Author’s response to reviews

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

Authors:

Malin Carmland (malin.carmland@clin.au.dk)
Melissa Kreutzfeldt (melissa.sos.kreutzfeldt@rsyd.dk)
Jakob Holbech (jakob.holbech@rsyd.dk)
Niels Andersen (trolle@ph.au.dk)
Troels Jensen (tsjensen@clin.au.dk)
Flemming Bach (flemming.bach@rm.dk)
Søren Sindrup (soeren.sindrup@rsyd.dk)
Nanna Finnerup (finnerup@clin.au.dk)

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Author’s response to reviews:

Dear Dr. Dietrich Haubenberger

Thank you very much for your correspondence regarding our manuscript “Effect of lacosamide in peripheral neuropathic pain: study protocol for a randomized, placebo-controlled, phenotype-stratified trial” to be considered for publication in “Trial” as a trial protocol.

We appreciate very much the reviewers’ thorough and helpful comments. We have responded to the comments and marked changes in the revised manuscript with red. We hope that the manuscript is acceptable with the revision.

Yours sincerely,
Nanna Finnerup
Response to reviewers:

Reviewer #1:

This protocol is written according to the SPIRIT guidance. It is a RCT, however the main objective and analysis is a non-randomised comparison of the two sub-groups. If this is the case should this study be described as a RCT? Perhaps the main comparison should be that comparing lacosamide versus placebo. Secondary analyses could then include an a priori sub-group analysis and the per protocol analysis comparing the two sub-groups? Please justify.

Answer: The reviewer raises a good point. However, we believe that the randomization and blinding is needed to justify that any difference is not explained by a difference in the response to placebo. So while we agree that the primary objective is not based on randomization, randomization and blinding is crucial for the supportive objective and the conclusions that can be drawn from the study.

Since this manuscript was submitted 5 months ago, the study has started, and we cannot make changes. Also our main purpose of the study is to examine if lacosamide is more effective in a specific pain phenotype than the other. The focus is the phenotyping and understanding of mechanisms of neuropathic pain more than lacosamide. Previous studies have examined lacosamide versus placebo with mixed results and suggested that only some patients respond. Our hypothesis is that lacosamide is effective in one and not the other phenotype and thus the overall effect is not relevant to this hypothesis and we want to power the study to our main hypothesis and have a sufficient number of patients with each phenotype.

Sample size: What is the justification for the minimal clinically important difference of 1.25? What is the justification for a SD of 1.6? As the main analysis planned is of a non-randomised comparison why are you so confident that there will be no baseline imbalance?

Answer: The SD of 1.6 is based on the previous study with another sodium channel blocker in the same population (ref 5: Demant et al.). We judge that a difference of 1.25 NRS points is
clinical relevant and that it is reasonable that it is lower that the relevant drug-placebo difference. We base the expectation on no baseline imbalance on our previous study in the same population with the same phenotypes (ref 5: Demant et al.), where there were no difference in baseline pain intensity (median (range) was 6 (4-9) in both groups).

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 Grammar: P8 line 47 male partner has had a vasectomy and is their sole partner.

Answer: This is changed

P14 line 30-33 meaning is unclear. Please re-write after addressing my first comment above.

Answer: The PP analysis is the primary and this the ITT is the secondary. If there is a phenotype difference, the group is heterogeneous, and it is not justified to calculate the effect of lacosamide in the combined population. The primary aim of our study is not to repeat previous studies and examine the effect in the whole population but we want to understand the mixed results from previous studies and test if lacosamide is more effective in one that the other phenotype. Therefore, the effect in the whole population is exploratory and only relevant if there is no phenotype difference.

Reviewer #2:

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?

Answer: The diagnosis will always be confirmed on site by the investigators from symptomatology, clinical assessment and earlier paraclinical investigations (e.g neurophysiology, radiology). There will not be a panel, but the primary investigators (MEC and MK), who are both MDs and neurology registrars, will perform the pain history and neurological
examination and if they are in doubt, they will confer the patients with the senior investigators and additional tests may be requested. Only patients with a confirmed probable or definite neuropathic pain will be included. On page 6, we have added: “Before inclusion, the diagnosis of probable or confirmed neuropathic pain will be confirmed by the investigator by a detailed pain history, focused clinical and neurological examination, and evaluation of previous paraclinical examinations. “

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.

