PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Phase III, international, multi-centre, double-blind, dose increment, parallel-arm, randomised controlled trial of duloxetine versus pregabalin for opioid-unresponsive neuropathic cancer pain: A JORTC-PAL16 Trial Protocol
AUTHORS	Matsuoka, Hiromichi; Clark, Katherine; Fazekas, Belinda; Oyamada, Shunsuke; Brown, Linda; Ishiki, Hiroto; Matsuda, Yoshinobu; Hasuo, Hideaki; Ariyoshi, Keisuke; Lee, Jessica; Le, Brian; Allcroft, Peter; Kochovska, Slavica; Fujiwara, Noriko; Miyaji, Tempei; Lovell, Melanie; Agar, Meera; Yamaguchi, Takuhiro; Satomi, Eriko; Iwase, Satoru; Phillips, Jane; Koyama, Atsuko; Currow, David

VERSION 1 – REVIEW

REVIEWER	Igor Dykukha Almirall Hermal GmbH, Medical Affairs
REVIEW RETURNED	31-Mar-2021

GENERAL COMMENTS	General considerations The study is aimed to address an important unmet need and is going to provide a valuable information about efficacy, safety and tolerability of typical representatives of two major classes of the second-line treatment for the opioid-resistant cancer neuropathic pain - duloxetine comparing to pregabalin. I fully support the author's choice of the prospective, parallel-arm, double-blind RCT study design to address the scientific question. Abstract 1. Introduction: The exclusion of the patients with chemotherapy-induced neuropathic pain (CINP) is important for understanding the study design/results, because, for instance, the efficacy of duloxetine was proved in RCTs so far particularly in CINP. 2. Introduction: "both classes of drugs …" (plural) 3. Introduction: It is not possible to measure "net effect" in this study, because that would require a comparison to placebo, e.g. as a third arm. Please re-phrase. 4. Methods (suggestion): "…(LANSS) of ≥12 despite of an adequate trial of regular opioid medication…."? 5. Methods: Please add a sentence that dose escalation is until day 14 and that from day 14 till 21 it is dose de-escalation period to avoid withdrawal effects. 6. Methods: "…mean difference in BPI item 3" in order to clarify the statistical parameter – it is a mean. 7. Methods: "…patients will be enrolled between…" or "…patients will be recruited into study between…", not "examined". Strengths and limitation of this study 1. Bullet-point 1. Please clarify that it were patients with chronic neuropathic cancer pain (NCP), not induced by the chemotherapy.

	2. Bullet-point 2. Instead of “collaborative” nature of study, I would stress the high-quality DB-RCT multi-center study design. Both compared interventions are not necessarily harmful, I strongly recommend saying “safety and tolerability” instead of “harm” (see also my comment below). 3. Bullet-point 3. In my opinion, exclusion of CINP is not necessarily makes comparison more accurate, because for instance duloxetine has a proved effect in CINP in a 1 DB crossover RCT with 231 patients (Smith et al. JAMA 2013), while for pregabalin positive effect in CINP was reported only in one observational study with 23 patients (Saif et al. Anti-cancer Res 2010) and in a case series (Atreya, Indian Journal of Palliative Care 2016). I think that clinical focus on CNP not related to chemotherapy might be further rationale to exclude CINP patients. Main manuscript 1. Introduction: I am afraid, a single RCT cannot answer a question about first-line / second-line recommendation. Apart of evidence, guidelines consider also other issues like, for instance, existing standard of care, other available treatments (including non-pharmacological) or regulatory status (label). Please kindly re-phrase the statement “The results of this RCT will clarify the first-line standard treatment for NCP”, e.g. “study may help to clarify”. 2. Introduction: Please check and shortly summarise recent treatment guidelines, for instance https://www.awmf.org/fileadmin/user_upload/Leitlinien/128_D_Ges_fuer_Palliativmedizin/128-001OLkengl_S3_Palliative_care_2021-03.pdf (Germany). 3. Methods: A sub-study is planned. In SPIRIT Checklist, item 26b should be probably marked with “Yes" instead of “N/A”. 4. Box 1, inclusion criteria: You may consider clarification of the first inclusion criterion, e.g. “…who are in investigator’s opinion are feasible for the therapy with duloxetine and/or pregabalin”. 5. Box 1, inclusion criteria: I believe, the second inclusion criterion can be combined with the third one, i.e. “Insufficient response to an adequate opioid medication (….) defined as pain related to cancer with a worst pain score of ≥4 or greater on BPI item 3 (worst pain intensity) score in the past 24 hours”. 6. Box 1, inclusion criteria: It is “KPS/AKPS” in the time and event schedule (Table 1). Please ensure consistency throughout the text. 7. Box 1, inclusion criteria: The last inclusion criterion allowing continuation of the other adjuvant analgesics including antidepressants, anticonvulsants, NMDA antagonists might need further clarification (e.g. in discussion section), because of 1) risk of drug-drug interactions (how it is managed in the study), 2) masking/confounding of the true effect of the study intervention. 8. Box 1, exclusion criteria: Do you mean “women with childbearing potential who do not agree to use an adequate contraception”? If needed, please re-phrase “may possibly be pregnant”. 9. Recruitment: Please clarify whether or not an additional consent for the sub-study required. 10. Randomisation: I understand the idea to stratify the randomisation for as many confounders as possible, but still it is not quite clear, whether all of them are crucial for the robustness of the primary endpoint. Some confounders looks exploratory (a hypothetic assumption). The interactions could be explored post-hoc as a sensitivity (sub-group) analysis. On the other hand: 1) impact on statistical power (was stratification considered during calculation of the sample size?); 2) more complicated statistical analysis with adjustments to all confounders (strata).

