adverse effects include dry mouth, anorexia, insomnia and constipation. Other potential adverse effects are fever, diarrhoea, flatulence, gastroenteritis, tooth disorders, peripheral oedema, arthritis, agitation, leg cramps, hypertonia, abnormal thinking, bronchitis, dyspnoea, pruritus, amblyopia, menstrual disorders, seizures, ecchymosis bleeding disorders and interstitial nephritis.

This information about sibutramine was obtained from RxList <http://www.rxlist.com> on 26th June 2000.

In addition to orlistat, two other drugs are currently licensed in the UK for the treatment of obesity.[32] One of these is the bulk-forming agent methylcellulose (Celevac®, Monmouth, UK), which is deemed to reduce food intake by producing a feeling of satiety. However, there is little evidence to support this claim.[35] Patients taking this drug must be advised to maintain an adequate fluid intake. Contraindications to its use are gastrointestinal obstruction, and adverse effects include flatulence, abdominal distension and gastrointestinal obstruction. The other is phentermine (Duromine®, 3M and Ionamin®, CHS), which is a catecholaminergic drug with sympathomimetic and stimulant effects. It is licensed for use as an adjunct to the treatment of selected patients with moderate to severe obesity, with prescription restricted to a maximum of 12 weeks. Phentermine is associated with the rare but serious risk of pulmonary hypertension which may be insidious, as well as a number of less serious adverse effects. Cautions include mild hypertension (avoid if moderate or severe), diabetes mellitus and a history of anxiety or depression, and associated contraindications are cardiovascular disease, glaucoma, hyperthyroidism, epilepsy, unstable personality, history of psychiatric illness, history of drug/alcohol abuse, pregnancy and breastfeeding.

This review will not assess the effectiveness of methylcellulose or phentermine. The clinical effectiveness and cost-effectiveness of sibutramine will be considered in a separate report.

It is generally agreed that pharmacological agents are unsuitable for use as a sole treatment, but, rather, should be employed as an adjunct to other weight-loss interventions, such as prescribed diet, exercise or behavioural therapy. Published guidelines for the management of obesity from the Royal College of Physicians and the Scottish Intercollegiate Guidelines Network endorse this view,[28,31] as do prescribing guidelines.[32] Further recommendations from the Royal College of Physicians state that anti-obesity drugs should not be prescribed for longer than 12 weeks initially. After this time, weight loss should be assessed and therapy should be discontinued in patients who have not achieved at least 5% reduction of initial weight. Prescription may be continued beyond this period for patients attaining at least 5% loss of initial body weight, provided body weight is continually monitored and weight is not regained.[31]

At present, drugs are not normally used for childhood obesity because of the risks of growth suppression. Most of the research literature has so far reflected their use in adults aged up to 75 years.[27]

Aim of the review

To assess systematically the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity. In this context, the term 'management' covers both weight-loss and weight-maintenance programmes. The review considers both overweight and obese people, and the main outcomes of interest are those reflecting changes in body weight, fat content or fat distribution. Other relevant health-related outcomes are also be considered.

Chapter 2
Methods

Search strategy

The following electronic databases were searched from inception to the end of June 2000 to locate information on the clinical effectiveness and cost-effectiveness of orlistat (using both generic and brand names) in the treatment of obesity.

- Allied and Complementary Medicine database
- BIOSIS
- British Nursing Index
- Cochrane Library CD-ROM (2000 issue 2)
- Cumulative Index to Nursing and Allied Health Literature
- Database of Abstracts of Reviews of Effectiveness
- DH-Data
- EconLit
- EMBASE
- Health Management Information Service database
- Health Technology Assessment database
- Index to Scientific and Technical Proceedings
- King's Fund Database
- MEDLINE
- National Research Register (2000 issue 1)
- NHS Economic Evaluation Database
- Office of Health Economics Health Economic Evaluations Database
- Science Citation Index
- Social Science Citation Index.

The search strategy used is provided in appendix 1.

In addition, searches were carried out on the internet using the Hoffmann-La Roche website, pharmaceutical databases, such as PharmInfo Net <http://www.pharminfo.com/> and RxList <http://www.rxlist.com>, biomedical search engines, such as OMNI <http://www.omni.ac.uk>, meta-search engines, such as The BigHub <http://www.thebighub.com/>, and general search engines, such as Alta Vista <http://www.altavista.com/>.

The reference lists of relevant reviews and included trials were checked in order to identify further eligible evaluations. When relevant conference abstracts were identified, authors were contacted and requested to provide a full report (for trials) or a bibliography (for reviews). In addition, material was submitted from the manufacturer of orlistat.

Inclusion and exclusion criteria

In order to be included in the review, studies had to fulfil criteria relating to study design, participant characteristics, interventions and outcomes.

Study design

Randomised controlled trials (RCTs), incorporating any duration of therapy and any length of follow-up, were considered for inclusion in the review. The exception to this was that, for company submissions, only RCTs with a duration of at least 1 year were selected. This post-hoc decision was taken in light of the time constraints of the review.

Participants

The following were included in the review:

- RCTs recruiting participants defined as being overweight or obese
- RCTs recruiting participants wishing to maintain weight loss, having been previously overweight or obese.

Definitions of obesity and being overweight varied between studies. Trials involving specific patient groups, such as those with diabetes, hypertension or hyperlipidaemia, were included in the review provided they met the above criteria.

However, studies recruiting participants who were not overweight or obese, but who wished to achieve weight loss were excluded. Evaluations for which mixed participants were recruited (e.g. some with healthy weight and some overweight/obese) were only included if results were presented separately for the overweight/obese patients. In addition, studies recruiting people with eating disorders, such as anorexia nervosa and bulimia nervosa, were excluded. In trials to which overweight/obese participants were recruited as well as those with the above eating disorders, only those where results were presented separately for the overweight/obese participants were included.

Interventions

Evaluations of orlistat used to treat overweight/obese patients or maintain weight loss in previously overweight/obese patients were considered for inclusion in the review. Orlistat could be combined with other strategies such as dietary restriction or behavioural programmes, and participants in control groups could receive placebo, an alternative anti-obesity pharmacological agent or an alternative anti-obesity intervention (e.g. based on dietary regimen, physical activity or behavioural modification).

Outcomes

The primary outcome of the review was an assessment of obesity/overweight status measured as changes in body weight, fat content or fat distribution.

- Measures of weight change include absolute weight change and percentage weight change relative to baseline.
- Measures of fat content include BMI, ponderal index, skin fold thickness, fat free mass and fat change.
- Measures of fat distribution include waist size, waist:hip ratio and girth:height ratio.

In order to be included, trials had to report measurements at baseline and post-intervention.

The secondary outcomes were physiological changes occurring in association with changes in body weight/fat content/fat distribution. The most common examples of these were changes in lipid profiles, glycaemic control among those with diabetes and BP among those with hypertension. Where available, data were recorded on patient-related quality of life (QoL).

Data on adverse effects and costs were also reviewed, where available.

Language restrictions

Only studies published in English, French, Dutch or German were considered for inclusion in the review.

Process of study selection

All titles and abstracts were assessed independently by two reviewers. If either reviewer considered a reference to be potentially relevant, a hard copy of the paper was retrieved for further consideration. Full papers were assessed against the selection criteria detailed above (see the pre-screen form in appendix 2). Pre-screening was performed independently by two reviewers, and disagreements were resolved through discussion or by recourse to a third reviewer.

Data extraction

The following data were extracted from each included trial: author(s), year of publication, country of study, study aim, method of randomisation, outcomes measured, setting of treatment, duration of treatment and follow-up, participant selection criteria, baseline comparability of groups, intervention characteristics, results per treatment arm, incidence of adverse effects and numbers of/reasons for withdrawal. Data were extracted by one reviewer into standardised structured tables (see appendix 3) and were checked by a second reviewer, and any disagreements about data were resolved through discussion. Where multiple publications of the same study were identified, every publication was examined to ensure that all relevant data for that particular study were recorded and data were presented as a single entry.

Quality assessment

Each included trial was assessed against a comprehensive checklist for methodological quality. The following aspects of quality were assessed: method of randomisation, participant selection criteria, sample size, comparability of treatment arms, blinding, statistical analysis and description of withdrawals (see appendix 4). Quality assessment was performed independently by two reviewers with disagreements resolved through discussion.

Methods of analysis/synthesis

A narrative summary of results has been presented here, with results grouped according to study endpoint and type of weight-management programme (weight loss or weight maintenance). Statistical pooling (meta-analysis) has been undertaken for groups of trials that were considered to be sufficiently similar. For continuous data, a pooled weighted mean difference (WMD) was generated and a summary relative risk (RR) was calculated for dichotomous variables.

The WMD is a method of meta-analysis used to combine measures on continuous scales (e.g. body weight) where the mean, standard deviation (SD) and sample size in each group are known. The

weight given to each study (i.e. how much influence each study has on the overall results of the meta-analysis) is determined by the precision of its estimate of effect and, in the statistical software in RevMan (as used in this review), is equal to the inverse of the variance. This method assumes that all of the trials have measured the outcome on the same scale.[36]

The RR is the ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in that group. An RR of 1.0 indicates no difference between comparison groups. For undesirable outcomes, an RR < 1.0 indicates that the intervention was effective in reducing the risk of that outcome.[36] In this review, the summary RR was calculated in terms of the risk of failure to achieve 5 or 10% loss of initial body weight.

A random-effects model was employed for both WMD and RR, and 95% confidence intervals (CIs) were presented with the central-effect estimates. The results of related statistical tests for heterogeneity have been presented with each analysis. Statistically significant heterogeneity was considered to be present when the associated *p*-value was < 0.10. The meta-analyses were generated using Metaview 4.1 (Review Manager 4.1, 2000 The Cochrane Collaboration).

Estimation of QoL, costs and cost-effectiveness and/or cost per quality-adjusted life-year

The following specialist sources were searched to identify relevant economic literature: EconLit, NHS Economic Evaluation Database and the Office of Health Economics Health Economic Evaluations Database. Identified economic evaluations were submitted to the same study selection and data-extraction process as studies of clinical effectiveness. Assessment of methodological quality was undertaken using principles outlined in published guidelines.[37] Data extraction and quality assessment tables for economic evaluations are shown in appendices 5 and 6, respectively.

Chapter 3
Results

Results of the search strategy

The search strategy (see chapter 2 and appendix 1) generated 658 references of possible relevance to this review. Once titles (and abstracts, where available) had been assessed, hard copies of 187 papers were examined (please note that these figures relate to the joint review of the two drugs orlistat and sibutramine). Overall, 14 RCTs of orlistat met the selection criteria of the review. These included 11 published RCTs,[38–48] and three RCTs identified from company submissions.[49–51] In addition, two economic evaluations were identified, one published[52] and one from company submissions.[53] Details of published studies are summarised in appendix 3 (RCTs) and appendix 5 (economic evaluation).

Quality assessment

Published RCTs (see appendix 4)

Eleven published trials of orlistat were included.[38–48] One trial reported the use of procedures to produce true randomisation,[41] in one it was unclear[44] and in all other trials it was not stated. All trials used concealment of randomisation (assumed from the use of the description 'double-blind'), but methods used to achieve concealment were not described. All trials reported participant selection criteria. Two trials provided details of an *a priori* power calculation for sample size.[41,44] Two trials allocated between 20 and 50 participants per group,[38,39] one trial recruited 60 participants per group[46] and eight trials recruited over 100 patients per group.[40–45,47,48] All reported baseline comparability of treatment groups, indicated intention to provide identical treatment to patients apart from the drugs under study and blinded patients. In all cases, it was unclear whether caregivers were blinded, although all the trials were described as double-blind. The same was true for blinding of outcome assessors, except in one trial where it was stated that they were blind.[44] None of the trials reported assessment of blinding of patients, caregivers or outcome assessors. All trials described statistical methods used, but three did not provide variance around central estimates.[40,44,46] Most of the trials did not require adjustment for baseline imbalance because study groups appeared to be comparable. The one exception to this was a trial in which baseline body weight was noted to be higher in orlistat-treated patients ($p < 0.05$),[45] however, methods used to adjust for this were not described. Eight trials described ways in which missing data were dealt with[38,40–45,48] and nine included analyses based on intention-to-treat (ITT).[38,40–45,47,48] All trials reported the number of withdrawals per treatment group with reasons. Patient adherence with the study regimen was assessed in 10 trials,[38–44,46–48] but in four of these this involved the run-in period only.[41,43,47,48]

RCTs from company submission

Three trials were included from the company submission.[49–51] The details relating to the methodological quality of these trials have been declared as commercial-in-confidence by the manufacturers of orlistat and are, therefore, not provided in this report.

Results from published RCTs of orlistat

The most important findings have been outlined in the text of the review. The reader may also refer to the data extraction table (appendix 3) for more detailed information, for example, for specific values in connection with study outcomes where these are not mentioned in the text. 'Significant' means statistically significant unless otherwise stated.

Eleven published trials of orlistat were identified.[38–48] Two trials had a 12-week endpoint,[38,39] two had a 6-month endpoint,[40,46] two had a 1-year endpoint,[41,47] four reported results of a 1-year weight-loss programme followed by a 1-year weight-maintenance programme[42–44,48] and one focused solely on weight maintenance.[45]

RCTs with a 12-week endpoint

Two RCTs conducted by the same research group were identified.[38,39] Both trials were small, recruiting numbers per treatment arm of approximately 20[39] and 45.[38] In the earlier trial,[39] obese, but otherwise healthy, patients were recruited that were aged 18–55 years with body weight 20–50%

above ideal measurement. The other trial had the following inclusion criteria: obese, but otherwise healthy, patients that were aged 25–60 years with a BMI of 27.8–35.0 kg/m^2 for men and 27.3–35.0 kg/m^2 for women.[38] Participants in both trials underwent a 4-week single-blind placebo run-in period during which they were instructed to commence a calorie-restricted diet with an energy deficit of 500 kcal/day, which continued during the double-blind treatment phase.[38,39]

In the earlier trial, participants were only eligible to enter the double-blind phase if they had achieved a weight loss of 0.5–4.0 kg during the run-in period. They were then randomly allocated to receive either orlistat 50 mg three times per day or placebo for 12 weeks.[39] For the other trial, patients were eligible to enter double-blind treatment if they had adhered to both the dietary and drug regimens. Adherence with the dietary programme was defined as a body-weight reduction of 0–4 kg (note that this includes no weight loss at all) and a deviation of less than 20% from the prescribed intake of total calories and calories as fat in three out of four calculations from dietary records. Adherence with the drug regimen was assessed by counting returned placebo capsules and at least 80% was required to have been used. This was a dose-ranging study in which patients were allocated to receive orlistat 120, 60 or 10 mg three times daily or placebo.[38]

Patients receiving the highest dose of orlistat (120 mg three times daily) lost significantly more weight compared with placebo (–4.74 versus –2.98 kg, $p = 0.001$, values adjusted for weight loss during run-in), however, comparisons between other groups did not result in a statistically significant difference.[38] For the other trial, patients in the orlistat group (50 mg three times daily) lost significantly more weight than those receiving placebo (–4.3 versus –2.1 kg, 95% CI for the difference in weight loss, 0.2 to 4.2), with weight loss being assessed from the start of randomisation.[39]

In terms of cardiovascular risk factors, cholesterol and triglyceride levels did not change during the study in either group in the earlier trial.[39] In addition, there were no significant changes in BP, heart rate, biochemical or haematological parameters in either group, however, it is unclear whether these outcomes were assessed from the start of the run-in period or from the start of randomisation.[39] For the dose-ranging trial, patients receiving the two higher doses of orlistat achieved significantly reduced levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C). LDL-C to high-density lipoprotein cholesterol (HDL-C) ratio was significantly reduced in patients treated with the highest dose of orlistat compared to those treated with placebo, but there were no statistically significant between-group differences in levels of triglycerides at 12 weeks.[38]

Adverse events and withdrawals

In one trial, one patient withdrew from the orlistat group due to adverse events, which included episodes of faecal incontinence. The incidence of adverse events did not differ significantly between groups, with the exception of gastrointestinal adverse events, which were more frequent in the orlistat group. Gastrointestinal effects included abdominal pain, liquid stools, faecal incontinence, urgency, oily stools, nausea, vomiting, flatulence and haemorrhoids, most of which were reported as mild or moderate in intensity. For most patients, serum levels of vitamins A and E remained within reference values during the trial, and changes in serum levels of vitamin D and β-carotene were not reported.[39]

In the dose-ranging trial, *p*-values were not provided for the between-group differences for changes in serum levels of vitamins A and D at 12 weeks. However, there were statistically significant reductions in serum levels of vitamin E in the orlistat 60 and 120 mg three times daily groups compared with placebo ($p < 0.01$ for both comparisons); the *p*-value was not reported for orlistat 10 mg three times daily versus placebo. Most adverse events were reported as mild to moderate and were described as being common in the orlistat groups, particularly at the two higher doses. Severe adverse events, defined as those that were very inconvenient to patients, were observed in small percentages of patients, again at the two higher doses. One patient in the orlistat 10 mg three times daily group and three in the 120 mg three times daily group withdrew due to adverse effects.[38]

Pooled analyses of RCTs with a 12-week endpoint

Results from both trials were pooled for change in body weight at 12 weeks comparing orlistat 50–60 mg three times daily with placebo.[38,39] The pooled between-group difference was not statistically significant with a WMD of –1.24 kg (95% CI, –2.65 to 0.16, $p = 0.08$; test for

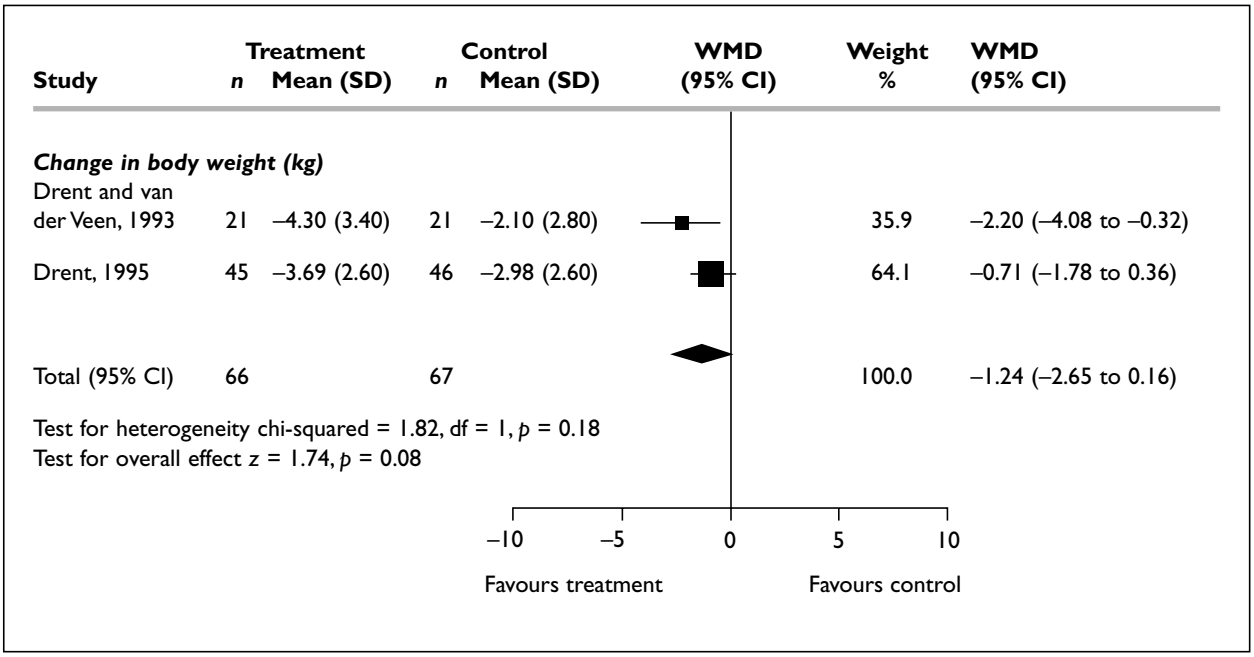

FIGURE 1 *Change in body weight at 12 weeks for orlistat 50–60 mg three times daily versus placebo*

heterogeneity chi-squared = 1.82, degrees of freedom (df) = 1, $p = 0.18$; see *Figure 1*).

RCTs with a 6-month endpoint

Two trials were identified,[40,46] one of which was a dose-ranging study.[40]

RCT by Micic and colleagues[46]

In the trial by Micic and colleagues,[46] patients aged 18–75 years with a BMI of at least 30 kg/m^2 were included. All patients underwent a 2-week single-blind placebo run-in period and commenced a calorie-restricted diet (minimum intake of 1200 kcal/day) with an energy deficit of 600 kcal/day, which continued in the double-blind phase. During the double-blind phase, patients were randomised to receive orlistat 120 mg three times daily or placebo and about 60 participants were allocated to each treatment arm.[46]

All reported changes were assessed relative to baseline values. At 24 weeks, the mean weight loss was –10.75 kg in the orlistat group and –7.34 kg in the placebo group. The results of tests of statistical significance were not reported. There was no statistically significant difference between groups for the number of patients achieving a reduction in BMI of < 4 kg/m^2, however, more patients in the orlistat group achieved a reduction of 4–12 kg/m^2 relative to placebo (48 versus 28%, $p < 0.05$).[46]

More patients in the orlistat group achieved reductions in total cholesterol and LDL-C levels and in the LDL-C:HDL-C ratio, however, the results of tests of statistical significance were not reported. Levels of HDL-C increased by 0.95% in orlistat patients and decreased by 2.5% in placebo patients and total triglyceride levels decreased by 5.32% and increased by 7.1%, respectively. There were no statistically significant differences between treatment and control groups in mean values of systolic BP (SBP) and diastolic BP (DBP). Analysis of heart rate, electrocardiogram (ECG) and laboratory tests showed no significant differences between groups.[46]

Adverse events and withdrawals

One orlistat-treated patient withdrew due to adverse events compared to none in the placebo group. In the orlistat group, 29 patients complained of gastrointestinal adverse events compared to 11 in the placebo group. Of these, 27 and eight patients, respectively, suffered from oily stools. The intensity of adverse effects was usually described as mild or moderate.[46]

RCT by van Gaal and colleagues[40]

Patients aged at least 18 years with a BMI of 28–43 kg/m^2 were eligible for inclusion in this dose-ranging trial.[40] All patients underwent a 4-week single-blind placebo run-in period during which a calorie-restricted diet was prescribed. The minimum daily intake was 1200 kcal/day and the energy deficit was 600 kcal/day. This continued during the double-blind treatment period when patients were randomised to receive

orlistat 240, 120, 60 or 30 mg three times daily or placebo. About 120 participants were allocated to each treatment arm.[40]

The percentage weight loss relative to initial weight at 24 weeks was 6.5% for placebo and 8.5, 8.8, 9.8 and 9.3% for orlistat 30, 60, 120 and 240 mg three times daily, respectively. It was unclear if the weight loss was dose-dependent. Analysis based on least squares mean (LSM) differences indicated that weight losses with orlistat 60, 120 and 240 mg three times daily were all significantly better than placebo ($p \leq 0.002$).[40] The LSM difference is the expected value of the treatment means for a balanced design with all the covariates at their mean value. It takes into account differences that exist between treatment groups at baseline for the covariates and adjusts for them.[43] The percentage of patients losing more than 10% of their initial body weight were 19, 28, 28, 37 and 38% for placebo and orlistat 30, 60, 120 and 240 mg three times daily, respectively, and the reductions in waist circumference were 3.5, 5.1, 5.9, 6.3 and 6.0 cm, respectively.[40]

Adverse events and withdrawals

The rate of withdrawal due to adverse events was 2% in the placebo group and 6, 5, 2 and 3% in the orlistat 30, 60, 120 and 240 mg three times daily groups, respectively, and the rates of adverse events were 69, 79, 83, 84 and 87%, respectively. Most adverse events were described as mild to moderate in intensity. With the exception of gastrointestinal adverse effects, they were considered to be mostly unrelated to treatment. Rates of gastrointestinal adverse events in the different groups were 46% for placebo and 61, 76, 71 and 83% for orlistat 30, 60, 120 and 240 mg three times daily, respectively. Most of the orlistat-treated patients experienced one or two episodes of gastrointestinal events, generally within the first few weeks of initiating treatment, and 11 patients withdrew due to gastrointestinal events, 10 of whom were treated with orlistat.[40]

No abnormalities associated with orlistat use were observed from laboratory tests or in terms of hepatocellular damage, ECG measurements or vital signs. The percentage of patients with low serum levels of fat-soluble vitamins on two or more consecutive occasions ranged between 3.3% for the placebo group and 12.8% for the group treated with the highest dose of orlistat, and it appeared to be dose-related.[40]

RCTs with a 1-year endpoint

Two trials with a 1-year endpoint were identified.[41,47]

RCT by Hollander and colleagues[47]

The trial by Hollander and colleagues[47] recruited only people with type 2 diabetes maintained on oral sulfonylureas for the 6 months prior to the trial. Additionally, eligible patients had a stable blood glucose, were aged over 18 years and had a BMI of 28–40 kg/m^2. All patients underwent a 5-week single-blind placebo run-in period. During this time a mildly hypocaloric diet was commenced. Those who achieved at least 70% adherence with the drug regimen during the run-in, assessed by counting returned placebo capsules, were eligible to enter the double-blind trial in which they were randomised to receive either orlistat 120 mg three times daily or placebo. About 160 participants were allocated to each treatment arm.[47]

ITT analysis of the LSM difference in weight loss between treatment groups was 2.4 kg in favour of orlistat ($p < 0.001$), calculated from the beginning of the run-in period to endpoint. In the orlistat group, 49% of patients lost at least 5% of their initial weight compared with 23% in the placebo group, and the between-group difference was statistically significant ($p < 0.001$). The respective figures for ≥ 10% loss of initial body weight were 18 and 9%, respectively ($p < 0.02$). The mean decrease in waist circumference was 4.8 cm with orlistat and 2.0 cm with placebo ($p < 0.01$).[47]

Orlistat patients achieved significantly better glycaemic control compared to placebo patients in terms of decreased glycosolated haemoglobin (–0.28 versus 0.18%, $p < 0.001$) and fasting plasma glucose (–0.02 versus 0.54 mmol/l, $p < 0.001$). A total of 43% of orlistat-treated patients decreased the dose of sulfonylureas, compared with 29% of the placebo group, and 12% of orlistat-treated patients discontinued sulphonylurea medication compared to none in the placebo group. The between-group difference for mean decrease in fasting insulin levels at 1 year was not statistically significant. Orlistat resulted in significantly greater improvements than placebo in several lipid parameters, including greater reductions in total cholesterol ($p < 0.001$), LDL-C ($p < 0.001$), triglycerides ($p < 0.05$), apolipoprotein B ($p < 0.001$) and LDL-C:HDL-C ratio ($p < 0.001$).[47]

Adverse events and withdrawals

At least one gastrointestinal adverse event was experienced by 79% of orlistat patients compared with 59% of placebo patients. Mild to moderate transient gastrointestinal events were reported with orlistat therapy, which usually occurred

early during treatment and usually resolved spontaneously. There were 12 withdrawals due to adverse events in the orlistat group and 23 in the placebo group. Withdrawals due to gastrointestinal adverse events totalled seven in the orlistat group and two in the placebo group. Serum levels of fat-soluble vitamins generally remained within the reference range, apart from levels of vitamin E and β-carotene, which were significantly lower with orlistat versus placebo at 1 year ($p < 0.001$). Vitamin D supplementation was required in 17% of orlistat patients and 7% of controls, vitamin E in 1% of both groups and β-carotene in 9% of the orlistat group. Prothrombin times did not differ between groups and did not fall below the reference range.[47]

RCT by Finer and colleagues[41]

In the second trial,[41] participants with a minimum age of 18 years and a BMI of 30–43 kg/m^2 were recruited. Patients with diabetes were excluded. All participants underwent a 4-week single-blind run-in phase, during which time they received placebo and commenced a low energy diet. Each individual patient's diet was calculated from estimated total daily energy expenditure minus 600 kcal/day, with a minimum prescribed energy intake of 1200 kcal/day. This dietary regimen continued for the first 24 weeks of the double-blind phase. After this, the prescribed daily energy intake was further reduced by 300 kcal/day for all patients regardless of whether or not body weight had stabilised. Those initially prescribed the minimum energy intake (1200 kcal/day) had their energy intake adjusted to 1000 kcal/day at the end of week 24 and maintained to the end of week 52. Patients were randomised to receive orlistat 120 mg three times daily or placebo for 1 year, and 114 participants were allocated to each treatment group.[41]

