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Clinical effectiveness of very low energy diets in the management of weight loss: a systematic review and meta-analysis of randomized controlled trials

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Conflicts of interest

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Abstract

Guidelines suggest that very low energy diets (VLEDs) should be used to treat obesity only when rapid weight loss is clinically indicated due to concerns about rapid weight regain.

Literature databases were searched from inception to November 2014. Randomized trials were included where the intervention included a VLED and the comparator was no intervention or an intervention that could be given in a general medical setting in adults that were overweight. Two reviewers characterised the population, intervention, control groups, outcomes, and appraised quality. The primary outcome was weight change at 12 months from baseline.

Compared with a behavioural programme alone, VLEDs combined with a behavioural programme achieved -3.9kg (95% CI -6.7 to -1.1) at one year. The difference at 24 months was -1.4kg (95%CI -2.6 to -0.2) and at 38-60 months was -1.3kg (95%CI -2.9 to 0.2). 19% of the VLED group discontinued treatment prematurely compared with 20% of the comparator groups, relative risk 0.96 (0.56 to 1.66). One serious adverse event, hospitalisation with cholecystitis, was reported in the VLED group and none in the comparator group.

VLEDs with behavioural programmes achieve greater long-term weight loss than behavioural programmes alone, appear tolerable, and lead to few adverse events suggesting they could be more widely used than current guidelines suggest.
Introduction

Obesity is a chronic relapsing condition linked to serious health consequences including type 2 diabetes, cardiovascular disease, musculoskeletal problems as well as many cancers (1-3). There is a pressing need for effective and sustainable interventions. Given the scale of the problem, much of the management of obesity needs to occur within the community and primary care is an important, but underused, setting.

Very low energy diets (VLEDs) are one option to manage obesity used in specialist settings and as part of self-management. A VLED provides <800kcal a day with high levels of protein and minimal carbohydrate, to encourage weight loss with minimal loss of lean tissue and supplemented with vitamins, minerals, electrolytes and fatty acids to ensure adequate nutrition (4). However these diets are not recommended for routine weight management. For example, the American Heart Association/American College of Cardiology/The Obesity Society 2013 guidelines (5) recommend that VLEDs should only be used in limited circumstances and only be provided by a trained professional with medical monitoring. In the UK, the Scottish Intercollegiate Guidelines Network (SIGN) guideline 115 (6) notes that long term maintenance with VLED is not superior to other obesity treatment options, while the National Institute for Health and Clinical Excellence (NICE) guidelines advise that these diets should be reserved for patients who have a clinical need for rapid weight loss such as prior to joint replacement or fertility treatment (7).

Previous systematic reviews have investigated the use of VLEDs for weight loss (8-12) and have concluded that VLEDs are effective in the short term (8, 11), but that their effectiveness in the longer term (12 months or more) is not certain (8, 9, 11). In 2006 Tsai et al. (11) reviewed six randomized controlled trials, but they were unable to use a consistent method for imputation of loss-to-follow up making conclusions on the population impact uncertain. Other reviews that have included a meta-analysis have included 1 to 3 studies and have concluded that there is insufficient evidence available to assess the potential benefits of VLEDs (10, 12). More recently, Mulholland et al. (9) reviewed longer term evidence on the
effectiveness of VLEDs, including a variety of study designs. They concluded that VLEDs could lead to long-term weight loss, reduced cardiovascular risk and respiratory disorders. However, they reported that their conclusions were limited by heterogeneity between the studies and did not perform a meta-analysis (9).

Here, we have examined the efficacy and safety of the use of VLEDs for weight loss, in contexts applicable to how they may be applied in a general medical setting. In addition, when available, we extracted data on health outcomes including systolic and diastolic blood pressure, HDL and LDL cholesterol, fasting blood glucose, psychological well-being, quality of life and adverse events.

Methods

Search strategy

Medline, Embase and the Cochrane Central Register of Controlled Trials Database were searched from database inception to November 2014. We also screened references from systematic reviews identified through our search and requested papers from authors for those we were unable to obtain or had abstracts only. The searches were not restricted by country or language. Grey literature such as the ISCRTN database, ANZCTR database and websites including Clinicaltrials.gov, Opengrey and Oaister were also searched. The results of the searches were documented and the references stored in a reference manager database. A sample search strategy (Medline) can be found in Supplementary Appendix 1.

