Author's response to reviews

Title: Can treatment with Cocculine improve the control of chemotherapy-induced emesis in early breast cancer patients? A randomized, multi-centered, double-blind, placebo-controlled Phase III trial

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Responses to Reviewers

Reviewer #1

**Major Compulsory Revisions**

1. **Comment 1:** In the abstract, the crucial statement “High percentages of patients …reported that nausea had no impact on their quality of life” implies that nausea as such does not affect the patients' quality of life. Instead, the authors wanted to say that high percentages of patients (irrespective of the treatment group) didn’t experience nausea: please reformulate.

   **Author response:** This sentence mentions the results of the primary endpoint analysis (i.e. nausea dimension of the FLIE score during the first course of chemotherapy). In this study, high percentages of patients (i.e. 205 patients (50.9%; 103 patients in the placebo and 102 in the homeopathy arms)) have reported that nausea has no impact on their quality of life (i.e. FLIE score >6, See Table 3). In addition, only a small percentage of patients experienced severe nausea and vomiting (See Table 6). The mentioned sentence was reformulated as follows (See Abstract, Results section, page 2): “A total of 205 patients (50.9%; 103 patients in the placebo and 102 in the homeopathy arms) had nausea FLIE scores > 6 indicative of no impact of nausea on quality of life during the 1st chemotherapy course. There was no difference between the 2 arms when primary endpoint analysis was performed by chemotherapy stratum; or in the subgroup of patients with susceptibility to nausea and vomiting before inclusion. In addition, nausea, vomiting and global emesis FLIE scores were not statistically different at any time between the two study arms. The frequencies of severe (Grade ≥ 2) nausea and vomiting were low in our study (nausea: P: 17.6% vs C: 15.7%, p=0.62; vomiting: P: 10.8% vs C: 12.0%, p=0.72 during the first course).”

2. Throughout the article, the authors use the brand name of the homeopathic remedy, which is not a good practice in a scientific article – please use the brand name only in the methods section in the context of the description of the complex homeopathic remedy.

   **Author response:** As Cocculine is a complex homeopathic medicine composed of 4 elements, the name Cocculine cannot be replaced easily. However, if the Editorial office considered that this particular point may disturb the reading, we are willing to change the term Cocculine with the name of the 4 components. The brand name Cocculine® is used only in the Methods section.

3. The homeopathic remedy was only given on day -1 to day 2 whereas nausea was assessed until day 6 – why? This should be explained / discussed in the discussion section. I think it would have been interesting to find out whether administration of the homeopathic remedy would have improved nausea on days 3 to 6 (especially when conventional anti-emetic medication was finished).

   **Author response:** The Cocculine treatment schedule used in this trial has been recommended by Boiron and is representative of Cocculine documentation (French Summary of Product characteristics of Cocculine, validated by French Agency [ANSM]). Of note, the Cocculine treatment schedule used in this study is the same than the one used in the study reported by Genre et al. 2003 (see attached abstract) and was evaluated as add on therapy.
Reviewer # 2

Major Compulsory Revisions:
1. “...However the trial plan is such that from the beginning you don’t expect positive results because: Except the last regime with Docetaxel the chemotherapy regime was not highly emetyogenic hence strong antiemetic therapy ie Ondansetron and steroid was adequate enough to take care of nausea and vomiting Cocculine had little space to do any thing over and above the therapy given

   Author response: A previous report using similar anti-emetic treatment has reported that “75% percent of patients with nausea and 50% of those with vomiting reported a negative impact on the performance of activities of daily living when queried with the Functional Living Index–Emesis (FLIE) questionnaire despite modern prophylactic anti-emetic treatment” – see reference #13).

   Since several clinical reviews have highlighted that homeopathy should not be substituted for proven therapies (cf. Jonas WB, Kaptchuk TJ, Linde K. A critical overview of homeopathy. Ann Intern Med. 2003 Mar 4;138(5):393-9), Cocculine was evaluated as add-on therapy in our trial.

2. Giving the same drug for all cases of Chemotherapy related vomiting violates the basic principles of Homeopathy”

   Author response: In this study, we have investigated the effect of a complex homeopathic medicine in a large population of randomized patients. This approach is justified by the followings:
   - In the daily practice, the side effects of conventional chemotherapy treatment are preferably treated routinely. Individual homeopathic prescription is therefore not easily compatible with routine clinical activity.
   - Individualized treatment is a time consuming and expensive approach and required the implication of an expert homeopath. Therefore, such approach was not easily applicable in the context of a multi-centered study.
   - Finally, individualized remedy is less feasible for double-blind randomized trials.
Major Compulsory Revisions

1. The authors should state clearly (also in the abstract) that the described treatment does not represent classical homeopathy, however complex homeopathy. This makes a significant difference regarding methodology. It is clear that side effects of conventional treatment may preferably be treated routinely and may not allow individual homeopathic prescription.
   