The between-group difference for mean percentage weight loss at 52 weeks analysed by ITT was statistically significant (8.5 versus 5.4% in the orlistat and placebo groups, respectively, $p = 0.016$). However, it was not clear if the change in body weight was assessed from the beginning of the run-in period or randomisation. The LSM difference from placebo for change in body weight was 2.0 kg (95% CI, –3.6 to –0.38, $p < 0.05$) for orlistat-treated patients based on ITT. The between-group differences for patients losing > 5 and 10% of initial body weight during double-blind treatment were statistically significant in favour of orlistat. The respective values were 35 versus 21% ($p = 0.02$) and 16 versus 6% ($p = 0.02$). The between-group difference for mean decrease in waist circumference at 1 year was not statistically significant.[41]

Changes in lipid levels were assessed from the beginning of randomisation. Orlistat-treated patients showed statistically significant decreases in serum levels of total cholesterol, LDL-C and LDL-C:HDL-C ratio compared with placebo ($p < 0.05$). However, there were no statistically significant between-group differences for triglycerides, lipoprotein A and very-low-density lipoprotein cholesterol (VLDL-C). Levels of HDL-C increased by similar amounts in both groups. In patients with an elevated level of LDL-C at baseline (≥ 3.36 mmol/l), the mean value decreased after 1 year by 7.1% in the orlistat group and 1.3% in the placebo group. There was a trend towards a reduction in fasting insulin and, to a lesser extent, in fasting glucose levels associated with weight loss in both groups.[41]

Adverse events and withdrawals

Nine patients (8%) in the orlistat group withdrew due to adverse events compared with seven (6%) in the placebo group. At least one gastrointestinal adverse event was reported by 82% of patients in the orlistat group and 56% in the control group. Most events occurred early in the study and were transient (≤ 4 days). Three orlistat-treated patients and one placebo-treated patient withdrew due to gastrointestinal adverse events. Supplementation of vitamins A, D and E was given to 1.8, 8.0 and 3.6%, respectively, of orlistat-treated patients compared with 0.9% of placebo patients for each vitamin. During the study, 7% of orlistat patients and 11% of placebo patients developed gallbladder abnormalities, and 3 and 2%, respectively, developed renal abnormalities.[41]

RCTs of weight loss/weight maintenance

Four RCTs reported results of a 1-year weight-loss programme followed by a 1-year weight-maintenance programme.[42–44,48]

RCT by Davidson and colleagues[42]

In the trial by Davidson and colleagues,[42] participants aged over 18 years with a BMI of 30–43 kg/m^2 were recruited. People with type 2 diabetes treated with drugs were excluded. All patients underwent a 4-week single-blind placebo run-in period when they were instructed to commence an energy-restricted diet. Those with a treatment adherence of at least 75%, assessed by counting returned placebo capsules, were randomised to receive orlistat 120 mg three

times daily or placebo for 1 year as a weight-loss regimen. Patients completing the first year of treatment, with a treatment adherence of ≥ 70%, were eligible to enter the weight-maintenance phase. Participants treated with orlistat during the first year were randomised to receive placebo or orlistat 60 or 120 mg three times daily. Participants taking placebo during the first year continued to take placebo during the second year. This was a large trial, with 657 participants allocated to the initial orlistat group and 224 to the placebo group.[42]

Changes in outcomes appeared to be reported from the beginning of randomisation. At the end of the first year, orlistat-treated patients lost significantly more weight than placebo (8.76 versus 5.81 kg, $p < 0.001$). There were statistically significant results in favour of orlistat for those losing at least 5 and 10% of initial weight (66 versus 44%, $p < 0.01$, and 39 versus 25%, $p < 0.004$, respectively). In addition, there were small, but statistically significant, improvements with orlistat versus placebo for mean decreases in DBP ($p = 0.009$) and SBP ($p = 0.002$) at 1 year.[42]

In terms of weight regain at the end of the second year, the mean values were 3.2, 4.3 and 5.6 kg for orlistat 120 and 60 mg three times daily and placebo, respectively ($p < 0.001$ for placebo versus 120 mg orlistat, and for 60 versus 120 mg orlistat). The mean percentage weight loss at 2 years was 7.6, 4.2 and 4.5% for orlistat 120 and 60 mg three times daily and placebo, respectively. Tests of statistical significance were not reported for these comparisons. Patients maintaining greater than 10% initial loss at 2 years were 34% in those receiving orlistat 120 mg three times daily for 2 years and 18% in those receiving placebo for 2 years ($p = 0.02$).[42]

Results for changes in lipid levels and indicators of glycaemic control were presented for those receiving orlistat 120 mg three times daily for 2 years and those receiving placebo for 2 years. Orlistat-treated patients had significantly lower levels of total cholesterol and LDL-C compared with placebo ($p < 0.001$ for both), however, the difference between groups was not statistically significant for HDL-C and triglycerides. Results from analysis of covariance suggested that the changes in lipid levels were independent of weight loss. More favourable results were also observed for orlistat for changes in fasting serum glucose ($p = 0.001$) and insulin levels ($p = 0.04$) over 2 years compared with placebo. The observed decrease in insulin levels appeared to be related to weight loss, rather than being an independent drug effect.[42]

Adverse events and withdrawals

During the first year, 61 patients (9%) in the orlistat group withdrew due to adverse effects compared with nine (4%) in the placebo group. The figures at the end of the second year were five (3.3%) for those receiving orlistat 120 mg three times daily for the full 2 years, nine (6%) for those receiving orlistat 120 mg three times daily during the first year and 60 mg three times daily during the second year, six (4%) for those receiving orlistat in the first year and placebo in the second year and four (3%) for patients receiving placebo for 2 years. At the end of 2 years, 79% of patients receiving orlistat 120 mg three times daily for the full 2 years reported at least one gastrointestinal adverse event compared with 59% for those receiving placebo for 2 years, and seven and two patients withdrew due to gastrointestinal adverse events, respectively. The authors stated that most gastrointestinal adverse events occurred early during treatment, were mild to moderate in intensity and resolved spontaneously. The adverse-event rate was lower in the second year than in the first year and did not differ significantly between groups. There were no apparent systematic differences in weight loss among participants who experienced several, one or no gastrointestinal adverse events. At the end of the second year, 14% of patients receiving 120 mg three times daily for 2 years and 7% of patients receiving placebo for 2 years required supplemental fat-soluble vitamins or β-carotene. Although serum levels of vitamins D and E decreased significantly in those receiving orlistat, values remained within the reference ranges.[42]

The incidence of breast cancer was assessed during this trial. Among those receiving orlistat 120 mg three times daily for 2 years, there were three cases of breast cancer diagnosed, two identified prior to starting the trial and one identified 32 days after randomisation. Among those receiving placebo for 2 years, there was one case of breast cancer identified prior to the start of the trial.[42]

RCT by Hauptman and colleagues[43]

In the trial by Hauptman and colleagues,[43] participants aged over 18 years with a BMI of 30–44 kg/m^2 were recruited. All eligible patients entered a 4-week single-blind placebo run-in period during which they commenced a reduced-energy diet with a prescribed intake of

5020 kJ/day for patients weighing < 90 kg initially and 6275 kJ/day for those weighing ≥ 90 kg initially. Patients with at least 75% adherence with the drug regimen during the run-in period, assessed by counting returned placebo capsules, were eligible to enter the double-blind trial. The above dietary regimen was continued throughout the first year of the double-blind trial and, in addition, patients viewed videos on behaviour modification. Patients were randomised to receive orlistat 120 or 60 mg three times daily or placebo, and about 210 participants were allocated to each treatment group. The second year constituted the weight-maintenance phase and the drug regimens continued as above. A weight-maintenance diet was prescribed for those who were still losing weight and patients were encouraged to walk briskly for 20–30 minutes three to five times per week.[43]

Changes in outcomes were calculated from randomisation. At the end of the first year, ITT analysis showed that both orlistat groups had achieved a significantly greater decrease in weight relative to placebo ($p = 0.001$). The mean weight loss in the orlistat 120 mg three times daily group was 7.94 kg compared with 7.08 kg for the 60 mg three times daily group and 4.14 kg in the placebo group. A similar pattern was seen for proportions of patients losing at least 5% (51, 49 and 31% for orlistat 120 and 60 mg three times daily and placebo, respectively) and 10% (29, 24 and 11%, respectively) of their initial weight, with both active treatment groups performing significantly better than placebo for both outcomes ($p < 0.001$).[43]

At the end of the second year, ITT analysis showed that both orlistat groups had achieved a significantly greater decrease in weight relative to placebo ($p = 0.001$). The mean weight loss in the orlistat 120 mg three times daily group was 5.02 kg compared with 4.46 kg for the 60 mg three times daily group and 1.65 kg in the placebo group. The percentage of initial body weight lost at 2 years was 5.01, 4.44 and 1.70% for orlistat 120 and 60 mg three times daily and placebo, respectively ($p < 0.001$ for both orlistat groups compared with placebo). Weight regain at 2 years, expressed as a percentage of the weight lost during the first year, was 38, 37 and 60% for orlistat 120 and 60 mg three times daily and placebo, respectively.[43]

At 2 years, both active treatment groups performed significantly better than placebo in terms of maintaining a weight loss of at least 5% of initial body weight (34% for both orlistat groups and 24% for the placebo group, $p < 0.03$ for orlistat 60 mg three times daily versus placebo and $p < 0.02$ for orlistat 120 mg three times daily versus placebo). A similar pattern was seen for proportions of patients maintaining a weight loss of at least 10% of initial body weight with values of 19, 15 and 7% for orlistat 120 and 60 mg three times daily and placebo, respectively ($p = 0.008$ for orlistat 60 mg three times daily versus placebo and $p < 0.001$ for orlistat 120 mg three times daily versus placebo).[43]

At the end of the first year, total cholesterol and LDL-C levels were significantly lower in both orlistat groups compared with placebo ($p = 0.001$), which was generally maintained during the second year. Between-group differences for triglycerides and glucose levels were never statistically significant. Fasting insulin levels in the orlistat 120 mg three times daily group were lower than the placebo group at 1 year ($p < 0.05$). DBP decreased in the orlistat 60 mg three times daily group at 1 year (–0.97 ± 0.01 mmHg, $p = 0.02$), but changes in the other two groups were not statistically significant. During the second year, no significant changes were observed between groups for DBP, but SBP in the orlistat 120 mg three times daily group was reduced relative to placebo ($p = 0.04$). Similar results were seen for ITT and completer analyses.[43]

Adverse events and withdrawals

Withdrawals due to adverse events over the 2 years were 11% in the 120 mg three times daily group and 7% in both the other groups, and rates did not differ significantly between groups. Patients reporting gastrointestinal adverse events over the 2 years were 79% in the orlistat 120 mg three times daily group ($p = 0.001$ versus placebo), 72% in the 60 mg three times daily group ($p = 0.003$ versus placebo) and 59% in the placebo group. Gastrointestinal adverse events occurred more frequently in orlistat-treated compared to placebo-treated patients ($p = 0.001$), and most were described as mild to moderate in intensity, were limited to one or two episodes per patient and occurred early during treatment. Few gastrointestinal adverse events were reported during the second year. Withdrawal rates due to gastrointestinal adverse events were 5.7, 4.7 and 1.4% in the 120 and 60 mg orlistat groups and the placebo group, respectively.[43]

Serum levels of vitamins A, D and E and β-carotene remained within reference ranges in all groups throughout the 2 years. Two consecutive low vitamin E and β-carotene values occurred signifi-

cantly more frequently in patients treated with orlistat than with placebo. The frequency of two consecutive low-level vitamin A and D values did not significantly differ between groups. Supplementation of β-carotene was required by 6.3% in the orlistat 120 mg three times daily group, 4.3% in the orlistat 60 mg three times daily group and 2.4% in the placebo group.[43]

RCT by Sjostrom and colleagues[44]

In this trial, obese patients were recruited from hospital waiting lists or by local advertising.[44] Patients aged at least 18 years with a BMI of 28–47 kg/m^2 were eligible to enter the trial. Those with pharmacologically treated diabetes were excluded. All patients underwent a 4-week single-blind placebo run-in period during which they commenced an energy-restricted diet. The energy content of the diet was calculated from each patient's estimated total daily energy expenditure minus 600 kcal/day. The minimum prescribed energy intake was 1200 kcal/day. Participants with more than 75% adherence during the run-in regimen, assessed by counting the number of returned placebo capsules, were eligible to enter the double-blind phase. For the weight-loss phase, the above dietary regimen was followed until week 24 when the prescribed energy intake was further reduced by 300 kcal/day and the minimum prescribed energy intake adjusted to 1000 kcal/day. Patients were randomised to receive orlistat 120 mg three times daily or placebo. At this stage, 340 participants were allocated to each treatment arm. After 1 year, patients could enter the weight-maintenance phase provided they demonstrated more than 75% adherence with the weight-loss regimen, assessed as above. During the second year, a weight-maintenance diet was commenced and patients were advised not to follow a hypocaloric diet during this time. They were re-randomised to either orlistat 120 mg three times daily or placebo.[44]

The LSM difference in weight loss during the first year was 3.9 kg in favour of orlistat ($p < 0.001$), calculated from the beginning of the run-in period to the end of the first year. At 1 year, 24% of orlistat-treated and 33% of placebo-treated patients lost 0.1–5.0% of initial body weight, 30 and 32%, respectively, lost 5.1–10.0% of initial body weight, 30 and 16% lost 10.1–20.0% of initial body weight and 9 and 2% lost > 20% of initial body weight. Patients with unchanged or increased body weight at the end of 1 year were 8 and 18%, respectively.[44]

During the second year, the LSM difference in weight loss between the group receiving placebo during the first year and orlistat during the second year and the group receiving orlistat during the first year and placebo during the second year was 3.6 kg in favour of the former ($p < 0.001$). The LSM difference in weight loss between the group receiving orlistat during both years and the group receiving placebo during both years was 2.4 kg in favour of orlistat ($p < 0.001$). At 2 years, 57% of patients receiving orlistat for 2 years maintained a weight loss of > 5% compared with 37% of those receiving placebo for 2 years.[44]

The group receiving orlistat during the first year and those receiving orlistat for 2 years had significantly greater reductions in total cholesterol, LDL-C, LDL-C:HDL-C ratio and serum glucose and insulin levels compared with the groups receiving placebo for the first year and for 2 years. There were significantly greater reductions in SBP and DBP at 1 year in the orlistat group versus placebo. Linear modelling showed that baseline risk-factor value and weight reduction were significant variables at 1 and 2 years for observed risk-factor changes. Treatment was also a significant predictor for change in total cholesterol at 1 year ($p = 0.0001$) and 2 years ($p = 0.0002$), change in LDL-C at 1 year ($p = 0.0003$) and 2 years ($p = 0.0463$), and change in LDL-C:HDL-C ratio at 2 years ($p = 0.0236$).[44]

Adverse events and withdrawals

During the first year, 12 of 345 patients (3.5%) reported gastrointestinal adverse effects in the orlistat group versus two of 343 patients (0.6%) in the placebo group. During the second year, two of 126 patients (1.6%) receiving placebo for 2 years, none of those receiving orlistat followed by placebo, five of 127 (3.9%) of those receiving placebo followed by orlistat and two of 135 (1.5%) of those taking orlistat for 2 years reported gastrointestinal adverse effects. There were no clinically or statistically significant changes in the mean values of any laboratory measurements during the study and the frequency of laboratory abnormalities was evenly distributed between groups.[44]

During the first year, 41 patients in the orlistat group and 18 in the placebo group had two or more consecutive low serum levels of fat-soluble vitamins, but only 16 and four patients, respectively, required supplements. During the second year, supplemental vitamins were received by four patients in the orlistat/orlistat group, one in the placebo/placebo group, three in the placebo/orlistat group and one in the orlistat/placebo group.[44]

RCT by Rossner and colleagues[48]

In the trial by Rossner and colleagues,[48] patients aged at least 18 years with a BMI of 28–43 kg/m^2 were recruited. People with drug-treated diabetes mellitus were excluded. All patients entered a 4-week single-blind placebo run-in period when they were instructed to commence a dietary regimen containing 30% of calories as fat with a daily energy deficit of 600 kcal. Patients who completed the run-in period and achieved at least 75% adherence with the treatment regimen (assessed by counting returned placebo capsules) were eligible to enter the double-blind study. For all patients, the diet described above continued throughout the first year. During the second year, dietary intake was adjusted to achieve weight maintenance rather than weight loss. Patients were randomised to receive orlistat 120 or 60 mg three times daily or placebo for 2 years, and approximately 240 participants were allocated to each treatment arm.[48]

The following data are based on ITT analyses. From the beginning of the run-in period to the end of the first year, the mean weight change was –9.4 kg in the orlistat 120 mg three times daily group, –8.5 kg in the orlistat 60 mg three times daily group and –6.4 kg in the placebo group ($p < 0.001$ for both orlistat groups versus placebo). The mean weight change from start of run-in to the end of 2 years was –7.4, –6.6 and –4.3 kg with orlistat 120 and 60 mg three times daily and placebo, respectively ($p < 0.005$ for orlistat 60 mg three times daily versus placebo and $p < 0.001$ for orlistat 120 mg three times daily versus placebo). More than 10% loss of initial body weight at 1 year was achieved by 38, 31 and 19% of patients treated with orlistat 120 or 60 mg three times daily or placebo, respectively ($p < 0.002$ for orlistat 60 mg three times daily versus placebo and $p < 0.001$ for orlistat 120 mg three times daily versus placebo). At the end of 2 years, 28% of patients in the orlistat 120 mg three times daily group had maintained > 10% loss of initial weight compared with 29% in the 60 mg three times daily group and 19% in the placebo group ($p < 0.05$ for both orlistat groups versus placebo). There were no statistically significant differences between groups for mean change in waist circumference at 1 year, however, at the end of 2 years, the values were –5.1 in the orlistat 120 mg three times daily group ($p < 0.05$ versus placebo), –4.7 in the 60 mg three times daily group and –3.1 in the placebo group.[48]

In terms of changes in lipid levels, both orlistat groups achieved statistically significant improvements in total cholesterol and LDL-C at 1 and 2 years compared with placebo ($p < 0.001$). Increased levels of HDL-C were seen in all groups at 1 and 2 years, but the between-group difference was statistically significant only for orlistat 120 mg three times daily versus placebo at 1 year ($p < 0.05$). Greater improvements in the LDL-C:HDL-C ratio were seen in the orlistat 60 mg three times daily group compared to placebo at 1 and 2 years ($p < 0.001$ for both 1 and 2 years) and in the orlistat 120 mg three times daily group versus placebo at 1 and 2 years ($p < 0.05$ at 1 year and $p < 0.001$ at 2 years). No statistically significant differences between groups were seen for triglyceride or VLDL-C levels at either time point.[48]

DBP was significantly lower in patients receiving orlistat 120 mg three times daily compared with placebo patients at 1 year ($p < 0.05$), but no statistically significant between-group differences were observed for measurements of SBP. Orlistat-treated patients appeared to achieve a better QoL at 1 and 2 years, as assessed using a 55-item self-administered questionnaire.[54]

Adverse events and withdrawals

During the first year, 26% of patients withdrew from the orlistat 120 mg three times daily group, 24% withdrew from the 60 mg three times daily group and 35% withdrew from the placebo group. Of these, 6, 7 and 2% withdrew due to adverse events and 3, 2 and 2% withdrew due to treatment failure, respectively. During the second year, the figures for withdrawal were 12% in the orlistat 120 mg three times daily group, 24% in the 60 mg three times daily group and 14% in the placebo group. Of these, 9, 10 and 3% withdrew due to adverse events and 3, 2 and 3% withdrew due to treatment failure, respectively. Gastrointestinal adverse events occurred more frequently in the orlistat groups, and caused nine patients in the group receiving orlistat 120 mg three times daily, 12 patients in the group receiving orlistat 60 mg three times daily and two in the placebo group to withdraw.[48]

Pooled analyses of RCTs with 1- and 2-year endpoints

Four trials were pooled that had analysed by ITT at 1 year.[42,43,47,48] The summary estimate showed that orlistat 120 mg three times daily achieved significantly greater weight loss compared with placebo (WMD = –2.90 kg, 95% CI, –3.61 to –2.19, $p < 0.00001$; test for heterogeneity chi-squared = 3.07, df = 3, $p = 0.38$; see *Figure 2*).

It should be noted that two of these trials calculated outcomes from the start of the run-in period,[47,48] whilst the other two calculated outcomes from the start of double-blind treatment.[42,43] The analysis was repeated after grouping trials according to the starting point of calculations. For the two trials calculating change in body weight from the start of the run-in period, the summary effect size was slightly smaller compared with the previous analysis (WMD = –2.54 kg, 95% CI, –3.62 to –1.47, $p < 0.00001$; test for heterogeneity chi-squared = 1.34, df = 1, $p = 0.25$; see *Figure 3*).[47,48] For the two trials calculating change in body weight from the start of the double-blind period, the summary effect size was slightly larger compared with the original analysis (WMD = –3.35 kg, 95% CI, –4.44 to –2.27, $p < 0.00001$; test for heterogeneity chi-squared = 0.59, df = 1, $p = 0.44$; see *Figure 4*).[42,43]

Two trials were not included in these meta-analyses because insufficient data were provided in the papers to calculate effect sizes.[41,44]

Two trials were pooled for change in percentage body weight at 1 year (WMD = –2.38%, 95% CI, –3.45 to –1.31, $p < 0.00001$; test for heterogeneity chi-squared = 1.05, df = 1, $p = 0.31$; see *Figure 5*).[42,47] It should be noted that one of these trials calculated the outcome from the start of the run-in period,[47] and the other calculated it from the start of double-blind treatment.[42] Four trials were excluded from this meta-analysis: two due to lack of variance data[41,44] and two because the outcome was not reported.[43,48]

Four trials were pooled for those achieving < 5% loss of initial weight at 1 year. This showed that orlistat 120 mg three times daily performed better than placebo (RR = 0.72, 95% CI, 0.63 to 0.82, $p < 0.00001$; test for heterogeneity chi-squared = 4.02, df = 3, $p = 0.26$; see *Figure 6*).[41–43,47] In one of the trials, the outcome was calculated from the start of double-blind treatment,[41] however, in the other three trials, it was not clear whether it had been calculated from the start of the run-in period or the start of double-blind treatment.[42,43,47] In three trials, analysis appeared to be by ITT[41–43] and in the other this was unclear.[47] It should be noted that two trials were not included in this analysis: one because the relevant figures were read from a graph and, therefore, may not have been accurate[48] and the other because the outcome was not reported.[44]

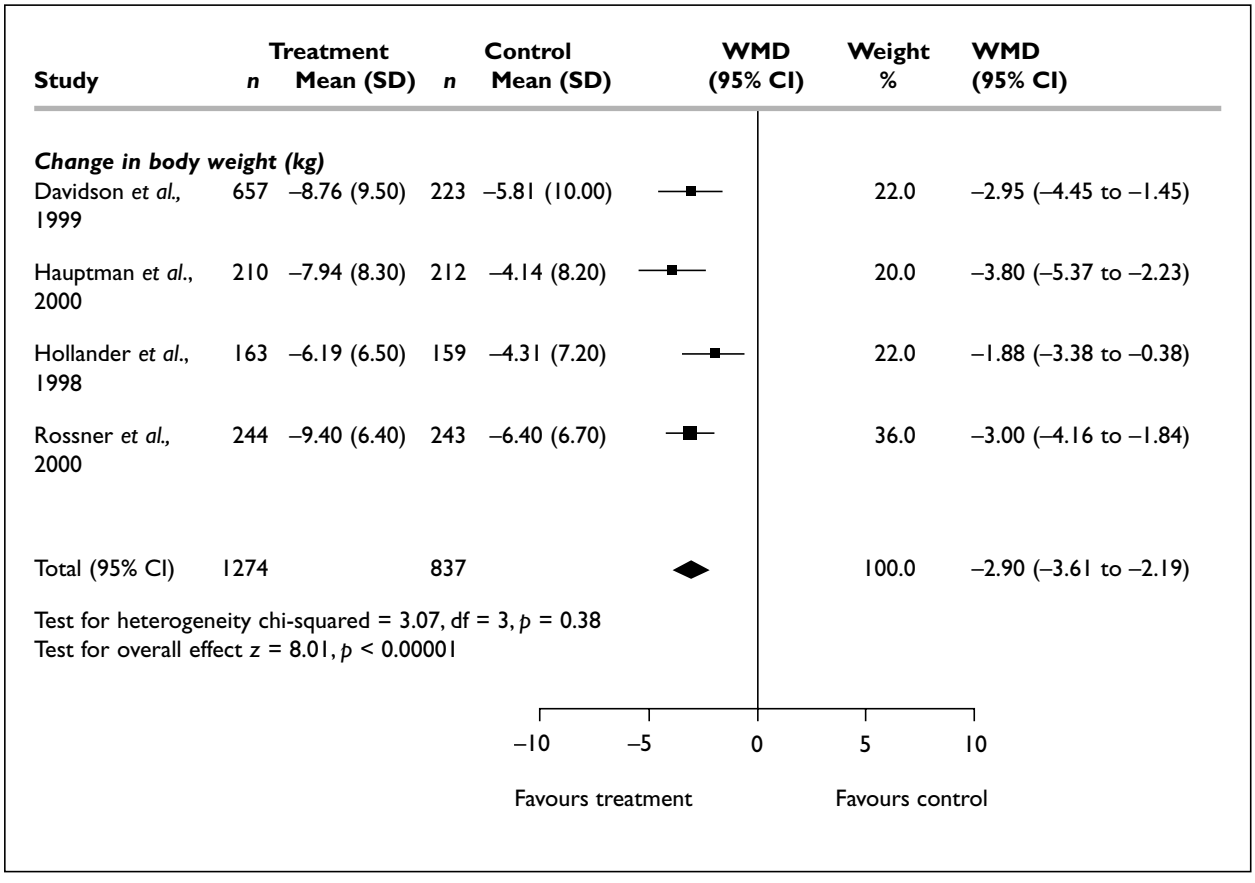

FIGURE 2 *Weight change at 1 year for orlistat 120 mg three times daily versus placebo*

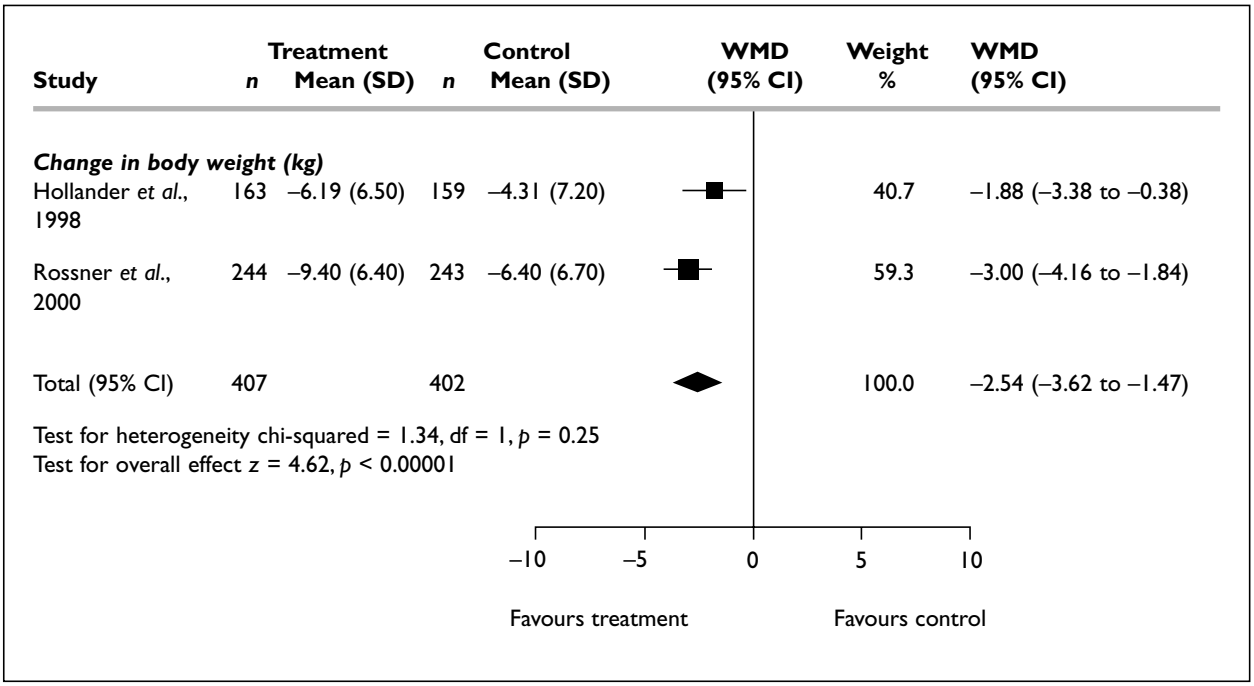

FIGURE 3 *Change in body weight at 1 year for orlistat 120 mg three times daily versus placebo*