Studies were included if they recruited adults (≥ 18 years) who were overweight (BMI ≥ 25 kg/m²) or obese (BMI ≥ 30 kg/m²), with or without co-morbidities related to excess adiposity. We excluded studies in pregnant women or people with eating disorders.

Only randomized controlled trials were eligible. Interventions had to incorporate a VLED (defined as 800kcal/day or less) for initial weight loss. Interventions that used VLEDs on a
few days each week and studies where a VLED was used only for weight-loss maintenance were excluded. The comparators were defined as either no intervention or an intervention that could be given in a general medical context, including primary care. We excluded studies with a VLED in the comparator programme as we were interested in the clinical effectiveness of VLEDs compared to other weight loss methods rather than between different types of VLED programmes. Studies were required to report a measure of weight change at 12 months (defined as 11-20 months) or greater from baseline. Data were also extracted on health outcomes including blood pressure, HbA1c, and lipids and also on adverse events and withdrawals during treatment.

Studies were excluded if they did not present sufficient information to allow critical appraisal and data extraction or such information was not available in trial protocols or from authors. Titles and abstracts were assessed for inclusion by a single reviewer with a sample checked by a second reviewer. If in doubt, the full paper was assessed.

Data extraction

Two people independently used a data extraction form to characterise the population, intervention, control groups, outcomes, and to appraise the quality. Disagreements were resolved by discussion or by a third reviewer.

In all trials, some participants are lost to follow-up and studies vary in whether and how they impute data. The practices they adopt can affect the effect size and so to reduce spurious heterogeneity from this we used baseline observation carried forward as a consistent method of imputation (13). This has the additional benefit of conservatism because people who find the treatment ineffective are less likely to attend for follow-up.

We also extracted data on changes in systolic and diastolic blood pressure, HDL and LDL cholesterol, fasting serum glucose, insulin, HbA1c, Beck Depression Index (BDI) (14), treatment withdrawal and adverse events. We also used BOCF to calculate change in these biomedical outcomes and BDI.
Quality assessment was based on the York CRD approach (15). Risk of bias was assessed on the basis of randomisation sequence, concealment of allocation, selective reporting and attrition.

We attempted to characterise the behavioural interventions using the 40 item taxonomy of weight loss techniques, CALO-RE (16). However, the studies reported the behavioural elements sparsely and this was uninformative so we dropped this in the interests of economy (however, these data are available on request).

Authors were contacted for missing data and clarifications as required.

Analysis
We conducted meta-analyses in Review Manager 5.2 (17) to examine the difference between intervention and comparator groups in weight change at 12 months, 24 months, and 38-60 months. Meta-analyses were conducted to examine the changes in biochemical outcomes and BDI at 12 months as well as adverse events.

We planned three different comparisons: VLED alone versus a behavioural programme, VLED plus a behavioural programme versus a brief intervention and VLED plus a behavioural programme versus a behavioural programme alone. In the latter group (which included the majority of the studies) we also conducted further subgroup analyses based on:

- With/without a pre-existing co-morbidity, as this could affect motivation to adhere
- Formulation of the VLED (liquid/meal replacement or regular food), as this could affect adherence
- VLED programme (single or multiple periods of VLED), as a second phase of VLED programme may act as a relapse prevention or rescue strategy and be expected to result in further weight loss.
All meta-analyses used a random effects model to account for differences in the intervention programmes and populations. Pooled results were calculated as mean differences in kilograms (kg) with 95% confidence intervals. The $I^2$ statistic was used to quantify statistical heterogeneity (18, 19). Where a study contributed more than one intervention arm to a subgroup we split the control group equally to avoid double-counting in the pooled result. We also conducted sensitivity analyses to explore the effect of excluding studies where there were significant differences in the intervention and/or comparator treatments compared to the other studies.