	11. Randomisation: If applicable, please mention per site recruitment caps (max, min number of patients). 12. Table 1: I suggest renaming the table to “Times and Events Schedule”, according to commonly used terminology. 13. Table 1: Consider using commonly used terms, i.e. “End of Sudy” (“EoS”) instead of “Exit”. I could not find in the text clarification for the abbreviation “WD” (is it “Early Termination”, “ET”?), please add a footnote. 14. Table 1: It is very common to design last visit in the study (End of Study Visit, EoS), which is D21, in the same way as “Early Termination” (ET) visit, i.e. “EoS/ET”. 15. Table 1: The assessments in down-titration period “D15-20” might need clarification (e.g. a footnote): assessment of AEs (Section “Clinician assessed”) is do-able only in case of in-patient cohort. 16. Table 1: “Sub-study (if consented)” (singular). Please keep in mind that Informed Consent procedure for the sub-study should be described in the appropriate section of the paper and reflected in the SPIRIT Checklist. 17. Page 17, line 42: According to ICH GCP it should be signed ICF (original). Please kindly correct wording to “a signed copy of”. 18. Page 17, line 56: Editorial correction: “the electronic data capture system VIEDOC 4”. 19. Harms: I strongly advise against using word “harm(s)” throughout the text, because in my opinion it is misleading. The medical treatment interventions are not necessarily harmful. Besides, commonly used terms in pharmacovigilance are ”safety” and “tolerability”. I recommend re-naming the section to “Safety assessments” and replace word “harm” everywhere in text. 20. Harms: Please note that there is already an updated version of CTCAE available – Ver. 5 (2017; https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Please consider using it or explicitly explain why you prefer to use the old one. 21. Page 18, line 41: do you mean “by health care providers”? 22. Measurement tools: Please consider using the wording “assessment tools” instead of “measurement tools”. 23. Measurement tools: The section about KPS and AKPS is missing. I presume, it is “Karnofsky Performance Status” and “Australia-modified Karnofsky Perfomance Status”? The disclosure of the abbreviation is missing in manuscript, please add it. Also, please explain in the section, how the two somewhat different scoring approaches will be analysed / matched within the common database. 24. CTCAE/PRO-CTCAE: Please see my comment above concerning availability of Version 5. 25. Interventions: I believe, this part of the study design might require the most attention, because 1) the starting dosages (30mg duloxetine or 50mg pregabalin daily) are lower than recommended in the approved labels (60mg and 150mg respectively; https://www.ema.europa.eu/en/documents/product-information/cymbalta-epar-product-information_en.pdf, https://www.ema.europa.eu/en/documents/product-information/lyrica-epar-product-information_en.pdf); 2) the study allows participation of patients with CL-Cr between 30 and 60 mL/min, so pregabalin dosage might need to be adjusted in some patients; 3) the primary endpoint assesses the effect a few days after end of the dose titration (which is performed based mostly on safety and tolerability situation, rather than efficacy). You might need to elaborate about chosen titration regime and treatment duration, as well as provide explanation to deviation from SmPC text, if any; 4) the deviation from the recommended posology in SmPC might influence external

	validity of the study. It was decided to use 1/2 of the recommended starting dose in case of duloxetine and 1/3 in case of pregabalin, which could be probably not so big deal should the study treatment would be longer. However, in case of 14 days treatment such "imbalanced" up-titration over 8 days may confound primary endpoint. 26. Page 23, line 34: See above my comment concerning "net effect". I suggest avoiding using of that term in the context. 27. Page 24, line 13: Editorial correction – "the most appropriate pain medication according to the local standard of care". Using of the wording "open label medication" is in my opinion false in the context. 28. Co-treatments: I suggest using a commonly used term "Concomitant therapy" instead of "Co-treatments". 29. Co-treatments: See above my comment regarding using of other adjuvant analgetics throughout the study. Without explanation/rationale this issue makes an impression of a strong confounding influencing both efficacy and safety outcomes. Further, it should be clear from the manuscript that there is no jeopardy to patients due to drug-drug interactions. 30. Primary endpoint: I trust is a "mean difference between", not "comparison". 31. Secondary endpoints: Karnofsky Performance Status will be measured repeatedly. May be it makes sense to analyse the data explorative and add an exploratory secondary endpoint. 32. Secondary endpoints: Consider adding end-point for the Global Impression of Change. 33. Statistical considerations: Handling of the missing data is crucial for consistency and robustness of the study results. Please describe imputation methodology for the missing data and describe, whether a sensitivity analyses for the primary endpoint (e.g. NRI, As Observed, LOCF) is planned. 34. Statistical considerations, statistical hypothesis: Stratified randomisation means adjustment for confounders, which statistically calculated as "LS mean" (less-squire mean). I presume, you are going to use Cochrane-Mantel-Haenzel (CMH) adjustment? Please expand on that a bit in the manuscript. 35. Statistical considerations, sample size: In situation of uncertainty about the comparative effect sizes, the superiority design might be risky, and perhaps it might have been advisable to go for the non-inferiority primary endpoint and perform superiority tests as secondary endpoints. In latter case, I would suggest prioritisation of the main secondary endpoints using the Holm's adjustment procedure for multiplicity. 36. Statistical considerations, sample size: Please mention, in case sample size was adjusted also for the stratified randomisation. 37. Ethical issues: I recommend to explicitly mention that ICH GCP requirements are considered in the study design and conduct. Based on the information in the manuscript it is very likely that the study has been designed in accordance to the ICH GCP standards. 38. Discussion: Please consider also systematic review van den Beuken-van Everdingen et al. Pain Practice 2017. 39. Discussion: There are uncertainties related to the effect size of pain reduction of the compared interventions in chronic, not chemotherapy-induced, neuropathic cancer pain, which might have been addressed by adding a placebo arm (e.g. duloxetine : pregabalin : placebo = 2:2:1). Please kindly add explanation why placebo arm was not deemed necessary/possible, though the effect of the both active interventions in this particular population has not been yet well established. Technical issues? Ethical concerns? Other?