   **Author response:** This clarification has been added in the abstract and throughout the MS. Following review of this MS, the discussion has been reorganised and partially rewritten (page 13-15). A discussion related to this topic was added in the Discussion Section, page 13-15 as follows:
   
   “Our study has evaluated the effect of a complex homeopathic medicine in a large randomized study. This strategy was chosen for the following reasons: (i) first of all, the management of side effects related to conventional treatment need to be integrated in the routine of daily clinical practice thus not allowing time-consuming individual homeopathic prescription, (ii) secondly, the use of homeopathy with an individualized remedy is expensive and required the implication of the same experienced homeopath that is difficult to set up in multicenter trial and (iii) finally, individualized prescription is not easily compatible with double-blind randomized trials 23.”

2. Data are missing for: Patients’ belief as to group (Cocculine or placebo), belief of homeopathy efficacy, comfort of homeopathy, side effects, etc. ("Clinical Research in Complementary Therapies" (Lewith et al, 2011, 2nd Ed.)) This should be discussed as a limitation.
   
   **Author response:** We agree with the reviewer, these data have not been collected and are missing. Of note, the reference mentioned by the Reviewer was not published at time of this trial was set up. Following review of this MS, the discussion has been reorganised and partially rewritten (page 13-15).

Minor Essential Revisions

1. Page 3, para 3, line 2: rewrite „In an European ...“
   
   **Author response:** This sentence has been corrected.
Major Compulsory Revisions:

1. “… though the discussion and conclusions need to focus on the study outcomes (efficacy and safety of the study drug). They should not focus on the low rates of CINV in both study arms, which may or may not be explainable by the attention patients received.  
   **Author response:** The discussion and conclusions have been rewritten in the Abstract (page 2) and in the Discussion Section, pages 13-15.

2. In addition, there is a need to clarify that the study drug is a “complex” and not “classic” homeopathic remedy, and controversial statements regarding the efficacy of homeopathy for other indications should be removed.
   
   **Author response:** The revised version of the MS mentioned that Cocculine is a complex homeopathic remedy in the title, abstract, and throughout the MS.  
   A discussion on this topic has been added page 13 as follows: “Our study has evaluated the effect of a complex homeopathic medicine in a large randomized study. This strategy was chosen for the following reasons: (i) first of all, the management of side effects related to conventional treatment need to be integrated in the routine of daily clinical practice thus not allowing time-consuming individual homeopathic prescription, (ii) secondly, the use of homeopathy with an individualized remedy is expensive and required the implication of the same experienced homeopath that is difficult to set up in multicenter trial and (iii) finally, individualized prescription is not compatible with double-blind randomized trials.”  
   Controversial statements regarding the efficacy of homeopathy for other indications have been removed (i.e. references to Pommier at al, study in the Background section, to the 1991 meta-analysis by Kleijnen et al., Linde et al.; Lancet 1997: 350:834-43 & Jacobs et al. in 2003 have been deleted from the discussion Section).

3. Finally, the study’s limitations have not been presented, such as the low prevalence of CINV in both arms (with sample size based on a 0.5 difference); no comparison between groups for patient-related factors influencing the development of CINV (tendency for motion sickness, pre-existing anxiety, history of alcohol consumption, other factors); etc.
   
   **Author response:** The unexpected low prevalence of CINV is discussed in the discussion (see pages 13-15). An analysis of the primary endpoint was performed in the stratum of patients with susceptibility to emesis (See Table 4). However, we have no information on the impact of pre-existing anxiety, history of alcohol consumption or other factor on endpoints analysis.

Minor Essential Revisions

1. Title: should read “reduce” and not “improve” chemotherapy-induced emesis and should read “multi-centered” and not “multicentric”
   
   **Author response:** The title has been corrected as follows: “Can treatment with Cocculine improve the control of chemotherapy-induced emesis in early breast cancer patients? A randomized, multi-centered, double-blind, placebo-controlled Phase III trial”.

2. Abstract: Conclusion: The conclusions of the study should focus on the studied outcomes, and not the low rates of CINV in both study arms.
   
   **Author response:** The conclusion has been rewritten as follows: “This double-blinded, placebo-controlled, randomised Phase III study showed that adding a complex homeopathic medicine (Cocculine) to standard anti-emetic prophylaxis does not improve the control of CINV in early breast cancer patients.”
3. Background - • page 3, 2nd paragraph: the toxic effects of anti-emetic medications need to be presented, as well as contraindications to their use

**Author response:** The main adverse events of anti-emetic medications (aprepitant and ondansetron) include asthenia/fatigue, constipation, diarrhea, anorexia, Hiccups. The contraindications are mainly related to drug-drug interactions as aprepitant is a moderate inhibitor of CYP3A4. However, the authors consider that such information are not relevant in the context of this MS since Cocculine was evaluated as add-on therapy.