**Results**

The literature search identified 2232 studies in total. 2227 of which were identified through database searches and five were identified from other sources (Figure 1). Sixty-seven full papers were retrieved and 18 were eligible for inclusion, which described 12 randomized controlled trials comprising 14 VLED intervention arms and 12 control arms. The main reason papers were excluded was because they were not randomized trials or did not report body weight after 12 months or more. One study was excluded as the LED contained more than 800kcal/day (20). Four studies were excluded as the intervention involved intermittent VLED use e.g. twice a week (21-24). Six trials were also excluded as they included a VLED in the comparator arm (25-30) and a further four were excluded as, although they initially met the inclusion criteria, they provided insufficient data for inclusion in the meta-analysis and the authors were unable to supply the missing data (31-34). A list of the 49 full papers excluded with grounds for exclusion is included as supplementary data in Table S1 in the Appendices.

**Characteristics of the studies (Table S2)**

The 12 trials randomized 522 adult participants to VLED and 452 adult participants to a comparator programme. The median number of participants was 76.5 (IQR 54 to 93).
Seven studies were carried out in Europe (one in the UK), four in the USA and one in Australia. The median percentage of female participants was 71% (IQR 61 to 80%), the median age 45.6 years (IQR 42.0 to 50.4 yrs), and median baseline BMI 38.2kg/m$^2$ (IQR 35.8 to 40.3kg/m$^2$). Two studies recruited patients with type 2 diabetes mellitus (35-38), one patients with obstructive sleep apnoea (39, 40), and one patients with asthma (41).

The median length of the initial VLED intervention was 10 weeks (IQR 8 to 12 weeks) and the median energy content of the VLED was 463kcal/day (IQR 420 to 541kcal/day). Two studies included a second “booster” period of VLED, which we termed “multiple VLED” in the meta-analyses (36-38, 42). Eight studies emphasised diet more than physical activity in the behavioural weight loss programme. The remaining four studies (35, 36, 39, 40, 43) emphasised diet and activity modification equally. Behavioural support was continued after the VLED phase in all the studies and included a median of 22 (IQR 14 to 50) contacts, typically provided weekly during the VLED and less frequently thereafter. In all cases, participants saw a nurse, dietician or psychologist providing specialist weight loss management support. The sessions were all face-to-face group sessions with the exception of the study by Purcell et al. (43), which delivered individual sessions. The study by Wing et al. (36) provided individual sessions for participants in the VLED + BT group, but group sessions for the BT group. The study by Tuomilehto et al. (39, 40) delivered both individual and group sessions to the VLED group. The data on duration of the sessions were sparse, but generally they lasted 1-1.5 hours. Intervention details are summarised in Table S2. The study by Wadden et al. randomized people to three groups and one constituted provision of a VLED without any behavioural support (44, 45).

In 10 trials the comparator comprised a behavioural programme where the behavioural programme was generally comparable with the VLED group in intensity and methods, but participants followed a modestly restricted energy deficit diet. The behavioural component of the intervention and comparator programmes was identical in intensity and content in seven
of the 10 trials. In Torgerson et al. (46, 47) there were 56 compared with 59 sessions and in Purcell et al. (43) there were 18 support sessions for the behavioural group compared with six for the VLED + BT group. In Wadden et al. (44, 45) the focus of the sessions differed between arms but not the intensity of support. During the last three months of the programme the sessions for the behavioural weight loss programme aimed at continued weight loss whereas the VLED + BT group focussed on relapse prevention, maintaining weight loss and strategies for handling weight regain.

In two trials the comparator was a brief intervention, meaning participants were given brief advice on the energy restricted diet, written materials, but little or no ongoing support. Tuomilehto et al. provided no in-person regular support and the behavioural intervention comprised a booklet and brief one-off advice only (39, 40). Rolland et al. provided a self-help booklet and asked participants to return for regular weighing and provided support on the telephone or by email if participants asked (48, 49).

Ten studies reported weight change at 12 months from baseline (defined as 11-20 months, median time point was 12 months (IQR 12 to 12)). Eight studies followed participants for longer; six studies at 24 months and four studies at 38-60 months. Reporting of other outcomes such as biomedical parameters and BDI was limited with seven studies reporting these outcomes at 12 months. Nine studies reported presumed side effects and/or adverse events. Eight studies reported on whether participants stopped the treatment programme prematurely.

**Risk of bias**

Most studies were classified as at unclear risk of bias because they did not report aspects of trial methods now expected in CONSORT (Table S3).