	40. Discussion: I am not sure, whether exclusion of some neuropathic conditions (chemotherapy-induced or central NCP) could significantly reduce population heterogeneity, because of methodological challenges in the differential diagnostics, but I appreciate the author's transparent position in the discussion section. 41. Discussion: The authors mention subgroup analyses. Perhaps that could be shortly described in the statistic part. Anyway, you answered "Yes" to the question 20b of the SPIRIT Checklist. (By the way, I could not find information about subgroup analyses on Page 18. Please kindly double-check the answer.) 42. Page 30: The deviation from the recommended posology in SmPC may influence external validity of the study, see my comment above. In case it is a local clinical practice in Japan/Australia, I would recommend explicitly mentioning that in the manuscript. 43. Page 30, line 52: See above my comment – in my opinion, it is "efficacy and safety", not "efficacy and harms". 44. Page 30, line 55: It is impossible to clarify treatment standard with one single RCT, see above my comment. Hence, I suggest editorial correction: "the results of the trial will help to clarify …." 45. Abbreviations: Please add disclosure for KPS, AKPS, PRO-AEs, BPI-SF, and check once again throughout the text, whether every abbreviation is explained. 46. Page 36, line 31: Is it "patient representatives"? I do not believe that it is appropriate to call patients "consumers" taking into account the study setting and nosology. 47. Study flowchart: I recommend using of wording "study treatment" here instead of "intervention" in order to avoid confusion with surgical studies, i.e. "within 1 week before treatment start" or "within 1 week before randomisation". 48. Study flowchart: The English translation of the time-points is misleading, e.g. "3 days after intervention". It should be "3 days after treatment start", because treatment with duloxetine/pregabalin was continuous, not a one-time intervention on D1. 49. Study flowchart: Please kindly ensure that all study assessments are included. For instance, I could not find KPS/AKPF or safety lab tests. 50. Study flowchart: Please add "(if consented), i.e. "Patient interview (if consented)".

REVIEWER	Jose Carlos Roche Bueno Lozano Blesa University Clinical Hospital
REVIEW RETURNED	12-May-2021

GENERAL COMMENTS	The Protocol has been well designed

REVIEWER	Diana Wilkie University of Florida
REVIEW RETURNED	05-Sep-2021

GENERAL COMMENTS	The authors present a protocol manuscript for a well designed study of selected type of neuropathic pain in palliative care patients with cancer. Except for minor copyediting that is required prior to publication, the manuscript is well conceived and written following the SPIRIT standards. The plans for statistical analysis are sketchy, especially how the missing data will be handled in a population known for health decline. It also is not clear if the patients will be inpatient or outpatient for the study period.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Igor Dykukha, Almirall Hermal Gmbh

Abstract

1. Introduction: The exclusion of the patients with chemotherapy-induced neuropathic pain (CINP) is important for understanding the study design/results, because, for instance, the efficacy of duloxetine was proved in RCTs so far particularly in CINP.

Response #1:

In accordance with the Reviewer's comment, we have clarified the exclusion of the patients with chemotherapy-induced neuropathic pain on the 1st paragraph. (page 3, lines 3-5)

2. Introduction: "both classes of drugs …" (plural)

Response #2:

In accordance with the Reviewer's comment, we have changed to "both classes of drugs …" (plural) (page 3, line 8)

3. Introduction: It is not possible to measure "net effect" in this study, because that would require a comparison to placebo, e.g. as a third arm. Please re-phrase.

Response #3:

We thank the Reviewer for this insightful comment. In accordance with the Reviewer's comment, we have changed from "the net effect" to "efficacy and safety". (page 3, line 9)

4. Methods (suggestion): "…(LANSS) of ≥12 despite of an adequate trial of regular opioid medication…."?

Response #4:

In accordance with the Reviewer's comment, we have revised the Methods section. (page 3, lines 14-15)

5. Methods: Please add a sentence that dose escalation is until day 14 and that from day 14 till 21 it is dose de-escalation period to avoid withdrawal effects.

