Orlistat for Overweight Subjects with Nonalcoholic Steatohepatitis

To the Editor:

We read with interest the article by Harrison et al.[1] on the use of Orlistat in overweight patients with nonalcoholic steatohepatitis (NASH). Their prospective randomized trial of 41 patients concluded that improvement in liver histology was not significantly different after 36 weeks of treatment with Orlistat/vitamin E compared to vitamin E alone. The mean weight loss between the two groups was higher in the Orlistat group but did not reach statistical significance (8.3% versus 6.0%). The authors therefore reanalyzed the data to compare those who lost $<$ or $\geq$ 5% body weight or $<$ or $\geq$ 9% body weight, respectively. Using these stratifications, they demonstrated that weight loss of 5% was associated with improvement in steatosis but not NAFLD activity score (NAS), whereas weight loss of 9% was also associated with an improvement in NAS.

Regarding design, there are no power calculations presented in the methods section, so there is no way of assessing if the trial was adequately powered to detect differences between the treatment groups. Also, three primary endpoints are listed; does this imply the study was powered for all three primary outcomes? We estimate that to detect a 10% reduction in weight could require up to 60 patients per group and question whether the study presented was adequately powered. The authors' data demonstrates greater loss of weight in the Orlistat group, but this did not reach statistical significance and could be due to power. With respect to the subgroup analysis, this does not appear to have been powered at the outset, and as such, descriptive statistics only should be presented.

Regarding analysis, it would be helpful if the authors could clarify why the percent weight loss is categorized into two further analyses: $<$5%, $>$5% and $<$9%, $>$9% and if these were preplanned or data-driven cut-points. As a continuous measure, the percent weight loss should be analyzed as a continuous variable since loss of information and bias are introduced by dichotomizing variables. The statistical analyses presented use a mix of parametric and nonparametric approaches; given the small size of the study, then nonparametric statistics are more appropriate (Spearman's correlation, Mann-Whitney tests).

No significant difference was observed in the histological improvements seen between the two groups at 36 weeks; however, a detailed histopathological description was only provided for liver biopsies at the start of the study. We would be interested to see a more detailed description of the histopathological changes at follow-up of the two treatment groups.

We know that the degree of weight loss achieved with Orlistat is variable. Orlistat may provide additional histological improvement compared with a similar degree of diet-induced weight loss, but only in the subset of patients who achieve $>$5%-10% weight loss. Indeed, previous studies have suggested that Orlistat can improve hepatic steatosis beyond its effect on weight reduction,[2] and exerts additional beneficial effects on inflammation and fibrosis.[3]

We feel it may be premature at this stage to discount a role for Orlistat in NASH. Given the magnitude of NASH in the West, there remains a pressing need for larger studies which are powered to detect differences in weight loss/NAS score.

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Reply:

We appreciate the comments of Dowman and colleagues in reference to our study with orlistat in nonalcoholic steatohepatitis.[1] Regarding study design, specifically with respect to the lack of a calculation for power, this study was designed as a pilot trial and not necessarily intended to definitively answer the question of whether orlistat therapy alone is efficacious. However, we have subsequently performed a retrospective power analysis using the values for weight loss reported in the article. The independent variables are treatment (control, orlistat) and time (before, after treatment). The dependent variable is body weight. The mean $\pm$ standard deviation (SD) of body weight before treatment is 225 $\pm$ 42 pounds. A 10% weight loss will be 22.5 pounds, an effect size of 0.54 SD. Four two-tailed, post hoc tests (two between and two within groups) are appropriate for this analysis, so a Bonferroni correction of $P = 0.05/4 \simeq 0.01$ was used. With SPSS Sample Power, version 2.0, we obtained a sample size estimate of 82 subjects per group for a power of 80% with a level of confidence of 95%. We concur that a larger sample size than was used in the article is needed to detect a 10% difference in weight loss between groups. With 23 subjects in one group and 18 in the other, we had the power to detect a 1.13 SD effect size or 25.4 pound difference in weight loss between groups. Presented as descriptive statistics, body weight in pounds was 226 (95% confidence interval [CI]: 153-299) in the orlistat group before treatment, 224 (95% CI: 132-316) in the control group before treatment, 208 (95% CI: 132-284) in the orlistat group after treatment, and 210 (95% CI: 120-300) in the control group after treatment.

Regarding analysis, as previously noted in our article, there were no significant differences in histopathology between the two groups, so further case-by-case analysis was not thought to be helpful in this pilot trial. Subsequently, when no treatment effect was observed, the data were pooled and categorized by weight loss. The observed weight losses were 6.0% in the control group and 8.3% in the orlistat group. The 5% and 9% cut-points bracket the observed weight loss values and split the group sizes by a 2:3 ratio. Power analyses were not performed. Power is not an issue when statistically significant differences are found. However, increasing the number of hypothesis tests increases the probability of a Type I error. The results of Spearman correlation analysis between weight change $\geq$ 5% and changes in dependent variables were the quantitative insulin-sensitivity check index (QUICKI; $r = -0.327$, $P = 0.039$, $n = 40$) and steatosis ($r = -0.388$, $P = 0.013$, $n = 40$). The results of Spearman correlation analysis for weight change $\geq$ 9% were QUICKI ($r = -0.385$, $P = 0.014$, $n = 40$), steatosis ($r = -0.453$, $P = 0.003$, $n = 40$), ballooning ($r = -0.326$, $P = 0.040$, $n = 40$), inflammation ($r = -0.321$, $P = 0.044$, $n = 40$), adiponectin ($r = 0.461$, $P = 0.002$, $n = 41$), and the NAFLD activity score (NAS; $r = -0.419$, $P = 0.007$, $n = 40$). We agree that larger studies are needed to fully delineate the efficacy of orlistat in the treatment of nonalcoholic steatohepatitis. However, quantification of a specific weight loss goal that is associated with clinical and histopathologic improve-