**Meta analysis**
Weight change at 12 months

In trials where participants were randomized to a behavioural weight loss programme, participants lost 6.4kg, but adding a VLED to a similar intensity programme resulted in a mean weight loss of 10.3kg, a difference of -3.9kg (95% CI -6.7 to -1.1) weight-loss (Figure 2). One study comparing a VLED combined with a behavioural programme (VLED + BT) with a brief intervention (39, 40) showed an additional -7.2kg (95% CI -9.9 to -4.5) loss. One study compared a VLED alone with a behavioural programme (44, 45). The behavioural programme led to a 4.5kg (95% CI -0.1 to 9.0) greater weight loss than the VLED arm.

Subgroup analyses at 12 months

We performed subgroup analyses among the nine studies that compared VLED + BT with BT group (Figures S2-4). There was no evidence that trials of VLED to treat a medical condition led to greater weight loss relative to control than trials where the VLED was for weight loss only. Likewise there was no evidence of subgroup differences for meal replacements versus regular food or a single period of use versus multiple periods.

Sensitivity analysis

We conducted a sensitivity analysis excluding studies where the comparator programme prescribed a diet with fewer than 1000kcal/day. This excluded only one study (42) and did not change the results (difference -4.0kg (95% CI -7.3 to -0.8)). In addition, we excluded the trial by Purcell et al. (43) because the weight loss programme for the comparator behavioural programme group was a third of the intensity of VLED + BT group. Excluding this study did not change the results (difference -4.2kg (95% CI -7.4 to -1.1)).

Weight change at 24 months

Six trials provided data at 24 months. In trials where participants were randomized to a behavioural weight loss programme, participants lost 2.8kg, but adding a VLED to a similar
intensity programme resulted in a mean weight loss of 4.2kg, a difference of -1.4kg (95% CI -2.6 to -0.2). VLED + BT compared with a brief intervention gave a difference of -3.7kg (95% CI -6.0 to -1.4) (Figure S5).

**Weight change at 38-60 months**

Four trials provided data at 38-60 months. In trials where participants were randomized to a behavioural weight loss programme, participants lost 2.1kg, but adding a VLED to a similar intensity programme resulted in a mean weight loss of 3.4kg, a difference of -1.3kg (95% CI -2.9 to 0.2) (Figure S6). VLED alone compared with a behavioural programme showed an effect in favour of the comparator who lost, on average, 1.3kg (95% CI -3.3 to 5.8) more than the VLED.

**Secondary outcomes**

There was little evidence that VLED + BT led to greater improvements in lipids, blood glucose, systolic blood pressure, or insulin than BT alone (Table 1 and Figures S7 to 13) but data were very limited. There was some evidence that VLED + BT led to a greater improvement in diastolic blood pressure than BT alone (-4.2mmHg (95% CI -6.3 to -2.1)), but again data were limited (Figure S13).

**Beck Depression Inventory**

Four studies assessed change in depression at 12 months and there was no evidence of any greater improvements among participants using a VLED + BT compared to BT alone (n=3; difference -0.90 (95% CI -2.98 to 1.17, p=0.77, I²=0%)) or VLED alone versus BT (n=1; difference 3.85 (95% CI -1.20 to 8.90)) (Figure S14).

**Discontinuation of treatment**

In most studies, the proportion of people who stopped adhering to the programme was similar in the intervention and comparator groups, with 19% stopping the VLED + BT
programme prematurely compared with 20% in the BT group. Meta-analysis of these proportions (Figure 3) showed that participants were as likely to stop adhering to the VLED programme as the behavioural programme (RR 0.96 (95% CI 0.56 to 1.66)).

**Adverse Events**

Six studies did not report adverse event data by trial arm (36-38, 41, 44-47, 50, 51). One study reported that no adverse events were deemed related to treatment, but gave no further details (39, 40). There was only one serious adverse event reported in any of the studies that was classified as probably related to the intervention, which was cholecystitis leading to a cholecystectomy (43). The majority of the events reported were transient effects such as tiredness, dizziness and cold intolerance. The most frequently reported of these effects was transient alopecia (RR 3.5 (95% CI 0.8 to 15.4) (all the available data on adverse effects are summarised in Table 2).