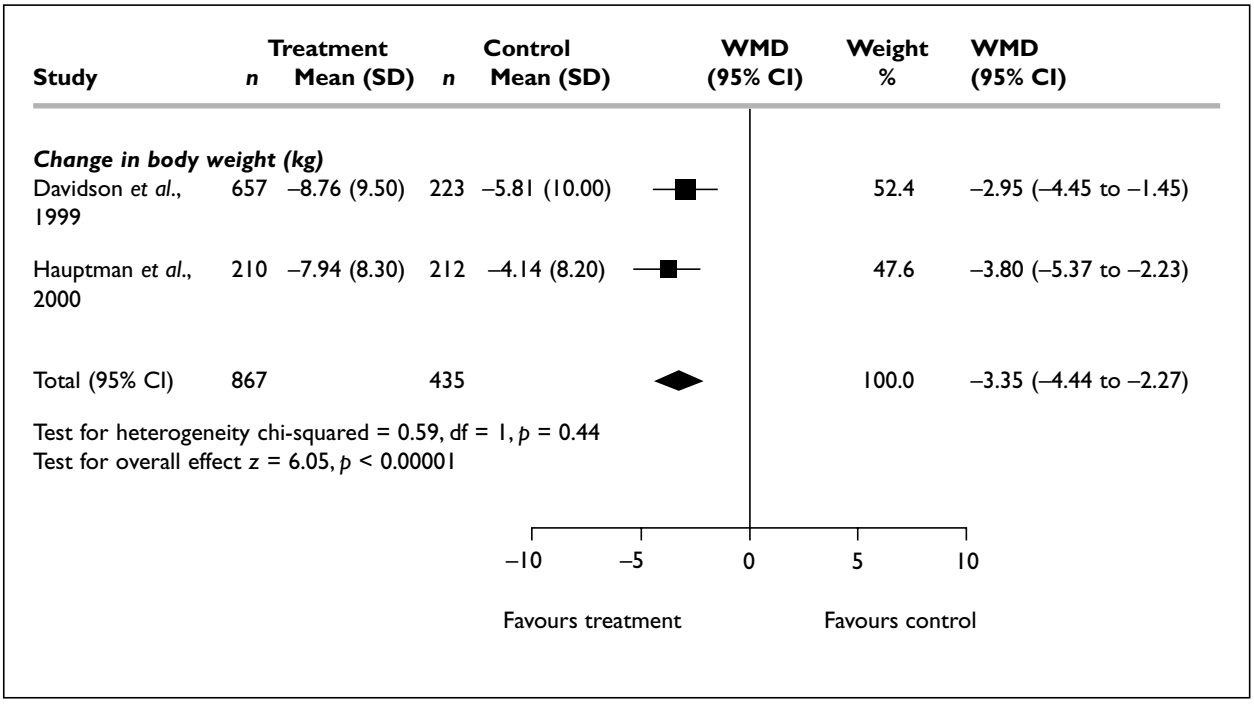

FIGURE 4 *Change in body weight at 1 year for orlistat 120 mg three times daily versus placebo*

Five trials were pooled for the risk of achieving < 10% loss of initial body weight at 1 year. This analysis also showed that orlistat 120 mg three times daily performed more favourably than placebo (RR = 0.85, 95% CI, 0.80 to 0.91, $p < 0.00001$; test for heterogeneity chi-squared = 4.84, df = 4, $p = 0.3$; see *Figure 7*).[41–43,47,48] In four of these trials, the starting point used for calculation of the outcome was unclear (i.e. whether at the start of run-in or double-blind treatment),[42,43,47,48] but in the other trial, calculations were from the start of double-blind treatment.[41] In three trials, ITT analysis was undertaken,[41–43] and in two it was unclear whether this had been done.[47,48] One trial was excluded from the analysis because results were not reported in terms of achieving at least 10% loss of initial weight.[44]

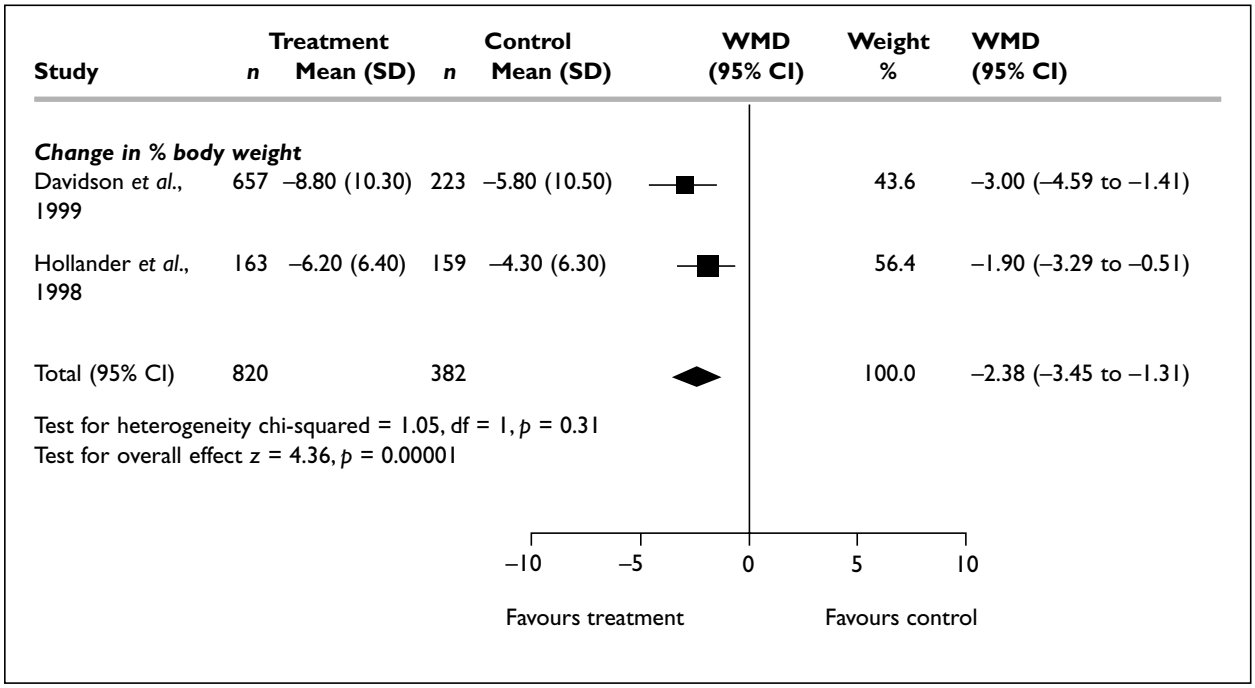

FIGURE 5 *Change in percentage body weight at 1 year for orlistat 120 mg three times daily versus placebo*

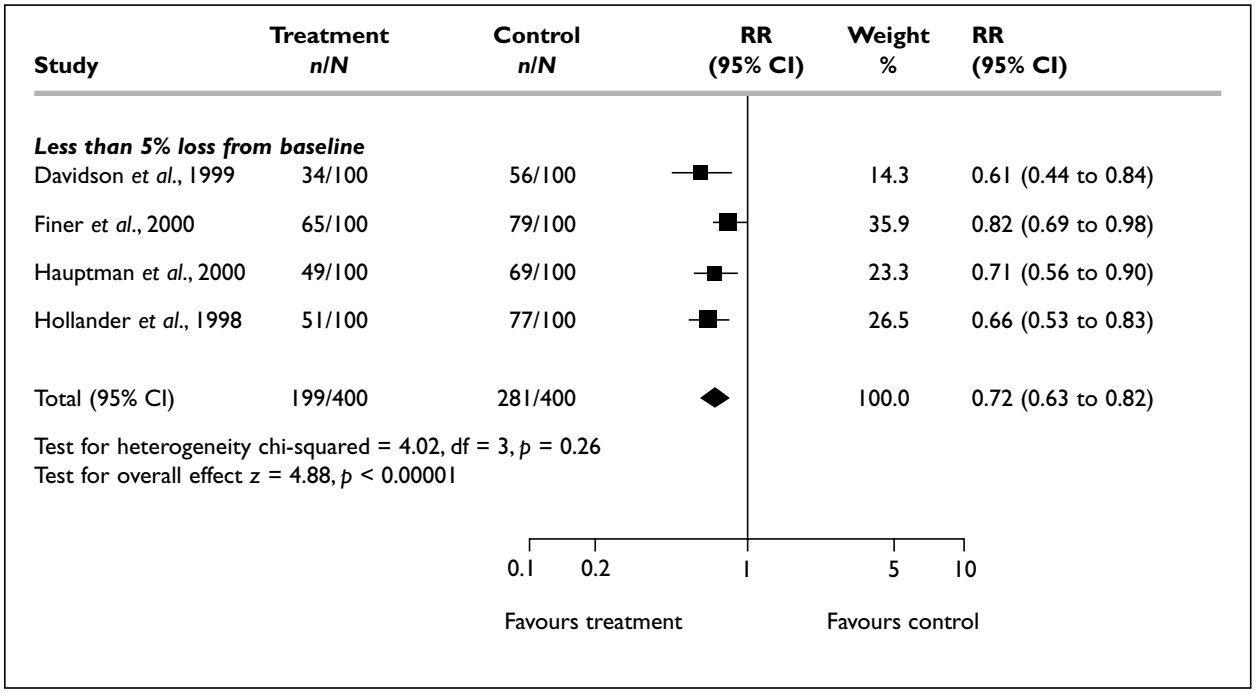

FIGURE 6 *RR of failure to achieve at least 5% loss of initial weight at 1 year for orlistat 120 mg three times daily versus placebo*

Two trials were pooled for change in body weight at 2 years with orlistat 120 mg three times daily versus placebo.[43,48] The pooled result was in favour of orlistat (WMD = –3.19 kg, 95% CI, –4.25 to –2.12, $p = 0.00001$; test for heterogeneity chi-squared = 0.05, df = 1, $p = 0.82$; see *Figure 8*).

Two trials were pooled for change in percentage body weight at 2 years with orlistat 120 mg three times daily versus placebo.[42,43] The pooled result favoured orlistat (WMD = –3.23 kg, 95% CI, –4.77 to –1.69, $p = 0.00004$; test for heterogeneity chi-squared = 0.02, df = 1, $p = 0.9$; see *Figure 9*).

Three trials were pooled for the risk of failing to maintain 10% loss of initial body weight at 2 years with orlistat 120 mg three times daily versus placebo.[42,43,48] Again, the pooled result was

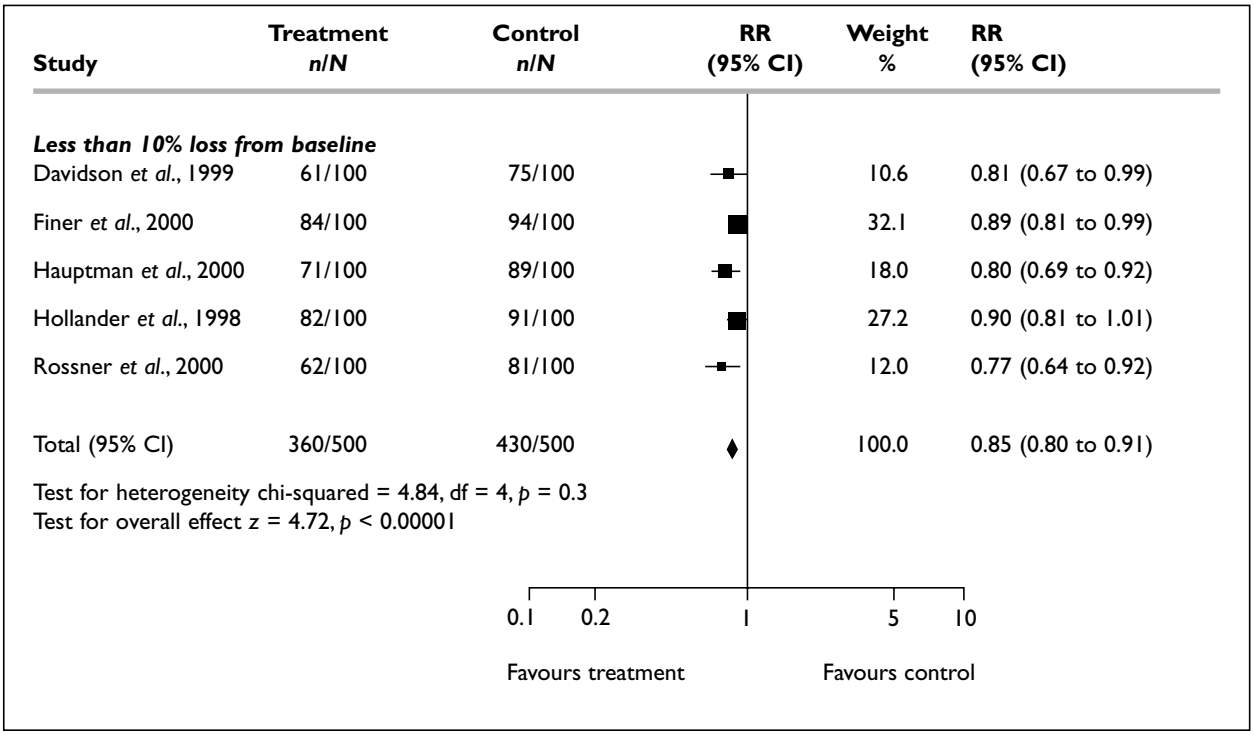

FIGURE 7 *RR of failure to achieve at least 10% loss of initial weight at 1 year for orlistat 120 mg three times daily versus placebo*

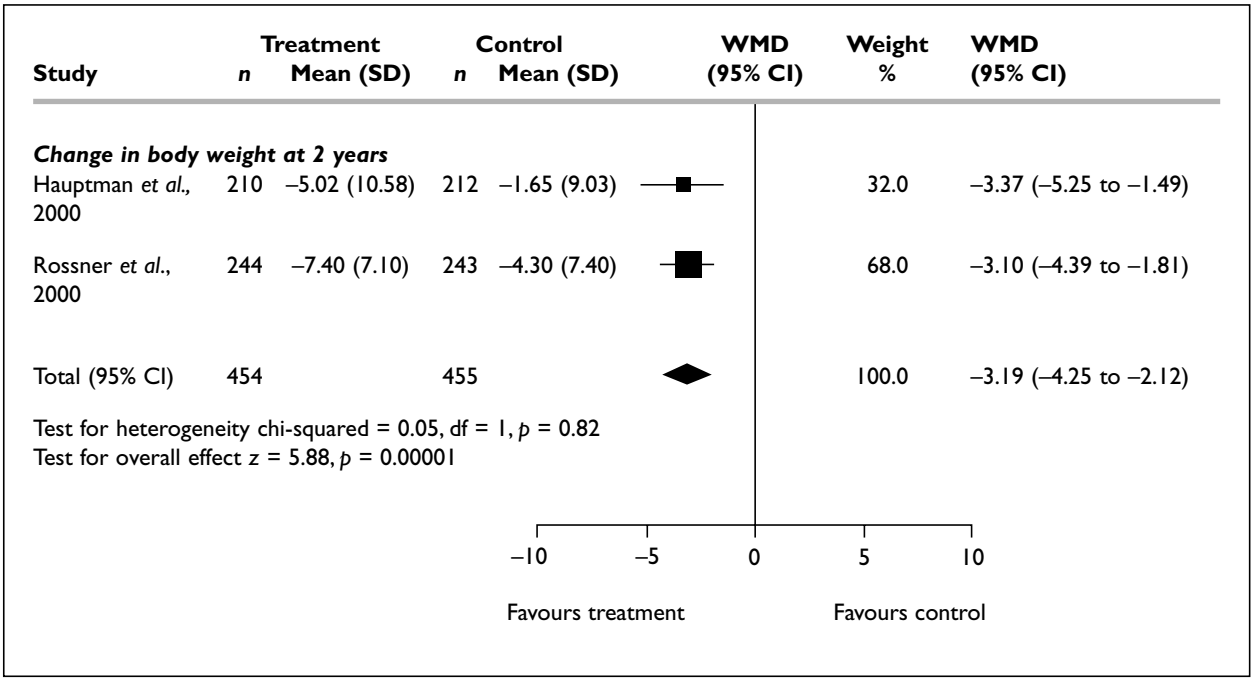

FIGURE 8 *Change in body weight at 2 years for orlistat 120 mg three times daily versus placebo*

significantly in favour of orlistat (RR = 0.86, 95% CI, 0.79 to 0.93, $p = 0.0001$; test for heterogeneity chi-squared = 1.10, df = 2, $p = 0.58$; see *Figure 10*).

RCTs focusing on weight maintenance

One RCT was identified which was a dose-ranging study for weight maintenance.[45] Participants aged at least 18 years with a BMI of 28–43 kg/m^2 were recruited, with exclusion of those with type 2 diabetes. All patients underwent a 6-month run-in period for weight loss. During this time, an energy-reduced diet was prescribed, which was designed to produce weight loss at the rate of 0.5–1.0 kg per week. All participants received dietary counselling, attended four sessions on

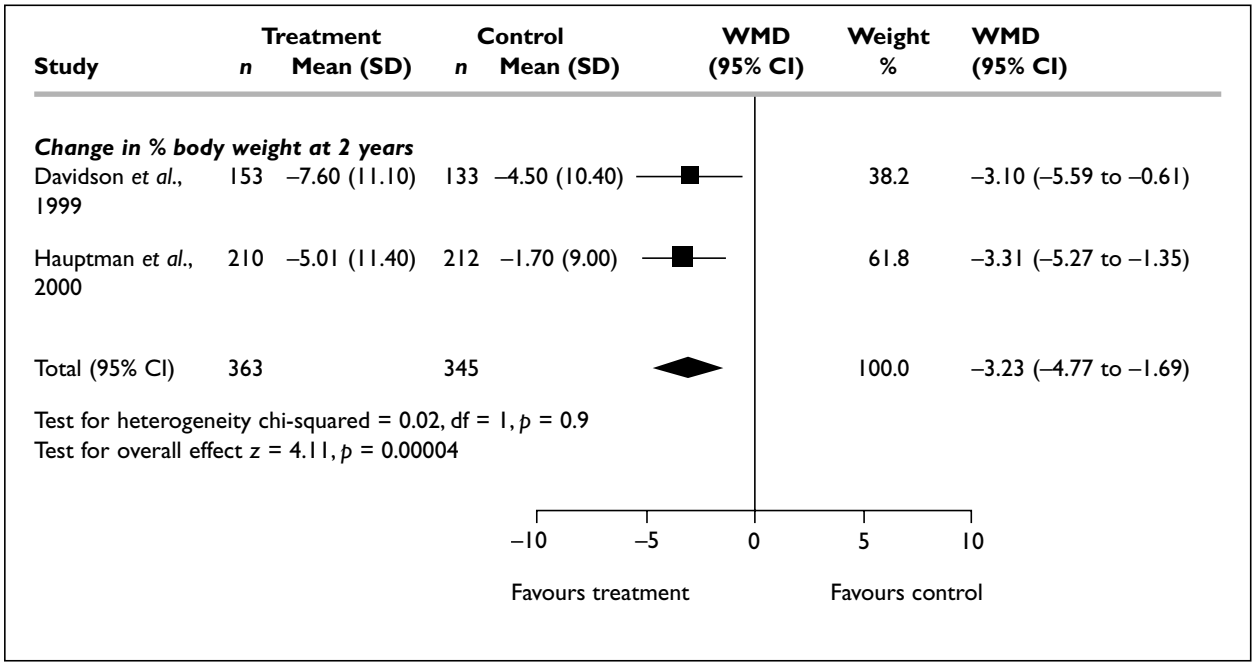

FIGURE 9 *Change in percentage body weight at 2 years for orlistat 120 mg three times daily versus placebo*

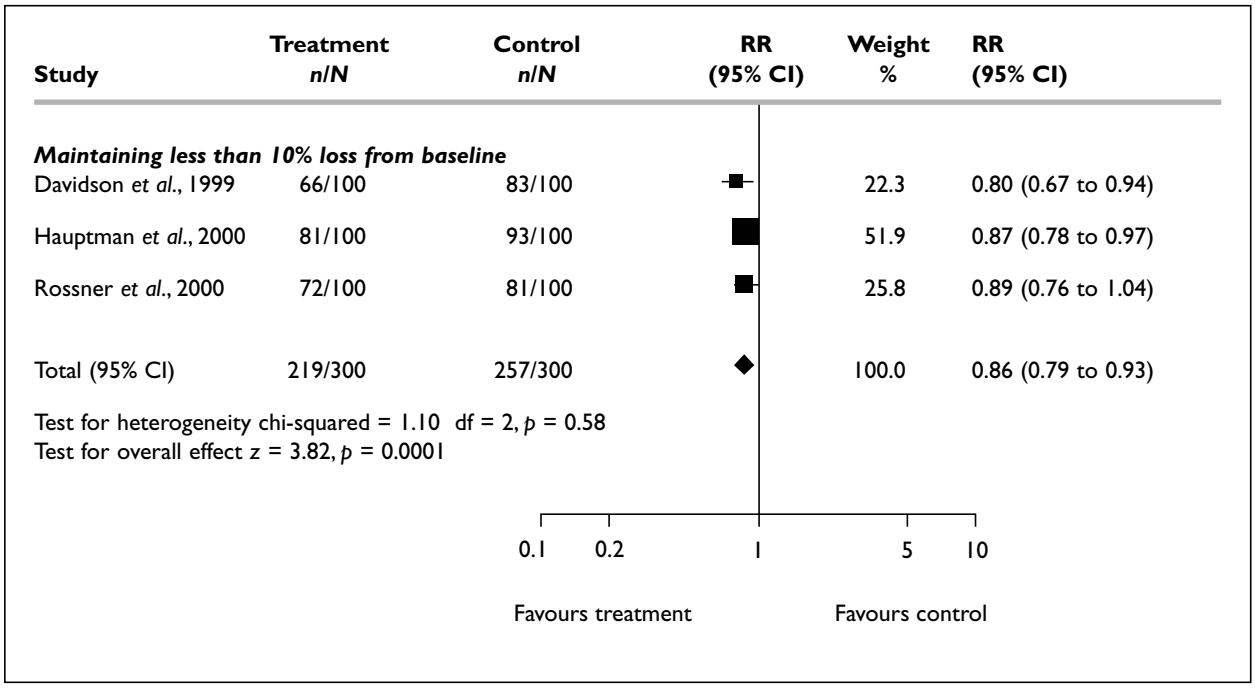

FIGURE 10 *RR of failure to maintain 10% loss of initial body weight at 2 years for orlistat 120 mg three times daily versus placebo*

behavioural modification and were encouraged to walk briskly for 20–30 minutes five times per week. Patients losing at least 8% of their initial body weight during the run-in period were eligible to enter the double-blind phase of the trial, which was designed to achieve weight maintenance. At this time, each individual's energy requirements were reassessed and an increase in energy intake was prescribed that matched anticipated metabolic requirements over the ensuing year. Dietary and behavioural counselling were provided. If patients regained weight, a reduced energy diet was not initiated, but they were encouraged to maintain the higher body weight. Patients were randomised to receive orlistat 120, 60 or 30 mg or placebo three times daily for 1 year, and about 180 participants were allocated to each treatment arm.[45]

The mean overall weight loss during the 6-month run-in period was approximately 10 kg. The mean weight loss after 1 year of double-blind treatment relative to body weight at the start of the run-in period was 7.24 kg with orlistat 120 mg three times daily, 6.16 kg with orlistat 60 mg three times daily, 5.15 kg with orlistat 30 mg three times daily and 5.93 kg with placebo. However, the between-group difference was statistically significant only for orlistat 120 mg three times daily versus placebo ($p < 0.001$). Analysis of weight regain during double-blind treatment, expressed as a percentage of the weight lost during the run-in period, revealed a 32.4, 47.2, 53.3 and 56.0% weight gain with orlistat 120, 60 and 30 mg and placebo three times daily groups, respectively ($p < 0.001$ for 120 mg dose versus placebo).[45]

After randomisation, 24% of patients receiving orlistat 120 mg three times daily did not regain any weight or continued to lose weight compared with 16.3% in the placebo group. After 1 year of double-blind treatment, body weight was greater than initial body weight in 5.4% of patients in the 120 mg dose group compared with 18.3% in the placebo group. A weight loss of > 5% of initial body weight was sustained in 62% of patients treated with orlistat 120 mg three times daily compared with 50% of placebo patients.[45]

Significant reductions in total cholesterol and LDL-C levels from initial values were seen in all orlistat groups compared with placebo. These levels increased in the placebo group. Changes in the LDL-C:HDL-C ratio were significantly different only for the 30 mg dose group compared with placebo. For fasting glucose and insulin levels, mean increases of 1–2% above initial values were noted in the orlistat 30 mg and placebo groups compared with slight reductions of about 1% in the other two orlistat groups. Changes in BP and waist circumference did not differ significantly between groups.[45]

Adverse events and withdrawals

There were 27 withdrawals due to adverse events in the orlistat 120 mg group, 17 in each of the orlistat 60 and 30 mg groups and five in the placebo group. The percentage of patients reporting at least one adverse event was about 7–8% greater in the orlistat groups compared with placebo. This difference was mainly accounted for by more gastrointestinal adverse events in the orlistat groups, with similar rates for adverse events involving other body systems across groups. The percentage of patients reporting gastrointestinal events was 95, 92, 82 and 68% in the orlistat 120, 60 and 30 mg three times daily and the placebo groups, respectively. Most gastrointestinal adverse events were reported as mild to moderate in intensity, occurred early during treatment and were resolved without intervention. Most patients experienced one or two episodes. The rates of withdrawal due to gastrointestinal adverse events were 12% in the 120 mg group, 7% in the 60 mg group, 5% in the 30 mg group and < 1% in the placebo group. The mean serum levels of vitamins A, D and E and β-carotene remained within the reference ranges. However, vitamin E and β-carotene levels were significantly lower in the orlistat groups compared with placebo at the end of the study ($p < 0.001$).[45]

RCTs from company submission

A further three trials on orlistat, submitted by the drug company, were included.[49–51] The results of these trials relating to both clinical effectiveness and adverse effects have been declared as commercial-in-confidence by the manufacturer of orlistat. Therefore, only details concerning participant and intervention characteristics are provided here. All three trials had an endpoint of 1 year.

In the first trial,[49] patients aged 18–75 years with a BMI of 28–38 kg/m^2 were recruited. In addition, eligible patients had to have at least one of the following risk factors: a fasting blood glucose of ≥ 6.7 mmol/l on at least two occasions or be diagnosed with type 2 diabetes; a total plasma cholesterol of > 6.5 mmol/l, a plasma LDL-C of ≥ 4.2 mmol/l on at least two occasions or be receiving lipid lowering drugs; or a DBP of > 90 mmHg on at least two occasions or be receiving antihypertensive treatment. All patients underwent a 2-week single-blind placebo run-in period during which they started a hypocaloric diet containing 30% of calories as fat with an energy deficit of 600 kcal/day. This dietary regimen continued throughout the double-blind treatment phase and, additionally, patients received dietary counselling and weight-control self-help information and were encouraged to walk for 30 minutes every day. Patients were randomised to receive either orlistat 120 mg three times daily ($n = 190$) or placebo ($n = 186$), and after 6 months of therapy, patients could opt to reduce their energy intake by a further 300 kcal/day.[49]

In the second trial, patients aged 18–80 years with a BMI of at least 28 kg/m^2 were recruited. In addition, eligible patients had to have at least one risk factor relating to raised lipid

levels, impaired glycaemic control or raised BP. A mildly hypocaloric diet was prescribed for all patients and they were randomised to receive either orlistat 120 mg three times daily (n = 265) or placebo (n = 266) for 1 year.[50]

In the third trial, obese patients with hypertension were recruited. All patients were prescribed a hypocaloric diet with an energy deficit of 600 kcal/day and a multivitamin supplement. Lifestyle intervention literature was made available, there were periodic meetings with a dietician and moderate exercise was encouraged. Patients were randomised to receive orlistat 120 mg three times daily (n = 278) or placebo (n = 276) for 1 year.[51]

Economic evaluations

Published economic evaluations

Appendix 5 shows a data extraction table and appendix 6 summarises the quality assessment.

One published report described a cost–utility analysis of orlistat in the treatment of obesity.[52] Data from three double-blind RCTs were used to assess the effectiveness of orlistat.[42,44,47] The interventions included orlistat 120 mg three times daily plus a hypocaloric diet versus placebo with diet. All trials started with a 4- or 5-week run-in period of placebo plus diet and had a 1- or 2-year follow-up. The main outcomes were mean weight loss and the proportion of patients who lost > 5% of initial body weight.