Response #5:

In accordance with the Reviewer's comment, we have added the sentence in the Abstract and Methods section. (page 3, line 18- page 4 line 1, page 19, lines 14-15)

6. Methods: "…mean difference in BPI item 3" in order to clarify the statistical parameter – it is a mean.

Response #6:

In accordance with the Reviewer's comment, we have added "mean" in the Methods section. (page 4, line 2)

7. Methods: "…patients will be enrolled between…" or "…patients will be recruited into study between…", not "examined".

Response #7:

In accordance with the Reviewer's comment, we have changed to "A sample size of 160 patients will be enrolled between February 2020 and March 2023. (page 4, line 3)

Strengths and limitation of this study

1. Bullet-point 1. Please clarify that it were patients with chronic neuropathic cancer pain (NCP), not induced by the chemotherapy.

Response #1:

In accordance with the Reviewer's comment, we have added "not induced by the chemotherapy" to the Bullet-point 1.

2. Bullet-point 2. Instead of "collaborative" nature of study, I would stress the high-quality DB-RCT multi-center study design. Both compared interventions are not necessarily harmful, I strongly recommend saying "safety and tolerability" instead of "harm" (see also my comment below).

Response #2:

In accordance with the Reviewer's comment, we have revised our manuscript to "The high-quality DB-RCT multi-center study design and adequately powered trial designed to provide a clinically meaningful outcome, and enable the safety and tolerability following intervention to be prospectively and systematically evaluated."

3. Bullet-point 3. In my opinion, exclusion of CINP is not necessarily makes comparison more accurate, because for instance duloxetine has a proved effect in CINP in a 1 DB crossover RCT with 231 patients (Smith et al. JAMA 2013), while for pregabalin positive effect in CINP was reported only in one observational study with 23 patients (Saif et al. Anti-cancer Res 2010) and in a case series (Atreya, Indian Journal of Palliative Care 2016). I think that clinical focus on CNP not related to chemotherapy might be further rationale to exclude CINP patients.

Response #3:

In accordance with the Reviewer's recommendation, we revised our manuscript focusing on NCP not related to chemotherapy.

Main manuscript

1. Introduction: I am afraid, a single RCT cannot answer a question about first-line / second-line recommendation. Apart of evidence, guidelines consider also other issues like, for instance, existing standard of care, other available treatments (including non-pharmacological) or regulatory status (label). Please kindly re-phrase the statement "The results of this RCT will clarify the first-line standard treatment for NCP", e.g. "study may help to clarify".

Response #1:

In accordance with the Reviewer's comment, we revised our manuscript. (page 7, lines 13-14)

2. Introduction: Please check and shortly summarise recent treatment guidelines, for instance https://www.awmf.org/fileadmin/user_upload/Leitlinien/128_D_Ges_fuer_Palliativmedizin/128-001OLkengl_S3_Palliative_care_2021-03.pdf (Germany).

Response #2:

In accordance with the Reviewer's recommendation, we have summarized recent three treatment guidelines including
"https://www.awmf.org/fileadmin/user_upload/Leitlinien/128_D_Ges_fuer_Palliativmedizin/128-001OLkengl_S3_Palliative_care_2021-03.pdf (Germany)". (page 6, lines 9-10)

3. Methods: A sub-study is planned. In SPIRIT Checklist, item 26b should be probably marked with "Yes" instead of "N/A".

Response #3:

In accordance with the Reviewer's comment, we revised our SPIRIT Checklist.

4. Box 1, inclusion criteria: You may consider clarification of the first inclusion criterion, e.g. "…who are in investigator's opinion are feasible for the therapy with duloxetine and/or pregabalin".

Response #4:

In accordance with the Reviewer's recommendation, we revised Box1.

5. Box 1, inclusion criteria: I believe, the second inclusion criterion can be combined with the third one, i.e. "Insufficient response to an adequate opioid medication (….) defined as pain related to cancer with a worst pain score of ≥4 or greater on BPI item 3 (worst pain intensity) score in the past 24 hours".

Response #5:

In accordance with the Reviewer's recommendation, we have combined the second inclusion criterion with the third one.

6. Box 1, inclusion criteria: It is "KPS/AKPS" in the time and event schedule (Table 1). Please ensure consistency throughout the text.

Response #6:

In accordance with the Reviewer's recommendation, we have revised Box1.We use just AKPS, so we have omitted KPS from the Box1. Please see Response #23.

7. Box 1, inclusion criteria: The last inclusion criterion allowing continuation of the other adjuvant analgesics including antidepressants, anticonvulsants, NMDA antagonists might need further clarification (e.g. in discussion section), because of 1) risk of drug-drug interactions (how it is managed in the study), 2) masking/confounding of the true effect of the study intervention.

Response #7:

Although patient safety will be ensured by avoiding the use of drugs that are contraindicated in the drug instructions due to drug-drug interactions, we will permit the possibility of masking/confounding of the true effect of the study intervention due to the priority of proceeding with a pragmatic trial. We have added this point on the Discussion section.

8. Box 1, exclusion criteria: Do you mean "women with childbearing potential who do not agree to use an adequate contraception"? If needed, please re-phrase "may possibly be pregnant".

Response #8:

We are not trying to ask about contraceptive intentions, so we think the current description is fine.

9. Recruitment: Please clarify whether or not an additional consent for the sub-study required.

Response #9:

An additional consent is required for the sub-study and this is now clarified. (page 8, line 5)

10. Randomisation: I understand the idea to stratify the randomisation for as many confounders as possible, but still it is not quite clear, whether all of them are crucial for the robustness of the primary endpoint. Some confounders looks exploratory (a hypothetic assumption). The interactions could be explored post-hoc as a sensitivity (sub-group) analysis. On the other hand: 1) impact on statistical power (was stratification considered during calculation of the sample size?); 2) more complicated statistical analysis with adjustments to all confounders (strata).