4. • page 3, 3rd paragraph: the last sentence states that homeopathic medicines are used by patients with cancer for “symptomatic relief, general supportive care as well as for adverse effects of cancer treatments”. This sentence needs to be clarified, since there is significant overlap between these terms, and a reference should be provided.

**Author response:** This sentence has been rewritten as follows (page 4) :” Overall, homeopathic approaches are used by cancer patients to alleviate their pain resulting from the disease itself or from conventional anti-cancer treatment 15.”

5. • page 3, end of 3rd paragraph: Here would be a good place for an explanation of the difference between “complex homeopathy” and “classic” homeopathy. There is no need to go into a further explanation of the principles of homotoxicology.

**Author response:** An explanation of the difference between complex and classical homeopathy has been added in the Background section page 5 as follows: “Different homeopathic practices coexist: the “classical” or “individualised” homeopathy using single homeopathic medicine that is prescribed according to the individual’s condition and history, (ii) the “clinical” homeopathy that uses the same homeopathic medicine for a group of patients with the same disease and (iii) the “complex” homeopathy that uses more than one homeopathic medicine, in a fixed combination or concurrently, for a particular condition.”

6. • page 3, 4th paragraph: The first sentence needs to be supported by a reference.

**Author response:** This sentence has been rewritten as follows (page 5): Cocculine is a homeopathic medicinal product registered in France for treatment of nausea and travel sickness composed of 4 homeopathic components (Coccus indicus 4 CH, Tabacum 4 CH, Nux vomica 4 CH, Petroleum 4 CH produced by Boiron, France, according to European Pharmacopoeia). Cocculine has been registered by French agency (ANSM), the summary of product characteristics is available only in French language.

7. Methods: • page 5, 2nd paragraph: A more detailed description of the computer program used for randomization would further increase the methodological quality of the study (Jadad/Oxford quality scoring system)

**Author response:** A more detailed description of the computer program used for randomization has been added page 6 as follows: “Randomisation was conducted centrally via a computer-generated system, using permuted blocks of four patients (the Jadad/Oxford score was ≥ 3/5). Patients were stratified by participating centre and type of chemotherapy regimen (FAC50 or FEC100 versus TAC). Allocation list was generated by the study statistician before the beginning of the study. Investigators asked the coordinating center by fax for a treatment allocation number”.

8. • page 7, top of the page: A description of the placebo tablets (shape, size, etc.) should be provided.

**Author response:** A description of the placebo tablets is provided in the revised MS, page 7 : “The placebo tablets were identical seemingly in the active tablets (packaging, colour, shape...). The placebo tablets were inert and contained only (Saccharose (75%), lactose (24%), and Magnesium stearate (1%)) without any homeopathic components”.

9. • page 6, 3rd paragraph: references 18 and 19 should be switched with 27-28 from the current reference list.

**Author response:** The reference list has been updated and corrected.
10. • page 7, 1st paragraph: the term “AE” needs to be written in full the first time it is mentioned. • same sentence: NCI-CTCAE v3.0 should have a cited reference
Author response: This has been corrected in the revised version of the MS.

11. Results: • page 9, 2nd and 3rd paragraphs: There seems to be a bit of confusion regarding the numbering of the tables. The numbers presented for median nausea severity (0.56 [P] vs. 0.58 [C], p=0.62) appear in Table 5 and not Table 4, as listed. The same is true for the occurrence of nausea during the 1st cycle (p=0.48), which is presented in Table 6 and not Table 4, as listed.
Author response: The numbering of tables has been corrected throughout the revised version of the MS.

12. • page 10, 1st paragraph: the term “SAE” needs to be written in full (i.e., “severe AE”) the first time it is used.
Author response: This has been corrected in the revised version of the MS.

13. Discussion: • page 11, 1st paragraph, 7th line: “Several clinical trials have shown the effectiveness of homeopathic medicines in allergic rhinitis, dermatological complaints and childhood diarrhea.22” This is a very problematic statement. Subsequent studies did not concur with the conclusions of the study by Jacobs e al. regarding childhood diarrhea, and the efficacy of homeopathy for allergic rhinitis and dermatological complaints remains to be proven. Most important, this information is not relevant to the discussion of the present study’s findings, and should be removed.
Author response: This statement has been removed.