The prevalence of obesity and the associated morbidity and mortality figures were derived from literature reviews as well as QoL gains due to weight loss and cost data. The perspective adopted was that of the NHS and, therefore, only direct costs (outpatient appointments, general practitioner consultations and drugs) were included. Health benefits were quantified in terms of changes in QoL associated with weight loss.

The results were as follows.

- The annual average cost of orlistat treatment for 100 patients (treated for 2 years) was £73,436.
- Orlistat resulted in obese people losing an additional 3–4% of initial body weight over diet alone. For both orlistat and placebo, there was a rebound effect (weight regain) during the second year. The additional 1-year weight loss over placebo for patients with type 2 diabetes was 1.9%.
- The proportion of patients achieving at least 5% loss of initial body weight over 2 years, based on an ITT analysis, was 17.5% (95% CI, 7.4 to 27.3) greater for orlistat than for placebo and the number needed to treat was 6 (95% CI, 4 to 14).
- The number of quality-adjusted life-years (QALYs) gained in a year of 100 patients treated with orlistat, compared to placebo, was estimated at 1.601.
- The incremental cost–utility of orlistat treatment was £45,881 (range £19,452 to £55,391) per QALY gained.

Sensitivity analyses were performed for the costs of orlistat, different withdrawal rates, different response rates (completers who lost 5% of initial body weight or more) and different utility gains. The analysis seemed reasonably stable to these sensitivity analyses.

The authors commented that utilities have been calculated on the basis of the published trial results. However, trial data were not consistent with the European Medicines Evaluation Agency's (EMEA) prescription indication for orlistat (loss of ≥ 2.5 kg by diet in 4 weeks pre-treatment and loss of ≥ 5% of body weight after 12 weeks of orlistat treatment). Therefore the cost/QALY gained figures obtained here may be different from those obtained in clinical practice.

Economic evaluations from company submissions

One report was identified which described a cost–utility analysis of orlistat in the treatment of obesity.[53] Details of the model used and the methodological quality of the study have been declared as commercial-in-confidence by the manufacturer of orlistat and, therefore, only brief details of the intervention and the outcome measurements used are provided here.

Clinical effectiveness data were derived from the re-analysis of a published RCT.[44] The interventions included orlistat 120 mg three times daily plus a hypocaloric diet versus placebo plus diet. The trial started with a 4-week run-in period of placebo plus diet. The main outcomes were mean weight loss and the proportion of patients who lost > 5% of initial body weight.

Chapter 4

Discussion and conclusions

Note that, where possible, the mean difference between treatment and control groups is shown in terms of ITT analyses, and relates to a 120 mg three times daily dose of orlistat.

Clinical effectiveness

Most of the trials showed greater weight loss in orlistat groups versus placebo (statistically significant) at all endpoints,[38–44,48] and results from several trials showed that orlistat was associated with better maintenance of weight loss.[42–45,48] Findings from a small dose-ranging trial suggested that orlistat 120 mg three times daily was the optimum regimen in terms of weight loss.[38] This was supported by results of pooled analyses at 1 year.[42,43,47,48] In addition, pooled analysis of two small trials showed that orlistat within the dose range 50–60 mg three times daily did not produce weight loss that was significantly different from placebo at 12 weeks.[38,39]

For participants without diabetes at both 12 weeks and 6 months, the mean difference in favour of orlistat was approximately 1.7 kg.[38,40] At 1 year, the WMD from pooled analyses was 2.9 kg.[42,43,47,48] For trials involving a 1-year weight-maintenance programme following a 1-year weight-loss regimen, the mean difference measured from baseline at the end of the second year was 3.2 kg.[43,48] In one trial evaluating a 6-month weight-loss regimen (diet only) followed by a 1-year weight-maintenance programme using orlistat, the mean difference calculated from the start of the weight-loss phase was 1.3 kg in favour of orlistat.[45]

In obese patients with type 2 diabetes, orlistat 120 mg three times daily produced a significantly greater weight loss at 1 year compared with placebo (mean difference 1.8 kg). In addition, some parameters of glycaemic control and lipid concentration also showed a significantly greater improvement with orlistat than with placebo.[47] Orlistat also produced significant improvements in glycaemic control in participants without diabetes.[42,43]

Most trials showed statistically significant improvement in at least some lipid concentration parameters.[38,41,42,44,45,48] Findings from one trial suggested that improvements in lipid levels were independent of weight loss.[42] However, another study showed no statistically significant between-group differences.[39] Results from three RCTs indicated that orlistat produced significant reductions in BP relative to placebo.[44,46,48]

The distinction between statistical significance and clinical significance may be an important issue in orlistat trials. Many of the included RCTs demonstrated statistically significant differences between groups in terms of change in body weight in favour of orlistat. However, the mean difference between treatment groups was sometimes small, and it is possible that the differences observed were not clinically significant. This may also apply to other outcomes, such as changes in lipid levels, indicators of glycaemic control and BP.

Adverse effects

The incidence of gastrointestinal adverse events was consistently higher in orlistat groups compared with placebo,[38,40–48] and orlistat use was associated with lower serum levels of fat-soluble vitamins and/or a requirement for supplementation.[38,40–43,45,47,48] One dose-ranging study suggested that decreases in the serum levels of fat-soluble vitamins were dose-related.[40]

Health professionals should carefully consider the adverse effect profile associated with orlistat use, particularly in connection with gastrointestinal adverse effects. Some of the weight loss in orlistat-treated patients is probably explained by patients reducing their dietary fat intake in order to avoid symptoms, such as fatty stools, increased defaecation and oily spotting.[55] In most of the trials included in this review, it is reported that the majority of adverse effects were mild or moderate in intensity. It may be useful if qualitative research was conducted in this area to discover the impact of these adverse effects from the patients' perspective and to gain more information about patients' preferences for treatment.

Economic evaluations

Of the two economic evaluations identified,[52,53] one was a published Development and Evaluation

Committee (DEC) report in which the incremental cost–utility of orlistat treatment was estimated as £45,881 per QALY gained (range £19,452 to £55,391).[52] For this evaluation, weight loss was estimated as 3–4% during the first year of treatment (1.9% for people with type 2 diabetes), with weight regain in the second year. Utilities were calculated on the basis of findings from three published trials,[42,44,47] however, as acknowledged by the authors of the DEC report, the data in the trials were not consistent with the EMEA's prescription indications for orlistat. Therefore, the figures obtained for the cost/QALY gained may be different from those obtained in clinical practice. In the trial used for clinical effectiveness data in the industry submission, patients were stratified according to weight loss after the 4-week run-in phase (< 2 or > 2 kg), but all participants stayed in the trial.[44] It is not possible to provide a comparison of the two economic evaluations here due to the manufacturer's declaration that details of the company model and associated methodological quality are commercial-in-confidence.

Limitations of the trials

In general, the methodological quality of included trials was moderate or good. Relatively few trials reported the use of methods to produce true randomisation. However, all the trials were described as double-blind and were placebo-controlled.

All included trials reported selection criteria for participants, reported group comparability at baseline and expressed an intention to provide identical treatment to participants, apart from the drugs under study. Relatively few described the use of an *a priori* power calculation to estimate required sample size and it is possible that some trials lacked sufficient statistical power to detect statistically significant between-group differences for some outcomes.

Patients were blind in all trials by the use of identical placebo, but it was less clear whether caregivers and outcome assessors were also blind. In reality, this is likely to have been the case, since all trials were double-blind, and it is probable that provision of care and outcome assessment were carried out by the same staff. Due to the gastrointestinal adverse events that can occur with the use of orlistat,[55] there is the possibility that patients and study personnel may have been able to guess that the active drug was being administered rather than placebo. Indeed, in two trials, this was highlighted as a potential problem.[39,42] It is possible that study results could have been biased if blinding was no longer valid. None of the trials included methods to determine the success of blinding of patients, care providers or outcome assessors. In view of the potential difficulties involved, an assessment of the effectiveness of blinding would have been useful.

All trials described the statistical methods used for data analysis and most reported results in terms of a central value with associated variance. More than half of the trials described methods to deal with missing data and most performed analyses based on ITT. Failure to use ITT analysis may have caused bias brought about by non-random withdrawal of participants from the study.

Some trials that performed analysis by ITT employed the last observation carried forward (LOCF) method.[43,48] This method involves filling in missing values by using the last observed value for that case and, therefore, assumes that the outcome remains constant at the last observed value after withdrawal. Some problems have been identified with the use of this approach: if patients continue to take prescribed anti-obesity medication after withdrawal, the LOCF is likely to underestimate the true treatment effect in those taking the active drug, and if patients discontinue medication and subsequently regain weight, the LOCF is likely to overestimate the true treatment effect.[56]

It has been suggested that analyses based on actual treatment received following withdrawal are of more value in explaining the biological effects of treatment. To this end, the multiple imputation model has been proposed, which involves analysis based on treatment actually received after withdrawal as opposed to that to which participants were originally assigned. This involves a sensitivity analysis incorporating imputations obtained for a range of alternative assumptions of dose after withdrawal. The range of assumptions include continuation on the same treatment as that immediately prior to withdrawal, reversion to control treatment after withdrawal and assignment to treatment group dose that is the closest to the actual recorded dose after withdrawal. Ideally, trials should incorporate follow-up of withdrawals in order to record information on dosage received. Future trialists may wish to consider using the multiple imputation model as an alternative to the LOCF.[56]

Most trials reported number of withdrawals per group and the accompanying reasons. The majority of trials included an assessment of patient adherence with the trial regimen. However, this was usually based on counting returned capsules (drug regimen) or assessing food intake from patients' self-reported account (dietary regimen) and both methods are potentially unreliable.

Most of the trials included in this review comprise a single-blind placebo run-in period prior to double-blind treatment. Opinions differ as to the optimal approaches to analysis in trials of this type. One view is that the inclusion of weight loss occurring during the run-in period together with that achieved during double-blind treatment can be misleading, as the outcomes relating to the double-blind period are the most important.[57] Another view is that the run-in period is an important part of treatment because many risk-factor improvements occur during this time, and it should, therefore, be viewed as part of the whole treatment package.[58] Improved reporting and clarity in trials, relating to whether statistical calculations take the beginning of the run-in period or double-blind treatment as the starting point, would assist in interpretation of results.[59] One solution could be to report outcomes occurring during run-in separately to those for the double-blind period (starting from randomisation). Additional analyses could integrate outcomes during run-in and double-blind phases.

Generalisability of the results

Use of orlistat in younger people

Since most of the trials included in this review stipulated a minimum participant age of 18 years, no information is available on the possible effects of orlistat in children and adolescents. Childhood obesity is an area of concern in the UK and other developed societies, but has been more difficult to define and classify compared with adult obesity.[5,26] However, a definition of overweight and obesity in children, based on pooled international data for BMI and linked to the adult obesity cut-off point of 30 kg/m^2, has recently been proposed.[60] Despite this progress, options to prevent and treat obesity in younger people remain relatively limited. The World Health Organisation recommends that interventions in obese children should be designed to prevent weight gain rather than produce weight loss.[26] Another report emphasises the importance of a structured and multidisciplinary approach in this age group.[61] A previous systematic review found that family therapy and strategies to reduce sedentary behaviour may be promising interventions.[27] The issue of whether to use pharmacotherapy in childhood obesity is contentious. The Royal College of Physicians does not recommend the use of anti-obesity drugs in children due to the lack of data about adverse effects on growth, development and future eating behaviour.[31] Another source reflects the same concerns, but explains that further research may help to identify subgroups of younger people who may benefit from combining pharmacotherapy with dietary and physical activity modification.[62] During the course of this review, one clinical trial protocol was identified, involving the evaluation of orlistat in younger people with severe obesity (defined as a BMI for age above the 95th percentile according to the National Health and Nutrition Examination Survey data). The population to be studied will comprise 12–17 year-old African-American and Caucasian children and adolescents who have one or more obesity-related risk factors (hypertension, hyperlipidaemia, sleep apnoea, hepatic steatosis, insulin resistance, impaired glucose tolerance or type 2 diabetes). Results of this clinical trial are awaited with interest (see conclusions).

Use of orlistat in older people

Most of the trials included in this review focused on patients under 75 years of age, reflecting a lack of information on the effectiveness and safety of orlistat in older people. Despite the paucity of research in this age group, obesity is clearly an important health problem in older age. In 1998, it was estimated that 48% of men in England aged 75 years and over were overweight and 16% were obese. The respective figures for women in the same age group were 37 and 20%.[4]

Two articles have highlighted pertinent issues around the use of pharmacotherapy in older people.[63,64] Aspects to be taken into account when prescribing include impaired gastric absorption and motility and the effects of altered body composition on drug distribution. As an individual ages, fat mass increases whilst fat-free mass reduces. These changes affect the absorption of drugs according to whether they are lipophilic (fat-soluble) or hydrophilic (water-soluble). The higher proportion of fat mass present in older people means that lipophilic drugs will have a higher distribution volume, whereas with hydrophilic drugs, although there is a smaller volume of distribution, the concentration achieved may be higher. Both of these phenomena can cause problems with drug toxicity meaning that the

prescription regimen may need to be adjusted. In addition, impaired renal and hepatic function, with the high likelihood of concurrent morbidities, and use of polypharmacy, that might produce the possibility of drug interactions, need to be considered when planning pharmacotherapy in older people.[63,64] It has been suggested that appropriate adjustment of drug regimens in older people can be achieved, but that careful selection, dosing and monitoring in this age group are necessary. It is important that clinically significant effects, as distinct from those observed under controlled conditions, should be recognised.[64]

Although evidence exists to suggest that weight loss is beneficial to health,[20] a debate exists as to the usefulness and appropriateness of pharmacotherapy in obese elderly patients. One view is that weight loss in older people who are relatively fit and independent should not be encouraged. This is because weight loss leads to loss of fat-free mass as well as loss of fat mass, and this could contribute to lower levels of muscular strength and functional independence.[63] A further area of concern is the depletion of fat-soluble vitamins in a group who tend to already consume a sub-optimal level of vitamins and minerals.[63]

Given the lack of research in this age group and the fact that the elderly population in developed societies is increasing, further research on the clinical effectiveness and safety of orlistat in this group would be welcome.

Gender

The issues of gender differences in terms of obesity and response to anti-obesity treatment is an area that may require further study. More men than women are overweight (46 versus 32% in England in 1998) but a slightly higher proportion of women than men are obese (19 versus 17% from the same survey).[4] Gender differences also occur in terms of fat distribution: men tend to have more frequent central (abdominal) obesity, whilst thighs and buttocks are the commonest body areas for fat deposition in women. Of these two types of fat distribution, central obesity is more likely to be associated with hyperlipidaemia, coronary heart disease, hypertension and impaired glycaemic control.[65] All of the trials included in this review recruited participants of both sexes and, in general, there were larger proportions of female participants. None of the trials incorporated stratification of results according to gender, with one exception where mean decrease in waist circumference was presented separately for males and females.[41] Future trials could usefully stratify results in this way to determine whether the treatment effects of anti-obesity drugs are different between men and women.

Other demographic variables

It is possible that factors such as ethnicity and social class may also influence patients' response to treatment for obesity. Asian people are considered to be at particular risk of developing obesity,[7] and, in general, the prevalence of obesity is inversely related to social class or household income, although this trend is more distinct in women,[4] but there is no definitive explanation for the latter association.[5] Several of the trials included in this review reported the baseline distribution of different ethnic groups,[41–43,45,47] however, none presented results according to ethnic group and none reported baseline distribution of social class or household income. It would be useful if future research could investigate the impact of treatment on different ethnic or social groups in order to help determine the best patients to target for anti-obesity pharmacotherapy.

Trials versus clinical practice

This review has identified some issues relating to the compatibility between trials and clinical practice in terms of patient characteristics and patient management.

Patient characteristics

In terms of patient characteristics, there are issues relating to methods of recruitment in clinical trials and the relationship between selection criteria used in trials as opposed to those used to select patients for treatment in clinical practice.

In several of the included trials, the methods used for recruiting patients were not described. Recruitment methods involving advertising may attract participants who wish to lose weight for cosmetic reasons. Such trials may not reflect the use of anti-obesity drugs in patients with identified risk factors such as hypertension, impaired glycaemic control and hyperlipidaemia, and may not be informative as to the effectiveness of drugs in improving risk-factor profiles. Another recruitment strategy might involve enlisting patients attending specialist obesity clinics, but these patients may represent the most refractory cases and, therefore, the treatment effect of orlistat may be underestimated compared with that observed in a more general population. It would be useful if future trials could incorporate

selection criteria that reflect characteristics of people likely to be selected for treatment in clinical practice.

National prescribing guidelines state that orlistat should be used in the management of patients with a BMI of 30 kg/m^2 or more or in those with a BMI of at least 28 kg/m^2 in the presence of other risk factors (i.e. hypertension, diabetes or hyperlipidaemia).[32] Of the 14 included trials, eight adhered to these guidelines,[41–43,46,47,49–51] five had selection criteria allowing recruitment of patients not meeting the recommended criteria[38,40,44,45,48] and in one it was unclear since inclusion criteria relating to baseline BMI were not provided.[39]

For orlistat trials that matched the recommendations, most reported statistically significant results in favour of the active drug relative to placebo in terms of weight loss for both participants with[47] and without[41–43,46] diabetes and also produced statistically significant favourable results in terms of weight maintenance compared with placebo.[42,43] One trial recruiting patients with type 2 diabetes also showed statistically significant improvements in indicators of glycaemic control,[47] and a trial of participants without diabetes showed improvements in BP, glycaemic control and some indicators of hyperlipidaemia with orlistat compared to placebo.[42] However, findings for these outcomes from other trials were less clear.

It would be useful if future trials used participant inclusion criteria that were matched with recommended indications for drug use. Alternatively, baseline data and results could be stratified according to whether recruited patients met the recommended criteria or not.

Patient management

National prescribing guidelines indicate that treatment with orlistat should be initiated only in patients who have already achieved a weight loss of at least 2.5 kg in 4 weeks using a dietary programme alone,[32,33] and that treatment should be discontinued after 12 weeks in patients who lose less than 5% of body weight as measured from the start of drug therapy.[33] European prescribing guidelines also reflect these recommendations and state that the duration of treatment with orlistat should not be longer than 2 years.[34]

Most of the orlistat trials included in this review incorporated a 4-week single-blind placebo run-in period during which time patients were instructed to follow a hypocaloric diet (precise parameters vary slightly between trials). It may be considered that this phase loosely corresponds to the requirement in clinical practice for patients to undergo a 4-week period of treatment involving dietary modification (albeit without placebo) in an attempt to lose ≥ 2.5 kg prior to treatment with orlistat. However, weight loss during the run-in period was not always reported in the trials and, apart from three exceptions, was not used as an eligibility criterion for orlistat treatment. In one trial, it was stipulated that patients had to lose 0.5–4 kg during run-in in order to progress to double-blind treatment[39] and in another trial, by the same research group, the criterion was loss of 0–4 kg during the run-in (however, this includes no weight loss at all).[38] In a third trial, patients were required to lose ≥ 8% of initial body weight during a 6-month run-in period using diet alone in order to be eligible to participate in a double-blind trial of weight-maintenance therapy.[45] Most of the trials did not report proportions of patients losing ≥ 5% of body weight (measured from the start of randomisation) at 12 weeks and none used failure to achieve this as a rationale for discontinuing treatment. It is possible that future trials could match the recommended prescription indications more closely in one of two ways.

Firstly, a protocol could be established to withdraw treatment in patients who fail to lose at least 5% of body weight measured after 12 weeks of double-blind treatment. Therapy could then be continued in successful cases. In terms of the general use of anti-obesity drug therapy, the recommendations of the Royal College of Physicians also reflect the principle of discontinuing treatment in patients who have not lost at least 5% of body weight at 12 weeks. A further recommendation relating to those who are successful in achieving this outcome is that drugs may be continued beyond this initial period provided body weight is continually monitored and weight is not regained.[31] This pattern of care could be reflected in trials.

An alternative approach may be for trials to report rates of at least 5% loss at 12 weeks, but to retain the patients who fail to achieve this and, thereafter, stratify results according to success or failure of this outcome. Trials should also try to match the pre-treatment phase and withdraw those not losing 2.5 kg during the run-in period if they are to correspond with the scheme proposed in the licensing indications.

It is apparent that management of patients recruited for trials does not closely correspond to management of patients in clinical practice.

It is likely that management of patients in the placebo arm of trials represents more intensive management than is normally seen in usual clinical practice. For example, patients are likely to attend clinic more often and receive closer dietary supervision in trials. Placebo-controlled RCTs in which all participants receive identical treatment with the exception of the study medication should give an indication of the effects of the active drug over and above the rest of the treatment package and the placebo effect. However, it may be useful if future trials could try to replicate management of patients in everyday clinical practice and attempt to assess the effectiveness of anti-obesity drugs combined with usual clinical management over and above usual clinical management without drugs.

For most obese people, obesity is a chronic condition with a tendency towards patterns of weight loss and weight regain over time. In light of this, longer-term data on the effectiveness and safety of orlistat would be helpful. The maximum recommended prescription duration for orlistat is 2 years.[34] Several trials included in this review involve evaluation of the use of orlistat for 2 years (i.e. a 1-year weight-loss programme followed by a 1-year weight-maintenance programme),[42–44,48] but no data were identified beyond this point.

Sponsorship of trials

It should be noted that most of the trials included in this review were described as being sponsored by the manufacturer. In one case, the sponsorship was unclear, but it was apparent that the trialists had a connection with the drug company.[43]

Comparison with other systematic reviews

One other comparable systematic review of effectiveness was identified, prepared as a DEC report, which evaluated the effectiveness and safety of orlistat in the treatment of obesity.[52] Several differences were noted between the DEC report and this current review. Firstly, only four electronic databases were searched: MEDLINE, EMBASE, The Cochrane Library and the Internet (Alta Vista), whereas the current review included searches of 19 different electronic databases plus internet searches. Few details of the review process were provided in the DEC report, for example, screening tools for papers, the number of reviewers involved in study selection and appraisal, independence of decision-making and methods for resolving disagreements. Inclusion criteria for trials were not described in detail and there was no structured presentation of assessment of methodological quality of included trials, although certain quality-related aspects were discussed, such as use of the ITT protocol. Three trials were included that have also been included in the current review.[42,44,47] The current review included 11 published trials of orlistat, however, several of these will have been published after the completion of the DEC report. It appears that the DEC report excluded shorter-term trials from the systematic review,[38–40] however, this was not explained as an exclusion criterion, and details of shorter-term trials were shown in tables of adverse effects in appendices. An economic analysis was also included in the DEC report and this has already been discussed. The main conclusions from the DEC report were:

- whilst orlistat promotes weight reduction for some people in the short term, discontinuation of treatment results in weight regain
- the protocols of the trials included in the review do not coincide with the licensed indication for orlistat and so generalisability is limited
- there is a lack of long-term data on the effectiveness and safety of orlistat use.

Conclusions

Implications for clinical practice

Many of the trials included in this review demonstrated statistically significant differences between groups in terms of absolute weight loss, proportions of patients achieving at least 5 or 10% loss of initial body weight and weight maintenance in favour of orlistat compared with placebo. Sometimes the mean difference between treatment groups was small, and healthcare professionals involved in the care of obese patients will need to decide whether these differences are clinically significant. In addition, the possibility of adverse effects in orlistat-treated patients should be taken into account. The optimum regimen was 120 mg three times daily. Between-group differences in other outcomes, such as changes in lipid levels, indicators of glycaemic control and BP, were less consistent across trials in terms of statistical significance. In studies where the between-group differences for these outcomes were statistically significant, clinicians should judge whether the differences observed were of clinical importance. The cost per QALY for orlistat was estimated at £45,881.[52]

Implications for future research

In general, the methodological quality of included trials was moderate or good. However, possible difficulties with maintenance of blinding were identified. This is an important consideration as both the patient and the investigators may have been able to recognise the use of orlistat due to associated gastrointestinal adverse effects. It would be useful if future trials could attempt to assess the effectiveness of blinding in patients and those assessing outcomes. It is recommended that ITT analysis is incorporated into future trials, however, the optimum methods for achieving this are under debate.

Further research is required in younger and older patients to assess the effects of orlistat in these age groups. In addition, results could be usefully stratified by variables such as gender, ethnicity and social class in order to assist clinicians in identifying the types of patients most likely to benefit from treatment. In order to assist with generalisability of results, patient selection in trials should match the criteria for treatment in clinical practice, and trials should be structured to correspond with recommended treatment protocols for orlistat.

Forthcoming research

One ongoing trial was identified from the National Research Register, which is entitled "Clinical trial of orlistat – a pancreatic lipase inhibitor". The lead researcher is Professor RL Kennedy at the Department of Medicine, Sunderland Royal Hospital, UK. The trial was started on 1st November 1999 and expires on 1st November 2001. Another trial was identified from internet searches as a clinical trial protocol (protocol number: 98-CH-0111) entitled "Safety and efficacy of orlistat in African-American and Caucasian children and adolescents with obesity-related comorbid conditions". It was started last year and expires in 2003, and is being led by Dr Jack Yanovski (Developmental Endocrinology Branch, NICHD, NIH, Bethesda, USA).

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The views expressed are those of the authors, who are also responsible for any errors.

References

1. Department of Health. Obesity: reversing the increasing problem of obesity in England. A report from the nutrition and physical activity task forces. London: Department of Health; 1995.
2. Knight I. The heights and weights of adults in Great Britain. London: HMSO; 1994.
3. Colhoun H, Prescott-Clarke P. Health survey for England, 1994. London: HMSO; 1996.
4. Erens B, Primatesta P. Health survey for England: cardiovascular disease. London: The Stationery Office; 1998.
5. Garrow J, Summerbell C. Obesity. In: Stevens A, Raftery J, Mant J, editors. Health care needs assessment: the epidemiologically based needs assessment reviews. 3rd series. Abingdon; Radcliffe Medical Press; 2000. Electronically available on http://hcna.radcliffe-online.com/obframe.html
6. Prentice AM, Jebb SA. Obesity in Britain: gluttony or sloth? *BMJ* 1995;**311**:437–9.
7. NHS Centre for Reviews and Dissemination. Ethnicity and health; reviews of literature and guidance for purchasers in the areas of CVD, mental health, and haemoglobinopathy. York: University of York; 1996. Report No. 5. p. 1–224.
8. Guillaume M, Lapidus L, Beckers F, Lambert A, Bjorntorp P. Familial trends of obesity through three generations: the Belgian–Luxembourg child study. *Int J Obes Relat Metab Disord* 1995;**19**:55–9.
9. Grio R, Porpiglia M. Obesity: internal medicine, obstetric and gynecological problems related to overweight. *Panminerva Med* 1994;**36**:138–41.
10. Parsons T, Power C, Logan S, Summerbell C. Childhood predictors of adult obesity: a systematic review. *Int J Obes Relat Metab Disord* 1999;**23**:S1–107.
11. Flegal K, Troiano R, Pamuk E, Kuczmarski R, Campbell S. The influence of smoking cessation on the prevalence of overweight in the United States. *N Engl J Med* 1995;**333**:1165–70.
12. Health Education Authority. Obesity in primary health care. A literature review. London: Health Education Authority; 1995.
13. Deegan PC, McNicholas WT. Pathophysiology of obstructive sleep apnoea. *Eur Respir J* 1995;**8**:1161–78.
14. Grunstein RR, Wilcox I. Sleep-disordered breathing and obesity. *Baillieres Clin Endocrinol Metab* 1994;**8**:601–28.
15. Richman RM, Elliott LM, Burns CM, Bearpark HM, Steinbeck KS, Caterson ID. The prevalence of obstructive sleep apnoea in an obese female population. *Int J Obes Relat Metab Disord* 1994;**18**:173–7.
16. Rossner S, Lagerstrand L, Persson HE, Sachs C. The sleep apnoea syndrome in obesity: risk of sudden death. *J Intern Med* 1991;**230**:135–41.
17. Han T, van Leer E, Seidell J, Lean M. Waist circumference action levels in the identification of cardiovascular risk factors: prevalence study in a random sample. *BMJ* 1995;**311**:1401–5.
18. Ohlson L, Larsson B, Svardsudd K, Welin L, Eriksson H, Wilhelmsen L, *et al.* The influence of body fat distribution on the incidence of diabetes mellitus. *Diabetes* 1985;**34**:1055–8.
19. Haffner S, Mitchell B, Hazuda H, Stern M. Greater influence of central distribution of adipose tissue on incidence of non-insulin diabetes in women than in men. *Am J Clin Nutr* 1991;**53**:1312–17.
20. Goldstein D. Beneficial effects of modest weight loss. *Int J Obes Relat Metab Disord* 1992;**16**:397–415.
21. Lee I, Paffenbarger RS. Change in body weight and longevity. *JAMA* 1992;**268**:2045–9.
22. Hamm P, Shekell RB, Stamler J. Larger fluctuations in body weight during young adulthood and twenty-five-year risk of coronary death in men. *Am J Epidemiol* 1989;**129**:312–18.
23. Lissner L, Odell PM, D'Agostino RB. Variability of body weight and health outcomes in the Framingham population. *N Engl J Med* 1991;**324**:1839–44.
24. Blair SN, Shaten J, Brownell K, Collins G, Lissner L. Body weight change, all-cause mortality, and cause-specific mortality in the Multiple Risk Factor Intervention Trial. *Ann Intern Med* 1991;**119**:749–57.
25. Jeffery RW. Does weight cycling present a health risk? *Am J Clin Nutr* 1996;**63**(Suppl):452S–5S.
26. World Health Organisation. Obesity: preventing and managing the global epidemic. Report of a World Health Organisation consultation on obesity. Geneva: World Health Organisation; 1998.
27. NHS Centre for Reviews and Dissemination. Systematic review of interventions in the treatment and prevention of obesity. York: University of York; 1997. Report No. 10. p. 1–149.