**Discussion**

A VLED together with a behavioural programme led to an additional 3.9 kg weight loss than a similar behavioural programme alone at 12 months. There were limited data at longer follow up, but the data showed that some of this weight loss advantage is maintained up to 60 months. One trial provided inconclusive evidence that offering a VLED without a behavioural programme was less effective than a behavioural programme alone. There were very limited data on other biomedical outcomes, but no evidence of an advantage of the VLED + BT over BT alone. The evidence suggested that adherence to the VLED + BT programme was similar to that for the BT programme. Subgroup analyses at 12 months showed no significant differences in weight loss between subgroups offered liquid or food based VLED, multiple or single VLED programmes, or whether participants were being treated for a medical condition. There was only one SAE reported, cholecystitis, which was deemed likely to be due to the VLED, and transient alopecia was the only common adverse event reported.
**Strengths and limitations**

These findings are consistent with previous systematic reviews that have considered the use of VLEDs in weight loss management. The reviews by Avenell (12), Tsai (11) and Franz (10) only included randomized controlled trial data. However, since these reviews (most recently in 2007) more studies have been published. This, together with a more comprehensive literature search than most previous reviews has allowed us to include more data from randomized controlled trials. We were able to pool data from nine trials at 12 months, totalling 974 participants, whereas in previous reviews meta-analyses have typically been based on data from only 1-3 trials.

Previous reviews have chosen to include study types such as cohort studies in their analyses as well as randomized controlled trials (8, 9). By restricting the review to randomized trials we reduced the scope for bias to influence the results. National clinical guidelines base recommendations for effective treatments almost exclusively on data from randomized trials. We found little evidence for bias but we were unable to assess quality in one or more domains in many trials because information was not presented. Most trials predated widespread adoption of CONSORT and this could explain why methodological details were lacking and we regard the data as robust. Applying a consistent method to account for loss to follow-up removed one source of heterogeneity between trials and also minimised the scope for bias. We were able to extract data with up to 5 year follow up allowing some pooling of data at these longer follow up periods. We also applied a consistent coding scheme to describe the behavioural components of these programmes that support motivation and adherence and reported on adherence.

There were some limitations. Despite contacting authors, we excluded a few trials where there were insufficient data presented to allow inclusion in the meta-analysis or other key aspects of the methods or results were missing. However, based on the published data
these trials appear to give similar results to those we could include and we feel exclusion is unlikely to have biased the findings. A study by Bliddal et al (20), which included a LED with 810kcal/day was excluded. The difference between 800kcal/day and 810kcal/day is clinically unimportant. However, as laid down in the PRISMA statement (52) we adhered to our predetermined inclusion criteria, which were based on the internationally recognized definition of a VLED being 800kcal/day or less, and therefore excluded the study. The results from this study were similar to our findings. Inclusion of this study in the meta-analysis of VLED+BT compared with BT alone at 12 months gives a difference of -4.2kg (95%CI -6.7 to -1.8) and therefore, would not have changed our conclusions. Few trials followed up participants for longer than a year so mean differences in weight loss were imprecisely estimated but there was still evidence of superiority of VLED + BT over BT at 24 months. Data on outcomes other than weight were especially sparse so it remains unclear whether VLED and a behavioural programme lead to better health outcomes than a behavioural programme alone. However, data suggest that weight loss leads to linear reductions in blood pressure and LDL and increases in HDL (53, 54) so it seems reasonable to assume that greater weight loss leads to greater health benefits, though this cannot be established from this review alone.

Implications
Several current guidelines caution against the use of VLEDs for the treatment of obesity, except where rapid weight loss is required, and warn about weight regain. These trials conducted by obesity specialists suggest that in this context, VLEDs appear to be well-tolerated and appear to have a long-term advantage over behavioural programmes alone. Weight regain does occur beyond 12 months but the rate of regain does not outweigh the advantages of greater initial weight loss. This is consistent with the finding from a direct comparison of two treatments that the rate of weight loss does not affect the proportion of weight regained within 144 weeks (43). Accordingly, this review provides strong evidence that current prohibitions on use are unnecessary and provide reassurance that routine use in
specialist obesity clinics should be considered when behavioural treatments alone have not produced sufficient weight loss. However, the trials reviewed provide no evidence to suggest that providing a VLED without behavioural support is effective compared with behavioural support, but suggest that adding a VLED to a behavioural programme is effective. The data in this meta-analysis derive largely from trials conducted by obesity specialists. Perhaps as a consequence, the behavioural programme appears to have been rather more effective than is the case when behavioural programmes are conducted in everyday medical contexts (55). Despite this, the descriptions of both the behavioural programme accompanying VLEDs and the behavioural programme alone suggest that such programmes are similar to most weight control programmes (56) and there is no reason to assume that the programmes could not be implemented in routine care. A trial in everyday medical context providing behavioural support plus a VLED compared with behavioural support is required to confirm this.