Response #10:

We believe that the adjustment factors we chose are established confounders, and we selected these as essential for adjustment. We have cited the literature to show the reasons for the selection of each stratification factor. The reasons for choosing the six stratification factors are as follows

(1) Degree of pain: It is known that the meaning of pain relief differs depending on the pre-treatment NRS, such as the fact that the higher the pre-treatment pain score, the lower the NRS is likely to be, and we classified the patients based on whether they were suffering from severe pain or not as described in the NCCN guideline.(Ref 2, 21)

(2) Opioid dose: There is no clear definition of high or low dose, but opioids above 90 mg have been reported to increase the risk of delirium (Ref 22), and the criteria for low dose were based on Ref 23. Low doses of opioids include the possibility that an element of nociceptive pain may remain.

(3) According to a previous study, a clear association of elevated pain levels with psychiatric symptoms such as depression and anxiety has indicated in oncological patients. (Ref 24).

(4)-(6)：It is well known that pharmacokinetics changes with race and body weight, affecting drug efficacy, and that treatment effects vary by site. According to the previous studies, one of the most common variables used for adjustment were study site, race, and body weight (Ref 25,26).

(page 11, lines 7-13)

Regarding the interactions, in accordance with the reviewers' comments, we will consider conducting a post-hoc analysis.

We did not consider stratification when calculating the sample size, but we would like to examine more complicated statistical analysis with adjustments for all confounders post-hoc, as the reviewer suggested.

11. Randomisation: If applicable, please mention per site recruitment caps (max, min number of patients).

Response #11:

We have not set recruitment caps (max, min number of patients) per site.

12. Table 1: I suggest renaming the table to “Times and Events Schedule”, according to commonly used terminology.

Response #12:

In accordance with the Reviewer’s recommendation, we have renamed the Table.

13. Table 1: Consider using commonly used terms, i.e. “End of Sudy” (“EoS”) instead of “Exit”. I could not find in the text clarification for the abbreviation “WD” (is it “Early Termination”, “ET”?), please add a footnote.

Response #13:

In accordance with the Reviewer's recommendation, we have used EoS and ET, then added footnotes.

14. Table 1: It is very common to design last visit in the study (End of Study Visit, EoS), which is D21, in the same way as "Early Termination" (ET) visit, i.e. "EoS/ET".

Response #14:

In accordance with the Reviewer's recommendation, we have revised Table1.

15. Table 1: The assessments in down-titration period "D15-20" might need clarification (e.g. a footnote): assessment of AEs (Section "Clinician assessed") is do-able only in case of in-patient cohort. **Response #15:**

In accordance with the Reviewer's comment, we have corrected the error in the assessment date from D15-20 to D21.Please see Table1.

16. Table 1: "Sub-study (if consented)" (singular). Please keep in mind that Informed Consent procedure for the sub-study should be described in the appropriate section of the paper and reflected in the SPIRIT Checklist.

Response #16:

In accordance with the Reviewer's comment, we have described the informed consent procedure for the sub-study and reflected in the SPIRIT checklist. (page 8 line 5, SPIRIT checklist)

17. Page 17, line 42: According to ICH GCP it should be signed ICF (original). Please kindly correct wording to "a signed copy of".

Response #17:

In accordance with the Reviewer's recommendation, we have revised our manuscript. (page 14, line 3)

18. Page 17, line 56: Editorial correction: "the electronic data capture system VIEDOC 4".

Response #18:

In accordance with the Reviewer's comment, we have revised our manuscript. (page 14, line 10)

19. Harms: I strongly advise against using word "harm(s)" throughout the text, because in my opinion it is misleading. The medical treatment interventions are not necessarily harmful. Besides, commonly used terms in pharmacovigilance are "safety" and "tolerability". I recommend re-naming the section to "Safety assessments" and replace word "harm" everywhere in text.

Response #19:

In accordance with the Reviewer's strong recommendation, we have changed to the word "safety" instead of "harm" everywhere in the text.

20. Harms: Please note that there is already an updated version of CTCAE available – Ver. 5 (2017; https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Please consider using it or explicitly explain why you prefer to use the old one.

Response #20:

We conducted an RCT using CTCAE – Ver. 4 as well in a previous study (Matsuoka et al. BMJ Open 2017, JPSM 2019). We aimed to obtain comparable data to this previous study.

21. Page 18, line 41: do you mean "by health care providers properly"?

Response #21:

Yes, we mean "by health care providers properly". In accordance with the Reviewer's comment, we have changed our manuscript. (page 15 line 5)

22. Measurement tools: Please consider using the wording "assessment tools" instead of "measurement tools".

Response #22:

In accordance with the Reviewer's recommendation, we have revised our manuscript. (page 15 line 7)

23. Measurement tools: The section about KPS and AKPS is missing. I presume, it is "Karnofsky Performance Status" and "Australia-modified Karnofsky Perfomance Status"? The disclosure of the abbreviation is missing in manuscript, please add it. Also, please explain in the section, how the two somewhat different scoring approaches will be analysed / matched within the common database.