28. Scottish Intercollegiate Guidelines Network. Obesity in Scotland. Integrating prevention with weight management. Edinburgh: Scottish Intercollegiate Guidelines Network; 1996. Report No. 8.

29. Douketis J, Feightner J, Attia J, Feldman W and the Canadian Task Force on Preventive Health Care. Periodic health examination, 1999 update. 1. Detection, prevention and treatment of obesity. *CMAJ* 1999;**160**:513–25.

30. National Heart, Lung and Blood Institute and National Institute of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. Bethesda, MD: National Institutes of Health; 1998. Report No. 98-4083.

31. Royal College of Physicians. Clinical management of overweight and obese patients with particular reference to the use of drugs. London: Royal College of Physicians; 1998.

32. British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary 40. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain; 2000.

33. MIMS (Monthly Index of Medical Specialities). London: Haymarket Publishing Services; 2000 Aug.

34. European Agency for the Evaluation of Medicinal Products. Committee for proprietary medicinal products European Public Assessment Report (EPAR): xenical. London: EMEA; 1998. p. 1–39.

35. Glenny A-M, O'Meara S. Chapter 70: Obesity. In: McGraw-Hill Clinical Medicine Series: Clinical Pharmacology. New York: McGraw-Hill. In press.

36. Clarke M, Oxman A, editors. Cochrane Reviewers' Handbook 4.1. In: Review Manager (RevMan) (Computer program). Version 4.1. Oxford: The Cochrane Collaboration, 2000 Jun.

37. Drummond M, O'Brien B, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes. Second edition. Oxford: Oxford University Press; 1999.

38. Drent ML, Larsson I, William-Olsson T, Quaade F, Czubayko F, von Bergmann K, *et al.* Orlistat (RO 18-0647), a lipase inhibitor, in the treatment of human obesity: a multiple dose study. *Int J Obes Relat Metab Disord* 1995;**19**:221–6.

39. Drent ML, van der Veen EA. Lipase inhibition: a novel concept in the treatment of obesity. *Int J Obes Relat Metab Disord* 1993;**17**:241–4.

40. van Gaal LF, Broom JI, Enzi G, Toplak H. Efficacy and tolerability of orlistat in the treatment of obesity: a 6-month dose-ranging study. *Eur J Clin Pharmacol* 1998;**54**:125–32.

41. Finer N, James WP, Kopelman PG, Lean ME, Williams G. One-year treatment of obesity: a randomized, double-blind, placebo-controlled, multicentre study of orlistat, a gastrointestinal lipase inhibitor. *Int J Obes Relat Metab Disord* 2000;24:306–13.

42. Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, *et al.* Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat – a randomized controlled trial. *JAMA* 1999;**281**:235–42.

43. Hauptman J, Lucas C, Boldrin MN, Collins H, Segal KR. Orlistat in the long-term treatment of obesity in primary care settings. *Arch Fam Med* 2000;**9**:160–7.

44. Sjostrom L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HPF, *et al.* Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients [published commentary appears in *Lancet* 1998;**352**:160–1]. *Lancet* 1998;**352**:167–72.

45. Hill JO, Hauptman J, Anderson JW, Fujioka K, O'Neil PM, Smith DK, *et al.* Orlistat, a lipase inhibitor, for weight maintenance after conventional dieting: a 1-y study. *Am J Clin Nutr* 1999;**69**:1108–16.

46. Micic D, Ivkovic-Lazar T, Dragojevic R, Jorga J, Stokic E, Hajdukovic Z. [Orlistat, a gastrointestinal lipase inhibitor, in therapy of obesity with concomitant hyperlipidemia]. *Med Pregl* 1999;**LII**:323–33.

47. Hollander PA, Elbein SC, Hirsch IB, Kelley D, McGill J, Taylor T, *et al.* Role of orlistat in the treatment of obese patients with type 2 diabetes: a 1-year randomized double-blind study. *Diabetes Care* 1998;**21**:1288–94.

48. Rossner S, Sjostrom L, Noack R, Meinders AE, Noseda G. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. *Obes Res* 2000;**8**:49–61.

49. Roche. Industry submission; 2000. Report No. M37004.

50. Roche. Industry submission; 2000. Report No. M37009.

51. Roche. Industry submission; 2000. Report No. M37049.

52. Foxcroft D, Ludders J. Orlistat for the treatment of obesity. Southampton: Wessex Institute for Health Research and Development; 1999. Report No. 101. p. 1–49.

53. Roche. Cost–utility analysis of orlistat. Company submission; 2000.

54. Mathias S, Williamson C, Colwell H, Cisternas M, Pasta D, Stolshek B, *et al.* Assessing health-related quality of life and health state preference in persons with obesity: a validation study. *Qual Life Res* 1997;**6**:311–22.

55. Garrow J. Flushing away the fat. Weight loss during trials of orlistat was significant, but over half was due to diet. *BMJ* 1998;**317**:830–1.

56. Little R, Yau L. Intent-to-treat analysis for longitudinal studies with drop-outs. *Biometrics* 1996;**52**:1324–33.

57. Lekkerkerker JFF, Diemont WL, Koopmans PP. Orlistat and weight loss. *Lancet* 1998;**352**:1473–4.

58. Sjostrom L, Rissanen A, Golay A. Orlistat and weight loss – reply. *Lancet* 1998;**352**:1474.

59. Begg C, Cho M, Eastwood S, Horton R, Moher D. Improving the quality of reporting of randomized controlled trials – the CONSORT statement. *JAMA* 1996;**276**:637–9.

60. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000;**320**:1240–3.

61. Trent ME, Ludwig DS. Adolescent obesity, a need for greater awareness and improved treatment. *Curr Opin Pediatr* 1999;**11**:297–302.

62. Epstein LH. Helping obese youngsters lose weight: what works...what doesn't? *Consultant* 1998;**38**:2462–75.

63. Dvorak R, Starling RD, Calles-Escandon J, Sims EH, Poehlman ET. Drug therapy for obesity in the elderly. *Drugs Aging* 1997;**11**:338–51.

64. McDonagh M. An overview of age-specific pharmacokinetics and pharmacodynamics. *The Aging Male* 2000;**3**:81–6.

65. Legato MJ. Gender-specific aspects of obesity. *Int J Fertil Women's Med* 1997;**42**:184–97.

Appendix 1

Search strategy

The search strategy below was used for the joint review of orlistat and sibutramine.

#1 explode "Obesity"/ all subheadings
#2 "Body-Weight"/ all subheadings
#3 "Hyperphagia"/ all subheadings
#4 "Adipose-Tissue"/ all subheadings
#5 weight or overweight or obese or obesity or antiobesity
#6 food or appetite or satiety
#7 adiposity or overeating
#8 hyperphagia or fat
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 orlistat
#11 xenical
#12 tetrahydrolipstatin
#13 sibutramine
#14 meridia in ti,ab
#15 #10 or #11 or #12 or #13 or #14
#16 #9 and #15

This strategy was used for the MEDLINE database and was adapted, as appropriate, for the other databases searched.

Appendix 2

Pre-screen form

(1) Paper (author and year)

(2) Study design (eligible for inclusion: RCT)

(3) Participants (eligible for inclusion: overweight/obese or maintaining weight loss)

(4) Interventions (eligible for inclusion: orlistat)

(5) Outcomes (eligible for inclusion: body weight, fat content or fat distribution assessed at both baseline and post-intervention)

(6) Language (eligible for inclusion: English, French, German or Dutch)

(7) Decision

Appendix 3

Data extraction table for RCTs

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Drent and van der Veen, 1993[39] ***Country*** The Netherlands ***Aim*** To investigate the additional weight-reducing potential and tolerability of orlistat in obese patients receiving dietary treatment ***Method of randomisation*** Not stated ***Outcomes*** Change in body weight, dietary intake (assessed from diaries), BP, heart rate, adverse events, adherence with drug regimen (assessed by counting number of returned capsules), vitamin A and E levels, lipid levels, ECG, haematology, blood chemistry, urinalysis ***Setting and length of treatment*** 4-week run-in as outpatients followed by 12-week DB phase	***Population*** People responding to an advertisement in their local newspaper ***Inclusion criteria*** *For run-in* Obese but otherwise healthy outpatients, aged 18–55 years, body weight 20–50% above ideal according to the 1983 Metropolitan Life Insurance Tables *For DB study* Adherence with the dietary regimen during run-in (defined as body weight reduction of 0.5–4 kg, and by completion of diaries), adherence with the drug regimen (assessed by counting placebo capsules – at least 80% used) during run-in ***Exclusion criteria*** GI disorder, use of laxatives or drugs that could affect body weight	***4-week SB placebo run-in period for all patients*** Basal calorific requirement calculated for each patient according to gender, age and actual weight. The calculated daily intake was multiplied by 1.3 to adjust for mild–moderate daily activities, and then reduced by 500 to obtain weight loss. Patients were instructed to follow this 500 kcal-reduced diet containing 30% calories as fat, and to complete a diary recording their dietary intake, physical activities and defaecation pattern. All received placebo capsules tds with main meals (n = 52) ***Standard care for all patients during DB phase*** Dietary regimen as above C: placebo tds (n = 21) I: orlistat 50 mg tds (n = 23)	***Gender*** (male/female) C: 3/16 I: 3/17 ***Age*** (mean ± SD in years) C: 41.6 ± 8.2 I: 41.9 ± 8.1 ***Weight*** (mean ± SD in kg) C: 81.9 ± 7.9 I: 85.5 ± 12.1 ***BMI*** (mean ± SD in kg/m^2) C: 30.0 ± 2.6 I: 30.6 ± 3.7 Patients were normolipidaemic at baseline, with vitamin A and E levels within the range of reference values	***Statistical techniques*** ANOVA with repeated measurements and unpaired and paired t-tests ***Weight loss during run-in*** (mean ± SD in kg) Overall: 2.63 ± 1.08 C: 2.61 ± 1.17 I: 2.65 ± 1.01 ***Weight loss between randomisation and end of 12-week period*** (mean ± SD in kg) C: 2.1 ± 2.8 I: 4.3 ± 3.4 95% CI for difference, 0.2 to 4.2 ***Cardiovascular changes*** Cholesterol and triglyceride levels unchanged, and no significant changes in BP, heart rate, biochemical or haematological parameters in either group	***Total withdrawals*** C: two (both due to motivation problems) I: three (one due to non-adherence with diet, one due to dissatisfaction with amount of weight lost and one due to adverse events, including some episodes of faecal incontinence) ***GI adverse events*** (number of patients in C/I) Abdominal pain 4/12 Liquid stools 1/8 Faecal incontinence 0/2 Urgency 0/1 Oily stools 0/3 Nausea 0/5 Vomiting 1/4 Flatulence 2/5 Haemorrhoids 0/1 Most were mild or moderate No significant difference in the adverse events (other than GI) between groups ***Vitamin A and E levels*** For most patients, levels remained within reference values during the study	***Limitations of study, as noted by study authors*** Although the study was DB, the adverse events enabled some patients to guess that they had received orlistat, especially when complaints were more than mild ***Sponsorship*** Hoffmann-La Roche

continued

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Drent *et al.*, 1995[38] ***Countries*** The Netherlands, Denmark, Germany, Sweden ***Aim*** To evaluate the efficacy and tolerability of orlistat in 10, 60 and 120 mg tds dosages plus a mildly hypocaloric diet ***Method of randomisation*** Not stated. Patients stratified according to gender ***Outcomes*** Change in body weight, anthropometry, vital signs, adverse events, serum lipid levels, serum levels of vitamins A, D and E, adherence with dietary regimen ***Setting and length of treatment*** Multicentre study involving five clinics with 4-week run-in followed by 12-week DB study	***Population*** Not stated ***Inclusion criteria*** *For run-in* Obese but otherwise healthy, aged 25–60 years, BMI 27.8–35.0 kg/m^2 for men and 27.3–35.0 kg/m^2 for women, waist:hip ratio ≥ 0.9 for men and ≥ 0.8 for women, accustomed to three main meals/day, consistent regular physical activity, women to be surgically sterile, 1 year postmenopausal or using reliable mechanical contraceptives *For DB phase* Patients adhering to the dietary regimen (defined as body weight reduction of 0–4 kg and a deviation of less than 20% from prescribed intake of total calories and calories as fat in three of 4-day calculations from dietary records) and adhering to the drug regimen during run-in (assessed by counting placebo capsules – at least 80% used) ***Exclusion criteria*** History of cardiac disease requiring medication, oedema of non-cardiac origin, history of drug hypersensitivity or allergic conditions that may interfere with the study, transaminases 100% above upper reference value, serum creatinine > 160 µmol/l, proteinuria > 500 mg/dl, use of drugs influencing body weight and serum lipid or vitamin levels, Cushing's syndrome, diabetes mellitus requiring drug treatment or other endocrine abnormalities other than l-thyroxine-stabilised hypothyroidism, history of substance abuse, history of GI disorders, pancreatitis, pancreas lipase deficiency or lactose intolerance, history of eating disorders, any abnormality of potential clinical significance	***4-week SB placebo run-in period for all patients*** Basal calorific requirement calculated for each patient according to gender, age and actual weight. The calculated daily intake was multiplied by 1.3 to adjust for mild–moderate daily activities. The energy intake was estimated from 4-day dietary records, and the average estimated energy requirement was then reduced by 500 kcal in order to obtain weight loss. Patients were instructed to follow a 500 kcal-reduced diet containing 30% calories as fat, and to complete a dietary diary during the whole 16-week study period. All received placebo capsules tds with main meals (n = 237) ***Standard care for all patients during DB study*** Dietary regimen as above. At all clinic visits, diet diaries were discussed with the dietician C: placebo tds (n = 46) I1: orlistat 10 mg tds (n = 48) I2: orlistat 60 mg tds (n = 45) I3: orlistat 120 mg tds (n = 47)	***Gender*** (male/female) C: 18/28 I1: 21/27 I2: 20/25 I3: 20/27 ***Age*** (mean ± SD in years) C: 43.4 ± 8.5 I1: 44.9 ± 9.2 I2: 43.5 ± 8.4 I3: 44.6 ± 9.3 ***Weight*** (mean ± SD in kg) C: 90.0 ± 11.6 I1: 92.1 ± 12.3 I2: 92.6 ± 12.5 I3: 94.1 ± 12.9 ***BMI*** (mean ± SD in kg/m^2) C: 31.1 ± 2.1 I1: 31.5 ± 2.2 I2: 31.5 ± 2.3 I3: 31.4 ± 2.5 ***Waist:hip ratio*** (mean ± SD) C: 0.91 ± 0.07 I1: 0.93 ± 0.07 I2: 0.92 ± 0.07 I3: 0.94 ± 0.06 ***Total cholesterol*** (mean ± SD in mmol/l) C: 5.5 ± 0.8 I1: 5.6 ± 1.0 I2: 5.6 ± 1.0 I3: 5.6 ± 1.1 ***LDL-C*** (mean ± SD in mmol/l) C: 3.7 ± 0.7 I1: 3.6 ± 0.7 I2: 3.8 ± 0.8 I3: 3.9 ± 1.1 ***Triglycerides*** (mean ± SD in mmol/l) C: 1.5 ± 1.7 I1: 2.1 ± 2.4 I2: 1.5 ± 1.1 I3: 1.6 ± 0.9	***Statistical techniques*** ANOVA and ANCOVA. Safety population analysis included those who had received at least one dose of medication after randomisation. ITT analysis as above plus at least one body weight measurement. Standard efficacy analysis included those adhering to drug and dietary regimens for ≥ 4 weeks of randomised treatment. For ITT and standard efficacy analyses, the last available body weight was used as a week 12 value ***Weight change at 12 weeks adjusted for weight loss during run-in*** (mean ± SEM in kg by ITT) C: –2.98 ± 0.38 I1: –3.61 ± 0.38 I2: –3.69 ± 0.39 I3: –4.74 ± 0.38 p = 0.001 for C versus I3, other comparisons not significant ***Standard efficacy analysis at 12 weeks*** (mean ± SEM) C: –3.20 ± 0.42 I1: –3.64 ± 0.45 I2: –3.85 ± 0.44 I3: –4.76 ± 0.41 p = 0.009 for C versus I3, other comparisons not significant ***Change in total cholesterol at 12 weeks adjusted for baseline levels*** (mean ± SD in mmol/l by ITT) C: 0.22 ± 0.55 I1: 0.10 ± 0.73 I2: –0.10 ± 0.67 I3: –0.22 ± 0.53 p = not significant for C versus I1, p = 0.011 for C versus I2, p = 0.001 for C versus I3 ***Change in LDL-C at 12 weeks adjusted for baseline levels*** (mean ± SD in mmol/l by ITT) C: 0.13 ± 0.39 I1: 0.14 ± 0.68 I2: –0.14 ± 0.42 I3: –0.19 ± 0.51 p = not significant for C versus I1, p = 0.012 for C versus I2, p = 0.003 for C versus I3 ***Change in LDL-C:HDL-C ratio at 12 weeks adjusted for baseline levels*** (mean ± SD by ITT) C: –0.07 ± 0.63 I1: 0.02 ± 0.62 I2: –0.13 ± 0.60 I3: –0.39 ± 0.71 p = not significant for C versus I1, p = not significant for C versus I2, p = 0.033 for C versus I3 ***Change in triglycerides at 12 weeks adjusted for baseline levels*** (mean ± SD in mmol/l by ITT) C: 0.05 ± 0.94 I1: –0.36 ± 1.44 I2: 0.03 ± 0.65 I3: –0.20 ± 0.61 p = not significant for C versus I1, I2 and I3 ***Change in serum levels of vitamin A at 12 weeks*** (mean ± SEM in µmol/l by ITT) C: –0.034 ± 0.059 I1: –0.004 ± 0.059 I2: –0.042 ± 0.059 I3: –0.095 ± 0.058 p-values not stated	***Number of withdrawals due to GI adverse events*** C: 0 I1: 0 I2: 0 I3: 3 ***Number of withdrawals due to circumoral paresthesia*** C: 0 I1: 1 I2: 0 I3: 0 ***Number of withdrawals due to asthenia*** C: 0 I1: 0 I2: 0 I3: 1 (one patient suffered from both GI complaints and asthenia) ***Reasons for withdrawals other than adverse events*** C: 6 I1: 4 I2: 3 I3: 2 ***Total number of withdrawals*** C: 6 I1: 5 I2: 3 I3: 5	***Study limitations, as noted by the study authors*** Patients may under-report their food intake in the diet diaries, however, this should be the case across all treatment groups ***Sponsorship*** Hoffmann-La Roche

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Authors, year, country, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
continued Drent *et al.*, 1995[38]				***Change in serum levels of vitamin D at 12 weeks*** (mean ± SEM in nmol/l by ITT) C: –15.4 ± 3.7 I1: –12.1 ± 3.8 I2: –23.3 ± 3.8 I3: –13.8 ± 3.7 *p*-values not stated ***Change in serum levels of vitamin E at 12 weeks*** (mean ± SEM in µmol/l by ITT) C: 0.81 ± 0.91 I1: –0.69 ± 0.91 I2: –3.16 ± 0.91 I3: –3.48 ± 0.89 $p < 0.01$ for C versus I2 and C versus I3, *p*-value for C versus I1 not stated ***Adverse events*** Mild–moderate adverse events were common in the orlistat groups, particularly at the two higher doses. Severe (very inconvenient) events were observed in small percentages of patients, again at the two higher dosages ***Adherence with dietary regimen*** Information from diet diaries indicated that patients adhered to dietary regimen		

continued

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Micic *et al.*, 1999[46] ***Country*** Yugoslavia ***Aim*** To investigate the effect of orlistat on weight reduction and serum lipid levels, and to assess tolerability ***Method of randomisation*** Not stated ***Outcomes*** Body weight, sitting BP and heart rate, serum lipid levels, standard laboratory tests for blood and urine, adverse events, patient adherence ***Setting and length of treatment*** Endocrinology centres. 2-week run-in followed by 24-week DB trial	***Population*** Not stated ***Inclusion criteria*** *For run-in* Age 18–75 years, BMI ≥ 30 kg/m^2, serum LDL-C ≥ 4.2 mmol/l. If female, had to use adequate contraception, be surgically sterile or postmenopausal *For DB phase* Unclear – adherence with run-in regimen? ***Exclusion criteria*** Total serum triglycerides > 4.5 mmol/l, pregnancy, lactation, of childbearing potential not using adequate contraception, history of myocardial infarction, coronary artery bypass grafting or coronary angioplasty during 6 months prior to screening, significant cardiac, respiratory, renal, neurological, GI or endocrine disease that may impact on study parameters or safety, history of GI surgery for weight loss, history of postoperative adhesions, active GI disease, pancreatic disease, type 2 diabetes, proliferative retinopathy and clinical nephropathy, history of cancer (except successfully treated skin or cervical cancers), history of bulimia or laxative abuse, abnormal laboratory values 100% above reference range, fat-soluble vitamin deficiencies, received investigational new drug within last 3 months, history of psychological illness or condition interfering with patient's ability to understand study requirements, use of appetite suppressants, fish oil supplements, retinoids, systemic steroids, anticoagulants or acarbose (2-month wash-out period prior to randomisation required)	***2-week SB placebo run-in for all patients*** Commenced individually determined mild hypocaloric diet with a minimum intake of 1200 kcal/day and a deficit of 600 kcal/day plus placebo twice daily (*n* = 120) ***Standard care for all patients during DB study*** Continued dietary regimen as above C: placebo tds with main meals for 24 weeks (*n* = 59) I: orlistat 120 mg tds with main meals for 24 weeks (*n* = 60)	***Gender*** (male/female) C: 13/46 I: 18/42 ***Age*** (mean ± SD in years) C: 43.95 ± 10.72 I: 45.47 ± 8.06 ***Weight*** (mean ± SD in kg) C: 97.67 ± 6.13 I: 100.3 ± 20.2 ***BMI*** (mean ± SD in kg/m^2) C: 36.28 ± 5.23 I: 36.08 ± 6.25 Study authors stated that there were no statistically significant differences between groups in terms of lipid levels, vital signs and serum and urine laboratory tests	***Statistical techniques*** Two-sided tests used for all analyses. Chi-squared, Mann–Whitney, Fischer, McNemarov, *t*-test for dependent samples, *t*-test for independent samples, repeated-measures ANOVA (with and without factor-therapeutic group) and regression ***Number (%) of patients with weight loss/gain after 4 weeks of therapy*** C: 41 (73.2%)/15 (26.8%) I: 53 (91.4%)/5 (8.6%) $p < 0.05$ ***Number (%) of patients with weight loss/gain at 24 weeks*** C: 43 (87.8%)/6 (12.2%) I: 50 (100.0%)/0 (0.0%) $p < 0.05$ ***Mean (%) weight loss at 24 weeks*** C: 7.34 kg (7.5%) I: 10.75 kg (10.7%) *p*-value not reported ***Number (%) of patients with BMI reduction of < 4 kg/m^2 at 24 weeks*** C: 31 (72.1%) I: 26 (52.0%) p = not significant ***Number (%) of patients with BMI reduction of 4–12 kg/m^2 at 24 weeks*** C: 12 (27.9%) I: 24 (48.0%) $p < 0.05$ ***Changes in serum lipid levels at 24 weeks*** *Total cholesterol* C: decreased by 5.9% I: decreased by 13.9% *LDL-C* C: decreased by 5.9% I: decreased by 19.4% *HDL-C* C: decreased by 2.54% I: increased by 0.95% *LDL-C:HDL-C ratio* C: decreased by 5.3% I: decreased by 20.3% *Triglycerides* C: increased by 7.10% I: decreased by 5.32% *p*-values not reported for analysis of lipid levels, however, authors state that between-group differences were statistically significant ***Vital signs and laboratory tests*** Sitting SBP in patients of I showed significant reductions throughout the trial ($p = 0.05$ at 24 weeks). There were no statistically significant changes in patients of C. Sitting DBP in patients of I showed statistically significant reductions throughout the trial ($p = 0.001$ at 24 weeks), and in C patients after week 20 ($p = 0.008$ at week 24). There were no significant differences between I and C in mean values of SDP and DBP. Analysis of heart rate, ECG and laboratory tests showed no significant differences within groups over time or between groups	***Total withdrawals*** One patient withdrew during the run-in. Ten patients from each study group withdrew during DB treatment. Overall withdrawal = 16.8% ***Reasons for withdrawal*** (number of patients in C/I) Irregular visits 0/1 Contact lost 1/1 Adverse event 0/1 Patient's decision 9/6 Protocol violation 0/1 ***Number of completers*** C: 49 I: 50 ***Number (%) of patients available for analysis of efficacy and tolerability*** C: 56/59 (95.0%) I: 58/60 (96.7%) ***Number (%) of patients not available for analysis of efficacy*** C: 0 (0.0%) I: 2 (3.3%) ***Number (%) of patients not available for analysis of efficacy or tolerability*** C: 3 (5.0%) I: 0 (0.0%) ***Number (%) of patients with adverse events or new disease*** C: 7/59 (11.9%) I: 18/60 (30.0%) ***Number of patients with GI adverse events*** C: 11 I: 29 ***Of these, number of patients with oily stools*** C: 8 I: 27 ***Other adverse events*** (number of patients in C/I) Depression 1/0 Discopathy 1/0 Headache 0/1 Breast abscess 0/1 Tonsillitis 1/0 In one patient of I, oily stools with diarrhoea led to interruption of therapy Intensity of adverse events was usually mild–moderate ***Patient adherence with drug regimen (assessed by counting returned capsules)*** Adherence was about 90% in both groups (which was considered satisfactory)	***Limitations of the study, as noted by the study authors*** None stated ***Sponsorship*** Hoffmann-La Roche