Answer: We thank the reviewer for this very relevant question. Radicular pain syndromes will be included if there is clear neuropathic pain fulfilling the grading criteria (inclusion criteria 2) and if there are not other causes of pain in the same area that cannot be distinguished from neuropathic pain (exclusion criteria 1), this could be cases where there is pain in the leg in an area with sensory loss and a MRI confirming a relevant nerve root lesion/compression. CRPS is not included and we also do not include trigeminal neuralgia. On page 7-8 we have added: “Patients with peripheral neuropathic pain following peripheral nerve injury (including amputation), painful polyneuropathy, postherpetic neuralgia, and painful radiculopathy will be included. Patients with central neuropathic pain, e.g. pain due to stroke, multiple sclerosis and spinal cord injury will not be included. Patients with trigeminal neuralgia, which is sometimes partly a central neuropathic pain and has different treatment recommendations, will not also be included. Patients with CRPS type I or II will not be included.”

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

Thank you

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.
Answer: In response to the reviewer’s comments above, we have now specified that we do not include central neuropathic pain.

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.

Answer: Yes, we are aware of this risk and ideally a larger trial would always be preferred. However, in the recent trial by de Greef et al. only 1/12 patients dropped out during the lacosamide treatment due to reasons not related to trial medication and we have adapted an even slower titration. The de Greef trial is now published and we have updated ref 14.

Reviewer #3:

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.

Answer: We appreciate the point about the effect of lacosamide not being proven. However, if the effect of lacosamide depends on the sensory phenotype, further non-stratified studies will not be able to prove an effect. We believe that there is reasonable evidence from previous clinical trials that the effect of sodium channel blockers depend on the underlying mechanisms of the pain and the best predictor may be sensory phenotyping. Studies in lacosamide do suggest that some patients respond as the trials are not completely negative.

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

Answer: This was a specific request from the Danish Medicines Agency. They considered it a phase 2 trial since lacosamid isn’t approved in Denmark for the treatment of neuropathic pain (new indication).
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.

Asnwer: We agree that ideally we would compare the drug-placebo difference between the two phenotypes and compare the effect of lacosamide. If we only compare the drug-placebo difference between the two phenotypes, any difference between groups can occur just because of a difference between the placebo response. This was the case e.g. in Campbell et al. Pain 2012;153:1815-23, where the larger drug-placebo difference in the capsaicin responders was explained by a lower placebo response, while the effect to the drug was identical. Thus we believe we need to show both that the effect of lacosamide is different and that the effect of lacosamide is better than placebo and ideally that the drug-placebo is different. Powering the study to be able to show that the drug-placebo difference is different is not possible with the available funding and numbers of patients that can be recruited in Denmark. However, we believe that the present design is also feasible to reasonable address the hypothesis.

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.

Answer: As responded to reviewer 1, we believe that the randomization and blinding is needed to justify that any difference is not explained by a difference in the response to placebo. While we agree that the primary objective is not based on randomization, randomization and blinding is crucial for the supportive objective and the conclusions that can be drawn from the study.

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?

Answer: We thank the reviewer for the comment. Our aim is to test if the effect of lacosamide is better in the irritable nociceptor phenotype. If we only tested the effect of lacosamide in the irritable nociceptor phenotype only, we would not know if it is also effective in the non-nociceptor phenotype (and thus depriving a certain group of patients a treatment that might be effective) and more importantly, if the effect depends on the phenotype. Our interest is to understand if phenotyping patients based on their sensory profile is useful for differentiating underlying mechanisms/predicting the response to a sodium channel blocker rather than testing the clinical relevant effect of lacosamide.

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?

Answer: The ratio 2:1 is adopted because we expect the difference between lacosamide and placebo is larger than the difference between the effect to lacosamide in the two phenotypes. Thus we calculate the sample size based on a minimally relevant treatment vs placebo effect of 1.5 NRS. Yes, the calculations were based on the 80% and 5%. On page 13, we have added: “and a 80% power and a 5% risk of type I error,”

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.)

Answer: The reviewer raises a highly relevant point, which we have discussed. We base the expectation on no baseline imbalance on previous study in the same population with the same phenotypes (ref 5: Demant et al.), where there were no difference in baseline pain intensity
(median (range) was 6 (4-9) in both groups). When we looked at the Demant study, we saw no impact on the results whether or not we included baseline data. Therefore, we decided not to include baseline data. We agree that the reviewer is correct that adjusting for baseline pain intensity could be an advantage, but we did not include that in the prespecified statistical plan in the now approved protocol. We acknowledge that more data are needed to make such decisions and in the discussion, we have added: “It would have been advantageous to have done a thorough analysis of previous studies to access whether the best statistical plan should be a regression analysis including e.g. baseline pain intensity, center, and escape medication.”