14. • page 11, end of 1st paragraph: “Meta-analyses of clinical trials evaluating the effectiveness of homeopathic medicines…..” The conclusions of the 1991 meta-analysis by Kleijnen et al. regarding the efficacy of homeopathy (as well as the subsequent semi-positive meta-analysis by Linde et al.; Lancet 1997: 350:834-43) have been contested in later studies. It is beyond the scope of this article to debate the efficacy of homeopathy for anything other than CINV.
Author response: This statement has been removed.

15. • page 13, 2nd paragraph: citation #30 does not appear in the reference list.
Author response: The reference list has been updated and corrected.

16. • page 13, end of 2nd paragraph and Conclusions: The purpose of the study was to examine the efficacy of Cocculine on CINV, primarily following the 1st cycle of chemotherapy. The message of the paper should be that the study treatment was no better than placebo. Other study outcomes, such as the low reported frequency of CINV in both study arms, can be mentioned but should not be the focus of the discussion or conclusions reached from the results.
Author response: Discussions and conclusions have been rewritten (pages 13-15).

17. Acknowledgements: • it should be mentioned who provided the study drug and the place preparation(Boiron?)
Author response: Boiron, France has provided the study drug. This has been added in the Acknowledgement section of the revised MS.

Reviewer # 5

Major Compulsory Revisions

1. According to which guidelines or considerations have the investigators choosen the Cocculine treatment schedule (2-6-4 tablets, why not 3-3-3 or only by symptoms f.e.)?
Author response: The Cocculine treatment schedule used in this trial has been recommended by Boiron and is representative of Cocculine documentation (French Summary of Product characteristics of Cocculine, validated by French Agency [ANSM]). Of note, the Cocculine treatment schedule used in this study is the same than the one used in the study reported by Genre et al. 2003 (see attached abstract) and was evaluated as add on therapy.

2. I was not able to find any results of taking rescue medication. This would be interesting.
The use of anti-emetic concomitant medication has been analysed for all enrolled patients. There was no statistical difference in the use of rescue anti-emetic medication (Zophren, Solupred, Cocculine, Nux Vomica, Tabaccum, data not shown) between the study arms.

3. A prior study with CINV treatment with Cocculine was mentioned and discussed. Unfortunately, this study is not listed by Pubmed (or is there a mistake in the reference list?). Please attach the full text of this study with your re-submission if possible. Which assessment of vomiting and nausea was used in this other study? Are there further explanations of controversial results to this study?

Author response: The prior study with Cocculine has been conducted by Genre et al (GENRE D, TARPIN C, BRAUD AC, CAMERLO J, PROTIÈRE C, EISINGER F et al. Randomized double-blind study comparing homeopathy (cocculine) to placebo in prevention of nausea/vomiting among patients receiving adjuvant chemotherapy for breast cancer. Proceedings of the 26th annual San Antonio Breast Cancer Symposium 2003 Dec 3-6; San Antonio, USA. P. no. 637) and presenting at an annual Breast Cancer Symposium. The abstract is attached to our online submission and this reference is listed in the reference list (N°16).

4. Are there limitations of your study? I would like to see a discussion about classical homeopathy (single remedies in higher dilutions) and complex remedies (a mix of different less diluted substances). Might be a treatment with a single medication (i.e. only Nux vomica for every patient in the verum group) more efficient than in higher potencies? Classical homeopathy with an individualized remedy is expensive and less feasible for double-blind randomized trials.

Author response: A discussion on this topic was added page 12 as follows: “Our study has evaluated the effect of a complex homeopathic medicine in a large randomized study. This strategy was chosen for the following reasons: (i) first of all, the management of side effects related to conventional treatment need to be integrated in the routine of daily clinical practice thus not allowing time-consuming individual homeopathic prescription, (ii) secondly, the use of homeopathy with an individualized remedy is expensive and required the implication of the same experienced homeopath that is difficult to set up in multicenter trial and (iii) finally, individualized prescription is not easily compatible with double-blind randomized trials.”

Minor Essential Revisions

1. The authors displayed a lot of different types to analyse vomiting and emesis: the FLIE score, the diaries and investigator assessment and the demonstration of results after different cycles of chemotherapy. This was a little bit confusing.

Author response: Clarifications have been added in the written text throughout the revised MS.

2. In the written text of results the numbering of the tables is wrong: patients characteristics at baseline are shown in table 3, table 2 was not mentioned, FLIE scores were shown in table 4, patient self-evaluation in table 5 and investigators assessment in table 6. Please rearrange this.

Author response: The table numbering has been corrected in the revised version of this MS.

3. “...patients and...” has to be deleted in the first sentence in Results in the abstract.

Author response: This sentence has been corrected in the revised version of this MS.

3. The writing is acceptable but needs some further corrections

Author response: The full MS has been reviewed by Rob Steiner, a Senior Medical Writer.