Previous trials have investigated other potential weight management interventions in primary care. The Lighten Up trial (57) compared a range of commercial weight reduction programmes to minimal intervention and found a mean difference of between 0.9 to 2.5kg additional weight loss for the commercial providers at 12 months, while Jebb et al. (58) compared a group based behavioural weight loss programmes offered by a commercial provider (WeightWatchers) to standard primary care management and found a mean of 3.2kg additional weight loss for the commercial provider at 12 months. In the UK, systems are already in place to allow referrals from primary care to these group based behavioural weight loss programmes. Our results imply that adding VLEDs to these kinds of behavioural programmes would lead to an additional 3.9kg weight loss at 12 months. In these studies the treatment was provided within a research or specialist setting and studies are warranted to explore the use of referral schemes to providers offering a VLED programme.

Conclusions
Adding a VLED to a behavioural weight loss programme produces greater weight loss in the medium and longer-term than a behavioural programme alone. Such programmes appear well-tolerated. Current advice against their use for routine weight loss in medical clinics should be reconsidered.

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**Ethical approval**

None needed.

**Author’s contributions**

HMP, SAJ and PA designed the study. HMP, SAJ, and PA drafted the paper with additional input from DJ, AL and AC. HMP conducted the statistical analyses and HMP, SAJ and PA wrote the results. Data extractions were carried out by HMP, DJ, AL and AC. All authors have read and agreed the final version of the manuscript.
References


Figure 1: Review flow chart

Figure 2: Forest plot BOCF weight change at 12 months

Figure 3: Forest plot – dropouts from treatment
**Table 1: Summary of biomedical parameter analyses, 12 months data, BOCF**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Difference</th>
<th>95% CI</th>
<th>I²</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>-0.90 mmol/L</td>
<td>-2.5 to 0.7</td>
<td>86%</td>
<td>210</td>
</tr>
<tr>
<td>HbA1c</td>
<td>-1.23%</td>
<td>-3.4 to 1.0</td>
<td>92%</td>
<td>129</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>24 pmol/L</td>
<td>-14.7 to 62.7</td>
<td>0%</td>
<td>129</td>
</tr>
<tr>
<td>HDL</td>
<td>0.06 mmol/L</td>
<td>0.00 to 0.13</td>
<td>39%</td>
<td>129</td>
</tr>
<tr>
<td>LDL</td>
<td>0.22 mmol/L</td>
<td>-0.01 to 0.45</td>
<td>NA</td>
<td>93</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.49 mmHg</td>
<td>-6.0 to 9.0</td>
<td>69%</td>
<td>293</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-4.19 mmHg</td>
<td>-6.3 to -2.1</td>
<td>0%</td>
<td>293</td>
</tr>
</tbody>
</table>
Table 2: Summary of reported adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>VLED percentage* (number)</th>
<th>Comparator percentage* (number)</th>
<th>Peto odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cardiovascular event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• New abnormal ECG</td>
<td>0 (0)</td>
<td>2.0 (1)</td>
<td>0.05 (0.00 to 3.2)</td>
</tr>
<tr>
<td>Any musculoskeletal event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Raised serum urate requiring allopurinol</td>
<td>5.8 (1)</td>
<td>0 (0)</td>
<td>8.3 (0.16 to 6421.4)</td>
</tr>
<tr>
<td>Any gastrointestinal event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cholecystitis and cholecysectomy</td>
<td>0.76 (1)</td>
<td>0 (0)</td>
<td>7.9 (0.16 to 396.9)</td>
</tr>
<tr>
<td>• Hepatic dysfunction</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Any renal dysfunction</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Any skin or subcutaneous tissue event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Transient alopecia</td>
<td>42.2 (49)</td>
<td>13.8 (8)</td>
<td>3.5 (0.8 to 15.4)</td>
</tr>
</tbody>
</table>

* The denominator in the percentage calculation is the number of participants in those trials that reported on the given adverse event.