**Reviewer’s report**

**Title:** Effect of lacosamide in peripheral neuropathic pain: study protocol for a randomized, placebo-controlled, phenotype-stratified trial

**Version:** 0  **Date:** 21 Apr 2019

**Reviewer:** John Markman

**Reviewer's report:**

This is an exceptionally well-conceived and important study. The manuscript is well written. The proposed trial represents an attempt to replicate the methodology of the landmark Demant study. This is critically important because the Demant study was the first successful example of pain phenotype stratification.

It is also important to characterize further the analgesic efficacy of lacosamide for chronic neuropathic pain conditions given the conflicting clinical trial results (using BOCF assumptions) from the neuropathy studies.

Additional detail is needed as to how the investigators will "verify" neuropathic pain--is there an independent panel that will review the screened patients from the referring centers? More explicit detail as to how predominantly-nociceptive syndromes will be excluded is also needed. For example, it is not clear if subjects with chronic lumbar radicular pain syndromes or complex regional pain syndrome will be included in the proposed study population. Clarification as to how syndromes, such as those in which active peripheral inflammation may be sensitizing peripheral nociceptors, will be handled and the relevance of ongoing peripheral inflammation to phenotypic differentiation is needed.

The assessment of expectation and blinding are critical elements of the design. Inclusion of these elements strengthens the proposed design.

The authors should clarify the use of the term "peripheral" neuropathic pain as used in the title and elsewhere in the manuscript. My understanding is that they propose to exclude central neuropathic etiologies (e.g. post stroke pain, Spinal cord injury related pain) but some readers will be confused by the mechanistic investigation of descending modulation-- a form of modulation that localizes to the central nervous system.
The relatively low anticipated drop out rate of 1:6 for a lacosamide-naive population seems overly optimistic and, as the authors concede, there is a risk that the study's assay sensitivity from such a small sample will be too low to detect a true treatment difference using a drug that did not consistently show significant analgesic benefit in far larger pivotal studies.

**Level of interest**
Please indicate how interesting you found the manuscript:

An article of importance in its field

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Quality of figures**
All images and figures within the manuscript should be genuine i.e. without evidence of manipulation. No specific feature within an image may be enhanced, obscured, moved, removed, or introduced. If you have concerns about the veracity of the figures you should choose the first option below.

**Statistical review**
Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?
4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

1. No
2. No
3. No
4. No
5. No
6. No

"I declare that I have no competing interests"

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal

Were you mentored through this peer review?

No