continued

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
van Gaal, 1998[40] ***Countries*** Austria, Belgium, Brazil, Finland, Germany, Italy, Sweden, UK, Switzerland ***Aim*** To determine the weight-reducing efficacy and tolerability of orlistat and to define the optimal dosage regimen ***Method of randomisation*** Not stated ***Outcomes*** Change in body weight, vital signs, ECG, adverse events, clinical chemistry, haematology, serum levels of vitamins A, D and E and β-carotene, urinalysis, waist and hip circumference, faecal fat excretion, plasma levels of orlistat, gallbladder ultrasound, adherence with drug regimen (assessed by counting the number of returned capsules), adherence with dietary regimen (assessed by diet diaries) ***Setting and length of treatment*** 14 centres. 4-week run-in followed by 24-week DB phase	***Population*** Not stated ***Inclusion criteria*** *For run-in* Age ≥ 18 years, BMI 28–43 kg/m^2, women of childbearing potential eligible if using adequate contraceptive measures *For DB phase* At least 70% adherence with drug regimen during run-in, no proven evidence of multiple gallstones (assessed by ultrasound) or symptomatic cholelithiasis, lipid-soluble vitamin levels within the clinical reference range, no clinically significant GI disorder ***Exclusion criteria*** Weight loss > 4 kg in the 3 months before screening, history or presence of significant medical disorders (including diabetes mellitus, cardiovascular disease, uncontrolled hypertension and pancreatic disease), previous GI surgery for weight reduction, history of postoperative adhesions, history or presence of cancer (with the exception of treated basal cell carcinoma), psychiatric or neurological disorders requiring medications or liable to prejudice patient adherence, evidence of alcohol or substance abuse, bulimia or laxative abuse, pregnancy, lactation, postmenopausal women who were amenorrhoeic for less than 1 year, use of drugs capable of influencing body weight or plasma lipids during the month prior to study entry, concomitant use of anticoagulants, digoxin, anti-arrhythmics or lipid-soluble vitamin supplements	***4-week SB placebo run-in for all patients*** Nutritionally balanced hypocaloric diet designed to result in weight loss of 0.25–0.5 kg/week, containing 30% calories as fat, 50% as carbohydrate, 20% as protein and maximum cholesterol of 300 mg/day. Total daily energy expenditure estimated for each patient from basal metabolic rate multiplied by 1.3 to account for mild to moderate activity levels. The minimum prescribed calorie intake was 1200 kcal/day with a deficit of 600 kcal/day. If BMI was recorded as ≤ 22 kg/m^2 on two consecutive visits, prescribed calories were increased to maintain weight. Placebo tds (n = 676) ***Standard care for all patients during DB study*** Dietary regimen continued as above C: placebo tds with main meals (n = 123) I1: orlistat 30 mg tds with main meals (n = 122) I2: orlistat 60 mg tds with main meals (n = 123) I3: orlistat 120 mg tds with main meals (n = 120) I4: orlistat 240 mg tds with main meals (n = 117)	***Gender*** (% male) C: 22% I1: 25% I2: 24% I3: 21% I4: 25% ***Age*** (mean ± SD age in years) C: 43 ± 11 I1: 40 ± 11 I2: 42 ± 11 I3: 40 ± 11 I4: 44 ± 11 ***BMI*** (mean ± SD in kg/m^2) C: 35 ± 4 I1: 35 ± 4 I2: 34 ± 4 I3: 35 ± 4 I4: 34 ± 4	***Statistical techniques*** Safety analyses included those who had received at least one dose of trial medication after randomisation and had a subsequent safety observation. ITT analyses included those who had received at least one dose of study medication and had a subsequent efficacy observation. Null hypothesis was tested using ANOVA and ANCOVA. For each centre, the placebo-adjusted 95% CI of orlistat effect (based on LSM) was calculated, and the placebo-adjusted LSM differences from each centre were used in a Michaelis–Menton model to assess the dose–response relationship ***Diet diaries*** There were no differences between groups in energy or fat consumption ***Weight loss during run-in*** All treatment groups lost similar amounts of weight (about 3 kg) ***Mean % weight loss at 24 weeks in relation to initial weight*** C: 6.5% I1: 8.5% I2: 8.8% I3: 9.8% I4: 9.3% ***LSM differences in body weight from placebo at 24 weeks*** (in kg) I1: 0.95 I2: 1.86 I3: 2.55 I4: 2.81 $p \leq 0.002$ for C versus I2, $p \leq 0.001$ for C versus I3, $p \leq 0.001$ for C versus I4 ***Patients that lost > 10% initial body weight*** C: 19% I1: 28% I2: 28% I3: 37% I4: 38% p-values not reported ***Mean change in waist circumference*** (in cm) C: –3.5 I1: –5.1 I2: –5.9 I3: –6.3 I4: –6.0 p-values not reported ***Mean change in daily faecal fat excretion*** (in g) C: –0.1 I1: +11.5 I2: +15.4 I3: +18.5 I4: +23.5 p-values not reported ***Pharmacokinetics*** Analysis of plasma samples confirmed that the overall absorption of orlistat was very low	***Total withdrawals during run-in*** Overall 63/767 (9%) ***Most common reasons for withdrawal (number of patients overall)*** Entry violation 13 Lost to follow-up 12 Did not cooperate 11 Patients with adverse events 8 ***Total withdrawals during DB treatment*** C: 22% I1: 24% I2: 23% I3: 19% I4: 17% ***Reasons for withdrawals during DB treatment*** (% of patients in C/I1/I2/I3/I4) Refused treatment 8/7/7/3/5 Adverse events 2/6/5/2/3 Lost to follow-up 7/6/6/7/5 Did not cooperate 1/3/2/3/4 Administrative 2/2/3/3/0 Protocol violation 1/1/1/1/0 Entry violation 0/0/0/1/0 ***Patients with adverse events*** C: 69% I1: 79% I2: 83% I3: 84% I4: 87% Most adverse events were mild–moderate. With the exception of GI events, they were judged to be mostly unrelated to treatment ***Patients with GI adverse events*** C: 46% I1: 61% I2: 76% I3: 71% I4: 83% ***Number of patients with severe GI adverse events*** C: 1 I1: 9 I2: 8 I3: 2 I4: 10 Most of the orlistat-treated patients experienced one or two episodes of GI events, generally within the first few weeks of initiating treatment. Most episodes were mild–moderate in severity	***Limitations of the study, as noted by the study authors*** None stated ***Sponsorship*** Hoffmann-La Roche

continued

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
continued van Gaal, 1998[40]					Three patients (2%) in C and 18 patients (4%) in the orlistat groups withdrew due to various adverse events: 11 due to GI events, 10 of whom were treated with orlistat ***Withdrawals due to adverse events related to treatment*** C: two (one due to abnormal GTT and one due to urticaria) I1: five (one due to faecal incontinence, one due to flatulence, one due to liquid stools, one due to abdominal pain and one due to polymyalgia rheumatica) I2: two (one due to abdominal pain and one due to depression) I3: two (one due to gastritis and one due to liquid stools) I4: one (due to faecal incontinence Serious adverse events were reported by two patients in C and 12 patients in the four orlistat groups. Four were considered as possibly related to treatment (one due to faecal incontinence and one due to diverticulitis in I1 and one each in I2 and I4 due to abdominal pain). All patients apart from the one in I4 withdrew No clinically relevant abnormalities related to orlistat were found in laboratory values or in terms of hepatocellular damage, vital signs or ECG. There was no evidence to support the notion of increased cholelithiasis associated with orlistat use ***Patients with low levels of fat-soluble vitamins on ≥ two consecutive occasions*** C: 3.3% I1: 4.2% I2: 6.7% I3: 4.2% I4: 12.8% ***Number of patients who received supplemental fat-soluble vitamins*** C: 2 I1: 2 I2: 0 I3: 4 I4: 8 There were significant differences in the levels of vitamins D (I4 only) and E and β-carotene between C and orlistat-treated groups at 24 weeks (LSM difference $p \leq 0.001$)	

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Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Hollander *et al.*, 1998[47] ***Country*** USA ***Aim*** To determine the efficacy of orlistat when used in obese patients with type 2 diabetes in terms of weight loss, glycaemic control and lipid status ***Method of randomisation*** Method not stated. Stratification according to weight loss and glucose control during run-in: 1st stratum – weight loss ≤ 2 kg, glucose 5.6–8.9 mmol/l; 2nd stratum – weight loss ≤ 2 kg, glucose 9.0–12.2 mmol/l; 3rd stratum – weight loss > 2 kg, glucose 5.6–8.9 mmol/l; 4th stratum – weight loss > 2 kg, glucose 9.0–12.2 mmol/l ***Outcomes*** Change in body weight, glycaemic control, lipid levels, waist circumference, standard laboratory measurements (haematology, clinical chemistry, urinalysis and faecal occult blood), levels of vitamins A, D and E and β-carotene, prothrombin time, adverse events ***Setting and length of treatment*** 12 centres. 5-week run-in followed by 52-week DB phase	***Population*** Not stated ***Inclusion criteria*** *For run-in* Aged > 18 years, BMI 28–40 kg/m^2, type 2 diabetes maintained on oral sulfonylureas for the 6 months prior to trial, stable plasma glucose on a second-generation sulfonylurea agent (glyburide or glypizide) as the only oral hypoglycaemic agent at trial entry *For DB phase* At least 70% adherence with drug regimen during run-in (assessed by counting capsules), glycated haemoglobin of 6.5–10% at screening, fasting plasma glucose level of 5.6–12.2 mmol/l at the end of week 4 of run-in, blood levels of fat-soluble vitamins above the lower limit of reference range ***Exclusion criteria*** Pregnancy, lactation, women of childbearing potential not taking adequate contraceptive measures, clinically relevant condition that might affect study outcomes, significant complications associated with diabetes, weight loss > 4 kg during the previous 3 months, history of recurrent nephrolithiasis or symptomatic cholelithiasis, GI surgery for weight loss, history of bulimia or laxative abuse, use of any drugs that might influence body weight or plasma lipids during the 8 weeks prior to trial	***5-week SB placebo run-in for all patients*** Nutritionally balanced, mildly hypocaloric diet containing 30% calories as fat, 50% as carbohydrate and 20% as protein, with a maximum of 300 mg/day of cholesterol. Patients instructed in dietary requirements and procedures for completing food intake records. All previous vitamin supplements were discontinued and patients were prescribed placebo and oral hypoglycaemic agent (glypizide or glyburide) at doses determined by patient's physician. Constant doses were maintained during the 2 weeks prior to randomisation (n = 391) ***Standard care for all patients during DB study*** Hypocaloric diet with an energy deficit of 500 kcal/day. Additional dietary counselling and supplements given to patients with two consecutive fat-soluble vitamin measurements below reference range C: placebo tds with meals for 52 weeks (n = 159) I: orlistat 120 mg tds with meals for 52 weeks (n = 163)	***Gender*** (male/female) C: 85/74 I: 79/83 ***Age*** (mean ± SD in years) C: 54.7 ± 9.7 I: 55.4 ± 8.8 ***Race numbers*** (white/black/Hispanic/other) C: 140/9/6/4 I: 141/13/4/4 ***Weight*** (mean ± SD in kg) C: 99.7 ± 15.4 I: 99.6 ± 14.5 **BMI** (mean ± SD in kg/m^2) C: 34.0 ± 3.4 I: 34.5 ± 3.2 ***Fasting plasma glucose*** (mean ± SD in mmol/l) C: 9.09 ± 1.87 I: 8.85 ± 1.68 ***Glycated haemoglobin*** (mean ± SD) C: 8.2 ± 1.07% I: 8.05 ± 0.98%	***Statistical techniques*** ITT analysis included patients who had received at least one dose of study medication and a subsequent efficacy observation. Safety analysis included those who had received one dose of trial medication and a subsequent safety observation. ANOVA and ANCOVA were used to test the null hypothesis. The placebo-adjusted 95% CI of orlistat treatment effect (LSM) was determined ***Weight loss during run-in*** (mean ± SEM in kg) C: 2.24 ± 0.14 I: 2.07 ± 0.15 ***% weight loss from beginning of run-in to endpoint*** (mean ± SEM by ITT) C: 4.3 ± 0.5% I: 6.2 ± 0.5% LSM difference between treatment groups (2.4 kg) was statistically significant (p < 0.001) ***% weight loss from beginning of run-in to endpoint for completers*** (mean ± SEM) C: 4.2 ± 0.5% I: 6.3 ± 0.4% (p < 0.001) ***Weight loss*** (mean ± SEM in kg by ITT) C: 4.31 ± 0.57 I: 6.19 ± 0.51 p < 0.001 ***Patients that lost ≥ 5% of initial body weight*** C: 22.6% I: 48.8% p < 0.001 ***Patients that lost ≥ 10% of initial body weight*** C: 8.8% I: 17.9% p < 0.017 ***Decrease in fasting plasma glucose levels during run-in*** (mean ± SEM in mmol/l) C: 1.16 ± 0.13 I: 0.98 ± 0.13 p-value not given ***Additional change in fasting plasma glucose levels from randomisation to endpoint*** (mean ± SEM in mmol/l) C: 0.54 ± 0.15 I: –0.02 ± 0.14 p < 0.001 ***Values in subset of patients with fasting plasma glucose ≥ 7.77 mmol/l at start of DB phase*** (mean ± SEM in mmol/l) C: 0.36 ± 0.27 I: –0.47 ± 0.19 p < 0.001 ***Decrease in fasting plasma insulin levels at endpoint*** (mean ± SEM) C: 4.3 ± 6.3% I: 5.2 ± 4.4% p = not significant Mean glycated haemoglobin levels decreased during run-in by about 7.5% in both groups ***Additional change in glycated haemoglobin levels from randomisation to endpoint*** (mean ± SEM) C: 0.18 ± 0.11% I: –0.28 ± 0.09% p < 0.001 ***Values in subset of patients with glycated haemoglobin levels > 8% at start of DB phase*** (mean ± SEM) C: –0.05 ± 0.29% I: –0.53 ± 0.18% p < 0.001 ***Patients that decreased/discontinued sulfonylureas*** C: 28.9%/0.0% I: 43.2%/11.7% ***Changes in lipid levels*** Decreases were similar in both groups during run-in. After randomisation, I patients demonstrated improved parameters versus patients in C, with statistically significant differences for total cholesterol, LDL-C (p < 0.001), LDL-C:HDL-C ratio (p < 0.001), triglycerides (p = 0.036) and apolipoprotein B (p < 0.001) ***Change in waist circumference at endpoint*** (mean ± SEM in cm) C: –2.0 ± 0.5 I: –4.8 ± 0.5 p < 0.01	***Number (%) of withdrawals during DB phase*** C: 44/159 (28%) 23 withdrawals due to adverse events I: 24/163 (15%) 12 withdrawals due to adverse events ***Number (%) of completers*** C: 116/159 (72%) I: 139/163 (85%) ***Reasons for withdrawal*** Adverse events, loss to follow-up, non-adherence, administrative, protocol violations and treatment failure. Numbers per reason were not provided except for non-adherence (n = 4) ***Number (%) of withdrawals due to raised plasma glucose levels on ≥ three occasions despite maximum sulfonylurea medication*** C: 15 (8.8%) I: 5 (2.5%) ***Patients who experienced ≥ one GI adverse event*** C: 59% I: 79% GI events usually occurred early during treatment, were mild to moderate in intensity, were generally transient and resolved spontaneously ***Number of withdrawals due to GI adverse events*** C: 2 I: 7 There was no evidence for the development of gallstones or renal stones after orlistat treatment Mean plasma levels of vitamins A, D and E and β-carotene remained within the reference ranges throughout the study. After 52 weeks, mean vitamin E and β-carotene levels were significantly lower in I versus C (p < 0.001). However, there was no significant change in vitamin E:LDL-C ratio in either group Supplementation was required for vitamin D in 7% of C patients and 17% of I patients, for vitamin E in 1% of both groups and for β-carotene in 9% of patients in I Prothrombin times did not differ between groups and did not fall below the reference range	***Limitations of the study, as noted by the study authors*** None stated ***Sponsorship*** Hoffmann-La Roche

continued

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Finer *et al.*, 2000[41] ***Country*** UK ***Aim*** To assess the efficacy and tolerability of orlistat in producing and maintaining weight loss over a 12-month period ***Method of randomisation*** Blinded code numbers, randomised in blocks of four, were printed on the labels of DB medication (matching orlistat and placebo) and supplied in identical blister packs to each study centre. Patients were randomised in blocks to give equal numbers of orlistat and placebo patients. Patients were stratified according to weight lost during run-in (≤ 2 and > 2 kg) ***Outcomes*** Change in body weight, waist circumference, serum lipid levels, fasting serum insulin and glucose levels, plasma levels of vitamins A, D and E and β-carotene, haematology, fasting blood chemistry, urinalysis, faecal occult blood, sitting BP, heart rate, adherence, adverse events ***Setting and length of treatment*** Five centres. 4-week run-in followed by 52-week DB phase	***Population*** Obese patients recruited by local advertisement or referred by general practitioners ***Inclusion criteria*** *For run-in* Age ≥ 18 years, BMI 30–43 kg/m^2, women of childbearing potential taking adequate contraceptive measures *For DB phase* > 75% compliance with drug regimen (calculated from number of returned capsules) during run-in ***Exclusion criteria*** Weight loss > 4 kg in the 3 months prior to screening, history of any serious disease (including diabetes), uncontrolled hypertension, previous GI surgery for weight reduction, history of postoperative adhesions, history or presence of cancer, psychiatric or neurological disorder requiring chronic medication or liable to prejudice adherence, evidence of alcohol or substance abuse, bulimia or laxative abuse, pregnancy, lactation, postmenopausal women who were amenorrhoeic for < 1 year, taking drugs capable of influencing body weight, resins for lipid lowering, anticoagulants, digoxin or lipid-soluble vitamin supplements within the previous month	***4-week SB placebo run-in for all patients*** Nutritionally balanced low-energy diet providing 30% of energy from fat and designed to give an individually tailored energy deficit of 600 kcal/day, to produce a weight loss of 0.25–0.5 kg/week. The lowest prescribed energy intake was 1200 kcal/day. Alcohol consumption was limited to 150g/week. Placebo tds with meals (n = 267) ***Standard care for all patients during 52-week DB study*** Dietary regimen as above until end of week 24, when prescribed daily energy intake was reduced by 300 kcal/day in all patients, regardless of whether or not body weight had stabilised. Patients prescribed 1200 kcal/day at screening had energy intake adjusted to 1000 kcal/day at the end of week 24 and maintained to end of week 52 C: placebo tds with meals (n = 114) I: orlistat 120 mg tds with meals (n = 114)	***Gender*** (male/female) C: 13/95 I: 12/98 ***Age*** (mean ± SD in years) C: 41.4 ± 10.0 I: 41.5 ± 10.5 ***Race numbers*** (white/black/other) C: 104/1/3 I: 103/2/5 ***Weight*** (mean ± SD in kg) C: 98.4 ± 15.0 I: 97.9 ± 12.9 ***BMI*** (mean ± SD in kg/m^2) C: 36.8 ± 3.7 I: 36.8 ± 3.6 ***Patients with elevated LDL-C levels (≥ 3.36 mmol/l)*** C: 53% I: 52% ***Patients with elevated SBP (≥ 140 mmHg)*** C: 2% I: 5.5% ***Patients with elevated DBP (≥ 90 mmHg)*** C: 22% I: 18%	***Statistical techniques*** ANOVA was used to the test null hypothesis. For each centre, 95% CI of treatment difference based on LSM was provided and the LSM difference from each centre used to explore any centre by treatment interaction. The LSM was compared as the primary endpoint for analysis. ITT analysis included patients who were assessed clinically and received at least one dose of study medication, and included observed data and data from the LOCF to week 52. Completer analysis included patients who completed 52 weeks of treatment without protocol violation ***Average % weight loss at 52 weeks*** (by ITT) C: 5.4% I: 8.5% p = 0.016 ***Average % weight loss of completers at 52 weeks*** C: 5.5% I: 8.8% p = not significant ***At 24 weeks*** The LSM difference from placebo for change in body weight was –1.8 kg (95% CI, –2.96 to –0.56; p = 0.004) for orlistat-treated patients in the ITT population. For completers, the changes was –2.4 kg (95% CI, –3.82 to –0.88; p = 0.002) ***At 52 weeks*** The LSM difference from placebo for change in body weight was –2.0 kg (95% CI, –3.6 to –0.38; p < 0.05) for orlistat-treated patients in the ITT population. For completers, the change was –2.5 kg (95% CI, –5.38 to 0.42; p = 0.092) When ITT data were stratified by weight loss during run-in, those losing > 2 kg during run-in lost more weight at 52 weeks with orlistat than those losing ≤ 2 kg during run-in ***Patients losing > 10% of initial body weight, including run-in*** (by ITT) C: 17% I: 28% p = 0.04 ***Patients losing > 10% of initial body weight during DB treatment only*** (by ITT) C: 6% I: 16% p = 0.02 ***Patients losing > 5% of initial body weight during DB treatment only*** (by ITT) C: 21% I: 35% p = 0.02 ***Mean decrease in waist circumference at 52 weeks in females with measurement of ≥ 88 cm at baseline*** (in cm) C: 5.1 I: 6.3 p = not significant	***Reasons for withdrawals during run-in*** Lost to follow-up 18 Did not cooperate 7 Adverse events 5 Entry violation 5 Administrative 2 Protocol violation 1 Refused treatment 1 ***Total number (%) of withdrawals during run-in*** Overall 39/267 (15%) ***Reasons for withdrawals during 52-week DB study*** (number of patients in C/I) Lost to follow-up 18/15 Did not cooperate 8/7 Adverse events 7/9 Administrative 5/3 Protocol violation 3/5 Refused treatment 5/2 Treatment failure 2/0 ***Total withdrawals during 52-week DB study*** C: 48 I: 41 ***ITT analysis*** Ten patients were excluded from ITT analysis: six due to insufficient safety assessments and four due to insufficient evaluations for efficacy, leaving 108 in C and 110 in I ***Number of completers*** C: 66 I: 73 ***Number of completers that underwent analysis*** C: 61 I: 59	***Limitations of the study, as noted by the study authors*** Larger and longer trials are necessary to adequately evaluate adverse effects such as gallstone and renal stone formation in association with the use of orlistat Patients prescribed orlistat may require fat-soluble vitamin supplements because more patients with low or marginal vitamin levels may be met in clinical practice (as opposed to trials) ***Sponsorship*** Hoffmann-La Roche

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Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
continued Finer *et al.*, 2000[41]				***Mean decrease in waist circumference at 52 weeks in males with measurement ≥ 102 cm at baseline*** (in cm) C: 3.9 I: 4.1 p = not significant ***Patients that had regained weight between 24 and 52 weeks*** C: 1.34% I: 0.6% ***Lipid levels*** Orlistat-treated patients showed significant decreases ($p < 0.05$) in serum levels of total cholesterol and LDL-C and LDL-C:HDL-C ratio compared with placebo. There were no significant between-group differences for triglycerides, lipoprotein A and VLDL-C. HDL-C levels increased by similar amounts in both groups. In patients with elevated LDL-C (≥ 3.36 mmol/l) at start of DB treatment, the mean value decreased after 52 weeks by 1.3% in C and 7.1% in I There was a trend towards a reduction in fasting insulin and, to a lesser extent, in fasting glucose levels associated with weight loss in both groups Between weeks 24 and 52, DBP tended to fall in patients with elevated levels (≥ 90 mmHg) at baseline	***Adverse events*** 82.1% of patients in I versus 56.4% in C had at least one GI event. 59% of patients in I and 15.4% in C had at least one of the following events: loose stools, increased defaecation, abdominal pain, uncontrolled oily discharge, faecal urgency, nausea/ vomiting, discoloured faeces, flatulence or decreased defaecation. Most events occurred early in the study and were generally transient (≤ 4 days) Three patients in I withdrew due to GI adverse events (one due to abdominal pain, one due to liquid stools and one due to increased defaecation) and one patient in C withdrew due to oesophagitis Other reported adverse events included upper respiratory tract infection (I: 6.3%, C: 5.4%), pharyngitis (I: 6.3%, C: 2.7%), influenza (I: 12.5%, C: 10.0%), headache (I: 10.9%, C: 8.9%) and back pain (I: 4.5%, C: 2.7%) Supplementation of vitamins A, D and E was given to 1.8, 8.0 and 3.6%, respectively, of I patients, compared with 0.9% for each of C patients During the study, 7% of I and 11% of C patients developed gallbladder abnormalities and 3 and 2%, respectively, developed renal abnormalities	

continued

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Davidson *et al.*, 1999[42] ***Country*** USA ***Aim*** To test the hypothesis that orlistat combined with dietary intervention is more effective than placebo for weight loss and maintenance over 2 years, and to examine the effectiveness of 2-year orlistat administration in improving BP, lipid levels and carbohydrate metabolism abnormalities ***Method of randomisation*** The method of randomisation was not stated. Randomisation was conducted in two stages: year 1 (weight loss) and year 2 (weight maintenance). Participants were stratified at year 1 randomisation according to whether > 2 or < 2 kg were lost during run-in ***Outcomes*** Change in body weight, standing waist circumference, BP, levels of vitamins A, D and E and β-carotene, prothrombin time, fasting serum glucose and insulin levels, glucose tolerance, lipid levels, adverse effects ***Setting and length of treatment*** 18 clinical research centres. 2-year study	***Population*** Not stated ***Inclusion criteria*** *For run-in* Age > 18 years, BMI 30–43 kg/m^2, adequate contraception in women of childbearing potential, no weight loss (> 4 kg) in previous 3 months *For year 1 (weight loss)* Participants with a treatment adherence of ≥ 75% during run-in (assessed by counting returned placebo capsules) were randomised to placebo or orlistat 120 mg *For year 2 (weight maintenance)* Participants who completed the first year of treatment, with an adherence of ≥ 70% entered the maintenance phase. Participants treated with orlistat during year 1 were randomised to receive placebo or orlistat 60 or 120 mg tds. Participants taking placebo during year 1 continued to take placebo during year 2 ***Exclusion criteria*** Frequent change of smoking habits, smoking cessation within last 6 months, history or presence of substance abuse, excessive alcohol intake, significant cardiac, renal, hepatic, GI, psychiatric or endocrine disorder, drug-treated type 2 diabetes, concomitant use of medications that alter appetite or lipid levels	***4-week SB placebo run-in for all patients*** Controlled-energy diet providing 30% of energy intake as fat. Energy intake was prescribed for each participant on the basis of estimated daily maintenance energy requirement. All vitamin and mineral preparations were discontinued 8 weeks prior to beginning the study (*n* = 1187) ***Standard care for all patients during weight-loss (DB) phase*** Controlled-energy diet continued (as above) with four behaviour modification sessions on weight-loss strategies. Dieticians provided instruction on dietary intake recording and later used participants' food diaries for counselling. Participants were encouraged to walk briskly for 20–30 minutes three–five times/week C1: placebo tds with meals for 52 weeks (*n* = 224) (ITT *n* = 223) I1: orlistat 120 mg tds with meals for 52 weeks (*n* = 668) (ITT *n* = 657) ***Standard care for all patients during maintenance phase*** Weight-maintenance diet with four seminars on weight-maintenance strategies C2: placebo in weight-loss phase followed by placebo tds with meals for 52 weeks (*n* = 133) C3: orlistat 120 mg in weight-loss phase followed by placebo tds with meals for 52 weeks (*n* = 138) I2: orlistat 120 mg in weight-loss phase followed by orlistat 60 mg tds with meals for 52 weeks (*n* = 152) I3: orlistat 120 mg in weight-loss phase followed by orlistat 120 mg tds with meals for 52 weeks (n = 153)	***Gender*** (male/female) C1: 26/197 I1: 113/544 ***Age*** (mean ± SD in years) C1: 44.0 ± 0.7 I1: 43.3 ± 0.6 ***Race percentages*** (white/black/Hispanic) C1: 79.4/15.7/4.0 I1: 81.3/13.4/4.3 ***Weight*** (mean ± SD in kg) C1: 100.6 ± 0.9 I1: 100.7 ± 0.6 ***BMI*** (mean ± SD in kg/m^2) C1: 36.5 ± 0.9 I1: 36.2 ± 0.1 ***Patients with abnormal oral glucose tolerance test results*** (impaired/diabetes) C1: 5.8%/4.5% I1: 6.1%/4.0% ***Patients with abnormal fasting insulin level*** C1: 30.5% I1: 36.7% ***Patients with abnormal LDL-C level*** C1: 35.9% I1: 32.1% ***Patients with abnormal HDL-C level*** C1: 12.1% I1: 15.2% ***Patients with abnormal triglyceride level*** C1: 5.4% I1: 10.5% ***Patients with a DBP > 90 mmHg*** (untreated/ treated) C1: 7.2%/1.8% I1: 5.5%/2.7%	***Statistical techniques*** ITT analysis using LOCF included those receiving at least one dose of medication during DB treatment, with at least one body-weight measurement before and after randomisation. ANOVA and ANCOVA were used to assess between-group differences in mean change in body weight and to compare weight change in year 1 with that in year 2. ANCOVA was used to evaluate changes in risk factors using baseline values as covariates ***Overall mean weight loss during run-in*** Approximately 2.3 kg (2.3% of initial body weight) ***Weight loss at the end of year 1*** (mean ± SEM in kg) C1: 5.81 ± 0.67 I1: 8.76 ± 0.37 $p < 0.001$ ***% weight loss at end of year 1*** (mean ± SEM) C1: 5.8 ± 0.7% I1: 8.8 ± 0.4% $p < 0.001$ ***Patients with a weight loss at end of year 1 of > 5% initial weight*** C1: 43.6% I1: 65.7% $p < 0.01$ ***Patients with a weight loss at end of year 1 of > 10% initial weight*** C1: 24.8% I1: 38.9% $p < 0.004$ ***Weight regain at the end of year 2*** (mean ± SEM in kg (%)) C3: 5.63 ± 0.42 (63.4%) I2: 4.26 ± 0.57 (51.3%) I3: 3.2 ± 0.45 (35.2%) $p < 0.001$ for C3 versus I3, $p < 0.001$ for I2 versus I3 ***% weight loss at the end of year 2*** (mean ± SEM) C2: 4.5 ± 0.9% C3: 4.2 ± 0.8% I3: 7.6 ± 0.9% ***Patients maintaining > 10% weight loss at the end of year 2*** C2: 17.5% I3: 34.1% $p = 0.02$ ***Change in SBP at 1 year*** (mean ± SEM in mmHg) C1: from 118.6 ± 0.9 to 119.6 ± 1.3 I1: from 119.4 ± 0.5 to 118.6 ± 0.6 $p = 0.002$ ***Change in DBP at 1 year*** (mean ± SEM in mmHg) C1: from 76.1 ± 0.6 to 77.4 ± 0.9 I1: from 76.9 ± 0.4 to 75.9 ± 0.4 $p = 0.009$	***Reasons for withdrawals during 4-week run-in*** (number of patients (%)) Lost to follow-up 43 (3.6%) Administrative 53 (4.5%) Adverse events 23 (1.9%) Did not cooperate 64 (5.4%) Treatment failure 0 (0.0%) Protocol violation 12 (1.0%) Entry violation 98 (8.3%) Refused treatment 1 (0.1%) ***Total % of withdrawals during 4-week run-in*** Overall 24.8% ***Reasons for withdrawals during year 1*** (number of patients (%)) Lost to follow-up C1: 21 (9.4%) I1: 59 (8.8%) Administrative C1: 21 (9.4%) I1: 42 (6.3%) Adverse events C1: 9 (4.0%) I1: 61 (9.1%) Did not cooperate C1: 16 (7.1%) I1: 26 (3.9%) Treatment failure C1: 11 (4.9%) I1: 6 (0.9%) Protocol violation C1: 5 (2.2%) I1: 13 (1.9%) Entry violation C1: 1 (0.4%) I1: 3 (0.4%) Refused treatment C1: 2 (0.9) I1: 0 (0.0) ***Total % of withdrawals during year 1*** C1: 38.3% I1: 31.3%	***Limitations of the study, as noted by study authors*** The high withdrawal rate and the potential bias due to lack of treatment efficacy in the placebo group and GI events in the orlistat group, which could have caused unplanned unblinding, may have resulted in under- or over-estimation of the effectiveness of orlistat. However, application of the LOCF approach to the ITT population should minimise the opposing sources of bias ***Reviewer's comments*** Most results are based on comparisons between those receiving placebo for 2 years and those receiving orlistat 120 mg for 2 years, and other treatment combinations are not taken into account. The analysis of change in body weight (mean ± SEM) during the 2 years (presented as a figure in the paper) is based on the groupings for year 2, and the year 1 comparison between placebo and orlistat 120 mg is not shown ***Sponsorship*** Hoffmann-La Roche

