Reviewer’s report

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

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Reviewer: Igor Karp

Reviewer's report:

The study addresses the effect of lacosamide therapy on peripheral neuropathic pain, and its main objective seems to be about the role of the irritable nociceptor phenotype as a potential modifier of the efficacy of the lacosamide therapy. While the topic is of medical importance, and the study has several merits, I am not fully convinced that pursuit of the stratification topic at the current stage of knowledge - namely, at a point when the very existence of effect of lacosamide therapy on pain is still in question - is truly justifiable. Further, there are several issues that, in my opinion, require clarification and/or reconsideration. I present these issues in my comments below.

1) The rationale for referring to the trial as being "phase 2" is unclear.

2) The authors intend to address the potential role of the irritable-nociceptor phenotype as a predictive biomarker of "an increased response to lacosamide" by restricting the analysis to patients on the lacosamide treatment only. However, response to lacosamide cannot be examined without data on patients on the placebo treatment. Thus, it is unclear why the authors do not intend to address this objective by testing for the effect-modifying role of the phenotype status (by using data from both the lacosamide and placebo treatment groups.) On p.15, the authors state that "It would require an unrealistic high number of patients to power the study to show a difference in the drug-placebo differential between the two groups of patients" but I do not think this is a justifiable reason for not addressing the topic of phenotype-differential effect of lacosamide in an appropriate manner.

3) On the other hand, if comparing the outcomes between patients with and without the irritable nociceptor was justified, it would still be unclear why there would be a need for this to be done in a randomized trial, because the irritable-nociceptor phenotype status is not randomized.

4) The rationale for addressing the supportive objective, involving contrasting the lacosamide treatment versus placebo, in each of the phenotype-status subgroups separately is unclear, especially as the effect of the lacosamide treatment in humans remains to be established (in
patients with either phenotype). It appears that the hypotheses of the existence of effect of the treatment in patients with and without the irritable nociceptor are correlated, so testing them separately from each other does not seem justifiable. Insofar as the authors hypothesize that the magnitude of the effect (if it indeed exists) of the lacosamide treatment is greater in patients with the irritable nociceptor than in patients without it, would it not be more efficient (and ethical) to carry out an RCT on efficacy of the lacosamide treatment in patients with the irritable nociceptor only?

5) The sample size calculations for the "supportive objective" are not fully clear. Why is the treatment:placebo allocation ratio of 2:1 adopted? And were these calculations based on the 80% power and 5% alpha level?

6) The authors state that "statistical analysis of the primary outcome will be performed by t-test", but the justification for the use of t-test is not obvious, especially given the (relatively) small sample size and no information on the distribution of the outcome variable. Further, the authors state that "Since we do not expect differences in baseline between the two phenotypes [5] or a major impact of baseline pain intensity on the outcome, we do not plan to include these as covariates in the analyses", but the reason for not expecting "differences in baseline" is not clear (but in any case, from the precision perspective, it may be beneficial to adjust for prognostically-relevant characteristics in analysis even if they are perfectly balanced between the study groups.)

7) According to the Study Drugs section, "allowed escape medicine is paracetamol, up to 4,000 mg daily", but under which circumstances exactly its use is "allowed" is not specified. Further, it is unclear how/if the information on the use of paracetamol will be used in statistical analysis (aside from it serving as a "secondary outcome"). Further, it is unclear how exactly what scale will be adopted for representation of the secondary outcome of "Use of escape medication (paracetamol) during the treatment period": will it be binary, and if yes will the categories be "any use versus none"?

8) The authors state that "Non-dichotomous secondary outcomes will be performed by t-test or Mann-Whitney U test, where applicable" (p.13), but it is unclear which of the two secondary outcomes (pain relief and use of escape medication) will involve Mann-Whitney U test.

9) The justification for the "tertiary" outcomes #3 ("Mean values of the daily pain ratings for the other 11 weeks") and #4 ("Presence of 30% and 50% reduction of pain (from pain diary, baseline vs. last week of treatment)") is unclear, given their similarity to the primary outcome. The same issue applies to the "tertiary" outcome #6 ("The intensity of pain symptoms assessed by the Neuropathic Pain Symptom Inventory").

10) The trial will be "multicenter" but it is unclear whether the multicenter nature of the trial will be taken into account in data analysis. Furthermore, won't randomization be carried out in the center-based strata?
11) The authors state that "The aim is to enroll 108 patients with peripheral neuropathic pain who will be randomized to a 12-week treatment with lacosamide or placebo up to 400 mg/day in a 2:1 ratio", but this is not really the aim of the study but (part of its) methodology.

12) The meaning of some of the exclusion criteria is unclear - specifically, "Woman of childbearing potential" and "Patients inappropriate for placebo treatment". I suggest that the authors develop and provide specific, operational definitions of these criteria.

13) The rationale for distinguishing four types of outcome (primary, secondary, tertiary, and "other") is not quite clear. Further, the authors refer to an "explorative outcome" (pp.13-14), but it is unclear what this means.

14) In the abstract, the authors state that "Secondary and tertiary outcomes include analyses of the intention-to-treat population, the Patient Global Impression of Change (PGIC), pain relief, the number needed to treat (NNT), …" but analyses are not outcomes, and nor are "the intention-to-treat population" and "the number needed to treat".

15) The authors state that ""Personalized" or "precision" pain medicine is an algorithm that predicts the efficacy of individualized treatment on the basis of measurable individual phenotypic or genotypic patient characteristics (biomarkers)" but medicine is not an algorithm, so this definition is incorrect. Furthermore, taking a single phenotypic characteristic into account when assessing a treatment's efficacy is not tantamount to developing a fully-individualized algorithm.

16) The authors state (Abstract, and p.4 of the manuscript) that there were "very large placebo responses" in previous studies, but an (observed) change in the outcome is not necessarily a "placebo response", so I suggest that this phrase be modified.

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