Response #23:

At first, the eligibility criterion is the same for both indicators at 50 or above, so there is no impact on the eligibility evaluation by parallel using KPS and AKPS. Originally, it was planned to use KPS in Japan and AKPS in Australia based on the general practice in each country. Before implementing the study protocol in Japan, it turned out that the assessment by AKPS was also possible in Japan and that KPS was unnecessary. So, we will choose only AKPS and have added the disclosure of the abbreviation of it. (page 18, lines 15-18)

24. CTCAE/PRO-CTCAE: Please see my comment above concerning availability of Version 5.

Response #24:

We thank the Reviewer for this insightful comment. We conducted an RCT using CTCAE – Ver. 4 in a previous study (Matsuoka et al. BMJ Open 2017, JPSM 2019). We aimed to obtain comparable data to this previous study.

25. Interventions: I believe, this part of the study design might require the most attention, because 1) the starting dosages (30mg duloxetine or 50mg pregabalin daily) are lower than recommended in the approved labels (60mg and 150mg respectively; https://www.ema.europa.eu/en/documents/product-information/cymbalta-epar-product-information_en.pdf, https://www.ema.europa.eu/en/documents/product-information/lyrica-epar-product-information_en.pdf); 2) the study allows participation of patients with CL-Cr between 30 and 60 mL/min, so pregabalin dosage might need to be adjusted in some patients; 3) the primary endpoint assesses the effect a few days after end of the dose titration (which is performed based mostly on safety and tolerability situation, rather than efficacy). You might need to elaborate about chosen titration regime and treatment duration, as well as provide explanation to deviation from SmPC text, if any; 4) the deviation from the recommended posology in SmPC might influence external validity of the study. It was decided to use 1/2 of the recommended starting dose in case of duloxetine and 1/3 in case of pregabalin, which could be probably not so big deal should the study treatment would be longer. However, in case of 14 days treatment such “imbalanced” up-titration over 8 days may confound primary endpoint.

Response #25:

1) As the starting dose differs between Australia and Japan, it was necessary to determine a uniform dose for the international study.

The starting dose of duloxetine in Japan is 20 mg in the setting for palliative care (Matsuoka et al. JJCO 2019,) while in the West it is usually 30 mg or 60 mg. We chose 30 mg for the starting dose of duloxetine because we assumed that it was also tolerable for Japanese patients.

In the same setting, the starting dose of pregabalin in Japan is 50 mg (Matsuoka et al. JJCO 2019), while in the West it is usually 25-100mg from the results of recent systematic review and meta-analysis (Kane C et al., Palliative Medicine 2018). Taking these results into consideration, we assume that starting 150 mg pregabalin is not tolerable and 50 mg is safe for patients in both countries. We have added this point on the Discussion section. (page 26 lines 9-10, page 28 lines 9-17)

2) Because we set the dose of pregabalin that is suitable even for patients with CL-Cr 30-60 mL/min in the study, such patients are not excluded and dose adjustment is not required.

3) The observation period of the previous study (Caraceni et al., JCO) that we referred to was 10 days. As the subject was a vulnerable cancer patient, we considered that seven days after the end of the dose titration is sufficient for the primary endpoint assessment and that a total of 2 weeks (3 weeks including the tapering period) study period is enough for other assessments, especially safety.

4) For both arms, the dose is increased to the maximum dose one week (Day 8) before the evaluation of the primary endpoint (Day 14), and the analgesic effects of both duloxetine and pregabalin are stable one week after reaching the maximum dose. The titration schedule is therefore less likely to

impact the assessment of the primary endpoint, if there is any imbalance of starting doses.

26. Page 23, line 34: See above my comment concerning “net effect”. I suggest avoiding using of that term in the context.

Response #26:

In accordance with the Reviewer’s comment, we have changed from “the net effect” to “efficacy and safety”. Please see Abstract Response #3. (page 7, lines 10,12-13)

27. Page 24, line 13: Editorial correction – “the most appropriate pain medication according to the local standard of care”. Using of the wording “open label medication” is in my opinion false in the context.

Response #27:

In accordance with the Reviewer’s recommendation, we have revised our manuscript. (page 21, lines 1-2 9)

28. Co-treatments: I suggest using a commonly used term “Concomitant therapy” instead of “Co-treatments”.

Response #28:

In accordance with the Reviewer’s recommendation, we have revised our manuscript. (page 21, line 4)

29. Co-treatments: See above my comment regarding using of other adjuvant analgetics throughout the study. Without explanation/rationale this issue makes an impression of a strong confounding influencing both efficacy and safety outcomes. Further, it should be clear from the manuscript that there is no jeopardy to patients due to drug-drug interactions.

Response #29: In accordance with the Reviewer’s recommendation, we have discussed the drug-drug interactions in the Discussion section. (page 26, lines 7-8, page 27, lines 2-7)

30. Primary endpoint: I trust is a “mean difference between”, not “comparison”.

Response #30:

In accordance with the Reviewer’s recommendation, we have revised our manuscript to “The primary endpoint is a mean difference between study arms of the worst pain intensity over the previous 24 hours at day 14 measured using the BPI items 3.” (page 21, line 14)

31. Secondary endpoints: Karnofsky Performance Status will be measured repeatedly. May be it makes sense to analyse the data explorative and add an exploratory secondary endpoint.

Response #31:

In accordance with the Reviewer's comment, we will try to implement it in the post-hoc analysis.