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Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
continued Davidson *et al.*, 1999[42]				***Change in waist circumference at 2 years*** (mean ± SEM in cm) Placebo: –2.38 ± 1.0 Orlistat: –4.52 ± 0.8 $p < 0.05$ Note that it was unclear exactly which groups these were ***Total cholesterol levels at 2 years*** (mean ± SEM in mmol/l) C2: 5.19 ± 0.10 I3: 5.04 ± 0.09 $p < 0.001$ ***LDL-C levels at 2 years*** (mean ± SEM in mmol/l) C2: 3.22 ± 0.09 I3: 3.14 ± 0.08 $p < 0.001$ ***HDL-C levels at 2 years*** (mean ± SEM in mmol/l) C2: 1.36 ± 0.04 I3: 1.28 ± 0.03 $p = 0.11$ ***Triglyceride levels at 2 years*** (mean ± SEM in mmol/l) C2: 1.56 ± 0.16 I3: 1.51 ± 0.08 $p = 0.64$ Changes in lipid levels were independent of weight loss ***Change in fasting serum glucose levels over 2 years*** (mean ± SEM in mmol/l) C2: from 5.60 ± 0.03 to 5.80 ± 0.06 I3: from 5.62 ± 0.03 to 5.67 ± 0.05 $p = 0.001$ ***Change in fasting serum insulin levels over 2 years*** (mean ± SEM in pmol/l) C2: from 86.37 ± 4.71 to 86.32 ± 6.89 I3: from 84.02 ± 3.46 to 66.52 ± 3.92 $p = 0.04$ The decrease in insulin levels appeared to be related to weight loss rather than an independent drug effect	***Reasons for withdrawals during year 2*** (number of patients (%)) Lost to follow-up C2: 15 (11.3%) C3: 15 (10.9%) I2: 22 (14.5%) I3: 17 (11.1%) Adminstrative C2: 2 (1.5%) C3: 6 (4.3%) I2: 2 (1.3%) I3: 8 (5.2%) Adverse events C2: 4 (3.0%) C3: 6 (4.3%) I2: 9 (5.9%) I3: 5 (3.3%) Did not cooperate C2: 5 (3.8%) C3: 4 (2.9%) I2: 6 (3.9%) I3: 6 (3.9%) Treatment failure C2: 3 (2.3%) C3: 6 (4.3%) I2: 4 (2.6%) I3: 3 (2.0%) Protocol violation C2: 3 (2.3%) C3: 6 (4.3%) I2: 5 (3.3%) I3: 3 (2.0%) Entry violation C2: 0 (0.0%) C3: 0 (0.0%) I2: 0 (0.0%) I3: 0 (0.0%) Refused treatment C2: 3 (2.3%) C3: 0 (0.0%) I2: 2 (1.3%) I3: 2 (1.3%) ***Total % of withdrawals during year 2*** C2: 26.5% C3: 31.0% I2: 32.8% I3: 28.8% Completion rates at end of year 2 were not significantly different between treatment groups ***Adverse events*** 59% of patients in C2 and 79% in I3 had ≥ one GI event. Most occurred early during treatment, were mild–moderate in intensity and resolved spontaneously There were no apparent systematic differences in weight loss among participants who experienced several, one or no GI adverse effects ***Number of withdrawals due to GI adverse events*** C2: 2 I3: 7 The adverse event rate was lower in year 2 than in year 1 and did not differ significantly between groups ***Patients that required supplemental fat-soluble vitamins or β-carotene*** C2: 6.5% I3: 14.1% Levels of vitamin D and E decreased ($p = 0.001$ and $p = 0.03$, respectively) in I in year 1, but remained within the reference ranges ***Patients diagnosed with breast cancer during the 2-year study*** C2: one patient (identified prior to starting the study) I3: two participants (one identified prior to starting the study and one 32 days after randomisation)	

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Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Hauptman *et al.*, 2000[43] ***Country*** USA ***Aim*** To evaluate the long-term efficacy and tolerability of orlistat within primary care settings for the treatment of obesity ***Method of randomisation*** Not stated ***Outcomes*** Change in body weight, waist circumference, serum lipid levels, fasting serum glucose and insulin levels, BP, adverse events, haematology, blood chemistry including levels of vitamins A, D and E and β-carotene, prothrombin time, urinalysis, 24-hour urine test, faecal occult blood ***Setting and length of treatment*** 17 primary care centres. 4-week run-in followed by a 52-week DB weight-loss phase and then a 52-week DB weight-maintenance phase	***Population*** Not stated ***Inclusion criteria*** *For run-in* Age >18 years, BMI 30–44 kg/m^2 *For DB phase* ≥ 75% adherence with drug regimen during run-in (assessed by counting returned capsules) ***Exclusion criteria*** Pregnancy, lactation, women of childbearing potential not taking adequate contraceptive measures, weight loss of > 4 kg during the 3 months prior to study; history of significant cardiac, renal, hepatic or GI disorders, uncontrolled hypertension or any other clinically significant condition, GI surgery for weight reduction, bulimia or laxative and/or substance abuse, abnormal laboratory measures, changes in smoking habits in the 6 months prior to study, use of any drug that might influence body weight or food intake during the 8 weeks prior to screening	***4-week SB placebo run-in for all patients*** Nutritionally balanced reduced-energy diet, providing 30% energy as fat, 50% as carbohydrate, 20% as protein and a maximum of 300 mg/day of cholesterol. Alcohol consumption was limited to a maximum of 10 drinks/week. The prescribed energy intake was 5020 kJ/day for patients who weighed < 90 kg initially and 6275 kJ/day for those who weighed ≥ 90 kg initially. Dietary guidance was provided by a study physician. Placebo tds (n = 796) ***Standard care for all patients during DB study*** Year 1: dietary regimen as above for 52 weeks. Videos on behaviour modification techniques showed at four points Year 2: weight-maintenance diet for further 52 weeks, which included a prescribed energy intake increase of 1255 kJ/day for those who were still losing weight at 52 weeks or no dietary adjustment for those whose weight remained stable. Patients were given weight-management and diet leaflets designed to assist with weight maintenance at four points. Patients completed 3-day diet diaries at 10 points during the study, having received instructions from staff and viewed a video on food records. Patients were encouraged to walk briskly for 20–30 minutes three–five times/week C: placebo tds with main meals for 104 weeks (n = 212) I1: orlistat 60 mg tds for 104 weeks (n = 213) I2: orlistat 120 mg tds for 104 weeks (n = 210)	***Characteristics of patients randomised at the beginning of year 1*** ***Gender*** (male/female) C: 47/165 I1: 47/166 I2: 44/166 ***Age*** (mean ± SEM in years) C: 41.6 ± 0.7 I1: 42.6 ± 0.8 I2: 43.2 ± 0.7 ***Race numbers*** (white/black/American-Indian/Hispanic/other) C: 193/15/0/4/0 I1: 200/9/0/2/2 I2: 184/19/1/6/0 ***Weight*** (mean ± SEM in kg) C: 101.8 ± 1.00 I1: 100.4 ± 1.00 I2: 100.5 ± 0.98 ***BMI*** (mean ± SEM in kg/m^2) C: 36.1 ± 0.3 I1: 35.8 ± 0.3 I2: 36.0 ± 0.2	***Statistical techniques*** ITT analyses included patients who had received ≥ one dose of DB medication and had ≥ one follow-up body-weight measurement. ANOVA and ANCOVA were used to assess group differences in changes in body weight. The 95% CI of treatment difference based on the LSM was also determined. LOCF technique was used for 1- and 2-year analyses using observed actual values rather than derived data. Chi-squared was used to analyse differences in proportions ***Weight change at 1 year*** (mean ± SEM in kg by ITT) C: –4.14 ± 0.56 I1: –7.08 ± 0.54 I2: –7.94 ± 0.57 p = 0.001 for C versus I1 and C versus I2 ***Weight change at 1 year for completers*** (mean ± SEM in kg) C: –4.26 ± 0.58 I1: –7.92 ± 0.70 I2: –8.78 ± 0.73 p = 0.001 for C versus I1 and C versus I2 ***Weight change at 2 years*** (mean ± SEM in kg by ITT) C: –1.65 ± 0.62 I1: –4.46 ± 0.61 I2: –5.02 ± 0.73 p = 0.001 for C versus I1 and C versus I2 ***Weight change at 2 years for completers*** (mean ± SEM in kg) C: –1.54 ± 0.58 I1: –4.58 ± 0.68 I2: –5.16 ± 0.78 p = 0.02 for C versus I1, p = 0.002 for C versus I2 ***Patients who lost ≥ 5% of initial weight at 1 year*** (by ITT) C: 30.7% I1: 48.8% I2: 50.5% p < 0.001 for C versus I1 and C versus I2	***Total number (%) of withdrawals during run-in*** Overall 161/796 (20%) ***Number (%) of withdrawals during year 1 (weight-loss phase)*** C: 90/212 (42%) I1: 59/213 (28%) I2: 59/210 (29%) ***Number (%) of withdrawals during year 2 (weight-maintenance phase)*** C: 31/122 (25%) I1: 34/154 (22%) I2: 34/151 (23%) ***Reasons for withdrawal during 2-year DB phase*** (% of patients in C/I1/I2) Lost to follow-up 16.5/13.1/15.2 Administrative 17.5/7.5/6.7 Adverse events 7.1/6.6/11.0 Did not cooperate 5.2/5.2/4.3 Protocol violation 3.8/5.2/4.3 Treatment failure 3.8/3.3/1.9 Refused treatment 3.3/2.8/0.5 Died 0/0/0.5 (one patient due to acute myocardial infarction after 301 days of treatment) Rates of withdrawal due to adverse events did not differ significantly between groups ***Total number (%) of withdrawals during 2-year DB phase*** C: 121 (57.1%) I1: 94 (46.2%) I2: 97 (46.2) p < 0.05 for C versus I1 and C versus I2 ***Number of completers at the end of year 2*** C: 91 I1: 120 I2: 117 ***Patients reporting GI adverse events over 2 years*** C: 59% I1: 72% I2: 79% p = 0.003 for C versus I1, p = 0.001 for C versus I2 Specific GI events (faecal urgency, oily spotting, oily stools, flatus with discharge, oily evacuation, increased defaecation and faecal incontinence) occurred more frequently in I1 and I2 versus C (p = 0.001). Most were mild–moderate in intensity, were limited to only one or two episodes per patient and occurred early during treatment. Few GI events were reported during year 2	***Limitations of the study, as noted by the study authors*** One aspect of the study was that it did not relate to actual clinical practice: if patients started to regain weight in year 2, they were instructed not to resume a reduced-energy diet, but rather avoid further weight gain. Under realistic clinical practice conditions, patients who relapsed would probably be encouraged to reduce their energy intake for a period to reverse the weight gain ***Sponsorship*** Not stated, but first author is based at Hoffmann-La Roche, Nutley, NJ, USA

continued

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
continued Hauptman *et al.*, 2000[43]				***Patients who lost ≥ 10% of initial body weight at 1 year*** (by ITT) C: 11.3% I1: 24.4% I2: 28.6% $p < 0.001$ for C versus I1 and C versus I2 ***Patients who maintained ≥ 5% of initial weight loss at 2 years*** (by ITT) C: 24.1% I1: 33.8% I2: 34.3% $p < 0.03$ for C versus I1, $p < 0.02$ for C versus I2 ***Patients who maintained ≥ 10% of initial weight loss at 2 years*** (by ITT) C: 6.6% I1: 14.6% I2: 18.6% $p = 0.008$ for C versus I1, $p < 0.001$ for C versus I2 ***% of initial weight lost at 2 years*** (mean ± SEM in kg) C: 1.70 ± 0.62 (1.65 ± 0.62) I1: 4.44 ± 0.61 (4.46 ± 0.61) I2: 5.01 ± 0.79 (5.02 ± 0.73) $p < 0.001$ for C versus I1 and C versus I2 ***Weight regain at year 2, expressed as % lost in year 1*** C: 60% I1: 37% I2: 38% ***Cardiovascular risk factors*** At 1 year, total cholesterol and LDL-C levels were significantly lower in I1 and I2 versus C ($p = 0.001$), and this was generally maintained during year 2. Differences between groups for triglycerides and glucose levels were non-significant at all times. Fasting insulin levels were lowere in I2 than C at 1 year ($p < 0.05$). DBP decreased in I1 at 1 year (–0.97 ± 0.01 mmHg, $p = 0.02$). Changes in C and I2 not significant during year 2 and no significant changes between groups for DBP, but SBP in I2 was reduced ($p = 0.04$) versus C. Similar pattern of results for ITT and completers	***Number (%) of withdrawals due to GI events*** C: 3 (1.4%) I1: 10 (4.7%)I2: 12 (5.7%) ***Fat-soluble vitamins*** Vitamins A, D and E and β-carotene levels remained within reference ranges in all groups during the 2 years. Two consecutive low vitamin E and β-carotene values occurred more frequently with orlistat than with placebo ($p < 0.05$). The frequency of two consecutive low-level vitamin A and D values did not significantly differ between groups. β-carotene supplementation was required by 2.4, 4.3 and 6.3% of patients in C, I1 and I2, respectively	

continued

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Sjostrom *et al.*, 1998[44] ***Countries*** Sweden, Finland, Denmark, France, The Netherlands, Switzerland ***Aim*** To assess the efficacy and tolerability of orlistat in producing and maintaining weight loss and to assess its effects on cardiovascular risk factors ***Method of randomisation*** Random number codes. Randomisation in blocks of four (investigators blind) to give equal numbers of patients in both groups. Patients were stratified according to weight loss during run-in (≤ 2 or > 2 kg). Patients were reassigned at the end of year 1 for the weight-maintenance phase ***Outcomes*** Change in body weight, fasting serum levels of glucose, insulin and lipids, haematology, clinical chemistry (including levels of vitamins A, D and E), prothrombin time, β-carotene levels, urinalysis, plasma orlistat levels, adverse events ***Setting and length of treatment*** 15 centres. 4-week run-in followed by a 52-week DB weight-loss phase and then a 52-week DB weight-maintenance phase	***Population*** Obese patients recruited from hospital waiting lists or by local advertising ***Inclusion criteria*** *For run-in* Age ≥ 18 years, BMI 28–47 kg/m^2, women of child-bearing potential using adequate contraception *For weight-loss DB phase* > 75% adherence with run-in regimen (assessed by counting returned placebo capsules) *For weight-maintenance DB phase* > 75% adherence with regimen ***Exclusion criteria*** Serious disease including uncontrolled hypertension and pharmacologically treated diabetes, weight loss of > 4 kg in the 3 months prior to screening, prior surgery for weight reduction, history of postoperative adhesions, bulimia or laxative abuse, use of drugs that could influence body weight or lipid levels in the month prior to study entry, drug or alcohol abuse	***4-week SB placebo run-in for all patients*** Reduced-energy diet containing 30% energy as fat (minimum prescribed energy intake was 1200 kcal/day with an energy deficit of 600 kcal/day). Energy content of diet calculated from patients' estimated basal metabolic rate multiplied by 1.3 to estimate the total daily energy expenditure. Placebo tds with meals (n = 743) ***Standard care for all patients during year 1 of DB study*** Dietary regimen as above up to week 24, when the prescribed energy intake was reduced by 300 kcal/day. Patients initially prescribed the minimum energy intake had their energy intake adjusted to 1000 kcal/day. If two consecutive measurements of low plasma levels of fat-soluble vitamins were recorded, additional dietary counselling or vitamin supplementation was provided C1: placebo tds with meals for 52 weeks (n = 340) I1: orlistat 120 mg tds with meals for 52 weeks (n = 343) ***Standard care for all patients during year 2 of DB study*** Weight-maintenance diet – patients were advised not to use hypocaloric diet C2: placebo during year 1 followed by placebo tds with meals for 52 weeks (n = 123) C3: orlistat during year 1 followed by placebo tds with meals for 52 weeks (n = 138) I2: placebo during year 1 followed by orlistat 120 mg tds with meals for 52 weeks (n = 125) I3: orlistat during year 1 followed by orlistat 120 mg tds with meals for 52 weeks (n = 133)	***Gender*** (male/female) C1: 57/283 I1: 59/284 ***Age*** (mean (range) in years) C1: 44.3 (18.0–77.0) I1: 45.2 (20.0–76.0) ***Weight*** (mean (range) in kg) C1: 99.8 (64.2–137.2) I1: 99.1 (61.0–148.6) ***BMI*** (mean (range) in kg/m^2) C1: 36.1 (29.2–43.5) I1: 36.0 (28.3–47.2) ***Waist circumference*** (mean (range) in cm) C1: 105.9 (71–135) I1: 105.4 (70–149) ***Cardiovascular risk factors*** Baseline values did not differ between groups	***Statistical techniques*** ITT analyses included patients who had received at least one dose of test medication and at least one follow-up body measurement. For withdrawals, the LOCF was used to the end of year 1 or 2 in the LSM calculations. The null hypothesis was tested with general linear models. ANCOVA was used to assess year 1 weight loss with the following variables: treatment, centre and weight-loss stratification after run-in. During year 2 analyses, weight change from the start of the run-in to the end of year 1 was used as a covariate ***Mean (%) weight loss from start of run-in to the end of year 1*** (in kg) C1: 6.1 (6.1%) I1: 10.3 (10.2%) Thus the decrease in weight was 68% greater in I1 than in C1 (the LSM weight-loss difference from randomisation was 3.9 kg (p < 0.001) ***Patients who lost > 20% of initial body weight at the end of year 1*** C1: 2.1% I1: 9.3% ***Patients who lost 10.1–20.0% of initial body weight at the end of year 1*** C1: 15.6% I1: 29.5% ***Patients who lost 5.1–10.0% of initial body weight at the end of year 1*** C1: 31.5% I1: 29.7% ***Patients who lost 0.1–5.0% of initial body weight at the end of year 1*** C1: 32.7% I1: 23.6% ***Patients with unchanged or increased body weight at year 1*** C1: 18.2% I1: 7.9% ***Effect of orlistat during year 2*** I2: LSM difference in weight loss versus C3 = 3.6 kg (SEM 0.6, p < 0.001) I3: LSM difference in weight loss versus C3 = 2.4 kg (SEM 0.6, p < 0.001)	***Number of withdrawals during year 1*** Five early withdrawals (four had no safety assessment and one received no trial medication) reduced the year 1 ITT population from 688 to 683 patients, and 544 completed treatment. At the end of year 1, 18 patients withdrew mainly due to non-adherence, and 253 patients from C1 and 273 from I1 were reassigned for year 2 ***Number of withdrawals during year 2*** At the end of year 2, the ITT population consisted of 519 patients (75% of those randomised), and 435 (63% of those randomised) completed treatment. Analysis of patients completing year 2 gave similar results to the ITT analysis ***Number (%) of patients who withdrew due to GI adverse events in year 1*** C1: 2/343 (0.6%) I1: 12/345 (3.5%) ***Number (%) of patients who withdrew due to other adverse events in year 1*** C1: 7/343 (2.0%) I1: 11/345 (3.2%) ***Number (%) of patients who withdrew for other reasons in year 1*** C1: 74/343 (21.6%) I1: 38/345 (11.0%) ***Number (%) of patients who withdrew due to GI adverse events in year 2*** C2: 2/126 (1.6%) C3: 0/138 (0.0%) I2: 5/127 (3.9%) I3: 2/135 (1.5%) ***Number (%) of patients who withdrew due to other adverse events in year 2*** C2: 1/126 (0.8%) C3: 4/138 (2.9%) I2: 1/127 (0.8%) I3: 1/135 (0.7%) ***Number (%) of patients who withdrew for other reasons in year 2*** C2: 21/126 (16.7%) C3: 17/138 (12.3%) I2: 19/127 (15.0%) I3: 18/135 (13.3%) Serious adverse events were reported by 24 patients in C1 and 25 in I1 in year 1, and one in each group was possibly treatment-related. Two serious adverse events occurred that were possibly treatment-related in the year 2	***Limitations of the study, as noted by the study authors*** None stated ***Sponsorship*** Hoffmann-La Roche

continued

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
continued Sjostrom *et al.*, 1998[44]				At 2 years, 57.1% of patients in I3 maintained a weight loss of > 5% compared with 37.4% in C2 ***Cardiovascular risk factors*** I1 and I3 had significantly greater reductions in total cholesterol, LDL-C, LDL-C:HDL-C ratio, glucose and insulin versus C1 and C2, respectively, at both 1 and 2 years, respectively. There were also significantly greater reductions in SBP and DBP at 1 year in I1 versus C1 Linear modelling showed that baseline risk-factor value and weight reduction were significant variables at 1 and 2 years for observed risk-factor changes. Treatment was also a significant predictor for change in total cholesterol at 1 (p = 0.0001) and 2 years (p = 0.0002), and for change in LDL-C at 1 (p = 0.0003) and 2 years (p = 0.0463). At 2 years, treatment was also a significant predictor for change in LDL-C:HDL-C ratio (p = 0.0236)	***Number of withdrawals in year 1*** CI: 83 I1: 61 ***Number of withdrawals in year 2*** CI: 45 I1: 46 There were no clinically or statistically significant changes in any laboratory measurements during the study, and the frequency of laboratory abnormalities was similar in all groups In year 1, 41 patients in I1 and 18 in C1 had two or more consecutive low vitamin concentrations, and 16 and four patients, respectively, received supplements. In year 2, supplements were received by four patients in I3, one in C2, three in I2 and one in C3 Pharmacokinetic analysis of blood samples showed minute concentrations of unchanged orlistat in the plasma of a few patients at 24, 52 and 104 weeks, indicating low systemic absorption of orlistat after 2 years of treatment	

continued

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Rossner *et al.*, 2000[48] ***Countries*** Sweden, The Netherlands, Germany, Switzerland ***Aim*** To determine the effect of orlistat on long-term weight loss, weight maintenance and obesity-related risk factors ***Method of randomisation*** Not stated. Patients were stratified according to weight loss during run-in, however, exact parameters of stratification were not explained ***Outcomes*** Change in body weight, waist and hip circumferences, lipid levels, ECG, BP, fasting blood glucose and insulin levels, quality of life (assessed by a 55-item self-administered questionnaire[54]), food intake (assessed with diaries), adverse events, serum levels of fat-soluble vitamins and β-carotene ***Setting and length of treatment*** 14 centres. 4-week run-in followed by a 2-year study (1 year of weight loss and 1 year of weight maintenance)	***Population*** Not stated ***Inclusion criteria*** *For run-in* Age ≥ 18 years; BMI 28–43 kg/m^2; women of childbearing potential were eligible if using adequate contraception *For DB phase* Completion of run-in period with ≥ 75% adherence (assessed by counting returned capsules) ***Exclusion criteria*** Pregnancy, lactation, any clinically significant condition that might affect the outcome of the study, weight loss of > 4 kg during the previous 3 months, smoking cessation within previous 6 months, prior GI surgery for weight reduction, history of postoperative adhesions, history of bulimia or laxative abuse, use of any drug that might influence body weight or serum lipids during the 8 weeks before screening, uncontrolled hypertension, drug-treated diabetes mellitus, history of symptomatic cholelithiasis	***4-week SB placebo run-in for all patients*** Nutritionally balanced diet containing 30% of calories as fat with an energy deficit of 600 kcal/day and placebo tds. All vitamin supplements were discontinued (n = 783) ***Standard care for all patients during DB study*** Diet as above for 1 year. Diet as above for year 2 with adjustment of the daily energy intake to a level equivalent to the estimated total daily energy expenditure minus 10% of kcal/day for those losing ≥ 3 kg between weeks 40 and 52. Supplements were given to those with vitamin or β-carotene levels below reference ranges for two consecutive measurements. There were fewer clinic visits during year 2 C: placebo tds with main meals for 2 years (n = 243) I1: orlistat 60 mg tds with main meals for 2 years (n = 242) I2: orlistat 120 mg tds with main meals for 2 years (n = 244)	***Gender*** (male/female) C: 31/206 I1: 56/183 I2: 40/202 ***Age*** (mean ± SD in years) C: 44.3 ± 10.8 I1: 44.7 ± 10.7 I2: 43.6 ± 11.4 ***Weight*** (mean ± SD in kg) C: 97.7 ± 14.6 I1: 99.1 ± 14.3 I2: 96.7 ± 13.8 ***BMI*** (mean ± SD in kg/m^2) C: 35.3 ± 4.1 I1: 35.2 ± 3.9 I2: 34.7 ± 3.7 ***Number (%) of patients with a LDL-C level of ≥ 3.362 mmol/l (treated or untreated)*** C: 127/237 (54%) I1: 131/239 (55%) I2: 125/242 (52%) ***Number (%) of patients with a LDL-C level of < 3.362 mmol/l (treated)*** C: 1/237 (0.4%) I1: 2/239 (0.8%) I2: 0/242 (0%) ***Number (%) of patients with a HDL-C level of < 0.905 mmol/l*** C: 45/237 (19%) I1: 76/239 (32%) I2: 65/242 (27%) ***Number (%) of patients with a triglyceride level of ≥ 2.54 mmol/l*** C: 24/237 (10%) I1: 30/239 (13%) I2: 20/242 (8%) ***Number (%) of patients with a fasting insulin level of ≥ 90 pmol/l*** C: 103/237 (43%) I1: 111/239 (46%) I2: 93/242 (38%) ***Number of patients with DBP ≥ 90 mmHg (untreated or treated)*** C: 47/237 (20%) I1: 63/239 (26%) I2: 45/242 (19%) ***Number (%) of patients with a DBP of < 90 mmHg (treated)*** C: 20/237 (8%) I1: 22/239 (9%) I2: 17/242 (7%) ***Number (%) of patients with a waist circumference of ≥ 100 cm*** C: 141/237 (59%) I1: 145/239 (61%) I2: 133/242 (55%)	***Statistical techniques*** The safety analysis included those who had received at least one dose of trial medication after randomisation and had a subsequent safety observation. The ITT analyses were based on LOCF and included participants who had received at least one dose of study medication and had a subsequent efficacy observation. The null hypothesis was tested using ANOVA and ANCOVA. The placebo-adjusted 95% CI of orlistat treatment effect was also determined based on the LSM ***Weight change from the start of run-in to the end of year 1*** (mean ± SD in kg by ITT) C: –6.4 ± 6.7 I1: –8.5 ± 7.3 I2: –9.4 ± 6.4 p < 0.001 for C versus I1 and C versus I2, LSM ***Weight change from the start of run-in to the end of year 1 for completers*** (mean ± SD in kg) C: –7.0 ± 6.8 I1: –9.6 ± 7.3 I2: –9.8 ± 6.3 p < 0.002 for C versus I2, LSM Patients in C achieved significant weight loss at the end of year 1 in both the ITT and completers analyses (p < 0.001) ***Weight change from the start of run-in to the end of year 2*** (mean ± SD in kg by ITT) C: –4.3 ± 7.4 I1: –6.6 ± 8.3 I2: –7.4 ± 7.1 p < 0.005 for C versus I1, p < 0.001 for C versus I2, LSM ***Weight change from the start of run-in to the end of year 2 for completers*** (mean ± SD in kg) C: –4.3 ± 7.5 I1: –6.8 ± 8.4 I2: –7.6 ± 7.0 p = 0.012 for C versus I1, p < 0.001 for C versus I2, LSM	***Total number (%) of withdrawals during run-in*** Overall 54/783 (7%) ***Total number (%) of withdrawals during year 1*** C: 85/243 (35.0%) I1: 57/242 (23.6%) I2: 63/244 (25.8%) ***Total number (%) of withdrawals during year 2*** C: 22/158 (14.0%) I1: 45/185 (24.3%) I2: 22/181 (12.2%) ***Reasons for withdrawal during year 1*** (number of patients (%)) Adverse event C: 4 (1.6%) I1: 16 (6.6%) I2: 15 (6.1%) Treatment failure C: 5 (2.1%) I1: 4 (1.7%) I2: 6 (2.5%) Refused treatment C: 24 (9.9%) I1: 12 (5.0%) I2: 20 (8.2%) Lost to follow-up C: 21 (8.6%) I1: 12 (5.0%) I2: 6 (2.5%) Did not cooperate C: 20 (8.2%) I1: 10 (4.1%) I2: 12 (4.9%) Protocol violation C: 5 (2.1%) I1: 2 (0.8%) I2: 2 (0.8%) Entry violation C: 1 (0.4%) I1: 0 (0.0%) I2: 0 (0.0%) Administrative C: 5 (2.1%) I1: 4 (1.7%) I2: 2 (0.8%) Died during study C: 0 (0.0%) I1: 0 (0.0%) I2: 0 (0.0%) ***Reasons for withdrawal during years 1 and 2*** (number of patients (%)) Adverse event C: 7 (2.9%) I1: 24 (9.9%) I2: 21 (8.6%) Treatment failure C: 8 (3.3%) I1: 4 (1.7%) I2: 6 (2.5%) Refused treatment C: 33 (13.6%) I1: 25 (10.3%) I2: 23 (9.4%) Lost to follow-up C: 23 (9.5%) I1: 16 (6.6%) I2: 11 (4.5%) Did not cooperate C: 24 (9.9%) I1: 16 (6.6%) I2: 15(6.1%) Protocol violation C: 6 (2.5%) I1: 4 (1.7%) I2: 4 (1.6%) Entry violation C: 1 (0.4%) I1: 0 (0.0%) I2: 0 (0.0%) Administrative C: 5 (2.1%) I1: 12 (5.0%) I2: 5 (2.0%) Died during study C: 0 (0.0%) I1: 1 (0.4%) I2 0 (0.0%)	***Limitations of the study, as noted by the study authors*** None stated ***Sponsorship*** Hoffmann-La Roche