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"?

Answer: Paracetamol is allowed during all study periods for all types of pain (this is now added on page 7). We do not plan to include paracetamol in the statistical analysis. Paracetamol is often used to treat other types of pain during the trial and there is no evidence for an effect in neuropathic pain and we do not expect that it will have an impact on the primary outcome, therefore, as is standard in trials of neuropathic pain, we examine the use of paracetamol in the two periods separate from the main results. We will calculate and compare the average number of tablets taking during the study periods and number of patients taking any dose. This is added on page 10.

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.

Answer: Thank you for pointing this out, this was meant to cover both secondary and tertiary outcomes. The secondary outcomes will be assessed using Mann-Whitney U test. This is now added on page 14.

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").

Answer: Mean value for all weeks are included as tertiary outcome to provide information for the weeks prior to the last week of treatment. 30% and 50% pain reduction are included as these outcome are often used in systematic reviews and provide additional data to reduction in average pain intensity since that is normally U-shaped (see e.g. Moore et al. Numbers-needed-to-treat analyses, Pain 2010; 151:592-7). Evaluating pain symptoms are included as a tertiary outcomes as several studies suggest that symptoms can be used as profiling and sodium channel blockers may be more effective for certain symptoms (eg. Paroxysmal pain) than others. This study could provide explorative results that could be tested in further trials (see e.g. Freeman et al. Sensory profiles ... Pain 2014;1555:367-76; Attal et al. Neuropathic pain: are there distinct subtypes. Pain 2008;138:343-53). These outcomes are recommended for chronic pain treatment trials (Edwards et al. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommenations. Pain;2016;157:1851-71).

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?

Answer: Randomisation will be carried out centrally (for both participating centres) at the pharmacy and not center-based and center is not taken into account in the analyses (now added on page 14). We have many years of collaboration between the centers and include detailed descriptions of SOP and training sessions and the investigators include some patients together to standardize every step as much as possible. Stratification based on center has implications for running the study as this will increase the risk that not all produced medication will be used because of limited shelf life. However, we do agree that it is a judgement and that we need more data from previous trials to justify this. This limitation is included in the discussion on page 16.

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.

Answer: Thank you, we have changed “aim” to “plan”.

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.
Answer: We thank the reviewer for these comments. The manuscript is shortened compared to the protocol that is submitted and approved by the ethical committee and national competent authority due to a word limit. We have added a bit more of the text related to exclusion criteria 6: “Acceptable effective contraception is defined in the Clinical Trials Facilitation Group (CTFG) http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf). “Women of childbearing potential” is phrased as it is in our protocol and standard use, also in the CTFG guideline. We can of course expand but not completely sure about the suggestion from the reviewer. The term “Patients inappropriate for placebo treatment” is as it is described in the approved protocol. This is considered according to judgment by the investigator.

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.

Answer: We have many outcomes. The separation into secondary and tertiary outcomes is meant to grade/hierarchically order these. Tertiary outcome are to be considered more explorative compared to primary and secondary outcomes. By other outcomes we meant to separate “positive effect” outcomes (primary, secondary, and tertiary) from side effects and other assessment such as assessment of blinding and patient expectation. This is as described in the approved protocol.

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”.

Answer: Thank you, we have changed to: “Secondary and tertiary outcomes include the Patient Global Impression of Change (PGIC), pain relief, presence of 30%- and 50% pain reduction, sleep disturbance, depression, and anxiety.”

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.
Answer: We appreciate this comment. We have changed the sentence on page 3 to: “There is an increasing interest in identifying predictive biomarkers associated with a specific tractable pain mechanism linked to a drug with a known mechanism of action [3, 4].”

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.

Answer: We agree with the reviewer that sometimes, placebo response is mixed with placebo effect and that the change during a placebo treatment is not only due to a placebo effect. However, it is generally accepted that the placebo response is defined as “as the change in pain observed after administration of the placebo treatment”. The placebo effect, however, is measured as the difference in pain across an untreated and a placebo-treated group/condition, thereby separating changes in the placebo group from spontaneous fluctuations in pain, regression to the mean, and other confounding factors (see eg Vase and Wartolowska, Br J Anaesth 2019). Thus the term placebo response is meant to cover all changes during the placebo treatment and not only the placebo effect. This is clarified on page 4 and we hope this answers the reviewers comment.

Additional comment:

During the review process a revised protocol has been approved (version 2.1, this is noted) and on page 13 we have now mentioned that we will take blood samples for future genetic analyses.