Author's response to reviews

Title: Fluvoxamine for fatigue in primary biliary cirrhosis and primary sclerosing cholangitis: a randomised controlled trial.

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Author's response to reviews: see over
Dear editor,

Below you find a point-to-point reply to the questions asked by the reviewers. If you have any additional questions, please do not hesitate to contact me.
As you requested, I am prepared to obtain an ISRCTN.

Kind regards,

Pieter ter Borg

Reviewer: Keith Lindor

A few things that should be discussed in the manuscript include:
1) How was the agent picked (known to be a sedating antidepressant)?

Fluvoxamine was chosen because of several reasons:
- There was extensive local experience with this drug
- Fluvoxamine is one of the oldest SSRI's, and therefore the possibility of unexpected toxicity was low
- In contrast to other SSRI's, there is a documented correlation between serum concentration and effect in patients with depression, which could be used in future studies using this particular drug.

This has been further clarified in the revised manuscript.

2) How was the dose arrived at?

The dose chosen in the present study is a widely used dose in the treatment of depression. Since previous data on the effects on fatigue were lacking, this dose was used in the present study.

This has been further clarified in the revised manuscript.

3) Was there any difference in response between men and women.

There were no significant differences in response between men and women. This has been stated in the revised manuscript.

Reviewer: Martin Prince

1. The main weakness of the trial is that it is severely underpowered. The power calculation is based upon very optimistic estimates of benefit with active drug and similarly optimistic estimates of difference between placebo and active arms. This point should be made more strongly in the discussion- the authors state that a small beneficial effect may have been missed. In a study of this size a substantial beneficial effect may have been missed although it would unlikely from the data presented. The methods for performing the power calculation are not stated, I presume that a non-parametric method has been used. It is important to state this, as it is necessary for the reader to see that a non-parametric method has been used in the power calculation as these statistics were then used in the analysis.
The manuscript has been revised to more strongly state that the effect estimates were rather optimistic, and that this may have resulted in not finding a smaller effect than intended in the power calculation. The power calculation was performed using the sampsi command in the statistical software package Stata 5. We intended to perform the analysis using Student’s t-test, however given the smaller than planned sample size and the relatively large number of patients who discontinued treatment, we believed that the distribution of data did not allow such analysis. However, when despite this data distribution an analysis using the Student’s t-test was performed, this did not result in any different study outcomes.

The manuscript has been revised to clearly state the reason for the non-parametric analysis, although originally an analysis using parametric tests was planned. Altogether, we believe that using non-parametric tests was the only reliable method of analyzing the current data set, since Student’s t-test can only be used if the data set is sufficiently normally distributed, although the results and conclusions would not have been different if Student’s t-test would have been used.

2. The authors state that subgroup analysis was performed analysing the data for patients with PBC and PSC separately. As there are no space constraints in this electronic journal, this data should be published. An important role for this paper is to inform future systematic reviews and meta analyses. These reviews are usually specific to individual diagnoses.

We fully agree with the reviewer that data on PBC and PSC should be presented separately. The manuscript has been revised and tables including data on patients with PBC and PSC have been added.

1. Figure 2 adds little additional data not contained in table 3 and may be removed. The text states that figure 3 contains both intention to treat and per protocol analysis. Only one set of data appears to be actually represented.

Although figure 2 adds little additional data, we would appreciate this figure to be included in the manuscript since it clarifies the lack of effect of fluvoxamine. However, if the editor prefers so, this figure can be deleted. The text incorrectly states that figure 2 contains per protocol data. This has been changed.