32. Secondary endpoints: Consider adding end-point for the Global Impression of Change.

Response #32:

In accordance with the Reviewer's comment, we will try to implement this in the post-hoc analysis.

33. Statistical considerations: Handling of the missing data is crucial for consistency and robustness of the study results. Please describe imputation methodology for the missing data and describe, whether a sensitivity analyses for the primary endpoint (e.g. NRI, As Observed, LOCF) is planned.

Response #33:

All statistical procedures will be developed in the future, so the word "were" was changed to "will be". In addition, "before data evaluation" was changed to "through a blinded data review before data fixation". We plan to examine them through a blinded data review and finalize them in the statistical analysis plan before data fixation. For the primary endpoint, the current policy is to employ observed case analysis when the number of missing observations is very small, and to employ multiple imputation when there are a certain number of missing observations and the missing mechanism is considered to be missing at random. (page 22, line 18- page 23, lines 1-3)

34. Statistical considerations, statistical hypothesis: Stratified randomisation means adjustment for confounders, which statistically calculated as "LS mean" (less-squire mean). I presume, you are going to use Cochrane-Mantel-Haenzel (CMH) adjustment? Please expand on that a bit in the manuscript.

Response #34:

The purpose of employing confounding factors at the time of randomisation is to "ensure comparability between groups (reduce bias)," while the purpose of adjusting confounding factors at the time of analysis is to "improve precision". In this study, stratified randomisation is used to ensure comparability between groups. Even if some imbalance in confounding factors between groups occurs as a result of randomization, we accept it as a result of randomization, at least in the primary endpoint, i.e., our policy is not to adjust at the time of analysis. Therefore, as the reviewer suggested, we plan to make inferences based on simple arithmetic averages rather than LS means based on CMH adjustments. Post hoc adjustment analysis by stratification factors may be conducted.

35. Statistical considerations, sample size: In situation of uncertainty about the comparative effect sizes, the superiority design might be risky, and perhaps it might have been advisable to go for the non-inferiority primary endpoint and perform superiority tests as secondary endpoints. In latter case, I would suggest prioritisation of the main secondary endpoints using the Holm's adjustment procedure for multiplicity.

Response #35:

We wish to express our deep appreciation to the Reviewer for his insightful comment on this point. As the reviewer pointed out, "The non-inferiority primary endpoint and perform superiority tests as secondary endpoints" may be a better choice. However, after discussions among researchers, we came to the conclusion that we should verify the superiority of the primary endpoint, as this is why we planned and started this study.

36. Statistical considerations, sample size: Please mention, in case sample size was adjusted also for the stratified randomisation.

Response #36:

As we have outlined in "**Response #10**", the sample size calculation does not take stratification into account.

37. Ethical issues: I recommend to explicitly mention that ICH GCP requirements are considered in the study design and conduct. Based on the information in the manuscript it is very likely that the study has been designed in accordance to the ICH GCP standards.

Response #37:

Australia has adopted the ICH GCP for the conduct of clinical trials and this study meets those requirements, but there are some differences between the Japan's Clinical Trials Act and ICH GCP. As there are two different regulations required across jurisdictions we have added the sentence "(The study will be performed in accordance with the Declaration of Helsinki,) the Australian adoption of ICH GCP and the Japan's Clinical Trials Act." instead of "ICH GCP". (page 24, lines 17-18)

38. Discussion: Please consider also systematic review van den Beuken-van Everdingen et al. Pain Practice 2017.

Response #38:

We referred this systematic review on the discussion. (page 25, line 10）

39. Discussion: There are uncertainties related to the effect size of pain reduction of the compared interventions in chronic, not chemotherapy-induced, neuropathic cancer pain, which might have been addressed by adding a placebo arm (e.g., duloxetine: pregabalin: placebo = 2:2:1). Please kindly add explanation why placebo arm was not deemed necessary/possible, though the effect of the both active interventions in this particular population has not been yet well established. Technical issues? Ethical concerns? Other?

Response #39:

We had discussed the necessity of placebo arm, on the other hands Gabapentinoids (gabapentin and pregabalin) are one of the most widely used therapies for neuropathic cancer pain (not for just cancer pain, nor CIPN). Phase III studies revealed moderate analgesic effects of gabapentinoids (gabapentin and pregabalin) compared with placebo in combination with opioids for neuropathic cancer pain, not

for just cancer pain, not for CIPN. From the results of these 2 RCTs, we concluded that it was no longer ethical to use a placebo arm. There is no longer the equipoise required to justify such an arm.

We have added this point on the Discussion section. (page 26, line 9, page 27 lines 17-18, page 28, lines 1-4）

40. Discussion: I am not sure, whether exclusion of some neuropathic conditions (chemotherapy-induced or central NCP) could significantly reduce population heterogeneity, because of methodological challenges in the differential diagnostics, but I appreciate the author's transparent position in the discussion section.

Response #40:

As the Reviewer mentioned in "Strengths and limitation of this study Bullet-point 3", I think that clinical focus on neuropathic cancer pain not related to chemotherapy nor central neuropathic pain might significantly reduce population heterogeneity.

41. Discussion: The authors mention subgroup analyses. Perhaps that could be shortly described in the statistic part.

Anyway, you answered "Yes" to the question 20b of the SPIRIT Checklist. (By the way, I could not find information about subgroup analyses on Page 18. Please kindly double-check the answer.)