continued

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
continued Rossner *et al.*, 2000[48]				At the end of year 2, the mean weight loss in C was statistically significant in the ITT analysis ($p < 0.05$) but not in the completers population ***Patients with > 5% loss of initial weight at 1 year*** C: 43% 11: 61% 12: 62% $p < 0.001$ for C versus 12 Note that these values were read from a graph ***Patients with > 5% loss of initial weight at 2 years*** C: 38% 11: 55% 12: 68 % $p < 0.001$ for C versus 12 Note that these values were read from a graph ***Patients with > 10% loss of initial weight at 1 year*** C: 18.8% 11: 31.2% 12: 38.3% $p < 0.002$ for C versus 11, $p < 0.001$ for C versus 12 ***Patients who maintained > 10% loss in year 2*** C: 18.6% 11: 29.0% 12: 28.2% $p < 0.05$ for C versus 11 and C versus 12 ***Mean change in waist circumference at 1 year*** (in cm) C: –4.7 11: –6.0 12: –6.2 p = not significant ***Mean change in waist circumference at 2 years*** (in cm) C: –3.1 11: –4.7 12: –5.1 $p < 0.05$ for C versus 12 ***% change in total cholesterol from start of DB treatment*** (mean ± SD by ITT at 1/2 years) C: 0.11 ± 11.25/6.14 ± 13.41 11: –3.04 ± 12.33/2.04 ± 15.38 12: –6.45 ± 11.90/0.29 ± 12.79 $p < 0.001$ for C versus 11 and C versus 12 at years 1 and 2 ***% change in LDL-C from start of DB treatment*** (mean ± SD by ITT at 1/2 years) C: –1.48 ± 16.67/7.70 ± 18.10 11: –5.65 ± 17.88/1.28 ± 21.53 12: –9.68 ± 16.08/0.17 ± 18.47 $p < 0.001$ for C versus 11 and for C versus 12 at years 1 and 2 ***% change in HDL-C from start of DB treatment*** (mean ± SD by ITT at 1/2 years) C: 14.03 ± 18.25/14.59 ± 20.39 11: 14.60 ± 18.69/16.99 ± 22.26 12: 10.75 ± 17.83/14.12 ± 21.03 $p < 0.05$ for C versus 12 at year 1 ***LDL-C:HDL-C ratio*** (mean ± SD by ITT at day 1/1 year/2 years) C: 3.24 ± 1.16/2.81 ± 1.00/3.06 ± 1.01 11: 3.28 ± 1.11/ 2.70 ± 0.95/2.82 ± 0.94 12: 3.12 ± 1.07/2.64 ± 0.94/2.87 ± 1.05 $p < 0.001$ for C versus 11 at 1 and 2 years and C versus 12 at 2 years, $p < 0.05$ for C versus 12 at year 1 ***% change in triglycerides from start of DB treatment*** (mean ± SD by ITT at 1/2 years) C: 1.31 ± 35.37/5.51 ± 37.68 11: –0.82 ± 34.25/8.13 ± 77.64 12: –1.87 ± 35.82/1.47 ± 40.80 p = not significant	***Total number (%) of withdrawals during years 1 and 2*** C: 107 (44.0%) 11: 102 (42.1%) 12: 85 (34.8%) 11 participants with no follow-up assessments were excluded from the safety and efficacy analyses, and two additional participants who had a follow-up safety assessment but no efficacy assessment were excluded from ITT analysis ***Adverse events*** The authors reported that, with the exception of more frequent GI events in orlistat-treated patients, the adverse-event profiles were similar in all three groups throughout the study, were generally mild–moderate and resolved spontaneously. They reported that the GI events with orlistat generally occurred early during treatment, were mild–moderate in intensity, resolved spontaneously and were limited to only one or two episodes per patient ***Number of severe GI events over 2 years*** C: 8 11: 16 12: 25 The majority of adverse events (38/49) occurred during year 1 ***Number (%) of withdrawals due to adverse events*** C: 6 (2.5%) 11: 23 (9.6%) 12: 19 (7.9%) ***Number (%) of withdrawals due to GI adverse events*** C: 2 (0.8%) 11: 12 (5%) 12: 9 (3.7%) ***Patients diagnosed with breast cancer during the trial*** C: one (postmenopausal) 11: one (diagnosed 36 days after randomisation) 12: three (postmenopausal) No clinically significant changes were observed in any laboratory parameters, and treatment with orlistat had no clinically significant effect on pulse rate or ECG	

continued

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
continued Rossner *et al.*, 2000[48]				***VLDL-C levels*** (mean ± SD in mmol/l by ITT at day 1/ 1 year/2 years) C: 0.72 ± 0.46/0.58 ± 0.37/0.59 ± 0.37 I1: 0.78 ± 0.71/0.72 ± 0.74/0.72 ± 0.74 I2: 0.67 ± 0.46/0.56 ± 0.41/0.53 ± 0.39 *p* = not significant ***Lipoprotein A levels*** (mean ± SD in mg/l by ITT at day 1/1 year/2 years) C: 284.14 ± 357.93/296.84 ± 389.03/284.29 ± 340.52 I1: 280.22 ± 346.07/266.15 ± 337.33/209.31 ± 259.77 I2: 328.54 ± 409.07/257.36 ± 316.79/233.14 ± 291.71 $p < 0.05$ for C versus I2 at 1 year, $p < 0.001$ for C versus I2 at 2 years ***DBP*** (mean ± SD in mmHg by ITT at day1/1 year/2 years) C: 81.2 ± 9.8/79.9 ± 11.0/81.2 ± 9.9 I1: 81.5 ± 10.3/79.5 ± 10.0/81.71 ± 10.3 I2: 79.5 ± 9.4/78.6 ± 10.2/79.9 ± 9.5 $p < 0.05$ for C versus I2 at 1 year ***SBP*** (mean ± SD in mmHg by ITT at day1/1 year/2 years) C: 127.3 ± 16.1/125.4 ± 18.6/128.5 ± 17.5 I1: 128.4 ± 14.5/125.7 ± 15.9/129.6 ± 16.7 I2: 125.5 ± 14.9/122.8 ± 16.0/124.9 ± 16.5 *p* = not significant ***% change in fasting blood glucose levels from start of DB treatment*** (mean ± SD by ITT at 1/2 years) C: 2.23 ± 7.45/1.89 ± 8.76 I1: –0.41 ± 8.94/–0.53 ± 9.87 I2: 0.33 ± 7.62/–0.01 ± 12.32 $p < 0.05$ for C versus I1 and C versus I2 at 1 year ***% change in fasting insulin levels from start of DB treatment*** (mean ± SD by ITT at 1/2 years) C: –1.63 ± 63.98/10.72 ± 68.97 I1: –6.42 ± 49.16/3.22 ± 55.48 I2: –11.39 ± 54.78/6.29 ± 61.11 $p < 0.05$ for C versus I1 and C versus I2 at 2 years ***Quality of life*** Orlistat-treated patients reported significantly greater satisfaction with their weight-loss medication than placebo patients after 1 and 2 years ($p < 0.001$ for I2 and $p < 0.05$ for I1). Patients in I2 also expressed greater satisfaction with losing weight ($p = 0.011$) and their weight-loss programme ($p = 0.002$) at 2 years. Overall satisfaction with treatment, as expressed by the treatment index, was significantly greater with orlistat compared with placebo at 2 years ($p < 0.05$ for I1 and $p < 0.001$ for I2). Orlistat-treated patients also reported less overweight distress than placebo, and this became statistically significant in I2 at 2 years ($p < 0.05$). There were no significant differences between treatment groups in depression scores after either 1 or 2 years	***Number of patients requiring vitamin supplementation*** C: 1 I1: 14 I2: 12 73% of the incidences of low vitamin levels occurred during year 1. The differences in mean plasma values for vitamins D and E and β-carotene between orlistat-treated and placebo patients were statistically significant ($p < 0.001$). The vitamin E:LDL-C ratio increased during orlistat treatment (indicating no loss of vitamin E protection against LDL-C-induced atherogenesis) ***Patients affected by GI adverse events*** (C/I1/I2) Fatty/oily stool 4.6%/24.2%/31.7% Faecal urgency 5.4%/10.0%/14.4% Oily spotting 0.8%/13.3%/14.5% Increased defaecation 2.9%/7.9%/8.2% Faecal incontinence 1.3%/3.1%/7.4% Flatus with discharge 0.8%/6.2%/4.9% Oily evacuation 0.4%/3.7%/4.7% ***Number of withdrawals due to GI adverse events*** (C/I1/I2) Fatty/oily stool 0.0%/0.0%/0.4% Faecal urgency 0.4%/1.3%/0.0% Oily spotting 0.0%/0.0%/0.4% Increased defaecation 0.0%/0.4%/0.0% Faecal incontinence 0.0%/1.3%/0.4% Data were not available for flatus with discharge or oily evacuation	

continued

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Hill *et al.*, 1999[45] ***Country*** USA ***Aim*** To assess the effectiveness of orlistat in preventing weight regain and to assess the long-term effects of orlistat on obesity-related cardiovascular disease risk factors ***Method of randomisation*** Not stated. Stratification according to weight loss during run-in (≤ or > 10% of initial body weight) ***Outcomes*** Body weight, waist circumference, serum lipid levels, fasting serum glucose and insulin levels, vital signs, BP, haematology, clinical chemistry, urinalysis, levels of fat-soluble vitamins and β-carotene, faecal fat content, adverse events ***Setting and length of treatment*** 17 clinical research centres. 6-month run-in for weight loss followed by 1-year DB phase for weight maintenance	***Population*** Not stated ***Inclusion criteria*** *For run-in (weight loss)* Age ≥ 18 years, BMI 28–43 kg/m^2 *For DB phase (maintenance)* Loss of ≥ 8% of initial body weight during run-in ***Exclusion criteria*** History of significant medical disorder, uncontrolled hypertension, recurrent nephrolithiasis, symptomatic cholelithiasis, active GI disorders, type 2 diabetes, pancreatic disease, cancer, pregnancy, lactation, history or presence of substance abuse, eating disorders, excessive alcohol intake, significantly abnormal laboratory results, previous GI surgery for weight loss, history of postoperative adhesions, taking medications known to influence body weight, appetite or lipid levels during 8 weeks prior to screening	***6-month run-in for all patients*** Nutritionally balanced reduced-energy diet containing 30% energy as fat, 50% as carbohydrate and 20% as protein with a deficit of 4180 kJ/day to produce a weight loss of 0.5–1.0 kg/week. The deficit was based on the estimated energy expenditure, calculated from each individual's basal metabolic rate, taking into account gender, age and weight. Individuals were given a daily energy intake equivalent to their basal metabolic rate multiplied by 1.3. Participants received dietary counselling, attended a four-session behavioural modification programme and were encouraged to walk briskly for 20–30 minutes five times/week. All previous vitamin supplements were discontinued and standard daily multivitamin and multimineral tablets were prescribed. Patients were asked to record food and drink intake for 3 consecutive days at seven time points (n = 1313) ***Standard care for all patients during DB study*** Individuals' energy requirements were reassessed and an increase in energy intake was prescribed to match anticipated metabolic requirements over ensuing year. Dietary and behavioural counselling was provided throughout the year. If patients regained weight during this period, a reduced-energy diet was not initiated, but encouragement given to maintain this higher weight. Patients were asked to record food and drink intake for 3 consecutive days at four time points	***Gender*** (male/female) C: 28/156 I1: 29/157 I2: 35/136 I3: 23/156 ***Age*** (mean ± SEM in years) C: 46.4 ± 0.7 I1: 46.8 ± 0.8 I2: 46.1 ± 0.7 I3: 45.9 ± 0.7 ***Race numbers*** (white/black/Hispanic/other) C: 164/9/8/3 I1: 164/14/5/3 I2: 155/10/5/1 I3: 153/9/17/0 ***Weight*** (mean ± SEM in kg) C: 90.8 ± 0.9 I1: 89.3 ± 0.9 I2: 92.4 ± 0.9 I3: 89.7 ± 0.9 I2 was significantly different from other groups (p < 0.05), which was due to the higher proportion of males in I2 ***BMI*** (mean ± SEM in kg/m^2) C: 32.8 ± 0.2 I1: 32.6 ± 0.2 I2: 32.9 ± 0.2 I3: 32.8 ± 0.2 ***Serum lipid levels*** Similar across all groups	***Statistical techniques*** ITT analysis included those who received at least one dose of medication and for whom at least one body-weight measurement was taken before and after randomisation. Safety analysis included those who had received at least one dose of medication and who had had at least one follow-up safety evaluation. LOCF data were used. Completers analysis included those with ≥ 70% adherence to drug regimen (assessed by counting returned capsules). ANCOVA was used to assess between-group differences in % weight regain, with weight loss during run-in as the covariate. Placebo-adjusted treatment differences and 95% CI were based on LSM. Comparisons of the changes in risk-factor variables over time between groups were assessed with ANOVA and ANCOVA, with change in body weight as the covariate. Chi-squared was used for categorical analysis of frequency distributions ***Weight loss during run-in*** Approximately 10 kg overall ***Weight change after 1-year DB treatment relative to body weight at start of run-in*** (mean ± SEM in kg) C: –5.93 ± 0.69 I1: –5.15 ± 0.55 I2: –6.16 ± 0.49 I3: –7.24 ± 0.52 p < 0.001 for C versus I3 ITT weight-loss results were similar to those of completers ***Mean % weight regain during 1-year DB phase expressed as % of the weight lost during run-in*** C: 56.0% I1: 53.3% I2: 47.2% I3: 32.4% p < 0.001 for C versus I3 ***Patients with mean % weight regain expressed as % of weight lost during run-in*** *≤ 25% regain* C: 29.9% I1: 32.3% I2: 30.4% I3: 47.5% p < 0.05 for I3 versus all other groups *25–50% regain* C: 22.8% I1: 20.4% I2: 25.7% I3: 22.9% *50–75% regain* C: 15.2% I1: 18.3% I2: 25.1% I3: 17.3% *> 75% regain* C: 32.1% I1: 29.0% I2: 18.7% I3: 12.3% I2 and I3 significantly different from I1 and C (p < 0.05)	***Total number (%) of withdrawals during 6-month run-in*** Overall 584/1313 (44%) ***Main reasons for withdrawal during run-in*** Failure to meet the 8% weight-loss goal 35% Lost to follow-up 27% Did not attend appointments 14% Did not cooperate 9% Protocol violation 9% ***Number (%) of withdrawals during DB study*** C: 50/188 (27%) I1: 47/187 (25%) I2: 40/173 (23%) I3: 55/181 (30%) ***Number of withdrawals during DB study due to adverse events*** C: 5 I1: 17 I2: 17 I3: 27 ***Number of completers*** C: 138 I1: 140 I2: 133 I3: 126 Seven participants were excluded from the safety analysis because of no follow-up safety assessments. Two participants were excluded from the ITT analysis due to no follow-up efficacy assessments ***Adverse events*** During the 1-year DB phase, the % of patients reporting at least one adverse event was about 7–8% greater with orlistat compared with placebo. This difference was mainly accounted for by more GI events in I1, I2 and I3, with similar rates for adverse events involving other body systems across groups ***Patients reporting GI adverse events*** C: 68.1% I1: 82.3% I2: 91.8% I3: 95.0% Most were mild–moderate in intensity, occurred early during treatment and resolved without intervention. Most patients experienced one or two episodes ***Number of withdrawals due to GI adverse events*** C: 0.5% I1: 5.4% I2: 7.0% I3: 11.7%	***Limitations of the study, as noted by the study authors*** Some re-adjustments in body weight would occur in most patients because the prescribed dietary intake was increased at the time of randomisation. As a result, this study may have underestimated the benefits of orlistat in weight maintenance. Furthermore, patients who began to gain weight were asked to maintain the higher weight rather than resume an energy-reduced diet. Under actual clinical practice conditions, patients would be encouraged to reduce their energy intake ***Sponsorship*** Hoffmann-La Roche

continued

Authors, year, country, aim and design details	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
continued Hill *et al.*, 1999[45]		C: placebo tds for 1 year (n = 188) I1: orlistat 30 mg tds for 1 year (n = 187) I2: orlistat 60 mg tds for 1 year (n = 173) I3: orlistat 120 mg tds for 1 year (n = 181)		23.5% of I3 patients did not regain any weight or continued to lose weight after randomisation versus 16.3% in C. After the 1-year DB phase, body weight was greater than initial body weight in 5.4% of I3 patients versus 18.3% in C. 61.8% in I3 sustained a weight loss of > 5% of initial weight versus 49.8% in C ***Obesity-related risk factors after 1-year DB treatment*** Reductions in total cholesterol and LDL-C levels from initial values were significantly greater in I1, I2 and I3 versus C. Total and LDL-C levels increased in C. Changes in LDL-C:HDL-C ratio were significantly different only for C versus I1. For fasting glucose and insulin levels, mean increases of 1–2% above initial values were noted in C and I1 compared with slight reductions (about 1%) in I2 and I3. Changes in BP and waist circumference did not differ significantly between groups. Faecal fat values increased in a dose-dependent manner with orlistat	***Fat-soluble vitamins*** Mean levels of vitamins A, D and E and β-carotene remained within reference ranges. However, vitamin E and β-carotene levels were significantly lower with orlistat than placebo at the end of the study ($p < 0.001$)	

ANCOVA, analysis of covariance; ANOVA, analysis of variance; C, control group (C1/C2/C3/C4, first/second/third/fourth control group); CI, confidence interval; DB, double blind; DBP, diastolic blood pressure; ECG: electrocardiogram; GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; I, intervention group (I1/I2/I3/I4, first/second/third/fourth intervention group); ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LOCF: last observation carried forward; LSM, least squares mean; SB, single blind; SBP, systolic blood pressure; SD, standard deviation; SEM, standard error of the mean; tds, three times per day; VLDL-C: very-low-density ipoprotein cholesterol

Appendix 4

Quality assessment table for RCTs

Study	Davidson *et al.*, 1999[42]	Drent and van der Veen, 1993[39]	Drent *et al.*, 1995[38]	Finer *et al.*, 2000[41]	Hauptman *et al.*, 2000[43]	Hill *et al.*, 1999[45]	Hollander *et al.*, 1998[47]	Micic *et al.*, 1999[46]	Rossner *et al.*, 2000[48]	Sjostrom *et al.*, 1998[44]	van Gaal *et al.*, 1998[40]
Method of generating sequence of randomisation	NS	NS	NS	True randomisation	NS	NS	NS	NS	NS	Unclear	NS
Concealed randomisation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Selection criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
A priori power calculation	NS	NS	NS	Yes	NS	NS	NS	NS	NS	Yes	Unclear
Number of participants per group at baseline	224, 668	21, 23	46, 48, 45, 47	114, 114	212, 213, 210	188, 187, 173, 181	159, 163	60, 60	243, 242, 244	340, 343	123, 122, 123, 120, 117
Baseline comparability	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intended identical treatment (except study interventions)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Attempt to blind patients	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Attempt to blind carers	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Attempt to blind outcome assessors	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
Check to what extent blinding was successful patients/carers/assessors	NS for all	NS for all	NS for all	NS for all	NS for all	NS for all	NS for all	NS for all	NS for all	NS for all	NS for all
Description of statistical methods used	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Measures of central tendency and variance	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Adjustment for baseline imbalance	NA	NA	NA	NA	NA	NS	NA	NA	NA	NA	NA
Methods for dealing with missing data described	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Intention-to-treat analysis	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Withdrawals reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Patient adherence assessed	Yes	Yes	Yes (diet)	Yes (run-in only)	Yes (run-in only)	NS	Yes (run-in only)	Yes	Yes (run-in)	Yes (up to 1 year)	Yes

NS, not stated; NA, not applicable

Appendix 5

Data extraction table for economic evaluations

Authors, year, country of origin, type of evaluation and currency	Interventions and main clinical outcomes	Sources of data	Methods and perspective	Results	Sensitivity analysis	Additional comments
Foxcroft and Ludders, 1999[52] ***Country*** UK ***Type of economic evaluation*** Cost–utility analysis ***Currency*** British £	***Intervention*** All double-blind RCTs of orlistat versus placebo. All used placebo plus diet as control *Sjostrom* et al., *1998*[44] – 4-week placebo run-in plus diet – 120 mg orlistat tds plus hypocaloric diet (1200 kcal with 30% fat and 600 kcal deficit; at the end of week 24, 1000 kcal minimum, further 300 kcal reduction) – crossover in second year (patients reassigned to orlistat or placebo plus eucaloric diet) *Davidson* et al., *1999*[42] – 4-week placebo run-in plus hypocaloric diet – 120 mg orlistat tds plus diet (diet not specified), subgroup received 60 mg orlistat tds – first year: 120 mg orlistat versus placebo – second year: orlistat patients reassigned to orlistat (120 or 60 mg) or placebo, and all patients switched to eucaloric diet *Hollander* et al., *1998*[47] – 5-week placebo run-in plus hypocaloric diet – 120 mg orlistat tds plus diet (diet not specified) – 1-year follow-up ***Outcomes*** Mean weight loss and number of patients who lost > 5% of initial body weight	***Efficacy data*** – Sjostrom *et al.*, 1998 – Davidson *et al.*, 1999 – Hollander *et al.*, 1998 ***Prevalence, mortality and morbidity*** – Health Survey for England (webpage, March 1999) – Manson *et al.*, 1995 – NHS Centre for Reviews and Dissemination, 1997 (report 10) – McIntyre, 1998 ***QoL estimates*** – James *et al.*, 1997 – Index of Health related QoL – Fontaine *et al.*, 1996 – Barofsky *et al.*, 1997 – Lean *et al.*, 1998; 1999 – van Gemert *et al.*, 1998 – Karlsson *et al.*, 1998 – Shah *et al.*, 1994 ***Cost data*** – Quesenberry *et al.*, 1998 – West, 1998 – Roche computer model – Portsmouth and Southeast-Hampshire Health Authority	***Methods*** Systematic literature review of studies evaluating the use of orlistat as an adjunct to diet in the treatment of obesity Outcomes were based on ITT analysis. Since the denominator to be used in an ITT calculation was unclear in both 2-year RCTs, authors re-analysed the data on an ITT basis and performed sensitivity analysis for different interpretations of the ITT denominator Health benefits were quantified in terms of changes in QoL associated with weight loss Side-effects (gastrointestinal problems and potential vitamin malabsorption) were considered mild and transient, and are summarised in an abstract but not incorporated in the analysis ***Perspective*** The perspective adopted was that of the NHS. Direct costs included were outpatient appointments, general practitioner consultations and drugs; indirect costs were not included	***Costs*** Average annual cost of orlistat treatment for 100 persons (treated for 2 years) = £73,436 ***Benefits*** *Weight loss* – additional 3–4% of initial body weight over diet alone for obese people (weight regain in second year) – 1.9% for type 2 diabetes *% who lost > 5% over 2 years* Absolute RR = 17.5% (95% CI, 7.4 to 27.3) NNT = 6 (95% CI, 4 to 14) *% who lost > 10% over 2 years* Absolute RR = 8.6% (95% CI, 2.7 to 14.8) NNT = 12 (95% CI, 7 to 37) *QoL estimates* QoL values for obese patients ranged from 0.680 (case 1) to 0.940 (case 2) depending on the degree of disability Case 1: 0.181 QALYs per year gained with > 10% weight loss Case 2: 0.050 QALYs per year gained with > 10% weight loss Two independent experts rated that 0.10 and 0.19 QALYs could be gained per year with 10 kg (10%) weight loss Based on case 1: number of QALYs gained in a year of 100 persons treated with orlistat = 1.601 ***Synthesis*** The incremental cost–utility of orlistat treatment = £73,436/1.601 (£45,881 per QALY gained)	The analysis seems reasonably stable to the wide-ranging parameters of the multi-way sensitivity analysis ***Basic assumptions:*** – benefits of weight loss are the same across the whole spectrum of obesity and weight loss – costs = £73,436 (sensitivity analyses: A: £55,618, B: £88,658) – Drop-out rates: 52% orlistat versus 57% placebo (sensitivity analyses: C: 33 versus 40%) – Response rates: 34.1% of completers for orlistat lost > 10% of initial body weight versus 17.5% placebo (sensitivity analyses: D: 57.1% of completers for orlistat lost > 5% of initial body weight versus 37.4% placebo) – Utility gain of 10 kg weight loss = 0.181 (sensitivity analyses: E: 0.076, F: 0.260) Basic analysis: Cost/QALY gained = £45,881 (range £19,452 to £55,391) ***Cost/QALY gained for sensitivity analyses*** A: £34,792 B: £55,391 C: £32,860 D: £35,822 E: £13,541 F: £131,918 Orlistat prescribed in primary care = £26,635 (extreme values range £9,779 to £66,505)	***Limitations as mentioned by the authors*** This report considers the effectiveness of orlistat in achieving weight loss and reducing certain risk factors linked to adverse health events. These proxy outcomes may not fully show the benefits or disbenefits that orlistat has on obesity-related mortality and morbidity A societal perspective may have shown greater value for money as there are potential benefits and/or savings that have not been considered, e.g. increasing the employment rate in the obese Utilities have been calculated on the basis of the published trial results, but trial data were not consistent with the EMEA's prescription indication for orlistat. Therefore, the figures obtained for cost/QALY gained here may be different from those obtained in clinical practice

NNT, number needed to treat; QALY, quality-adjusted life-year; ITT, intention-to-treat; tds, three times daily; EMEA, European Medicines Evaluation Agency

Appendix 6

Quality assessment table for economic evaluations

Study	**Foxcroft and Ludders, 1999**[52]
Well-defined question	Properly addressed
Comprehensive description of alternatives	Properly addressed
Effectiveness established	Properly addressed
Relevant costs and consequences identified	Properly addressed
Costs and consequences measured accurately	Properly addressed
Costs and consequences valued credibly	Properly addressed
Costs and consequences adjusted for differential timing	Not properly addressed
Incremental analysis of costs and consequences	Properly addressed
Allowance made for uncertainty in estimates of costs and consequences	Properly addressed
Results/discussion included all issues of concern to users	Properly addressed

Appendix 7

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We look forward to hearing from you.

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