PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for a multi-institutional, randomised, double-blinded, placebo-controlled phase Ⅲ trial investigating additive efficacy of duloxetine for neuropathic cancer pain refractory to opioids and gabapentinoids: the DIRECT study
AUTHORS	Matsuoka, Hiromichi; Ishiki, Hiroto; Iwase, Satoru; Koyama, Atsuko; Kawaguchi, Takashi; Kizawa, Yoshiyuki; Morita, Tatsuya; Matsuda, Yoshinobu; Miyaji, Tempei; Ariyoshi, Keisuke; Yamaguchi, Takuhiro

VERSION 1 - REVIEW

REVIEWER	Pickering, Gisèle CPC/CIC Inserm 1405 University Hospital Clermont-Fd France
REVIEW RETURNED	11-May-2017

GENERAL COMMENTS	Interesting paper, but duloxetine adverse events and inefficacy in pain trials should be more precisely reported.

REVIEWER	Jongen, Joost Erasmus MC, Rotterdam, Netherlands
REVIEW RETURNED	14-May-2017

GENERAL COMMENTS	This is a well written and sound research protocol. I have only two minor comments: 1) The authors propose a one-sided t-test, probably to increase statistical power. However, this means that they'll miss the chance that placebo is better than duloxetine. 2) Sample size calculation is based on a difference in NRS score of one point and a SD of 1.5 point. Could they add a reference on which this SD is based? Furthermore, even if they would find a statistically significant difference, one NRS point difference is hardly clinically significant

VERSION 1 – AUTHOR RESPONSE

RESPONSE TO REVIEWER 1:
We wish to express our appreciation to Dr. Pickering G for insightful comments, which have helped us significantly improve the paper.
Comment 1:
Interesting paper, but duloxetine adverse events and inefficacy in pain trials should be more precisely reported.

Response:
We thank the reviewer for this insightful comment. In accordance with the reviewer’s comment, we

added duloxetine adverse events and inefficacy in pain trials in the introduction section. (See from page 6 line 22 to page 7 line 2)

RESPONSES TO REVIEWER 2:

We wish to express our appreciation to Dr. JLM Jongen for insightful comments, which have helped us significantly improve the paper.

Comment :

This is a well written and sound research protocol. I have only two minor comments.

Comment 1:

The authors propose a one-sided t-test, probably to increase statistical power. However, this means that they'll miss the chance that placebo is better than duloxetine.

Response:

We thank the reviewer for this insightful comment. As you've pointed out, we will miss the chance whether placebo is better than duloxetine or not, however, our primary interest is to clarify whether duloxetine is more effective than placebo and we adopted a one-sided test from the practical sample size perspective. (See page 15 line 11 to 12)

Comment 2 :

Sample size calculation is based on a difference in NRS score of one point and a SD of 1.5 point. Could they add a reference on which this SD is based? Furthermore, even if they would find a statistically significant difference, one NRS point difference is hardly clinically significant

Response:

We strongly appreciate the reviewer's comment on this point. In accordance with the reviewer's comment, we added reference on which this SD was acquired (Matsuoka et al. 2012 Anticancer Research). As there was no data of the optimal minimal clinically important differences of duloxetine in cancer neuropathic pain at the planning stage of the study, we quoted the meta-analysis which showed one NRS point difference compared to placebo in neuropathic non-cancer pain using duloxetine (Quilici et al. 2009 BMC Neurology) for a clinical significant difference. Recently, Hui et al. reported that the optimal cutoff was ≥ one NRS point for improvement in cancer pain (Hui et al. 2015 Cancer). As the estimation of clinical significant difference matched with the recent report, we did not recalculate sample size in the middle of study. We cited Hui's study in the manuscript. (See page 15 line 4 to 8).

As we agree with the reviewer's comments that 33% decrease or 50% decrease can be more interpretable end-points, we will add these ad-hoc analyses. (See page 14 line 10 to 11)