Response #41:

In accordance with the Reviewer's recommendation, we have added the description of subgroup analysis in the text (page 23, lines 16-18) and answered "Yes" to the SPIRIT checklist.

42. Page 30: The deviation from the recommended posology in SmPC may influence external validity of the study, see my comment above. In case it is a local clinical practice in Japan/Australia, I would recommend explicitly mentioning that in the manuscript.

Response #42:

As we mentioned in **Response #25**, the starting dose differs between Australia and Japan, it was necessary to determine a uniform dose for the international study.

The starting dose of duloxetine in Japan is 20 mg in the setting for palliative care (Matsuoka et al. JJCO 2019,) while in the West it is usually 30 mg or 60 mg. We chose 30 mg for the starting dose of duloxetine because we assumed that it was also tolerable for Japanese patients.

In the same setting, the starting dose of pregabalin in Japan is 50 mg (Matsuoka et al. JJCO 2019), while in the West it is usually 25-100mg from the results of recent systematic review and meta-analysis (Kane C et al., Palliative Medicine 2018). Taking these results into consideration, we assume that starting 150 mg pregabalin is not tolerable and 50 mg is safe for patients in both countries.

We have added this point on the Discussion section. (page 26 lines 9-10, page 28 lines 9-17)

43. Page 30, line 52: See above my comment – in my opinion, it is “efficacy and safety”, not “efficacy and harms”.

Response #43:

In accordance with the Reviewer’s recommendation, we revised our manuscript. (page 29, line 7)

44. Page 30, line 55: It is impossible to clarify treatment standard with one single RCT, see above my comment. Hence, I suggest editorial correction: “the results of the trial will help to clarify ….”

Response #44:

In accordance with the Reviewer’s comment, we revised our manuscript. (page 29, line 9)

45. Abbreviations: Please add disclosure for KPS, AKPS, PRO-AEs, BPI-SF, and check once again throughout the text, whether every abbreviation is explained.

Response #45:

In accordance with the Reviewer’s comment, we have added some abbreviations after reading through the text. (page 33-34)

46. Page 36, line 31: Is it “patient representatives”? I do not believe that it is appropriate to call patients “consumers” taking into account the study setting and nosology.

Response #46:

It means “patient and caregivers representatives”. In accordance with the Reviewer’s comment, we revised our manuscript. (page 31, lines 14-16, page 32, lines 1-2)

47. Study flowchart: I recommend using of wording “study treatment” here instead of “intervention” in order to avoid confusion with surgical studies, i.e. “within 1 week before treatment start” or “within 1 week before randomisation”.

Response #47:

In accordance with the Reviewer’s recommendation, we revised our Figure.

48. Study flowchart: The English translation of the time-points is misleading, e.g. “3 days after intervention”. It should be “3 days after treatment start”, because treatment with duloxetine/pregabalin was continuous, not a one-time intervention on D1.

Response #48:

In accordance with the Reviewer’s recommendation, we have revised our Figure.

49. Study flowchart: Please kindly ensure that all study assessments are included. For instance, I could not find KPS/AKPF or safety lab tests.

Response #49:

As we mentioned in **Response #23,** at first, the eligibility criterion is the same for both indicators at 50 or above, so there is no impact on the eligibility evaluation by parallel using KPS and AKPS. Originally, it was planned to use KPS in Japan and AKPS in Australia based on the general practice in each country. Before implementing the study protocol in Japan, it turned out that the assessment by AKPS was also possible in Japan and that KPS was unnecessary. So, we will choose only AKPS and add all study assessments to the flowchart.

50. Study flowchart: Please add "(if consented), i.e. "Patient interview (if consented)".

Response #50:

In accordance with the Reviewer's recommendation, we revised our Figure.

Reviewer: 2

Dr. Jose Carlos Roche Bueno, Lozano Blesa University Clinical Hospital Comments to the Author:

The Protocol has been well designed

Response to Reviewer 2:

We thank the Reviewer for this comment.

Reviewer: 3

Dr. Diana Wilkie, University of Florida

Comments to the Author:

The authors present a protocol manuscript for a well designed study of selected type of neuropathic pain in palliative care patients with cancer. Except for minor copyediting that is required prior to publication, the manuscript is well conceived and written following the SPIRIT standards. The plans for statistical analysis are sketchy, especially how the missing data will be handled in a population known for health decline. It also is not clear if the patients will be inpatient or outpatient for the study period.

Response to Reviewer 3:

All statistical procedures will be developed in the future. We plan to examine them through a blinded review and finalize them in the statistical analysis plan before data fixation. For the primary endpoint, the current policy is to employ observed case analysis when the number of missing observations is very small, and to employ multiple imputation when there are a certain number of missing observations and the missing mechanism is considered to be missing at random. (page 22, line 18-

page 23, lines 1-3) In accordance with the Reviewer's recommendation, we have clarified the participants (i.e., both inpatients and outpatients) (Abstract page 3 line 16, page 8 line 8)

VERSION 2 – REVIEW

REVIEWER	Igor Dykukha Almirall Hermal GmbH, Medical Affairs
REVIEW RETURNED	21-Oct-2021

GENERAL COMMENTS	Thank you for your detailed response and for taking into considerations my comments.

REVIEWER	Diana Wilkie University of Florida
REVIEW RETURNED	14-Nov-2021

GENERAL COMMENTS	The revisions are appropriate. Minor editing is still required in the text and reference list.